University of Rhode Island

DigitalCommons@URI

Open Access Dissertations

2008

The Formulation and Process Development of a Novel Multiparticulate Extended Release Pharmaceutical Delivery Platform for a Highly Water Soluble Compound

Cyrus D. Agarabi

University of Rhode Island

Follow this and additional works at: https://digitalcommons.uri.edu/oa_diss

Recommended Citation

Agarabi, Cyrus D., "The Formulation and Process Development of a Novel Multiparticulate Extended Release Pharmaceutical Delivery Platform for a Highly Water Soluble Compound" (2008). *Open Access Dissertations*. Paper 499.

https://digitalcommons.uri.edu/oa_diss/499

This Dissertation is brought to you for free and open access by DigitalCommons@URI. It has been accepted for inclusion in Open Access Dissertations by an authorized administrator of DigitalCommons@URI. For more information, please contact digitalcommons-group@uri.edu.

THE FORMULATION AND PROCESS DEVELOPMENT OF A NOVEL
MULTIPARTICULATE EXTENDED RELEASE PHARMACEUTICAL
DELIVERY PLATFORM FOR A HIGHLY WATER SOLUBLE COMPOUND

BY

CYRUS D. AGARABI

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN
PHARMACEUTICAL SCIENCES

UNIVERSITY OF RHODE ISLAND

2008

DOCTOR OF PHILOSOPHY DISSERTATION

OF

CYRUS D. AGARABI

APPROVED:

Dissertation Committee:

Major Professor

Three handwritten signatures are written on three horizontal lines. The top signature is 'John T. Neuloh'. The middle signature is 'J. L. ...'. The bottom signature is 'W. Lee'.

A handwritten signature, 'Harold O'Neil', is written above a horizontal line.

DEAN OF THE GRADUATE SCHOOL

UNIVERSITY OF RHODE ISLAND

2008

ABSTRACT

This research compared a traditional drug development approach with an enhanced “Quality by Design” (QbD) approach to foster greater process and formulation understanding. Propranolol HCl extended release capsules and Metoprolol Succinate extended release tablets served as targets for development. The formulation and process parameters utilized well-established techniques, such as wet granulation, extrusion, spheronization, and fluid bed processing with commercially available aqueous or organic polymeric systems.

Propranolol HCl extended release capsules were a benchmark for current generic pharmaceutical process development to identify basic parameters for a suitable product. Metoprolol Succinate extended release tablets utilized the ICH Q8 annex guidelines approach to identify target profiles, and then; define, test, and link Critical Quality Attributes (CQAs). Preliminary data supported factor and level selections for the 2^3 full factorial and Box-Behnken experimental designs for elements of a conceptual design space.

Physical and chemical characterization of commercially available competitors established product target profiles. Particle size distribution, sphericity, moisture content, and dissolution profiles were studied as CQA's. Preliminary studies for the immediate release beads identified the water quantity during granulation, kneading time during granulation, and the duration of spheronization as significant factors for particle size generation, and sphericity. The traditional approach determined an organic system was necessary for Propranolol HCl to yield a stable extended release product. The aqueous sustained release coating studies for

Metoprolol Succinate found the polymer coating level, humidified curing condition, and curing duration were important factors. Altering the excipient blend formulation during initial tableting trials minimized segregation and bead damage.

The full factorial design for the development of immediate release beads identified spheronization time as a statistically significant factor in determining the standard deviation and relative standard deviation for sphericity. The Box-Behnken design for sustained release beads found the polymer coating levels to be a statistically significant main effect for the dissolution profile. Significant surface damage was apparent throughout the full factorial tableting design, with a “best case” approach yielding an improved dissolution profile. Traditional approaches incorporated into the QbD approach facilitate variable and level selection throughout the development process. Data generated via these statistical methods supports process understanding and future decision-making.

ACKNOWLEDGEMENTS

I would like to express my gratitude to the following people for their unwavering support throughout this process: Dr. Needham, Dr. Palinaswamy, the Staff at Cherokee Pharma Inc., my friends and family.

ABSTRACT	ii
ACKNOWLEDGEMENTS.....	iv
LIST OF FIGURES	x
LIST OF TABLES	xiii
LIST OF EQUATIONS.....	xv
Chapter 1 Study Overview	1
1.0 Introduction	1
1.1 Statement of the Problem	1
1.2 Objectives of the Study	2
1.3 Study Approach.....	6
Chapter 2 Pharmaceutical Regulatory Environment.....	10
2.0 Introduction	10
2.1 Regulatory Background of Generic Pharmaceuticals	10
2.2 Current State of Pharmaceutical Regulations for Manufacturing.....	13
2.2.1 PAT Background.....	14
2.2.2 Design Space-Background	15
2.2.3 Quality by Design (QbD) Background	16
2.3 Organic Solvents	23
2.3.1 Class 1 Solvents: Solvents to be Avoided.....	24
2.3.2 Class 2 Solvents: Solvents to be Limited	24
2.3.3 Class 3 Solvents: Solvents with Low Toxic Potential	24
2.4 Legal Background	24
2.5 Chapter Review	26
Chapter 3 Target Product Profiles	28
3.0 Introduction	28
3.1 Reverse Engineering Background	28
3.2 Deformulation Background.....	29
3.3 Pharmaceutical Deformulation.....	30
3.4 Techniques	31
3.4.1 SEM.....	31
3.4.2 Particle Size Analysis.....	32
3.4.3 Dissolution	32
3.5 Propranolol Hydrochloride Extended Release Capsules	33
3.5.1 Current Manufacturer's of Propranolol HCl Extended Release Capsules	35
3.5.2 Recent Research for Propranolol HCl Extended Release	35
3.6 Metoprolol Succinate Extended Release Tablets	36
3.7 Metoprolol Succinate Formulations	37
3.8 Recent Research for Metoprolol Succinate.....	38
3.8.1 Watson.....	38
3.9 Materials	43
3.9.1 SEM Studies.....	43
3.9.2 Physical Characterization and Particle Size Evaluations	43
3.9.3 Dissolution Studies.....	43
3.10 Methods.....	44

3.10.1 SEM Sample Preparation Methods	44
3.10.2 Physical Characterization and Particle Size Evaluations	45
3.11 Analytical Methods	45
3.11.1 Dissolution-Propranolol HCl	45
3.11.2 Dissolution-Metoprolol Succinate	46
3.11.3 Analytical Calculations of Concentration for Dissolution	47
3.11.4 Concentration Determined by High Performance Liquid Chromatography	47
3.11.5 Propranolol Hydrochloride Assay Method	48
3.11.6 Metoprolol Succinate Assay Method	49
3.12 Results/Discussion	49
3.12.1 SEM and Deformation of Competitors	49
3.12.2 Results- Wyeth Inderal LA Extended Release Capsules	50
3.12.3 Results-Par Propranolol HCl Extended Release Capsules.....	53
3.12.4 Results- Actavis Propranolol HCl Extended Release Capsules.....	57
3.13 Metoprolol Succinate	60
3.13.1 Astra-Zeneca (Brand).....	61
3.13.2 Ethex	65
3.13.3 Sandoz	68
3.14 Particle Size Analysis Results-Propranolol HCl	72
3.15 Metoprolol Succinate Particle Size Distribution Results.....	73
3.15.1 Results- Propranolol HCl Extended Release Capsules- Fill Weight	75
3.15.2 Results-Metoprolol Succinate Extended Release Tablets-Dimensions/Fill Weight	75
3.15.3 Results- Dissolution Profile- Propranolol HCl Extended Release Capsules	76
3.15.4 Results-Dissolution of Metoprolol Succinate Extended Release Tablets.....	79
3.16 Chapter Review	81
Chapter 4 Critical Quality Attributes	82
4.0 Introduction	82
4.1 Stress-Strain Relationship.....	82
4.2 IR Bead Processing	83
4.2.1 Granulation.....	83
4.2.2 Wet Granulation	84
4.2.3 High Shear Wet Granulation.....	86
4.2.4 Extrusion	88
4.2.5 Spheronization.....	89
4.2.6 Fluid Bed Drying.....	92
4.3 Controlled Release Background	95
4.3.1 Fluid Bed Spray Coating.....	95
4.4 Curing	97
4.5 Bead Top Coating.....	98
4.6 Tablet Background	99
4.7 Key Excipients for Formulation	101
4.7.1 Fillers/Bulking Agents	101

4.7.2 Granulating Agent	102
4.7.3 Binding Agents.....	103
4.8 Polymers.....	104
4.8.1 Methylcellulose	104
4.8.2 Ethylcellulose	105
4.8.3 Plasticizers.....	106
4.8.4 Other Inactive Ingredients for Tabletting.....	107
4.9 Identifying Critical Quality Attributes (CQA's).....	108
4.9.1 Particle Size Distribution	108
4.9.2 Sphericity	110
4.9.3 Moisture Content.....	111
4.9.4 Dissolution Profile	112
5.0 Introduction.....	114
5.0.1 Phase II: Formulation and Process Development of an Immediate Release Drug Pellet	114
5.0.2 Phase III: The Creation and Evaluation of Coated Controlled Release Pellets	118
5.0.3 Phase IV: The Creation and Evaluation of a Multiparticulate Compressed Oral Tablet	122
5.1 IR Bead Formulation Materials.....	124
5.1.1 Propranolol	124
5.1.2 Metoprolol Succinate	124
5.2 SR Bead Formulation Materials.....	124
5.2.1 Propranolol HCl	124
5.2.2 Metoprolol Succinate	125
5.2.3 Materials- Sustained Release Bead Top Coating	125
5.2.4 Materials- Tabletting.....	125
5.2.5 Excipient Granule (Formulation #1) for Metoprolol Succinate SR Tabs.....	126
5.2.6 Excipient Dry Blend (Formulation #2) for Metoprolol Succinate SR Tabs	126
5.2.7 Excipient Dry Blend (Formulation #3) for Metoprolol Succinate SR Tabs	126
5.3 Processing Methods.....	127
5.3.1 Propranolol HCl IR Bead Processing.....	127
5.3.2 General Metoprolol Succinate IR Bead Processing	130
5.3.3 Exploratory Metoprolol Succinate IR Bead Processing.....	130
5.3.4 Sustained Release Coating and Curing Methods	133
5.3.5 General Spray Coating Methods	133
5.3.6 Aquacoat ECD Trials- Propranolol HCl	133
5.3.7 Aquacoat ECD Solids Concentration Trials- Propranolol HCl.....	134
5.3.8 Organic Ethylcellulose Coating Trials	134
5.3.9 Aquacoat ECD Trials- Metoprolol Succinate	134
5.3.10 Curing Trials Overview.....	134
5.3.11 Methods-Sustained Release Bead Top Coating	135
5.3.12 Tabletting Methods-Blending	135

5.3.13 Methods-Tabletting	136
5.4 Analytical Methods	136
5.4.1 Dissolution and Concentration	136
5.4.2 Comparison of Dissolution Profiles	136
5.5 General Statistical Methodology	137
5.5.1 Statistical Methods-Exploratory Batches	137
5.6 Physical Characterization Methods.....	139
5.6.1 Particle Size Distribution Analysis	139
5.6.2 Loss on Drying (LOD)	139
5.6.3 Sphericity	139
5.7 Exploratory/Traditional Results.....	141
5.8 Results-Propranolol	142
5.8.1 Propranolol IR Statistical Results	143
5.8.2 Initial Processing Information.....	145
5.8.3 Identifying the Critical Parameters	146
5.8.4 Confirmation/Optimization of Critical Parameters	146
5.8.5 Doubling the Batch Size.....	147
5.9 Results Propranolol HCl SR	149
5.9.1 Results- Effects of Curing Oven	152
5.9.3 Metoprolol Succinate IR Exploratory Statistical Results.....	160
5.9.4 Particle Size Distribution	160
5.9.5 Metoprolol Succinate IR Exploratory Statistical Results- Sphericity	162
5.9.6 Results-Metoprolol Succinate Exploratory Batches-New Approach.....	165
5.9.7 Results- Top Coating.....	172
5.10 Results-Exploratory Tabletting Study	174
Chapter 6 Design Space	176
6.0 Introduction	176
6.1 Statistical Methods-DOE Batches.....	176
6.1.1 Full Factorial Design for Metoprolol Succinate IR Bead Processing	177
6.1.2 Box-Behnken Designs.....	178
6.1.3. Statistical Methods- Metoprolol Succinate SR Box Behnken Design	179
6.1.4 Statistical Methods- Metoprolol Succinate Tablet.....	180
6.2 Metoprolol Succinate IR Bead DOE-Results.....	181
6.2.1 Statistical Results for Metoprolol Succinate DOE IR Bead Formulations	182
6.2.2 Confirmation/Batch Size Increase of DOE Results for Metoprolol IR Beads	192
6.3 Metoprolol Succinate SR Doe Results	196
6.4 DOE Results for Metoprolol Succinate Tablets	200
6.4.1 SEM for Metoprolol Succinate Tablet DOE	201
6.4.2 Dissolution of Metoprolol Succinate Multiparticulate Tablets	206
Chapter 7 Conclusions.....	208
7.1 Establishment of Target Product Profiles.....	208
7.2 CQA Identification.....	208
7.3 Linking CQA's to Process Parameters	209

7.4 Supporting Elements of a Design Space.....	211
7.5 Exploratory Traditional Methods vs. QbD.....	213
7.6 Study Limitations	214
7.7 Future Studies	214
BIBLIOGRAPHY	216
APPENDIX 1	228
APPENDIX 2	229
APPENDIX 3	232
APPENDIX 4.....	235
APPENDIX 5.....	237
APPENDIX 6	249
APPENDIX 7	250
APPENDIX 8.....	251
APPENDIX 9	258

LIST OF FIGURES

Figure 1 Adapted Overview of Pharmaceutical Development Described in Q8 Annex (ICH 2007)	4
Figure 2 Formulation and Processing Variable Overview	6
Figure 3 Hierarchy of Manufacturing Control Strategy (Low 2006).....	17
Figure 4 Example of an Ishikawa Diagram (ICH 2007)	19
Figure 5 Propranolol Hydrochloride Chemical Structure (Wyeth 2007).....	33
Figure 6 Metoprolol Succinate Chemical Structure (Astra-Zeneca 2007).....	36
Figure 7 Inderal LA 160mg Whole Pellet.....	51
Figure 8 Inderal LA 160mg Cross Section	52
Figure 9 Inderal LA Cross Sectional Polymer Coating	52
Figure 10 Propranolol HCl ER Caps 160mg- Cross Section after Dissolution	53
Figure 11 Par Propranolol 160mg	55
Figure 12 Par Propranolol 160mg Cross-Section.....	56
Figure 13 Par Propranolol 160mg- Cross Sectional Polymer Coating	56
Figure 14 Actavis Propranolol 160mg Whole Pellet	58
Figure 15 Actavis Propranolol 160mg Cross-Section.....	59
Figure 16 Actavis Propranolol 160mg Cross Sectional Polymer Coating	60
Figure 17 Astra-Zeneca 25mg- Whole Pellet.....	63
Figure 18 Astra-Zeneca 25mg- Cross Section	64
Figure 19 Astra-Zeneca 25mg- Cross Sectional Polymer Coating	64
Figure 20 Ethex 100mg- Whole Pellet.....	66
Figure 21 Ethex 100mg- Cross Section	67
Figure 22 Ethex 100mg- Cross Sectional Polymer Coating	68
Figure 23 Sandoz 25mg- Whole Pellet	71
Figure 24 Sandoz 25 mg- Cross Section.....	71
Figure 25 Sandoz 25 mg- Cross Sectional Polymer Coating.....	72
Figure 26 Particle Size Distribution of Propranolol HCl Extended Release Beads...	72
Figure 27 Comparison of Dissolution of Inderal LA 160mg Capsules and Par Propranolol Extended Release 160mg Capsules Using USP I Method	78
Figure 28 Comparison of Toprol XL 100mg and 200mg Dissolution Profile.....	80
Figure 29 Example Stress-Strain Curve for Uniaxial Tension (Hoag, Vivek et al. 2008)	83
Figure 30 Overview of Critical Factors During Granule Formation (Ennis 2005)....	85
Figure 31 Schematic of a Bottom-Driven Vertical High Shear Granulator with Horizontal Chopper Shaft (NiroPharma 2003)	86
Figure 32 An Adapted Schematic of an Early Spheronizer (Nakahara 1966)	90
Figure 33 Schematic of Fluid Bed Drying of Wet Material (Olsen 1989).....	92
Figure 34 Cross Sectional Schematic of a Standard Bottom Spraying Configuration with a Wurster Column (Olsen 1989).	95
Figure 35 Adaptation of Blaine's ASTM Des. C 205-55 for Estimating the Surface Area of Small Particles and Polymer Coating Requirements (Degussa 2007a).97	

Figure 36 Effect of Particle Size on Dissolution Profile (Dashevsky, Kolter et al. 2004)	109
Figure 37 Example of a Design Space for a Drying Operation (ICH 2007).....	111
Figure 38 Processing Steps for the Immediate Release Pellet	114
Figure 39 Ishikawa Diagram-Immediate Release Beads	117
Figure 40 Phase III-General Methodology for a SR Pellet	118
Figure 41 Ishikawa Diagram-Sustained Release Beads.....	120
Figure 42 Phase IV-General Methodology	122
Figure 43 Ishikawa Diagram-Multiparticulate Tabletting	123
Figure 44 Example of Propranolol IR Bead Drying Cycle	128
Figure 45 Example of a Metoprolol IR Bead Drying Cycle	132
Figure 46 Screenshot of Sphericity Measurements.....	140
Figure 47 Propranolol IR Main Effects Plot for Sieve # 18.....	143
Figure 48 Propranolol IR Bead Yield vs. Mean Sphericity	144
Figure 49 Propranolol IR Bead-Round (RB005055/56 Blend).....	148
Figure 50 Comparison of High and Low Polymeric Coating Suspension Solids	150
Figure 51 Curing Propranolol Aqueous SR Beads in a Vacuum Oven vs. Humidity Chamber	152
Figure 52 Metoprolol Succinate IR Beads Exploratory Batch Overview of Mean Sphericity vs. Yield (%).	157
Figure 53 Main Effects Plot for the Reduced Model of Particle Size Target % Yield for Metoprolol Succinate IR Exploratory	160
Figure 54 Main Effects Plot for Mean Sphericity for Metoprolol Succinate IR Exploratory Batches	162
Figure 55 Main Effects Plot for Sphericity Standard Deviation for Metoprolol Succinate IR Exploratory Batches	164
Figure 56 Exploratory Metoprolol Succinate SR Beads	169
Figure 57 Exploratory Metoprolol Succinate SR Beads for Tabletting Studies	171
Figure 58 Metoprolol Succinate SR Low Polymer Coating Level with Topcoat	173
Figure 59 Metoprolol Succinate SR Low Polymer Coating Level with Top Coat-Cross Section.....	173
Figure 60 Overview of Dissolution Profiles for the Metoprolol Succinate Exploratory Tabletting Study	174
Figure 61. Metoprolol IR Bead- Dumbbells (RB014005)	183
Figure 62. Metoprolol IR Beads-Rods (RB014005)	184
Figure 63. Main Effects Plot of Metoprolol Succinate DOE Sphericity Standard Deviation	187
Figure 64. Interaction Plot for Metoprolol Succinate DOE Sphericity Standard Deviation	187
Figure 65. Main Effects Plot for Metoprolol Succinate DOE RSD (%) of Sphericity	190
Figure 66. Interaction Plot of Metoprolol Succinate DOE Sphericity RSD (%)	190
Figure 67. Loss on Drying at 48°C End Drying Temperature	191
Figure 68. Metoprolol IR Bead- Round (RB014013/023/024 Blend)	193
Figure 69. Metoprolol IR Bead Loss on Drying Curve as a Function of Time	194

Figure 70. Contour Plots for F ₂ Values of Metoprolol Succinate SR DOE	198
Figure 71. High Polymer Coating Level with Topcoat Uncompressed	201
Figure.72. High Polymer Coating with Topcoat and a 30/70 Blend at 2kp Tabletted	202
Figure 73 Metoprolol Succinate High Polymer Level with Topcoat, 30/70 Blend at 5kp Tablet Hardness.....	202
Figure 74. Cross Sectioned Tablet of Metoprolol Succinate High Polymer Level with Topcoat with a 30/70 Blend and 2kp Hardness.	203
Figure 75. Metoprolol Succinate High Polymer Level with Topcoat, 50/50 Blend Tabletted at 2Kp	203
Figure 76 Metoprolol Succinate High Polymer Level Top Coated with a 50/50 Blend, Tabletted to 5kp.	204
Figure 77. Metoprolol High Polymer Coating with a Topcoat 50/50 Blend at 2kp.	204
Figure 78. Metoprolol Succinate SR Tablets at High and Low Hardness with and without #25 Beads Loaded.....	206

LIST OF TABLES

Table 1 Different Approaches to Pharmaceutical Development (ICH 2007)	21
Table 2 Propranolol Extended Release Capsules Inactive Ingredients	34
Table 3 Propranolol HCl Extended Release Formulation (Chen 2006).....	35
Table 4 Inactive Ingredients of Metoprolol Succinate Formulations.....	37
Table 5 Watson Metoprolol Succinate Formulation and Function (Sriwongjanya, Yuk et al. 2008).....	38
Table 6 Metoprolol Succinate Sustained Release Formulation (Ravishankar, Patil et al. 2006).....	40
Table 7 Metoprolol Succinate Extended Release Formulation (Dias 2007).....	41
Table 8 Metoprolol Succinate Extended Release Formulation (Niazi 2004)	42
Table 9 USP Dissolution Test 1 Acceptance Criteria (USP 2007b)	46
Table 10 Metoprolol Succinate USP Dissolution Acceptance Criteria (USP 2007c)	46
Table 11 Inderal LA Propranolol HCl Extended Release Capsule Formulation and Hypothesized Function.....	50
Table 12 Par Propranolol HCl Extended Release Capsule Formulation and Hypothesized Function.....	54
Table 13 Actavis Propranolol Formulation.....	57
Table 14 Astra-Zeneca Metoprolol Succinate Formulation and Theorized Function	62
Table 15 Ethex Metoprolol Succinate Formulation and Theorized Function.....	65
Table 16 Sandoz Metoprolol Succinate Formulation.....	69
Table 17 Methacrylic Acid Copolymer Types (Degussa 2007b).....	69
Table 18 Approximate Particle Size Distribution of 100mg Metoprolol Succinate Tablets (N=3)	73
Table 19 Average Fill Weights for Propranolol HCl 160mg Capsules	75
Table 20 Metoprolol Succinate SR Tablet Dimensions/Fill Weight	75
Table 21 Common Categories and Examples of Binders, Adapted from (Cantor, Augsburger et al. 2008).....	103
Table 22 Propranolol IR Experimental Overview	129
Table 23 Overview of the Coded Process Parameter for Metoprolol IR Beads Exploratory Batches	131
Table 24 Sieve screen size conversion to microns and inches.....	139
Table 25 Propranolol IR Bead Particle Size Distributions.....	142
Table 26 Propranolol Aqueous SR Results Organized by Coating Level	149
Table 27 Propranolol Organic SR Coating Acceptable Dissolution Results	155
Table 28 Exploratory Batches-Processing Parameters and Results Overview	156
Table 29 Analysis of Variance for Target % Using Adjusted SS for Tests of Reduced Model	160
Table 30 Analysis of Variance for Mean Sphericity, Using Adjusted SS for Tests	162
Table 31 Analysis of Variance for Sphericity Std. Dev., Using Adjusted SS for Tests	163
Table 32 Overview of Significant Coded Variables from Exploratory Batches.....	165

Table 33 Processing Parameters and Results for 2 Phase Water Addition for Metoprolol Succinate IR Beads	167
Table 34. Overview of the Full Factorial Metoprolol Succinate IR Bead DOE	177
Table 35. Box Benhken-3 Factor/3 Level Design for SR Metoprolol Succinate.....	179
Table 36. Metoprolol Succinate Multiparticulate Tablet 2 ³ Factorial Design.....	180
Table 37. Overview of the Process Parameters and Results	181
Table 38. Estimated Effects and Coefficients for Mean Sphericity (Coded Units) Metoprolol Succinate IR Bead DOE.....	184
Table 39. Analysis of Variance for Mean Sphericity (Coded Units) Metoprolol Succinate IR Bead DOE.....	185
Table 40. Estimated Effects and Coefficients for Sphericity Standard Deviation (Coded Units) Metoprolol Succinate IR Bead DOE	186
Table 41. Analysis of Variance for Standard (Coded Units) Sphericity Standard Deviation (Coded Units) Metoprolol Succinate IR Bead DOE	186
Table 42. Estimated Effects and Coefficients for Sphericity RSD (%) (Coded units) Metoprolol Succinate IR Bead DOE.....	188
Table 43. Analysis of Variance for Sphericity RSD (%) (Coded units) Metoprolol Succinate IR Bead DOE.....	189
Table 44. Metoprolol IR Bead DOE Run #7 Confirmation Trials.....	192
Table 45. Metoprolol Succinate SR DOE Results	196
Table 46. Estimated Regression Coefficients for Metoprolol Succinate F2 Values	197
Table 47. Analysis of Variance for Metoprolol Succinate F2 Values	197
Table 48. Tablet Friability for the DOE Batches	200

LIST OF EQUATIONS

Equation 1. Calculation for % Dissolved at the First Sample Point	47
Equation 2. Calculating % Drug Dissolved at n Hours.....	47
Equation 3. Calculating F1 Value for a Given Time Point.....	47
Equation 4. Formula for Calculating Percent Content of Drug by HPLC Assay	48
Equation 5. Drying Rate (Parikh 1992).....	93
Equation 6. f_2 Equation	136
Equation 7. Aspect Ratio for Pellet Sphericity Measurements	140

Chapter 1 Study Overview

1.0 Introduction

This chapter serves to orient the reader with the challenges associated with drug development and the use of organic solvents in the pharmaceutical industry. The objectives and overview of the approach to the research proposed are described. Additionally, the potential benefits of this work for the pharmaceutical community and the general public are presented.

1.1 Statement of the Problem

Tablet manufacturing has been described as a “paradox”; formulating and manufacturing a mass of raw materials into a usable product is complicated, and then upon administration, the tablet must release the active ingredients in the desired manner requiring additional design considerations (Swarbick 2007). To improve formulation and process understanding during development, aspects of the Quality by Design (QbD) approach described by the International Conference on Harmonization (ICH) to guide experimentation can be used to enhance innovative efforts in the marketplace. This approach is different from the traditional method of drug development by supporting a risk-based approach to the identification and evaluation of critical parameters that negatively impact product characteristics. Experimental design to evaluate formulation and processing parameters with benchmarks gained through reverse engineering (product characterization of marketed competitors) serves as an improved model for generic drug development.

Utilizing reverse engineering techniques to understand how the products are formulated and manufactured is not a novel concept. Generic pharmaceutical manufacturers use reverse engineering to understand the performance of innovator products in order to model their formulations to mimic the marketed product closely enough to gain FDA approval. While this method of deconstruction to copy the original product may be effective, it does not improve the product design or manufacturing practices. Instead of attempting to duplicate ineffective, expensive, or other disadvantageous methods, improvements can be made to the drug product, delivery system and manufacturing process to provide a well understood generic product. This conceptual generic product development strategy will serve as the intellectual basis of this work and will provide generic manufacturers with an understanding of the advantages of implementing these methodologies. As a result of improved product development, consumers of generic products will ultimately reap the rewards of a more competitive market with theoretically lower costs and decreased time to market entry.

1.2 Objectives of the Study

The primary aim of the study is the comparison of formulation and process development for two extended release water-soluble pharmaceutical compounds, propranolol HCl and metoprolol succinate. Propranolol HCl development will largely be empirical, from raw ingredients to a final sustained release capsule using a traditional approach. General information gained through the traditional development process of propranolol HCl will be used to support decisions for a QbD

developmental approach of metoprolol succinate extended release tablets. While the development of a single drug product is dependent on its chemical and physical properties, the traditional approach can be understood and improved to yield a stronger process understanding. Process understanding can be gained through the use of multivariate statistical approaches to support a design space. Utilizing a systemic approach facilitates understanding of the material attributes and process parameters that are linked to a drug product's critical quality attributes (CQA's). Figure 1 is an adapted overview of the ICH Q8 Annex strategy for Pharmaceutical Development, from concept through commercialization. The Q8 strategy provides a general framework of drug development, which will be applied to metoprolol succinate throughout this research.

Figure 1 Adapted Overview of Pharmaceutical Development Described in Q8 Annex (ICH 2007)

Throughout the development and product life cycle, changes in formulation and manufacturing practices offer opportunities to gain greater knowledge of product characteristics and performance under various conditions. Inclusion and analysis of relevant experimental and experiential information can be used to create, support, and expand the control and design spaces. While absolute operational and process understanding is impossible, it is important to recognize what is known and operate within those parameters. This project will use the sequential approach presented by the ICH Q8 annex to guide the enhanced product development approach to support elements of a conceptual design space. Scale up, development of a control strategy, and product life cycle management are important aspects for commercialization, but are beyond the scope of this work. Due to equipment and financial limitations, development will avoid costly high tech machinery and utilize a practically based QbD approach of statistical methodology and process understanding to support elements of the design space.

A secondary objective is the evaluation of aqueous systems in place of organic solvents where feasible, as an environmentally friendlier alternative. It can be hypothesized that both brand and select generic products utilize organic solvents in selected aspects of their manufacturing. Solvent usage is not limited to sustained release coatings, and may be used during the production of immediate release beads. Therefore, both the immediate release bead preparations and the sustained release coatings provide areas where aqueous systems may be explored.

1.3 Study Approach

Figure 2 Formulation and Processing Variable Overview

The formulation and process development aspects of the project are divided into four phases based on common processing steps where intermediate testing occurs. Figure 2. serves as an overview of the study approach for drug product development, with processing steps presented in squares, and potential variables as rounded squares. Phase I deformulates the competitor's products and uses physical, chemical, and published literature to support the development of product profile targets. Phase II evaluates the formulation and process development of an immediate release bead, from raw ingredients to final dried beads. Phase III is the development of a sustained release bead, which spray coats and cures the polymer system onto the immediate release beads. Phase IV topcoats the sustained release beads, before blending and compressing them into multiparticulate sustained release tablets. Identification and evaluation of intermediate metrics will facilitate a comprehensive system understanding in addition to the final product characterization. Evaluation throughout the process will bolster process understanding and a systemic approach to support formulation and production changes. Each stage of development has an impact on the final product; therefore it is essential to understand processing ranges and yields for each stage.

Drug development does not occur in a vacuum, therefore it must be fluid and flexible in order to adapt to changes. For example, the development of spherical immediate release beads in a controlled particle size distribution is an important intermediate goal. The traditional approach would strive to optimize the batch yield and proceed to the next phase. Optimization of a poorly understood process is not a wise allocation of time and resources. In contrast, the goal for the immediate release

beads should be to evaluate the output over a reasonable processing range to understand the impacts of variability and processing conditions. Therefore, when the second phase of development begins, sustained release coating and curing, and the data suggests an adjusted particle size distribution, the necessary changes are made based on process understanding.

The ICH Q8 approach for drug development is divided into four stages for this research:

1. Targets will be identified utilizing deformation/reverse-engineering methods of currently manufactured brand and generic competitors.
Characterization of marketed product's vital metrics serves to support benchmarks for both the propranolol HCl and metoprolol succinate formulations.
2. Identification and justification of CQA's for the target multiparticulate formulations
3. Linking specific factors to CQA's and exploring the preliminary relationships utilizing "traditional" approaches.
 - a. Development of an uncoated immediate release drug pellet through the evaluation of formulation and wet granulation processing parameters.
 - b. Evaluation of polymer coating to the pellets developed in phase 1 to yield an extended release dissolution profile.
 - c. Metoprolol Succinate extended release tablet formulation and process parameters for the final dosage form.

4. Evaluating the selected factors by design of experiment and other QbD approaches to support elements of a conceptual design space.

Chapter 2 Pharmaceutical Regulatory Environment

2.0 Introduction

Generic pharmaceuticals are a vital element of healthcare and often deliver quality medications at a fraction of the price of the brand product. This chapter aims to familiarize the reader with the current regulatory, legal landscape and competitive climate of the generic pharmaceutical market.

2.1 Regulatory Background of Generic Pharmaceuticals

The “Drug Price Competition and Patent Term Restoration Act of 1984”, commonly referred to as the Hatch-Waxman Act, legalized the approval of Abbreviated New Drug Application (ANDA) submissions for generic equivalents to currently marketed products (Mathias, Dole et al. 1984). This act specifically required generic manufacturers to demonstrate the following: 1) The innovator product was currently approved. 2) There were no patent infringements related to their product. 3) All required in vitro and in vivo bioequivalency studies met the Food and Drug Administration (FDA) requirements. The key advantage of this new avenue for drug approval was the removal of duplicate and costly clinical trials for generic products, since the innovator previously established safety and efficacy for initial market approval. Additionally, generic manufacturers must comply with Current Good Manufacturing Practice regulations (cGMP’s), in order to market their products.

Bioequivalency studies became the clinical standard that generic products had to meet in order to gain FDA approval. The Code of Federal Regulations part 320.1 defines bioavailability and bioequivalence as the following: “Bioavailability is the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action....” While “Bioequivalence is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study (CFR:320.1 2003).” Recently the FDA expressed interest in receiving feedback on the regulatory process and has issued the “Guidance for Industry: Bioequivalence Recommendations for Specific Products”, which describes the agency’s goal to streamline the process and become more efficient through improved communication with manufacturers and the public (FDA 2007a).

For approval of multiple strengths of a narrow therapeutic index drug to avoid duplicitous bioequivalency testing the FDA’s Guidance on In Vitro/ In Vivo correlations for extended release products must be met. In addition to the acceptance criteria, one of the following three situations must be satisfied:

1. Bioequivalence has been established for all strengths of the reference-listed product.
2. Dose proportionality has been established for the reference listed product, all reference-listed products are compositionally proportional or qualitatively the

same and have the same release mechanism, and the In Vitro dissolution profiles of all strengths are similar.

3. Bioequivalence is established between the generic product and the reference listed product at the highest and lowest strengths, and for the reference listed product, all strengths are compositionally proportional or qualitatively the same and have the same release mechanism, and the In Vitro dissolution profiles are the same.

Acceptance Criteria: The difference in predicted means of C_{max} and AUC should be no more than 10% based on dissolution profiles of the highest strength and the lower strength product (FDA 1997a).

The goals of the Hatch-Waxman act were to expedite and expand the availability of more affordable generic drugs, while simultaneously providing incentives for the development of innovative and novel products. This legislation created the framework for the birth of the generic pharmaceutical industry, which has grown and evolved over the past two decades. The Food and Drug Administration has worked with the pharmaceutical industry and outside agencies to create rules and regulations to govern the approval and manufacture of generic drug products. In the fiscal year of 2007 (ended September 30, 2007), the Office of Generic Drugs received a record high 877 ANDA's, and approved over 600 of those submissions (Wechsler 2007).

In addition to demonstrating bioequivalency to the innovator product, new generic drug products must be adequately labeled, and manufactured in compliance with good manufacturing practices (cGMP's) for the FDA to approve the ANDA

(Holovac 2004) Generic pharmaceutical manufacturers can make minor formulation modifications, such as limited excipient (inactive ingredients) substitutions, and changes to the manufacturing method, such as processing equipment and procedure, as long as the final product is found to be bioequivalent to the innovator.

Manufacturers must use caution about radical formulation changes to a reference-listed drug when submitting an ANDA. The FDA states, “Any product variations because of differences in excipients (e.g. absorption enhancers or hydrophobic agents) or other changes in formulation that may significantly affect absorption of the active drug ingredient or active moiety should be submitted in separate applications (FDA 1998).”

Meeting regulatory requirements and a manufacturer’s desire to improve a product’s process and/or formulation must be balanced. Advances in manufacturing technology, equipment, and materials should be explored in order to gain a competitive advantage in the marketplace. While the exclusivity associated with being first to the generic market is highly desirable, an efficient formulation and process will reap long-term profits and allow sustainability throughout the product lifecycle.

2.2 Current State of Pharmaceutical Regulations for Manufacturing

Current pharmaceutical leaders have recognized the limitations of cGMP’s examples include dubious and repetitive product testing, validation procedures and extensive documentation for well-understood process changes. Within the pharmaceutical industry, there is apprehension over the interpretation of the new

regulations by the agency's field representatives. Trepidation over regulatory backlash has hindered process improvements in the past and became an object of industry and FDA focus for change (Hussain 2002). In response, the FDA released Guidance for Industry, which addressed the use of Process Analytical Techniques (PAT) (FDA 2004a) and Pharmaceutical cGMP's for the 21st century (FDA 2004b). These documents are supported by a number of GMP guidelines including: Q8 Guideline on Pharmaceutical Development (FDA 2006a), Q9 Guideline on Quality Risk Management (FDA 2006b) and Q10 Guideline on Quality Systems which is still under development (Joneckis 2006) to encourage innovation in the pharmaceutical industry.

2.2.1 PAT Background

The FDA defines PAT as:

A scientific, risk-based framework intended to support innovation and efficiency in pharmaceutical development, manufacturing, and quality assurance. The framework is founded on process understanding to facilitate innovation and risk-based regulatory decisions by industry and the Agency. The framework has two components: (1) a set of scientific principles and tools supporting innovation and (2) a strategy for regulatory implementation that will accommodate innovation (FDA 2004a).

The definition for PAT presented does not define the overall strategy of the initiative, but serves as an introduction to the regulatory practice. A practical definition of PAT is given as "systems for continuous analysis and control of manufacturing processes based on real-time measurements, or rapid measurements during processing, of quality and performance attributes of raw and in-process

materials and processes to assure acceptable end product quality at the completion of the process” (Hussain 2002).

These revised guidance documents have created a new era for the pharmaceutical industry. The documents shift away from conventional thinking, an example is a current guidance document for the submission of products using on line process controls in place of end product sterility testing for terminally moist heat sterilized products. Parametric release is defined as “a sterility assurance release program where demonstrated control of the process enables a firm to use defined critical process controls in lieu of sterility testing...(FDA 2008c).” Traditionally, these sterile products were subject to end product testing, which sampled a small amount of material and was limited to identifying only the most serious of contaminants due to scientific limitations. Through greater process understanding, the decision was made to validate and control the process parameters to monitor the product bioburden. The process understanding, approach supports an environment of continuous improvements.

2.2.2 Design Space-Background

The new focus is to understand the product, the manufacturing process, and operations. This approach has been described as the “design space”, defined by the FDA as:

...the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory postapproval change process.

Design space is proposed by the applicant and is subject to regulatory assessment and approval (FDA 2006c).

Within the design space, the control space has been described as a: “Multi-dimensional space that encompasses process operating parameters and component quality measurements that assure process or product quality. It is a subset of the design space” (Desai 2006). Exploration and understanding of these areas will lead to the identification of critical parameters, as well as metrics and methods to capture their impact on the process, enabling quality management through a risk based approach. A new control strategy aims to minimize risks associated with failures when critical and non-critical process parameters fall outside the control space but remain within the design space.

2.2.3 Quality by Design (QbD) Background

The FDA has recognized, similarly to outside industries, that quality must be built into the design of the product, and that it cannot be achieved through testing or inspection alone. In order to promote the idea of incorporating quality into product development, the ICH adopted “Quality by Design (QbD).” QbD is defined as, “A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management (ICH 2007)”.

By the standards of the 21st century the development and manufacturing of pharmaceutical products is generally considered to be inefficient when compared to other industries (FDA 2004a). The FDA has introduced cGMP’s for the 21st century (FDA 2004b) to facilitate the improvement of pharmaceutical manufacturing through

the use of a risk-based approach. Figure 3 depicts a conceptual representation of the hierarchy of manufacturing control strategy. Data generated through experimental designs provide the framework for creating and supporting the manufacturing practices. Changes to the control space, within the design space, supported by adequate data as defined by the manufacturer would conceivably not require supplemental FDA approval.

Figure 3 Hierarchy of Manufacturing Control Strategy (Low 2006).

This understanding will lead to the identification of critical parameters, as well as metrics and methods to capture their impact on the process, which enables quality management utilizing a risk based approach. A new control strategy aims to minimize the risks associated with failures when the critical and non-critical process parameters fall outside the control space but remain within the design space. The ICH presents the concept of Critical Quality Attributes (CQA), defined as “A

physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (ICH 2007).” Ideally all CQAs should be evaluated early in development, but the process of continuous improvement necessitates vigilance throughout the development and life cycle of the product as guided by the ICH Q10 documentation. The first step is to identify all of the factors, which may impact the product throughout the process, and then to identify those factors with the theorized greatest impacts to evaluate experimentally. Changes in formulation and manufacturing practices offer opportunities to gain greater knowledge of product characteristics and performance under different conditions. Inclusion and analysis of relevant experimental and experiential information can be used to create, support, and expand the control and design spaces. Figure 4. is an example of an Ishikawa diagram, which can be used as a tool to identify key areas of interest in a tableting process.

Figure 4 Example of an Ishikawa Diagram (ICH 2007)

Table 1 is an overview of the differences that can be found between the “minimal” (traditional), and “enhanced“(QbD) developmental approaches. The ICH recognizes in the Q8 Annex that manufacturers will most likely utilize tools from both of these approaches, with their processes’ described between the two extremes. The emphasis is to incorporate these techniques from the initial stages throughout the entire product life cycle. A hybrid approach between the two extremes, would help to introduce new techniques to well established systems to encourage improvement. For many small to medium manufacturers, an incremental approach may be the only economically feasible option. Knowledge gained from utilizing the QbD approaches on a small scale or through a partial implementation can serve to guide improvement for future expansions and products.

Table 1 Different Approaches to Pharmaceutical Development (ICH 2007)

Aspect	Minimal Approach	Enhanced, quality by design Approach
Overall Pharmaceutical Development	<ul style="list-style-type: none"> • Mainly empirical • Developmental research often conducted one variable at a time 	<ul style="list-style-type: none"> • Systematic, relating mechanistic understanding of input material attributes and process parameters to drug product CQAs • Multivariate experiments to understand product and process • Establishment of design space • PAT tools utilised
Manufacturing Process	<ul style="list-style-type: none"> • Fixed • Validation primarily based on initial full-scale batches • Focus on optimisation and reproducibility 	<ul style="list-style-type: none"> • Adjustable within design space • Lifecycle approach to validation and, ideally, continuous process verification • Focus on control strategy and robustness • Use of statistical process control methods
Process Controls	<ul style="list-style-type: none"> • In-process tests primarily for go/no go decisions • Off-line analysis 	<ul style="list-style-type: none"> • PAT tools utilised with appropriate feed forward and feedback controls • Process operations tracked and trended to support continual improvement efforts post-approval
Product Specifications	<ul style="list-style-type: none"> • Primary means of control • Based on batch data available at time of registration 	<ul style="list-style-type: none"> • Part of the overall quality control strategy • Based on desired product performance with relevant supportive data
Control Strategy	<ul style="list-style-type: none"> • Drug product quality controlled primarily by intermediate and end product testing. 	<ul style="list-style-type: none"> • Drug product quality ensured by risk-based control strategy for well understood product and process • Quality controls shifted upstream, with the possibility of real-time release or reduced end-product testing
Lifecycle Management	<ul style="list-style-type: none"> • Reactive (i.e., problem solving and corrective action) 	<ul style="list-style-type: none"> • Preventive action • Continual improvement facilitated

The FDA has given the pharmaceutical industry an opportunity to enter the 21st century of manufacturing by expanding the control space of their operations while still staying within safe operating conditions in the design space. PAT, the design space, and QbD has excited many in the pharmaceutical industry, who see the potential to continuously improve processes as they occur in other manufacturing industries.

This drastic change in the regulatory mindset has raised many questions regarding feasibility and practicality. The FDA has promoted the adoption of these techniques on a general level. For example, PAT has become an industry “buzzword” with much of the knowledge only attainable through consultants, and/or is guarded closely within the industry. Current seminars and workshops address very specific ideas of using novel techniques for limited areas, such as specific assays used during processing to verify quality (Tyler 2006). Some consultants may propose vague “buzzword” laden approaches to improvements without scientific background and appear to be more oriented to selling their services. Widespread adoption of these new approaches has been slow due to a lack of technical knowledge and trepidation over the interpretation of these guidance documents by regulators.

Moving toward an “enhanced” developmental approach is still in its early stages with skepticism and uncertainty of how the FDA will regulate this new area. While the long-term benefits of manufacturing improvements are clear, it may be difficult to make the argument for a sizable investment in innovation on a product currently being developed for fear of clinical failure and the uncertainties of FDA

product approvals. Further, if a product will be approved, companies want to avoid delaying or jeopardizing the approval process due to changes in manufacturing approaches. Additionally, there are concerns over technological limitations, which prevent online process monitoring and understanding for complex products such as protein drugs (Glaser 2006).

2.3 Organic Solvents

The advantages of aqueous systems over organic solvents has been widely accepted in the pharmaceutical industry for over the past 20 years (McGinity 1997). Organic solvents require specialized equipment and recovery systems for production. Due to the volatility of the solvents, explosion proof equipment and processing areas are necessary. Systems for solvent scrubbing and recovery are necessary to minimize the environmental impacts and contain waste materials (Olsen 1989). Organic waste produced in the manufacturing of pharmaceuticals including: liquids, volatile gasses, and solid materials, all contribute to make the pharmaceutical industry one of the leading producers of organic waste. It is estimated that “the pharmaceutical industry has the highest waste generation and the highest amount of organic waste used per mass of product produced for any commercial sector (Slater and Savelski 2007)”. Beyond the environmental impacts of organic solvents, there are health related concerns for residual levels consumed by end product users. In response, the International Conference on Harmonization (ICH) has identified acceptable residual levels and categorizes the residual organic solvents with regard to their associated risks:

2.3.1 Class 1 Solvents: Solvents to be Avoided

Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.

Examples: Benzene, Carbon Tetrachloride, 1,2-Trichloroethane.

2.3.2 Class 2 Solvents: Solvents to be Limited

Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity.

Solvents suspected of other significant but reversible toxicities.

Examples: Methylene Chloride, Methanol, Xylene.

2.3.3 Class 3 Solvents: Solvents with Low Toxic Potential

Solvents with low toxic potential to man; no health-based exposure limit is needed. Class 3 solvents have PDEs of 50 mg or more per day.

Examples: Acetone, Isopropyl Alcohol, Ethanol(ICH 2005).

Specialized equipment, waste disposal, analytical testing for residuals, and many other considerations raise the cost of organic processing (Olsen 1989). Ideally, aqueous systems can be substituted for organic solvents during development. Unfortunately due to pharmaceutical feasibility, organic solvents are still used where aqueous systems are inadequate. In cases where organic solvents are necessary, the risk classification and environmental impacts should be minimized.

2.4 Legal Background

Traditionally, manufacturers in many industries would develop novel products and kept their methodologies secret. These “trade secrets” became targets of commercial espionage and could be stolen by competitors. In order to protect innovation, patents become an important and useful barrier that manufacturers use to block or slow their competitors. A general “utility” patent offers 20 years of protection from the date of filing, and allows multiple claims on a single patent

(USPTO 2006). Additionally, patents may be bought, sold, or licensed and they can generate new revenue streams for the owners. Patents are particularly useful in the pharmaceutical industry to keep competitors out of the market. The following list of commonly utilized types of patents are employed by the pharmaceutical industry (Kanfer, Walker et al. 2004):

- 1) Patenting a New Chemical Entity or Active Pharmaceutical Ingredient (API).
- 2) Patenting the processing methods or synthesis of the API and/or drug product.
- 3) Patenting the formulation of the drug product (API and excipient blend).
- 4) Patenting the API's use in combination with other API's to create a new drug product.
- 5) Patenting the specific polymorphic crystals and other related chemical structures of the API.
- 6) Use patents for specific clinical indications.

In addition to patents, manufacturers can gain exclusivity to market a product if they meet requirements set by the FDA. While the US Patent and Trademark Office grant patents, the FDA approves market exclusivity. A New Chemical Entity (NCE) is granted a five-year exclusivity from the date of approval (FDA 2007b), while an innovative change to an existing product by the New Drug Application holder can yield a three year exclusivity. A six-month pediatric exclusivity is available to manufacturer's who perform additional studies of their drug products on pediatric

populations. Patent challenge, otherwise known as 180-day exclusivity, is the most important type of exclusivity for generic manufacturers. Competition for this exclusivity has become so fierce that guidance documentation has been developed to address procedures for when multiple ANDA's are submitted on the same day. A multiple first applicant approach has been adopted and allows any of the ANDA's submitted on that day to be reviewed and approved in order to share the exclusivity (FDA 2003a). This intense competition for exclusivity highlights the demand for efficient development and submission for generic products.

The generic pharmaceutical industry has seen strong growth, with Teva Pharmaceuticals, Mylan Inc., and Watson Pharmaceuticals, three leading manufacturers of generic drug products, increasing gross sales in 2007 by 60%, 28%, and 20%, respectively (Standard and Poor's January 14, 2008). The Standard and Poor's reports do not separate sales due to acquisitions and mergers from in house pharmaceutical sales. This may result in inflated gross sales, (White and Sondhi 2007) this may be especially true for Teva due to their recent rapid expansion via acquisitions(Standard and Poor's January 14, 2008). In this fast paced and competitive market, strong formulation and process development is key to a manufacturer's long-term growth and survival.

2.5 Chapter Review

This chapter gives a brief overview of the current legal and regulatory climate of the generic pharmaceutical industry, and addresses challenges associated with developing a generic product. Opportunities for advancement in

pharmaceutical product/process development are outlined in the study aims. A rationale for the justification of the research is presented with perceived significance for the pharmaceutical industry and consumers.

Chapter 3 Target Product Profiles

3.0 Introduction

The first step proposed by the ICH Q8 Annex is to establish target product profile, consisting of chemical and physical targets. Scanning Electron Microscopy (SEM) of cross-sectioned drug beads allowed visualization of polymer coating thickness, and general formulation and manufacturing techniques. Basic physical characterization of the dosage forms established particle size distributions of the dosage form, as well as tablet/capsule fill weights and dimensions. Dissolution studies evaluated the drug release profile to identify variability and trends within the USP acceptance criteria. These imaging, physical, and chemical tests evaluated propranolol HCl and metoprolol succinate to gain an understanding of the competition and support the establishment of a target product profile. This chapter provides a general overview of reverse engineering and deformation techniques utilized to create targets for the drug products during development. Product characterization of multiple manufacturers for the two target products was performed to identify different approaches in drug development.

3.1 Reverse Engineering Background

Theoretically, the simplest method for one manufacturer to create an identical drug product as their competitor is to steal the formulation and a copy of the master batch record using corporate espionage techniques. Fortunately for manufacturers, there are laws to prevent such activities. The Economic Espionage Act (EEA)(1996) protects trade secrets in the United States, while the Agreement on Trade-Related

Aspects of Intellectual Property Rights (TRIPS) (1994) protects patents globally among countries that are part of the World Trade Organization (WTO). Reverse engineering is an appealing alternative to avoid criminal and litigious consequences.

Reverse engineering is defined as “the process of extracting the knowledge or design blue-prints from anything man-made (Eilman 2005).” Classically general manufacturers used reverse engineering techniques in order to gain insight into the methods of their competitors. Semiconductors, software source code, and protected digital media have received protection from reverse engineering techniques because of the efficiency of reverse engineers (Samuelson and Scotchmer 2002). Currently the EEA and TRIPS laws do not specifically sanction or condemn the practice of reverse engineering, which leaves room for enforcement interpretation.

3.2 Deformulation Background

The term “deformulation” is often used interchangeably with reverse engineering, but must be considered as a tool within the broader definition of reverse engineering. Business sectors related to the pharmaceutical industry such as the polymer and paint industries, utilize deformulation techniques. A general definition of deformulation is “A comparative analysis of unknown materials, utilizing product specific methodology to separate and identify each unknown component in the formula” (Chen, Tseng et al. 2001). In the paint industry this methodology may be applied for several different reasons, such as: a loss of documentation during formulation, to investigate a competitors product to ensure that there is no patent infringement, investigation of whether competitors marketing claims are supported

by their formulation, and the identification of advantages held by the competition (Bruck and Willard 2006). While the polymer industry is complex and requires extensive methodology to understand the molecular weights, copolymerization, and other necessary attributes for optimal performance (Nuwaysir, Wilkins et al. 1990), deformation can provide critical information.

3.3 Pharmaceutical Deformation

In the pharmaceutical industry, the term deformation is often used when referring to understanding the genetic structures of existing bacteria and viruses in order to reengineer the function to meet their objectives. Two examples of current published research are: the reverse engineering of bacteria to create highly efficient antibiotic producing organisms (Lum, Huang et al. 2004), while vaccine discovery has been expedited and improved by applying these strategies to genomics (Zagursky 2003).

Pharmaceutical development groups must perform a thorough analysis of chemical and physical properties during the development of a generic product, which could be viewed as deformation. Generic drug manufacturers have an advantage over other industries because both active and most inactive ingredients that appear in the final product are listed on the labeling. Inactive ingredients of oral dosage forms are not required to be listed on the label, while all other routes must list inactive ingredients and concentrations found in the final dosage form (CFR:201.100 2007). While it is not required, it is customary for the manufacturer of oral dosage forms to list inactive ingredients used in the final product. The inactive ingredients listed are

useful for the formulation scientist, but information about quantities, molecular weights or grades of materials, and methods must be determined in order to fully understand the target product. This aspect is most important when a branded product is no longer available and there are only generic equivalents on the market.

The process of product characterization is product specific, but general techniques utilized for the dosage form are useful. For solid oral dosage forms such as tablets and capsules, an important characteristic is the dissolution profile of the product. While this information may be available through research journals or other references, it is important to understand that manufacturers do experience variability within their approved specification ranges. This can be especially true for controlled release products, with acceptable but significant batch-to-batch dissolution variations. Therefore, looking at multiple lots and/or multiple manufacturers is an important step in understanding fluctuations which may occur (Kanfer, Walker et al. 2004). Additional areas for consideration are the formulation's structural characteristics, chemical and physical parameters.

3.4 Techniques

3.4.1 SEM

SEM is a quantitative method for identifying physical and structural parameters of controlled released oral dosage forms. Images obtained using SEM are of high resolution and have a three dimensional appearance attributed to the instrument's large depth field, which allows a large amount of the sample to be in focus at one time (Crowder, Hickey et al. 2003). Multiparticulate systems can be

analyzed to gain a stronger understanding of the manufacturing techniques utilized. By separating the internal components of active and inert ingredients of the multiparticulate system, the formulation scientist can use SEM to focus on the active system in the formulation. Images of the surface morphology can be useful to understand the film integrity and the impact of damage during processing. Cross sectional imaging can give valuable information on polymer coating thickness and core structure characteristics (Metha and Jones 1985).

3.4.2 Particle Size Analysis

Sieving is a useful method for determining the particle size distribution of the discharged product. Sieves are usually cylindrical open containers with predetermined and calibrated mesh sizes stacked upon each other with increasing aperture size, with the largest openings on top to catch agglomerated particles, and the smallest screen on the bottom to remove the fines (Crowder, Hickey et al. 2003).

3.4.3 Dissolution

Dissolution testing has been used extensively for drug development and the four approved apparatuses are described in detail in the USP chapter <711> (USP 2007a). This research focused on Apparatus 1 (basket) and Apparatus 2 (paddle), to follow the appropriate compendial dissolution procedures for the developed products. The Reference Listed Drug (RLD) is defined as “the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA (CFR:314.94 2008).” The dissolution profiles for the RLD strength serve as an important target during drug development.

3.5 Propranolol Hydrochloride Extended Release Capsules

Propranolol Hydrochloride acts as a non-selective beta-blocker, and is indicated for the treatment of hypertension, angina pectoris, migraine, and hypertrophic subaortic stenosis. The drug has a pKa of about 9.45, is readily soluble in water (1g/20ml) and ethanol (1g/20mL), practically insoluble in ether (Troy 2005). Propranolol is nearly completely absorbed from the gastrointestinal tract, and is >90% protein bound throughout the body with a half-life of 3.4 to 6 hours. After administration, constant blood concentrations of drug for approximately 12 hours are apparent before an exponential decline over the following 12 hours of the extended release period (American Society of Health-System Pharmacists 2008b).

Propranolol HCl extended release capsules (Inderal LA, Wyeth) is available in 60mg, 80mg, 120mg, and 160mg. The Reference Listed Drug product is the 160mg extended release capsule (FDA 2008b). All of the capsule strengths comply with the USP dissolution test I. Propranolol has a molecular weight of 295.80 Da, a chemical formula of $C_{16}H_{21}NO_2 \cdot HCl$, and the chemical structure found in Figure 5 (Wyeth 2007).

Figure 5 Propranolol Hydrochloride Chemical Structure (Wyeth 2007)

Table 2 Propranolol Extended Release Capsules Inactive Ingredients

(Wyeth 2007)(Brand)	(Par 2007)	(Mylan 2007)	(Actavis-Elizabeth 2008)
Cellulose	Ethylcellulose	Ammonio Methacrylate Copolymer	Black Iron Oxide
Ethylcellulose	Gelatin- Capsules	Black Iron Oxide	D&C Yellow #10 Aluminum Lake
Gelatin Capsules	Methylcellulose	D&C Red #28 Aluminum lake	Ethylcellulose
Hypromellose	Microcrystalline Cellulose	D&C Yellow #10 Aluminum Lake	FD&C Blue #1 Aluminum Lake
Titanium Dioxide	Titanium Dioxide	Dibutyl Sebecate	FD&C Blue #2 Aluminum Lake
		Ethylcellulose	FD&C Red #40 Aluminum Lake
		FD&C Blue #1 Aluminum Lake	Gelatin
		FD&C Blue #2 Aluminum Lake	Hydroxypropyl Cellulose
		FD&C Red #40 Aluminum Lake	Opacode S-1-8114/8115
		Gelatin	Pharmaceutical Glaze
		Hydroxypropyl cellulose	Povidone
		Hypromellose	Propylene glycol
		Microcrystalline cellulose	Sugar Spheres
		Polyethylene glycol	Talc
		Propylene Glycol	Titanium Dioxide
		Shellac Glaze	
		Sodium Lauryl Sulfate	
		Talc	
		Titanium Dioxide	

3.5.1 Current Manufacturer's of Propranolol HCl Extended Release Capsules

Table 2. provides an overview of the currently marketed propranolol HCl extended release capsules. Formulation and processing strategies are discussed in conjunction with the SEM imaging in the results section.

3.5.2 Recent Research for Propranolol HCl Extended Release

Propranolol HCl has been used extensively as a model drug for many applications due to its availability and relative low cost. Recently patented formulations for extended release Propranolol HCl is found in Table 3.

Table 3 Propranolol HCl Extended Release Formulation (Chen 2006)

Formulation 1	Quantity (%)	Formulation 2	Quantity (%)	Function
Core		Core		
Propranolol HCL, USP (<75 Microns)	51.17	Propranolol HCL, USP (<75 Microns)	49.56	Active Ingredient
Sugar Spheres, NF 30/35	18.73	Sugar Spheres, NF 35/40	9.75	Inert Core
Microcrystalline Cellulose, (PH 105) NF	21.76	Microcrystalline Cellulose, (Vivapur Type 99)	27.84	Filler
Ethylcellulose 10 Cps	5.04	Ethylcellulose 10 Cps	4.11	Binder
Sustained Release Coating		Sustained Release Coating		
Ethylcellulose, NF 45 Cps	2.48	Ethylcellulose, NF 10 Cps	6.42	Sustained Release Polymer
Acetyl Tributyl Citrate	0.25	Acetyl Tributyl Citrate	0.419	Plasticizer
Hydroxypropyl Methylcellulose, (E5) USP	0.25	Hydroxypropyl Methylcellulose, (E5) USP	1.028	Pore Former/Water soluble Polymer
Talc, USP	0.33	Talc, USP	0.824	Antisticking

***Cps is Centipoise, a measure of viscosity.**

The formulation uses a blend of isopropyl alcohol and ethanol to create an organic solvent slurry with the ethylcellulose, Propranolol HCl and the microcrystalline cellulose. The slurry is applied to the inert cores (Sugar Spheres®) in a fluid bed processor. The active drug layered beads are then sustained release coated with an ethylcellulose, acetyl tributyl citrate, HPMC E5, and talc solution

dissolved in isopropyl alcohol and acetone. Chen's patent for Propranolol extended release capsules demonstrates strong correlation to Inderal for *in vitro* dissolution and the *in vivo* fasting condition, but failed the fed state condition due to a spike at the first time point.

3.6 Metoprolol Succinate Extended Release Tablets

Metoprolol Succinate is a beta-1 selective blocker indicated for the treatment of hypertension, angina pectoris, and heart failure. The drug is freely soluble in water and sparingly soluble in ethanol, with a molecular weight 652.8 Da (Astra-Zeneca 2007). The RLD strengths of Toprol XL are 50mg and 200mg (FDA 2008a), which interestingly creates two similar but distinct product targets. The 25mg and 50mg strengths, and the 100mg and 200mg strengths are dose proportional to each other. Figure 6 is the chemical structure of Metoprolol Succinate.

Figure 6 Metoprolol Succinate Chemical Structure (Astra-Zeneca 2007)

The drug has a pKa of 9.68, is 11-12% bound to albumin, the half-life ranges from 3-7 hours, and is predominately metabolized in the liver by CYP2D6 with a 50% first pass effect. Interestingly, the oral steady state bioavailability of the extended release tablets is approximately 77% of the immediate release equivalent

metoprolol tartrate. Peak plasma concentrations are 25-50% of the levels attained by equivalent Metoprolol tartrate dosing, time to plasma concentration max ($C_{p_{max}}$) is 7 hours (American Society of Health-System Pharmacists 2008a).

3.7 Metoprolol Succinate Formulations

Table 4 is an overview of the excipient formulations used by manufacturers of Metoprolol Succinate extended release tablets. Each formulation and the theorized function of each excipient ingredient are presented in the results section, except the Watson formulation found in the “Recent Research for Metoprolol Succinate” section.

Table 4 Inactive Ingredients of Metoprolol Succinate Formulations

Astra-Zeneca (Brand) (Astra-Zeneca 2007)	Ethex (Ethex 2007)	Sandoz	Watson*(Sriwongjanya, Yuk et al. 2008)
Cellulose Compounds	Calcium Stearate	Colloidal Silicon Dioxide	Cellulose Acetate Butyrate, CAB 171-15
Paraffin	Carboxymethylcellulose Sodium	Crospovidone	Crospovidone
Polyethylene Glycol	Carnauba Wax	Hypromellose	Eudragit S100
Silicon Dioxide	Croscarmellose Sodium	Magnesium Stearate	Glycerol Monostearate
Sodium Stearyl Fumarate	Glycerol Behenate	Methacrylic Acid Copolymer	Hydroxypropylcellulose (E-5)
Titanium Dioxide	Hydrogenated Vegetable Oil	Microcrystalline Cellulose	Lutrol F68 (Poloxamer 188 NF)
	Hypromellose	Polyethylene Glycol	Microcrystalline Cellulose
	Maltodextrin	Polysorbate 80	Opadry White/HPMC
	Methacrylic Acid Copolymer	Sugar Spheres	Polysorbate 80
	Microcrystalline Cellulose	Talc	Silicon Dioxide/Talc
	Polydextrose	Titanium Dioxide	Sugar Spheres/Celphere
	Polyethylene Glycol		
	Povidone		
	Sodium Stearyl Fumarate		
	Titanium Dioxide		
	Triacetin		
	Triethyl Citrate		
	Vinyl Acetate Copolymer		

*The Watson brand is not yet commercially available (Watson-Pharmaceuticals 2007), therefore, the ingredients list is theoretically based on the company's patent.

3.8 Recent Research for Metoprolol Succinate

3.8.1 Watson

Table 5 Watson Metoprolol Succinate Formulation and Function (Sriwongjanya, Yuk et al. 2008)

Formulation Step	Estimated Content % per formulation step	Function
Phase I		Development of an IR Bead
Core		
Sugar Spheres 60/80 NF/Celphere CP-203		Inert core for drug layering
IR Drug Layering		
Metoprolol Succinate	70-99	Active Ingredient
HPMC (E-5)	1-25	Binder
Polysorbate 80	0-0.5	Surfactant
IR Beads		
Silicon Dioxide/Talc		Anti-Sticking Agents
Phase II		Development of an SR Bead
SR Polymer Coating		
IR Drug loaded beads		Active Ingredient
Cellulose Acetate Butyrate, CAB 171-15	75-90	Polymeric Membrane
Eudragit S100	5-15	Polymeric Membrane/Channeling Agent
Lutrol F68 (Poloxamer 188 NF)	2-10	Plasticizer/Emulsifier
Phase III		Development of a Multiparticulate Tablet
Tabletting Ingredients		
SR Drug Loaded Beads	25-45	Active Ingredient
IR Drug Loaded Beads**	2-8	Active Ingredient
Glyceryl Monostearate	5-30	Lubricant
Microcrystalline Cellulose	30-50	Flow/Disintegrant/ Filler
Crospovidone		Disintegrant
Tablet Coating		
Opadry White/HPMC		Sealant/Pigment

**** Note that the patent entails either SR beads alone or a combination of IR and SR beads. For SR beads only, the IR bead content is substituted with SR beads.**

Watson is currently licensing its exclusivity rights for the 50mg strength of Metoprolol Succinate, and intends to pursue their submitted ANDA after March 18, 2008 when Astra-Zeneca's extended exclusivity period for pediatric studies expires (Watson-Pharmaceuticals 2007). Table 5. is an overview of the metoprolol succinate formulation patent developed by (Sriwongjanya, Yuk et al. 2008), which is the property of Watson Pharmaceuticals via the acquisition of ANDRX Pharmaceuticals. This formulation utilizes a water/acetone solvent system for the sustained release polymer coating and follows a similar process as the innovator.

Table 6 Metoprolol Succinate Sustained Release Formulation (Ravishankar, Patil et al. 2006)

	Function	Quantities
Sodium Core (Any of the following:)	Base for drug/polymer layering	(425-850 Um) Undisclosed, 70% 600-850 Um)
Sodium Citrate		
Sodium Acetate		
Sodium Chloride		
Sodium Succinate		
Modulating Layer		
Eudragit NE30D	Polymeric Modulator	20%
Polysorbate 80	Plasticizer	2% of NE30D Weight
Glyceryl Monostearate	Glident	5% of NE30D Weight
IR Drug Layering		
Metoprolol Succinate	Active Ingredient	28%
Polyvinyl Pyrrolidone	Binder	1.36
Colloidal Silicon Dioxide	Anti-Caking	0.27
Sustained Release Coating		
Eudragit RS30D	Polymer Membrane	35%
Talc	Glident	50% of RS30D
Triethyl Citrate	Plasticizer	20% of RS30D
Curing		
Colloidal Silicon Dioxide	Anti-Caking	1%

Table 6. is the patented formulation by Ravishankar, Patil et. al. 2006, with ut a two-polymer system approach for their dosage form. The Eudragit® NE30D polymer acts to quench the ionic charges of the salt cores and create a suitable surface for drug layering. While the Eudragit® RS30D acts to slow the release of the Metoprolol Succinate from the drug loaded cores. The authors targeted a “chronopharmaceutical” profile, which attempts to control the release of drug based on the circadian rhythm to optimize the therapeutic dosing regimen. The *in vitro* and *in vivo* release of the drug was designed to slowly release the drug initially and then

more rapidly release the drug after the 7-hour period. A traditional zero order release profile would require optimization of both polymeric layers to adequately match the brand product and sustain the release over a 20 hour period. Additionally, the research focused on the sustained release pellets, which were not tabletted into a final dosage form. Compression of the coated pellets cannot be overlooked, as there can be a significant impact on the release profile.

Table 7 Metoprolol Succinate Extended Release Formulation (Dias 2007)

	Function	Quantity (g)
Core		
Celphere CP-203 (150-300 μm)	Drug Layering Core	100
Drug-binder solution		
Metoprolol Succinate	Active Ingredient	300
Opadry® 03F59040	Film Coating system	15
Polyvinyl Pyrolidone	Binder	9
Purified Water	Solvent	1412
Seal coat		
		1% Weight Gain
Opadry® 03F59040	Film Coating system	4.2
Purified Water	Solvent	137
Barrier Coat		
		26% Weight Gain
Surelease E-7-19040	Polymeric Membrane	445
Purified Water	Solvent	297
Top Coat		
		3% Weight Gain
Opadry® 03F59040	Film Coating system	16.8
Purified Water		523
Tablet Additives		
Cushioning Agent*	Coated bead protection	(70% w/w) 231
Tablet		
		Final weight 330g

Table 7. is Dias 2007 formulation, which utilized a multi step formulation on the inactive microcrystalline (Celphere®) cores. Opadry is a film coating system

composed of polymer, plasticizer, and pigment to form an adhesive film with high tensile strength (Colorcon 2008a). The seal coat acts as a barrier between the Metoprolol drug layer and the sustained release layer. The Surelease polymeric suspension system acts to sustain the drug's release over the dosing interval. The topcoat is necessary to prevent "blocking," a static buildup that prevents material flow at the end of processing of the Surelease polymer (Colorcon 2006). The topcoat can also act to aid in the cushioning of the polymer-coated beads to protect the barrier coating from damage. Tablet cushioning agents (*in the table) explored were: Pre-gelatinized maize starch (Starch[®] 1500), microcrystalline cellulose (Avicel[®] PH102) and spray-dried lactose (Lactopress[®]). The agents were studied as dry blends and hot melt extruded granules. Additionally, the effect of compression force on the pellets was studied. The research concluded that low compression force coupled with a high level of either hot melt extruded microcrystalline cellulose or starch granules provided the greatest protection.

Table 8 Metoprolol Succinate Extended Release Formulation (Niazi 2004)

	Function	Quantity/ 1000 Tablet (g)
Core		
Metoprolol Succinate	Active Ingredient	95.0
Polyoxol 40 hydrogenated castor oil	Polymeric Membrane	25.0
Hydroxypropyl Methyl Cellulose	Carrier material	230.0
Aluminum Silicate	Carrier material	94.0
Alcohol	Solvent	QS
Tablet Additives		
Sodium Stearyl Fumurate	Lubricant	As needed

Table 8. is Niazi, 2004's formulation that gives a simplified granulation procedure where metoprolol is mixed with the castor oil, and then mixed with the

HPMC and aluminum silicate. The components are then granulated with alcohol and dried. The dried granules are lubricated and compressed. This method of formulation is significantly different from the previous examples because of the use of an organic solvent and wet granulation, as oppose to drug layering. The drug release properties of a granulated formulation may experience different diffusional release characteristics than a drug-layered core. Binder selection and concentration, drug layering thickness and density, and other variables can impact the dissolution profiles. The author does not give dissolution profile and tablet characteristics; therefore it is difficult to hypothesize the performance of this delivery system.

3.9 Materials

3.9.1 SEM Studies

Inderal LA 160mg capsules (Wyeth), propranolol HCl ER caps 160 mg (Actavis Elizabeth), propranolol HCl ER caps 160 mg (Par Pharmaceuticals), Toprol XL 25mg (Astra-Zeneca), metoprolol succinate 100mg tablets (Ethex), and metoprolol succinate 25mg tablets (Sandoz) were used.

3.9.2 Physical Characterization and Particle Size Evaluations

Inderal LA 160mg capsules (Wyeth), propranolol HCl ER caps 160 mg (Actavis Elizabeth), propranolol HCl ER capsules 160 mg (Par Pharmaceuticals), and Toprol XL Tablets 100mg and 200mg (Astra-Zeneca).

3.9.3 Dissolution Studies

Inderal LA (Propranolol HCl) ER 160 mg capsules (Wyeth), propranolol HCl ER caps 160 mg (Par Pharmaceuticals), hydrochloric acid, deionized water (in house),

sodium phosphate monobasic, phosphoric acid, anhydrous dibasic sodium phosphate, citric acid monohydrate, and acetonitrile were all of analytical grade.

Toprol XL (Metoprolol Succinate) extended release 100mg, and 200 mg tablets (Astra-Zeneca), potassium phosphate monobasic, sodium phosphate monobasic, phosphoric acid, sodium hydroxide, and analytical grade deionized water prepared in house. The water system consists of Millipore[®] pre filters for municipal water to feed a Waters[®] Elix 5 reverse osmosis system, and is stored in a 60-L Waters[®] Reservoir equipped with a UV Automatic Sanitation Module[®] (ASM), which feeds the Waters[®] A-10 Gradient reverse osmosis system equipped with a terminal 0.22 μm filter, where the analytical water is dispensed.

3.10 Methods

3.10.1 SEM Sample Preparation Methods

The contents of sample capsules were emptied while tablet samples were placed in approximately 100ml of purified water, USP and manually agitated until the drug and water-soluble components were in solution. The remaining insoluble material was screened and the active beads were separated from the other excipients. Samples were air dried, cross-sectioned with a razor blade, and analyzed by scanning electron microscopy (SEM) on a JSM-5900 JEOL (Japan). Magnification and background settings were adjusted based on the sample type. Whole pellet and cross sectional samples were imaged and measured using the instrument's software. One set of Inderal LA 160mg beads were studied after completion of the USP dissolution procedure.

3.10.2 Physical Characterization and Particle Size Evaluations

Propranolol HCl capsules were weighed, emptied, and the beads were sieved through screens #16-30 mesh. U.S. Standard Test Sieves (Newark, Clifton, NJ), which meet ASTM E-11 (Formerly the American Society for Testing and Materials) specification were used to screen the material. The quantity retained on each screen was weighed and calculated as a percent of the total weight.

Toprol XL Tablets were weighed and measured with a Mitutoyo® CD-8"CSX digital caliper. The tablets were gently broken apart and screened through sieves #25-60 mesh. U.S Standard Test Sieves (Newark, Clifton, NJ), which meet ASTM E-11 Specification were used to screen the material. The quantity retained on each screen was weighed and calculated as a percent of the total weight.

3.11 Analytical Methods

3.11.1 Dissolution-Propranolol HCl

A Hanson® SR-8 dissolution apparatus was used in accordance with the USP test method 1 for propranolol hydrochloride extended release capsules. Key settings: apparatus 1, basket speed 100 rpm, 2 phase media, 900 mL of dissolution media. 0.1N hydrochloric acid buffer with a pH of 1.2 for the first 1.5 hours and a sodium phosphate monobasic pH 6.8 buffer from 1.5 hours to 24 hours. The bath temperature was maintained at $37 \pm 0.5^{\circ}\text{C}$ throughout the dissolution. 10mL samples were taken at the sampling time points, with the acceptance criteria found in Table 9. Concentration was primarily determined following the USP method using a Hewlett Packard® 8453 UV spectrophotometer at 320 nm absorbance. The general

method was confirmed by high performance liquid chromatography following the USP method.

Table 9 USP Dissolution Test 1 Acceptance Criteria (USP 2007b)

Dissolution Test 1	
Time (hours)	Amount Dissolved
1.5	Not more than 30%
4	Between 35% and 60%
8	Between 55% and 80%
14	Between 70% and 95%
24	Between 81% and 110%

3.11.2 Dissolution-Metoprolol Succinate

A Hanson SR-8 Dissolution apparatus was used for the USP test method for Metoprolol Succinate extended-release tablets. The key settings are: Apparatus 2, Paddle speed 50 rpm, pH 6.8 phosphate buffer, 500mL dissolution media volume. The sample volume was 5mL with sampling time points and acceptance criteria in Table 10, additional and alternative time points may be sampled where appropriate. Concentration was primarily determined using high performance liquid chromatography.

Table 10 Metoprolol Succinate USP Dissolution Acceptance Criteria (USP 2007c)

Time (Hours)	Amount Dissolved
1	Not more than 25%
4	Between 20% and 40%
8	Between 40% and 60%
20	Not less than 80%

3.11.3 Analytical Calculations of Concentration for Dissolution

$$\% \text{ Dissolved at first sample point, A} = \frac{r_u}{r_s} \times C_{std} \times P \times \frac{DVO}{\# \text{ Units}} \times \frac{100}{LC}$$

Equation 1. Calculation for % Dissolved at the First Sample Point

Where:

r_u	Absorbance or Peak area of drug in the sample preparation
r_s	Average absorbance or peak area of the drug in the working standard
C_{std}	Concentration of Metoprolol Succinate in the Working Standard, in mg/mL.
P	Purity factor of drug Reference Standard in decimal form.
DVO	Initial dissolution volume, in mL
# Units	# of dosage units
100	Conversion factor for percent.
LC	Label Claim (concentration)

% Dissolved at n hours, $A_1 = B + F_1$

Equation 2. Calculating % Drug Dissolved at n Hours

Where,

$$F_1 = A \times \frac{SV}{DVO} \text{ and } B = \frac{r_u}{r_s} \times C_{std} \times P \times \frac{DV_n}{\text{Units}} \times \frac{100}{LC}$$

Equation 3. Calculating F1 Value for a Given Time Point

Where:

SV	Sampled volume, amount removed at the previous time points
DV_n	Dissolution volume at n hours, in mL

This calculation method was used to determine the concentration of the drugs throughout the dissolution period to account for concentration lost due to sampling.

3.11.4 Concentration Determined by High Performance Liquid Chromatography

Propranolol HCl and Metoprolol Succinate were assayed for concentration on a Waters® 2695 separation module equipped with a column heater, an auto sampler,

and degasser. The system was equipped with a Waters® 2487 dual λ absorbance detector for UV/Vis detection. All methods had to meet system suitability criteria of less than a 2.0 % relative standard deviation (RSD) of five injections of the reference solution. Additionally, an in process standard was injected after every six injections of sample solution and with a reference standard which must be less than 3.0 % RSD. The concentration was determined using equation 4.

$$\% \text{ Content of Drug} = \frac{AT \times WR \times PF \times 100 \times MW}{AC \times WT \times LC}$$

Equation 4. Formula for Calculating Percent Content of Drug by HPLC Assay

Where:

- AT Area of the drug peak from the sample solution.
- AC Area of the drug peak from the reference solution.
- WR Weight (mg) of reference substance taken.
- WT Weight of the sample in mg.
- MW Average mass of the capsule or tablet content in mg.
- PF Purity factor % Purity of working standard on an as needed basis.
- LC Label claim for content of drug per unit.
- 100 Percent conversion factor

3.11.5 Propranolol Hydrochloride Assay Method

The Propranolol Hydrochloride USP monograph assay method was used, an overview of the method is given here. The system was equipped with a Symmetry shield®, RP18, 150 mm x 4.6 mm 5 μ m and the UV detector was set to 220 nm. An isocratic method was employed, with a flow rate of 2.0 ml/min, a sample injection

volume of 10 μ L, an average retention time of 2-4 minutes, and a sample run time of 6 minutes. A Phosphate Buffer with a pH of 3.0, and a mobile phase of blended buffer and acetonitrile (75:25 respectively).

3.11.6 Metoprolol Succinate Assay Method

The Metoprolol Succinate USP monograph assay method was used, an overview of the method is given here. The system was equipped with a Nova-Pack[®], C18, 150 mm x 3.9 mm 4 μ column, and the UV detector was set to 280 nm. An isocratic method was employed, with a flow rate of 1.5ml/min, a sample injection volume of 25 μ L, an average retention time of 2-4 minutes, and a sample run time of 7 minutes. A phosphate buffer with a pH of 3.0, and a mobile phase of blended buffer and acetonitrile (75:25 respectively) were used in the method.

3.12 Results/Discussion

3.12.1 SEM and Deformation of Competitors

The deformation of the competitors provided formulation and manufacturing strategies to guide developmental targets for metoprolol succinate and propranolol HCl. This section is divided by product and manufacturer to examine the SEM results and the inactive ingredients. Manufacturing techniques and formulation approaches are supported by patents, literature, and the experimental SEM images. For cases where concrete information was unavailable, formulation function and utilization are based on traditional methodology and a hypothetical "best guess." Due to a lack of sample availability, the Mylan formulation of

Propranolol HCl was not investigated, fortunately the formulation is similar to the Actavis product, which can be used to understand the general development approach.

3.12.2 Results- Wyeth Inderal LA Extended Release Capsules

Based on early patents and the current list of inactive ingredients in Table 11, the brand product consists of a simplistic formulation utilizing organic solvents. Drug loaded cores are prepared via wet granulation with microcrystalline cellulose using alcohol, and/or methylene chloride, or an alcohol/water mix as the granulating agent (Guley, DeMeals et al. 1981) The sustained release coating is comprised of an ethylcellulose and Hypromellose blend in a methylene chloride/methanol solvent mix in a range from 1.5-5% (Guley and Farina 1992).

Table 11 Inderal LA Propranolol HCl Extended Release Capsule Formulation and Hypothesized Function.

Formulation Step	Function
Phase I	Development of an IR Bead
Drug Loaded Core	
Cellulose (MCC)	Core material
Propranolol HCl	Active Ingredient
Phase II	
SR Polymer Coating	Development of an SR Bead
IR Drug Loaded Beads	Active Ingredient
Ethylcellulose	SR Polymeric membrane
Hypromellose	Pore Forming agent
Phase III	Top Coat/Aesthetics
Titanium Dioxide	Pigment
Hypromellose	Binder
Phase IV	Encapsulation
Gelatin Capsules	Dosage Form

Figure 7 Inderal LA 160mg Whole Pellet

Figure 7, the whole particle imaged showed sphericity near 1.0, which cannot be generalized to all of the beads in the dosage form, but is a good example of the desired bead. The surface morphology was smooth and free of cracks or defects.

Figure 8 Inderal LA 160mg Cross Section

Figure 9 Inderal LA Cross Sectional Polymer Coating

Figures 8 and 9 of Inderal LA display the thin coating level of polymer used to achieve the sustained release profile, and support the theorized organic polymer system for the sustained release profile.

Figure 10 Propranolol HCl ER Caps 160mg- Cross Section after Dissolution

The porous core after dissolution, seen in Figure 10, indicates that the production method utilized a wet granulation with extrusion/spheronization approach to create pellets of the desired size. The material remaining after dissolution are water insoluble excipients, such as microcrystalline cellulose, ethylcellulose, etc....

3.12.3 Results-Par Propranolol HCl Extended Release Capsules

The Par formulation is similar to Inderal LA, based on the inactive ingredient list in Table 12.and the SEM figures. The Par formulation appears to have followed a similar formulation approach to the brand product.

Table 12 Par Propranolol HCl Extended Release Capsule Formulation and Hypothesized Function.

Formulation Step	Function
Phase I	Development of an IR Bead
Drug Loaded Core	
Microcrystalline Cellulose	Core material
Propranolol HCl	Active Ingredient
Phase II	
SR Polymer Coating	Development of an SR Bead
IR Drug Loaded Beads	Active Ingredient
Ethylcellulose	SR Polymeric membrane
Methylcellulose	Pore Forming agent
Phase III	Top Coat/Aesthetics
Titanium Dioxide	Pigment
Methylcellulose	Binder
Phase IV	Encapsulation
Gelatin Capsules	Dosage Form

Figure 11 is the whole bead image for the Par formulation of propranolol HCl at a magnification of 100x. The bead appears to have a smooth defect free surface morphology, and a bead sphericity near 1.0.

Figure 11 Par Propranolol 160mg

Figure 12 is a 100x magnification of the cross-sectioned bead, with the drug loaded core and the sustained release polymer coating visible. Figure 13 is a 2500x magnification of the edge of a cross sectioned bead, which shows a thicker coating of polymer than the brand product. More polymers are likely necessary due to the smaller particle size distribution yielding a greater surface area.

Figure 12 Par Propranolol 160mg Cross-Section

Figure 13 Par Propranolol 160mg- Cross Sectional Polymer Coating

3.12.4 Results- Actavis Propranolol HCl Extended Release Capsules

The Actavis formulation in Table 13 is markedly different than the extrusion/spheronization techniques used by the other manufacturers, using a drug layering approach on sugar spheres.

Table 13 Actavis Propranolol Formulation

Component	Function
Phase I	Development of an IR Bead
Sugar Spheres	Inert core for drug layering
Povidone	Binder
Metoprolol Succinate	API
Phase II	Development of an SR Bead
Propylene glycol	Plasticizer
Ethylcellulose	SR Polymer
Hydroxypropyl Cellulose	Pore Former
Phase III	Top Coating
Titanium Dioxide	Pigment
Talc	Lubricant
Hydroxypropyl Cellulose	Binder
Phase IV	Encapsulation
Gelatin	Encapsulation
Phase V	Capsule Identification
Opacode S-1-8114/8115	Ink System
Pharmaceutical Glaze	Moisture barrier/Opacode Component
Propylene glycol	Plasticizer/Opacode Component
Black Iron Oxide	Capsule Pigment
D&C Yellow #10 Aluminum Lake	Capsule Pigment
FD&C Blue #1 Aluminum Lake	Capsule Pigment
FD&C Blue #2 Aluminum Lake	Capsule Pigment
FD&C Red #40 Aluminum Lake	Capsule Pigment

The solubility of Propranolol HCl in water would likely result in an extremely long processing time, and may employ an aqueous polymer coating. The Actavis formulation utilizes a drug layering approach, which may utilize an organic, aqueous or organic/aqueous solvent system. Research has effectively used ethanol/water (60:40 respectively) to load the required drug amount (Dashevsky and Mohamad 2006). Aqueous systems alone have been used to layer the drug (Percel, Vishnupad et al. 2002). Either approach would conceivably be a time consuming process due to the drug's solubility and the quantity necessary to achieve the target potency (Jones 1989).

Figure 14 Actavis Propranolol 160mg Whole Pellet

Figure 14 is the whole bead of the Actavis formulation of propranolol HCl, which contains a speckled appearance. The SEM software determined the speckles to be titanium dioxide from the topcoat.

Figure 15 shows the inert core (Sugar Sphere[®]), the drug layer, and the sustained release-coating layer. The magnified sustained release layer in Figure 16 indicates a thick polymeric coating level and may indicate the use of an aqueous polymer. A topcoat is applied after the sustained release polymer to give an aesthetically pleasing bead and provide a protective coating for the sustained release system. Interestingly, both the Mylan and Actavis formulations utilize pharmaceutical glaze (shellac) which historically has been used as a seal coat to provide an adequate moisture barrier (Kottke and Rudnic 2002). The Opacode S product family of pharmaceutical ink utilizes pharmaceutical glaze (Shellac) and requires a solvent system, such as IPA (Colorcon 2008c). Due to the dual colored capsule (pink and gray) and information printed on the capsule, a large amount of pigments and other excipients are required.

Figure 15 Actavis Propranolol 160mg Cross-Section

Figure 16 Actavis Propranolol 160mg Cross Sectional Polymer Coating

3.13 Metoprolol Succinate

Metoprolol succinate brand and generic marketed products were deformed using SEM imaging, physical and chemical techniques. The list of ingredients is presented with their theorized function to describe the formulation approach. SEM imaging was performed on the whole bead to identify surface morphology and sphericity. Cross-sectioned imaging was used to identify drug and/or polymer coating thicknesses and manufacturing strategies, such as drug layering vs. extrusion/spheronization.

3.13.1 Astra-Zeneca (Brand)

Table 14 is an overview of the formulation and theorized function for Toprol XL. Based on a formulation and process patent (Jonsson 1990), sustained release Metoprolol Succinate tablets are prepared by the following steps: 1) Metoprolol Succinate is dissolved in ethanol 95% and sprayed onto the inert silicon dioxide cores in a fluidized bed granulator. 2) The drug-loaded cores are spray coated in the fluidized bed granulator with the sustained release polymer coating with methylene chloride and isopropyl alcohol as the organic solvents. 3) Inactive microcrystalline cellulose based granules are prepared through wet granulation. 4) The inactive granules, the drug loaded beads, and a lubricant are mixed and compressed into tablets. 5) The tablets are coated with a coating solution in a coating pan.

Table 14 Astra-Zeneca Metoprolol Succinate Formulation and Theorized Function

Formulation Step	Function
Phase I	Development of an IR Bead
Core	
Silicon Dioxide 0.15-0.3 mm (diameter)	Inert core for drug layering
IR Drug Layering	
Metoprolol Succinate	Active Ingredient
Phase II	
SR Polymer Coating	Development of an SR Bead
Polymer Coating	
IR Drug Loaded Beads	Active Ingredient
Cellulose Compounds (Ethylcellulose 10-50 Cps/HPMC Blend)	Polymeric membrane
Polyethylene Glycol	Plasticizer
Phase III	Development of a Multiparticulate Tablet
Tablet Additives	
Microcrystalline Cellulose (Avicel®)	Disintegrant/Tabletting Agent
Sodium Stearyl Fumarate	Lubricant
Tablet Coating	
Hydroxypropyl Methylcellulose	Binder
Polyethylene Glycol	Plasticizer
Titanium Dioxide	Pigment
Paraffin	Sealant/Coating Agent

The sustained release coated pellets are 0.4—0.6mm in diameter with a density of 1.2-1.3g.cm³ (Abrahamsson, Alpsten et al. 1996). The small inert cores have a large surface area and utilize a combination of the following organic solvents: isopropyl alcohol, ethanol 95%, and/or methylene chloride in order to avoid agglomeration during drug layering and sustained release coating to ensure a uniform distribution of the material.

The beads appear to be spherical, based on the SEM image in Figure 17, with a sphericity of the beads near 1.0. The surface is relatively smooth and without visual cracking or defect.

Figure 17 Astra-Zeneca 25mg- Whole Pellet

Figure 18 is a cross-sectioned bead at 100x magnification; the bead is comprised of the silicon dioxide core, a drug layer, and a sustained release layer.

Figure 19 is a 250x magnification focused on the sustained release layer of the bead.

Sizing was calculated by the system software and gives an approximate range between 32-45µm.

Figure 18 Astra-Zeneca 25mg- Cross Section

Figure 19 Astra-Zeneca 25mg- Cross Sectional Polymer Coating

3.13.2 Ethex

Table 15 is a list of the ingredients in the formulation and the theorized function for each component

Table 15 Ethex Metoprolol Succinate Formulation and Theorized Function

Formulation Step	Function
Phase I	
Core	Development of an IR Pellet
Metoprolol Succinate	Active Ingredient
Microcrystalline Cellulose	Core Material
Carboxymethylcellulose Sodium	Binder
Phase II	
SR Polymer Coating	Development of an SR Bead
Polymer Coating	
Methacrylic Acid Copolymer	Polymeric Membrane
Vinyl Acetate Copolymer	Polymeric Membrane
Triacetin	Plasticizer
Triethyl Citrate	Plasticizer
Phase III	Development of a Multiparticulate Tablet
Tablet Additives	
Sodium Stearyl Fumarate	Lubricant
Maltodextrin	Cushioning agent
Polydextrose	Cushioning agent
Hypromellose	Cushioning agent
Povidone	Pore former
Carboxymethylcellulose Sodium	Disintegrant
Glycerol Behenate	Lubricant
Calcium Stearate	Lubricant
Tablet Coating	
Polyethylene Glycol	Binder/Plasticizer
Titanium Dioxide	Color
Carnauba Wax	Sealant
Hydrogenated Vegetable Oil	Sealant/Lubricant

This formulation appears to use the greatest amount of different inactive ingredients to create a viable dosage form. The impact and cost of each excipient

should be well understood when creating a generic product. While the individual excipient may not be particularly expensive to purchase, it is important to consider the costs associated with maintaining cGMP material for production and the extensive handling and documentation required for use. Additionally, all of the inactive ingredients must be examined to ensure that there are no compatibility issues or long-term stability implications. Based on the processing methodology and magnitude of excipients, this formulation is theoretically the most expensive and identifying specific excipients with their functions is challenging.

Figure 20 is a whole pellet and displays a dumbbell like shape, which may be attributed to the immediate release bead processing during extrusion/ spheronization. The bead is not as spherical as the brand product, and visual observations indicated a significantly larger particle size distribution.

Figure 20 Ethex 100mg- Whole Pellet

Figure 21 is a 75x magnification of a cross-sectioned bead, which does not contain an inert core or separate drug layering. Figure 22 is a 100x magnification of the sustained release polymer level with approximately 9-11 μ m thickness. Based on the ingredient list and the SEM images, the Ethex[®] formulation is the only currently marketed product theorized to be manufactured using a wet granulation process.

Figure 21 Ethex 100mg- Cross Section

Figure 22 Ethex 100mg- Cross Sectional Polymer Coating

3.13.3 Sandoz

Table 16 contains the Sandoz formulation for metoprolol succinate, with the theorized function for each ingredient. This formulation is unique in the approach to sustained release coating by employing Methacrylic acid copolymer alone.

Table 16 Sandoz Metoprolol Succinate Formulation

Formulation Step	Function
Phase I	Development of an IR Bead
Core	
Sugar Spheres	Inert core for drug layering
IR Drug Layering	
Metoprolol Succinate	Active Ingredient
Polyethylene Glycol	Binder
Phase II	Development of an SR Bead
SR Polymer Coating	
Polymer Coating	Active Ingredient
Methacrylic Acid Copolymer	Polymeric membrane
Colloidal Silicon Dioxide (Syloid)	Anti-Sticking agent
Polysorbate 80	Plasticizer
Phase III	Development of a Multiparticulate Tablet
Tablet Additives	
Magnesium Stearate	Lubricant
Microcrystalline Cellulose	Flow/Filler/Cushioning agent

Methacrylic acid copolymer, USP is a general name describing a number of different systems, commercially available examples of this polymer can be seen in Table 17.

Table 17 Methacrylic Acid Copolymer Types (Degussa 2007b)

Trade Name	Methacrylic acid Copolymer USP/NF Grade	Solubility	Release Site
L100	A	$\geq$ pH 6.0	Jejunum
L12.5			
S100	B	$\geq$ pH 7.0	Ileum/Colon
S12.5			
L100-55	C	$\geq$ pH 5.5	Duodenum
L30D-55			

While all three grades of Methacrylic acid copolymer are used for enteric coating, each has a specific pH solubility, which allows for targeted colonic delivery.

All of the polymers in Table 17 may utilize organic solvent systems, while grade C polymers have the option for dispersion in an aqueous system. An aqueous dispersion, Eudragit L30-55D, is commercially available and Eudragit L100-55 can be redispersed in water from a powder. If a grade C polymer were used, a sustained release profile would be difficult to achieve due to rapid dissolution of the polymer in the small intestines resulting in immediate drug release. Additionally, the two grade C polymers contain polysorbate 80 and sodium lauryl sulfate for aqueous dispersion. Polysorbate 80 is utilized in the formulation but sodium lauryl sulfate is not, which would indicate this grade of polymer was not used. Therefore, it can be hypothesized that a thick coat of a grade B polymer or a blend of A and B grade Methacrylic acid copolymer are employed in order to yield a zero order kinetic release throughout the gastrointestinal tract (Degussa 2007b).

Figure 23 is a whole pellet of the Sandoz metoprolol succinate 25mg at 75x magnification. The beads appear relatively spherical and dumbbells were not found. Figure 24 is a 75x magnification of the cross-sectioned bead with a drug layering approach is similar to the branded product, and the sugar sphere, drug layer, and sustained release layer are clearly visible. Figure 25 is a 500x magnification of the cross-sectioned bead, focused on the sustained release layer. The image shows a range of polymer thickness from approximately 37-52 μm .

Figure 23 Sandoz 25mg- Whole Pellet

Figure 24 Sandoz 25 mg- Cross Section

Figure 25 Sandoz 25 mg- Cross Sectional Polymer Coating

3.14 Particle Size Analysis Results-Propranolol HCl

Figure 26 Particle Size Distribution of Propranolol HCl Extended Release Beads

Figure 26 depicts the unique particle size distributions for branded and generic Propranolol HCl. Interestingly, the Actavis and Par Propranolol HCl extended release beads are shifted to smaller particle size distributions. The shift to smaller particles indicates a larger amount of polymer was needed to compensate for the increased bead surface area to match the dissolution profile of the other competitors. A marginal increase in the polymer level can be seen by the SEM of the cross section of the Par in Figure 27. Additionally, the cross section of Actavis Propranolol HCl in Figure 27 shows a significantly larger amount of polymer applied, which may indicate that an aqueous polymer was employed for the intermediately distributed beads.

3.15 Metoprolol Succinate Particle Size Distribution Results

Table 18 Approximate Particle Size Distribution of 100mg Metoprolol Succinate Tablets (N=3)

Mesh Cut	Weight (mg)	% Retained	Observations
#25	15.2	1.47	Granules
#30	66.1	6.41	Granules
#35	356	34.53	80% SR Beads/ 20% Granules
#45	190.6	18.49	Mostly SR Beads
#60	23	2.23	Granules
Pan	180	17.46	Fine Excipients
Shell Coating	200	19.40	Mix of Top Coat and compressed excipients
Total	1030.9		

This small sampling of branded tablets yields an estimate of the target end process particle size for the SR beads prior to tableting. Excipient granules and beads could be differentiated and estimated with the naked eye. Table 18 shows that qualitatively the bulk of the active beads are retained on sieve sizes #35 and #45. The excipient granules are spread out over the range of the sieves, with a significant

amount of fine excipients comprised of crushed excipient granules during tableting and fine excipients (i.e. lubricant).

3.15.1 Results- Propranolol HCl Extended Release Capsules- Fill Weight

Table 19 Average Fill Weights for Propranolol HCl 160mg Capsules

Brand	Average Gross Weight (mg) (n=10)	Average Capsule Weight (mg) (n=10)	Average Net Fill weight (mg) (n=10)
Wyeth	341.0	73.0	268.0
Par	349.4	73.0	276.4
Actavis	343.5	73.1	270.4

Table 19 shows that all of the marketed products have similar fill weights, and provide a reasonable fill weight to target.

All of the products used size 1 capsules to encapsulate the extended release beads. The Mylan brand was unavailable for evaluation.

3.15.2 Results-Metoprolol Succinate Extended Release Tablets-Dimensions/Fill Weight

Table 20 Metoprolol Succinate SR Tablet Dimensions/Fill Weight

Tablet Strength (mg)	Tablet Shape	Length (in)	Length (mm)	Width (in)	Width (mm)	Thickness (in)	Thickness (mm)	Average Tablet Weight (n=10)	Standard Deviation	RSD (%)
100	Scored Round	0.401	10.18	NA	NA	0.1595	4.05	366.76	7.90277	2.15
200	Scored Oval	0.6785	17.23	0.2585	6.56	0.3425	8.7	703.9	5.03918	0.72

The Metoprolol Succinate 100mg tablets are slightly more than half of the weight of the 200mg tablets, which supports the dose proportionality of the RLD. The high dose tablets were selected for initial development, 25mg and 50mg tablets were not evaluated. Table 20 provides information about target weights and tablet dimensions for tooling selection.

3.15.3 Results- Dissolution Profile- Propranolol HCl Extended Release Capsules

Figure 27 is a comparison of Inderal LA 160mg and Par pharmaceutical's generic Propranolol extended release 160mg capsule dissolution profiles. Due to an initial erroneous run and limited sample availability the Par brand and Inderal LA were run in the same bath to examine the product trends. Appendix 1. displays the complete experimentation performed to determine the mean Inderal LA profile used during the development of this product. The Par generic follows the same trend as the brand product but has a quicker initial release before matching the innovator at the 22-hour time point. The error bars represent the calculated standard deviation of the samples at that point, and indicate a difference in the profiles. Previous exploratory work (not shown) determined that the Actavis formulation exhibited a slower dissolution than the branded product. Mylan's Propranolol extended release capsule formulation was unavailable at the time and therefore not studied. Variation between the manufacturers was expected, but all FDA approved generics met the USP I dissolution criteria.

Propranolol HCl extended release capsules are comprised of sustained release coated beads; each strength is adjusted by fill weight and are proportional dosage forms. The FDA's approval of lower strengths of the dosage form without an In

vitro/In vivo correlation is possible if the bioavailability data are available for the highest strength (FDA 1997a). The USP monograph acceptance criteria and the brand product's dissolution profile served to guide formulation and process development.

Inderal 160mg vs Par 160mg Extended Release Capsules (n=3)

Figure 27 Comparison of Dissolution of Inderal LA 160mg Capsules and Par Propranolol Extended Release 160mg Capsules Using USP I Method

3.15.4 Results-Dissolution of Metoprolol Succinate Extended Release Tablets

Figure 28 is the USP II dissolution profiles of Astra-Zeneca's Toprol XL-100mg and 200mg dosage forms, with the USP low and high levels of acceptance criteria. The standard error bars for the dissolution profiles overlap and the profiles can be considered equivalent. The Toprol XL 100mg and 200mg strength dissolution profiles are considered dose similar, and the formulation is dose proportional. The Ethex Metoprolol Succinate Tablets do not comply with the USP monograph dissolution acceptance criteria and were subsequently not evaluated (Ethex 2007).

Toprol XL 100mg and 200mg Extended Release Tablets (n=6)

Figure 28 Comparison of Toprol XL 100mg and 200mg Dissolution Profile

3.16 Chapter Review

SEM imaging was used in conjunction with published formulation ingredient lists to facilitate the identification of component activity. The imaging supported a bead sphericity target of ~ 1.0 for Propranolol HCl. The identification of dumbbells in the Ethex formulation of metoprolol succinate supported a more flexible sphericity target in anticipation of potential formulation or processing difficulties. The sieving studies identified a controlled particle size distribution for both Propranolol HCl and metoprolol succinate. The Propranolol HCl competitors each had a tailored particle size distribution but varied in their tailored approach, with the brand product having the largest mean particle sizes. The Metoprolol Succinate beads were significantly smaller than the Propranolol HCl beads, and also showed a tailored approach to particle size distribution. The dissolution profiles of both Propranolol HCl and Metoprolol Succinate brand products were within the USP acceptance criteria, and served as the targets for drug release for the target products.

Chapter 4 Critical Quality Attributes

4.0 Introduction

This chapter gives an overview of current techniques used to formulate and process multiparticulate sustained release in order to support the selection of Critical Quality Attributes (CQA's). Wet granulation, extrusion/spheronization and fluid bed drying are the primary processing techniques explored for immediate release pellets, which were utilized in the development of the experimental dosage forms in order to provide a viable platform for the water-soluble drugs. The second area of interest is in polymeric membrane formulations and processing conditions required to create a viable controlled release. Finally, a basic overview of top coating and tableting are discussed to support the selection of the CQA's.

4.1 Stress-Strain Relationship

Throughout the manufacturing process ingredients are subject to stress and strain, which can impact product properties. Tensile strength testing is used to calculate stress (σ), where the force applied to the material is divided by the cross-section of the sample and strain (ϵ) where; the resulting length of the sample is divided by the initial length (With 2006). Figure 29. is a simplified example of a stress-strain relationship, where the material begins by experiencing reversible elastic deformation, then moves to viscoelastic deformation. The elastic region displays extension length proportional to the load applied and is reversible upon removal of the load, while viscoelastic material can experience any of the following when a load is applied: immediate elastic deformation, slow elastic deformation, or

a plastic deformation (McArthur and Spalding 2004). Viscoelastic behavior is seen for many amorphous materials used throughout pharmaceutical manufacturing, including tableting (Hoag, Vivek et al. 2008). Beyond the “yield” (elastic limit), the material is experiencing irreversible plastic deformation, until it reaches a final “rupture” point where fracture occurs. Fracture is a disruption of the continuous connective nature throughout the system, which can result in a weakened unit (With 2006).

Figure 29 Example Stress-Strain Curve for Uniaxial Tension (Hoag, Vivek et al. 2008)

4.2 IR Bead Processing

4.2.1 Granulation

Common reasons for granulating pharmaceutical material described by (Parikh 2005) include: Increased drug distribution uniformity, densification of

material, enhanced flow rates and rate uniformity, easier metering or volumetric dispensing, dust reduction, and improved product appearance.

Extensive research has been conducted on difficulties associated with the granulation process, examples include studies focused on: high shear granulation (Devay, Mayer et al. 2006), extrusion/spheronization (Chatchawalsaisin, Podczek et al. 2005) (Sriamornsak, Nunthanid et al. 2007), and fluid bed processing (Lipsanen, Antikainen et al. 2007) (Rajniak, Mancinelli et al. 2007). Common general equipment used in wet granulation processes are: high shear mixers, low shear mixers and fluid bed granulators. While each method has its distinct advantages and disadvantages, high shear granulation will be explored in this research.

4.2.2 Wet Granulation

Wet granulation uses liquid to wet the seed particles to create controlled conditions of agglomeration. Liquid binding forces are responsible for the particle size generation, while solid bridging is the key factor for granule strength (Crowder, Hickey et al. 2003). Figure 30. gives an overview of the rate processes of agitative agglomeration that includes: wetting, growth, consolidation, and breakage. The figure also describes the critical formulation and process variables, which are responsible for the final granule characteristics.

Figure 30 Overview of Critical Factors During Granule Formation (Ennis 2005)

The general steps of the wet granulation process are: 1. Weighing and blending all active and inactive ingredients. 2. Preparing a damp mass. 3. Screening the damp mass into granules. 4. Drying the granulation. 5. Sizing the granules through dry screening (Ansel, Allen et al. 1999). The sized particles can then be further processed with sustained release coating or blended with excipients for tableting.

Water-soluble drugs are well suited to wet granulation methods which can use water as the granulating liquid to provide adhesion of the particles to one another. Water acts to raise the contact angle of water soluble materials at the solid liquid interface to enhance the distribution of the drug throughout the mass (Cantor, Augsburger et al. 2008). Challenges associated with this approach are found during

the establishment of a compatible uniform formulation due to possible drug migration and robust processing parameters to create a pharmaceutically viable product (Allen, Popovich et al. 2005).

4.2.3 High Shear Wet Granulation

Figure 31 Schematic of a Bottom-Driven Vertical High Shear Granulator with Horizontal Chopper Shaft (NiroPharma 2003)

Figure 31 is a schematic of a typical vertical high shear granulator for wet granulation. Dry material is introduced to the granulator through the load port and can be mixed with the main impeller to achieve a uniform dry blend. Dust created

from dry materials is captured in the product filter to prevent external contamination. Granulating liquids, such as water or organic solvents, are introduced through the spray port during main impeller and/or chopper mixing. When an acceptable granule is formed, the wet mass exits the system through the discharge port.

Granule growth in a high shear granulator is largely dominated by coalescence or layering. Coalescence is the agglomeration of materials based on collision and binding of granules to one another. Binders facilitates fine particle adherence to larger particles, to achieve layering (Gokhale, Sun et al. 2005). Adequate water is essential for success for both of these methods of granule growth. Two types of water are inherent in the system: internal water, which is captured within the particles during agglomeration, and “free” surface water remaining from the addition of granulating liquids. Both forms of water are necessary to create bonding strength and plasticity to allow coalescence and layering (Ghebre-Sellassie 1989).

High shear granulation has been shown to create denser particles with lower porosity to slow disintegration times compared to alternative methods of single step extrusion granulation (Keleb, Vermeire et al. 2004b) and fluid bed granulation (Gao, Jain et al. 2002) approaches. This method’s unique physical properties are associated with the high shear granulation’s adhesion of material with water before repeated cutting and compaction to yield a denser and harder material (Gao, Jain et al. 2002).

Research has shown the importance of shear on a granule’s growth and its final properties. (Oulahna, Cordier et al. 2003) found that higher impeller speeds

during processing result in lower granule porosity and friability, with a narrower particle size distribution overall. This research also found that granule size is a critical factor for a granule's properties regardless of the impeller speed and increasing shear alone does not result in more homogenous granules.

4.2.4 Extrusion

Extrusion can be defined as “a method of applying pressure to a mass until it flows through an orifice or defined opening. It is a technique that determines two dimensions of an agglomeration of particles (Hicks and Freese 1989).” The two dimensions of the particles defined by extrusion are: 1) the cross sectional diameter which is a function of the screen size the material passes through. 2) The length of the extrudate, which is dependent on the formulation and processing parameters.

There are a number of different types of extruders, but all achieve the same objective of converting a wet mass into cylindrical particles. A wet mass can be created using high or low shear granulation, and is forced through a screen with holes of uniform diameter to create spaghetti like rods. The extrudate hangs down and breaks under its own weight into similar lengths. The critical formulation parameter during extrusion is the material's plasticity, which must break but avoid adherence to other particles during spheronization (Mehta, Singh Rekhi et al. 2005). Water in the formulation, added during granulation, aids the extrusion process by increasing the plasticity of the material, and provides lubrication to the die during processing (Tomer and Newton 1999). The final extrudate should be a cohesive unit,

with suitable firmness and plasticity to withstand the remaining downstream processes(O'Connor and Schwartz 1989).

Extrusion is typically viewed as an intermediate processing step, with formulation adjustments made in the previous granulation step. Current research in extrusion focuses on formulation properties and different types of extruders used. Examples include: examining different base excipients (Almeida-Prieto, Blanco-Mendez et al. 2007), use of twin screw extruders (Keleb, Vermeire et al. 2004a), and hot melt extrusion (Andrews, Jones et al. 2008). Equipment modifications and operational parameters have been studied to evaluate non-formulation based variables. The study of water distribution and loss during extrusion is important for aqueous wet granulation formulations. Research has demonstrated water migration during slower speeds of extrusion resulting in wetter extrudates early in the process (Tomer and Newton 1999). The authors associated this phenomenon with slow extrusion speeds allowing water greater time to travel through void spaces to the die. Additionally, the loss of surface water has been associated with evaporation due to a rise in temperature of the extruder and die during processing (Vervaet, Baert et al. 1995).

4.2.5 Spheronization

The spheronizer was patented over 40 years ago to rapidly create small (<2.0 mm diameter) uniform spherical granules using crossing grooves to cut and rub the material (Nakahara 1966). Figure 32 is comprised of A) Motor to drive the system.

B) A cross-hatched friction plate, which spins to shape the material. C) A sidewall to contain the product. D) A material loading port. E) A material discharge port.

Figure 32 An Adapted Schematic of an Early Spheronizer (Nakahara 1966)

Spheronization occurs after extrusion, where the cylindrical particles are broken into short lengths by contact with the rotating frictional plate, and collisions at the particle/particle level and the particle/wall interface to create spherical shapes with nearly uniform diameters. The centrifugal force generated by the rotating plate throws the material to outside of the plate where it climbs up the sidewall before

gravity results in a tumbling (“rope like”) motion back to the friction plate, where it repeats the same cycle (Nakahara 1966). The cross hatch angle, pattern, and groove distance (space between edges) can all be adjusted to improve the efficiency of spheronization for different sized beads (Hicks and Freese 1989).

(Reitz and Kleinebudde 2008) evaluated jacketed vessels for temperature control during processing to alter product viscosity, plasticity and sticking more basic spheronizer research focuses on spheronization speed and duration.

Spheronization speeds are generally evaluated to yield an optimal rope like movement of the material (Dukic-Ott, Remon et al. 2007) and adequately densify the material (Vervaet, Baert et al. 1995). Spheronization cycle times directly impact the sphericity of a particle by increasing the number of collisions the material undergoes during a cycle, and serves as an important area for research (Pinto, Lameiro et al. 2001). In general, the longer the cycle is run the greater chance the material will be round, but there is also an increased chance for unintended particle size growth.

4.2.6 Fluid Bed Drying

Figure 33 Schematic of Fluid Bed Drying of Wet Material (Olsen 1989)

Figure 33 depicts how a wet mass can be dried using a fluid bed dryer instead of a traditional oven (tray) dryer. Granules, pellets or other wet materials are first loaded into the product container of fluid bed dryer. The air inlet introduces air into the system through the lower plenum; the air is heated, cooled, and humidified depending on the equipment configuration (Olsen 1989).

The air passes through a lower screen (distribution plate); screen mesh sizes are changed for different products to accommodate varying loads and to alter the

flow pattern and restriction of airflow to lift the product. Heated air will lift and dry the wet mass; the drying rate is described by Equation 5:

$$\frac{dw}{dt} = \frac{h \cdot A}{H} * \Delta T$$

Equation 5. Drying Rate (Parikh 1992)

Where $\frac{dw}{dt}$ is the mass transfer rate (drying rate), h is the heat transfer coefficient, A is the surface area, H is the latent heat of evaporation, and ΔT is the temperature difference between the air and the material surface. Heat transfers to the material during drying to supply latent heat to evaporate the liquid, while simultaneously mass transfers as the internal liquid/vapor diffuses and evaporates from the surface (Parikh 1992).

Physical interactions with other particles, chamber walls, and the air distribution plate will aid in the breakage of agglomerated particles that may have formed during earlier stages of processing. A critical balance must be maintained during fluidization for drying; over fluidization will break the particles and create excess dust resulting in concentration or excipient loss, while under fluidization can leave particles wet, agglomerated and unsuitable for further processing (Olsen 1989). The air then passes through the expansion chamber, where cooling occurs, and to the filter housings.

Filters may consist of bags, cartridges, or a drying screen similar in design to the air distribution plate on the bottom of the chamber. Filter pore size must be selected carefully to balance adequate airflow to sustain fluidization, and prevent the escape of API or excipients. Generally, a smaller pore size is chosen when drying

become clogged during processing, thereby limiting the airflow. The filters are shaken or “blown back” using compressed air to reintroduce the drug or excipients to the immediate release pellets to prevent concentration loss during processing. While every effort is made to keep the material off the filters and on the product, filters may gradually become clogged and decrease the fluidization level. It is critical to monitor the filter pressure and product pressure for machinery equipped with these gauges. Adjustments to the fan speed during processing may be required to maintain an optimal fluidization height and must be evaluated to understand and control the process parameters (Parikh 1991).

An “air blast” or a “bed blast” can be utilized to lift the product off the air distribution plate during the process if necessary. This technique closes the valves above the filters on the top of the chamber to allow vacuum pressure to build just above the product chamber. The valves are rapidly opened and a large amount of vacuum pressure pulls the material off of the air distribution plate. The abrupt movement can lift and break up wet materials that may have formed large agglomerates. Standard operating parameters designed to avoid over agitation of the product and may not sufficiently lift the wet materials early in the drying stages when it is heaviest. After the fluid bed is discharged, it is important to separate process generated agglomerates and fine particles (also referred to as “fines”) from the usable material (Olsen 1989).

Sieving is performed to remove agglomerated particles, fines, and undesirable particle sizes that may be generated during processing. This controls the

particle size of the immediate release pellets that will be subsequently coated for sustained release.

4.3 Controlled Release Background

4.3.1 Fluid Bed Spray Coating

Figure 34 Cross Sectional Schematic of a Standard Bottom Spraying Configuration with a Wurster Column (Olsen 1989).

Figure 34 depicts the schematic of the product container where spray coating using a bottom spray nozzle with a Wurster column is used for the addition of liquid materials to the fluidizing solid materials. Within the coating chamber, (A), temperature controlled air is drawn through the air distribution plate, (C), via a motor drawing vacuum to lift and fluidize the solid material. The Wurster column, (B), acts to create capillary action and create an ideal spray zone, where the spray nozzle,

(D), can introduce liquid coating materials to the fluidizing solid material. The spray nozzle, (D), is also capable of introducing atomizing air to the system to aid in the lift, and capillary action of the Wurster column, in addition to controlling the droplet size of the materials being sprayed. After the air passes the fluidized material it enters the expansion chamber, (E), and is filtered prior to exiting the system (Olsen 1989).

Drug layering on inactive cores, the addition of polymeric membranes and other excipients to drug loaded pellets for sustained release or protection are common uses for this configuration. The formulation and operating conditions during spraying are critical for the successful production of a product.

When spraying polymeric membranes onto drug loaded beads, it is important to understand the impact of the starting material. Figure 35 is a useful estimator of particle surface area based on diameter, in order to estimate the required polymer quantity. As the particle size increases, the surface area and the amount of polymer required for 1 mg/cm^2 decreases. This is important when considering the target formulation's particle size distribution to understand the impacts on polymer coating thickness.

Figure 35 Adaptation of Blaine's ASTM Des. C 205-55 for Estimating the Surface Area of Small Particles and Polymer Coating Requirements (Degussa 2007a).

4.4 Curing

After completion of the aqueous sustained release coating process, the film applied may not completely coat the immediate release bead. This is due to the incomplete coalescence of the polymer particles into a homogenous film, resulting in variable drug release from the beads (Bodmeier, Guo et al. 1997). Curing is a processing step that may use heat and/or humidity to facilitate the rapid coalescence of the polymer into a uniform coating to protect the beads to create a uniform drug release profile. The extreme conditions of curing, such as: high temperature, high humidity, and long durations of curing have been studied. The results are highly dependent on the polymer coating material used and cannot be generalized among

polymer systems(Siepmann, Muschert et al. 2008). Curing polymers has also been found to reduce the brittleness when compared to uncured beads, which is advantageous during tableting to minimize bead crushing (Abbaspour, Sadeghi et al. 2007). For Aquacoat ECD aqueous dispersion, the manufacturer recommends a curing cycle of two hours at 60°C (FMC-BioPolymer 2006). Curing approximately 10-12°C above the T_g allows relaxation of polymer chains and an alteration of the film wetting properties reduces instability during storage for beads coated with an Aquacoat ECD and DBS (Wheatley and Steuernagel 1997).

4.5 Bead Top Coating

A protective excipient blend is of primary importance to minimize bead crushing during tableting, top coating aqueous ethylcellulose beads may offer an additional level of protection during processing (Dias 2007). Mannitol, polyethylene oxide, polyethylene glycol and microcrystalline cellulose have also been explored as protective excipients to provide cushioning, especially for high potency beads in poorly uniform blends (Torrado and Augsburgers 2008). Opadry II Y-30-18037, contains a proprietary blend of triacetin (plasticizer), Hypromellose, Lactose monohydrate, and titanium dioxide, triethyl citrate (Spectrum, Gardenia, California) was used as a plasticizer to provide additional flexibility. The Opadry II top coating suspension is advertised to act as an environmental moisture protection for water sensitive drugs to enhance product stability and shelf life. Additionally, strong film mechanics for protection against peeling and cracking support the use predominantly for tablets (Colorcon 2008b).

4.6 Tablet Background

Compressed oral tablets for immediate release applications are a well-established pharmaceutical dosage form for the generic market, with formulation and manufacturing practices studied extensively. Materials experience volume reduction until consolidated into a solid unit; tableting traditionally places material into a die and then uses a set of punches to reduce the volume under pressure (Hoag, Vivek et al. 2008). Advantages of tablets over other dosage forms include: ease of administration, low cost to manufacture, ease of packaging and shipping, and product stability and tamper resistance (Kottke and Rudnic 2002). The tableting of multiparticulate modified release systems offers additional advantages over standard tablets. The primary advantage of a multiparticulate system is the enhanced surface area and distribution in the gastrointestinal tract as compared to a traditional single unit system. This can yield decreased inter/inpatient drug release variability, potentially diminish food effects, avoid “dose dumping” if the system is damaged, and facilitate the combination of multiple incompatible drugs (Torrado and Augsburger 2008).

Compaction acts to transform the raw ingredients into a final dosage form through the following mechanisms: Initial volume reduction rearranges particles closer together until interparticulate friction prevents movement. Further volume reduction is achieved through reversible (visco)elastic deformation, and proceeds to irreversible plastic deformation which contributes to the tablet’s strength, or undergoes brittle fracture which yield crumbling tablets of poor quality (Kottke and Rudnic 2002). This compaction results in the formation of chemical (i.e.

electrostatic, Van der Waal forces) and physical (i.e. mechanical interlocking, solid bridges formed via melting) interparticulate bonds to create a viable tablet (Hoag, Vivek et al. 2008)

Direct compaction may be a viable approach to a limited number of products as an effective tableting method. These products do not require adjustments to their flow properties, density, and/or particle size distribution, to yield appropriate physical parameters for an acceptable dissolution profile (Parikh 2005). For many drugs, wet granulation is used to create viable drug granules for compression. Creating an appropriate size distribution and shape/morphology of intermediate pellets for tableting into a multiparticulate dosage form, with proper physical parameters such as compressibility attributes bulk/tap density and flow properties are complicated. Varying granule properties such as: particle size, sphericity, and porosity can all influence the granular deformation during tableting. Plastic deformation is primarily seen during tableting, but porous and irregular granules may experience fragmentation and breakage (attrition) resulting in rapid drug release (Hoag, Vivek et al. 2008).

One common tableting technique matches the active and excipient particle sizes in order to gain better homogeneity to minimize segregation due to the flow properties of the powders during the blending steps. If homogeneity and adequate flow is not achieved, the dissolution properties, tablet weight, hardness, and manufacturability may all be adversely effected (Crowder, Hickey et al. 2003).

4.7 Key Excipients for Formulation

4.7.1 Fillers/Bulking Agents

There are a number of fillers and bulking agents used to create a core structure for the active ingredient. Examples include: lactose, sugars, dicalcium phosphate, starch (pregelatinized), and microcrystalline cellulose (MCC) (Chan and Heng 2005). The choice of core material is dependent on the active ingredient and dissolution profile target. Two examples: 1) For water soluble drugs within a sustained release product, an insoluble core (i.e. mcc) will slowly release the drug via diffusion through the insoluble structure. 2) For poorly water soluble drugs, it is necessary to use a soluble filler (i.e. starch) to facilitate the release of the drug from the inert matrix (Dukic-Ott, Remon et al. 2007).

MCC is ubiquitously found throughout pharmaceutical manufacturing in a multitude of functions, available in a range of mean particle sizes and grades. It is primarily used for oral capsules/tablets as a binder and diluent in wet granulation and direct compression (Weller 2003). MCC primarily undergoes plastic deformation during compression, in contrast to crystalline lactose and sucrose which may be more prone to experience fracturing (Hoag, Vivek et al. 2008). MCC's addition to an excipient blend improve the plastic characteristics during compression and lubricant efficiency to protect sustained release coatings on the beads during compression (Torrado and Augsburg 2008).

Smaller mean particle sized grades of MCC (e.g. Avicel PH-101 ~50 μ m (FMC-BioPolymer 2008) are utilized in wet granulation, due to their beneficial rheological properties as a wet mass during extrusion and spheronization (Faure,

York et al. 2001). Avicel PH-102 (~100 μm) (FMC-BioPolymer 2008) may be used during tableting to provide excipient protection for smaller coated beads, but potential formulation dependent segregation issues must be understood (Torrado and Augsburgers 2008). Larger sized grades of MCC (e.g. Avicel PH 200 ~200 μm) have been found to yield lower tablet weight variations, while maintaining compactibility similar to smaller sized materials (Doelker, Massuelle et al. 1995). In addition to MCC's enhanced compactibility, wetting and drying occur at a rapid and even pace to prevent variable distribution of soluble ingredients in the granule (Cantor, Augsburgers et al. 2008).

4.7.2 Granulating Agent

A variety of granulating agents can be employed depending on the physicochemical properties of the dry mass of excipients and active ingredient(s). Water, ethanol, acacia, alginate, pectin, HPMC, sodium carboxy methylcellulose (CMC), polyvinylpyrrolidone (PVP), citric acid and calcium chloride solution (in water) were studied as granulating agents for the wet granulation process (Sriamornsak, Nunthanid et al. 2007). This research found that the higher viscosity agents resulted in dumbbell formation, while low viscosity watery agents with calcium chloride, which reduced the swelling potential of the excipient blend and yielded desirable spheres

Water has become the primary granulating agent of choice, with organic or hydro alcoholic solvent blends employed when hydrolysis of the active ingredient or other concerns are apparent (Cantor, Augsburgers et al. 2008). The amount of water

used during granulation will dictate the properties of the intermediate materials throughout process. If the mass is over wetted during granulation agglomerates may form during the spheronization process and yield an undesirable particle size distribution and shape (Vervaet, Baert et al. 1995). Conversely, if the mass is not sufficiently wet to lubricate the extrusion die, excessive die pressure and heat due to friction can result in a failed process (Tomer and Newton 1999).

4.7.3 Binding Agents

Binders provide cohesion for bonding of solid particles to promote size enlargement to produce granules and improve the blend flow during processing (Hamed, Moe et al. 2005). Binder selection is critical and can impact the formulation's friability, hardness, disintegration time, and dissolution rate. Binders are not required if the formulation can yield a evenly distributed granule, hard enough to withstand processing conditions with acceptable flow and compaction properties. There are a number of binders which are commonly used and can be divided into three categories, see Table 21.

Table 21 Common Categories and Examples of Binders, Adapted from (Cantor, Augsburger et al. 2008)

Binder Category	Examples	Comments
Sugars	Sucrose, Glucose, Sorbital	Primarily used for Chewable Tablet
Natural Polymers/Gums	Pregelatinized Starch, Acacia, Gelatin, Sodium Alginate	Pregelatinized Starch is most common
Synthetic Polymers	Polyvinyl Pyrrolidone (PVP), Poly Ethylene Glycol (PEG),	Most popular choice for wet/dry mixing, to avoid health concerns over naturally sourced binders
Semi Synthetic Polymers	Hydroxypropylmethylcellulose (HPMC), methylcellulose, Hydroxypropylcellulose (HPC), Sodium Carboxymethylcellulose (CMC), Ethylcellulose, and Methacrylates (Eudragits)	

4.8 Polymers

Polymers can be made from a variety of natural or synthetic materials, and are used throughout the pharmaceutical industry to conquer challenging formulations. Cellulose is a natural polymer found in the fibrous tissues of cotton and wood, which pass unchanged through the human digestive tract (Kim 2004). Many unique derivatives of this natural polymer have been created for diverse formulation applications. Alternatives to cellulose based polymers include derivatives of acrylic acid, synthetics: such as poly vinyl acetate (PVA), polyvinyl pyrrolidone (PVP), and natural ingredients such as waxes and shellac (Kottke and Rudnic 2002).

4.8.1 Methylcellulose

Hydroxypropylmethyl cellulose (HPMC) is soluble in water, isopropyl alcohol (IPA), and hydro alcoholic mixtures depending on the grade of material (Harwood 2002). The polymer is used in many areas of the pharmaceutical industry, including film coating and sustained release matrix tablets. The HPMC acts to form viscous gels to control the diffusion of water and drug release and when it is combined with a water insoluble polymer, such as ethylcellulose, it facilitates the creation of a “non-continuous film” (Dow 2008), or commonly referred to as a pore former. HPMC can be used as an effective pore former when combined with ethylcellulose for both organic and aqueous systems. Upon hydration HPMC acts to open channels within the polymeric matrix and facilitates drug release (Bodmeier, Guo et al. 1997). Research has indicated that the use of HPMC can result in flocculation and unstable coating systems when used with aqueous dispersions of

ethylcellulose (Ong 2006b) The flocculation was overcome when the dispersion was adequately mixed, which is consistent with standard processing parameters (Ong 2006a). High concentrations (30-40% of Polymer weight) of HPMC can result in the dissociation of carboxylic groups of the ethyl cellulose resulting in cracks and a loss of membrane controlled drug release (Gunder, Lippold et al. 1995). Overall the challenges of coating with HPMC in aqueous systems are considered greater than in organic systems, due to stricter processing controls to prevent undesirable results (Nagai, Obara et al. 1997).

4.8.2 Ethylcellulose

Ethylcellulose is a hydrophobic polymer, used to coat granules and/or tablets to create a sustained release profile (Dahl 2002). Ethylcellulose is brittle due to inter chain hydrogen bonding and bulky glucose subunits and requires plasticization (Bodmeier and Paeratakul 1994). The hydrophobicity of the polymer necessitates that it be dissolved in an organic solvent or be dispersed in an aqueous system. While aqueous or organic systems may be employed for ethylcellulose, the film formation mechanism is different. Organic solvents dissolve the ethylcellulose and other components to form a film when the organic solvent evaporates leaving the individual polymer molecules in contact (Osterwald 1984).

In contrast, aqueous systems undergo the following film forming process: 1) Individual polymer spheres containing hundreds of polymer chains dispersed in water coat the surface. 2) As water evaporates, the interfacial tension between the remaining water and polymer spheres increases and results in an ordered arrangement of polymer spheres. 3) Capillarity resulting from the increased

interfacial tension provides a driving force to overcome the repelling forces and cause deformation to fuse and coalesce the particles together (Wheatley and Steuernagel 1997).

In addition to avoiding the negatives of organic solvents, highlighted in chapter 1; aqueous systems offer several additional advantages: the lower viscosity dispersion allows a greater amount of polymer to be applied per unit of volume, and lower water vapor transmission rates due to the coalescence of small latex spheres (Wheatley and Steuernagel 1997).

Aquacoat[®] ECD and Surelease[®] are commercially available ethylcellulose aqueous dispersions. The Surelease[®] system is ready for use after the addition agitation of water to the desired solids concentration, and a 15 minute mixing time (Colorcon 2006). A disadvantage of the Surelease[®] system is the need for additional barrier coating, adding processing time and material expenses. In addition to ethylcellulose, the Aquacoat[®] ECD system contains, cetyl alcohol, and sodium lauryl sulfate which act as an emulsifier and stabilizer, respectively. The Aquacoat[®] ECD system requires the addition of a plasticizer, and a 30 minute mixing time before it is ready for application (FMC-BioPolymer 2006).

4.8.3 Plasticizers

Organic and aqueous ethylcellulose dispersions require plasticizers due to their brittle nature to prevent cracking, improve flexibility, reduce the polymer's glass transition (T_g) temperature to promote uniform film (Bodmeier, Guo et al. 1997). Plasticizers provide flexibility to the polymer by increasing the free space between the polymer chains and decrease rigid polymer-polymer binding (Aulton,

Abdul-Razzak et al. 1981). Additionally, plasticizers facilitate water uptake into the film to improve the coating's permeability to drugs (Lippold, Gunder et al. 1999). Common plasticizers used are hydrophobic, such as Dibutyl Sebecate, Polyvinyl Acetate Phthalate, and mineral oil, or hydrophilic, such as: Polyethylene Glycol (PEG), Triethyl Citrate (TEC), and Triacetin (Rowe, Shesky et al. 2002). TEC and DBS (15-30%) are both capable of decreasing the Tg and subsequently reducing the minimum film formation temperature (MFT) for Aquacoat dispersions to improve coalescence and film formation (Obara and McGinity 1995). Research has shown a greater association between the hydrophobic DBS than the hydrophilic TEC with Aquacoat (Tarvainen, Sutinen et al. 2003). DBS is initially emulsified in the water phase of the system, prior to incorporation into the polymer phase within 30 minutes of mixing (Bodmeier, Guo et al. 1997). DBS at approximately 24% of the polymer weight has been demonstrated to adequately plasticize and soften the ethylcellulose spheres to facilitate continuous film formation by reducing the glass transition temperature of Aquacoat from 89°C to 42-44°C (Wheatley and Steuernagel 1997).

4.8.4 Other Inactive Ingredients for Tableting

Other inactive ingredients that are used in the formulation of tablets are lubricants and disintegrants. Lubricants act to overcome the increased friction generated during compression between the tablet and die walls (Armstrong 2008). Examples of lubricants used in tableting include: Stearic acid and its salts (calcium, magnesium, zinc), hydrogenated vegetable oil, waxes, and mineral oils (Kottke and Rudnic 2002).

Tablet disintegrants are defined as, “Any solid, pharmaceutically acceptable material included in the formulation that acts to cause the tablet matrix to break up when the tablet comes into contact with aqueous media (Moreton 2008).” This broad definition encompasses many excipients, examples include: Carboxymethylcellulose Sodium, Povidones, starches, and alginates (Rowe, Shesky et al. 2002).

4.9 Identifying Critical Quality Attributes (CQA's)

CQA's are factors that affect a final product's potency, stability, and drug release (ICH 2007). Numerous factors would satisfy the requirements for consideration as a CQA, but attempting to study all of them would be unfeasible. Identification of the CQAs for this developmental process was selected based on the ICH Q8 guidelines, product deformation characterization, current literature and available equipment.

4.9.1 Particle Size Distribution

The particle size distribution generated at the completion of the granulation process is identified as a potential CQA in the ICH Q8 Annex. The importance of the particle size distribution on down stream processes is widely recognized and must be monitored (ICH 2007). Products with tailored particle size distributions have narrower specifications for acceptance criteria, with poor process control resulting in highly variable and poor yields (Dukic-Ott, Remon et al. 2007). The yield can have a significant impact on the profitability and sustainability of a product throughout its life cycle. For sustained release products, understanding how the

formulation and process effect the immediate release bead particle size distribution is critical. Variable particle size distribution will yield varying surface areas for coating and can drastically affect the dissolution profile of the system. Figure 36. depicts research comparing particle sizes when coating and tableting, on the extended release dissolution profile.

Figure 36 Effect of Particle Size on Dissolution Profile (Dashevsky, Kolter et al. 2004)

In Dashevsky's research, both pellets were coated to 20% w/w gain with a polymer for modified release. It is clear from Figure 36. that the smaller sized pellets release the drug faster due to an increased surface area and consequently a thinner polymer coating than the larger particles. While smaller pellets in general undergo less mechanical stress during compression and improved distribution into

the void space, pellet rupturing appears similar for both sizes for this research (Dashevsky, Kolter et al. 2004)

4.9.2 Sphericity

The sphericity of a pellet indicates the roundness of material, by direct comparison of perpendicular lengths of the material or by how well the material rolls (Vervae, Baert et al. 1995). The closer the measured ratio is to 1.0, the rounder the material. Rounder sustained release coated pellets have been associated with a more uniform drug release, than irregularly shaped material (Chopra, Alderborn et al. 2002). This research concluded that rounder pellets had more uniform polymeric coating, while dumbbell shaped pellets experienced disproportionate coating at the body and edges resulting in variable drug release. Mathematically, rounder pellets will increase the surface area for hydration and drug release.

The pellet sphericity can also impact down stream processes. Spherical pellets will move through the manufacturing process easier and create a more uniform dosage form. Conversely, pellets with an aspect ratio of >1.2 have been found to cause variability during filling operations for capsules (Chopra, Podcizek et al. 2002).

4.9.3 Moisture Content

Figure 37 Example of a Design Space for a Drying Operation (ICH 2007).

Figure 37 is given by the Q8 annex as an example of a drying operation design space. The target endpoint was set between 1-2% moisture content, and the drying is dependent upon the temperature path. If the material is dried too rapidly there can be excessive particle attrition and damage, conversely if the drying is performed too slowly the additional moisture in the product can result in an impurity formation (ICH 2007). From a practical stand point, over drying will generate a greater amount of dust, which may be composed of active ingredients and result in potency loss. High levels of moisture content can have adverse effects during

compression, causing changes in the mechanical strength of tablets due to excess lubrication (Kottke and Rudnic 2002). Excessive moisture in the final product can result in concerns over microbial growth, and an long term instability of the drug product (Petereit and Weisbrod 1999).

4.9.4 Dissolution Profile

A simplistic definition of the dissolution rate is “the amount of active ingredient in a solid-dosage form dissolved in unit time under standardized conditions of liquid-solid, interface, temperature, and media composition (Hanson 1991).” The dissolution profile provides information about critical factors and can guide scientists towards understanding their effects when changes occur. It is important to identify and understand the process and formulation factors, which must be controlled to yield a useful dissolution profile and a viable pharmaceutical product. Post approval, dissolution testing most often serves as a quality control function to determine acceptable variability and monitor variations during manufacturing, determine stable release profiles over time, and support regulatory changes (FDA 1997a).

The FDA provides three levels of *in vivo/in vitro* correlations as detailed in the guidance document: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations (FDA 1997a). In general the level assigned to the correlation is based on the following (Shah and Williams 1994) :

Level A: Superimposable *in vitro/in vivo* profiles, “point-to-point” correlation.

Level B: Comparable mean *in vitro/in vivo* dissolution time using statistical moment analysis, considered a single point correlation.

Level C: Mean *In vitro* dissolution time correlated to one pharmacokinetic parameter, considered a one-point correlation.

Ideally the formulation provides a Level A correlation, but often the anticipated bioavailability cannot be adequately projected through dissolution alone prior to performing the *in vivo* studies. While it is an imperfect method, it is widely considered as the most sensitive predictor of *in vivo* performance (Banakar 1991).

5.0 Introduction

This chapter outlines the general approach for each phase of drug development to initially link the materials and processes to CQA's. The Risk Assessment approach used Ishikawa diagrams to help identify potential factors for study. The materials and methodology used for this section and throughout the rest of the study are given. The results of the traditional/exploratory batches are given to guide the design of experiments.

5.0.1 Phase II: Formulation and Process Development of an Immediate Release Drug Pellet

Figure 38 Processing Steps for the Immediate Release Pellet

Propranolol HCl will serve as the drug for the "traditional" approach to the formulation of a generic marketed product. The formulation parameters are guided by the desire to closely mimic the marketed product's dissolution profile. The bulk of the research for phase II manufacturing process serves as an opportunity to identify variables to understand the Critical Quality Attributes (CQA's). The results found during the development of Propranolol HCl guided the factor selection for the formulation and processing of Metoprolol Succinate. The selected factors will

initially be evaluated for Metoprolol Succinate using exploratory batches to determine feasible operating parameters. The factors will be narrowed down and the operating levels will be fixed for a factorial experiment to support the QbD approach.

Figure 38 is an overview of the process from raw ingredient to dry immediate release bead. There are a number of processing steps involved in converting the raw materials into a viable drug pellet, which could then be coated with a polymer and ultimately encapsulated or compressed into a tablet. Critical parameters were identified during the process for investigation. The process begins with a dry mixing of the excipients and active ingredients, using only the impeller blade. After the dry ingredients are adequately mixed, purified water, USP, is added as the granulating agent. During water addition, the impeller blade and the chopper mixes and shear the material in a Jaygo-10L high shear mixer, to create a wet mass. The mass is then extruded using a Nica® E140 extruder with a screen size adequate to yield the desired particle size distribution. The extrudates are then spheronized with an Aeromatic Fielder® S450 spheronizer into moist round pellets. The moist pellets are then dried using a Mendel® MFB-1 fluid bed processor to the desired moisture level, as determined by loss on drying (%) by an Ohaus® MB200.

Experiments comparing the effects of the duration of shearing (kneading), spheronization parameters, and the amount of liquid added for granulation are areas of interest to identify the variables that link to the Critical Quality Attributes (CQA's). An Ishikawa diagram, Figure 39 was first prepared to determine variables of interest for the IR bead formulation and process. The key metrics of the pellets

will include the particle size distribution and sphericity of the produced IR beads.

The final pellet product will then serve as the basis for polymer coating and
tableting into a multiparticulate dosage form.

Figure 39 Ishikawa Diagram-Immediate Release Beads

5.0.2 Phase III: The Creation and Evaluation of Coated Controlled Release Pellets

Figure 40 Phase III-General Methodology for a SR Pellet

Figure 40 is an overview of the processing steps and potential variables for the development of a sustained release bead. In addition to difficulties associated with standard formulation and processing techniques, creating oral compressed tablets capable of delivering extended release profiles introduces a new dimension of challenges. The selection of an appropriate polymer system for targeted delivery and the desired release profile requires investigation and formulation studies.

Traditionally, non-aqueous and organic solvent systems were utilized to enhance the solubilization of polymers. A clear polymeric solution will form uniform coatings on substrates with reproducible film characteristics to create an extended release product. Solvent processing can be seen in product patents (Dhalinder 1993), but are generally not described in depth in literature, because it is viewed as an intermediate processing step; a classic example can be seen in the formulation of Metoprolol Succinate (Ragnarsson, Sandberg et al. 1987) (Sandberg, Rangarsson et al. 1988). Due to environmental hazards, pollution, and costs associated with handling, processing, and disposal of solvents, some manufacturers may prefer aqueous

polymeric coating systems to solve their needs for polymer application. However, more environmentally friendly and theoretically cost effective over the long term, aqueous polymer coatings can be difficult to process due to their delicate nature. The coating process is highly dependent on processing conditions, with inconsistent results often due to a lack of process control or inappropriate processing parameters. Additionally, aqueous polymer dispersions may experience variability or inappropriate physicochemical properties dependent on the polymer(s) selection (Porter and Bruno 1990). Figure 41 is an Ishikawa diagram for the development of sustained release beads, which describes potential variables for exploration.

Figure 41 Ishikawa Diagram-Sustained Release Beads

The immediate release pellets developed in *Phase III* will be coated with aqueous polymers first to evaluate the feasibility of the system against benchmarks set by the marketed product. For products, which cannot reasonably use aqueous systems, an organic solvent system will be employed. Each polymer system required the development of individual processing parameters in order to ensure a quality outcome. Functional polymer selection, coating thickness, curing conditions and curing duration are vital factors in the creation of a controlled release pellet. The primary metric was the pellets' dissolution profiles over their controlled release periods. The USP monographs for Propranolol Hydrochloride Extended Release Capsules (USP 2007b) and Metoprolol Succinate Extended Release Tablet (USP 2007c) dissolution methodology will be followed to evaluate the release profiles. For Propranolol HCl, Ultra Violet (UV) Spectroscopy was used for concentration determination, and the method was verified by high performance liquid chromatographic (HPLC). Metoprolol Succinate did not use UV spectroscopy due to interference and concentration was determined via HPLC. Scanning electron microscopy (SEM) or other visual imaging methods will be used to evaluate the surface morphology and coating patterns on the pellets. Pellets will be sieved to determine the particle size distribution. Additional physical characterization will be performed as needed.

5.0.3 Phase IV: The Creation and Evaluation of a Multiparticulate Compressed Oral Tablet

Figure 42 Phase IV-General Methodology

Figure 42 is an overview of the development steps for the creation of a multiparticulate sustained release tablet. Top-coated sustained release beads were combined with different excipient blends to act as fillers, cushioning agents, and binders. The blend is compressed to form a multiparticulate tablet, which is ultimately top-coated to prevent damage and water incursion. Experimental evaluations of the sustained release polymer content, excipient blend, and compaction force, measured as hardness will be evaluated to create a robust tablet dosage form. Figure 43 is an Ishikawa diagram of potential factors that could be explored for the formulation of a sustained release multiparticulate tablet. The final experimental dosage form's dissolution profile will be compared with the marketed product to compare the performance of the product over the extended release period. Additionally, the an objective is to demonstrate process understanding to show improvement towards meeting the USP monograph for the drug product, to support the QbD approach.

Figure 43 Ishikawa Diagram-Multiparticulate Tableting

5.1 IR Bead Formulation Materials

5.1.1 Propranolol

Propranolol hydrochloride, USP (SIMS, Italy), Microcrystalline Cellulose (Avicel PH 101) (FMC Biopolymer, Philadelphia, Pennsylvania) (d₉₀ <106 µm), and Purified Water, USP (in house).

5.1.2 Metoprolol Succinate

Metoprolol Succinate, USP (Esteve Quimica, Barcelona, Spain) (98.1% <200 µm), Microcrystalline Cellulose (Avicel PH 101) (FMC Biopolymer, Philadelphia, Pennsylvania), and Purified Water, USP (in house).

5.2 SR Bead Formulation Materials

5.2.1 Propranolol HCl

Formulated drug loaded immediate release pellets from Phase II,
Aqueous Coatings: Purified Water, USP (in house), Aquacoat ECD (FMC Biopolymer, Philadelphia, Pennsylvania), Dibutyl Sebecate, NF (Spectrum, Gardena, California), HPMC E6 (Dow, Midland, Michigan).
Organic Coatings: Ethocel 10 cp (Colorcon, West Point Pennsylvania), HPMC E15 (Dow, Midland, Michigan), Dibutyl Sebecate, NF (Spectrum, Gardena, California), Talc (Spectrum, Gardena, California), Isopropyl Alcohol, USP (100%) (Spectrum, Gardena, California), and Purified Water, USP (in house).

5.2.2 Metoprolol Succinate

Formulated drug loaded immediate release pellets from Phase II, Syloid 244 FP, NF (Grace Davidson, Columbia, Maryland), Aquacoat ECD (FMC Biopolymer, Philadelphia, Pennsylvania), Dibutyl Sebecate, NF (Spectrum, Gardena, California), and Purified Water, USP (in house).

5.2.3 Materials- Sustained Release Bead Top Coating

Metoprolol Succinate Sustained Release coated and cured beads from Phase III of the study, Opadry II Y-30-18037 (Colorcon, West Point, Pennsylvania), Triethyl Citrate, NF (Spectrum Chemicals, Gardena, California), Purified Water, USP (in house).

5.2.4 Materials- Tabletting

Metoprolol Succinate top coated beads, Microcrystalline Cellulose, NF (Avicel PH 102[®]) (FMC Biopolymer, Philadelphia, Pennsylvania), Microcrystalline Cellulose, NF (Avicel PH 200[®]) (FMC Biopolymer, Philadelphia, Pennsylvania), Crospovidone, NF (Polyplasdone[®] XL-10) (International Specialty Products, Wayne, New Jersey), Povidone, USP (Plasdone[®] K29/32) (International Specialty Products, Wayne, New Jersey), Lactose Monohydrate (80m) (Kerry Bio-Science, Tralee, Ireland), Starch 1500, NF (Colorcon, West Point, Pennsylvania), Hydrogenated Vegetable Oil, NF (Lubritab[®]) (J. Rettenmaier & Sohne, Rosenberg, Germany).

5.2.5 Excipient Granule (Formulation #1) for Metoprolol Succinate SR Tabs

Microcrystalline Cellulose NF (PH102), Crospovidone NF K29/32, Pregelatinized Starch (1500) NF, Lactose Monohydrate NF, and Purified Water, USP were granulated. All dry ingredients were first screened through a #25 sieve to remove large particles, prior to processing. Low shear wet granulation was performed on the Jaygo 10-L mixer, at a low impeller speed without the chopper blade. The granules were dried in a Freas[®] Scientific 625 oven, until an LOD of less than 5% was achieved. The granules were milled in a Fitzpatrick[®] Comminutor, with a screen size of 60 and knives facing forward.

5.2.6 Excipient Dry Blend (Formulation #2) for Metoprolol Succinate SR Tabs

Microcrystalline Cellulose, NF (PH102) Crospovidone, NF K29/32 Pregelatinized Starch (1500), NF Lactose Monohydrate, NF were screened through a #25 sieve and Hydrogenated Vegetable Oil, (Lubritab[®]) was screened through a #30 sieve to remove large particles prior to blending.

5.2.7 Excipient Dry Blend (Formulation #3) for Metoprolol Succinate SR Tabs

Microcrystalline Cellulose, NF (PH102), Microcrystalline Cellulose, NF (PH200), Crospovidone, NF XL-10, were screened through a #25 sieve and Hydrogenated Vegetable Oil, (Lubritab) was screened through a #30 sieve to remove large particles prior to blending.

5.3 Processing Methods

5.3.1 *Propranolol HCl IR Bead Processing*

The approach to development was to evaluate a selected factor while holding the other parameters constant to determine their effects, and to use visual observations to make adjustments. Early development utilized 400g batch sizes, while the final three lots RB005054, RB005055, and RB005056 were 800g batches to evaluate the process parameters effects of doubling the batch size. Propranolol HCl followed the general processing procedure described above. During wet granulation, impeller blade speed and chopper speeds were fixed throughout water addition and kneading. A 1.0mm stainless steel screen was used during extrusion to yield larger extrudates. The experimental process parameters can be seen for Propranolol immediate release bead production in Table 22. An example of the fluid bed drying cycle and processing parameters for the spheronized moist pellets can be seen in Figure 44. The moisture content specification was set to not more than 2.5%, based on the initial moisture content of the active ingredient and the excipient to ensure an adequately dry product.

Propranolol (RB005056) IR Bead Drying

Figure 44 Example of Propranolol IR Bead Drying Cycle

Table 22 Propranolol IR Experimental Overview

Raw and Coded Process Parameters									
Trial	H2O Amount (g)	H2O Amount Coded	H2O Addition g/min/500g batch	H2O Addition Coded	Kneading Time Coded	Spheronization RPM (Avg)	Spheronization RPM Coded	Spheronization Time (min)	Spheronization Time Coded
91907	200	Low	25	Low	Low	600	High	2.5	Low
92007	265	Low	30	Low	Low	550	High	2.5	Low
RB005008	275	Medium	83.33	High	Low	600	High	3	Low
RB005009	325	High	55	High	Low	366.66	Low	3	Low
RB005010	300	High	55	High	Low	475	High	4	Low
RB005013	290	High	50	Low	Low	300	Low	2	Low
RB005021	275	Medium	50	Low	Low	520	High	5	High
RB005022	290	High	50	Low	Low	336	Low	4.75	High
RB005023	275	Medium	50	Low	High	450	Low	6	High
RB005048	275	Medium	75	High	Low	460	High	5	High
RB005049	275	Medium	68.75	High	High	460	High	5	High
RB005054	275	Medium	62.5	High	High	440	Low	5	High
RB005055	275	Medium	50	Low	High	450	Low	6	High
RB005056	275	Medium	62.5	High	High	450	Low	6	High

5.3.2 General Metoprolol Succinate IR Bead Processing

Metoprolol Succinate followed the general processing procedure described above. During wet granulation, impeller blade speed and chopper speeds were fixed throughout water addition and kneading. A 0.6 mm stainless steel screen was used during extrusion to yield finer extrudates. An example of the fluid bed drying parameters for the spheronized moist pellets can be seen in Figure 45. The moisture content specification was set to not more than 2.5%, based on the initial moisture content of the active ingredient and the excipient to ensure an adequately dry product.

5.3.3 Exploratory Metoprolol Succinate IR Bead Processing

Initial exploratory batches were run based loosely on the processing parameters observed during the development of the Propranolol HCl IR beads. The raw and coded process parameters can be seen in Table 23.

Table 23 Overview of the Coded Process Parameter for Metoprolol IR Beads Exploratory Batches

Raw and Coded Process Parameters										
Trial	H2O Amount (g)	H2O Coded	H2O Addition g/min batch	H2O Addition Coded	Kneading Time (min)	Kneading Time Coded	Spheronizer RPM (Avg)	Spheronizer RPM Coded	Spheronizer Time (min)	Spheronizer Time Coded
RB005081	200	High	80	Low	1	High	628	Low	7	High
RB005107	180	High	90	Low	1	High	680	Low	5	Low
RB005108	190	High	95	Low	2	High	800	High	4	Low
RB005109	170	Low	85	Low	1	High	600	Low	2	Low
RB005119	180	High	180	High	0	Low	767	Low	6	Low
RB005120	140	Low	120	High	0.66	High	800	High	7	High
RB005122	150	Low	150	High	0.25	Low	800	High	5	Low
RB005123	160	Low	160	High	0.5	Low	800	High	9	High

Figure 45 Example of a Metoprolol IR Bead Drying Cycle

5.3.4 Sustained Release Coating and Curing Methods

5.3.5 General Spray Coating Methods

Drug loaded immediate release pellets produced in phase II were spray coated in the Mendel Fluid Bed[®] processor. For aqueous trials, the inlet temperature was set to 65°C, the product temperature was maintained between 35°C-45°C. Organic trials operated at an inlet temperature of 50°C, and maintained the product temperature between 32°C-42°C. The fan speed was adjusted during processing to maintain adequate fluidization. The Wurster column height was fixed at a setting of 6, the spray nozzle had an internal bore size diameter of 0.8mm, the spray rate was between 2-5g/min with an atomizing air range between 0.2-1.2 bar and Tygon[®] 3350 tubing used to deliver the coating material via an external peristaltic pump. The machine was adequately purged during organic solvent processing to prevent an explosion.

5.3.6 Aquacoat ECD Trials- Propranolol HCl

Immediate release beads were coated with an Aquacoat ECD aqueous dispersion. Dibutyl Sebecate, NF acted as a plasticizer, and Hydroxypropylmethyl Cellulose E6, was used as a pore former, both were added as fixed percentage of polymer weight throughout experimentation. Varying polymer concentrations were evaluated at 6 different levels from 4-15% polymer level. Screening studies will utilize subsampling to determine the effects of polymer levels within a batch. Subsamples and final samples were cured where appropriate.

5.3.7 Aquacoat ECD Solids Concentration Trials- Propranolol HCl

Immediate release Propranolol HCl beads were coated to the same polymer weight gain (% w/w) using two different concentrations of polymer in the coating suspension. The low concentration coating suspension formula had 40% less solids than the high concentration coating suspension. The coating suspensions were prepared and administered following the same procedures in the coating level trials.

5.3.8 Organic Ethylcellulose Coating Trials

Immediate release Propranolol HCl beads were coated to two different levels of polymer weight gain, but contained the same solids content. The polymer levels were significantly lower than the aqueous polymer levels applied. Curing was performed at various conditions and durations in the VWR® 9005 Stability Chamber.

5.3.9 Aquacoat ECD Trials- Metoprolol Succinate

Immediate release beads were coated with an Aquacoat ECD aqueous dispersion. Dibutyl Sebecate, NF acted as a plasticizer, and was added as fixed percentage of polymer weight throughout experimentation. Varying polymer concentrations were evaluated from 3-30% polymer level. Screening studies utilized sub sampling to determine the effects of polymer levels within a batch. Subsamples and final samples were cured where appropriate.

5.3.10 Curing Trials Overview

Uncured and cured material will be compared to understand the effects of curing. Non-humidified curing was performed in either the VWR® 1415 Vacuum oven (without pulling vacuum), or the Freas® Scientific 625 convection oven. While

both humidified and dry curing trials will be performed in a VWR® 9005 Stability Chamber. The baseline curing for all batches was performed in dry heat at 60°C for 2 hours. Curing studies compared dry heat, humidification, and duration were performed to understand the effects on the sustained release beads.

5.3.11 Methods-Sustained Release Bead Top Coating

Cured sustained release beads were charged into the Mendel Fluid Bed (MFB-1) processor. Inlet temperature was set to 65°C, product temperature was maintained between 40-45°C, the fan frequency was adjusted during the coating process to sustain adequate fluidization, the coating suspension was sprayed at approximately 3g/min, through a nozzle with an inner bore diameter of 0.8mm, and Tygon 3350 tubing was used. After the top coating suspension was applied, the beads continued to fluidize for 5-15 minutes to allow the beads to dry. A wide range of top coating quantities was studied, from low (<3%) to high (>15%) to evaluate the cushioning and protective effects of the topcoat.

5.3.12 Tabletting Methods-Blending

A 1:1 ratio of excipient blend to active top coated beads were blended, with the exception of Lubritab® which was added at 3-8% tablet weight at the final stage of blending. A Patterson Kelley® V-Blender, equipped with a 4-qt shell, and a shell speed of 25 rpm was used for blending. All excipients except the Lubritab® were blended for 4 minutes, top coated Metoprolol succinate beads were then added and blended for 4 minutes, and finally Lubritab® was added and blended for 5 minutes. The final blend was tested for LOD to ensure an acceptable level of moisture in the tablet.

5.3.13 Methods-Tabletting

A Natoli® Type BB bilayer tablet press, with a 13/32" (.4062) diameter standard cup with Natoli® tooling was used: The tooling dimensions are: cup volume 0.0025 in³, cup area 0.1341 in², perimeter 1.2761 in., Upper tip size 0.4043 in., lower tip size 0.4050 in., die size 0.4062. The metoprolol succinate blended with excipients was loaded directly into the feed frame and compressed on the tablet press by manually rotating the turret. The theoretical tablet fill weight was calculated and tablets prepared within 3-5% of the desired target were accepted for sampling. Pre compression was set low, resulting in 1-2kp hardness depending on the blend. Low hardness and high hardness samples were prepared by adjusting the compression force on the main compression cam, and analyzed by a DR. Schleuniger Pharmatron 6D hardness tester. Samples were tested during the beginning, middle, and end of the run to ensure that hardness was maintained within ± 1 Kp.

5.4 Analytical Methods

5.4.1 Dissolution and Concentration

USP methodology described in Chapter 3 was used.

5.4.2 Comparison of Dissolution Profiles

$$f_2 = 50 \log \left[\frac{100}{1 + \frac{\sum_{i=1}^n (T_i - R_i)^2}{n}} \right]$$

Equation 6. f_2 Equation

Equation 6 is the f_2 equation, where T_i is the concentration of the sample at a time point, R_i concentration of the reference product at that time point, and n is the number of sample points. This equation is a tool to aid in comparing dissolution profiles for sustained release drug products. The comparison of the profiles is critical for supporting changes to products currently on the market (FDA 1997b). An f_2 values greater than 50 suggest that the formulations are sufficiently similar (FDA 1995). Additionally, this method is used during development to compare novel formulations against currently marketed products (Dias 2007).

5.5 General Statistical Methodology

Minitab and Microsoft Excel software was employed for the design and analysis of the experiments. Exploratory data was fit into appropriate general linear models to study the significance of their main effects. A Full factorial design was employed for phase II and while a box benhken design was used for phase III. The analysis of variance (ANOVA) and DOE will be used to determine main effects and interactions between independent and dependent factors. Dissolution profiles will be the primary metric by which sustained release bead and final product formulations and processing parameters will be evaluated. Each method, statistical, mathematical or graphical interpretation of dissolution profiles has drawbacks, (O'Hara, Dunne et al. 1998); therefore, appropriate methodology will be chosen on an individual basis.

5.5.1 Statistical Methods-Exploratory Batches

Table 25 gives the coded trial parameters and the percentage of material yielded on each sieve size. The coded variables and the yields from each of the trials

were fitted into a general linear model and the ANOVA using the Tukey's method. For complete results for the general linear model using the Tukey's method for all of the sieve sizes, see Appendix 2. The Tukey's method was used to compare multiple processes to simultaneously evaluate if the means are equal (NIST/SEMATECH 2006b). The Tukey's method is useful for making comparisons across multiple factors and is an extension of the ANOVA method (Cobb 1998). The model's R^2 value indicates the fraction of the total variability in the responses that the model can account for (NIST/SEMATECH 2006a); The adjusted R^2 value corrects the R^2 for the sample size and for the number of terms in the model, with low values indicating a potential pooling error (Gardiner and Gettinby 1998).

Tables 22 and 23 previously presented in the process methods section gives the specific and coded process parameters for Propranolol and Metoprolol, which were investigated during the exploratory batches to create the general linear model and represents unbalance nested retrospective design. This design was used because the trials were not a balanced or a crossed design, where each variable is evenly tested. The results for the full general linear model for the ANOVAs is presented in Appendices 2 and 4, the results section presents the reduced general linear models. Model reduction was performed in accordance with statistically valid methods. Variables were evaluated in the full model and removed in a step wise approach with careful consideration of the impacts on the R^2 and adjusted R^2 (Colton 2004).

The main effects plots indicate the major changes in the response value. Evaluation of the slope is the critical parameter for the main effects plot; with a steep slope indicating a strong effect, and a near 0 slope indicating little effect (Gardiner

and Gettinby 1998). The plots do not indicate significance, but aid in visualizing which factors have the greatest impacts.

5.6 Physical Characterization Methods

5.6.1 Particle Size Distribution Analysis

U.S.A. Standard Test Sieves (Newark, Clifton, NJ), which meet ASTM E-11 Specification were used to screen the material. Sieve sizes and their dimensional conversions used for both Metoprolol Succinate and Propranolol HCl are listed in Table 24. Deblinding of screens was performed as needed when sample particles size and shape resulted in screen blinding.

Table 24 Sieve screen size conversion to microns and inches

Sieve #	Microns	Inches
14	1400	0.0555
16	1180	0.0469
18	1000	0.0394
20	850	0.0331
25	710	0.0278
30	600	0.0234
35	500	0.0197
45	355	0.0139
60	250	0.0098

5.6.2 Loss on Drying (LOD)

An Ohaus MB200 was used to determine the LOD of the immediate release beads. All samples were at least 5.0g, and the LOD was calculated as the percentage of weight lost after 10 minutes at 105°C.

5.6.3 Sphericity

The immediate release pellet sphericity was determined on a Nikon TE2000-E inverted research microscope set to 4X magnification. The width and length were

calculated with the NIS-Elements AR software for at least 20 beads per sample and used to calculate the aspect ratio, see Figure 46. for a screenshot of the sphericity measurements.

Figure 46 Screenshot of Sphericity Measurements

The larger value of each bead was considered the length (l) and the shorter value was treated as the width (w), where:

$$\frac{l}{w} = \text{Sphericity (Aspect Ratio)}$$

Equation 7. Aspect Ratio for Pellet Sphericity Measurements

Early experimentation using 50 bead readings yielded only ~3.5% reduction in RSD and <0.05 difference between the calculated mean sphericity. Additionally the

small sample space on the microscope made large sample sizes infeasible, especially with larger sized beads. 5.6.4 Tablet Friability

Tablet friability was performed on a Vankel® Friabilator, in accordance with the USP <1216>, on the compressed multiparticulate tablets without a top coating. The sample weight taken was as close to 6.5g of whole tablets for each test, and run for 100 rotations. A maximum mean loss of 1.0% was considered acceptable.

5.7 Exploratory/Traditional Results

The traditional immediate release approach is presented in this section for Propranolol HCl and Metoprolol Succinate. The development of the final exploratory drug products is presented separately. Results from these studies will be incorporated into the enhanced QbD approach to support the drug development process.

5.8 Results-Propranolol

Table 25 Propranolol IR Bead Particle Size Distributions

	Coded Process Parameters					% Retained Sieve #							Sphericity		
Trial	H2O Amount Coded	H2O Addition Coded	Kneading Time Coded	Spheronization RPM Coded	Spheronization Time Coded	14 (1400µm)	16 (1180µm)	18 (1000µm)	20 (850µm)	25 (710µm)	Pan	% Target	Mean Sphericity	Std. Dev. Sphericity	Sphericity RSD (%)
91907	Low	Low	Low	High	Low	0	0	0.36	31.57	20.67	47.4	31.93			
92007	Low	Low	Low	High	Low	0	0	8.8	59.3	19.4	12.5	68.1			
RB005008	Medium	High	Low	High	Low	1.12	8.21	56.3	30.09	4.27	0.02	86.39			
RB005009	High	High	Low	Low	Low	3.2	8.4	47	37.7	3.4	0.3	84.7			
RB005010	High	High	Low	High	Low	0.34	1.5	26.2	59.1	8.2	4.9	85.3			
RB005013	High	Low	Low	Low	Low	0.8	5.42	42.2	41.22	9.8	0.56	83.42			
RB005021	Medium	Low	Low	High	High	0.14	1.6	49.5	41.45	6.3	1.01	90.95	1.12	0.09	8.31
RB005022	High	Low	Low	Low	High	13.79	15.87	57.91	11.4	1	0.02	69.31	1.15	0.19	16.28
RB005023	Medium	Low	High	Low	High	0.97	4.82	58.78	30.85	4.32	0.26	89.63	1.16	0.11	9.75
RB005048	Medium	High	Low	High	High	1	3.36	67.44	22.96	4.86	0.38	90.4	1.1	0.12	10.96
RB005049	Medium	High	High	High	High	4.6	13.5	60.79	17.48	3.37	0.18	78.27	1.15	0.15	13.16
RB005054*	Medium	High	High	Low	High	15.77	30.21	45.79	7.32	0.84	0.07	53.11			
RB005055*	Medium	Low	High	Low	High	1.32	10.31	60.28	24.43	3.52	0.14	84.71	1.23*	0.22	17.78*
RB005056*	Medium	High	High	Low	High	0.66	7.11	58.79	27.91	5.31	0.23	86.7			

* Represents 800g batches

**The mean sphericity and RSD (%) was determined for the blended beads

5.8.1 Propranolol IR Statistical Results

The ANOVA from the general linear model for the material retained on all of the sieve sizes and the overall target (%) yield are in Appendix 4. Due to its greatest importance for yield, only sieve size 18 results are presented in this section. The only factor that can be considered to be statistically significant from this data is the amount of water added during the wet granulation of the material. The R^2 value of 88.74% and the adjusted R^2 of 78.59% is a good indicator of fit for the data. Appendix 2 presents the full general linear models for all of the sieve sizes used.

Figure 47 is the mean effects plot which indicates that the medium level (275g) of water amount added yields the greatest amount of particles retained on sieve #18. The high level of water yielded a lower amount of size #18 beads, but was better than the low level of water. The other factors are not statistically significant, but the means are useful in supporting processing decisions.

Figure 47 Propranolol IR Main Effects Plot for Sieve # 18

Propranolol IR Bead Yield vs Mean Sphericity

Figure 48 Propranolol IR Bead Yield vs. Mean Sphericity

Figure 48 compares the batches with regard to the amount (adjusted to a 1% scale) versus the mean sphericity ratio. Note that not all batches were analyzed for sphericity; due to availability and undesirable characteristics (failed batches), which may give the appearance that, all mean sphericities are relatively uniform (1.1-1.23). Early batches did not produce spherical beads, but served to guide development to improve the shape. A “Target” column was placed on the left side, to indicate the theoretical targets for each value. Due to particle size growth anticipated in the sustained release coating phase a tailored particle size distribution of ~65% retained on sieve size # 18 and ~35% retained on sieve size #20, and a sphericity near 1.0 was set. The batches can be divided into separate phases throughout the development: Initial processing information, identifying critical processing parameters, confirmation/optimization of those parameters, doubled batch size to understand the impacts of batch size.

5.8.2 Initial Processing Information

The early batches 091907-RB005013 were essential to determining general processing parameters and their effects. Batch RB005008 had the best yield for sieve sizes #18, #20, and overall yield (%). The first consideration during development was to identify the appropriate amount of water during the high shear granulation. Kneading time and spheronization can both impact the particle sizes generated but the granulating liquid will dictate all of the downstream processes (Ghebre-Sellassie 1989) and should be identified and evaluated early on. The batch

used a medium amount of water (275g) and was selected as the model for the next developmental phase.

5.8.3 Identifying the Critical Parameters

Lots RB005021, RB005022, and RB005023, were the pivotal batches for the selection of the water level amount added during high shear granulation. Lots RB005021 and RB005023 both used medium (275g) amounts of water, while RB005022 used a high (290g) amount. The particle size distributions were relatively similar between the two lots with a medium amount of water, but the high water batch yielded an unacceptably high level of material retained on sieve #16, and an insufficient yield on sieve #20. Some of the process parameters were varied for each lot to explore their impacts, and RB005023 yielded the most promising results and guided the remainder of the development process.

5.8.4 Confirmation/Optimization of Critical Parameters

In order to optimize the yield of the process, RB005048 was modeled after RB005023, but varied a number of the process parameters. The granulation water was added at a faster rate (50g/ml to 75g/ml), the kneading time was reduced, and the spheronization speed was increased slightly (450 to 460 rpm). These parameters increased the amount of surface water available (Gokhale, Sun et al. 2005) and may have resulted in greater particle size growth during spheronization due to greater adhesive forces in the formulation (O'Connor and Schwartz 1989). These parameters also yielded the best sphericity ratio and supported the decision to move to a larger batch size of 800g. Note: RB005049 was a failed batch that was attempted to optimize the process parameters.

5.8.5 Doubling the Batch Size

The process parameters were then evaluated at twice the batch size to explore the impacts of the increased load. RB005054 was first prepared according to the parameters developed in RB005048, with minor adjustments; the water was added at a slower rate (75 to 62.5 g/min) and slightly slower spheronization speed (460 to 440 rpm) in anticipation of the larger batch size. The batch yielded larger particles than had been anticipated, with unacceptable retention of sieve sizes #14 and #16. In response to the failed batch, the addition rate water was reduced (62.5 to 50 g/min), the spheronizer rpm was raised slightly (440 to 450 rpm) and the spheronization time was increased (5 to 6 min) to RB005055. This improved the yield to an acceptable level of 84.7% within the desired target. Finally, RB005056 was run following the same parameters as the previous batch, RB005055, with the exception of an increased water addition rate back to the RB005054 level (50 to 62.5g/min) and yielded the best results of the three batches. The small changes between RB005054 and RB005055 in process parameters may be responsible for a portion of the improvement, but an uncharacteristically erroneous batch cannot be ruled out. This incremental improvement approach was successful in generating basic process parameters and demonstrated reproducibility between the final two batches.

Figure 49 Propranolol IR Bead-Round (RB005055/56 Blend)

Batches RB005055 and RB005056 were blended together and an example of a spherical bead is seen in Figure 49. The pellets are reasonably round, and the surface morphology contained smoothed bumps and appears consistent with acceptable bead formations (Mehta 1989). This blend was subsequently used for further experimentation for the development of a sustained release bead.

5.9 Results Propranolol HCl SR

Table 26 Propranolol Aqueous SR Results Organized by Coating Level

% Propranolol Released Over Time (hrs)											
Batch #	Coating Level (Coded)	Coating Conc. (Coded)	Curing Method	1.5	3.5	5.5	7.5	10	22	24	F2 Value
RB005053	2	Low	2hrs @ 60c Vacuum Oven	14	35.5	50.5	61.1	69.9	87.8	87.7	96.3
RB005053	4	Low	2hrs @ 60c Vacuum Oven	16.5	33.6	45	53.7	62.3	77.9	80	58.2
RB005026	5	High	2hrs @ 60c Vacuum Oven	10.1	26.4	41.1	51.9	63.9	82.4	82.4	56.3

Table 26 is an overview of the Propranolol HCl sustained release coatings which displayed an acceptable f_2 values over 50. The coating levels, concentration, curing methods, and dissolution data for all of the batches is found in Appendix 6. An f_2 value of 96.3 is nearly point-to-point, and indicates that the coded coating level 2 and low solids content for the coating suspension yield the best results. While higher coating levels 4 and 5 resulted in an overall slower release of the drug from the sustained release beads.

Low vs High Polymer Concentration at a Fixed Polymer Concentration (Level 3)

Figure 50 Comparison of High and Low Polymeric Coating Suspension Solids

Figure 50 compares the differences in the dissolution profiles of beads coated with a low and high polymeric concentrated formula applied to the same final percentage (% w/w). The dissolution profile slows considerably when the concentration of the solids within the coating suspension is decreased. The decreased solids in the coating suspension results in a greater amount of water being applied the system, which increases the humidity in the chamber and will reduce the product temperature if the inlet temperature and fan frequency is not adjusted. The benefits of increased processing time and humidity will result in a longer mean residence time for the polymer to adhere to the bead surface. A lower polymeric solid's concentration will result in a longer overall coating period to reach the desired polymer concentration, which must be balanced to ensure a feasibly cost effective process. For example: To apply a 10% (w/w) polymer coating to a 1.0Kg batch of IR beads at a spray rate of 5g/min, the required processing time for a coating suspension with a polymeric concentration of 10%, would be 20 min. If the coating suspension were diluted to 5% polymer, the processing time would double to 40 minutes. While the spray rate increases with the batch size, the doubling of the processing time may increase to an unacceptable level for large batches (i.e. 300-500Kg).

5.9.1 Results- Effects of Curing Oven

Figure 51 Curing Propranolol Aqueous SR Beads in a Vacuum Oven vs. Humidity Chamber

Figure 51 compares two batches where the same polymer content was applied but cured with different ovens. The VWR 1415 vacuum oven was compared against curing in the VWR 9005 humidity chamber. A marked difference can be seen when comparing the two sets of data. Additional studies, not shown here, depict that curing in the Freas convection oven appears to slow down the release of the drug overall, while curing in the VWR 9005 stability chamber shows a sharp increase in drug release at the first sampling point. All of the chambers were set to 60°C and the materials were cured for 2 hours. Interestingly, the VWR 9005 chamber and the VWR 1415 vacuum oven are both closed systems, which may prevent the escape of moisture from the system. The VWR 9005 chamber operated at ambient humidity; with 18-25% RH observed during curing and is dependent on the humidity of the day. The VWR 1415 vacuum oven visibly condensed the moisture from the coated beads on the front door which had a glass viewing plate, the system humidity was measured to be <10% RH when curing at 60°C. The Freas 625 convection oven is an open system, which sweeps across the heater in a single pass of air before exiting the system, this system operates at a lower relative humidity (5-8% RH) because it can effectively wick away moisture.

When moisture remains in the polymeric coating the pores created by the HPMC E6 remain hydrated and act to channel the drug through the sustained release coating (Bodmeier, Guo et al. 1997). An adequate amount of moisture is necessary to maintain polymer flexibility and prevent cracking, but saturating pores with moisture must be avoided. (Gunder, Lippold et al. 1995) explored an Aquacoat, DBS, and HPMC coating system for a water-soluble compound and determined that

in an acidic medium (pH 1.2) the HPMC pores open and will irreversibly close within 1-2hrs. Subsequently, a change to the alkaline media will not reopen the pores, and diffusion proceeds slowly. Additionally, HPMC has been shown to potentially cause flocculation when combined with ethylcellulose and result in an unstable dosage form (Wong and Bodmeier 1996).

Further complicating the balance of moisture in the system is the need to pass long term accelerated stability studies. ICH guidelines dictate that a product must not have appreciable degradation (>5%) in their dissolution profile throughout the stability study. The two acceptable accelerated conditions are 30°C and 60% (RH) for 6 months, or 40°C and 75% (RH) for three months (ICH 2003). Additionally, room temperature must be maintained as a control to confirm normal storage conditions seen by the patients. Preliminary stability data of 10 days at 40c/75% RH confirm that even the vacuum cured beads show an unacceptably sharp increase in drug release. Aqueous ethylcellulose systems with HPMC based pore formers have shown increased drug release over time due to physical changes in the coating layer such as hydrolysis and changes in coalescence, as well as drug migration into the coatings (Siepmann, Siepmann et al. 2005). This instability resulted in the experimentation of an organic solvent ethylcellulose sustained coating solution.

Table 27 Propranolol Organic SR Coating Acceptable Dissolution Results

Batch #	Coating Level Coded	Curing Method	Propranolol HCl Released (%)							F2 Value
			1.5	3.5	5.5	7.5	10	22	24	
RB005072	1	6 hrs @ 50C Chamber 2	9.0	35.4	52.9	64.3	75.0	92.2	92.7	72.0
RB005064	2	6hrs @ 50c Chamber 2	7.8	29.5	45.1	56.9	70.1	92.7	95.3	65.5
RB005064	2	2 hrs @ 50C Freas	6.9	28.8	46.7	60.4	72.0	94.3	95.8	64.8
RB005064	2	18 hrs @ 50C Freas	7.8	30.4	44.8	55.6	65.4	83.1	85.6	64.3
RB005064	2	6 hrs @ 60c Freas	11.0	37.4	54.5	67.5	79.0	97.1	99.9	61.5
RB005064	2	24 hrs @ 50C Freas	8.3	36.2	54.8	67.5	80.1	99.8	100.3	57.7
RB005072	1	2 hrs @ 45C Chamber 2	7.6	36.5	55.1	68.7	79.9	99.9	103.7	56.8
RB005064	2	24hrs @ 50c Chamber 2	16.8	41.2	58.0	69.5	82.2	100.5	102.6	54.2
RB005072	1	18 hrs @ 45C Chamber 2	7.9	39.5	57.7	69.9	82.1	100.4	101.1	53.8
RB005072	1	24 hrs @ 45C Chamber 2	8.1	38.1	57.6	70.4	83.9	100.6	103.0	52.9
RB005072	1	24 hrs @ 50C Freas	9.7	37.6	57.2	72.1	84.4	100.1	101.1	52.8
RB005064	2	18 hrs @ 60C Freas	12.3	46.4	64.0	73.8	83.8	93.2	94.3	50.6
RB005064	1	Uncured	5.6	22.7	37.3	49.2	61.5	83.6	85.3	50.4

Table 27 is an overview of all of the formulations which could be considered similar to the reference dissolution profile, where f_2 is greater than 50. The complete experimental results for the organic sustained release coating of Propranolol HCl are in Appendix 7.

The organic ethylcellulose coatings are not as markedly adversely affected by curing in the humidity chamber as the aqueous dispersions. This would indicate a more uniform coating of the sustained release layer, able to seal the particle and protect against the moisture in the chamber from saturating pores in the film or pockets of plasticizer in the film (Bodmeier, Guo et al.

1997). Batch RB005072, with a low coating level and a curing condition of 6 hours @ 50°C was selected as the final formulation for long-term stability studies, (not included in this study)5.9.2 Immediate Release Beads- Metoprolol Succinate Exploratory

Table 28 Exploratory Batches-Processing Parameters and Results Overview

Trial	Processing Parameters					Yields			Comments	Sphericity			
	H2O Amount (g)	H2O Addition g/min batch	Kneading Time (min)	Spheronizer RPM (Avg)**	Spheronizer Time (min)	Final Prod. Temp °C	LOD (%)	Target %		Observed Shape	Mean Sphericity	Standard Deviation	RSD (%)
RB005077*	153	50	2	680/550	2.5	45.2	1.2	63.36	300g Reshaped/ Respheronized	Rods/dumbbells	1.36	0.28	20.46
RB005081	200	80	1	300/628	1 / 7	51.6	1.2	91.77	Reextruded/ Respheronized	More dumbbells	1.31	0.28	25.80
RB005107	180	90	1	680	5	51.3	1.3	86.47	Straight run	More Rods/Some dumbbells	1.35	0.29	21.58
RB005108	190	95	2	800	4	51.6	1.3	53.53	Straight run	Too big	1.39	0.30	21.74
RB005109	170	85	1	600	2	51.1	1	94.26	Straight run	Rods formed	1.76	0.40	22.68
RB005119	180	180	0	500/767	0/6	50.5	1.9	73.81	Fast addition- Reextruded/ Respheronized then good shape	Agglomerated Then Round/few dumbbells	1.18	0.23	19.04
RB005120	140	120	40 sec	800	7	50.2	1.6	82.7	Fast Addition-Straight Batch-Dry side	More Dumbbells than Rods	1.52	0.28	18.48
RB005122	150	150	15 Sec	800	5	50	1.4	90.4	Fast Addition- Straight Batch	Dumbbell shaped	1.58	0.33	20.67
RB005123	160	160	30 sec	800	9	48.6	1.7	85.78	Fast Addition- Straight Batch	Dumbbells	1.32	0.20	15.03

*RB005077 was not included in the general linear model because the batch size was only 300g.

**Average spheronization speed does not include the standardized first minute, and is a time weighted average. If two values are present a respheronization process was necessary and reflects the original and respheronized values respectively.
See Appendix 4 for full particle size distribution.

Figure 52 Metoprolol Succinate IR Beads Exploratory Batch Overview of Mean Sphericity vs. Yield (%).

To adequately assess the effects of the processing parameters, the material generated within the target particle size distribution and the mean sphericity ratio must be well understood. Figure 52. depicts both the mean sphericity and the target yield (adjusted to a 1% Scale for easier viewing) of the metoprolol succinate IR beads. It is the goal for the two values to be as close to 1 as possible, and can be considered inversely related for the interpretation of this graph. The processing parameters found in Table 26. must be considered when evaluating the output data.

The best target yield was produced for lot RB005109, with greater than 94% of the particles within the desired target particle size distribution. Unfortunately, this batch also yielded the worst mean sphericity ratio with the formation of rods. The formation of the rods may have caused a skewed distribution to appear, specifically with large narrow particles retained on #30 instead of on #25, which was more commonly seen in the other batches.

The best sphericity ratio was found in RB005119, which had initially formed large agglomerates after the completed process and required a re-extrusion and re-spheronization to achieve a desirable shape. This suggests that the additional processing of extrusion and spheronization facilitated the distribution and removal of water from the system. The water level, 180g in this batch was in an intermediate range of 140-200g as compared to the other batches but was added extremely rapidly (180 g/min) and did not undergo kneading. Excess water during extrusion can over saturate the material and make the extrudates difficult to process in the spheronizer. Conversely, insufficient water can create a high viscous mass that is difficult to cut and can result in machine blockage (Keleb, Vermeire et al. 2004b). These process

parameters imply that the water added remained as surface water and due to the lack of kneading did not get fully incorporated into the wetted mass. The primary extrusion and spheronization contained a large amount of surface water, which resulted in the initial agglomeration of the materials. The initial processing also acted to remove a portion of the water from the damp mass. While some water was removed during extrusion via heat transfer and friction, water migration in the formulation was most likely prevalent yielding disproportionately wet extrudates similarly to research conducted by (Vervaet, Baert et al. 1995).

The wet extrudates were then spheronized and visible condensation was formed on the cover during processing due to centrifugal force driving the surface liquid off of the beads, and squeezing out the internal water to the bead surface (O'Connor and Schwartz 1989). The spheronizer's purge air supplies compressed air to the system to facilitate the lift of the wet material during processing, which subsequently dries the formulation further. After the initial process was completed the re-extrusion served to redistribute the remaining water into the formulation. The re-spheronization cycle was able to shape the extrudates into a desirable shape, because they contained sufficient water incorporated into the core material and surface water. As the extrudates undergo the spheronization cycle, adequate water must be present at the surface to allow adhesion of smaller particles to reduce the formation of fine particles, but must be balanced with internal water to allow uniform extrusion and particle size growth (Gokhale, Sun et al. 2005). Reprocessing steps should be considered as a last resort to create a viable formulation; only after all other approaches have been exhausted

5.9.3 Metoprolol Succinate IR Exploratory Statistical Results

5.9.4 Particle Size Distribution

Table 29 Analysis of Variance for Target % Using Adjusted SS for Tests of Reduced Model

Source	DF	Seq SS	Adj SS	Adj MS	F	P
H2O Coded	1	282.63	604.74	604.74	7.94	0.048
Spheronizer RPM Coded	1	554.59	609.84	609.84	8.00	0.047
Spheronizer Time Coded	1	85.56	85.56	85.56	1.12	0.349
Error	4	304.83	304.83	76.21		
Total	7	1227.61				

S = 8.72965 R-Sq = 75.17% R-Sq (adj) = 56.55%

Figure 53 Main Effects Plot for the Reduced Model of Particle Size Target % Yield for Metoprolol Succinate IR Exploratory

The reduced model ANOVA found that the amount of water used during granulation and the speed of the spheronizer (rpm's) are both statistically significant.

While spheronization time was found not to be statistically significant, it remains in the reduced model in order to follow the proper reduction approach. Figure 53. shows that lower spheronization speed and lower water amount had greater yields within the target. Lower amount of water will tend to yield smaller particles, while slower spheronization will prevent excessive particle agglomeration. The particle size distribution within the target % yield is important but must be considered with the sphericity data, prior to making any processing decisions.

While spheronization time was found not to be statistically significant, it remains in the reduced model in order to follow the proper reduction approach. Figure 53. shows that lower spheronization speed and lower water amount had greater yields within the target. Lower amount of water will tend to yield smaller particles, while slower spheronization will prevent excessive particle agglomeration. The particle size distribution within the target % yield is important but must be considered with the sphericity data, prior to making any processing decisions.

5.9.5 Metoprolol Succinate IR Exploratory Statistical Results- Sphericity

Table 30 Analysis of Variance for Mean Sphericity, Using Adjusted SS for Tests

Source	DF	Seq SS	Adj SS	Adj MS	F	P
H2O Coded	1	0.112813	0.188576	0.188576	47.32	0.002
Kneading Time Coded	1	0.057604	0.072630	0.072630	18.22	0.013
Spheronizer Time Coded	1	0.050030	0.050030	0.050030	12.55	0.024
Error	4	0.004975	0.004975	0.001244		
Total	7	0.025688				

S = 0.0631302 R-Sq = 93.26% R-Sq (adj) = 88.20%

Figure 54 Main Effects Plot for Mean Sphericity for Metoprolol Succinate IR Exploratory Batches

The amount of water added, the kneading time, and the spheronization time were all found to be significant factors for the mean sphericity of the beads. These findings are in agreement with (Baert, Vermeersch et al. 1993) which found that the amount of granulation water added, the spheronization speed, and the spheronization time are the most important factors that determine pellet sphericity. Figure 54. shows that higher levels of water, lower kneading times, and higher spheronization time all contribute to the improvement (closer to 1.0 is the goal) of the mean sphericity. The sphericity is improved by having more available surface water, which occurs due to the higher level of water added and the diminished kneading time, and longer spheronization time which increases the bead contact with the spheronizer walls and friction plate to improve the roundness. These conditions may negatively effect the particle size distribution and yield larger particles.

Table 31 Analysis of Variance for Sphericity Std. Dev., Using Adjusted SS for Tests

Source	DF	Seq SS	Adj SS	Adj MS	F	P
H2O Coded	1	0.001513	0.007811	0.007811	6.28	0.066
Kneading Time Coded	1	0.008229	0.010971	0.010971	8.82	0.041
Spheronizer Time Coded	1	0.010971	0.010971	0.010971	8.82	0.041
Error	4	0.004975	0.004975	0.001244		
Total	7	0.025688				

S = 0.0352668 R-Sq = 80.63% R-Sq (adj) = 66.11%

Figure 55 Main Effects Plot for Sphericity Standard Deviation for Metoprolol Succinate IR Exploratory Batches

The ANOVA for the sphericity standard deviation determined kneading time and spheronization time to be statistically significant. Low kneading time and high spheronization time both decrease the standard deviation of the bead sphericity, while the amount of water does not play a significant role. Higher time in the spheronizer allows the material more time to contact the surfaces for rounding and approach or reach their maximal roundness (Baert, Vermeersch et al. 1993). Lower kneading times will disperse less water through the mass and leave more available surface water during extrusion and spheronization.

5.9.6 Results-Metoprolol Succinate Exploratory Batches-New Approach

Based on the raw data and the statistical interpretations, the greatest challenge is generating a spherical bead, while maintaining adequately sized particles. Table 32 is an overview of the significant variables and the levels, which yield the desired results.

Table 32 Overview of Significant Coded Variables from Exploratory Batches

Response	H2O Amount	H2O Addition Rate	Kneading Time	Spheronization Speed	Spheronization Time
% Target Yield	Low	NS	NS	Low	NS
Mean Sphericity	High	NS	Low	NS	High
Std. Dev. Sphericity	NS	NS	Low	NS	High

It is apparent from the table that the water amount necessary is not in agreement. Interestingly, the water addition rate was not found to be significant for any of the responses. Research has indicated that slow addition of the granulating water coupled with kneading would incorporate the granulating liquid into the system and improve the sphericity, the negative impacts of this approach was that the particle size distribution would skew to the larger size (Devay, Mayer et al. 2006). Conversely, rapid addition of water resulted in smaller particles due to the process of faster agglomeration but may yield poorly shaped pellets (Mehta, Singh Rekhi et al. 2005).

To achieve the correct balance of internal and surface water in the formulation, a new approach was implemented during the high shear granulation stage. An initial slow water addition phase was performed, followed by a rapid addition of water. Previous research had used this technique of slow addition (50g/min) followed by faster addition (100g/min) to successfully create dense beads

(Gao, Jain et al. 2002). This method theoretically allowed more time for initial agglomeration by forming liquid bridges, and supports particle growth during compaction and cutting to promote bead hardening and densification. The remaining processes followed the results seen in Table 32, low kneading time, low spheronization speed, and high spheronization time. The new process parameters and the results are found in Table 33.

Table 33 Processing Parameters and Results for 2 Phase Water Addition for Metoprolol Succinate IR Beads

Trial	Processing Parameters					Yields			Sphericity			
	H2O Amount (g)	H2O Addition G/min batch	Kneading Time (min)	Spheronizer RPM (Avg)	Spheronizer Time (min)	Final Prod. Temp	LOD (%)	Target %	Observed Shape	Mean Sphericity	Std Dev	RSD (%)
RB005124	170	80 for 1.5 min, 200 for 15 sec	15 sec	772	8	48.2	1.6	92.41	Spheres	1.2	0.15	12.16
RB005128	340	160 for 1.5 min, 400 for 15 sec*	15 sec	772	8	50	2.3	86.15	Spheres	1.16	0.15	13.03

*The water content and addition rate were doubled from RB005128 because the batch size was doubled.

The two-phase water addition coupled with the process parameters derived via statistical methodology successfully yielded a sufficiently round bead within the desired particle size distribution. The water amount and addition rate were doubled for the 800g batches, while the remaining process parameters remained the same. The larger batch yielded a slightly more spherical bead but lost some of the target % yield. The improved sphericity may be attributed to the increased load in the spheronizer, which results in more inter particle interactions, and a greater mass cascading onto the friction plate at the end of the rope like cycle to improve shaping. Research has shown that load can have both negative and positive impacts on shape and particle size distribution (Vervaet, Baert et al. 1995). The water added during granulation may have been distributed more evenly when kneading due to more advantageous surface to volume ratios than smaller loads. Additionally, variability within the process is expected, and doubling the batch size may not have identical yields if linear parameters are employed.

Figure 56 Exploratory Metoprolol Succinate SR Beads

Figure 56 is a graph depicting early exploratory coating levels; the medium and high level of polymer bracket the brand profile. This batch was performed to give a minimum starting point for bead coating experiments. The range of polymer concentration's used is approximately half the range that were ultimately used. The development strategy must account for a level of bead crushing, which will be highly dependent on the amount of protection provided by the excipient granule blends and top coating during tableting (Abbaspour, Sadeghi et al. 2005).

To hedge against damage to the beads during compression, Figure 57 is a coating trial, which examined a range of polymer levels two to three times of that seen in Figure 56. A significant decrease in drug release is present from the previous data present. The early points of 1 and 4 hour shows that the rate of initial hydration is similar for all of the beads. A divergence in the profiles from the lowest and highest profiles appears at 8 hours due to slower diffusion rates associated with the thicker polymer levels. Polymer levels 2 and 3 are similar and can be attributed to only a 2% coating thickness difference, which may not significantly impact the coating thickness for the standard curing cycle but may have an impact when cured under extreme conditions. Therefore, polymer levels 2 through 4 served as the polymer concentrations studied for the design of experiment factor.

Figure 57 Exploratory Metoprolol Succinate SR Beads for Tableting Studies

5.9.7 Results- Top Coating

Top coating with Opadry II suspension was found to have no negative or positive effects on the sustained release beads, data not shown. Overall, top coating at any level provided an improvement to the sustained release profile of any of the experimental tablets. Top coating the beads up to 15% w/w was studied, and the particle size distributions were found to grow too large and negatively affect the product yield. A final top coating level less than 10% was selected and fixed based on the exploratory studies for the future DOE. Figure 58 and 59 show cross sections of the finalized sustained release coating with a top coating. The topcoat can be seen to be significantly thinner than the sustained release, as it was applied at approximately 25% of the sustained release coating level. In addition to providing added protection, the topcoat imparts an aesthetic white finish to the beads.

Figure 58 Metoprolol Succinate SR Low Polymer Coating Level with Topcoat

Figure 59 Metoprolol Succinate SR Low Polymer Coating Level with Top Coat-Cross Section

5.10 Results-Exploratory Tableting Study

Figure 60 Overview of Dissolution Profiles for the Metoprolol Succinate Exploratory Tableting Study

Figure 60 is an overview of the dissolution data for the exploratory tableting study to screen three potential excipient blends. The granulated excipient blend provided very little protection during compression. This failure may be a result of the granules being too dense and/or brittle. Granules can lose some of the beneficial compactibility properties that they exhibit as raw materials after undergoing the granulation and drying processes (Abbaspour, Sadeghi et al. 2005). Particle size control of the granules was limited by the available mesh screens for the communitor, which ultimately discouraged further evaluation of wet granulation techniques for excipient granules.

The dry blend contained MCC 102, crospovidone, pregelatinized starch 1500, and lactose monohydrate. On initial inspection the high hardness tablets appear to exhibit slow drug release, but at the four-hour time point the release is consistent with unprotected beads experiencing crushing. The initial time point demonstrated poor tablet disintegration, and artificially prevented drug release by limiting the contact between the drug beads and the dissolution media (Moreton 2008). The poor disintegration may be caused by the grade of Crospovidone, and the binding ability of the other excipients.

The second dry blend used Avicel 102 and 200 in a 1:1 ratio, and polyplasdone XL-10 (30-50 μ m) to improve the disintegration of the tablets. This blend provided the best protection out of the three-excipient options. The addition of Avicel 200 raised the mean particle size of the excipient granulation and offered greater protection. This blend was chosen as the final formulation to examine during the design of experiment studies.

Chapter 6 Design Space

6.0 Introduction

Current research for granulation utilizing PAT and QbD approaches incorporate both on line monitoring and statistical design methodologies to characterize their formulations to support a design space. On line methodologies focus on monitoring the power consumed, torque produced by the blades, and near infrared spectroscopy for moisture content. Much of the on line monitoring is focused on parameters which are related to the flow properties and drug distribution, which have not yet been fully investigated in the literature (Cantor, Augsburger et al. 2008).

It is important to consider that not all recent research correlates these techniques to feasible end points. One example, utilized formulation and simulation to test the power consumption monitoring method for high shear granulation (Leuenberger, Puchkov et al. 2008). The author's found that a true granule "end point" during processing could not be derived and that a tailored individualized formulation approach was necessary. QbD is a general approach with many tools that can aid process understanding, an exploration of some of those approaches are described in this section.

6.1 Statistical Methods-DOE Batches

The 2^3 factorial design were analyzed for the estimated effects and coefficients, and an ANOVA of main effects and 2-way interactions to determine significant factors and interactions. All of the full model outputs can be seen in the

Appendices. Proper model reduction techniques were followed where necessary.

Main effects and interaction plots are given for significant factors. Both main effects and Interaction plots with intersecting lines are indicative of factor interactions for that response, but do not indicate statistical significance.

6.1.1 Full Factorial Design for Metoprolol Succinate IR Bead Processing

The experimental process parameters can be seen for the full factorial design for Metoprolol Succinate immediate release bead production in Table 34. The factors and levels were chosen based on the findings from the exploratory batches. The spheronizer was run at 600 rpm for one minute, and checked for excessive balling for all experiments. The spheronizer was then set to 775rpm, run for two minutes, and checked again. Then the spheronizer was run for the remaining time, either three minutes (low) or 6 minutes (high).

Table 34. Overview of the Full Factorial Metoprolol Succinate IR Bead DOE

Randomized Order	H2O Amount (g)	Kneading Time (Sec)	Spheronization Time (Min)
1	175	30	5
2	175	30	8
3	165	15	5
4	165	30	5
5	165	30	8
6	175	15	5
7	175	15	8
8	165	15	8

6.1.2 Box-Behnken Designs

The ICH Q8 annex recommends the use of response surface techniques to visualize factor effects and interactions to support the design space (ICH 2007). Two prominent methods of response surface techniques are the central composite and Box-Behnken designs. The Box-Behnken approach has the advantage of requiring fewer total runs because it only requires three levels for each factor instead of five, while remaining a balanced incomplete block design (Wu and Hamada 2000). The surface plots and contour plots that can be generated by this method are useful tools to aid in the visualization of the design space. The Box-Behnken designs have been used in pharmaceutical research such as (Zidan, Sammour et al. 2007) and (Shah, Zidan et al. 2007) to characterize critical factors for a novel delivery system.

6.1.3. Statistical Methods- Metoprolol Succinate SR Box Behnken Design

Table 35. Box Behnken-3 Factor/3 Level Design for SR Metoprolol Succinate

StdOrder	RunOrder	PtType	Polymer Coating Level	Curing Condition	Curing Time
8	1	2	1	0	1
10	2	2	0	1	-1
2	3	2	1	-1	0
3	4	2	-1	1	0
13	5	0	0	0	0
15	6	0	0	0	0
1	7	2	-1	-1	0
9	8	2	0	-1	-1
11	9	2	0	-1	1
12	10	2	0	1	1
5	11	2	-1	0	-1
4	12	2	1	1	0
14	13	0	0	0	0
7	14	2	-1	0	1
6	15	2	1	0	-1

The coded variables in Table 35 represent the following: -1 is the low level, 0 is the middle point, and 1 is the high level. A standard order (stdorder) is generated in accordance with the Box Behnken design; Minitab then randomizes the order in the Run Order column. The point type (PtType) is coded as 0 to represent the center point, and a 2 represents the face of the cube. The polymer coating level incrementally rises from the low level by 2% w/w, the exact coating levels cannot be described due to formulation confidentiality. The range of curing conditions was 60°C, 60°C/50% RH, and 60°C/75% RH. The curing time range was 2 hours, 4 hours, and 8 hours.

6.1.4 Statistical Methods- Metoprolol Succinate Tablet

Table 36. Metoprolol Succinate Multiparticulate Tablet 2^3 Factorial Design

StdOrder	RunOrder	SR Polymer level	Blend (MCC 200:102)	Hardness (Kp)
5	1	-1	1:1	5
6	2	1	1:1	5
4	3	1	3:7	2
1	4	-1	1:1	2
3	5	-1	3:7	2
8	6	1	3:7	5
2	7	1	1:1	2
7	8	-1	3:7	5

The standard order (StdOrder) of the 2^3 factorial design order is given in the first column of Table 36, with the Minitab randomized run order in the second column. The coded sustained release polymer level differs by 3%, with the low value equivalent to the high coded value developed during phase III. The high value for tableting represents the need to explore additional coating to prevent rapid release caused by crushing during tableting. Both levels of coated beads were top coated to the same percentage weight gain with the Opadry II topcoat suspension. The dry blend formulation #3 was selected for the tableting study. The ratio factor represents the amount of MCC 200 to MCC 102 within the excipient blend, while keeping all other inactive ingredient quantities constant. The tablet fill weights were adjusted to a concentration of 95mg Metoprolol Succinate to prevent biasing due to different polymer concentration application. The hardness was manually adjusted and determined by a DR. Schleuniger Pharmatron 6D hardness tester, prior to obtaining samples.

6.2 Metoprolol Succinate IR Bead DOE-Results

Table 37. Overview of the Process Parameters and Results

	Process Parameters						Sphericity			
Trial	H2O Amount (g)	Kneading Time (Sec)	Spheronization Time (Min)	Randomized Order	Target %	LOD %	Observed Shape	Mean Sphericity	Std. Dev. Sphericity	Sphericity RSD (%)
RB005148	175	30	5	1	90.63	1.6	Dumbbells/ Spheres	1.26	0.22	17.11
RB005149	175	30	8	2	90.92	1.6	Mostly Spherical*/ Few Dumbbells	1.34	0.19	14.2
RB014003	165	15	5	3	90.74	1.8	Rods/ Dumbbells	1.39	0.24	17.3
RB014004	165	30	5	4	92.53	1.3	Dumbbells> Rods> Spheres	1.45	0.21	14.31
RB014005	165	30	8	5	91.22	1.4	Dumbbells/ Rods	1.35	0.24	17.43
RB005150	175	15	5	6	79.83	1.5	Rounder Rods/Spheres	1.28	0.27	21.42
RB005151	175	15	8	7	89.99	1.8	Mostly Spherical	1.23	0.15	12.55
RB014006	165	15	8	8	91.37	1.5	Dumbbells/ Spheres	1.26	0.18	14.14

6.2.1 Statistical Results for Metoprolol Succinate DOE IR Bead Formulations

Table 37 is an overview of the process parameters and results of the Metoprolol Succinate immediate release bead formulations. The table characterizes the visual observations and it implies that differences can be seen between rods and spheres to make processing decisions. Appendix 5. contains all of the full statistical models for the sieve sizes collected and the target yield (%), with none of the factors or interactions showing statistical significance. This would imply that the particle size yields are not different enough that the processing parameters at these levels to have a significant impact. Model reduction techniques did not result in significant factors or improvement of the R^2 values.

It is not uncommon to find insignificant correlations between chosen variables and physical parameters. A 2^3 factorial design examining comparing high shear granulation impeller speed and binder flow was not statistically significant for three responses: Time parameter of dissolution, shape parameter of dissolution, and mean particle size diameter (Devay, Mayer et al. 2006). Interestingly, the mean particle size diameter for the responses in the study ranged from ~513-770 μm , which would result in retention on sieves #35 and #25 respectively. While statistically insignificant, the acceptance criteria set commercially may be based on the desired mean size retained and could imply a practically significant difference.

Figures 61 and 62 are examples of dumbbells and rods, respectively, generated during the DOE. These undesirable shapes are visible with the naked eye or can be evaluated with a standard optical microscope. It is important to consider

that even in acceptable batches there may be limited formation of dumbbells and/or rods, and screening may not be sufficient to eliminate. Therefore it is critical to understand the overall shape of the batch to anticipate future problems, which may arise in down stream processes.

Figure 61. Metoprolol IR Bead- Dumbbells (RB014005)

Figure 62. Metoprolol IR Beads-Rods (RB014005)

Table 38. Estimated Effects and Coefficients for Mean Sphericity (Coded Units)
Metoprolol Succinate IR Bead DOE

Term	Effect	Coef	SE Coef	T	P
Constant		1.32000	0.01031	128.06	0.000
Water Level	-0.08500	-0.04250	0.01031	-4.12	0.054
Kneading Time	0.06000	0.03000	0.01031	2.91	0.101
Spheronization Time	-0.05000	-0.02500	0.01031	-2.43	0.136
Water Level * Spheronization Time	0.06500	0.03250	0.01031	3.15	0.088
Kneading Time * Spheronization Time	0.04000	0.02000	0.01031	1.94	0.192

S = 0.0291548 R-Sq = 95.75% R-Sq (adj) = 85.12%

Table 39. Analysis of Variance for Mean Sphericity (Coded Units) Metoprolol Succinate IR Bead DOE

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Main Effects	3	0.026650	0.026650	0.0088833	10.45	0.089
2-Way Interactions	2	0.011650	0.011650	0.0058250	6.85	0.127
Residual Error	2	0.001700	0.001700	0.0008500		
Total	7	0.040000				

The estimated effects in Table 38 has the water level at a P value of 0.054, but this does not meet the general acceptance criteria of $P < 0.05$. This implies that the mean sphericity ratio range of 1.26-1.45 does not have a great enough difference associated with the selected factors at those ranges to be significant. The DOE did find significant results for processing factors with regard to the sphericity standard deviation and the sphericity RSD %. The standard deviation is a key measurement in manufacturing and is used extensively to support Six Sigma approaches for continuous improvement. Where Six Sigma links higher processing variability with product defects, and conversely lower standard deviations are associated with high quality performance (Welch 2003). The RSD is independent of units and is useful to compare the standard deviation with the mean to give an indication of the relative precision of the data (Gardiner and Gettinby 1998c).

Table 40. Estimated Effects and Coefficients for Sphericity Standard Deviation (Coded Units) Metoprolol Succinate IR Bead DOE

Term	Effect	Coef	SE Coef	T	P
Constant		0.21215	0.000451	470.78	0.001
Water Level	-0.00695	-0.00348	0.000451	-7.72	0.082
Kneading Time	0.00047	0.00023	0.000451	0.52	0.696
Spheronization Time	-0.04488	-0.02244	0.000451	-49.80	0.013
Water Level * Kneading Time	-0.01173	-0.00587	0.000451	-13.02	0.049
Water Level * Spheronization Time	-0.02801	-0.01400	0.000451	-31.08	0.020
Kneading Time * Spheronization Time	0.04647	0.02323	0.000451	51.56	0.012

S = 0.00127456 R-Sq = 99.98% R-Sq (adj) = 99.89%

Table 41. Analysis of Variance for Standard (Coded Units) Sphericity Standard Deviation (Coded Units) Metoprolol Succinate IR Bead DOE

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Main Effects	3	0.0041252	0.00412518	0.00137506	846.45	0.025
2-Way Interactions	3	0.0061622	0.00616220	0.00205407	1264.43	0.021
Residual Error	1	0.0000016	0.00000162	0.00000162		
Total	7	0.0102890

Figure 63. Main Effects Plot of Metoprolol Succinate DOE Sphericity Standard Deviation

Figure 64. Interaction Plot for Metoprolol Succinate DOE Sphericity Standard Deviation

Tables 40 and 41 show that Spheronization is a significant main effect, and all three of the two-way interactions are significant factors for the sphericity standard deviation. The main effects plot; Figure 63 indicates that high spheronization time has the greatest impact on reducing the sphericity standard deviation. All of the interactions are statistically significant, but Figure 64 shows that kneading time and spheronization time have the largest interaction effect. The interaction between the water level and the spheronization time is the second strongest, with kneading time and water level the weakest.

Table 42. Estimated Effects and Coefficients for Sphericity RSD (%) (Coded units)
Metoprolol Succinate IR Bead DOE

Term	Effect	Coef	SE Coef	T	P
Constant		16.058	0.04000	401.44	0.002
Water Level	0.525	0.262	0.04000	6.56	0.096
Kneading Time	-0.590	-0.295	0.04000	-7.38	0.086
Spheronization Time	-2.955	-1.478	0.04000	-36.94	0.017
Water Level * Kneading Time	-0.740	-0.370	0.04000	-9.25	0.069
Water Level * Spheronization Time	-2.935	-1.467	0.04000	-36.69	0.017
Kneading Time * Spheronization Time	3.060	1.530	0.04000	38.25	0.017

S = 0.113137 R-Sq = 99.98% R-Sq (adj) = 99.84%

Table 43. Analysis of Variance for Sphericity RSD (%) (Coded units) Metoprolol Succinate IR Bead DOE

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Main Effects	3	18.7115	18.7115	6.2372	487.28	0.033
2-Way Interactions	3	37.0508	37.0508	12.3503	964.87	0.024
Residual Error	1	0.0128	0.0128	0.0128		
Total	7	55.7752				

Table 42 shows that spheronization time and all of the two-way interactions are significant for the sphericity RSD %. Table 43 supports the main effects and interaction significance with the ANOVA. Figure 65 indicates that higher spheronization times will yield lower RSD%, while the other factors have minimal effects. Figure 66 indicates that the water level and spheronization time, as well as the kneading time and spheronization time have nearly same interacting effects. The interactions depict high water level, high spheronization time, and low kneading time to yield the lowest RSD %.

Figure 65. Main Effects Plot for Metoprolol Succinate DOE RSD (%) of Sphericity

Figure 66. Interaction Plot of Metoprolol Succinate DOE Sphericity RSD (%)

Figure 67. Loss on Drying at 48°C End Drying Temperature

Figure 67 is the LOD of the 400g-batch size experimental design trials separated by the amount of water added during granulation. All samples were dried to a product temperature of 48°C. The LOD range was from 1.3-1.8%, the low water level had an average LOD of 1.5% and the high water level had an average LOD of 1.6%. The 10g water difference between the two formulations did not result in a considerable difference in the LOD's. The product temperature target of 48°C served as a guide when the batch size was increased to 1.0 Kg. A lack of significant fine particle generation, as reflected in pan retention can be seen in Appendix 3, supports that there was not over agitation during the drying process.

6.2.2 Confirmation/Batch Size Increase of DOE Results for Metoprolol IR Beads

Table 44. Metoprolol IR Bead DOE Run #7 Confirmation Trials

Trial	Target %Yield	LOD % @48c	Mean Sphericity	Sphericity Std. Dev.	Sphericity RSD (%)
RB014013 (DOE Confirmation 400g)	93.07	1.6	1.28	0.2	15.45
RB014023 (1kg)	90.52	2.2	1.19	0.16	13.14
RB014024 (1kg)	91.37	2.2	1.12	0.11	10.13

The Metoprolol Succinate IR beads were run at the same processing conditions to confirm the initial findings from the DOE. The confirmation trial yielded >93% of the beads within the desired particle size distribution. The batch size was then increased to 1.0 Kg, with the water amount and rate doubling. The yields were both >90% and the mean sphericities showed improvement over the 400g batches. The increased batch size created better sphericity due to greater interactions between the material, the walls, and the spheronizer plate (Vervaet, Baert et al. 1995).

Figure 68. Metoprolol IR Bead- Round (RB014013/023/024 Blend)

Figure 68 is an SEM of a selected bead from the blend, which displayed good sphericity. There are no pores or cracking to indicate a weak or damaged bead. The beads from the three batches (RB014013, RB014023, and RB014024) were blended for the sustained release coating experiments.

Figure 69. Metoprolol IR Bead Loss on Drying Curve as a Function of Time

Figure 69 depicts the drying curve for Metoprolol IR beads for the 1.0 Kg batches to confirm the parameters at a higher batch load. LOD samples were taken every 5 minutes and after the drying cycle ended at 48°C. The values for the LOD (%) are presented below the RB014023 points, and above the RB014024 to avoid confusion. The first batch (RB014023) dried resulted in an increased LOD over the experimental design runs. This can be attributed to the increased load and a greater drying capacity required. Samples for the second batch (RB014024) were taken at 46°C, 48°C, and 50°C to confirm the first batch and understand the range around the target product temperature. Batch RB014024's found that at 48°C both batches yielded 2.2% LOD. 46°C did not yield a sufficiently dry pellet (2.8% LOD), while 50°C yielded a preferred LOD of 1.8%. The 1.0 Kg batch size requires a product temperature of at least 48°C to achieve an acceptable LOD with a specification of not more than 2.5%. An optimal LOD range of 1.5-2.0% occurs at a temperature above 48°C, with an acceptable yield at 50 C.

6.3 Metoprolol Succinate SR Doe Results

Table 45. Metoprolol Succinate SR DOE Results

Variables				% Metoprolol Succinate Released						
Polymer Coating Level	Curing Condition (°C/RH%)	Curing Time (Hrs)	Sample ID	1 hr	4 hr	8 hr	12 hr	16 hr	20 hr	F2
1	60/50	2	0908305	1.41	7.44	15.21	24.99	34.94	43.64	21.35
-1	60/0	4	0908298	9.13	26.38	38.85	49.26	46.39	55.09	31.24
1	60/50	8	0908306	1.57	8.31	18.25	33.46	48.42	59.37	26.88
0	60/0	8	0908301	1.74	8.98	18.99	28.55	37.74	46.56	22.95
0	60/0	2	0908294	3.89	13.19	23.71	33.83	43.46	51.92	26.02
1	60/75	4	0908309	1.63	4.51	11.79	24.05	40.33	55.66	22.84
0	60/50	4	0908300*	1.51	7.83	18.43	32.73	46.50	57.59	26.21
-1	60/50	8	0908310	1.55	8.00	21.66	39.59	55.54	66.80	30.70
0	60/75	8	0908311	2.75	5.66	10.71	21.07	34.60	49.55	21.03
0	60/50	4	0908300*	2.55	9.30	21.18	35.19	47.16	56.87	27.06
0	60/50	4	0908300*	1.79	8.33	18.57	30.45	41.44	50.31	24.17
-1	60/50	2	0908312	1.73	7.41	18.97	33.24	46.54	57.15	26.27
0	60/75	2	0908313	3.22	7.98	17.58	30.85	45.33	58.19	25.76
-1	60/75	4	0908314	3.83	9.67	21.57	38.17	54.64	68.60	30.76
1	60/0	4	0908299	7.07	19.28	28.79	29.54	38.28	46.11	24.34

*Denotes a center point of the experimental design

Table 45 is the results of the Metoprolol Succinate sustained release Box-Behnken design. The goal of the study was not to yield a high f_2 value, because these beads will be further processed and the drug release is expected to increase as a function of the damage experienced during the tableting process. Based on the exploratory tableting study there is reason to suspect damage may occur even with an improved excipient blend, therefore a thicker sustained release coating was studied. The f_2 value is given as the main indicator of dissolution profile to the brand product to understand the relative effects of the factors studied.

Table 46 is the estimated regression coefficients for the Metoprolol Succinate f_2 values, indicating that the polymer coating level is a significant factor. Table 47 are the ANOVA for the Metoprolol Succinate f_2 values, and indicates that the linear regression model is significant and there are no lack of fit concerns.

Table 46. Estimated Regression Coefficients for Metoprolol Succinate F2 Values

Term	Coef	SE Coef	T	P
Constant	24.7501	0.9201	26.899	0.000
Polymer Coating Level	-2.9450	0.8535	-3.451	0.006
Curing Conditions	-0.5200	0.8535	-0.609	0.556
Curing Time (Hrs)	0.0507	0.8323	0.061	0.953
Polymer Coating Level *	2.0558	1.2495	1.645	0.131
Polymer Coating Level				

S = 2.414 R-Sq = 60.0% R-Sq (adj) = 44.0%

Table 47. Analysis of Variance for Metoprolol Succinate F2 Values

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Regression	4	87.329	87.3295	21.8324	3.75	0.041
Linear	3	71.554	71.5690	23.8563	4.09	0.039
Square	1	15.775	15.7750	15.7750	2.71	0.131
Residual Error	10	58.274	58.2743	5.8274		
Lack-of-Fit	8	53.862	53.8622	6.7328	3.05	0.270
Pure Error	2	4.412	4.4121	2.2060		
Total	14	145.604				

Contour Plots of F2

Figure 70. Contour Plots for F₂ Values of Metoprolol Succinate SR DOE

Figure 70 are the contour plots generated by the design of experiments for Metoprolol Succinate sustained release studies. The Y- axis represents the first factor of the title, while the X-axis represents the second factor. The polymer coating level was the only factor found to be statistically significant, and the plots show that lower coating levels can be correlated with high f_2 values. The dissolution profiles are currently slower than the branded product and lower coating would increase the drug's release rate. The vertical delineations of the curing condition vs. the polymer concentration support that the polymer concentration is the primary factor in the interaction. Curing time and curing conditions indicate a reverse "C" curve which implies there are effects in the intermediate ranges on the f_2 value, that the extreme points high and low do not effect. The slowest release profiles were seen at the high polymer coating level and low curing time. Curing for the intermediate and high duration for the high polymer level did not alter the effects, signifying a potential coalescence effect. The high-level polymer beads cured at 60°C for 2 hours were chosen due to their low drug release rates for processing into multiparticulate tablets.

6.4 DOE Results for Metoprolol Succinate Tablets

Table 48. Tablet Friability for the DOE Batches

Lot#	Polymer Conc.	Blend Ratio (MCC 200:102)	Blend LOD (%)	Tablet Fill Weight (mg)	Hardness (kp)	Acceptable (%)	Pass/Fail
RB014064	1	1:1	2.5	449.5	2	85.56	Fail
					3	95.57	Fail
					4	98.66	Fail
					5	99.53	Pass
RB014065	-1	1:1	2.6	437	2	95.92	Fail
					5	100	Pass
RB014066	1	3:7	2.5	449.5	2	63.33	Fail
					5	98.76	Fail
RB014067	-1	3:7	2.7	437	2	98.31	Fail
					5	99.88	Pass

Table 48 is an overview of the friability results for the DOE batches, pass or fail determination is based on the USP Chapter <1216> for tablet friability, where not more than 1% of weight loss is allowed (USP 2007d). The results from this experiment found that all of the high hardness runs except RB014066 passed the friability test. This failure (98.76%) is most likely attributed to beads incorporated in the walls of the tablets becoming loose. Multiparticulate tablets incorporate the beads throughout the tablet and may create localized areas of beads towards the edges, which may result in a small loss of edge material during friability testing (Abbaspour, Sadeghi et al. 2005). It is important to consider that in a production environment, these tablets would receive an additional top coat, (i.e. Opadry) to protect against moisture, chipping, damage, and provide taste masking (Kottke and Rudnic 2002). Operating conditions during top coating for equipment such as pan coaters can be carefully selected to meet the tablet characteristics if necessary. In this situation, the friability data helps to support the understanding of the tablets that

would further be top coated, but must be considered in concert with the dissolution profile. Table 48 also describes the LOD (%) of the blend prior to compression and shows little moisture differences between the blends. The ANOVA was found to be not statistically significant, see Appendix 9 for the full model.

6.4.1 SEM for Metoprolol Succinate Tablet DOE

Figure 71. High Polymer Coating Level with Topcoat Uncompressed

Figure 71. is an SEM image of an uncompressed bead, which has been coated with a sustained release polymer and then top coated with an Opadry II suspension. The beads appear smooth and without defect, note that the light colored speckles are components of the top coating suspension. Figures 72 through 77 are the compressed high polymer level beads from both excipient blends with high and low hardness, as well as the tablet matrices they formed (for low hardness only).

Figure.72. High Polymer Coating with Topcoat and a 30/70 Blend at 2kp Tabletted

Figure 73 Metoprolol Succinate High Polymer Level with Topcoat, 30/70 Blend at 5kp Tablet Hardness

Figure 74. Cross Sectioned Tablet of Metoprolol Succinate High Polymer Level with Topcoat with a 30/70 Blend and 2kp Hardness.

Figure 75. Metoprolol Succinate High Polymer Level with Topcoat, 50/50 Blend Tabletted at 2Kp

Figure 76 Metoprolol Succinate High Polymer Level Top Coated with a 50/50 Blend, Tabletted to 5kp.

Figure 77. Metoprolol High Polymer Coating with a Topcoat 50/50 Blend at 2kp.

The SEM images depict varying degrees of surface cracking of the beads, from theoretically superficial to severe. Figure 75, the 1:1 blend ratio of MCC at 2Kp hardness appears to have the least amount of cracking on the surface for the individual bead and has some limited damage in Figure 77, in the tablet with the excipient blend. Bead damage is also visible in Figures 72 through 74, indicating that the 3:7 ratio excipient blend may also not serve to protect the beads during compression. Excipients must have good compressibility attributes, and be of similar size to the beads being tableted in order to provide protection from forces experienced during compression (Abbaspour, Sadeghi et al. 2005).

The bead's sphericity has an important impact on the final dosage form. Research examining the effects of a granule's shape and porosity on final tableting characteristics concluded the following: 1) Irregular shaped granules result in more complex behavior during compression and can induce granule fracturing. 2) Bed void space was increased as a function of irregular shaped granules to facilitate deformation during compression resulting in higher tablet tensile strength. 3) Lubricants provide less protection for irregularly shaped granules due to incomplete coverage and/or rupturing during compression (Johansson and Alderborn 2001). The void space created by the beads and excipient particles may be filled more effectively with the MCC PH-102 at a ratio of 1:1, than at 3:7 which does not contain adequately sized larger particles for cushioning.

6.4.2 Dissolution of Metoprolol Succinate Multiparticulate Tablets

Figure 78. Metoprolol Succinate SR Tablets at High and Low Hardness with and without #25 Beads Loaded

Figure 78 compares the theoretical “best case” scenario for the tableting study. Based on the SEM images and the dissolution profiles from the sustained release DOE, one could make the assumption that: the MCC 1:1 ratio and the high polymer concentration would create the best scenario for protecting the beads during compression. The tablets of the best-case scenario are compared with and without loading the sieve size #25 (the largest) beads of the blend. The best results are obtained for the formulation, which does not contain the #25 sieve sized beads compressed at 2 Kp. Interestingly, there is no significant difference between the formulations at the higher hardness, indicating that crushing of the beads is still occurring. A reduction in the particle size of the immediate release bead could have a positive effect on the final tablet product. The smaller sized beads would require more coating due to an increased surface area but would theoretically be able to fill the void spaces that are created during compression (Dashevsky, Kolter et al. 2004). (Badawy, Lee et al. 2000) found that a finer grade of active ingredient can alter the size of immediate release beads yielded and achieve a shift to a smaller particle size distribution.

Chapter 7 Conclusions

7.1 Establishment of Target Product Profiles

The first step of the ICH Q8 Annex was to establish the chemical and physical target product profiles. The current marketed competitors for propranolol HCl and metoprolol succinate extended release products were reformulated to establish targets to guide process development. The dissolution profiles served as an important target throughout the intermediate sustained release bead, and final multiparticulate extended release tablet development. Evaluation of variability and trends in drug release profiles within the USP acceptance criteria supported development decisions. SEM imaging provided visual indicators about the manufacturing practices, materials, and characteristics of the intermediate materials used by the marketed competition. The imaging determined uniform bead aspect ratios ~ 1.0 , indicating the production of spherical immediate release beads. Sieving studies found a tailored particle size distribution for both products and guided immediate release bead size targets. Additional physical characterization supported fill weight and tooling decisions for tablets and capsules.

7.2 CQA Identification

Identification of the CQAs for this developmental process was selected based on the ICH Q8 annex guidelines, product reformulation characterization, current literature and available equipment. Particle size distribution, particle sphericity, IR bead moisture content, and the sustained release dissolution profile were selected as the CQA's to be studied. The particle size distribution dictates both the surface area

available for polymer coating, and means particle size of beads during compression. Sphericity was chosen to facilitate bead flow through down stream process, and support even polymer coating application. High moisture contents have been identified as potentially causing long-term instability and potential microbial growth. Understanding the impacts of process and formulation changes on the dissolution profile during development is essential for guiding changes in the future.

7.3 Linking CQA's to Process Parameters

The general linear model of the process parameters and the yield determined statistically significant main effects. Particle size distribution was calculated based on individual sieve size retention and as a total yielded percentage. The amount of granulating water was found to be statistically significant for determining the particle size yield for both Propranolol HCl and metoprolol succinate. Identification of the water level is the critical process parameter because it will directly effect all downstream processing. During high shear granulation, controlling the process parameters to adjust the distribution of the water is important to facilitate extrusion and control the particle size distribution generated. Metoprolol succinate immediate release beads also found spheronization speed to be a significant factor for the determination of particle size distribution. Determination of an appropriate spheronization speed early in the process to create an optimal rope like formation and avoid irregular flow patterns of the beads must be carefully evaluated to avoid agglomeration and oversized bead generation.

Sphericity was measured as the mean aspect ratio and the standard deviation between the mean aspect ratio measurements. Kneading time and spheronization time were statistically significant for both mean sphericity and standard deviation of metoprolol succinate. Additionally, the granulation water amount was statistically significant for mean sphericity. Kneading time and granulating water can be directly attributed to the distribution and quantity of water available in the system to enhance the formulation's plasticity during processing. Longer durations of spheronization are associated with greater mean sphericity and lower sphericity variability due to increased particle interactions within the system.

The incorporation of HPMC into the aqueous ethylcellulose dispersion could not provide an adequate sustained release coating system for Propranolol HCl. Humidified and other extreme curing conditions stressed the polymeric coating and a lack of a uniform coating ultimately resulted in an unstable product. In contrast, an organic coating solution did not exhibit the same instability when humidified and extreme curing conditions were studied. Initial stability studies not presented in this work, suggest that the organic coated beads were stable and exhibited little changes over time to the dissolution profile.

The Aqueous dispersion studied for Metoprolol Succinate sustained release coating did not contain HPMC and provided a reliable and adaptable system. Curing conditions did impact the product, but to lesser degree than the Propranolol HCl sustained release beads. The sustained release bead profile was initially matched to the brand profile to understand a baseline level needed for coating. The polymer coating levels were then raised two to three times the initial polymer level in order to

compensate for potential bead crushing during tableting. Incremental increases of polymer level yielded an anticipated decrease in the drug release profile.

Bead top-coating experiments identified a medium level of coating to add adequate plasticity and extra degree of protection, without adversely affecting the drug release profile. High levels of top coating can result in beads growing to an unacceptably large size, which may have a negative impact during compression. A practical concern for the generation of oversized beads for a tailored system is the diminished product yield, which has financial and processing ramifications.

Preliminary tableting studies for metoprolol succinate identified the variable levels of protection provided by the different excipient granule blends. A mixed excipient blend of microcrystalline cellulose provided the greatest protection to the sustained release beads. Larger excipient particle sizes match the active beads and provide structural support, while smaller sized excipients fill void spaces created due to deformation during compaction. Tablet hardness ranges were established from 2kp to 5kp, at the low end of the acceptable range for passing tablet friability testing.

7.4 Supporting Elements of a Design Space

The metoprolol succinate immediate release beads utilized a 2^3 full factorial design to evaluate granulating water amount, kneading time, and spheronization time for the effects of these process conditions on the identified CQA's. These experiments yielded greater than 80% of the target particle size but found none of the factors or interactions statistically significant. The findings indicated that the factor levels had little effect on the final output and support an acceptable processing range.

The factors were also insignificant for the mean sphericity of the IR beads, but found spheronization time and all of the interactions significance in the relative and standard deviation of the sphericity measurements. This supported earlier work where longer spheronization times contributed to more uniformly round particles due to greater particle-particle and particle-system interactions. All of the trials met the moisture content specification of not more than 2.5%, and indicated that drying was within acceptable processing ranges. The IR bead with the lowest sphericity ratio was chosen for further development.

The Box-Behnken experimental design studied the polymer coating level, the humidification level during curing, and the duration of curing. Polymer coating level was statistically significant for the calculated f_2 of the dissolution profile. Contour plots depict the range and identified high polymer coating levels and short durations of curing were associated with low f_2 values. In contrast, high f_2 values are found for low polymer coating levels, intermediate curing duration, and low/medium levels of humidification. Understanding the range of the f_2 values was critical during development to support adjustment decisions to the sustained release profile.

A 2^3 full factorial experimental design was utilized to study the blend ratio of two microcrystalline cellulose particle sizes within the excipient blend, the amount of sustained release polymer coating applied to the active beads, and the hardness of the tablets. Friability studies indicated that 2kp hardness resulted in significant tablet breakage, while 5 kp hardness was acceptable. Visualization of bead damage during compression was performed with SEM, with significant damage to polymer coatings seen at 5kp hardness, and at the lower ratio of MCC 200:102. Therefore the “best

case” processing parameters for the tablets were further examined through dissolution testing. The dissolution profile was faster than the branded competitor but showed improvement over the previous experimental samples. Additionally, improvement was seen when beads retained on sieve #25, the largest mean particle size for the active beads was removed. This improvement indicated the importance of particle size during tableting, and would support movement in the target particle size distribution to a smaller size. Smaller sized beads fill void spaces more thoroughly and support plastic deformation during compression. The results from both the exploratory and DOE batches of immediate release beads indicate that a marked shift to a smaller particle size distribution would require a smaller extrusion screen and/or a micronized API with a smaller mean particle size distribution.

7.5 Exploratory Traditional Methods vs. QbD

The traditional methods promote local optimization, when an acceptable outcome is found; minor adjustments are made to optimize that outcome. This approach can be cost and time effective if the formulation scientist is able to discover an acceptable result in a timely fashion. If a complex interaction occurs or a problem arises in a formulation, it can be difficult to identify and quantify the cause and solution to the problem. Utilizing an appropriate design can improve the overall understanding of the system and aid in finding a global optimum.

It is important to consider that statistical significance is not equivalent to practical significance. Prudent judgment should be employed when analyzing results of the statistical methods to appropriately interpret the results and their implications.

The P value is a useful tool for determining significance but should not be the only guide to interpretation. A blended approach to drug development will save time where elaborate study designs are not necessary and support processing understanding to solve problems and changes to the system.

7.6 Study Limitations

Due to financial and resource constraints, not all generated samples could be tested and in certain situations the theoretical best guess batch was characterized. This limited the understanding of the design space edge of failure, as batches with negative traits were less likely to undergo full testing. Industrial pharmaceutical research often does not incorporate repetition into their statistical design due to the related costs associated. Therefore it is difficult to truly understand the product ranges and traits, especially in the event of a batch or analytical anomaly. The results found in the study cannot be generalized to cover all drugs, but may help to describe other drugs with similar physical characteristics.

7.7 Future Studies

Future work to establish point-to-point in vitro relationships and establish a level A bioequivalency rating should be pursued to support the commercialization of both of these products. Investigation of raw material physical characteristics and inter batch variability would be a useful tool to identify potential issues prior to beginning the process. Aspects of long term stability, pharmacokinetics, and scale up offer good opportunities to examine the relationships found in this study to a real world application for FDA approval. Other drugs with similar characteristics should

be studied to understand the applicability of the factors across drug product categories.

BIBLIOGRAPHY

- (1994). Final Act Embodying the Results of the Uruguay Round of Multilateral Trade Negotiations; Agreement on Trade-Related Aspects of Intellectual Property Rights Annex 1C. Pub. L. No.103-465: 319-351.
- (1996). Economic Espionage Act of 1996. Pub. L. No. 104-294: 18 United States Congress 1831-1839. Retrieved July 12, 2008 from <http://www.economespionage.com/EEA.html>.
- Abbaspour, M. R., F. Sadeghi, et al. (2007). "Thermal Treating as a Tool to Produce Plastic Pellets Based on Eudragit RS PO and RL PO Aimed for Tableting." European Journal of Pharmaceutics and Biopharmaceutics **67**: 260-267.
- Abbaspour, M. R., F. Sadeghi, et al. (2005). "Preparation and Characterization of Ibuprofen Pellets Based on Eudragit RS PO and RL PO or Their Combination." International Journal of Pharmaceutics **303**: 88-94.
- Abrahamsson, B., M. Alpsten, et al. (1996). "Gastro-Intestinal Transit of a Multiple-Unit Formulation (Metoprolol CR/ZOK) and a Non-Disintegrating Tablet with the Emphasis on Colon." International Journal of Pharmaceutics **140**(2): 229-235.
- Actavis-Elizabeth (2008). Propranolol Hydrochloride Capsule, Extended Release Product Label. Document # 40-9084, Rev. Feb/08.
- Allen, L., N. Popovich, et al., Eds. (2005). Ansel's Pharmaceutical Dosage Form's Drug Delivery Systems, 8th ed. . Baltimore, Lippincott Williams & Wilkins.
- Almeida-Prieto, S., J. Blanco-Mendez, et al. (2007). "Microscopic Image Analysis Techniques for the Morphological Characterization of Pharmaceutical Particles: Influence of the Software, and the Factor Algorithms Used in the Shape Factor Estimation." European Journal of Pharmaceutics and Biopharmaceutics **67**(3): 766-776.
- American Society of Health-System Pharmacists (2008a). Metoprolol Succinate Monograph. AHFS Drug Information. Bethesda: 1892-1901.
- American Society of Health-System Pharmacists (2008b). Propranolol Hydrochloride. AHFS Drug Information. Bethesda: 1908-1916.
- Andrews, G. P., D. S. Jones, et al. (2008). "The manufacture and characterisation of hot-melt extruded enteric tablets." European Journal of Pharmaceutics and Biopharmaceutics **69**(1): 264-273.
- Ansel, H. C., L. V. Allen, et al. (1999). Pharmaceutical Dosage Forms and Drug Delivery Systems, Lippincott Williams & Wilkins.
- Armstrong, N. (2008). Lubricants, Glidants, and Antiadherents. Pharmaceutical Dosage Forms: Tablets. L. Augsburger and S. Hoag. New York, Informa Healthcare. **Unit Operations and Mechanical Properties**: 251-267.
- Astra-Zeneca (2007). Toprol-XL (Metoprolol Succinate) Package Insert. Revised 07/07, Retrieved June 15, 2008 from <http://www.fda.gov/cder/foi/label/2008/019962s036lbl.pdf>.
- Aulton, M. E., M. H. Abdul-Razzak, et al. (1981). "The Mechanical Properties of Hydroxypropylmethylcellulose Films Derived from Aqueous systems. Part 1:

- The influence of plasticizers " Drug Development and Industrial Pharmacy 7: 649-668.
- Badawy, S., T. Lee, et al. (2000). "Effect of Drug Substance Particle Size on the Characteristics of Granulation Manufactured in a High-Shear Mixer." AAPS PharmSciTech 1: 33.
- Baert, L., H. Vermeersch, et al. (1993). "Study of parameters important in the spheronisation process." International Journal of Pharmaceutics 96: 225-229.
- Banakar, U. (1991). Pharmaceutical Dissolution Testing. New York, Marcel Dekker.
- Bodmeier, R., X. Guo, et al. (1997). Process and Formulation Factors affecting the Drug Release from Pellets Coated with Ethylcellulose-Pseudolatex Aquacoat. Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms. J. McGinity. New York, Marcel Dekker: 55-100.
- Bodmeier, R. and O. Paeratakul (1994). "Mechanical Properties of Dry and Wet Cellulosic and Acrylic Films Prepared from Aqueous Colloidal Polymer Dispersions Used in the Coating of Solid Dosage Forms " Pharmaceutical Research 11(6): 882-888.
- Bruck, M. L. and F. G. Willard (2006). "The Art and Science of Paint Deformulation: Knowing What's In The Mix Is Key, But Testing Can Be Tricky." Metal Finishing 104(9): 23-24.
- Cantor, S., L. Augsburger, et al. (2008). Pharmaceutical Granulation Processes, Mechanism, and the Use of Binders. Pharmaceutical Dosage Forms: Tablets. L. Augsburger and S. Hoag. New York, Informa Healthcare. **Volume 1: Unit Operations and Mechanical Properties**: 261-301.
- CFR:201.100 (2007). Labeling: Prescription Drugs for Human Use. Title 21 Food and Drugs, Code of Federal Regulations. pt 201.100. FDA.
- CFR:314.94 (2008). Application for FDA Approval to Market a New Drug. Title 21 Food and Drugs, Code of Federal Regulations pt.314. 94. FDA.
- CFR:320.1 (2003). Bioavailability and Bioequivalence Requirements. Title 21 Food and Drugs, Code of Federal Regulations pt. 320. 1. FDA.
- Chan, L. and P. Heng (2005). Drug Substance and Excipient Characterization. Handbook of Pharmaceutical Granulation Technology. D. Parikh. Boca Raton, Taylor & Francis Group: 79-107.
- Chatchawalsaisin, J., F. Podczek, et al. (2005). "The Preparation by Extrusion/Spheronization and the Properties of Pellets Containing Drugs, Microcrystalline Cellulose and Glyceryl Monostearate." European Journal of Pharmaceutical Sciences 24(1): 35-48.
- Chen, C. M. (2006). Controlled Release Oral Dosage Form of Beta-Adrenergic Blocking Agents. United States Patent Office. April 4. **7,022,342**.
- Chen, R., A. M. Tseng, et al. (2001). "Application of an Integrated Matrix-Assisted Laser Desorption/Ionization Time-of-Fight, Electrospray Ionization Mass Spectrometry and Tandem Mass Spectrometry Approach to Characterizing Complex Polyol Mixtures." Journal of the American Society for Mass Spectrometry 12(1): 55-60.

- Chopra, R., G. Alderborn, et al. (2002). "The influence of pellet shape and surface properties on the drug release from uncoated and coated pellets." International Journal of Pharmaceutics **239**(1-2): 171-178.
- Chopra, R., F. Podczek, et al. (2002). "The influence of pellet shape and film coating on the filling of pellets into hard shell capsules." European Journal of Pharmaceutics and Biopharmaceutics **53**(3): 327-333.
- Cobb, G. (1998). Comparisons, Contrasts, and Confidence Intervals. Introduction to Design and Analysis of Experiments. New York, Springer Verlag: 436-481.
- Colorcon (2006). Surelease Preparation and Use Guidelines, Retrieved June 19, 2008 from http://www.colorcon.com/literature/marketing/mr/Extended%20Release/Surelease%C2%AE/English/prep_use.pdf.
- Colorcon. (2008a). "Product Overview: Opadry Complete Film Coating System." Retrieved September 6, 2008, from <http://www.colorcon.com/products/coatings/immediate-release/Opadry/Product%20Overview>.
- Colorcon. (2008b). "Opadry II High Performance Film Coating Systems." Retrieved August 22, 2008, from http://www.colorcon.com/literature/marketing/fc/Opadry%20II/sales_bro_opadryII.pdf.
- Colorcon. (2008c). "SUPAC-IR-Printing Ink Changes Recommendations for Implementation." Retrieved October 19, 2008, from <http://www.colorcon.com/literature/regulatory/SUPAC%20IR-Recom%20for%20Implementation.pdf>.
- Colton, J. (2004). "Avoiding Mean Square Error Bias in Designed Experiments." Scientific Computing & Instrumentation (Reprint by Minitab Inc.): Retrieved August 1, 2008 from www.minitab.com/resources/articles/SCIAPr2004MSE.pdf.
- Crowder, T., A. Hickey, et al. (2003). A Guide to Pharmaceutical Particulate Science. Boca Raton, Interpharm/CRC.
- Dahl, T. (2002). Ethylcellulose. Handbook of Pharmaceutical Excipients, 4th ed. R. Rowe, P. Shesky and P. Weller. London, Pharmaceutical Press: 237-241.
- Dashevsky, A., K. Kolter, et al. (2004). "Compression of Pellets Coated with Various Aqueous Polymer Dispersions." International Journal of Pharmaceutics **279**(1-2): 19-26.
- Dashevsky, A. and A. Mohamad (2006). "Development of Pulsatile Multiparticulate Drug Delivery System Coated with Aqueous Dispersion Aquacoat® ECD." International Journal of Pharmaceutics **318**: 124-131.
- Degussa (2007a). Drug Surface Calculations and Determinations In EUDRAGIT Application Guidelines 10th ed. Darmstadt, Degussa, Pharma Polymers, Rohm GmbH.
- Degussa (2007b). Application Fields for Enteric Formulations. In Eudragit Application Guidelines 10th ed. Darmstadt, Degussa, Pharma Polymers, Rohm GmbH.
- Desai, P. (2006). Case Study: Approach for Filing with PAT. Real World Applications of PAT and QbD in Drug Process Development and Approval

- Workshop. American Association of Pharmaceutical Scientists, Crystal City, Virginia.
- Devay, A., K. Mayer, et al. (2006). "Investigation on Drug Dissolution and Particle Characteristics of Pellets Related to Manufacturing Process Variables of High-Shear Granulation." Journal of Biochemical and Biophysical Methods **69**(1-2): 197-205.
- Dhalinder (1993). Drug Preparation. United States Patent Office. September 21. **5,246,714**.
- Dias (2007). Application of an Aqueous Ethylcellulose Dispersion in Multiple-Unit Pellet System. Controlled Release Society. Reprinted by Colorcon, Long Beach, California.
- Doelker, E., D. Massuelle, et al. (1995). "Morphological, Packing, Flow and Tableting Properties of New Avicel Types." Drug Development and Industrial Pharmacy **21**: 643-661.
- Dow. (2008). "Controlled Release Systems." Retrieved August 27, 2008, from http://www.dow.com/dowexcipients/applications/controlled_release.htm.
- Dukic-Ott, A., J. P. Remon, et al. (2007). "Immediate Release of Poorly Soluble Drugs from Starch-Based Pellets Prepared Via Extrusion/Spheronisation." European Journal of Pharmaceutics and Biopharmaceutics **67**(3): 715-724.
- Eilman, E. (2005). Reversing: Secrets of Reverse Engineering. Indianapolis, Wiley Publishing, Inc.
- Ennis, B. J. (2005). Theory of Granulation: An Engineering Perspective. Handbook of Pharmaceutical Granulation Technology. D. Parikh. Boca Raton, Taylor & Francis Group: 7-78.
- Ethex (2007). Metoprolol Succinate Package Insert. P5081-4 Revised 06/07. St. Louis, MO: Retrieved May 10, 2008 from http://www.ethex.com/pages/pdf/58177036811_PIS.pdf.
- Faure, A., P. York, et al. (2001). "Process Control and Scale-Up of Pharmaceutical Wet Granulation Processes: A Review." European Journal of Pharmaceutics and Biopharmaceutics **52**(3): 269-277.
- FDA (1995). Federal Register. **60**: 61638-61642.
- FDA (1997a). Guidance For Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations. U.S. Department of Health and Human Services, Retrieved March 22, 2008 from <http://www.fda.gov/cder/Guidance/1306fnl.pdf>.
- FDA (1997b). Guidance for Industry: SUPAC-MR: Modified Release Solid Oral Dosage Forms. U.S. Department of Health and Human Services, Retrieved April 10, 2008 from <http://www.fda.gov/cder/Guidance/1214fnl.pdf>.
- FDA (1998). Guidance for Industry: Variations in Drug Products That May Be Included in a Single ANDA. Office of Generic Drugs. Center for Drug Evaluation and Research, U.S. Department of Health and Human Services.
- FDA (2003a). Guidance for Industry: 180-Day Exclusivity When Multiple ANDAs Are Submitted on the Same Day. Office of Generic Drugs. Center for Drug Evaluation and Research, U.S. Department of Health and Human Services.

- FDA (2004a). Innovation and Improvement in Pharmaceutical Manufacturing. Pharmaceutical cGMP's for the 21st Century. The PAT Team and Manufacturing Science Working Group Report: A Summary of Learning, Contributions, and Proposed Next Steps for Moving Towards the "Desired State" of Pharmaceutical Manufacturing. CDER, Retrieved May 15, 2008 from <http://www.fda.gov/Cder/gmp/gmp2004/manufSciWP.pdf>.
- FDA (2004b). Pharmaceutical cGMPs for the 21st Century- A Risk-Based Approach. CDER, Retrieved August 20, 2007 from http://www.fda.gov/Cder/gmp/gmp2004/GMP_finalreport2004.htm.
- FDA (2006a). Guidance for Industry: Q8 Pharmaceutical Development, U.S. Department of Health and Human Services, Retrieved August 9, 2008 from <http://www.fda.gov/Cber/gdlns/ichq8pharm.pdf>.
- FDA (2006b). Guidance for Industry: Q9 Quality Risk Management, Center for Drug Evaluation and Research, U.S. Department of Health and Human Services, Retrieved August 9, 2008 from <http://www.fda.gov/ohrms/dockets/98fr/05d-0288-gdl0002.pdf>.
- FDA (2006c). Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations: Retrieved September 2, 2007 from <http://www.fda.gov/Cber/gdlns/qualsystem.pdf>.
- FDA (2007a). Guidance for Industry: Bioequivalence Recommendations for Specific Products. Center for Drug Evaluation and Research. Office of Generic Drugs, U.S Department of Health and Human Services.
- FDA (2007b). Approved Drug Products with Therapeutic Equivalence Evaluations. Center for Drug Evaluation and Research, U.S. Department of Health and Human Services: 1069.
- FDA (2008a). Metoprolol Succinate. Electronic Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations Retrieved October 12, 2008 from <http://www.fda.gov/cder/ob/default.htm>.
- FDA (2008b). Propranolol HCl. Electronic Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, Retrieved October 12, 2008 from <http://www.fda.gov/cder/ob/default.htm>.
- FDA (2008c). Guidance for Industry: Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Product Terminally Sterilized by Moist Heat Processes. U.S. Department of Health and Human Services, Retrieved October 28, 2008 from <http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0391-gdl.pdf>.
- FMC-BioPolymer. (2006). "Aquacoat ECD Aqueous Coating." Retrieved September 4, 2008, from <http://www.fmcbiopolymer.com/Portals/bio/content/Docs/AquaCoat%20ECD%207706%20.pdf>
- FMC-BioPolymer. (2008). "Avicel for Solid Dosage Forms." Retrieved October 27, 2008, from <http://www.fmcbiopolymer.com/Products/Avicelforsoliddoseforms/tabid/2920/Default.aspx>.

- Gao, J. Z. H., A. Jain, et al. (2002). "Fluid Bed Granulation of a Poorly Water Soluble, Low Density, Micronized Drug: Comparison with High Shear Granulation." International Journal of Pharmaceutics **237**: 1-14.
- Gardiner, W. and G. Gettinby (1998). Response Surface Methods. Experimental Design Techniques in Statistical Practice. West Sussex, Horwood Publishing Limited: 322-358.
- Gardiner, W. and G. Gettinby (1998). Two-level Factorial Designs. Experimental Design Techniques in Statistical Practice. West Sussex, Horwood Publishing Limited: 207-233.
- Gardiner, W. and G. Gettinby (1998c). Introduction. Experimental Design Techniques in Statistical Practice. West Sussex, Horwood Publishing Limited: 1-18.
- Ghebre-Sellassie, I. (1989). Mechanism of Pellet Formation and Growth. Pharmaceutical Pelltization Technology. I. Ghebre-Sellassie. New York, Marcel Dekker: 123-143.
- Glaser, V. (2006). "Slow Adoption of PAT for Bioprocessing: Challenges Emanate from Technology Development and Design of Process." Genetic Engineering News: 38-40.
- Gokhale, R., Y. Sun, et al. (2005). High-Shear Granulation. Handbook of Pharmaceutical Granulation Technology. D. Parikh. Boca Raton, Taylor & Francis Group: 191-228.
- Guley, P., R. DeMeals, et al. (1981). Sustained Release Pharmaceutical Compositions. U. S. Patent. **4,248,858**.
- Guley, P. and J. Farina (1992). Preparation of Propranolol Hydrochloride Macrocrystals. U. S. Patent. **5,095,151**.
- Gunder, W., B. H. Lippold, et al. (1995). "Release of Drugs from Ethyl Cellulose Microcapsules (Diffusion Pellets) with Pore Formers and Pore Fusion." European Journal of Pharmaceutical Sciences **3**(4): 203-214.
- Hamed, E., D. Moe, et al. (2005). Binders and Solvents. Handbook of Pharmaceutical Granulation Technology. D. Parikh. Boca Raton: 109-128.
- Hanson, W. (1991). Theoretical Concepts. Handbook of Dissolution Testing. Eugene, Aster Publishing Corporation 13-26.
- Harwood, R. (2002). Hypromellose. Handbook of Pharmaceutical Excipients, 4th ed. R. Rowe, P. Shesky and P. Weller. London, Pharmaceutical Press: 297-300.
- Hicks, D. and H. Freese (1989). Extrusion and Spheronizing Equipment. Pharmaceutical Pelltization Technology. I. Ghebre-Sellassie. New York, Marcel Dekker: 71-100.
- Hoag, S., D. Vivek, et al. (2008). Compression and Compaction. Pharmaceutical Dosage Forms: Tablets. L. Augsburger and S. Hoag. New York, Informa Healthcare. **Volume 1: Unit Operations and Mechanical Properties**: 555-630.
- Holovac, M. A. (2004). "A Balancing Act in the United States Drug Industry: Pioneer and Generic Drugs, the Orange Book, Marketing Protection and the US Consumer." World Patent Information **26**: 123-129.

- Hussain, A. (2002). The Subcommittee on Process Analytical Technologies (PAT): Overview and Objectives. FDA's Advisory Committee for Pharmaceutical Science, Gaithersburg, Maryland.
- ICH (2003). Stability Testing of New Drug Substances and Products Q1A (R2), International Conference On Harmonisation, International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.
- ICH (2005). Impurities: Guideline for Residual Solvents Q3C (R3), Retrieved July 29, 2008 from <http://www.ich.org/LOB/media/MEDIA423.pdf>.
- ICH (2007). Draft Consensus Guideline: Pharmaceutical Development Annex to Q8, International Conference On Harmonisation Retrieved July 23, 2008 from <http://www.ich.org/LOB/media/MEDIA4349.pdf>.
- Johansson, B. and G. Alderborn (2001). "The effect of shape and porosity on the compression behavior and tablet forming ability of granular materials formed from microcrystalline cellulose." European Journal of Pharmaceutics and Biopharmaceutics **52**(3): 347-357.
- Joneckis, C. (2006). Implementing Q8, Q9, Q10. Parenteral Drug Association/Food and Drug Administration Joint Regulatory Conference, Washington, D.C.
- Jones, D. (1989). Solution and Suspension Layering. Pharmaceutical Pelletization Technology. I. Ghebre-Sellassie. New York, Marcel Dekker. **37**: 145-164.
- Jonsson (1990). Pharmaceutical Preparation. U. S. Patent. **4,957,745**.
- Kanfer, I., R. Walker, et al. (2004). Experimental Formulation Development. Generic Drug Product Development: Solid Dosage Forms. L. K. Shargel, I. New York, Marcel Dekker: 53-93.
- Keleb, E. I., A. Vermeire, et al. (2004a). "Twin Screw Granulation as a Simple and Efficient Tool for Continuous Wet Granulation." International Journal of Pharmaceutics **273**: 183-194.
- Keleb, E. I., A. Vermeire, et al. (2004b). "Single-Step Granulation/Tabletting of Different Grades of Lactose: A Comparison with High Shear Granulation and Compression." European Journal of Pharmaceutics and Biopharmaceutics **58**: 77-82.
- Kim, C. (2004). Polymer Science. Advanced Pharmaceutics: Physicochemical Principles. Boca Raton, CRC Press: 409-490.
- Kottke, M. and E. Rudnic (2002). Tablet Dosage Forms. Modern Pharmaceutics. G. R. Banker, C.T. New York, Marcel Dekker: 287-332.
- Leuenberger, H., M. Puchkov, et al. (2008). "Manufacturing Pharmaceutical Granules: Is the Granulation End-Point a Myth?" Powder Technology **In Press, Corrected Proof, Available online April 16**: Retrieved July 15, 2008 from [http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TH9-4S98V0K-3&_user=657938&_coverDate=04%2F16%2F2008&_rdoc=204&_fmt=high&_orig=browse&_srch=doc-info\(%23toc%235277%239999%2399999999%23999999%23FLA%23display%23Articles\)&_cdi=5277&_sort=d&_docanchor=&view=c&_ct=208&_acct=C000035679&_version=1&_urlVersion=0&_userid=657938&md5=3446db06426d25a1210a97151db1df13](http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TH9-4S98V0K-3&_user=657938&_coverDate=04%2F16%2F2008&_rdoc=204&_fmt=high&_orig=browse&_srch=doc-info(%23toc%235277%239999%2399999999%23999999%23FLA%23display%23Articles)&_cdi=5277&_sort=d&_docanchor=&view=c&_ct=208&_acct=C000035679&_version=1&_urlVersion=0&_userid=657938&md5=3446db06426d25a1210a97151db1df13).

- Lippold, B. C., W. Gunder, et al. (1999). "Drug Release from Diffusion Pellets Coated with the Aqueous Ethyl Cellulose Dispersion Aquacoat(R) ECD-30 and 20% Dibutyl Sebecate as Plasticizer: Partition Mechanism and Pore Diffusion." European Journal of Pharmaceutics and Biopharmaceutics **47**(1): 27-32.
- Lipsanen, T., O. Antikainen, et al. (2007). "Novel Description of a Design Space for Fluidised Bed Granulation." International Journal of Pharmaceutics **345**: 101-107.
- Low, D. (2006). Process Analytical Technology-from the perspective of a Biologicals Manufacturer. Real World Applications of PAT and QbD in Drug Process Development and Approval Workshop. American Association of Pharmaceutical Scientists, Crystal City, Virginia.
- Lum, A. M., J. Huang, et al. (2004). "Reverse Engineering of Industrial Pharmaceutical-Producing Actinomycete Strains Using DNA Microarrays." Metabolic Engineering **6**: 186-196.
- Mathias, C., B. Dole, et al. (1984). A Bill To Amend The Patent Laws of the United States: Drug Price Competition and Patent Term Restoration Act of 1984. .
- McArthur, H. and D. Spalding (2004). Mechanical Properties and Testing. Engineering Material Science: Properties, Uses, Degradation, Remediation. West Sussex, Horwood: 100-128.
- McGinity, J. (1997). Preface. Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms. J. McGinity. New York, Marcel Dekker. **79**.
- Mehta, A. (1989). Evaluation and Characterization of Pellets. Pharmaceutical Pelltization Technology. I. Ghebre-Sellassie. New York, Marcel Dekker: 241-265.
- Mehta, K., G. Singh Rekhi, et al. (2005). Extrusion/Spheronization as a Granulation Technique. Handbook of Pharmaceutical Granulation Technology. D. Parikh. Boca Raton, Taylor & Francis Group: 333-363.
- Metha, A. and D. Jones (1985). "Coated pellets under the microscope." Pharmaceutical Technology **9**: 52-60.
- Moreton, C. (2008). Disintegrants in Tableting. Pharmaceutical Dosage Forms: Tablets. L. Augsburger and S. Hoag. New York, Informa Healthcare. **Unit Operations and Mechanical Properties**: 217-249.
- Mylan (2007). Propranolol Hydrochloride Capsules, Extended Release Product Label. Rev. 05/07.
- Nagai, T., S. Obara, et al. (1997). Application HPMC and HPMCAS to Aqueous Film Coating of Pharmaceutical Dosage Forms. Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms. J. McGinity. New York, Marcel Dekker: 177-225.
- Nakahara, N. (1966). Method and Apparatus for Making Spherical Granules. U. S. P. Office. **3,277,520**.
- Niazi, S. (2004). Handbook of Pharmaceutical Manufacturing Formulations: Compressed Solid Products. Chicago, CRC Press.

- NiroPharma (2003). Aeromatic-Fielder High Sheer Processor, NPS-Aeromatic-HSG1001-GB / 2:
http://www.niroinc.com/html/pharma/phpdfs/high_shear_granulator.pdf.
- NIST/SEMATECH (2006a). Process Modeling. e-Handbook of Statistical Methods, Retrieved April 22, 2008 from
<http://www.itl.nist.gov/div898/handbook/pmd/section4/pmd44.htm>.
- NIST/SEMATECH (2006b). Tukey's Method. e-Handbook of Statistical Methods, Retrieved April 22, 2008 from
<http://www.itl.nist.gov/div898/handbook/prc/section4/prc471.htm>.
- Nuwaysir, L. M., C. L. Wilkins, et al. (1990). "Analysis of Copolymers by Laser Desorption Fourier Transform Mass Spectrometry." Journal of the American Society for Mass Spectrometry **1**: 66-71.
- O'Connor, R. and J. Schwartz (1989). Extrusion and Spheronization Technology. Pharmaceutical Pelltization Technology. I. Ghebre-Sellassie. New York, Marcel Dekker: 187-216.
- O'Hara, T., A. Dunne, et al. (1998). "A Review of Methods Used to Compare Dissolution Profile Data." Pharmaceutical Science & Technology Today **1**: 214-223.
- Obara, S. and J. W. McGinity (1995). "Influence of Processing Variables on the Properties of Free Films Prepared from Aqueous Polymeric Dispersions by a Spray Technique." International Journal of Pharmaceutics **126**(1-2): 1-10.
- Olsen, K. (1989). Fluid Bed Equipment. Pharmaceutical Pelltization Technology. I. Ghebre-Sellassie. New York, Marcel Dekker: 39-69.
- Ong (2006a). "Effect of Hypromellose as a Pore-Former in Aqueous Ethylcellulose Dispersion: Characterization of Dispersion Properties." Colorcon.
- Ong (2006b). "Hypromellose as a Former in Aqueous Ethylcellulose Dispersion: Stability and Film Properties." Colorcon.
- Osterwald, H. (1984). "Properties of Film-Formers and Their Use in Aqueous Systems." Pharmaceutical Research **2**(1): 14-18.
- Oulahna, D., F. Cordier, et al. (2003). "Wet Granulation: The Effect of Shear on Granule Properties." Powder Technology **130**: 238-246.
- Par (2007). Propranolol Extended Release Capsule Package Insert. (Rev 01/07) S282-01-1-02, <http://www.fda.gov/cder/foi/label/2007/078065lbl.pdf>.
- Parikh, D. (1991). "Airflow in Batch Fluid-Bed Processing." Pharmaceutical Technology **15**: 100-110.
- Parikh, D. (1992). "Understanding batch fluid bed drying." Powder and Bulk Engineering **4**: 1-5.
- Parikh, D. (2005). Introduction. Handbook of Pharmaceutical Granulation Technology. D. Parikh. Boca Raton, Taylor & Francis Group: 1-6.
- Percel, P., K. Vishnupad, et al. (2002). Timed Sustained Release Systems for Propranolol. U. S. Patent. **6,500,454**.
- Petereit, H.-U. and W. Weisbrod (1999). "Formulation and Process Considerations Affecting the Stability of Solid Dosage Forms Formulated with Methacrylate Copolymers." European Journal of Pharmaceutics and Biopharmaceutics **47**: 15-25.

- Pinto, J. F., M. H. Lameiro, et al. (2001). "Investigation on the Co-Extrudability and Spheronization Properties of Wet Masses." International Journal of Pharmaceutics **227**: 71-80.
- Porter, S. and C. Bruno (1990). Coating of Pharmaceutical Solid-Dosage Forms. New York, New York, Informa Healthcare.
- Ragnarsson, G., A. Sandberg, et al. (1987). "Development of a New Controlled Release Metoprolol Product." Drug Development and Industrial Pharmacy **13**: 1495-1509.
- Rajniak, P., C. Mancinelli, et al. (2007). "Experimental Study of Wet Granulation in Fluidized Bed: Impact of the Binder Properties on the Granule Morphology." International Journal of Pharmaceutics **334**: 92-102.
- Ravishankar, H., P. Patil, et al. (2006). "Modulated Release Metoprolol Succinate Formulation Based on Ionic Interactions: In Vivo Proof of Concept." Journal of Controlled Release **111**: 65-72.
- Reitz, C. and P. Kleinebudde (2008). "Spheronization of Solid Lipid Extrudates." Powder Technology **In Press, Corrected Proof, Available online April 16**: Retrieved October 12, 2008 from http://0-www.sciencedirect.com/heli. uri.edu /science? ob=MImg&_imagekey=B6TH9-4S98V0K-8-1C& cdi=5277&_user=657938&_orig=search&_coverDate=04%2F16%2F2008& _sk=999999999&view=c&wchp=dGLzVtz-zSkWb&md5=21ce4d5 1f2f870f9567ca05213f89581&ie=/sdarticle.pdf.
- Rowe, R., P. Shesky, et al., Eds. (2002). Handbook of Pharmaceutical Excipients, 4th ed. London, Pharmaceutical Press.
- Samuelson, P. and S. Scotchmer (2002). "The Law and Economics of Reverse Engineering." The Yale Law Journal **111**: 1575-1663.
- Sandberg, A., G. Rangarsson, et al. (1988). "Design of a New Multiple-Unit Controlled Release Formulation of Metoprolol - Metoprolol CR." European Journal of Clinical Pharmacology **33**: S3-S7.
- Shah, R. B., A. S. Zidan, et al. (2007). "Quality by Design: Characterization of Self-Nano-Emulsified Drug Delivery Systems (SNEDDs) Using Ultrasonic Resonator Technology." International Journal of Pharmaceutics **341**: 189-194.
- Shah, V. and R. Williams (1994). In Vivo and In Vitro Correlations: Scientific and Regulatory Perspectives. Generic and Bioequivalence. A. Jackson. Boca Raton, CRC Press: 101-111.
- Siepmann, F., S. Muschert, et al. (2008). "How to Improve the Storage Stability of Aqueous Polymeric Film Coatings." Journal of Controlled Release **126**(1): 26-33.
- Siepmann, F., J. Siepmann, et al. (2005). "Blends of Aqueous Polymer Dispersions Used for Pellet Coating: Importance of the Particle Size." Journal of Controlled Release **105**(3): 226-239.
- Slater, C. S. and M. Savelski (2007). "A Method to Characterize the Greenness of Solvents used in Pharmaceutical Manufacture." Journal of Environmental Science and Health, Part A **42**: 1595 - 1605.

- Sriamornsak, P., J. Nunthanid, et al. (2007). "Alginate-Based Pellets Prepared by Extrusion/Spheronization: A Preliminary Study on the Effect of Additive in Granulating Liquid." European Journal of Pharmaceutics and Biopharmaceutics **67**: 227-235.
- Sriwongjanya, M., S. Yuk, et al. (2008). Formulation and Process for Drug Loaded Cores. U. S. Patent. **7314640**.
- Standard and Poor's (January 14, 2008). Stock Report: Teva Pharmaceutical Industries Ltd. T. M. H. Company.
- Swarbick, J. (2007). Informa Healthcare. Encyclopedia of Pharmaceutical Technology. **6**.
- Tarvainen, M., R. Sutinen, et al. (2003). "Enhanced film-forming properties for ethyl cellulose and starch acetate using n-alkenyl succinic anhydrides as novel plasticizers." European Journal of Pharmaceutical Sciences **19**(5): 363-371.
- Tomer, G. and J. M. Newton (1999). "Water movement evaluation during extrusion of wet powder masses by collecting extrudate fractions." International Journal of Pharmaceutics **182**(1): 71-77.
- Torrado, J. and L. Augsburger (2008). Tableting of Multiparticulate Modified Release Systems. Pharmaceutical Dosage Forms: Tablets. L. Augsburger and S. Hoag. New York, Informa Healthcare. **Volume 2: Rational Design and Formulation**: 509-532.
- Troy, D. (2005). Propranolol HCl. Remington: The Science and Practice of Pharmacy. Philadelphia, Lippincott, Williams, & Wilkins: 1403.
- Tyler, S. (2006). Use of mass spectrometry, TGA, and DSC analysis for design of an API drying process and on-line monitoring for residual solvents removal. Real World Applications of PAT and QbD in Drug Process Development and Approval Workshop. American Association of Pharmaceutical Scientists, Crystal City, Virginia.
- USP (2007a). <711> Dissolution. USP30-NF25. Rockville, United States Pharmacopeial Convention: 277.
- USP (2007b). Propranolol Hydrochloride Extended-Release Capsule Monograph. United States Pharmacopeial Convention. USP30-NF25. Rockville, M.D.: 3058.
- USP (2007c). Metoprolol Succinate Extended Release Tablets Monograph. United States Pharmacopeial Convention. USP30-NF25 Rockville, M.D.: 2648.
- USP (2007d). <1216> Tablet Friability. USP30-NF25. Rockville, United States Pharmacopeial Convention: 1735.
- USPTO (2006). Manual of Patent Examiner Procedure, Eighth Ed. 5th Rev. Chapter 1500 Design Patents. United States Department of Commerce.
- Vervaet, C., L. Baert, et al. (1995). "Extrusion-spheronisation A literature review." International Journal of Pharmaceutics **116**(2): 131-146.
- Vervaet, C., L. Baert, et al. (1995). "Extrusion-Spheronisation: A Literature Review." International Journal of Pharmaceutics **116**: 131-146.
- Watson-Pharmaceuticals (2007). Press Release: Watson Enters Into Agreement to Permit Sandoz to Launch Metoprolol Succinate Extended-Release 50 mg Tablets; Relinquishes 180-Day Market Exclusivity. Corporate Website -

- Investor Relations, Retrieved July 10, 2008 from http://ir.watson.com/phoenix.zhtml?c=65778&p=irol-newsArticle_Print&ID=1004641&highlight=.
- Wechsler, J. (2007). "Generic Drugs For Everyone." Pharmaceutical Technology **31**: 4.
- Welch, J. (2003). What is Six Sigma? Six Sigma Continual Improvement for Business. W. Truscott. Burlington, Butterworth-Heinemann: 1-14.
- Weller, P. (2003). Cellulose, Microcrystalline Handbook of Pharmaceutical Excipients, 4th ed. R. Rowe, P. Shesky and P. Weller. London, Pharmaceutical Press: 108-111.
- Wheatley, T. and C. Steuernagel (1997). Latex Emulsions for Controlled Drug Delivery. Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms. J. McGinity. New York, Marcel Dekker: 1-54.
- White, G. and A. Sondhi (2007). Analyzing Financial Statements. Accountant's Handbook Volume 1: Financial Accounting and General Topics. D. R. Carmichael. Hoboken, John Wiley and Sons: 1-46.
- With, G. (2006). Constitutive Behavior. Structure, Deformation, and Integrity of Materials. Weinheim, Wiley-VCH. **Volume I: Fundamentals and Elasticity**: 23-40.
- With, G. (2006). Perspective and Outlook. Structure, Deformation, and Integrity of Materials. Weinheim, Wiley-VCH. **Volume II Plasticity, Visco-Elasticity, and Fracture**: 23-40.
- Wong, D. and R. Bodmeier (1996). "Flocculation of an Aqueous Colloidal Ethyl Cellulose Dispersion (Aquacoat) with a Water-Soluble Polymer, Hydroxypropyl Methylcellulose." European Journal of Biopharmaceutics **42**: 12-15.
- Wu, J. and M. Hamada (2000). Response Surface Methodology. Experiments: Planning, Analysis, and Parameter Design Optimization. V. Barnett. New York, Wiley Interscience: 387-435.
- Wyeth (2007). Inderal LA Capsules Package Insert. W10478C009 Rev 11/07, Retrieved on September 22, 2008 from <http://www.wyeth.com/content/ShowLabeling.asp?id=107>.
- Zagursky, R. (2003). "Vaccine Discovery Research by Reverse Engineering." Drug Discovery Today **8**: 972-973.
- Zidan, A. S., O. A. Sammour, et al. (2007). "Quality By Design: Understanding the Formulation Variables of a Cyclosporine A Self-Nanoemulsified Drug Delivery Systems by Box-Behnken Design and Desirability Function." International Journal of Pharmaceutics **332**: 55-63.

APPENDIX 1

Inderal LA 160mg Capsule Dissolution Profiles

	% Propranolol Released Over Time (hrs)						
Batch #	1.5	3.5	5.5	7.5	10	22	24
Inderal B08468	14.4	38.9	55.0	63.7	75.1	90.6	93.2
Inderal B08468	13.4	35.7	50.5	60.8	70.3	85.4	86.6
Inderal B08468	14.0	33.2	47.4	57.7	68.0	84.4	85.6
Inderal B08468	13.5	32.6	46.9	57.1	67.5	83.8	85.1
Inderal B08468	14.1	36.7	51.8	62.6	74.1	89.5	89.6
Inderal B08468	15.7	37.7	52.1	63.1	72.5	88.1	89.2
Mean	14.2	35.8	50.6	60.8	71.3	87.0	88.2
Std Dev	0.8	2.3	2.8	2.6	2.9	2.6	2.8

APPENDIX 2

Propranolol IR ANOVA

Propranolol IR ANOVA Sieves #14-Pan

Factor	Type	Levels	Values
H2O Amount Coded	Fixed	3	High, Low, Medium
H2O Addition Coded	Fixed	2	High, Low
Kneading Time Coded	Fixed	2	High, Low
Spheronization RPM Coded	Fixed	2	High, Low
Spheronization Time Coded	Fixed	2	High, Low

Analysis of Variance for 14, using Adjusted SS for Tests

Source	DF	Seq. SS	Adj. SS	Adj. MS	F	P
H2O Amount Coded	2	27.50	39.78	19.89	0.75	0.506
H2O Addition Coded	1	0.93	37.84	37.84	1.43	0.271
Kneading Time Coded	1	29.32	2.56	2.56	0.10	0.765
Spheronization RPM Coded	1	19.13	19.87	19.87	0.75	0.415
Spheronization Time Coded	1	77.73	77.73	77.73	2.94	0.130
Error	7	185.33	185.33	185.33	26.48	
Total	13	339.94				

S = 5.14539 R-Sq = 45.48% R-Sq (Adj.) = 0.00%

Analysis of Variance for 16, using Adjusted SS for Tests

Source	DF	Seq. SS	Adj. SS	Adj. MS	F	P
H2O Amount Coded	2	156.54	9.50	4.75	0.08	0.924
H2O Addition Coded	1	18.26	90.65	90.65	1.52	0.258
Kneading Time Coded	1	151.24	3.13	3.13	0.05	0.826
Spheronization RPM Coded	1	58.45	59.36	59.36	0.99	0.352
Spheronization Time Coded	1	38.88	38.88	38.88	0.65	0.446
Error	7	417.74	417.74	59.68		
Total	13	841.11				

S = 7.72510 R-Sq = 50.33% R-Sq (Adj.) = 7.76%

Analysis of Variance for 18, using Adjusted SS for Tests

Source	DF	Seq. SS	Adj. SS	Adj. MS	F	P
H2O Amount Coded	2	4463.83	1188.96	594.48	6.76	0.023
H2O Addition Coded	1	37.54	8.53	8.53	0.10	0.765
Kneading Time Coded	1	2.28	105.51	105.51	1.20	0.310
Spheronization RPM Coded	1	77.77	79.80	79.80	0.91	0.373
Spheronization Time Coded	1	145.45	145.45	145.45	1.65	0.239
Error	7	615.88	615.88	87.98		
Total	13	5342.75				

S = 9.37995 R-Sq = 88.47% R-Sq (Adj.) = 78.59%

Analysis of Variance for 20, using Adjusted SS for Tests

Source	DF	Seq. SS	Adj. SS	Adj. MS	F	P
H2O Amount Coded	2	831.7	106.0	53.0	0.28	0.762
H2O Addition Coded	1	0.6	221.1	221.1	1.18	0.313
Kneading Time Coded	1	183.3	53.5	53.5	0.29	0.610
Spheronization RPM Coded	1	244.7	251.5	251.5	1.34	0.284
Spheronization Time Coded	1	519.1	519.1	519.1	2.77	0.140
Error	7	1310.5	1310.5	187.2		
Total	13	3089.8				

S = 13.6824 R-Sq = 57.59% R-Sq (Adj.) = 21.23%

Analysis of Variance for 25, using Adjusted SS for Tests

Source	DF	Seq. SS	Adj. SS	Adj. MS	F	P
H2O Amount Coded	2	414.464	85.009	42.505	7.25	0.020
H2O Addition Coded	1	0.725	11.353	11.353	1.94	0.207
Kneading Time Coded	1	5.465	1.540	1.540	0.26	0.624
Spheronization RPM Coded	1	7.181	7.381	7.381	1.26	0.299
Spheronization Time Coded	1	15.271	15.271	15.271	2.61	0.150
Error	7	41.020	41.020	5.860		
Total	13	484.127				

S = 2.42074 R-Sq = 91.53% R-Sq (Adj.) = 84.26%

Analysis of Variance for Pan, using Adjusted SS for Tests

Source	DF	Seq. SS	Adj. SS	Adj. MS	F	P
H2O Amount Coded	2	1473.02	575.35	287.68	3.26	0.100
H2O Addition Coded	1	1.08	0.12	0.12	0.00	0.971
Kneading Time Coded	1	0.12	2.55	2.55	0.03	0.870
Spheronization RPM Coded	1	6.72	6.74	6.74	0.08	0.790
Spheronization Time Coded	1	0.21	0.21	0.21	0.00	0.962
Error	7	617.62	617.62	88.23		
Total	13	2098.77				

S = 9.39319 R-Sq = 70.57% R-Sq (Adj.) = 45.3%

Analysis of Variance for Target % Yield, using Adjusted SS for Tests

Source	DF	Seq SS	Adj SS	Adj MS	F	P
H2O Amount Coded	2	1752.7	1684.2	842.1	3.89	0.073
H2O Addition Coded	1	28.8	142.8	142.8	0.66	0.443
Kneading Time Coded	1	226.4	8.8	8.8	0.04	0.846
Spheronization RPM Coded	1	46.6	48.0	48.0	0.22	0.652
Spheronization Time Coded	1	115.0	115.0	115.0	0.53	0.490
Error	7	1515.6	1515.6	216.5		
Total	13	3685.0				

S = 14.7145 R-Sq = 58.87% R-Sq (adj) = 23.62%

APPENDIX 3

Metoprolol Succinate IR Bead Design of Experiments Results

	Process Parameters				% Retained Sieve #									Sphericity			
Trial	H2O Amt (g)	Kneading Time (Sec)	Spheronization Time (Min)	Random Order	20	25	30	35	45	60	Pan	Target %	LOD %	Observed Shape	Mean Sphericity	Std. Dev. Sphericity	Sphericity RSD (%)
RB005148	175	30	5	1	1.87	6.5	56	19.98	14.65	1	0	90.63	1.6	Dumbbells/ Spheres	1.26	0.22	17.11
RB005149	175	30	8	2	1.31	7.7	58.75	21.24	10.93	0.06	0	90.92	1.6	Mostly Spherical*/ Few Dumbbells	1.34	0.19	14.2
RB014003	165	15	5	3	1.6	5.22	52.76	21.48	16.5	2.44	0	90.74	1.8	Rods/ Dumbbells	1.39	0.24	17.3
RB014004	165	30	5	4	0.51	3.93	56.07	20.42	16.04	3.03	0	92.53	1.3	Dumbbells> Rods> Spheres	1.45	0.21	14.31
RB014005	165	30	8	5	0.26	6.04	54.75	19.42	17.05	2.44	0	91.22	1.4	Dumbbells/ Rods	1.35	0.24	17.43
RB005150	175	15	5	6	9.71	10.4	55.32	18.35	6.16	0.06	0	79.83	1.5	Rounder Rods/Spheres	1.28	0.27	21.42
RB005151	175	15	8	7	1.12	8.57	54.06	21.94	13.99	0.32	0	89.99	1.8	Mostly* Spherical	1.23	0.15	12.55
RB014006	165	15	8	8	0.5	6.76	54.53	20.75	16.09	1.33	0.03	91.37	1.5	Dumbbells/ Spheres	1.26	0.18	14.14

Metoprolol IR Bead Exploratory Batches Results

Processing Parameters						% Retained Sieve #										Sphericity				
Trial	H2O Amt (g)	H2O Addition g/min batch	Kneading Time (min)	Spheronizer RPM (Avg)	Spheronizer Time (min)	Final Prod. Temp °C	LOD (%)	20	25	30	35	45	60	Pan	Target %	Notes	Observed Shape	Mean Sphericity	Stand. Dev.	RSD (%)
RB005077	153	50	2	680/550	2.5	45.2	1.2	16	21	47.7	12.4	3.3	0	0	63.36	300g Reshaped/ Respheronized	Rods/dumbbells	1.36	0.28	20.46
RB005081	200	80	1	300/628	1 / 7	51.6	1.2	3.01	5.2	60.8	20.5	10.4	0.1	0	91.77	Reextruded Respheronized	More dumbbells	1.31	0.28	25.8
RB005107	180	90	1	680	5	51.3	1.3	5.09	8.4	58.6	17.6	10.3	0.1	0	86.47	Straight run	More Rods/Some dumbbells	1.35	0.29	21.58
RB005108	190	95	2	800	4	51.6	1.3	4.14	42	42.4	9.12	2.05	0	0	53.53	Straight run	Too big	1.39	0.3	21.74
RB005109	170	85	1	600	2	51.1	1	0.54	1.5	66	16.2	12.1	3.6	0.1	94.26	Straight run	Rods formed	1.76	0.4	22.68
RB005119	180	180	0	500/767	0/6	50.5	1.9	4.62	22	52.8	15	6	0	0	73.81	Fast addition-Reextruded Respheronized then good shape	Round/few dumbbells	1.18	0.23	19.04
RB005120	140	120	40 sec	800	7	50.2	1.6	0.38	10	56	15.5	11.2	4.9	1.9	82.7	Fast Addition-Straight Batch-Dry side	More Dumbbells than Rods	1.52	0.28	18.48
RB005122	150	150	15 Sec	800	5	50	1.4	0.19	2.3	61	16.6	12.8	5.5	1.6	90.4	Fast Addition-Straight Batch	Dumbbell shaped	1.58	0.33	20.67
RB005123	160	160	30 sec	800	9	48.6	1.7	0.34	8.2	56.4	15.5	13.9	5.3	0.3	85.78	Fast Addition-Straight Batch	Dumbbells	1.32	0.2	15.03
RB005124	170	80 for 1.5 min, 200 for 15 sec	15 sec	772	8	48.2	1.6	0.27	6.2	56	19.8	16.7	1	0.1	92.41	Slow, then fast addition	Good Spheres	1.2	0.15	12.16
RB005128	340	160 for 1.5 min, 400 for 15 sec	15 sec	772	8	50	2.3	0.67	13	51.5	21.7	12.9	0.1	0	86.15	800g- Slow water, then quick	Spheres	1.16	0.15	13.03

Metoprolol Succinate IR Bead Design of Experiments Confirmation Results

	% Retained Sieve #											
Trial	20	25	30	35	45	60	Pan	Target %	LOD @48c	Sphericity	Sphericity Std. Dev.	Sphericity RSD (%)
RB014013 (DOE Confirmation 400g)	0.3	5.46	52.73	23.47	16.87	1.17	0	93.07	1.6	1.28	0.2	15.45
RB014023 (1kg)	0.49	8.9	54.66	25.88	9.98	0.07	0.02	90.52	2.2	1.19	0.16	13.14
RB014024 (1kg)	0.39	8.18	58.32	23.95	9.1	0.04	0.01	91.37	2.2	1.12	0.11	10.13

APPENDIX 4

Full Model- Metoprolol Succinate Exploratory Batch

General Linear Model: Mean Spheric, Std. Dev. vs. H2O Coded, H2O Addition

Factor	Type	Levels	Values
H2O Coded	Fixed	2	High, Low
H2O Addition Coded	Fixed	2	High, Low
Kneading Time Coded	Fixed	2	High, Low
Spheronizer RPM Coded	Fixed	2	High, Low
Spheronizer Time Coded	Fixed	2	High, Low

Analysis of Variance for Target %, using Adjusted SS for Tests

Source	DF	Seq SS	Adj SS	Adj MS	F	P
H2O Coded	1	282.6	569.5	569.5	4.11	0.180
H2O Addition Coded	1	48.8	18.8	18.8	0.14	0.748
Kneading Time Coded	1	24.4	28.0	28.0	0.20	0.697
Spheronizer RPM Coded	1	483.5	502.9	502.9	3.63	0.197
Spheronizer Time Coded	1	111.5	111.5	111.5	0.81	0.464
Error	2	276.8	276.8	138.4		
Total	7	1227.6				

S = 11.7643 R-Sq = 77.45% R-Sq (adj) = 21.08%

Analysis of Variance for Mean Sphericity, using Adjusted SS for Tests

Source	DF	Seq SS	Adj SS	Adj MS	F	P
H2O Coded	1	0.112813	0.164413	0.164413	27.17	0.035
H2O Addition Coded	1	0.078204	0.002801	0.002801	0.46	0.566
Kneading Time Coded	1	0.001453	0.012043	0.012043	1.99	0.294
Spheronizer RPM Coded	1	0.000518	0.000226	0.000226	0.04	0.865
Spheronizer Time Coded	1	0.031297	0.031297	0.031297	5.17	0.151
Error	2	0.012103	0.012103	0.006052		
Total	7	0.236388				

S = 0.0777921 R-Sq = 94.88% R-Sq (adj) = 82.08%

Analysis of Variance for Std. Dev., using Adjusted SS for Tests

Source	DF	Seq SS	Adj SS	Adj MS	F	P
H2O Coded	1	0.001513	0.009016	0.009016	4.99	0.155
H2O Addition Coded	1	0.013538	0.000617	0.000617	0.34	0.618
Kneading Time Coded	1	0.000002	0.001417	0.001417	0.78	0.469
Spheronizer RPM Coded	1	0.000494	0.000350	0.000350	0.19	0.703
Spheronizer Time Coded	1	0.006528	0.006528	0.006528	3.61	0.198
Error	2	0.003613	0.003613	0.001806		
Total	7	0.125688				

S = 0.0425024 R-Sq = 85.94% R-Sq (adj) = 50.77%

Analysis of Variance for RSD (%), using Adjusted SS for Tests

Source	DF	Seq SS	Adj SS	Adj MS	F	P
H2O Coded	1	15.96	0.17	0.17	0.01	0.919
H2O Addition Coded	1	27.86	4.40	4.40	0.35	0.616
Kneading Time Coded	1	0.17	0.46	0.46	0.04	0.867
Spheronizer RPM Coded	1	2.21	2.18	2.18	0.17	0.719
Spheronizer Time Coded	1	0.04	0.04	0.04	0.00	0.962
Error	2	25.34	25.34	12.67		
Total	7	71.58				

S = 3.55963 R-Sq = 64.60% R-Sq (adj) = 0.00%

APPENDIX 5

Metoprolol Succinate IR DOE Results

Estimated Effects and Coefficients for 20 (coded units)

Term	Effect	Coef	SE Coef	T	P
Constant		2.110	0.8975	2.35	0.256
Water Level	2.785	1.393	0.8975	1.55	0.256
Kneading Time	-2.245	1.393	0.8975	1.55	0.364
Spheronization Time	-2.625	-1.313	0.8975	-1.46	0.382
Water Level * Kneading Time	-1.580	-0.790	0.8975	-0.88	0.541
Water Level* Spheronization Time	-1.950	-0.975	0.8975	-1.09	0.474
Kneading Time *Spheronization Time	2.220	1.110	0.8975	1.24	0.433

S = 2.53851 R-Sq = 90.56% R-Sq (adj) = 33.93%

Analysis of Variance for 20 (coded units)

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Main Effects	3	39.374	39.374	13.125	2.04	0.466
2-Way Interactions	3	22.455	22.455	7.485	1.16	0.578
Residual Error	1	6.444	6.444	6.444		
Total	7	68.272				

Estimated Effects and Coefficients for 25 (coded units)

Term	Effect	Coef	SE Coef	T	P
Constant		6.8900	0.3075	22.421	0.028
Water Level	2.8050	1.4025	0.3075	4.56	0.137
Kneading Time	-1.6950	-0.8475	0.3075	-2.76	0.222
Spheronization Time	0.7550	0.3775	0.3075	1.23	0.435
Water Level * Kneading Time	-0.6900	-0.3450	0.3075	-1.12	0.463
Water Level * Spheronization Time	-1.0700	-0.5350	0.3075	-1.74	0.332
Kneading Time * Spheronization Time	0.9000	0.4500	0.3075	1.46	0.382

S = 0.869741 R-Sq = 97.32% R-Sq (adj) = 81.25%

Analysis of Variance for 25 (coded units)

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Main Effects	3	22.6222	22.6222	7.5407	9.97	0.228
2-Way Interactions	3	4.8620	4.8620	1.6207	2.14	0.456
Residual Error	1	0.7564	0.7564	0.7564		
Total	7	28.2406				

Estimated Effects and Coefficients for 30 (coded units)

Term	Effect	Coef	SE Coef	T	P
Constant		55.2800	0.8875	62.29	0.010
Water Level	1.5050	0.7525	0.8875	0.85	0.552
Kneading Time	2.2250	1.1125	0.8875	1.25	0.429
Spheronization Time	1.4850	0.2425	0.8875	0.27	0.830
Water Level * Kneading Time	1.4600	0.2300	0.8875	0.26	0.839
Water Level * Spheronization Time	0.2600	0.1300	0.8875	0.15	0.907
Kneading Time * Spheronization Time	0.2300	0.1150	0.8875	0.13	0.918

S = 2.51023 R-Sq = 71.18% R-Sq (adj) = 0.00%

Analysis of Variance for 30 (coded units)

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Main Effects	3	14.9017	14.9017	4.9672	0.79	0.658
2-Way Interactions	3	0.6642	0.6642	0.2214	0.04	0.987
Residual Error	1	6.3013	6.3013	6.3013		
Total	7	21.8672				

Estimated Effects and Coefficients for 35 (coded units)

Term	Effect	Coef	SE Coef	T	P
Constant		20.4475	0.2575	79.41	0.008
Water Level	-0.1400	-0.0700	0.2575	-0.27	0.831
Kneading Time	-0.3650	-0.1825	0.2575	-0.71	0.607
Spheronization Time	0.7800	0.3900	0.2575	1.51	0.372
Water Level * Kneading Time	0.8300	0.4150	0.2575	1.61	0.354
Water Level * Spheronization Time	1.6450	0.8225	0.2575	3.19	0.193
Kneading Time * Spheronization Time	-0.6500	-0.3250	0.2575	-1.26	0.427

S = 0.728320 R-Sq = 94.52% R-Sq (adj) = 61.67%

Analysis of Variance for 35 (coded units)

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Main Effects	3	1.5224	1.5224	0.5075	0.96	0.618
2-Way Interactions	3	7.6348	7.6348	2.5449	4.80	0.321
Residual Error	1	0.5305	0.5305	0.5305		
Total	7	9.6877				

Estimated Effects and Coefficients for 45 (coded units)

Term	Effect	Coef	SE Coef	T	P
Constant		13.926	1.621	8.59	0.074
Water Level	-4.988	-2.494	1.621	-1.54	0.367
Kneading Time	1.483	0.741	1.621	0.46	0.727
Spheronization Time	1.178	0.589	1.621	0.36	0.778
Water Level * Kneading Time	1.233	0.616	1.621	0.38	0.769
Water Level * Spheronization Time	0.878	0.439	1.621	0.27	0.832
Kneading Time * Spheronization Time	-2.533	-1.2666	1.621	-0.78	0.578

S = 4.58559 R-Sq = 77.95% R-Sq (adj) = 0.00%

Analysis of Variance for 45 (coded units)

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Main Effects	3	56.92	56.92	18.973	0.90	0.630
2-Way Interactions	3	17.41	17.41	5.802	0.28	0.847
Residual Error	1	21.03	21.03	21.028		
Total	7	95.35				

Estimated Effects and Coefficients for 60 (coded units)

Term	Effect	Coef	SE Coef	T	P
Constant		1.3350	0.2150	6.21	0.102
Water Level	-1.9500	-0.9750	0.2150	-4.53	0.138
Kneading Time	0.5950	0.2975	0.2151	1.38	0.398
Spheronization Time	-0.5950	-0.2975	0.2150	-1.38	0.398
Water Level * Kneading Time	-0.2550	-0.1275	0.2150	-0.59	0.659
Water Level * Spheronization Time	0.2550	0.1275	0.2150	0.59	0.659
Kneading Time * Spheronization Time	-0.1700	-0.0850	0.2150	-0.40	0.760

S = 0.608112 R-Sq = 96.19% R-Sq (adj) = 73.34%

Analysis of Variance for 60 (coded units)

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Main Effects	3	9.0211	9.0211	3.0070	8.13	0.251
2-Way Interactions	3	0.3179	0.3179	0.1060	0.29	0.841
Residual Error	1	0.3698	0.3698	0.3698		
Total	7	9.7088				

Estimated Effects and Coefficients for Pan (coded units)

Term	Effect	Coef	SE Coef	T	P
Constant		0.003750	0.003750	1.00	0.500
Water Level	-0.007500	-0.003750	0.003750	-1.00	0.500
Kneading Time	-0.007500	-0.003750	0.003750	-1.00	0.500
Spheronization Time	0.007500	0.003750	0.003750	1.00	0.500
Water Level * Kneading Time	0.007500	0.003750	0.003750	1.00	0.500
Water Level * Spheronization Time	-0.007500	-0.003750	0.003750	-1.00	0.500
Kneading Time * Spheronization Time	-0.007500	-0.003750	0.003750	-1.00	0.500

S= 0.0106066 R-Sq = 85.71% R-Sq (adj) = 0.00%

Analysis of Variance for Pan (coded units)

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Main Effects	3	0.0003375	0.0003375	0.0001125	1.00	0.609
2-Way Interactions	3	0.0003375	0.0003375	0.0001125	1.00	0.609
Residual Error	1	0.0001125	0.0001125	0.0001125		
Total	7	0.0007875				

Estimated Effects and Coefficients for Target % (coded units)

Term	Effect	Coef	SE Coef	T	P
Constant		89.654	0.9912	90.45	0.007
Water Level	-3.623	-1.811	0.9912	-1.83	0.319
Kneading Time	3.343	1.671	0.9912	1.69	0.341
Spheronization Time	2.443	1.221	0.9912	1.23	0.434
Water Level * Kneading Time	2.522	1.261	0.9912	1.27	0.424
Water Level * Spheronization Time	2.782	1.391	0.9912	1.40	0.394
Kneading Time * Spheronization Time	-2.953	-1.476	0.9912	-1.49	0.376

S = 2.80368 R-Sq = 93.11% R-Sq (adj) = 51.74%

Analysis of Variance for Target % (coded units)

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Main Effects	3	60.521	60.521	20.174	2.57	0.423
2-Way Interactions	3	45.645	45.645	15.215	1.94	0.476
Residual Error	1	7.861	7.861	7.861		
Total	7	114.027				

Full Model

Estimated Effects and Coefficients for Mean Sphericity (coded units)

Term	Effect	Coef	SE Coef	T	P
Constant		1.32000	0.01250	105.60	0.006
Water Level	-0.08500	-0.04250	0.01250	-3.40	0.182
Kneading Time	0.0600	0.03000	0.01250	2.40	0.251
Spheronization Time	-0.0500	-0.02500	0.01250	-2.00	0.295
Water Level * Kneading Time	-0.01500	-0.00750	0.01250	-0.60	0.656
Water Level * Spheronization Time	0.06500	0.03250	0.01250	2.60	0.234
Kneading Time * Spheronization Time	0.04000	0.02000	0.01250	1.60	0.356

S = 0.0353553 R-Sq = 96.88% R-Sq (adj) = 78.12%

Analysis of Variance for Mean Sphericity (coded units)

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Main Effects	3	0.026650	0.026650	0.008883	7.11	0.267
2-Way Interactions	3	0.012100	0.012100	0.004033	3.23	0.383
Residual Error	1	0.001250	0.001250	0.001250		
Total	7	0.040000				

Estimated Effects and Coefficients for Standard (coded units)

Term	Effect	Coef	SE Coef	T	P
Constant		0.21215	0.000451	470.78	0.001
Water Level	-0.00695	-0.00348	0.000451	-7.72	0.082
Kneading Time	0.00047	0.00023	0.000451	0.52	0.696
Spheronization Time	-0.04488	-0.02244	0.000451	-49.80	0.013
Water Level * Kneading Time	-0.01173	-0.00587	0.000451	-13.02	0.049
Water Level * Spheronization Time	-0.02801	-0.01400	0.000451	-31.08	0.020
Kneading Time * Spheronization Time	0.04647	0.02323	0.000451	51.56	0.012

S = 0.00127456 R-Sq = 99.98% R-Sq (adj) = 99.89%

Analysis of Variance for Standard (coded units)

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Main Effects	3	0.0041252	0.00412518	0.00137506	846.45	0.025
2-Way Interactions	3	0.0061622	0.00616220	0.00205407	1264.43	0.021
Residual Error	1	0.0000016	0.00000162	0.00000162		
Total	7	0.0102890				

Estimated Effects and Coefficients for RSD (%) (coded units)

Term	Effect	Coef	SE Coef	T	P
Constant		16.058	0.04000	401.44	0.002
Water Level	0.525	0.262	0.04000	6.56	0.096
Kneading Time	-0.590	-0.295	0.04000	-7.38	0.086
Spheronization Time	-2.955	-1.478	0.04000	-36.94	0.017
Water Level * Kneading Time	-0.740	-0.370	0.04000	-9.25	0.069
Water Level * Spheronization Time	-2.935	-1.467	0.04000	-36.69	0.017
Kneading Time * Spheronization Time	3.060	1.530	0.04000	38.25	0.017

S = 0.113137 R-Sq = 99.98% R-Sq (adj) = 99.84%

Analysis of Variance for RSD (%) (coded units)

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Main Effects	3	18.7115	18.7115	6.2372	487.28	0.033
2-Way Interactions	3	37.0508	37.0508	12.3503	964.87	0.024
Residual Error	1	0.0128	0.0128	0.0128		
Total	7	55.7752				

Reduced Model

Estimated Effects and Coefficients for Mean Sphericity (coded units)

Term	Effect	Coef	SE Coef	T	P
Constant		1.32000	0.01031	128.06	0.000
Water Level	-0.08500	-0.04250	0.01031	-4.12	0.054
Kneading Time	0.06000	0.03000	0.01031	2.91	0.101
Spheronization Time	-0.05000	-0.02500	0.01031	-2.43	0.136
Water Level * Kneading Time	0	0	0	0	0
Water Level * Spheronization Time	0.06500	0.03250	0.01031	3.15	0.088
Kneading Time * Spheronization Time	0.04000	0.02000	0.01031	1.94	0.192

S = 0.0291548 R-Sq = 95.75% R-Sq (adj) = 85.12%

Analysis of Variance for Mean Sphericity (coded units)

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Main Effects	3	0.026650	0.026650	0.0088833	10.45	0.089
2-Way Interactions	2	0.011650	0.011650	0.0058250	6.85	0.127
Residual Error	2	0.001700	0.001700	0.0008500		
Total	7	0.040000				

APPENDIX 6

Propranolol HCl Aqueous SR Results

Batch #	Coating Level (Coded)	Coating Conc. (Coded)	Curing Method	% Propranolol Released Over Time (hrs)							F2 Value
				1.5	3.5	5.5	7.5	10	22	24	
RB005026	2	High	2hrs @ 60c Vacuum Oven	29.4	57.4	72.9	80.6	87.4	95.3	97.5	38.6
RB005026	5	High	2hrs @ 60c Vacuum Oven	10.1	26.4	41.1	51.9	63.9	82.4	82.4	56.3
RB005026	6	High	2hrs @ 60c Vacuum Oven	5.8	17.3	26.7	35.3	45.8	66.2	68	33.7
RB005026	6	High	2hrs @ 60c Vacuum Oven	10.3	34	28.6	38.4	45.7	74.8	76.9	38.9
RB005026	6	High	2hrs @ 60c Vacuum Oven	37.4	58.3	68.6	75.7	82.9	95.4	96.5	39.3
RB005051	1	Low	2hrs @ 60c Vacuum Oven	27	62.8	80.5	89.7	96.7	101.4	102.3	32
RB005051	3	Low	2hrs @ 60c Vacuum Oven	22.6	54.5	71.9	81.4	90.5	99.4	100.5	38.7
RB005053	2	Low	2hrs @ 60c Vacuum Oven	14	35.5	50.5	61.1	69.9	87.8	87.7	96.3
RB005053	4	Low	2hrs @ 60c Vacuum Oven	16.5	33.6	45	53.7	62.3	77.9	80	58.2
RB005053	4	Low	2hrs @ 60c Freas Oven	11.9	30.1	41.1	46.4	53.4	64.6	65.3	40.5
RB005059	4	High	2hrs @ 60c Chamber 2	44.5	63.8	71.6	76.5	80.7	88.9	88.8	36.2
RB005061	2	Low	2hrs @ 60c Chamber 2	41	47.6	51.3	54.3	57.3	64.7	65.6	38

APPENDIX 7

Propranolol Organic SR Dissolution Results

Batch #	Coating Level Coded	Curing Method	1.5	3.5	5.5	7.5	10	22	24	F2 Value
RB005064	1	Uncured	5.6	22.7	37.3	49.2	61.5	83.6	85.3	50.4
RB005064	2	Uncured	5.8	20.4	34.0	44.2	55.7	79.5	82.6	44.5
RB005064	2	24hrs @ 60c Chamber 2	15.3	50.9	70.3	81.5	91.1	102.5	103.5	40.5
RB005064	2	24hrs @ 60c/50% RH Chamber 2	18.3	62.0	81.4	92.2	98.8	103.2	104.4	32.0
RB005064	2	24hrs @ 50c Chamber 2	16.8	41.2	58.0	69.5	82.2	100.5	102.6	54.2
RB005064	2	24hrs @ 50c/50% RH Chamber 2	10.1	45.9	65.5	76.9	86.5	97.6	97.4	46.7
RB005064	2	6hrs @ 50c Chamber 2	7.8	29.5	45.1	56.9	70.1	92.7	95.3	65.5
RB005064	2	6hrs @ 50c/50% RH Chamber 2	12.8	46.9	68.6	81.8	93.9	109.9	111.1	39.0
RB005064	2	6 hrs @ 60c Freas	11.0	37.4	54.5	67.5	79.0	97.1	99.9	61.5
RB005064	2	24 hrs @ 60c Freas	15.2	49.4	70.6	82.9	93.6	106.0	107.3	38.9
RB005064	2	2 hrs @ 50C Freas	6.9	28.8	46.7	60.4	72.0	94.3	95.8	64.8
RB005064	2	24 hrs @ 50C Freas	8.3	36.2	54.8	67.5	80.1	99.8	100.3	57.7
RB005064	2	18 hrs @ 50C Freas	7.8	30.4	44.8	55.6	65.4	83.1	85.6	64.3
RB005064	2	18 hrs @ 60C Freas	12.3	46.4	64.0	73.8	83.8	93.2	94.3	50.6
RB005072	1	24 hrs @ 50C Freas	9.7	37.6	57.2	72.1	84.4	100.1	101.1	52.8
RB005072	1	24 hrs @ 50C Chamber 2	10.7	40.0	61.2	74.1	87.3	101.3	104.3	48.7
RB005072	1	24 hrs @ 45C Chamber 2	8.1	38.1	57.6	70.4	83.9	100.6	103.0	52.9
RB005072	1	2 hrs @ 45C Chamber 2	7.6	36.5	55.1	68.7	79.9	99.9	103.7	56.8
RB005072	1	6 hrs @ 45C Chamber 2	8.1	39.9	61.6	73.1	84.1	103.6	105.3	48.9
RB005072	1	18 hrs @ 45C Chamber 2	7.9	39.5	57.7	69.9	82.1	100.4	101.1	53.8
RB005072	1	6 hrs @ 50C Chamber 2	9.0	35.4	52.9	64.3	75.0	92.2	92.7	72.0

APPENDIX 8

Metoprolol SR Full Model Response Surface Regression/ANOVA

Response Surface Regression: Estimated Regression Coefficients for 1 hr

Term	Coef	SE Coef	T	P
Constant	2.00750	1.1367	1.766	0.138
Polymer Coating Level	-0.53053	0.6546	-0.810	0.454
Curing Conditions	-1.16079	0.6546	-1.773	0.136
Curing Time (Hrs)	-0.33000	0.6380	-0.517	0.627
Polymer Coating Level * Polymer Coating Level	1.06500	0.9391	1.134	0.308
Curing Conditions * Curing Conditions	2.40000	0.9391	2.556	0.051
Curing Time (Hrs) * Curing Time (Hrs)	-1.50750	1.0833	-1.392	0.223
Polymer Coating Level * Curing Conditions	-0.03500	0.9023	-0.039	0.971
Polymer Coating Level * Curing Time (Hrs)	0.23684	0.8782	0.270	0.798
Curing Conditions * Curing Time (Hrs)	0.83526	0.8782	0.951	0.385

S = 1.805 R-Sq = 77.2% R-Sq (adj) = 36.1%

Analysis of Variance for 1 hr

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Regression	9	55.0820	55.0820	6.1202	1.88	0.252
Linear	3	18.8032	13.2508	4.4169	3.39	0.111
Square	3	33.0913	33.0913	11.0304	3.39	0.111
Interaction	3	3.1874	3.1874	1.0625	0.33	0.807
Residual Error	5	16.2822	16.2822	3.2564		
Lack-of-Fit	3	15.7030	15.7030	5.2343	18.07	0.053
Pure Error	2	0.5792	0.5792	0.2896		
Total	14	71.3642				

Estimated Regression Coefficients for 1 hr using data in uncoded units

Term	Coef
Constant	-1.63000
Polymer Coating Level	-0.925263
Curing Conditions	-2.55289
Curing Time (Hrs)	1.56500
Polymer Coating Level * Polymer Coating Level	1.06500
Curing Conditions * Curing Conditions	2.40000
Curing Time (Hrs) * Curing Conditions	-0.167500
Curing Time (Hrs) * Curing Time (Hrs)	-0.0350000
Polymer Coating Level * Curing Time (Hrs)	0.0789474
Curing Conditions * Curing Time (Hrs)	0.278421

Response Surface Regression: 4 hr

Estimated Regression Coefficients for 4 hr

Term	Coef	SE Coef	T	P
Constant	8.6680	2.622	3.306	0.021
Polymer Coating Level	-1.3961	1.510	-0.925	0.398
Curing Conditions	-4.7757	1.510	-3.163	0.025
Curing Time (Hrs)	-0.6337	1.472	-0.431	0.685
Polymer Coating Level * Polymer Coating Level	2.6554	2.166	1.226	0.275
Curing Conditions * Curing Conditions	3.8179	2.166	1.763	0.138
Curing Time (Hrs) * Curing Time (Hrs)	-3.5334	2.498	-1.414	0.216
Polymer Coating Level * Curing Conditions	0.4850	2.081	0.233	0.825
Polymer Coating Level * Curing Time (Hrs)	0.5637	2.026	0.278	0.792
Curing Conditions * Curing Time (Hrs)	1.3536	2.026	0.668	0.534

S = 4.162 R-Sq = 80.6% R-Sq (adj) = 45.7%

Analysis of Variance for 4 hr

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Regression	9	359.951	359.951	39.9945	2.31	0.185
Linear	3	229.313	191.358	63.7859	3.68	0.097
Square	3	120.619	120.619	40.2065	2.32	0.192
Interaction	3	10.018	10.018	3.3393	0.19	0.897
Residual Error	5	86.616	86.616	17.3231		
Lack-of-Fit	3	85.498	85.498	28.4994	51.02	0.019
Pure Error	2	1.117	1.117	0.5586		
Total	14	446.566				

Estimated Regression Coefficients for 4 hr using data in uncoded units

Term	Coef
Constant	-0.0908333
Polymer Coating Level	-2.33553
Curing Conditions	-7.03158
Curing Time (Hrs)	3.71479
Polymer Coating Level * Polymer Coating Level	2.65542
Curing Conditions * Curing Conditions	3.81792
Curing Time (Hrs) * Curing Conditions	-0.392604
Curing Time (Hrs) * Curing Time (Hrs)	0.485000
Polymer Coating Level * Curing Time (Hrs)	0.187895
Curing Conditions * Curing Time (Hrs)	0.451184

Response Surface Regression: 8 hr

The analysis was done using coded units.

Estimated Regression Coefficients for 8 hr

Term	Coef	SE Coef	T	P
Constant	19.6420	2.970	6.614	0.001
Polymer Coating Level	-3.2791	1.710	-1.917	0.113
Curing Conditions	-6.0404	1.710	-3.532	0.017
Curing Time (Hrs)	-0.7325	1.667	-0.439	0.679
Polymer Coating Level * Polymer Coating Level	3.3158	2.454	1.351	0.234
Curing Conditions * Curing Conditions	2.5408	2.454	1.036	0.348
Curing Time (Hrs) * Curing Time (Hrs)	-4.4353	2.830	-1.567	0.178
Polymer Coating Level * Curing Conditions	0.0700	2.357	0.030	0.977
Polymer Coating Level * Curing Time (Hrs)	0.5830	2.295	0.254	0.810
Curing Conditions * Curing Time (Hrs)	0.2751	2.295	0.120	0.909

S = 4.715 R-Sq = 82.7% R-Sq (adj) = 51.7%

Analysis of Variance for 8 hr

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Regression	9	532.770	532.770	59.197	2.66	0.147
Linear	3	403.497	363.307	121.102	5.45	0.049
Square	3	127.499	127.499	42.500	1.91	0.246
Interaction	3	1.774	1.774	0.591	0.03	0.993
Residual Error	5	111.146	111.146	22.229		
Lack-of-Fit	3	106.347	106.347	35.449	14.78	0.064
Pure Error	2	4.798	4.798	2.399		
Total	14	643.916				

Estimated Regression Coefficients for 8 hr using data in uncoded units

Term	Coef
Constant	8.54250
Polymer Coating Level	-4.25079
Curing Conditions	-6.49895
Curing Time (Hrs)	4.68396
Polymer Coating Level * Polymer Coating Level	3.31583
Curing Conditions * Curing Conditions	2.54083
Curing Time (Hrs) * Curing Conditions	-0.492812
Curing Time (Hrs) * Curing Time (Hrs)	0.0700000
Polymer Coating Level * Curing Time (Hrs)	0.194342
Curing Conditions * Curing Time (Hrs)	0.0917105

Response Surface Regression: 12 hr

Estimated Regression Coefficients for 12 hr

Term	Coef	SE Coef	T	P
Constant	33.1944	3.688	9.001	0.000
Polymer Coating Level	-5.8158	2.124	-2.739	0.041
Curing Conditions	-3.5174	2.124	-1.656	0.159
Curing Time (Hrs)	-0.0300	2.070	-0.014	0.989
Polymer Coating Level * Polymer Coating Level	3.3550	3.047	1.101	0.321
Curing Conditions * Curing Conditions	-0.8900	3.047	-0.292	0.782
Curing Time (Hrs) * Curing Time (Hrs)	-3.7294	3.514	-1.061	0.337
Polymer Coating Level * Curing Conditions	1.4000	2.927	0.478	0.653
Polymer Coating Level * Curing Time (Hrs)	1.2703	2.849	0.446	0.674
Curing Conditions * Curing Time (Hrs)	-0.8242	2.849	-0.289	0.784

S = 5.854 R-Sq = 74.2% R-Sq (adj) = 27.6%

Analysis of Variance for 12 hr

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Regression	9	491.79	491.79	54.643	1.59	0.316
Linear	3	384.55	351.09	117.030	3.41	0.110
Square	3	89.71	89.71	29.905	0.87	0.514
Interaction	3	17.52	17.52	5.840	0.17	0.912
Residual Error	5	171.36	171.36	34.273		
Lack-of-Fit	3	160.13	160.13	53.375	9.50	0.097
Pure Error	2	11.24	11.24	5.620		
Total	14	663.15				

Estimated Regression Coefficients for 12 hr using data in Uncoded units

Term	Coef
Constant	22.8850
Polymer Coating Level	-7.93289
Curing Conditions	-2.14368
Curing Time (Hrs)	4.13375
Polymer Coating Level * Polymer Coating Level	3.35500
Curing Conditions * Curing Conditions	-0.890000
Curing Time (Hrs) * Curing Conditions	-0.414375
Curing Time (Hrs) * Curing Time (Hrs)	1.40000
Polymer Coating Level * Curing Time (Hrs)	0.423421
Curing Conditions * Curing Time (Hrs)	-0.274737

Response Surface Regression: 16 hr

Estimated Regression Coefficients for 16 hr

Term	Coef	SE Coef	T	P
Constant	45.5223	4.190	10.865	0.000
Polymer Coating Level	-4.9413	2.413	-2.048	0.096
Curing Conditions	0.8549	2.413	0.354	0.738
Curing Time (Hrs)	0.7538	2.352	0.321	0.762
Polymer Coating Level * Polymer Coating Level	2.9771	3.462	0.860	0.429
Curing Conditions * Curing Conditions	-3.1004	3.462	-0.896	0.411
Curing Time (Hrs) * Curing Time (Hrs)	-2.1394	3.993	-0.536	0.615
Polymer Coating Level * Curing Conditions	-1.5500	3.326	-0.466	0.661
Polymer Coating Level * Curing Time (Hrs)	1.2071	3.237	0.373	0.725
Curing Conditions * Curing Time (Hrs)	-1.6433	3.237	-0.508	0.633

S = 6.651 R-Sq = 60.4% R-Sq (adj) = 0.0%

Analysis of Variance for 16 hr

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Regression	9	337.42	337.42	37.491	0.85	0.610
Linear	3	223.64	195.67	65.222	1.47	0.328
Square	3	86.61	86.61	28.872	0.65	0.615
Interaction	3	27.16	27.16	9.055	0.20	0.889
Residual Error	5	221.21	221.21	44.242		
Lack-of-Fit	3	201.63	201.63	67.209	6.86	0.130
Pure Error	2	19.59	19.59	9.793		
Total	14	558.64				

Estimated Regression Coefficients for 16 hr using data in uncoded units

Term	Coef
Constant	38.3233
Polymer Coating Level	-6.95316
Curing Conditions	3.59368
Curing Time (Hrs)	2.62833
Polymer Coating Level * Polymer Coating Level	2.97708
Curing Conditions * Curing Conditions	-3.10042
Curing Time (Hrs) * Curing Conditions	-.0237708
Curing Time (Hrs) * Curing Time (Hrs)	-1.55000
Polymer Coating Level * Curing Time (Hrs)	0.402368
Curing Conditions * Curing Time (Hrs)	-0.547763

Response Surface Regression: 20 hr

Estimated Regression Coefficients for 20 hr

Term	Coef	SE Coef	T	P
Constant	55.6439	4.412	12.612	0.000
Polymer Coating Level	-5.1111	2.541	-2.012	0.100
Curing Conditions	3.8197	2.541	1.503	0.193
Curing Time (Hrs)	1.4225	2.476	0.574	0.591
Polymer Coating Level * Polymer Coating Level	3.3133	3.645	0.909	0.405
Curing Conditions * Curing Conditions	-1.8717	3.645	-0.513	0.629
Curing Time (Hrs) * Curing Time (Hrs)	-2.2172	4.204	-0.527	0.621
Polymer Coating Level * Curing Conditions	-0.9900	3.502	-0.283	0.789
Polymer Coating Level * Curing Time (Hrs)	1.4787	3.409	0.434	0.683
Curing Conditions * Curing Time (Hrs)	-1.3216	3.409	-0.388	0.714

S = 7.004 R-Sq = 65.4% R-Sq (adj) = 3.1%

Analysis of Variance for 20 hr

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Regression	9	463.79	463.79	51.533	1.05	0.507
Linear	3	370.67	325.61	108.536	2.21	0.205
Square	3	72.60	72.60	24.199	0.49	0.702
Interaction	3	20.53	20.53	6.842	0.14	0.932
Residual Error	5	245.28	245.28	49.056		
Lack-of-Fit	3	213.10	213.10	71.033	4.41	0.190
Pure Error	2	32.18	32.18	16.092		
Total	14	709.08				

Estimated Regression Coefficients for 20 hr using data in uncoded units

Term	Coef
Constant	47.1142
Polymer Coating Level	-7.57553
Curing Conditions	6.02237
Curing Time (Hrs)	2.93771
Polymer Coating Level * Polymer Coating Level	3.31333
Curing Conditions * Curing Conditions	-1.87167
Curing Time (Hrs) * Curing Conditions	-0.246354
Curing Time (Hrs) * Curing Time (Hrs)	-0.990000
Polymer Coating Level * Curing Time (Hrs)	0.492895
Curing Conditions * Curing Time (Hrs)	-0.440526

Response Surface Regression: F2

Estimated Regression Coefficients for F2

Term	Coef	SE Coef	T	P
Constant	26.0939	1.946	13.409	0.000
Polymer Coating Level	-2.8616	1.121	-2.554	0.051
Curing Conditions	-0.5868	1.121	-0.524	0.623
Curing Time (Hrs)	0.2700	1.092	0.247	0.815
Polymer Coating Level * Polymer Coating Level	1.9208	1.608	1.195	0.286
Curing Conditions * Curing Conditions	-0.4392	1.608	-0.273	0.796
Curing Time (Hrs) * Curing Time (Hrs)	-1.7147	1.854	-0.925	0.398
Polymer Coating Level * Curing Conditions	-0.2550	1.545	-0.165	0.875
Polymer Coating Level * Curing Time (Hrs)	0.5005	1.503	0.333	0.753
Curing Conditions * Curing Time (Hrs)	-0.4011	1.503	-0.267	0.800

S = 3.089 R-Sq = 67.2% R-Sq (adj) = 8.2%

Analysis of Variance for F2

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Regression	9	97.884	97.884	10.8760	1.14	0.467
Linear	3	71.554	65.434	21.8114	2.29	0.196
Square	3	24.333	24.333	8.1109	0.85	0.523
Interaction	3	1.997	1.997	0.6657	0.07	0.974
Residual Error	5	47.720	47.720	9.5439		
Lack-of-Fit	3	43.308	43.308	14.4358	6.54	0.135
Pure Error	2	4.412	4.412	2.2060		
Total	14	145.604				

Estimated Regression Coefficients for F2 using data in uncoded units

Term	Coef
Constant	20.8808
Polymer Coating Level	-3.69579
Curing Conditions	0.0815789
Curing Time (Hrs)	1.99521
Polymer Coating Level * Polymer Coating Level	1.92083
Curing Conditions * Curing Conditions	-0.439167
Curing Time (Hrs) * Curing Conditions	-0.190521
Curing Time (Hrs) * Curing Time (Hrs)	-0.255000
Polymer Coating Level * Curing Time (Hrs)	0.166842
Curing Conditions * Curing Time (Hrs)	-0.133684

APPENDIX 9

ANOVA of Tablet DOE Friability

Full Model

General Linear Model: % Usable versus SR Polymer I, Blend (MCC 2)

Factor	Type	Levels	Values
SR Polymer Level	Fixed	2	-1, 1
Blend (MCC 200:102)	Fixed	2	1:1, 3:7
Hardness (Kp)	Fixed	2	2, 5

Analysis of Variance for % Usable, using Adjusted SS for Tests

Source	DF	Seq SS	Adj SS	Adj MS	F	P
SR Polymer Level	1	274.83	274.83	274.83	3.81	0.301
Blend (MCC 200:102)	1	53.92	53.92	53.92	0.75	0.546
Hardness (Kp)	1	378.26	378.26	378.26	5.25	0.262
SR Polymer Level * Blend (MCC 200:102)	1	80.07	80.07	80.07	1.11	0.483
SR Polymer Level * Hardness (Kp)	1	238.82	238.82	238.82	3.31	0.320
Blend (MCC 200:102) * Hardness (Kp)	1	45.08	45.08	45.08	0.63	0.574
Error	1	72.06	72.06	72.06		
Total	7	1143.05				

S = 8.48882 R-Sq = 93.70% R-Sq (adj) = 55.87%

Reduced Model

General Linear Model: % Usable versus SR Polymer I, Blend (MCC 2, ...)

Factor	Type	Levels	Values
SR Polymer Level	Fixed	2	-1, 1
Blend (MCC 200:102)	Fixed	2	1:1, 3:7
Hardness (Kp)	Fixed	2	2, 5

Analysis of Variance for % Usable, using Adjusted SS for Tests

Source	DF	Seq SS	Adj SS	Adj MS	F	P
SR Polymer Level	1	274.83	274.83	274.83	4.69	0.163
Blend (MCC 200:102)	1	53.92	53.92	53.92	0.92	0.439
Hardness (Kp)	1	378.26	378.26	378.26	6.46	0.126
SR Polymer Level * Blend (MCC 200:102)	1	80.07	80.07	80.07	1.37	0.363
SR Polymer Level * Hardness (Kp)	1	238.82	238.82	238.82	4.08	0.181
Error	2	117.14	117.14	58.57		
Total	7	1143.05				

S = 7.65302 R-Sq = 89.75% R-Sq (adj) = 64.13%