2000

DEVELOPMENT, CHARACTERIZATION AND EVALUATION OF A PULSED-RELEASE TABLET DOSAGE FORM FOR LOW DOSE WATER SOLUBLE DRUGS

Suresh Palaniswamy
University of Rhode Island

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BY

SURESH PALANISWAMY

A DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

APPLIED PHARMACEUTICAL SCIENCES

UNIVERSITY OF RHODE ISLAND

2000

DOCTOR OF PHILOSHOPHY DISSERTATION

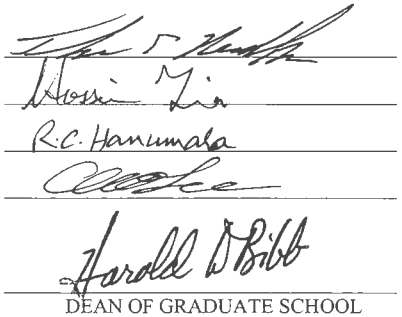
OF

SURESH PALANISWAMY

APPROVED:

Dissertation Committee

Major Professor



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2000

ABSTRACT

Various types of controlled release dosage forms such as wax matrix hydrophilic polymer matrix, osmotic pump and acrylic resin polymer encapsulated slow release for water soluble drugs have been developed and reported. However, there was no significant information available in the literature about the development and scale-up of pulse-release tablet dosage form for low dose water soluble drugs. This investigation was undertaken to develop, characterize and evaluate a new pulsed-release dosage form for a low dose water soluble drug with consistent drug release that combines polymer matrix and aqueous coating technology.

The effect of scale-up on granulation, compression and coating of pulse-release tablet formulation containing low dose active drug made with hydroxypropyl methylcellulose (HPMC) as base excipients were investigated for two different formulation. The controlled release matrix tablets produced were seal coated using aqueous polymer latex dispersion to retard the drug release from the tablet cores for a period of 3-4 hours. Immediate release coat was developed to apply the initial dose of the drug onto the seal coated tablets.

A factorial design was used to study the critical processing parameters that were known to influence coating process. The results of analysis of variance were used to predict the effect of various processing parameters on the response. Pair-wise comparisons of the dissolution results for two different scales and formulations using F_2 metrics established by FDA SUPAC guidelines were used to evaluate similarity between drug release characteristics.

Results indicate that adjustment of the blending time and headspace to blender capacity based on the size of the blenders used at various stages of scale-up is necessary to maintain constant blending geometry and equivalent mixing to produce uniform distribution of the active drug. Results also show that coating suspension spray rate and coating pan rotation speed significantly affect the coating uniformity. The content uniformity between tablets is significantly improved by using a low spray rate, low drug concentration in the coating solution and slower pan speed. Stability test results indicate that the developed formulation was stable when stored at ambient and accelerated storage conditions.

ACKNOWLEDGEMENTS

I would like to express my sincere thanks to my advisor, Dr. Thomas E. Needham for being as my major professor, for his interest, effort and guidance for assisting me in the graduate studies and research program.

This dissertation research was carried out entirely in the laboratories of TEVA Pharmaceuticals USA, Sellersville, PA 18960. I would like to extend my deep appreciation and gratitude to Dr. Dennis Szymanski (Vice President, Pharmaceutical Research and Development) for his continued support and encouragement even after his departure from TEVA. Also I would like to thank Dr. Kang Yang (Director, Pharmaceutical Research and Development) for his willingness and support during this project.

I want to thank Mr. Robert Gwozdz (TEVA Pharmaceuticals USA) for his assistance and support during this project. My deep appreciation goes to the entire analytical department who helped me in various analytical aspects of this project.

I want to thank Dr. Hossein Zia for his advice and assistance during my graduate studies. Also I want to thank Dr. Chong Lee (Department of Food Science and Nutrition, URI) and Dr. Hanumara R. Choudary (Computer Science and Statistics, URI) for serving on my Ph.D. dissertation committee. Also I extend my gratitude to Ms. Kathleen Hayes (Secretary, Department of Applied Pharmaceutical Sciences, URI) who always had a smile and a heart to help while I was at the school and off campus.

My parents who have been the greatest influence in my life, my father Palaniswamy, mother Lakshmi and brother Sekar. Through their love and sacrifice they allowed me to attain my goals otherwise were impossible.

To My Wife

Jothi and the little one

PREFACE

This thesis dissertation work has been prepared in accordance with the manuscript format option for dissertation preparation, as outlined in section 11-3 of The Graduate Manual of the University of Rhode Island. Contained within is a body of work divided into three sections.

Included in Section I is Introduction, which introduces the reader to the review and subject of this dissertation, a statement of the problem, and the specific objective of the research.

Section II is comprised of four manuscripts, containing the findings of the research, which comprises of this dissertation. The four manuscripts are presented in the format required by the journal to which they will be submitted.

Section III contains appendices containing, ancillary data (information essential to, but not usually included in published manuscripts) and other details pertaining to the understanding of the concepts presented in section II. This dissertation closes with a complete bibliographic listing of all the references cited in the dissertation, arranged in alphabetical order by the author's last name.

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SECTION I

INTRODUCTION

Typically, when a drug is either ingested or injected, the systemic drug level often exceeds the optimum therapeutic level for a brief period of time and then gradually declines from the therapeutic range to ineffective levels. Such "sawtooth" drug kinetic profiles are undesirable for many drugs, especially for drugs that have a low therapeutic index. Appropriately sustained drug blood levels can enhance therapeutic action and minimize undesirable side effects (1).

It is well known fact that patient compliance is better when drug dosage is administered only once or twice daily. It has been reported that as the number of doses per day increases, there is a greater risk that patients either forget or neglect to take every dose (2). Thus, it would be desirable to reduce the daily number of doses, especially in long-term chronic treatment.

With appropriate well designed controlled release dosage forms it is possible to reduce the frequency of dosing, maintain the therapeutic drug plasma concentration level for a longer periods of time, reduce undesirable toxic or adverse effects, and obtain a constant pharmacological action (3,4).

The oral route of administration has been recognized as convenient and more acceptable than any other route of drug administration (3). Because of the advantages offered by tablets such as, ease of administration, patient compliance, low cost manufacturability, packaging and shipping. A number of different designs and techniques were used to provide controlled release such as dissolution controlled, diffusion controlled, diffusion and erosion controlled, osmotically controlled and ion exchange. Thus tablets predominate in the oral controlled release market. Among the marketed

tablet formulations, non disintegrating matrix tablets are the most widely used. One of the earlier studies describing core tablets that release drugs through diffusion was by Sogren (4). In this study the tablet core was produced by direct compression of the granulated drug with insoluble plastic material so that a porous skeleton of the matrix material forms around the drug.

In addition, a source of concern with controlled release dosage forms is the difficulty in designing the formulation to obtain the desired drug release profile and manufacturability. Scale-up of solid dosage forms, particularly controlled release dosage forms, may lead to changes in the pharmaceutical characteristics and drug release profiles from the laboratory scale to the production scale, such inconsistencies are construed to be mainly the result of variations in raw materials and differences in equipment (5,6). To date, many studies have been performed to resolve the problem of variation in raw materials (7,8,9); however, difficulties in scale-up may also result from poor in-process controls or incorrect extrapolation of the results generated during small-scale studies. A major source of problems related to equipment differences is the failure to apply engineering models and scale-up factors when a process is transferred from pilot scale to production scale. In practice, this initial transfer to production scale is often empirical or trial and error rather than a systematic application of engineering principles.

Polymeric delivery systems may be used in a wide variety of pharmaceutical dosage forms. More recently, synthetic and semi-synthetic polymers have achieved wide use in tablet formulations, and polymeric coatings in the pharmaceutical industry. The oldest and most widely developed sustained release dosage forms involved coating with lipid substances such as: waxes (10) and fats i.e. Spansules®, which was one of the first

commercially available orally administered sustained release dosage form. The rate of drug release from such dosage form will depend upon the physical properties of the coating materials and of the drug itself.

Controlled Release Through Coated Particles

Since the introduction of the Spansule sustained release dosage form, there have been numerous studies on this type of coated particle dosage form. Coating of drug particles, granules or tablets with polymer can be achieved by pan coating or an air suspension coating process. A common procedure used to prepare drug-coated beads or granules is to coat nonpareil seeds with the drug and follow this with either a slowly dissolving wax or a polymer coat of varying thickness. There are a variety of slowly dissolving or disintegrating coatings available, such as those based on various combinations of carbohydrate sugars and cellulose, polyethylene glycol, polymeric materials or waxes. Examples of drug using coated granules include antihistamines (11,12), antihypertensives (13), and cardiac muscle dilators (14).

There have been a wide range of drugs formulated as sustained release coated granules and compressed into tablets, such as phenothiazines (15-18), anticholinesterase agents (19), and aspirin (20, 21). With tablet dosage forms, the concern for the thickness and area of the granular coating remains, with additional problem areas such as the influence of excipients and compression on the disintegration and dissolution of the tablets. Interestingly, the role of excipients on the dissolution pattern of compressed coated granules has not been fully clarified.

Controlled Release Through Microencapsulation

Microencapsulation has been defined as the process of enclosing small entities in a coating material to produce particles with modified characteristics (22). This process has been employed pharmaceutically to increase product stability (23,24), modify drug release, prevent drug incompatibility in formulations (24), and to improve certain physical characteristics of formulation such as compressibility and flow properties.

Coacervation has been credited to be the earliest process used to encapsulate pharmaceuticals (25). In 1949 Bungenberg de Jong (26) discussed both simple and complex coacervation but did not apply the process to coating particles. A specific comparison of simple and complex coacervation processes between gelatin and gum arabic was made. Indomethacin (27), steroids (28,29) and cod liver oil (30) have been encapsulated using simple and or complex coacervation. Because of their solubility, polymers used in the aqueous coacervation process are not effective for controlled release applications. A number of microencapsulation formulations for oral controlled release have been studied and reported. Salib (31) encapsulated phenobarbitone in ethylcellulose using the coacervation technique. Deasy et al. (32) encapsulated highly water-soluble drug, sodium salicylate using different viscosity grades of ethylcellulose. Holiday et al. (33) described the microencapsulation of aspirin to produce a sustained release dosage form. Baken and Powell (34) reported paracetamol, aspirin, potassium chloride and theophylline microcapsules; prepared using an ethylcellulose-polyethylene system for controlled release which showed excellent stability.

Drug Release from Polymer Controlled Release System

The release of drug from microcapsules is a mass transport phenomenon involving diffusion of drug molecules from a high concentration region to a low concentration region. Mathematical models used to describe the kinetics of drug release from microcapsules are usually divided into two categories, which are:

1. Drug release From Reservoir Device Microcapsules: In this system, a water-insoluble polymer film encases a core of drug (29,30,32,35). Assuming that the thermodynamic activity of the drug is maintained constant within the microcapsule, then the steady-state release rate from the reservoir to the external sink have been demonstrated by Baker and Lonsdale (36) and follows this type of release profile:

$$dq/dt = 4\Pi r_i r_o D k_d c_d/(r_o - r_i)$$

where: r_o = outside radius

r_i = inside radius

dq/dt = rate of release

D = diffusivity in the membrane

k_d = partition coefficient

c_d = concentration of drug in the donor solution

2. Drug Release From Matrix Microcapsules: In this system, the drug is dispersed throughout an insoluble polymer matrix. The drug release rate is dependent upon the drug diffusion rate. Based on a theoretical analysis of the law of simple diffusion. Higuchi (37) was able to mathematically derive an equation to describe the release of the drugs from a

homogenous matrix (monolithic solution) and from a granular matrix (monolithic dispersion).

For drug release from spherical pellets the equation can be simplified to:

$$1 + 2F\text{-}3F^{2/3} = Kt$$

Where F is the fraction of drug remaining in the pellet at time t, K is a constant, which varies with the type of matrix system.

For a homogenous matrix system: $K = 6DC_s/Aa_0^2$, where D is diffusion coefficient of the drug in the matrix polymer, C_s is the solubility of the drug in the matrix polymer, A is the initial concentration of the drug in the matrix and a_0 is the radius of the microsphere.

For a granular matrix system: $K = 6D\varepsilon C_s/\tau Aa_0^2$, where D is the diffusion coefficient of the drug in the dissolution medium, ε is the porosity which is the volume occupied by the drug granules, τ is the tortuosity of the matrix and C_s, A and a_0 are the same as above. These models assume that the pellets are not coated, the polymer is not erodable, does not swell and the loading is relatively low.

Controlled Release Through Matrix Tablets

Matrix tablets are used to provide controlled release. One type of matrix controlled release tablet is prepared by compressing a mixture of a hydrophilic polymer and drug (38). In contact with moisture, the tablet swells to form a gel barrier, effecting delayed release of drug. Huber et al. (39) proposed that drug release was controlled both by drug diffusion through and by attrition of the gel sheath formed around the tablet. Lapidus and Lordi (40) reported data characterizing the release of chlorpheniramine maleate from a hydroxypropyl methylcellulose ether matrix. Release patterns measured

from one face of flat-surfaced tablets could be linearized when plotted as a function of the square root of time. This suggested that equations originally derived by the Higuchi brothers (37,41) for drug release from insoluble tablet matrices and from homogeneous ointments were applicable to this system. A number of studies investigating the effects of excipients on the release of variety of drugs from matrix tablets followed, Huber and Christenson (42) investigated the release of tartrazine from two hydroxypropyl methylcellulose (HPMC) matrix tablets and found that higher viscosity grade HPMC released the tartrazine at a significantly slower rate. Sawayanagi et al. (43) examined the applicability of chitosan as a vehicle for making sustained release matrix tablets of water soluble drugs. Nakkano et al. (44) studied the release of theophylline from a hydroxypropyl cellulose matrix tablet. Ford et al. (45) investigated the effects of some formulation variables on the release rate of promethazine hydrochloride from hydroxypropyl methylcellulose (HPMC) tablet matrices. Baveja et al. (46) employed non-ionic hydroxypropyl methylcellulose (HPMC) and anionic sodium carboxy methylcellulose (Na CMC) to prepare a near zero-order release from hydrophilic matrix tablets. Jambhekar et al. (47) studied the release of drug through the planar surface of a non-disintegrating insoluble matrix tablet.

Another type of non-disintegrating controlled release tablet can be produced by compressing a mixture of insoluble inert plastic material and drug (4). Drug release is achieved by dissolution of the drug particles and is dependent upon the area of the interface between the plastic and the dissolving medium, the thickness of the diffusion layer which is the saturated solution formed at the interface between the solid and the liquid, and the difference in concentration between the diffusion layer and the solution.

When all of the drug has dissolved or leached out, the insoluble plastic skeleton still retains the original shape of the tablet. The release pattern may be controlled by varying the proportions of soluble and insoluble substances. Goodhart et al. (48) reported that phenylpropanolamine hydrochloride was released from a typical wax matrix by a diffusion mechanism. Farhadieh et al. (49) found that drug release from tablets compressed directly from mixtures of drug and methylacrylate-methylmethacrylate copolymer follow the square root of time dependence suggested by Higuchi. The magnitude of the release rate constant was found to be dependent on the matrix porosity and tortuosity as well as the solubility, diffusivity, and concentration of the drug. Khanna et al. (50) evaluated the drug release rate from two forms of Eudragit matrix tablets and reported the Eudragit RSPM in a concentration of 25% w/w was suitable for making sustained release tablets of propranolol hydrochloride. Fassihi (51) measured the compatibility of drug and polymer mixtures with directly compressible excipients. He found that the various formulation constituents affected tensile strength of tablets even at low compaction forces.

Both types of controlled release tablets mentioned above are designed to be nondisintegrating. Barkin et al. in a study that demonstrated significant therapeutic ramifications (52), pointed out that the widely used potassium chloride tablet formulations, usually in the form of wax matrix slow release tablets, can cause gastrointestinal ulceration, hemorrhage, obstruction and perforations (53,54). They suggested a microencapsulated potassium chloride preparation that does not use a wax matrix and which disperses polymer-coated potassium chloride crystals over a wide

surface area in the intestinal lumen for over 8 to 10 hours would represent a new generation of tablet.

Controlled Release Through Pulse-Release Tablets

A pulse-release tablet is one that provides the usual single dose of the drug immediately after administration and delivers the next dose after a period of time. Pulse-release tablets are not true sustained release products. However, the dosage form is designed to extend the activity of the second dose of the drug often after the effect of the first dose has diminished. Ideally, the lag time period should be only time-dependent. Also, a 4-6 hour lag time seems to be the upper limit for systemic administration due to gastrointestinal transit time. Drug release after the predetermined time should be rapid and complete. In this type of dosage form the core serves as the base onto which the initial dose is applied by usual coating techniques. Chlor-Trimetron Repetab® and Proventil Repetab® marketed by Schering-Plough illustrates this approach. The most important ingredient used in the barrier coating of Repetabs® a corn protein, zein. Zein is claimed to have time-dependent, erosion properties. Zein is a proven timed-release barrier, because it has been applied to Repetab® technology and commercialized to yield several successful products.

Water-soluble polymer to form a pulsed-release barrier

Gazzaniga et al. (55,56) developed oral delayed release systems based upon a retarding swellable hydrophilic coating and coined the name "Chronotrophic®" for their delivery system. A hydroalcoholic solution of hydroxypropyl methylcellulose was used

along with polyethylene glycol 400 or diethylphthalate, talc and polyvinyl pyrolidone in the barrier coating system. The authors demonstrated that the lag time was linearly correlated with coating weight gain and drug release was independent of the pH of the medium.

In an international patent, Shah (57) demonstrated the use of special grades of hydroxypropyl methylcellulose, e.g., Metolose® 60SH, 65SH, 90SH, and Methocel® F4M, as a hydrophilic matrix material to achieve bimodal drug release for several drugs, such as aspirin, ibuprofen, and adinazolam. Bimodal release is characterized by a rapid initial release, followed by a period of constant release, and finalized by a second rapid drug release.

Waxy material to form pulsed-release barrier

Tablets or capsules were coated with a hydrophobic wax-surfactant layer which was made from an aqueous dispersion of carnuba wax, beeswax, polyethylene sorbitan monooleate, and hydroxypropyl methylcellulose, to form the TimeClock®. The lag time for the system was found to be independent of normal physiological conditions, such as pH, food, and the anatomical position of the body (58).

Polyacrylic methacrylate copolymer to form pulsed-release barrier

Geoghegan et al. (59,60) described a sustained-release formulation containing diltiazem, fumaric acid, and talc coated onto non-pareil seeds using polyvinyl pyrolidone as the binding agent. Subsequently the drug layered pellets were coated with Eudragit RS®:Eudragit RL® (4:1). The drug release from this system showed a two hour delay.

Noda et al. (61,62) developed an organic acid-induced sigmoidal drug release system using a Eudragit RS polymer film as pulsed release barrier.

Enteric materials to form pulsed-release barrier

Various enteric materials, e.g., cellulose acetate phthalate, hydoxypropyl methylcellulose phthalate, polyvinylacetate phthalate, and the Eudragit® acrylic polymers, have been extensively used for gastroresistant, enterosoluble coatings to obtain pulse release in the intestine. An erodable association polymer system formed between a hydrogen-donating polymeric carboxylic acid of cellulose acetate phthalate and a hydrogen-accepting ethoxylated nonionic surfactant (Pluronic® F127) was investigated for its applicability to pulsatile drug delivery (63). Such association polymers are erodable at neutral or higher pH but insoluble at low pH. This type of dosage form is prepared either by coating the immediate release portion of the drug over an enteric or delayed release coated core tablet or by press-coating the granulation containing an initial dose of the drug over the core which has been coated with an enteric material.

Press coating technology for tablet dosage forms was used to form hydroxypropyl methylcellulose barriers with erodable and/or gellable characteristics to achieve time-programmed release of drugs by Conte et al. (64). From a technology and automated manufacturing perspective, press coating is a relatively complex and expensive process that requires advanced tableting equipment. On the other hand, multiple unit systems such as beads require a long coating process time to build up a pulsed-release barrier, due to the large surface area of the substrates to be coated. Additionally, a drug layering or core making process for multiple unit systems is time-consuming. Aqueous wax dispersion

was evaluated for controlled-release coating of beads (65). At the higher coating level, a two–hour lag time was achieved for the model drug theophylline and three hours was required for complete release of theophylline after the lag time. Thus, by combining the systems that have different release characteristics, oral drug preparations with various release patterns such as, repeat action, zero order, first order, bimodal, and sigmoidal patterns can be achieved. The findings reported in the literature so far did not combine the matrix system with the conventional coating technique to deliver a highly water soluble low dose drug that demonstrates an immediate release followed by a lag for 3-4 hours and the second dose in a zero order fashion. Hence, this study was undertaken to develop a pulsed-release delivery system using albuterol as a model drug.

Albuterol, a sympathomimetic amine derivative of ß-phenyl ethylamine, is a potent selective ß-adrenergic agonist with less $Beta_1$ adrenergic activity, and preferential $Beta_2$ adrenergic activity that provides bronchodilation with little myocardial stimulation (66). As a result it is used as a bronchodilator to treat chronic obstructive airway diseases in adults and children.

Albuterol is readily absorbed from the GI tract. Initial activity occurs within 15 minutes and lasts for a period of 4-5 hours. The drug is excreted in urine in about 24 hours with about 50 % of the orally administered drug is excreted within 3-4 hours. Maximum plasma albuterol concentration of about 18ng/ml is achieved within 2 hours after administration of 4 mg as syrup (66). The peak plasma concentration of albuterol and its metabolites are reported as 5.1-11.7 µg percent at 2.5 to 3 hours after an oral dose of 4 mg (66).

Albuterol is metabolized to a polar metabolite in humans, which has spectral and chemical properties different from the parent drug. Albuterol is contraindicated in patients with cardiovascular disorders. Teratogenic effects have been reported for albuterol in animals and oral administration of the drug has been shown to delay preterm labor (66).

However, owing to a short-half life of 3-5 hours the drug must be administered 3-4 times daily to maintain a therapeutic concentration. Unfortunately this requires careful observance of the treatment regimen a requirement that often interferes with the ability to achieve full therapeutic benefit from the treatment. Albuterol may be administered in a variety of dosage forms and is available on the market in the form of albuterol sulfate syrup, and tablets for oral administration, also in the form of albuterol for oral inhalation. The tablets are available as 2 mg and 4 mg immediate release and 4 mg repeat action tablets. The repeat action tablets are designed to deliver 2 mg immediately via a coated outer most layer and 2 mg slowly from the core for a period of 3-4 hours (66). The oral inhalation dosage form provides a metered dose of 90 μg of albuterol for each actuation. The only controlled release oral dosage form of albuterol on the US market is Proventil® Repetabs and the market potential of this dosage form is significant. The main objective of this pulsed-release dosage form is to improve compliance by reducing the number of doses from four to two per day.

Various types of controlled release dosage forms of albuterol have been developed and reported (67,68,69). These include wax matrix hydrophilic polymer matrix, osmotic pump and acrylic resin polymer encapsulated slow release. An extended release formulation of albuterol is marketed as Proventil® Repetabs but the detailed technology is

not reported. However first marketed in the 1950's using old technology, no further modifications in the design and processing methods of these dosage forms have been made presently. Contents as reported in the labeling of the marketed products of this type are derived from natural origin. These excipients show variability in content, drug release and often give less than reproducible results.

Processing of excipients obtained from natural origin is difficult and often prone to microbial contamination, which in turn requires strict quality control testing before processing into a dosage form. Organic solvents are needed in processing these materials which is hazardous. The recovery of these solvents also adds to the manufacturing cost.

This investigation was undertaken to develop a new pulsed-release dosage form with consistent drug release that combines polymer matrix and aqueous coating technology. This approach eliminates the use of organic solvents and uses an aqueous coating to retard drug release from the core for several hours after the first dose is released from the outermost layer. This method increases the efficiency of manufacturing and decreases variability by eliminating the use of excipients obtained from the natural origin, thereby giving a cost effective product, which is advantageous in this era of cost reduced health care.

Based on the above discussion, the specific objectives of this research were:

1. To develop two different controlled release formulations using matrix tableting technology to produce distinct drug release characteristics with a target release of 3 and 6 hours. To evaluate the processing parameters that affect tablet characteristics during scale-up from pilot to production size batches.
2. To evaluate aqueous coating techniques in an attempt to develop a seal coating that will protect and retard drug release from the controlled release matrix system. To study the effect of polymer coating level on drug release and identify the optimum polymer formulation required to retard drug release.
3. To develop a coating process that will allow coating of a small dose of drug onto core tablets that will meet USP standards for solid dosage forms. To study the effect of process variables that influence coating uniformity at both pilot and large scale production.
4. To identify the critical process variables that influence coating uniformity and to optimize these variables using statistical design of experiments. To evaluate the stability of the optimized formulation under ambient and accelerated storage conditions.

REFERENCES

1. Fatome, M., Courteille, F., Laval, J. D and Roman, V., Int. J. Radiat. Biol. Relat. Stud. Phys., Chem. Med., 52 (1), 21-29 (1987).
2. Malahy, B., American Journal of Hospital Pharmacy., 23 (6), 283-292 (1966).
3. Gunsel, W. C and Kanig, J. L., Tablets, in *Theory and Practice of Industrial Pharmacy* (2nd Ed.), Lea & Feiber, Philadelphia, p.321 (1976).
4. Sogren, J and Farykolf, L., Farm. Rev., 59, 171 (1960).
5. Avallone, H. L., Pharm. Eng., 10 (4), 38-41 (1990).
6. Chowhan, Z. T., Pharm. Technol.,12 (2), 26-44 (1988).
7. Russo, E. J., Pharm. Technol., 8 (11), 46-56 (1984).
8. Rowe, R. C., Int. J. Pharm. Tech. & Prod. Mfr., 3 (1), 3-8 (1982).
9. Gohel, M. C and Jogani, P. D., Pharm. Technol., (11), 54-62 (1999).
10. Blythe, R. H., U.S. Patent 2,783, 303 (1958).
11. Green, M. A., Ann. Allergy., 12, 273-283 (1954).
12. Rogers, H. L., Ann. Allergy., 12, 266-272 (1954).
13. Graham, H. V., J. Amer Geriat. Soc., 6, 671-674 (1958).
14. Ispen, J., Curr. Ther. Res., 13 (3), 193-208 (1971).
15. Mellinger, T. J., Amer. J. Psychiat., 121, 1119-1122 (1965).
16. Hollister, L. E., Curr. Ther. Res., 4 (9), 471-479 (1962).
17. Mellinger T. J., Mellinger, E. M and Smith, W. T., Clin. Pharmacol. Ther., 6, 486-491 (1965).
18. Vestre, D and Schiele, B. C., Curr. Ther. Res., 8 (12), 585-591 (1966).
19. Magee, K. R and Wasterberg, M.R., Neurology., 9, 348-351 (1959).

20. Cass, L. J and Frederick, W. S., Curr. Ther. Res., 7 (11), 673-682 (1965).

21. Ibid, 7, 683 (1965).

22. Luzzi, L. A., J. Pharm. Sci., 59 (10), 1367-1376 (1970).

23. Baken, J. A and Anderson, J. L., Microencapsulation, in *The Theory and Practice of Industrial Pharmacy* (2nd Ed.), Lea & Febiger, Philadelphia, p. 420 (1976).

24. Klaui, H. M., Hauseer, W and Huschke, G., Technological aspects of use of fat-soluble vitamins and carotenoids and of the development of stabilized marketable forms, in *Fat-soluble Vitamins* (R. A. Mortan Ed.), Pergamon, London, p.133 (1970).

25. Luzzi, L and Palmieri, A., An overview of pharmaceutical applications in Biomediacal Application of Microencapsulation, CRC Press, Inc., Boco Raton, Florida, p.9 (1983).

26. Bungenberg de Jong, H. G., *Colloid Science*, (H. R. Kruyt 2nd Ed.), Elsevier, Amsterdam, p.244 (1949).

27. Morse, L. D., U.S. Patent, 3,557,279 (1971).

28. Price, J. C and Palmieri, A., Microencapsulation of drugs suspended in oil, preparation and evaluation of prednisone and hydrocortisone microcapsules, in *Microencapsulation New Techniques and applications*, (T. Kondo Ed.), Techno Books, Tokyo, Japan, p.119 (1979).

29. Palmieri, A., Can. J. Pharm. Sci., 12 (10), 88-89 (1977).

30. Nixon, J. R., J. Pharm. Sci., 70 (4), 376-378 (1981).

31. Salib, N. N., Pharm Ind., 34 (9), 671-674 (1972).

32. Deasy, P. B., Brophy, M. R., Ecanow, B and Joy, M., Pharm. Pharmacol., 32 (1), 15-20 (1980).

33. Holiday, W. M., Berdick M., Bell, S. A and Kiritsis, G. C., U.S. Patent 3,488,418 (1960).

34. Baken, J. A and Powell, T. C., 8th International Symposium on Controlled Release of Bioactive Materials, Ft. Lauderdale, p. 158 (1981).

35. Samuelov, Y., Donbrow, M and Friedman M., J. Pharm. Sci., 68 (3), 325-329 (1979).

36. Baker R. W and Lonsdale, H. K., Controlled Release of Biologically Active Agents, Plenum Press, New York, p. 15 (1974).

37. Higuchi, T., J. Pharm. Sci. 52 (12), 1145-1149 (1963).

38. Christenson, G. L and Dale, L. B., U.S. Patent 3,065,143 (1960).

39. Huber, H. E., Dale, L. B and Christenson, G. L., J. Pharm. Sci., 55 (9), 974-976 (1966).

40. Lapidus, H and Lordi, N. G., J. Pharm. Sci., 55 (8), 840-843 (1966).

41. Higuchi, W. I., J. Pharm. Sci., 51 (8), 802-804 (1962).

42. Huber, H. E and Christenson, G. L., J. Pharm Sci., 57 (1), 164-167 (1968).

43. Sawayanagi, Y., Nambu, N and Nagai., Chem. Pharm. Bull., 30 (11), 4213-4215 (1982).

44. Nakkano, M., Ohmori N., Ogata, A., Sugimoto, K., Tobino, Y., Iwaoku, R and Juni, K., J. Pharm. Sci., 72 (4), 378-380 (1983).

45. Ford, J. L., Rubinstein, M. H and Hogan, J. E., Int. J. Pharm., 24, 327-338 (1985).

46. Baveja, S. K., Ranga Rao, K. V and Padmalatha Devi, K., Int J. Pharm., 39 (2), 39-46 (1987).

47. Jambhekar, S. S., Makoid, M. C and Coby, J., J. Pharm. Sci., 76 (2), 146-148 (1987).

48. Goodhart, F. W., McCoy, R. H and Ninger, F. C., J. Pharm Sci., 63 (11), 1748-51 (1974).

49. Farhadieh, B., Borodkin, S and Buddenhagen, J. D., J. Pharm. Sci., 60 (2), 209-12 (1971).

50. Khanna, S. K., Gode, K. D and Jayaswal, S. B., J. D., 18 (3), 103-108 (1980).

51. Fassihi, A. R., Int. J. Pharm., 37, 167-170 (1987).

52. Barkin, J. S., Harary, A. M., Shamblen, C. E and Lasseter, K. C., Annals of Internal Medicine., 98, 261 (1983).

53. Farquharson-Roberts, M. A., Giddings, A. E and Nunn, A. J., Brit. Med. J., 26 (3), 206 (1975).

54. Lubbe, W. F., Cadogan, E. S and A. Kannemeyer, H. R., N Z Med. J., 90 (647), 377-379 (1979).

55. Gazzaniga, A., Sangalli, M. E and Giordano, F., Eur. J. Pharm. Biopharm., 40 (4), 246-250 (1994).

56. Gazzaniga, A., Busetti, C., Moro, L., Sangalli, M. E and Giordano, F., S.T.P. Pharma Sciences., 5 (1), 83-88 (1996).

57. Shah, A. C., International Patent Application, WO8.700,044.

58. Pozzi, F., Furlani, P., Gazzangia, A., Davis, S. S and Wilding, I. R., J. Controller Release., 31, 99-108 (1994).

59. Geoghegan, E. J., Mulligan, S and Panoz, D., U.S. Patent, 4,891,230 (1990).

60. Geoghegan, E. J., Mulligan, S and Panoz, D., U.S. Patent, 5,616,345 (1997).

61. Noda, K., Hirakawa, Y., Yoshin, H and Narisawa, S., U.S. Patent 5, 395,628 (1995).

62. Narisawa, S., Nagata M., Ito, T., Yoshin, H., Hirakawa, Y and Noda, K., J. Controlled Release., 31, 253-260 (1993).

63. Xu, X and Lee, P. I., Pharm. Res., 10 (8), 1144-1152 (1993).

64. Conte, U., Maggi, L., Torre, M. L., Giunchedi, P and La manna, A., Biomaterials., 14 (13), 1017-1023 (1993).

65. Walia, P. S., Jo Meyer Stout, P and Turton, R., Pharm. Dev. Tech., 3 (1), 103-113 (1998).

66. Gerald, K. M., (Ed) "Drug Information", AHFS Published by ASHP, 617-619 (1988).

67. Bhalla, H. L and Sanzgiri, Y. D., Indian Journal of Pharmaceutical Sciences., 49:22-25 (1986).

68. Baveja, S. K., Ranga Rao K. V., Singh, A and Gombar, V. K., Int. J. Pharm., 41 (1), 55-62 (1988).

69. Palaniswamy, S., Masters Thesis, University of Rhode Island, Kingston, RI, USA, May (1994).

HYPOTHESIS TESTED HEREIN

It should be possible to develop a pulsed-release tablet dosage form for low dose water soluble drug using the conventional coating technique in conjunction with the matrix diffusion controlled release technique, which can release one dose of the drug as soon as ingested followed by the release of the second dose of the drug in a near zero-order release fashion for a period of 3-6 hours.

SECTION II

Manuscript I

An Approach to Scale-up of A Controlled Release Tablet Dosage Form For A Water Soluble Drug (To be submitted to Pharmaceutical Development and Technology)

Manuscript II

Development of Immediate Release Dose For A Pulsed-Release Tablet: Part–I: Seal Coat Development (To be submitted to Pharmaceutical Development and Technology)

Manuscript III

Development of Immediate Release Dose For A Pulsed-Release Tablet: Part–II: Immediate Release Coat Development (To be submitted to Pharmaceutical Development and Technology)

Manuscript IV

An Investigation of Uniformity of Aqueous Film Coating Containing Low Dose Active Drugs Using Statistical Design of Experiments (To be submitted to Pharmaceutical Technology)

MANUSCRIPT I

AN APPROACH TO SCALE-UP OF A CONTROLLED RELEASE TABLET DOSAGE FORM FOR A WATER SOLUBLE DRUG

ABSTRACT

The effect of scale-up on granulation and direct compression of controlled release tablet formulation containing low dose active drug made with hydroxypropyl methylcellulose (HPMC) as a base excipient was investigated. The model drug used was albuterol sulfate. Albuterol, a sympathomimetic amine is a potent selective beta adrenergic agonist used as a bronchodilator to treat chronic obstructive airway diseases in adults and children. The drug has a short half-life of 3-4 hours and must be administered 3-4 times daily to maintain a therapeutic plasma level.

Various concentrations of polymer and tableting excipients were evaluated and an optimum concentration, which gave near zero order release, was determined. Direct compression formulation containing < 2% of the drug developed at the pilot scale level was scaled up to a production size batch. A High Performance Liquid Chromatography (HPLC) assay method was used to determine the drug content in the formulation. Granulation and tablet characteristics were evaluated in an attempt to identify the optimum scale-up parameter for the large scale batches. To examine the impact of formulation and processing equipment on the drug content uniformity in the blend and tablet, statistical analysis along with, USP criteria for solid dosage form was applied. Batches manufactured at two different scales exhibited similar granulation and tablet properties for the two formulations studied.

Changes in the compression force significantly affected the tablet hardness for both formulations. However, the tablet hardness or the dwell time did not significantly affect the drug release. Observed F_2 values for both the scales of manufacturing, and all the pair-wise comparisons were > 83 suggesting that the drug release characteristics are

reproducible and similar based on SUPAC F_2 criteria. Stability studies indicate that the developed formulation was stable for a period of 3 months when stored at 25°C ambient conditions. The most important factor that should be considered in scaling-up of direct compression formulation of low dose active drug include adjustment of the blending time to blender rpm and capacity based on the size of the blenders used at various stages of scale-up.

1.0 Introduction

Scale-up of solid dosage forms, particularly controlled release dosage forms, can lead to changes in both pharmaceutical parameters and drug release profiles from laboratory scale to production scale. Such inconsistencies are construed to be mainly the result of variations in raw materials and equipment differences (1,2). To date, a number of studies have been performed to resolve the problem of variation in raw materials (3,4,5); However, difficulties in scale-up may also result from poor in-process controls or incorrect extrapolation from small-scale studies. A major source of problems related to equipment differences is the failure to apply engineering models and scale-up factors when a process is transferred from pilot scale to production scale. In practice, this initial transfer to production scale is often empirical or trial and error rather than a systematic application of engineering principles.

Until recently, there was no regulatory mechanism to evaluate the scale-up process except comparing the in-vitro dissolution profile of product at the various levels of scale-up to determine the reproducibility of the drug release and other product properties to be followed by bioequvalence studies characteristics. Recently SUPAC-IR and SUPAC-MR (Scale-up and Post Approval Change) guidelines for immediate release and modified release dosage forms were established by FDA (6).

Scaling-up of a dry granulation process should be achieved without problems as long as the mixing equipment geometry is similar. Issues related to blending are uniform mixing of excipients with drug, segregation of particles and end point control, all of which are a function of blender rpm and mixing time. Generally, production equipment is

much more efficient in mixing and milling than are similar types of laboratory-scale equipment. It is therefore important that the effects of this improved efficiency on the manufacturability and characteristics of the final dosage form be assessed during scale-up. The greatest difficulty observed as a result of the added efficiency of production equipment is overlubrication and its consequent effect on tablet hardness, capping and dissolution (3). Differences between tablet presses result in different compression times and may have an effect on the tablet's final characteristics. Such problems may arise with materials that undergo time-dependent stress relaxation. The differences attributable to press type have been related to the presence or absence of a gravity feed or a forced feed system in certain feed frames than to the event of compression itself (7).

The manufacture of matrix tablets by direct compression is an economical and simple process bearing a high commercial interest. Hydrophilic polymers such as HPMC, alginates and xanthum gum are well known and widely used in the development of controlled release formulations (8,9). However, there are some distinct disadvantages of these excipients that complicate the development and commercial production of tablets using these materials. These are the lack of flowability, hampering the direct compression process, poor mixing of granulation, affecting the drug content uniformity and compaction. In addition to these issues, it gets even more complicated when it comes to scale-up of dry granulation direct compression process for low dose active drug.

The goal of the present study is to systematically evaluate the relevant processing parameters on both pilot and production scales. This investigation includes the evaluation of granulation characteristics for a slow and fast releasing formulation using various grades of hydroxypropyl methylcellulose, on the small scale and production scale. Also

included were comparison of the tablet attributes, content uniformity, assay and dissolution profiles of the controlled release matrix tablets prepared from the direct compression granulation developed at two different scales for both the formulations. The results obtained from the two different scales were statistically analyzed to draw conclusions about the effect of scale-up on formulation characteristics and establish optimized process parameters.

2.0 Methods

2.1 Materials:

Albuterol Sulfate, USP obtained from (Propharmaco, Nobel Industries, Italy); Starch 1500, NF (Colorcon, West Point, PA); Lactose DT (Quest International Hoffman Estates, IL); Methocel® K 100 LV and K 15 M (Dow Chemical Company, Midland, MI); Magnesium Stearate, NF (Manllinckrot Inc., St. Louis, MO); Colloidal Silicon dioxide (Division Chemical, Baltimore, MD). All raw materials used complied with the current USP/NF grade specifications.

2.2 Equipment:

1 and 10 ft^3 V-Blender, (Gemco, Middlesex, NJ); Sieve Shaker (Sweco, Florance, KY); Micron Air Jet Sieve (Hosokawa Micron Powder Systems, Summit, NJ); Moisture Analyzer, Computrac Max 50 (Arizona Instrument, Tempe, AZ); Tablet Press Model Beta (Manesty, Liverpool, England); Tablet Press, Kikusui Model: Libra 836 KRCZ (Kikusui Seisakusho Ltd., Kyoto, Japan); SMI Force Monitoring System (SMI Inc., Pittstown, NJ); Vector Tablet Tester (Vector Corp., Marion, IA); Friability Tester (Erweka Instrument Corp., Milford, CT); Tap Density Apparatus, (J. Engelsmann A.G., Laudwishfen, GmbH, Germany); Tooling 9/32" Standard Concave, (Natoli Engineering Co., Chesterfield, MO); Bio-Dis Tester, (Vankel Industries Inc., Edison, NJ); Shimadzu LC-4A, High Performance Liquid Chromatography (HPLC) Equipped with a Shimadzu SPD-2AS spectrophotometer detector (Shimadzu, Japan).

2.3 Manufacturing Procedure:

Two types of tablets containing 2 mg of albuterol were manufactured with the aim of achieving an extended release formulation, one with a three hour and the other with a six hour release period. The batch sizes selected were 13.5 kg and 135 kg for the pilot scale and large scale which yielded 100,000 and one million (10X of the pilot scale) tablets, respectively. Two different formulations of albuterol sulfate tablets were prepared by blending the drug, polymer and filler excipients in a specified order for a total mixing time of 29 and 48 minutes using either a $1ft^3$ or $10ft^3$ V-blender respectively. The blends produced using the $1ft^3$ V-blender were compressed using a Manesty BetaPress (pilot scale) to determine the initial parameters, such as formulation component concentration, blending time, hardness, tablet weight variation and drug release.

The pilot scale formulation manufactured when scaled up to a batch size of 135 kg used a Kikusui Libra tablet press with 9/32" standard concave tooling for compression. The fill volume in the lower punch of the tablet machine was adjusted to a theoretical weight of 135 mg and compression force was adjusted to obtain a tablet hardness of 7-8 kilopounds (kp). Figure 1 shows the process flow diagram for controlled release tablet core manufacture.

2.3.1 Core Tablet Formulation

Table 1 shows typical albuterol sulfate controlled release core tablet formulation

Figure 1. Process Flow Diagram for Controlled Release Core Tablets

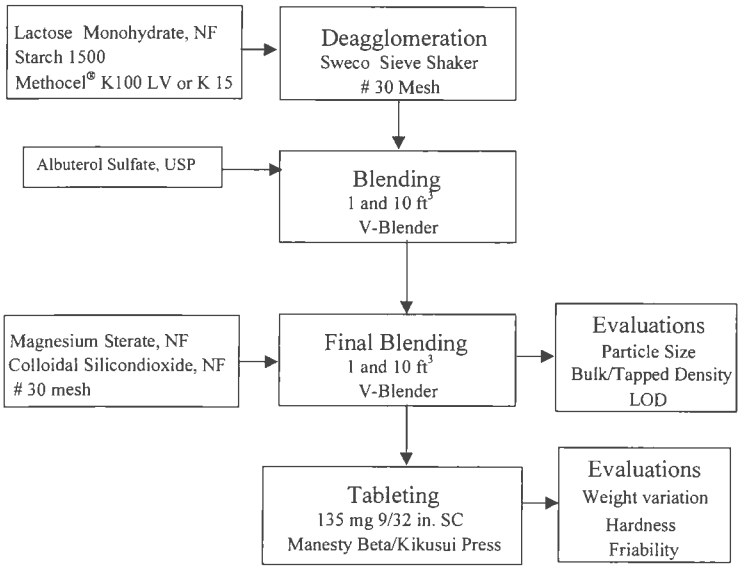


Table 1. Formula for Albuterol Sulfate Controlled Release Tablet Core

Ingredient	Formulation I		Formulation II	
	Percent (w/w)	mg/tablet	Percent (w/w)	mg/tablet
Albuterol Sulfate, USP	1.78	2.40	1.78	2.40
Methocel® (K100LV)	25.04	33.80	–	–
Methocel® (K15 M)	–	–	24.00	32.40
Starch 1500®	25.04	33.80	10.00	13.50
Spray Dried Lactose, NF	46.66	63.00	62.74	84.70
Colloidal silicon dioxide, NF	0.74	1.00	0.74	1.00
Magnesium Stearate, NF	0.74	1.00	0.74	1.00
Total	100.00	135.00	100.00	135.00

for a fast release (Formulation I) of three hours and a slow release (Formulation II) of six hours. Excipients were selected based on published information (10). Drug release from the matrix core tablets was controlled by a combined diffusion and erosion mechanism. This was achieved by inclusion of either a low viscosity (Methocel® K100LV) or a high viscosity (Methocel® K15 M) hydroxypropyl methylcellulose polymer along with the selection of appropriate ratio of soluble to insoluble filler excipients. Formulation, process and processing variables were chosen based on the results of an earlier study (10). Table 2 summarizes the unit operations for the two scales of manufacture.

2.4 Granulation Manufacture:

Dry granulation excipients lactose, pregelatinized starch, Methocel® (hydroxypropyl methylcellulose) K 100 LV or K 15 M were deagglomerated using a Sweco sieve shaker. The screened materials were then placed in either 1 or $10ft^3$ V-blender in the following order: Lactose, Albuterol Sulfate and Starch 1500 and mixed for 30 minutes. Methocel® was added to the pre-blend and mixed for additional 15 minutes. These excipients were premixed for a predetermined amount of time (27 minutes and 45 minutes for 1 and $10ft^3$ respectively). Optimum pre-blend mixing times were determined by evaluating drug content uniformity at various mixing intervals. Final blending of the granulation was completed by adding colloidal silicon dioxide and magnesium stearate (#30 mesh) and mixed for 2–3 minutes. The dry granules were then removed from the blender and stored for analysis and subsequent compression into tablets.

Table 2. Summary of Scales of Manufacture and Unit Operations

	Scale of Manufacture	
Parameter	**1X**	**10X**
Batch Size (kg)	13.5	135
Batch Size (units)	$1x10^5$	$1x10^9$
Raw Material	Same Source	Same Source
Manufacturing		
Deagglomeration	Sweco Sieve	Sweco Sieve
Blender Type (V)	1 ft^3	10ft^3
Tablet Press	Manesty Beta	Kikusui Libra

2.4.1 Granulation Properties

The granule properties examined include the following: granule size distribution, tap densities, angle of repose, percent compressibility (Carr index) and percent loss on drying. Blend samples of ~0.4 g (3 times the dose of 135 mg) were also collected from various locations (n=5) within each leg of the blender using an appropriate set of dies and a granulation sampling thief to determine the homogeneity of the final blend. Blend homogeneity was determined by assaying the individual samples collected from each location of the V-blender for content uniformity of albuterol sulfate. Composite samples collected from the drum after discharging the blend were used to determine bulk density, particle size and residual moisture. Residual moisture content (LOD) of the granules was determined using a thermogravimetric (Computrac Max 50, Arizona Instrument, Tempe, AZ) moisture analyzer. A sample weight of approximately 8 grams was spread onto an aluminum pan and placed in the analyzer. Table 3 lists the granulation parameters for the two different size batches manufactured.

2.4.2 Particle Size Analyses

Sieve analyses were performed to obtain a mean granule size and the weight distribution for the blend from each batch. A nest of standard sieves (mesh size 325, 200, 150, 100, 80, 60) with a micron jet sieve was used for these analyses. A 25 gram composite sample from the dry granulation blend was collected for the evaluation. The Sample was coned and quartered to obtain a sample weighing approximately 5 grams for analysis. The samples were added to the pre-weighed nest of sieves and allowed to shake

Table 3. Granulation Processing Parameters for V-Blender

Parameter	VB-1	VB-10
Blender Size (ft^3)	1	10
Capacity (L)	29	145
Batch Size (kg)	13.5	135
Blender (rpm)	23	14
Mixing Time - Pre Blend (min)	27	45
Mixing Time - Final Blend (min)	2	3

for 5 minutes with a vacuum pressure setting of 10.5 to 12 mm of water. The sieves were then reweighed to determine the weight fraction of granules retained on each sieve. These weights were converted to percent retained values using the initial total weight of the granules added and plotted against sieve size.

2.4.3 Bulk and Tap Densities

The bulk density of all the formulation components, and the tableting blend was evaluated. The bulk density of the granulation was determined by pouring an accurately weighed 100 gram sample into a clean dry 250 ml graduated cylinder tap density apparatus (J. Engelsmann A.G, GmbH, Germany). The density was then reported as the weight of the sample divided by the volume of the cylinder occupied upon pouring. The tapped density of each batch was then determined by subjecting the previously described graduated cylinder system to 200 taps from a height of approximately 2 cm. It was determined that 200 taps were sufficient to obtain a constant volume for the granulation. The tapped densities are also reported as weight per volume.

2.4.4 Carr Index and Angle of Repose

Bulk and tapped densities were used to calculate flowability and the indices of compressibility derived by Hausner (1967) (11) and Carr (1970)(11,12). The percent compressibility (Carr's index) was calculated as 100 times the ratio of the difference between tapped density and bulk density to tapped density. The drug excipient blend was placed in a powder funnel with 0.5 cm diameter opening supported using a retard stand such that the bottom of the orifice was 10 cm from the bench surface, the powder was

allowed to flow with the help of gravitational force. The angle of repose which is the angle (θ) obtained between the free standing powder heap and the horizontal plane was measured.

2.5 Tablet Manufacture:

The blended granulation was filled in the hopper of a Manesty BetaPress or an instrumented Kikusui Libra press (Kikusui, Seisakusho Ltd., Kyoto, Japan). The tablet press was setup to compress sixteen or thirty six 7-mm (9/32") shallow convex tablets per revolution. The target tablet weight was adjusted to 135 mg, and tablets were produced using a pre-compression and main compression force of 300 kg and 1700-2000 kg, respectively, to produce a target tablet hardness of 8 kp for the entire batch. Compression and ejection forces were analyzed. Instrumentation was used to monitor the precompression, main compression and ejection forces as well as machine speeds (rpm) at the large scale. Precompression force was kept constant for all formulations during the manufacture.

Table 4 shows equipment, batch sizes, and compression parameters for the controlled release tablet batches manufactured at two different scales for both formulations. Tablet samples were collected and stored in tightly sealed containers for subsequent physical characterization, assay and dissolution test. In-process and composite samples from the tableting runs were tested for weight, thickness, hardness and friability. Dissolution tests were conducted on compressed core tablets using USP apparatus 3, at 25 strokes per minute using 250 ml of phosphate buffer (pH 7.4) at 37 ±0.5°C.

Table 4. Tableting Parameters for Rotary Tablet Press

Parameter	Manesty	Kikusui
Number of Stations	16	36
Batch Size (kg)	13.5	135
Tooling Type	B	B
Tablet Punch Size	9/32"	9/32"
Compression Force (kg)	–	1700–2000
Granule Feed	FF[a]	IDF[b]
Tablets per minute (TPM)	480	2,160

a –Forced feeder; b –Induced die feeder

2.5.1 Weight Variation

The uniformity in weight of the compressed tablets were determined using the weight variation test procedure <905> specified in the United States Pharmacopoeia (USP 23) (13). For this test 30 tablets were randomly selected from the bulk sample for analysis. Ten of the selected tablets were individually weighed using a calibrated analytical balance (Sartorious Corp., Bohemia, NY) and the means and relative standard deviations calculated. USP acceptance criteria were applied in the evaluation of the results.

2.5.2 Tablet Thickness and Hardness

Thickness and hardness were measured individually by selecting 10 tablets randomly every fifteen minutes during tableting, using a Vector automatic tablet tester (Vector Corporation, Marion, IA). The crushing strength of 10 tablets from each batch was recorded in kilopounds (kp) and their means and percent relative standard deviations calculated.

2.5.3 Friability

The tablet friability, resistance to abrasion during handling and coating process, was measured using a Roche type friabilator (Erweka Instrument Corp., Milford, CT). Fifty tablets were randomly selected from the bulk sample for this test. The tablets were weighed and subjected to 100 rotations (25 rpm for 4 minutes) in the friabilator. The tablets were then removed from the friabilator, dusted and reweighed. Friability is reported as percent weight loss.

2.6 Assay and Drug Release Testing:

Blend uniformity, tablet content uniformity and assay was performed using a validated HPLC procedure. *In-vitro* drug release was studied in order to mimic *in-vivo* dissolution behavior. The media selected was a phosphate buffer pH 7.4 as recommended by USP 23. The dissolution study was performed using apparatus 3 (Reciprocating cylinder, Bio-Dis) (13). The temperature of the dissolution medium was maintained at 37 ± 0.5°C in all the studies. 250 ml of dissolution media was used in each cylinder and the stroke speed was set to 20/minute, sink conditions were maintained. Multipoint dissolution profiles were performed over a period of 6 hours by collecting samples at specified intervals and assaying by HPLC to determine the amount of drug released. Six tablets were used for each dissolution run and the percent labeled strength of albuterol sulfate dissolved was determined. Dissolution profiles were compared graphically and through the use of mathematical fit factor (F_2). The F_2 metrics equation provides a method to accurately compare dissolution profiles. The F_2 equation is expressed as (6):

$$F_2 = 50 \text{ LOG } \{[1+1/n \sum^{n}_{t=1} (R_t-T_t)^2]^{-0.5} \text{ x } 100\}$$

2.6.1 High Performance Liquid Chromatography Assay

An established HPLC assay method was used to test all samples (10). A reverse phase High Performance Liquid Chromatography (HPLC) assay was selected due to the advantage of direct analysis of aqueous samples, high sensitivity, and separation of excipients that would interfere in the assay (11,13). A reverse phase column, containing

packing L1 (Whatman partisil 10-ODS-3, 4.6x250 mm, C18, 10 μm) in conjunction with a variable wave length UV detector was used.

A number of mobile phase systems were tested. The one, that provided the best resolution, consisting of 70% methanol and glacial acetic acid in deionised degassed distilled water was chosen for the assay. The flow rate was 1.5 ml per minute, the UV detector set to 276 nm and the injection volume was 25 μl (using a WISP). A plot was obtained between peak area vs. concentration using standard solutions of albuterol sulfate for concentrations ranging from 0-20 μg/ml. The relationship thus obtained was linear ($r^2 > 0.9986$) and used for determining the concentration of albuterol sulfate in the dissolution sample.

3.0 Results and Discussion

3.1 Granulation Properties:

3.1.1 Flow Properties

Table 5 summarizes the granule properties for the different batch sizes. The values of Carr index were below 22.2%, indicating a good consolidation characteristic (11). Some materials have a high Carr index suggesting poor flow and low compressibility (7,11,14). Granulations that produce values in the range of 23% or below are considered to have fairly good compressibility characteristics (11,15). The measured angle of repose values for all the four batches ranged between 27–29° suggesting good flow characteristics that would enable uniform filling of granulation in the die cavities. Generally, flowability of blend is lower than excipient alone. A flow rate between 5–7 grams per second for all the batch sizes indicates smooth flow characteristics for the granulations. As we know from the literature granules with good flow characteristics provide even flow for a granulation through the hopper and various sections of the tablet press thereby minimizing tablet weight variation (15). There was no significant difference in flow characteristics between, all four granulation blends independent of the batch size.

3.1.2 Loss on Drying

Malamataris et al. (16) and Malamatris and Karidas (17) reported in-depth characterization of the effects of moisture content on the compression properties of hydroxypropyl methylcellulose (HPMC) and on the mechanical properties of tablets prepared with HPMC as the base excipient. Mosquera et al. investigated the effects

Table 5. Summary of Granule Properties

Batch Size (kg)	LOD (%)	Bulk Density (g/cm^3)	Tap Density (g/cm^3)	Carr Index (%)	Flow Rate (g/s)	Angle of Repose (θ)	Blend Uniformity	
							Mean	RSD
1X-I	3.65	0.57	0.73	21.9	5	28^o	101.3	1.7
1X-II	3.58	0.56	0.71	21.1	6	27^o	100.9	2.8
10X-I	3.71	0.55	0.74	21.7	6	29^o	100.9	1.6
10X-II	3.88	0.56	0.72	22.2	7	27^o	98.5	1.4

of HPMC moisture content on drug release from HPMC-based tablet (18). These authors studied the moisture content over the range of 2.25%–10.85% and found no significant effects on drug release profile. Granulation blend samples from both formulations were dried over a range of temperature starting with 85–155°C to identify the optimum drying temperature for moisture determination (Figure 2). To determine the moisture content, the blend sample was heated to 115°C, and moisture losses were recorded by the internal balance and automatically reported as percent moisture content. Moisture content as a function of loss on drying determined for both formulations at the two different scales ranged from 3.58–3.88 % and are similar to the findings reported earlier (16,17,18). This indicates that the moisture levels in the granulation are similar among the blends and did not have any effect on the physical characteristics of the granulation or tablets.

3.2 Blend Uniformity:

Usually the blender capacity should be kept between 70-100% of the working volume for uniform mixing and to avoid any potential particle segregation (3,19). The percent capacity utilization for each blend is presented in Table 6. These values were calculated using the bulk density measurements obtained from each blend. The percent capacity utilization was kept between 84-87% for both $1ft^3$ and $10ft^3$ blenders, which is considered as the optimum fill volume for these blenders (20). In addition, the mixing time for a blend should be adjusted to maintain the same number of revolutions at each scale of manufacture. Blending time is critical in achieving uniform mixing and good content uniformity (21).

Figure 2. Effect of Drying Temperature on Moisture Loss
Computrac Max 50 (Final Blend)
Batch Size 1X

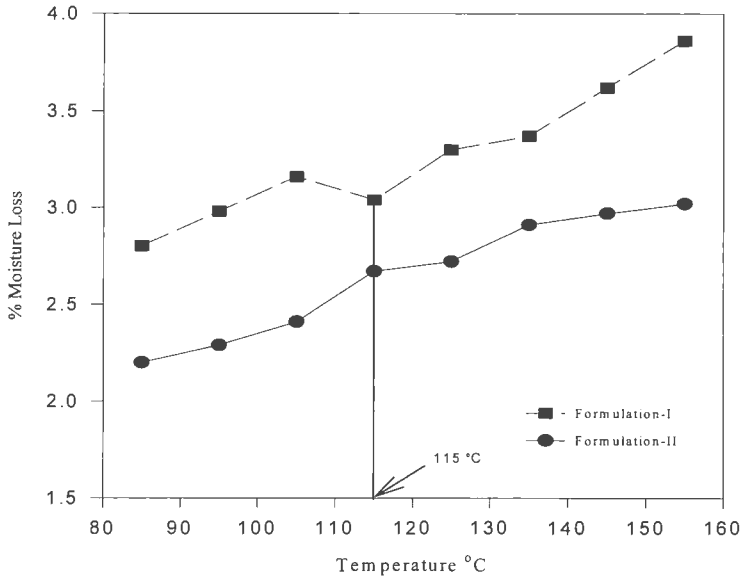


Table 6. Percent Capacity Utilization Data for $1ft^3$ and $10ft^3$ V-Blender

Batch Size (kg)	Actual Load (Kg)	Bulk Density (g/cm^3)	Capacity Utilization (%)	Mixing Time (min)
1X–I	13.5	0.57	83.6	29
1X–II	13.5	0.56	85.1	29
10X–I	135	0.55	86.7	48
10X–II	135	0.56	85.1	48

Over blending may also affect drug release and other tablet properties such as tablet disintegration and dissolution (22). The blending time for the small scale batch was 29 minutes and the adjusted blend time based on rpm for the large scale batch was 48 minutes; and was designed to produce a homogeneous blend of drug and excipients with uniform distribution of the drug within the blend. Homogeneity of the blend is determined by evaluating the individual assay results for samples taken from the various locations within the V-blender. The drug content uniformity results for the blend samples of both formulation show assay values in the range of 96.4–104.4% for the pilot scale batches and 96.6–102.9% for the scale-up batches respectively (Table 7). There was no significant difference in the drug content uniformity between the left and right arm of the V-shell. These results show the effectiveness of the blending process for both formulations in terms of the two blenders, batch size and blending time. The highest percent RSD value for the blend uniformity samples collected at multiple locations in the blender was found to be < 2.8%, indicating an excellent distribution of drug within the blend. Uniformly mixed blends produce uniformly compressed tablets that meet the USP content uniformity requirements. Based on this theory and due to low percent active in the blend (< 2%), combined with FDA recommendations for blend uniformity analysis for the products that require USP content uniformity, it was necessary to evaluate the drug content uniformity in the blend. Comparison of the blend uniformity assay values of the small scale and large scale blends show no statistically significant difference in the content uniformity assay values for formulation I (Table 18 Appendix I). Although formulation II showed a statistically significant difference in the blend uniformity for

Table 7. Blend Uniformity Results of Unit Dose Blend Samples from V-Blender

Blend Sample# / Location	1 ft^3 Formulation I	1 ft^3 Formulation II	10 ft^3 Formulation I	10 ft^3 Formulation II
	Assay %			
L1	101.0	103.8	101.4	101.0
L2	104.4	102.8	98.0	99.1
L3	101.5	104.0	100.9	98.0
L4	98.5	101.6	102.0	99.1
L5	101.9	96.5	101.4	99.1
R6	101.4	96.4	102.9	99.4
R7	102.4	99.7	102.3	96.8
R8	101.7	101.8	101.1	97.0
R9	98.5	99.2	100.8	96.6
R10	101.5	103.1	98.0	98.7
Average	101.3	100.9	100.9	98.5
Range	98.5–104.4	96.4–104.0	98.0–102.9	96.6–101.0
RSD	1.7	2.8	1.6	1.4

L – left arm of V-blender

R – right arm of V-blender

pilot and large scale the assay values for both the 1 ft^3 and 10 ft^3 blenders of both formulations are within the acceptable range of 90–110% with a RSD < 5% as stated in the FDA blend uniformity analysis guidance for the industry (23). ANOVA comparison of the blend uniformity assay results of all four batchs shows a statistically significant difference between the means of the content uniformity assay values. The blend uniformity mean assay value for $10ft^3$ scale of formulation II was found to be significantly different when compared with the small scale batch using the multiple range test. A complete statistical comparison of these results is included in (Table 19-20 Appendix I). Interestingly, the large scale blend has a smaller RSD compared to the small scale batches.

3.3 Granule Size Distribution:

The particle size of the ingredients used in a direct compression hydrophilic matrix formulation may have a significant impact on the performance and drug release characteristics (16,17). Differences in the particle size distribution between different materials in the formulation may influence the packing behavior of the materials and hence influence the material performance during granulation and tableting (11,24). Also tablet characteristics such as weight variation may be affected by differences in particle size and density (25). With this in mind, it was decided to determine the particle size distribution of the drug and the excipient blend used in the formulation.

The weight distribution of 5 g of granules was measured after 5 min of vibration over a nest of standard sieves (mesh size 325, 200, 150, 100, 80, 60). Table 8 shows the

Table 8. Weight Distribution of Granules for the Four Batches

Mesh Size (micron)	Percent Retained			
	1X-I	10X-I	1X-II	10X-II
60 (250)	6.2	6.0	4.0	6.0
80 (180)	9.6	8.7	7.0	5.0
100 (150)	9.0	10.0	15.0	14.0
150 (106)	13.0	12.0	17.0	19.0
200 (75)	16.0	16.5	21.0	23.0
325 (45)	21.2	21.0	19.0	17.0
Fines	27.0	26.0	17.0	15.0

sieve analysis results for all four batches. Figure 3 shows the particle size distribution histogram for the final blend at both scale for formulation I. About 16 percent of the particles are in the range of 180 to 250 microns, 59 percent of the particles are in the range of 45 to 150 microns and 27 percent ≤ 45 microns, this produces a fairly uniform blend. The particle size distribution for formulation II both scales (Figure 4) resembles an approximate bell shaped distribution. About 10 percent of the particles are in the range of 180 to 250 microns, 70% in the range of 45 to 150 microns and 17 percent ≤ 45 microns. There was no significant difference in particle size distribution between the small scale and large scale batches of both formulations. However, there was difference in particle size distribution between formulation I and II as expected due to the difference in excipient ratios between the two formulations. These results suggest that uniform mixing of the granulation have been achieved at both scales of blending. Studies show that excipients with angle of repose values < 30° and a particle size < 100 microns exhibit excellent flow characteristics (14, 26). Since the particle size of the blend was fairly uniform, this eliminates the potential problem of segregation of the excipients and an effective flow of granulation was achieved with direct scale-up and compression of the granulation.

3.4 Tablet Properties:

Tablets were compressed over a range of six hardness values between 5–10 kp for both the small scale and the large scale batches to study the effect of various tablet attributes such as weight, hardness, friability and drug release. After collecting samples in

Figure 3. Weight Distribution of Granules
Pilot and Full Scale Manufacture of Formulation I

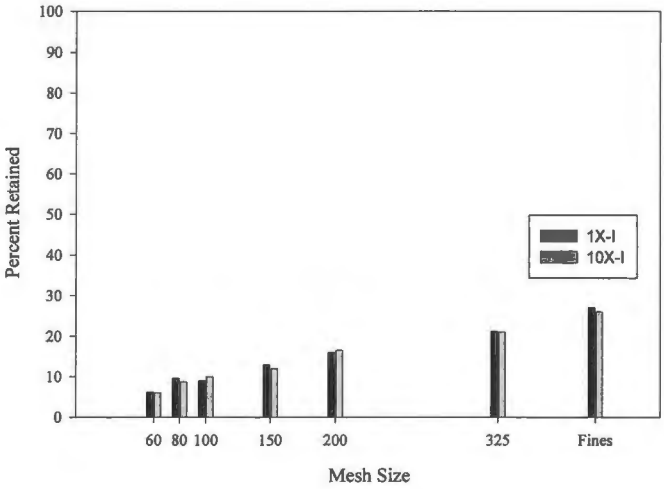
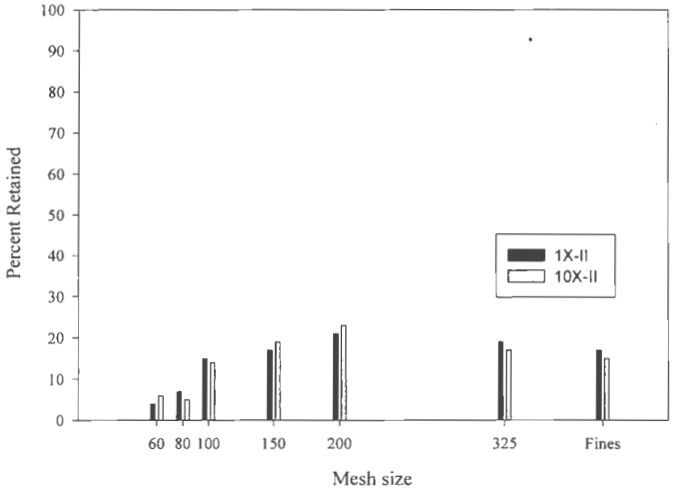


Figure 4. Weight Distribution of Granules
Pilot and Full Scale Manufacture of Formulation II



each hardness range the compression force was increased to the next level of hardness and samples collected. Tablet cores were randomly selected from each batch/range to measure these physical characteristics. Friability is a term used to describe the resistance of tablets to mechanical wear as shown by breakage, chipping, and abrasion during coating, high speed packaging and transportation. The resistance of a tablet to a mechanical wear is dependent on its ratio of stress to strain, and tensile strength (27). In addition, since these tablets are to be coated to delay drug release; it is important that the tablets withstand the physical stress encountered during the coating process (24, 27, 28). Since reliable methods of measuring the tensile strength of a tablet have not been developed, hardness (force applied in kilopounds (kp) required to break the tablets) is used as a measure of compressive tensile strength. To study the effect of compression force on the tablet hardness, tablets were compressed at various preset compression forces as described above. Tablet hardness increased as the compression force was increased showing an almost linear relationship for both formulations (Figure 5). A minimum hardness of 5.5 kp and 6 kp was required to form tablets that required a compression force of 500 kg for formulation I and II respectively. The highest compression force tested was 2000 kg that produced tablets of 10 kp hardness for formulation I and 9.5 kp for formulation II. To determine physical characteristics of the tablets, ten tablets from six levels of hardness (5–10 kp) were tested for weight, thickness, hardness and friability. The tablets produced using the Manesty BetaPress at small scale for both formulations at various target hardnesses were close to the theoretical hardness with minimal weight variation across the hardness range studied (Table 9 and 10). Tablets produced at lower

Figure 5. Effect of Compression Force on Tablet Hardness
Kikusui Libra Tablet Press

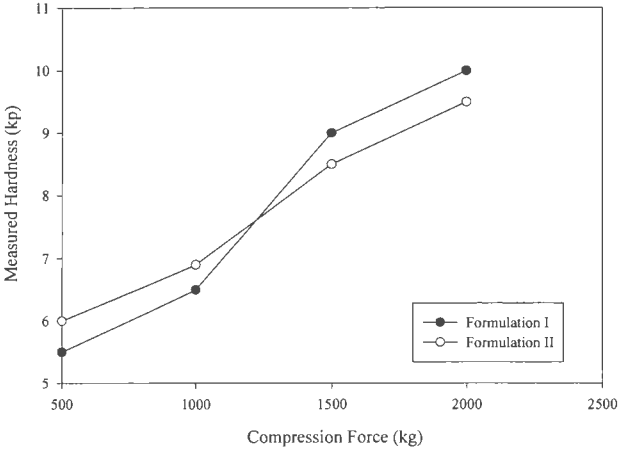


Table 9. Effect of Tablet Hardness on Physical Characteristics Using the Manesty BetaPress

Batch size 1X-I

Tests	Tablet Press Speed 25 RPM (400 TPM)					
Target Hardness (kp)	5	6	7	8	9	10
Hardness (kp)	4.9	6.3	7.2	8.2	9.1	9.9
Range	4.3–5.2	5.7–6.4	6.8–7.1	8.0–8.7	9.0–9.9	8.9–10.0
% RSD	4.2	3.8	3.1	2.9	3.5	3.2
Weight (mg)	135.1	136.3	135.0	136.0	137	137.0
Range	135.0–137.5	135.5–138.5	133.5–137.7	136.0–138.0	136.0–139.0	134.0–138.0
% RSD	0.5	0.4	0.6	0.5	0.7	0.4
Thickness (inches)	0.141	0.138	0.138	0.138	0.137	0.136
Range	0.140–0.141	0.138–0.140	0.137–0.138	0.137–0.139	0.136–0.138	0.135–0.137
% RSD	0.16	0.37	0.29	0.39	0.28	0.19
Friability (%)	0.03	0.02	0.01	0	0	0

Table 10. Effect of Tablet Hardness on Physical Characteristics Using the Manesty BetaPress

Batch size 1X-11

Tests	Tablet Press Speed 25 RPM (400 TPM)					
Target Hardness (kp)	5	6	7	8	9	10
Hardness (kp)	4.8	6.1	6.9	8.4	8.9	10.1
Range	4.4–5.2	5.8–6.5	6.3–7.3	8.0–8.9	9.0–10.0	8.9–10.2
% RSD	5.2	3.6	3.0	3.2	3.0	3.2
Weight (mg)	136.1	137.3	135.0	138.0	138	136.0
Range	135.0–136.7	136.5–138.5	133.0–137.0	136.0–139.0	136.0–140.0	134.0–138.0
% RSD	0.5	0.5	0.9	0.6	0.7	0.8
Thickness (inches)	0.141	0.140	0.138	0.138	0.137	0.136
Range	0.140–0.141	0.139–0.140	0.137–0.139	0.137–0.139	0.136–0.138	0.135–0.137
% RSD	0.17	0.36	0.28	0.41	0.47	0.38
Friability (%)	0.03	0.01	0	0	0	0

hardness 5 kp showed a larger variation in measured hardness, percent RSD values were 4.2 and 5.2 compared with 3.0 and 2.9 for the tablets set with higher hardnesses (8, 9 & 10 kp) for formulation I and II respectively. Tablet thickness was comparable between formulations and was influenced by the fill weight. Higher fill weight gave a thicker tablet and the lower fill weight produced thinner tablets.

Tablets produced at lower hardnesses were found to be friable for both formulations. This can be attributed to the softness of the tablet cores at lower compression force. However, the overall friability of these tablets across all hardnesses was less than 0.03%, which signifies that they should withstand the physical stress applied during coating process. Tablets produced using the Kikusui Libra press at large scale for both formulations at various compression forces produced tablets with a hardness closer to the theoretical hardness than was seen at the smaller scale (Table 11 and 12). A constant press speed of 60 rpm was selected for these hardness studies. Tablets produced at lower hardness at 5 kp exhibited larger RSD values compared with the tablets produced using compression forces in the range of hardnesses of 6–10 kp, indicating a better consolidation at higher compression force. Weight variation was minimal for both formulations at small and large scale suggesting that the granulation flow characteristics were uniform and is not affected by the type of feeder. This indicates that the formulation properties did not have any negative impact on the tablet physical characteristics.

A statistical evaluation (ANOVA) was performed to determine the statistical significance of the variability in measured average hardness values for both formulations

Table 11. Effect of Tablet Hardness on Physical Characteristics Using the Kikusui Libra Press

Batch size 10X-I

Tests	Tablet Press Speed 60 RPM (2160 TPM)					
Target Hardness (kp)	5	6	7	8	9	10
Hardness (kp)	4.8	6.1	6.9	8.4	8.9	10.1
Range	4.3–5.4	5.8–6.4	6.3–7.4	8.1–8.8	9.0–10.0	9.3–10.3
% RSD	5.1	3.0	2.8	3.0	2.7	2.6
Weight (mg)	136.1	137.3	135.0	136.5	138.0	136.0
Range	134.9–137.4	136.7–139.3	133.5–137.2	136.3–138.8	137.2–140.3	134.2–138.1
% RSD	0.5	0.5	0.9	0.6	0.7	0.8
Thickness (inches)	0.141	0.140	0.138	0.138	0.137	0.136
Range	0.140–0.141	0.139–0.140	0.137–0.139	0.137–0.139	0.136–0.138	0.135–0.137
% RSD	0.28	0.27	0.28	0.39	0.37	0.38
Friability (%)	0.02	0.02	0	0	0	0

Table 12. Effect of Tablet Hardness on Physical Characteristics Using the Kikusui Libra Press

Batch size 10X-II

Tests	Tablet Press Speed 60 RPM (2160 TPM)					
Target Hardness (kp)	5	6	7	8	9	10
Hardness (kp)	5.1	6.2	7.1	8.4	9.1	10.2
Range	4.6–5.3	5.8–6.3	6.7–7.3	8.0–8.7	9.0–10.0	8.9–10.3
% RSD	4.2	3.2	2.6	2.2	3.1	2.9
Weight (mg)	135.1	136.3	135.2	135.3	136.1	135.4
Range	135.0–136.1	136.2–138.5	133.0–138.0	133.0–137.0	136.1–139.0	134.0–137.5
% RSD	0.4	0.9	1.1	1.0	0.7	0.8
Thickness (inches)	0.141	0.137	0.136	0.136	0.136	0.136
Range	0.140–0.141	0.139–0.140	0.134–0.137	0.133–0.137	0.134–0.137	0.135–0.137
% RSD	0.16	0.63	0.82	0.92	0.49	0.39
Friability (%)	0.02	0.01	0.01	0	0	0

at both scales of manufacture. Among the comparisons made for 5–10 kp, there was no significant difference between average hardness was observed for 6–10 kp. However, there was a significant difference (P=0.0183) in average hardness was observed at 5 kp hardness, suggesting that at lower compression force, the consolidation of granulation is not uniform between tablets. A complete statistical analysis result is presented in (Table 21-26) Appendix I. Furthermore, comparison of weight, thickness and friability results for both formulations manufactured using two different tablet presses show similar results suggesting that there is no difference between small and large scale batches/presses.

3.4.1 Drug Content Uniformity

Homogeneity is confirmed by the results of the unit dose assay values and relatively small RSD values. FDA recommends blend uniformity analysis for the products that require content uniformity analysis (23). USP requires this test when the drug product contains less than 50 milligrams of the active ingredient per dosage form unit, or when the active ingredient is less than 50 percent of the dosage form unit by weight. Blend uniformity analysis or homogeneity testing can be applied to all dosage forms, but is recommended for those dosage forms for which the USP requires content uniformity testing. For this reason the content uniformity of the blend samples and the tablets produced with the corresponding blend was evaluated to see if there was a difference between assay/RSD for tablets and blend samples at various scales.

Table 13 compares the blend and tablet content uniformity results for small and large scale batches. It can be seen from these results that all the individual assay values

Table 13. Content Uniformity Results for Blend and Tablet Cores

Tablet Press	Manesty BetaPress				Kikusui Libra Press			
Batch Size	1X-I		1X-II		10X-1		10X-II	
Stage	Blend	Tablet	Blend	Tablet	Blend	Tablet	Blend	Tablet
Assay (%)	101.3	100.7	100.9	100.6	100.9	99.1	98.5	99.8
Range	98.5–104.4	98.9–102.7	96.4–104.0	97.1–105.4	98.0–102.9	97.3–100.6	96.6–101.0	98.5–102.1
RSD (%)	1.7	1.3	2.8	2.7	1.6	1.1	1.4	1.2

for the blend samples are within 96.6–104.4%, and the highest RSD value observed was 2.8% for formulation II at the small scale. The RSD values decreased as the batch size increased for both formulations. Furthermore, it can be seen that all the individual assay values for the corresponding tablet samples are within 97.1–105.4%, and the highest RSD value observed was 2.7% for formulation II at the small scale. Thus all pass USP requirements for solid dosage form content uniformity. The RSD values decreased as the batch size increased for both formulations. A statistical analysis using multiple sample comparison was performed to evaluate the difference between the blend and tablet content uniformity values. The analysis showed that there was no statistically significant difference between the content uniformity assay values of the blend sample and the corresponding tablet cores at the 5% level (ANOVA test results are presented in Table 27-30 Appendix I). The content uniformity values of the blend samples are reproducible in the corresponding tablet cores. These results suggest that a good homogeneity of the drug in the granulation have been achieved at both scales and is not affected by the additional handling and mixing during compression for both formulations.

3.4.2 Drug Release

In order to select a suitable tableting parameter, the effect of tablet hardness on drug release was also evaluated. Effect of tablet hardness on drug release is presented in Figure 6 and 7 for formulation I at two different scales. The dissolution profiles show a 100% drug release in 3 hours at all hardness ranges studied. Higher variability in drug release was observed at the 1 hour time point. The variability in drug release at early time

Figure 6. Effect of Tablet Hardness on Albuterol Sulfate Release for Batch Size 1X-I (Manesty BetaPress)

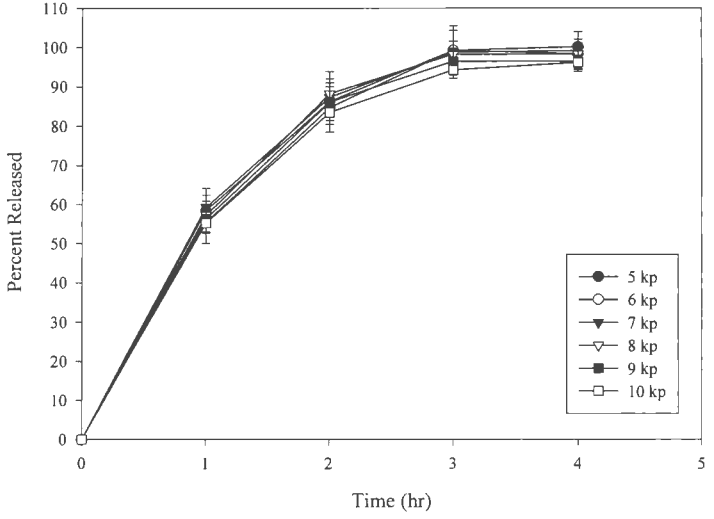
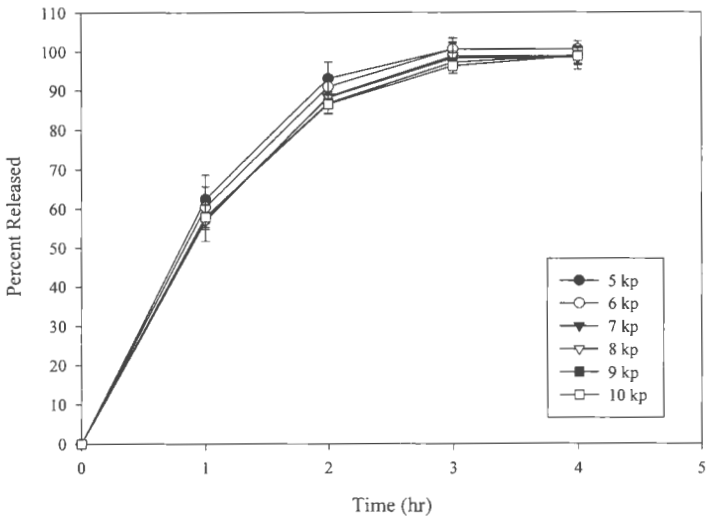


Figure 7. Effect of Tablet Hardness on Albuterol Sulfate Release for Batch Size 10X-I (Kikusui Libra Press)



point was larger (RSD = 6%) for both scales. This variability may be attributed to the difference in time of hydration and diffusion of the drug from the tablet matrix for the different hardness levels produced during manufacture. However, less variability (RSD < 2%) was observed at the later time points indicating that once the hydration is complete drug release is consistent between tablets. Furthermore, the time required for 50% and 75% drug release was determined for all hardnesses and a statistical evaluation was performed to determine if there were differences in dissolution time. The analysis of variance results for these comparisons did not show any statistically significant difference in time required for 50% and 75% drug release. Figure 8 and 9 show the effect of tablet hardness on drug release for formulation II at the two different scales. Again higher variability in drug release was observed at the 1 hour time point. However, a lower variability in dissolution was observed at the later time points indicating drug release is consistent after complete hydration of the tablets. In addition, the time required for 50% and 75% drug release was determined for all hardnesses and a statistical comparison of these results show no difference in time required for 50% and 75% drug release (Complete ANOVA results for these comparisons are included in Table 31-34 Appendix I). It can be seen from these results that there is no significant difference between the mean drug release obtained for various tablet hardness for formulation II manufactured using two different tablet presses.

Differences between tablet presses that result in different compression levels may have an effect on the final characteristics such as tablet hardness, disintegration and dissolution (3,7,29). Such problems may arise with materials that undergo time-

Figure 8. Effect of Tablet Hardness on Albuterol Sulfate Release for Batch Size 1X-II (Manesty BetaPress)

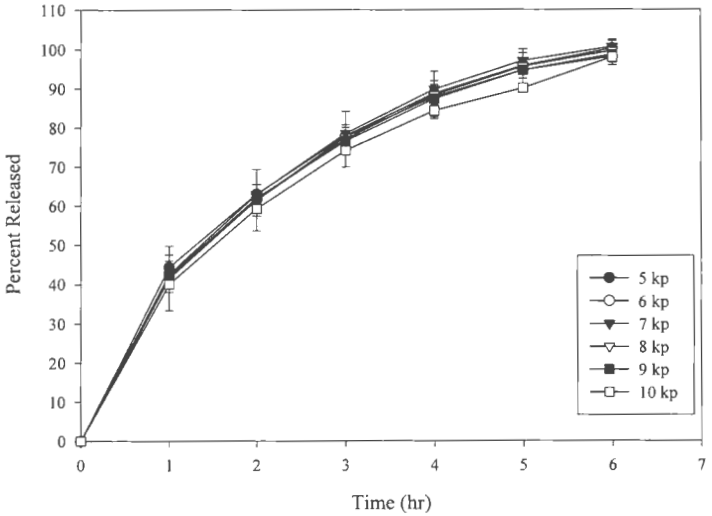
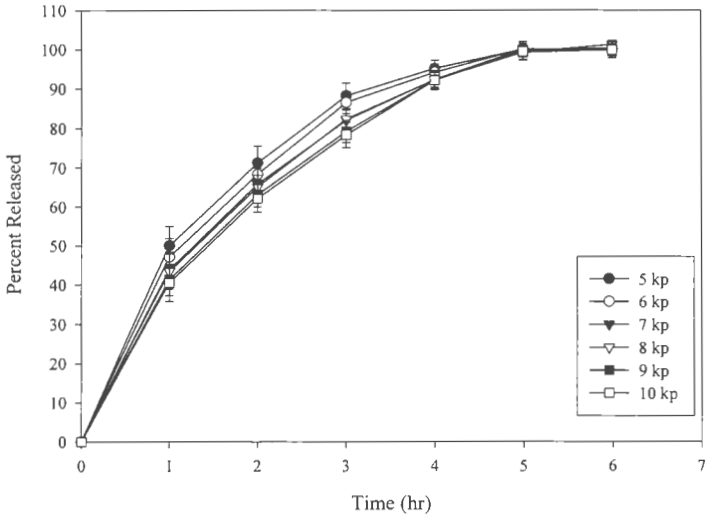


Figure 9. Effect of Tablet Hardness on Albuterol Sulfate Release for Batch Size 10X-II (Kikusui Libra Press)



dependent stress relaxation due to differences in dwell time related to variations in tablet press speed (7,30). In order to evaluate this behavior, the effect of tablet press speed with constant compression force that yielded tablets of 8 kp hardness was manufactured using the Kikusui Libra tablet press. Four different press speeds (40–70 rpm) were evaluated in an attempt to study the various tablet attributes and drug release for both formulations at the larger scale (Table 14 and 15). Since, it was not possible to adjust the press speed on the available Manesty betapress, the effect of tablet press speed on the tablet attributes was not evaluated at the pilot scale level for both formulations. For both formulations at the large scale, the speed of compaction had little effect on the tablet physical characteristics. The effect of compaction speed on the tablet hardness seemed to marginally increase with constant applied force. Average hardness ranged from 8.1–8.7 kp for various press speeds. This phenomenon was observed in both formulations. Although the hardness increased with increased press speed, it was not significant to impact the tablet physical characteristics. This is further evidenced by the fact that there was very small difference in the tablet weight and no difference in tablet thickness with the various press speeds. The tablet friability was not significantly affected by the press speed and the maximum value observed was < 0.04% for formulation I at 40 rpm. Furthermore, the mean dissolution values for tablets manufactured at various compression speeds also suggest that the drug release was not affected by varying the press speed. It can be seen from Figure 10 approximately 50% of the drug is released in the first hour with minimal variability between various samples. The variability in drug release is also minimal across all the samples tested for formulation I at various

Table 14. Summary of Tablet Press Speed Study Results (Tablet Hardness 8 kp)

Batch Size 10X-I (Kikusui Libra Press)

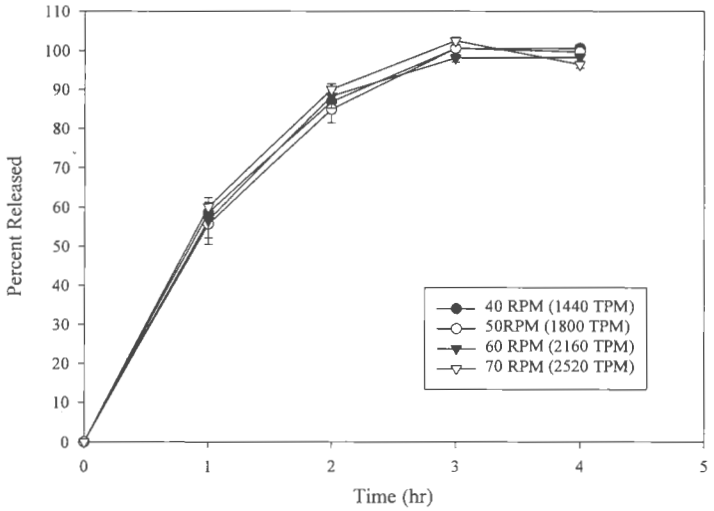
Tests	Tablet Press Speed RPM			
	40	50	60	70
Hardness (kp)	8.1	8.4	8.5	8.6
Range	7.7–9.0	8.2–8.7	8.2–9.0	8.0–9.1
% RSD	4.0	2.0	2.6	3.4
Weight (mg)	135.0	135.0	136.0	136.0
Range	134.0–137.0	133.0–137.0	135.0–138.0	134.0–138.0
% RSD	0.63	0.68	0.72	0.74
Thickness (inches)	0.137	0.137	0.137	0.137
Range	0.137–0.138	0.137–0.138	0.136–0.138	0.135–0.138
% RSD	0.30	0.32	0.40	0.42
Friability (Percent)	0.04	0.01	0	0.02

Table 15. Summary of Tablet Press Speed Study Results (Tablet Hardness 8 kp)

Batch Size 10X-II (Kikusui Libra Press)

Tests	Tablet Press Speed RPM			
	40	50	60	70
Hardness (kp)	8.1	7.8	8.4	8.7
Range	6.7–7.3	6.0–7.4	8.0–8.7	6.7–9.5
% RSD	2.6	3.6	2.2	3.6
Weight (mg)	134.6	135.3	135.8	135.2
Range	133.5–136.0	134.0–138.0	133.0–137.0	133.0–137.0
% RSD	0.53	0.79	1.01	0.76
Thickness (inches)	0.137	0.136	0.136	0.136
Range	0.137–0.138	0.134–0.137	0.133–0.137	0.134–0.137
% RSD	0.46	0.47	0.92	0.68
Friability (Percent)	0.02	0.01	0	0

Figure 10. Effect of Tablet Press Speed on Dissolution for Batch Size 10X-I (Kikusui Libra Press)



compaction speeds. Figure 11 depicts the dissolution profile for tablets manufactured at various press speeds at a constant compression force for formulation II, the dissolution profiles are similar suggesting that increased press speed did not have an effect on drug release. The variability in drug release at the early time points are large, approximately 40% of the drug release is observed at the second hour. However, the variability reduces as the dissolution time progresses and 100% drug release is observed at 5 hours as expected. Thus we can conclude from these results that both formulations are not sensitive to the dwell time which is invariably affected by the compression speed (30). Furthermore, the dissolution profiles for the two different formulations are not similar as the objective of the research with development of a fast and slow release controlled release tablets. Figure 12 compares the dissolution profile for both fast and slow release formulations. It can be seen from these results that the two formulations exhibit distinct dissolution profile. The formulation I that used low viscosity polymer and high concentration of starch released the drug faster as expected and formulation II used a high viscosity polymer produced a slow drug release extended up to six hours. Table 16 summarizes the tablet properties of all formulations manufactured at two different scales. The average weight of the tablets manufactured for all batches were acceptable and close to the theoretical weight of 135 mg. Average tablet hardness for the batches ranged from 8.0–8.3 kp indicating that a compression speed of 60 rpm is optimal for the large scale manufacture. A friability value of < 0.1% weight loss was observed for all formulations at both scales of manufacture.

Assay and content uniformity results for all batches manufactured met USP

Figure 11. Effect of Tablet Press Speed on Dissolution for Batch Size 10X-II (Kikusui Libra Press)

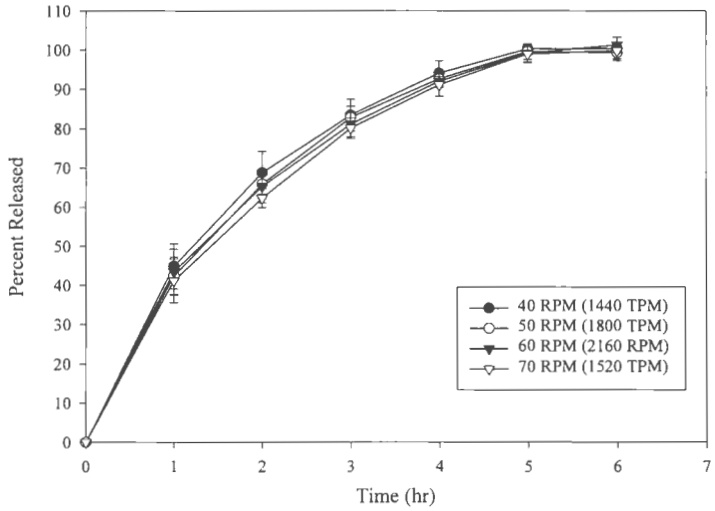


Figure 12. Dissolution Profile for Controlled Release Tablets

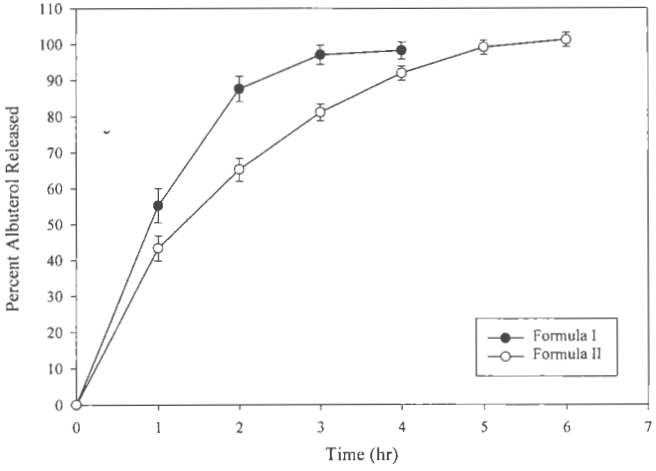


Table 16. Summary of Tablet Properties

Batch Size	Thickness (in.)	Hardness (kp)	Friability (%)	Assay (%)	Content Uniformity (%)	RSD (%)	F_2
1X–I	0.138	8.1	0.1	99.8	100.7	1.3	94.0
1X–II	0.137	8.2	0.0	100.3	100.6	2.7	83.6
10X–I	0.138	8.0	0.0	100.1	99.1	1.1	94.0
10X–II	0.138	8.3	0.0	100.2	99.8	1.2	83.6

specifications of (90–110%) for assay and content uniformity (90–110% and RSD < 6%) for solid dosage forms. The drug content uniformity of the tablets at both scales was acceptable with a smaller RSD value. (Table 16). Furthermore, the controlled release tablets manufactured for both formulations at different scales showed nearly superimposable dissolution characteristics (Figure 13 and 14).

Dissolution profiles were compared graphically and through the mathematical fit factor (F_2). The fit factor F_2 is 100 when the test and reference profiles are identical and approaches 0 as the dissimilarity increases (31). The pair-wise comparisons of the dissolution results for two different scales of these formulations evaluated using F_2 metrics show a value of 94 and 83.6 for formulation I and II respectively. An F_2 value of 50 or greater indicates that dissolution profiles are similar according to the F_2 metrics established by SUPAC guidelines (6,31). F_2 analysis results for these comparisons are included in Table 35-36 Appendix I. In addition, the batches manufactured at two different scales were stored in HDPE bottles and showed no change in assay or dissolution profiles when stored at controlled room temperature (20-25°C) for 3 months (Figure. 15-17).

Based on the evaluation of various compression study results, final tableting parameters were selected for the manufacture of the controlled release tablets cores. The tableting parameter that produced robust tablets with low friability, minimal weight variation and hardness was selected as the final compression parameter for manufacturing the controlled release tablets. Table 17 summarizes the optimum tableting parameters selected for the tablet manufacture. The press speed selected was 25 rpm for the Manesty

Figure 13. Effect of Scale-up and Type of Tablet Press on Drug Release
Formulation I

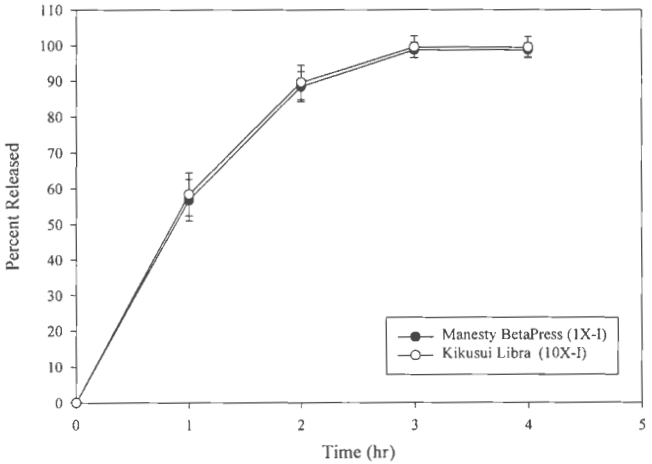


Figure 14. Effect of Scale-up and Type of Tablet Press on Drug Release Formulation II

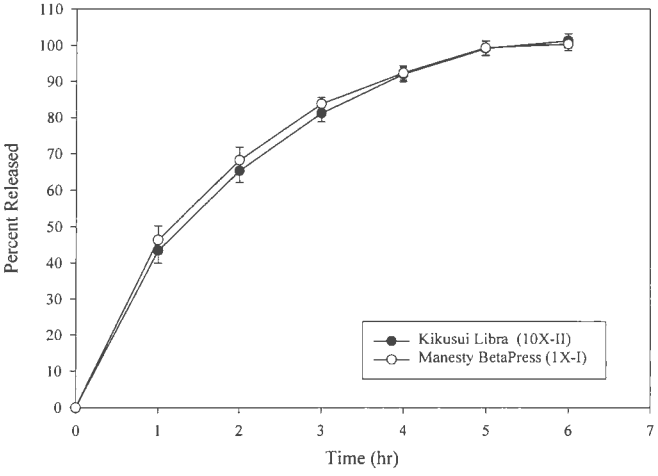


Figure 15. Dissolution Profile for Controlled Release Tablets Stored at 25°C/Ambient Condition (Formulation-I)

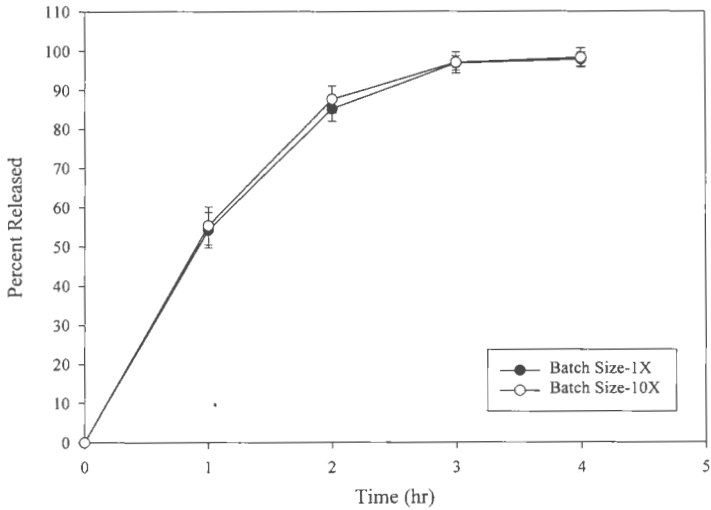


Figure 16. Dissolution Profile for Controlled Release Tablets
Storage Condition 25°C/Ambient Condition (Formulation-II)

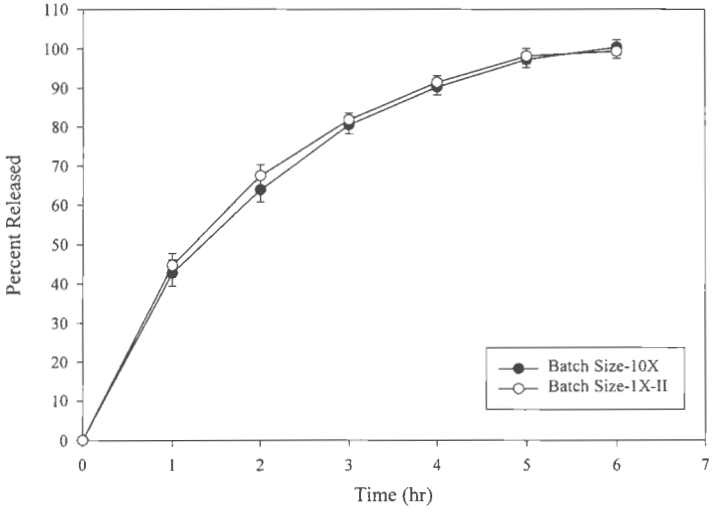


Figure 17. Controlled Release Tablet Assay
Storage Condition 25°C/Ambient

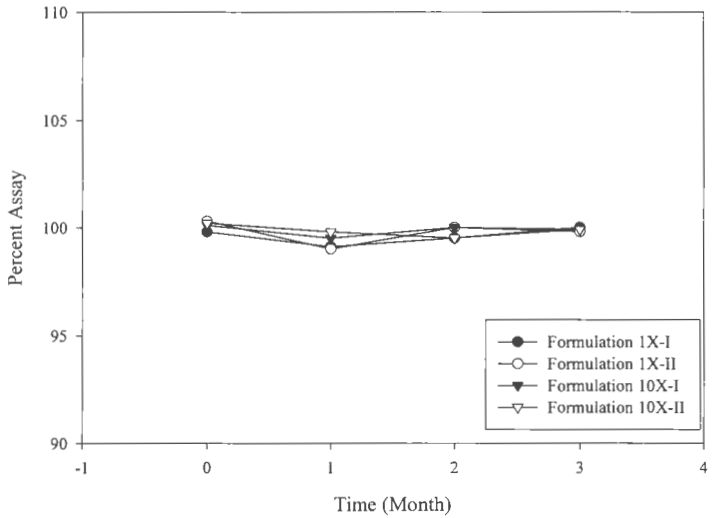


Table 17. Optimized Tableting Parameters

Tablet Press	Speed (rpm)	Fill Weight (mg)	Hardness (kp)	Compression Force (kg)	Friability (%)
BetaPress (Small scale)	25	135	8	N/A	<0.5
Kikusui Libra (Large scale)	60	135	8	1700-2000	<0.5

BetaPress for the small scale and 60 rpm for the Kikusui Libra press for the large scale production. The tablet weight 135 mg and 8 kp hardness was selected for both formulation I and II. Tablets thus produced using the established tableting parameters were used for further development and coating studies.

4.0 Summary and Conclusions

Over or inadequate mixing of granulation could potentially lead to segregation of particles and would result in non-homogenous blend. This may result in non uniformity of the drug substance in the dosage form and variability in the drug release. The blending equipment used for both small and large scale was geometrically similar. The most important factors that should be considered in scaling-up of the granulation process include adjustment of the blending time and head space to blender capacity based on the size of the blenders used at various stages of scale-up to maintain constant blending geometry and equivalent mixing. The batches manufactured at different scales exhibited similar granulation properties for the two formulations studied.

Tableting scale-up is principally different from that of mixing because there is no dimensional changes as the batch volume is increased due to process replication at higher speeds. Although selecting an appropriate compression force to obtain the desired hardness is critical in obtaining reproducible drug release characteristics. Our studies show that varying tablet hardness for both formulations did not influence drug release. The tablets produced using two different tablet presses for a range of speeds exhibited similar tablet characteristics and dissolution profiles. The statistical evaluation of the dissolution results indicate that there is no statistically significant difference between the mean drug release at the 5% level for two different batch sizes.

Furthermore, for both the scales of manufacture, all the pair-wise comparisons of the mean dissolution results for both formulations were equivalent based on SUPAC F_2 criteria. These findings indicate, appropriate in-process controls and the use of scaling

factors are essential for successful scale-up. Results also suggest that a direct scale-up of the controlled release tablet formulation with a mechanical robustness is possible from the pilot to the production scale. The proposed characterization technique gives an insight into the equipment capabilities and thus is suggested for use in scale-up of direct compression granulation and tableting processes.

REFERENCES

1. Avallone, H. L., Development and Scale-up of Pharmaceuticals, Pharm. Eng. 10 (4), 38-41 (1990).
2. Chowhan, Z. T., Aspects of Granulation Scale-up in High-Shear Mixers, Pharm. Technol., 12 (2), 26-44 (1988).
3. Russo, E. J., Typical Scale-up Problems and Experiences, Pharm. Technol., 8 (11), 46-56 (1984).
4. Augsburger, L. et al., An Approach Toward Establishing a Scientific Foundation for Interpreting Regulations and Workshop Reports on Scale-Up and Post Approval Changes, Pharm Res., 11 (10), S161 (1994).
5. Leuenberger, H., Scale-up of granulation Process with Reference to Process Monitoring, Acta Pharm. Technol., 29 (4), 274-280 (1983).
6. FDA Guideline for Industry-immediate release solid oral dosage form/scale-up and post approval changes (SUPAC-IR): Chemistry, manufacturing, and controls. In vitro dissolution and in vivo bioequivalence documentation, Federal Register, Vol. 60, No. 230, 30 November 1995, pp. 61638-61643.
7. Levin, M., Equipment Characterization for Solid Dosage Process Scale-Up Using Dimensionless Numbers and Performance Indices, 1 (4), 1261 (1999).
8. Mitchell, K., et al., Influence of concentration on the release of drugs from gels and matrices containing Methocel, Int. J. Pharm., 100, 175-179 (1993).
9. Talukdar, M and Kinget, R., Comparative study on xanthum gum and hydroxypropyl methylcellulose as matrices for controlled release drug delivery. Part 2. Drug diffusion in hydrated matrices Int. J. Pharm., 151, 99-107 (1997).

10. Palaniswamy, S., "Modified Release Adrenergic Drug for Twice a Day Dosing", Masters Thesis, University of Rhode Island, Kingston RI, USA, May (1994).

11. Wells. J. I., *Pharmaceutical Preformulation*, 1st Ed, Ellis Horwood Limited, Chichester, England, (1988).

12. Carr, R.L., Evaluating Flow Properties of Solids, Chem. Eng., 72, 163-168 (1965).

13. The United States Pharmacopoeia 23 Rev., United States Pharmacopoeial Convention, Inc 12601, Twinbrook Parkway, Rockville, MD 20852 (1995).

14. Mira, C., Garcia-Montoya, E., Perez-Lozanao, P., Garcia-Tobajas, A., Coderch, M., Gurrero, M., Minarro, M., Sune-Negre, J and Tico, J., Comparative Study of the Technological Parameters for Direct Compression (DC) Excipients, PharmaSci., 1 (4), 1281 (1999).

15. Lachman, L., Liberman, H. A and Kanig, J. L., *The Theory and Practice of Industrial Pharmacy*, 3rd Ed, Lea & Febiger (1987).

16. Malamataris S., Karidas, T and Goidas, P., Effect of Particle Size and Sorbed Moisture on Compression Behavior of some Hydroxypropyl Methylcellulose Polymers, Int. J. Pharm., 103, 205-215 (1994).

17. Malamataris, S and Karidas, T., "Effect of Particle Size and Sorbed Moisture on the Tensile Strength of Some Tableted Hydroxypropyl Methylcellulose (HPMC) Polymers", Int. J. Pharm., 104, 115-123 (1994).

18. Mosquera M. J., Cuŕa, M., Souto, C., Concherio, A., Martínez-Pacheco, R and Gómez-Amoza J. L., Effects of hydroxypropyl methylcellulose (HPMC) moisture content on hydrochlorothiazide release from HPMC-based tablets, Int. J. Pharm., 135, 147-149 (1996).

19. Hausberger, A., McDermott, T., Erhart L., Freel, D and Kirkman, C., Effect of Blender Scale, Blender Type and Sample Size on Blender/Granulation Homogeneity, PharmSci., 1 (1), S179 (1998).

20. Pichieri, A and Rohera, B. D., Study of effect of Scaling-up on the Content Uniformity of A Model Drug, PharmSci Supplement., 1 (4), 1262 (1999).

21. Pang, J., Wu, L., Chen, J. G., Markovitz, D and Hussain, M. A., Process Scale-up and Optimization for Low Strength DMP 543 Capsules", PharmSci., 1 (4), 1235 (1999).

22. Badaway, S. I. F and Menning, M. M., Effect of Over-Lubrication on Disintegration and Dissolution Rates of A Tablet Dosage Form for A Low Dose Compound, PharmSci., 1 (4), 250 (1999).

23. Blend Uniformity Analysis, CDER Guidance for Industry, August 3, 1999.

24. Mehta, A. M., Scale-up considerations in the fluid bed processor for controlled release products, Pharm. Technol., 12 (2), 46-47 (1988).

25. Schaible, D. J., Flow Characterization of Specialty Microcrystalline Cellulose Grades for Use in Direct Compression, PharmSci., 1 (1), S-644 (1998).

26. Sune-Negre J., Tico J., Minarro, M., Garcia-Montoya, E., Perez-Lozanao P., Coderch, M., Gurrero, M., Garcia-Tobajas, A and Mira C., Comparative Study of the Technological Parameters for Direct Compression (DC) Excipients in A Simple DC Formulation For Ibuprofen Tablets, PharmaSci., 1 (4), 1316 (1999).

27. Rowley, F. A., Common problems to avoid in aqueous coating, Pharm. Technol., 15 (10), 68-72 (1991).

28. Skultety, P. F., Rivera D., Dunleavy J and Lin C. T., Quantitation of The Amount and Uniformity of Aqueous Film Coating Applied To Tablets in a 24" Accela-Cota, Drug Dev. Ind. Pharm., 14 (5), 617-632 (1988).

29. Venkatesh, G. M., Lamey, K. A., Levin M and Murphy, S., Correlations Between a Hydraulic Compaction Simulator, Instrumented Manesty BetaPress and The Prester™, PharmaSci., 1 (4), 1297 (1999).

30. Levin, M., Equipment Characterization for Solid dosage Process Scale-Up Using Dimensionless Numbers and Performance Indices, PharmaSci., 1 (4), 1261 (1999).

31. Moore, J. W and Flanner, H., Mathematical Comparison of Dissolution Profiles, Pharm. Technol., 20 (6), 64-75 (1996).

MANUSCRIPT II

DEVELOPMENT OF IMMEDIATE RELEASE DOSE FOR A PULSED-RELEASE TABLET

PART I
SEAL COAT DEVELOPMENT

ABSTRACT

Acid polymers can be applied to solid dosage forms as enteric coatings from aqueous solutions of alkali salts, organic solvent solutions, or pseudolatex dispersions. Because of their insolubility in water, enteric resins historically have been applied using alcohol and other organic solvents. Current interest in enteric material focuses on water-insoluble resins that contain free carboxylic acid groups. These groups ionize at pH values higher than five and solubilize the resins, thereby releasing the drug from the core. The coatings from these resins resist water and gastric fluid but begin to dissolve in the intestine at pH 5-8.

This investigation was under taken to study the effect of various levels of polymer coating, identify the optimum polymer coating required to delay the drug release of the second dose from the matrix core for a period of 3 to 4 hours. Evaluate in-vitro drug release characteristics of a coated tablet under conditions that mimic the in-vivo dissolution behavior. Various levels of polymer coating were evaluated and an optimum concentration that results in adequate seal coating and delayed release was determined. The formulation developed during pilot studies was scaled-up to a production size batch. Various physical characteristics of the coated and uncoated tablets were evaluated as specified in the USP 23.

Two different types of Eudragit® polymers were used to coat controlled release core tablets containing 2 mg of albuterol by spraying from aqueous coating systems. Initially an Accela-Cota perforated coating pan was used to coat an aqueous polymer latex dispersion to retard the drug release from tablet cores for a period of 3-4 hours. These tablets were further coated with a mixture of polymer and drug to deliver 2 mg of

albuterol as immediate release. Scale-up coating parameters were determined for seal coating process.

A High Performance Liquid Chromatography assay method was used to determine drug release from dissolution samples. Dissolution testing was performed using USP apparatus 3 (Reciprocating cylinder). Drug release obtained from both formulations at two different scales showed differences in the release characteristics. The in-vitro dissolution data shows that the drug release can be delayed by the application of the Eudragit® S and Eudragit® L 30 D-55 polymers at a level of 4.7 mg/cm^2 and 5.6mg/cm^2 respectively. The results also demonstrate that Eudragit® S 100 and Eudragit® L 30 D-55 polymers can be successfully used in an aqueous system to obtain a delayed release effect.

1.0 Introduction

Frequently, a marginally delayed release of the active drug is sufficient enough to avoid plasma concentration peaks. In this way it is possible to improve compatibility without significantly delaying the therapeutic effect. A more substantial influence on pharmacokinetics is required where the active drug (such as albuterol sulfate) has a short half-life of two to three hours and is administered two to three times daily. In such cases a therapeutically effective blood level can be achieved by rapid release of an initial dose that is then followed by delayed release of the second dose. Active drug with uniform solubility over the entire pH range of the digestive tract, or at least in the predominant range from approximately pH 5 to 7, can be provided with delayed-release coatings of pH dependent and independent permeability coatings. This is achieved by mixing or combining water-insoluble permeable coating agents with enteric polymers containing carboxyl groups that dissolve between pH 5 and 7 (1).

Shellac is a naturally occurring resin that is processed from the secretion of the beetle *Kerria lacca.* Historically shellac was the material of choice for enteric coating (2). Despite the advantage that shellac films are considerably less permeable to water than films made from organic polymers, the pharmaceutical use of shellac as an adjuvant has greatly declined (3). Due to imperfect charge quality, which is more dependent on the method of refinement than the insect strain or host tree. Zein is another naturally occurring material that is an alcohol-soluble protein extracted from corn gluten that can be dissolved in ammoniated water to produce a coating system. Zein is an extremely versatile polymer for applications involving controlled release, taste masking, enteric and

delayed release coating (4). Unfortunately due to its natural origin this material suffers from the above-mentioned disadvantage (2,3).

Today, aqueous coating of enteric material is experiencing the type of success that film coating had nearly two decades ago. Acrylic copolymers are probably the fastest-growing type of enteric system to replace naturally occurring materials. Two of the most useful polymers in this category are Eudragit® L 30 D-55, a copolymer of methacrylic acid and ethyl acrylate, is a 30% solid in emulsion and Eudragit® S 100, a copolymer of methacrylic acid and methyl methacrylate (2). These polymers will be evaluated in this study to evaluate their efficacy in producing delayed release seal coating of core tablets.

Various types of coating pans are used for pharmaceutical coating. However, perforated pans are the equipment of choice when it comes to tablet coating, simply because of the efficiency and the economic advantage. These coating pans are available in various sizes and spray gun configurations. The number of spray guns employed depends on the size of the coating pan, small coating pans use one or two guns, larger pans use three to four guns. In larger coating pans, it is often beneficial to increase the number of spray guns to obtain broad area coverage and uniform spray patterns and droplet size. Variation in the size of the coating pan could lead to problems such as overwetting, sticking, picking and peeling due to inappropriate spray rates (5).

The goal of the present study is to systematically evaluate the relevant processing parameters of both a pilot scale (24") and a production scale (48") coating pan. These investigations include the evaluation of coated tablet characteristics of two different releasing formulations, fast and slow release, at small scale and production scale. The parameter to be evaluated includes the effect of polymer coating level, the

delayed release effect, coating uniformity and dissolution profiles of the coated tablets manufactured at two different scales.

2.0 Objective

The objective of the present study was to develop a seal coat for a controlled release matrix tablet in an attempt to retard drug release for a period of two to three hours followed by controlled release for a period of three to six hours in a near zero-order fashion. To identify the scale-up parameters, characterize and compare the coated tablet attributes, such as effect of polymer level, coating uniformity and dissolution profiles of the formulations manufactured at two different scales (pilot and production scale).

3.0 Methods

3.1 Materials:

Albuterol Sulfate, USP (Propharmaco, Nobel Industries, Italy); Starch 1500, NF (Colorcon, West Point, PA); Lactose DT (Quest International, Hoffman Estates, IL); Methocel® (Dow Chemical Company, Midland, MI); Magnesium Stearate, NF (Manllinckrot Inc., St. Louis, MO); Colloidal Silicon dioxide (Division Chemical, Baltimore, MD); Talc, USP (Amenda Drug and Chemical Co., Irvington, NJ); Opadry® II White (Colorcon, West Point, PA); Eudragit® S 100, Eudragit® L 30 D-55 (Rohm Pharma, GmBH, Germany); Ammonium Hydroxide, NF (Morflex Inc., Greensboro, NC); Triethylcitrate, NF (Morflex Inc., Greensboro, NC). All raw materials used complied with the current USP/NF grade specifications.

3.2 Equipment:

1 and 10 ft^3 V-Blender, (Gemco, Middlesex, NJ); Sieve Shaker (Sweco, Florance, KY); Micron Air Jet Sieve (Hosokawa Micron Powder Systems, Summit, NJ); Moisture Analyzer, Computrac Max 50 (Arizona Instrument, Tempe, AZ); Tablet Press Model: Beta (Manesty, Liverpool, England); Tablet Press, Kikusui Model: Libra 836 KRCZ (Kikusui, Seisakusho Ltd., Kyoto, Japan); SMI Force Monitoring System (SMI Inc., Pittstown, NJ); Vector Tablet Hardness Tester (Vector Corp., Marion, IA); Friability Tester (Erweka Instrument Corp., Milford, CT); Tap Density Apparatus (J. Engelsmann A. G., Laudwishfen, GmbH, Germany); Tooling 9/32" (Natoli Engineering Co., Chesterfield, MO); High Speed Disperser, Model: 89 (Premier Mill Corp., Reading, PA); Laser Diffraction Particle Size Analyzer, Mastersizer 2000 (Malvern Instruments, Southborough, MA); Peristaltic Pump, Masterflex Model: 7520-10 (Cole Parmer, Chicago, IL); pH meter, Model: 811 (Orion Research Inc., Cambridge, MA); Accela-Cota 24" and 48" (Thomas Engineering, Hoffman Estates, IL); Bio-Dis Tester (Vankel Industries Inc., Edison, NJ); Shimadzu LC-4A, High Performance Liquid Chromatography (HPLC) Equipped with a Shimadzu SPD-2AS spectrophotometer detector (Shimadzu, Japan).

3.3 Core Tablet Formulation:

Table 1 shows typical albuterol sulfate controlled release core tablet formulations that provide fast release (Formulation I) 3 hours and slow release (Formulation II) 6 hours respectively. Drug release was designed to be controlled by a combination of a diffusion and erosion mechanism from the matrix core tablets. This was achieved by inclusion of one of the low or high viscosity hydroxypropyl methylcellulose polymer, along with the selection of an appropriate ratio of soluble to insoluble filler excipients. Formulation, components, process and processing variables were chosen based on the results of an earlier study (5).

3.4 Manufacturing Procedure:

Controlled release albuterol sulfate tablets were prepared by blending the drug, polymer and filler excipients in a specified order using either a 1 ft^3 or 10 f^3V-blender. These blends were compressed using a Kikusui Libra tablet press with 9/32" standard concave tooling. The fill volume in the lower punch of the tablet machine was adjusted to a theoretical weight of 135 mg and the compression force was adjusted to obtain a tablet hardness in the range of 7-8 kilopounds. Table 2 shows tableting parameters for controlled release tablet batches. Figure 1 shows the manufacturing process flow diagram used in the manufacture of albuterol sulfate controlled release core tablets.

Table 1. Tablet Formulation for Albuterol Sulfate Controlled Release Tablet Cores

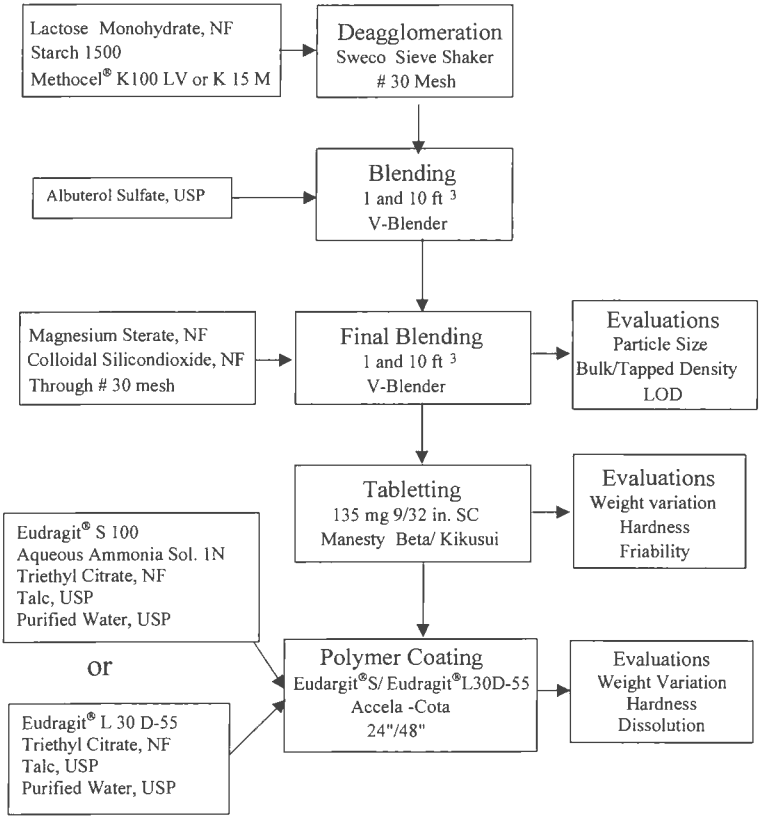
Ingredient	Formulation I		Formulation II	
	Percent w/w	mg/tablet	Percent w/w	mg/tablet
Albuterol Sulfate, USP	1.78	2.40	1.78	2.40
Methocel® (K100LV)	25.04	33.80	–	–
Methocel® (K15 M)	–	–	24.00	32.40
Pregelatinized Starch, NF	25.04	33.80	10.00	13.50
Spray Dried Lactose, NF	46.66	63.00	62.74	84.70
Colloidal silicon dioxide, NF	0.74	1.00	0.74	1.00
Magnesium Stearate, NF	0.74	1.00	0.74	1.00
Total	100.00	135.00	100.00	135.00

Table 2. Tableting Parameters for A Rotary Tablet Press

Parameter	Condition
Number of Stations	36
Batch Size (kg)	135
Tooling Type	B
Tool Size	9/32"
Compression Force (kg)	1200
Granule Feed	IDF[a]
Tablets per minute (TPM)	2160

[a] Induced die feeder

Figure 1. Process Flow Diagram for Albuterol Sulfate Controlled Release Tablets.



3.4.1 Granulation Manufacture

The dry granulation excipients, lactose, Starch 1500 (pregelatinized starch), Methocel® (hydroxypropyl methylcellulose) K 100 LV or K 15 M were deagglomerated using a Sweco sieve shaker. The screened materials were then placed in either a 1 ft^3 or a 10 ft^3 V-blender in the following order. Lactose, albuterol sulfate, pregelatinized starch and hyroxypropyl methylcellulose. These excipients were mixed for a (27minutes for 1 ft^3 and 45 minutes for 10 ft^3). Final blending of the granulation was completed by adding colloidal silicon dioxide and magnesium stearate (#30 mesh) and mixing for 2–3 minutes. The dry granules were then removed from the blender and stored for analysis and subsequent compression into tablets.

3.4.2 Sustained Release Matrix Core Tablet Manufacture

The manufactured granulation was filled in to the hopper of a Manesty BetaPress or an instrumented Kikusui press. The tablet press was setup to compress sixteen or thirty six 7-mm shallow convex tablets per revolution. The target tablet weight was adjusted to 135 mg, and tablets were produced using a pre-compression and main compression force of 300 kg and 1500 kg respectively to produce a target tablet hardness of 8 kp for the entire batch. Tablet samples were collected and stored in tightly sealed containers for subsequent physical characterization such as weight variation, thickness, hardness and friability. Assay and dissolution studies were also performed. The uniformity in weight of the compressed tablets were determined using the weight variation test procedure <905> specified in the United States Pharmacopoeia (USP 23). In-process and composite samples of the core tablets were tested for weight variation, thickness, hardness and

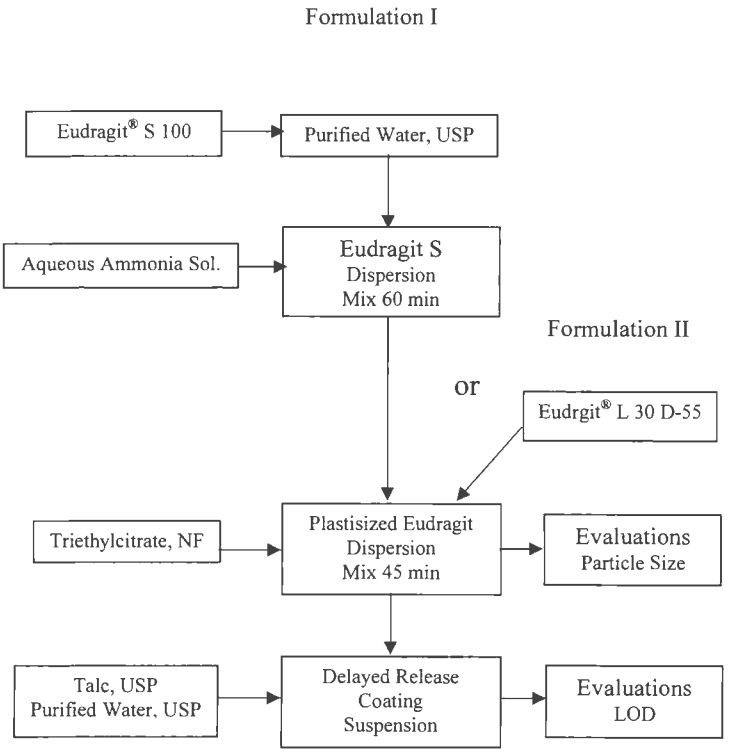
friability. Dissolution testing was conducted on compressed core tablets using an USP apparatus 3, at 25 strokes per minute using 200 ml of simulated intestinal fluid TS.

3.5 Tablet Coating:

3.5.1 Delayed Release Coating Suspension Preparation

Eudragit® S 100 and Eudragit® L 30 D-55 have different film forming properties, and require a certain degree of neutralization for aqueous coating. The recommended neutralization, level for Eudragit® S 100 (with 1 M NH_4OH) is 15% (mole) (6). Eudragit S® 100 powder was dispersed in purified water; to this dispersion a liquid ammonia solution was added and mixed for a predetermined time. Triethyl citrate was added to this mixture and mixed for additional time. Talc was dispersed separately in purified water using the Premier Mill dispersator; this dispersion was added to the Eudragit dispersion to form the coating suspension. For formulation II Eudragit® L 30 D-55 that was available as a latex dispersion, was plasticized with triethyl citrate. Talc was dispersed separately using the Premier Mill dispersator, in purified water; this dispersion was then added to the Eudragit® L 30 D-55 dispersion to form the coating suspension. Figure 2 shows the process flow diagram used to prepare the delayed release coating suspension for formulation I and II.

Figure 2. Process Flow Diagram for Delayed Release Coating Suspension Preparation.



3.5.2 Delayed Release Coating

A 24 or 48 inch Accela-Cota (Thomas Engineering, Hoffman Estates, IL) was loaded with approximately 12 or 130 kg of tablets equivalent to eighty nine thousand or one million tablets. The tablets were coated using either Eudragit S or L delayed-release coating suspension formulations presented in Table 3 and 4 respectively. The Eudragit coating suspension was sprayed through either one or three spray guns equipped with a 1-mm spray nozzle and using a, pan speed ranging from 4-8 rpm, airflow of 1600 ft^3/min, pan pressure of -0.05in. water, and a product temperature of 32°C. Spray to bed distance was maintained constant (10 inches) for all the coating trials. A Masterflex peristaltic pump equipped with silicon tubing was used to deliver the coating suspension. Processing parameters are listed in Table 5. Coated tablets were allowed to dry for 30 minutes at 40°C before cooling and discharge.

3.6 Assay and Drug Release Testing:

In-vitro drug release was studied at various pH's in order to mimic the *in-vivo* dissolution behavior. The pH's selected were 0.1 N hydrochloric acid pH 1.2, acetate buffer pH 4.7, and phosphate buffer pH 7.4 as recommended by USP 23. The dissolution study was performed using Apparatus 3 (Reciprocating cylinder, Bio-Dis) (8). The temperature of the dissolution medium was maintained at 37 ± 0.5°C in all studies. 250 ml of dissolution media was used in each cylinder, the stroke speed was set to 20/minute and, sink conditions were maintained. Multipoint dissolution profiles were constructed by collecting samples at specified intervals and assayed by HPLC to determine the amount

Table 3. Formula for Eudragit S Delayed Release Coating Suspension

Ingredient	Content	
	Percent w/w	mg/tablet
Eudragit® S 100	12.0	6.75
Aqueous Ammonia Solution 1N	6.1	–
Triethyl citrate, NF	6.0	3.38
Talc, USP	4.0	2.25
Purified Water, USP	71.9	–
Total	100.0[a]	12.38

[a] contains 22% w/w of total solids and 15% w/w of polymer

Table 4. Formula for Eudragit L Delayed Release Coating Suspension

Ingredient	Content	
	Percent w/w	mg/tablet
Eudragit® L 30 D-55	50.0[a]	9.45
Triethyl citrate, NF	1.5	0.95
Talc, USP	3.5	2.20
Purified Water, USP	45.0	–
Total	100.0[b]	12.6

[a] contains 15% w/w of polymer
[b] contains 20% w/w of total solids

Table 5. Coating Parameters for Accela-Cota for Delayed Release Coating

Parameter	C-24	C-48
Drum Size (Inches)	24	48
Batch Size (kg)	11	135
Pan (rpm)	12	4–6
Number of Spray Gun	1	3
Spray Rate (g/min/gun)	25	65
Bed to Spray Distance (inch)	8	10
Atomizing Air Pressure (Bar)	1	1.5
Inlet Air Temperature (^{o}C)	60	60
Product Temperature (^{o}C)	32	32
Drying Time (min)	30	30

of drug released. Blend uniformity, tablet assay and content uniformity were determined using a validated HPLC procedure.

3.7 High Performance Liquid Chromatography Assay:

A reverse phase High Performance Liquid Chromatography (HPLC) assay was selected due to the advantage of direct analysis of aqueous samples, high sensitivity, and separation of excipients that may interfere with the assay (8). A reverse phase column, containing packing L1 (Whatman partisil 10-ODS-3, 4.6x250 mm, C18, 10 μm) in conjunction with a variable wave length UV detector was used.

A number of mobile phase systems were tested. The one, that provided the best resolution, consisted of 70% methanol and glacial acetic acid in deionised degassed distilled water was chosen for the assay. The flow rate was 1.5 ml per minute, the UV detector set to 276 nm and the injection volume was 25 μl (using WISP). The linear relationship between peak area vs. concentration was determined using standard solutions of albuterol sulfate ranging from 0-20 μg/ml. to calculate the concentration of albuterol sulfate in the dissolution sample.

4.0 Results and Discussion

4.1 Granule properties:

Table 6 summarizes the granule properties. Values of Carr index ranged from 20.1–23.1%, indicating good flow and consolidation characteristics. Angle of repose values ranged between 27 – 29° which also suggest smooth flow characteristics for the granulations. Loss on drying values were similar for all formulations and ranged from 3.25 – 3.92%. Blend homogeneity is confirmed by the results of the mean unit dose assay values ranging from 99.5–101.2% with relatively small RSD values. The percent RSD variability for the blend uniformity samples collected at multiple locations in the blender was found to be ≤ 1.8%, indicating low variability and good blend uniformity. These results show the effectiveness of blending process for both formulations at both pilot and scale-up levels in terms of batch size and blending time.

4.2 Controlled Release Tablet Core Properties:

Friability is a term used to describe the resistance of tablets to mechanical wear as shown in breakage, chipping, and abrasion during coating, high-speed packaging and transportation. The resistance of a tablet to a mechanical wear is dependent on its ratio of stress to strain, and tensile strength. Twenty tablets were tested for weight, thickness, hardness and friability. Based on earlier compression study results, final tableting parameters were selected for the manufacture of the controlled release tablet cores. Table 7 summarizes the tablet properties for all formulations manufactured. Friability values of ≤ 0.3% were observed for all formulations at both scales of manufacture.

Table 6. Summary of Granule Properties

Batch Size (kg)	LOD (%)	Bulk Density (g/cm^3)	Tap Density (g/cm^3)	Carr Index (%)	Angle of Repose (θ)	Blend Uniformity	
						Mean	RSD
Pilot Formula I	3.53	0.57	0.71	20.1	28°	100.5	1.5
Pilot Formula II	3.58	0.56	0.72	21.1	27°	100.9	1.8
Scale-up Formula I	3.92	0.55	0.78	23.1	29°	101.2	1.6
Scale-up Formula II	3.25	0.56	0.70	22.2	27°	99.5	1.7

Table 7. Summary of Tablet Properties (Controlled release core)

Batch Size (kg)	Weight (mg)	Thickness (in.)	Hardness (kp)	Friability (%)	Assay (%)	Content Uniformity (%)	RSD (%)
Pilot Formula I	135.2	0.138	8.1	0.1	99.8	100.7	1.3
Pilot Formula II	135.6	0.137	8.0	0.1	100.3	100.6	2.7
Scale-up Formula I	134.9	0.138	8.0	0.0	100.1	99.1	1.1
Scale-up Formula II	135.4	0.138	8.2	0.3	100.2	99.8	1.2

A low friability value for compressed tablets suggests that the tablet cores are rugged and can withstand the mechanical stress generated during the coating process. Hence, these tablet cores are acceptable for the coating purposes. Assay and content uniformity results for all controlled release core tablet batches manufactured met USP specifications for assay and content uniformity for solid dosage forms. Tablets manufactured at two different scales were used for the coating studies.

4.3 Coated Tablet Properties:

4.3.1 Eudragit® S Coating

Tablets were initially coated with various levels of Eudragit S polymer to retard the drug release from the tablet cores and to serve as a seal coat over which the loading dose was applied as an immediate release. Coatings were applied in the range of 2.5–5.0% polymer weight gain based on tablet core weight. Table 8 shows the tablet physical characterization and film disintegration results for applied levels of polymer coating. It can be seen from these results that the tablet weight increases when the polymer application level was increased. The tablet hardness also increased gradually from 9.2–14.5 kp as the coating level increased. These results also show large variability of the cores in terms of weight, thickness, hardness and diameter at the initial stages of polymer application (2.3 mg/cm^2) and the variability reduced when the tablets received more coating 2.8 mg/cm^2 and above. Hence, the variability in the tablet weight with polymer levels of $\leq$ 2.8 mg/cm^2 can be explained by the fact that the tablets did not receive uniform coating of the material during the initial stages of the coating process.

Table 8. Tablet Characteristics for Various Levels of Eudragit S Polymer Coating

Coating Level (% w/w)	2.5	3.0	3.5	4.0	4.5	5.0
Polymer Applied (mg/cm^2)	2.3	2.8	3.3	3.7	4.2	4.7
Weight (mg)	141.2	142.4	143.7	144.9	146.2	147.4
RSD (%)	1.6	1.1	0.9	1.2	0.8	1.0
Thickness (mm)	3.51	3.52	3.54	3.56	3.57	3.59
RSD (%)	0.9	0.7	0.8	0.7	0.8	0.8
Hardness (kp)	9.2	11.7	12.5	13.1	13.9	14.5
RSD (%)	2.9	2.0	2.1	1.9	1.8	2.1
Diameter (mm)	7.19	7.21	7.23	7.25	7.26	7.27
RSD (%)	1.0	0.8	0.7	0.8	0.9	0.8
Disintegration Time[a]	150	216	252	312	348	342
(sec)	3.8	2.9	2.5	2.7	2.4	2.2

[a] Disintegration media phosphate buffer pH 7.4; n=6

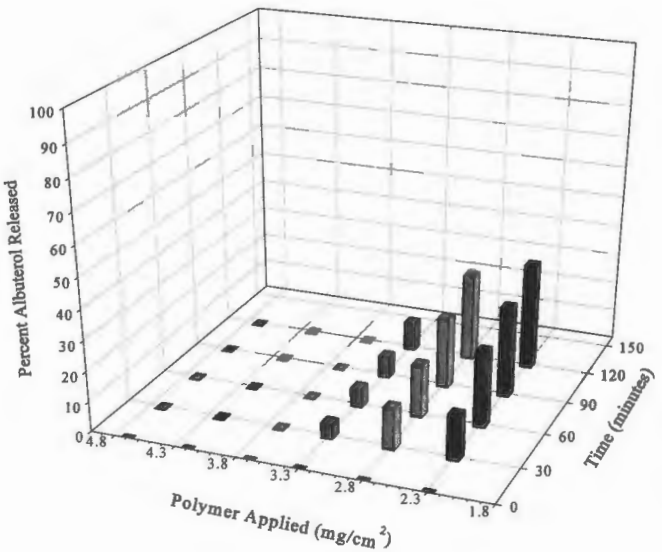
Reduced variability at higher coating levels suggests that the film coat is homogeneous and tablets are well sealed, which was further confirmed by the gastric-resistant test. Effect of coating thickness on film disintegration was determined for various levels of Eudragit S coating. Coating film disintegration time changed slightly for the tablets coated with 3.3 mg/cm^2 polymer (3.5% w/w). Coating film disintegration time increased as a result of increased coating film thickness, 150 seconds for tablets coated with 2.3 mg/cm^2 and 342 seconds for tablets coated with 4.7 mg/cm^2. Increasing the coating thickness from 3.7 mg/cm^2 and beyond had little effect on the film disintegration time.

Table 9 shows the coated tablet disintegration and dissolution properties in the gastric fluid. The film coatings disintegrate at low levels of polymer coating 3.3 mg/cm^2 indicating poor film integrity at these levels. It can be seen from these results that a release of 35.5% was observed at a coating thickness of 2.3 mg/cm^2 and that increasing the coating thickness improved the film integrity and reduces the drug release until no drug was released at > 3.7 mg/cm^2 applied coating level. The film was intact at a thickness of 3.7 mg/cm^2 and beyond. Furthermore, no drug release into the simulated gastric fluid was detected from the tablets coated with ≥ 3.7 mg/cm^2 during the 2-hour gastric resistance test. Figure 3 shows the effect of amount of polymer coating on drug release. Drug release is significantly affected by the amount of polymer applied at the lower level until 3.3 mg/cm^2 application. As the polymer applied increases the drug release gradually decreases and no drug release was observed after 3.7 mg/cm^2 of polymer application. Thus, we can conclude that to produce a delayed release effect a minimum of 3.7 mg/cm^2 of polymer coating is required for adequate seal coating, which

Table 9. Dissolution Results for Eudragit S 100 Film Coated Tablets (T_{120}) Simulated Gastric Fluid

Coating Level (%)	Polymer Applied (mg/cm^2)	Disintegration Time (min)	Albuterol Release (%)
2.5	2.3	2.8	35.5
3.0	2.8	3.5	29.0
3.5	3.3	5.5	9.5
4.0	3.7	Intact	0.0
4.5	4.2	Intact	0.0
5.0	4.7	Intact	0.0

Figure 3. Effect of Coating Film Thickness on Albuterol Release
Eudragit S Coating (Simulated Gastric Fluid)



is similar to the results reported earlier (9).

Table 10 shows the coated tablet properties for Eudragit S coated tablets for formulation I at both the pilot and scale-up. Although 3.7 mg/cm^2 polymer application gave adequate gastric-protection, 5% (4.7 mg/cm^2) polymer coating level was chosen to accommodate any variability in the coating process during routine manufacture. Results indicate a good recovery and efficiency (98.9%) for the tablets coated using the large coating pan (Accela-Cota 48"). However, the coating process using the small coating pan used in the pilot study shows poor recovery (91.5%) was not efficient when compared with the large coating pan. There is a clear indication that the large scale manufacturing process is more efficient than the small scale. Effect of moisture on drying temperature was studied to determine the optimum drying temperature for the coated tablets (Figure 4). Moisture loss measured as percent loss on drying was linear for a period of 480 minutes. After which the loss on drying was constant and no moisture loss observed. The maximum percent moisture loss observed was 3.3% w/w, which is similar to the loss on drying values obtained for the dry granulation and uncoated tablets, suggesting that the coating process did not impart any additional moisture to the tablet cores. Weight variation for the delayed release coated tablets was found to be comparable for the two different batch sizes, with reproducible LOD values.

Dissolution results for coated and uncoated tablets is presented in Figure (5). It can be seen form these comparisons that the uncoated tablets release drug faster than the coated tablets as expected. A polymer coating thickness of 3.7 mg/cm^2 produces a slower drug release approximately 10 percent slower compared with the uncoated tablets, and as the dissolution continues further almost all of the drug (100 percent) was released at the

Table 10. Summary Coating Properties of Eudragit® S Coated Tablets

Batch Size	% Polymer coated		Efficiency	Tablet Weight		Assay	LOD
	Theoretical	Actual	%	mg	%RSD	%	%
Pilot Formula I	5.0	4.9	91.5	147.7	1.6	99.8	2.8
Scale-up Formula I	5.0	5.0	98.9	147.3	1.2	98.9	3.6

Figure 4. Moisture Determination Eudragit S 100 Coating
Drying Temperature 50°C (n=100)

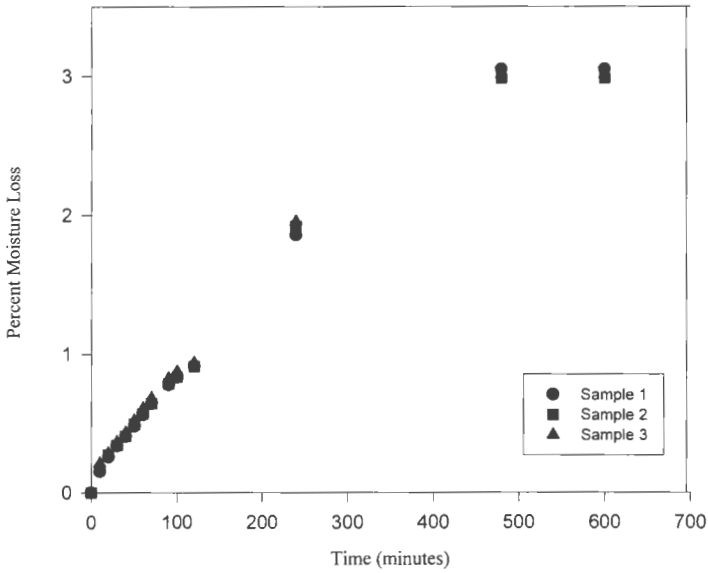
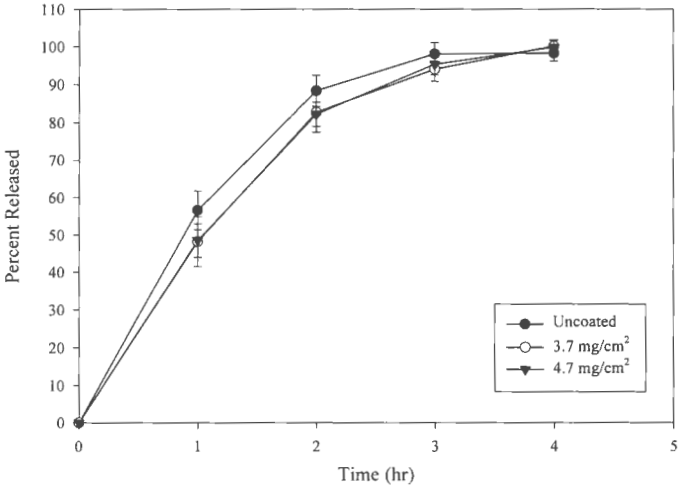


Figure 5. Effect of Eudragit S Coating on Albuterol Release



end of four hour. Tablets coated with 4.7 mg/cm^2 produced similar effect suggesting that the increased coating thickness beyond 3.7 mg/cm^2 did not have significant effect on the rate and extent of drug release.

4.3.2 Eudragit L 30 D-55 Coating

Tablets were initially coated with various levels of Eudragit L polymer to retard the drug release from the tablet cores and to serve as a seal coat over which the loading dose was applied as an immediate release. Coatings were applied in the range of 3–7% polymer weight gain based on tablet core weight. Table 11 shows the tablet physical characterization and film disintegration results for applied levels of polymer coating. It can be seen from these results that the tablet weight increases as expected when the polymer application level was increased. The tablet hardness also increased gradually from 8.6–15.8 kp as the coating level increased. These results also show large variability of the cores in terms of weight, thickness, hardness and diameter at the initial stages of polymer application (2.8 mg/cm^2) and the variability reduced as the tablets received more coating 4.2 mg/cm^2 and above. Therefore, the variability in the tablet weight with polymer levels of $\leq$ 3.7 mg/cm^2 can be explained by the fact that the tablets did not receive uniform coating of the material during the initial stages of the coating process. Reduced variability at higher coating levels suggests that the film coat is homogeneous and tablets are well sealed, which was further confirmed by the gastric-resistant test. Effect of coating thickness on film disintegration time was determined for various levels

Table 11. Summary Results for Various Levels of Eudragit L Film Coating

Coating Level (% w/w)	3.0	3.5	4.0	4.5	5.0	5.5	6.0	6.5	7.0
Polymer Applied (mg/cm^2)	2.8	3.3	3.7	4.2	4.7	5.1	5.6	6.1	6.5
Weight (mg)	140.4	141.3	142.2	143.1	144.0	144.9	145.8	146.00.	147.6
RSD (%)	1.4	1.2	1.2	1.0	0.7	0.8	0.9	8	0.8
Thickness (mm)	3.50	3.51	3.53	3.54	3.55	3.55	3.56	3.57	3.58
RSD (%)	0.9	0.7	0.8	0.7	0.8	0.7	0.6	0.6	0.7
Hardness (kp)	8.6	9.7	11.5	12.3	13.7	14.5	14.8	14.9	15.8
RSD (%)	2.9	2.0	2.1	1.9	1.8	2.1	2.3	1.8	2.5
Diameter (mm)	7.20	7.22	7.23	7.24	7.26	7.26	7.28	7.29	7.29
RSD (%)	1.0	0.8	0.7	0.6	0.6	0.5	0.4	0.5	0.5
Disintegration Time[a] (sec)	163	216	252	312	348	342	341	350	348
RSD (%)	3.8	2.9	2.5	2.7	2.4	2.2	2.8	2.6	2.7

[a] Coating film disintegration time, disintegration media phosphate buffer pH 7.4; n=6

of Eudragit L coating. Coating film disintegration time increased slightly as a result of increased coating film thickness, 163 seconds for tablets coated with 2.8 mg/cm^2 and 348 seconds for tablets coated with 6.5 mg/cm^2. Increasing the coating thickness from 4.7 mg/cm^2 and beyond had little effect on the film disintegration time and was similar to the effect observed with Eudragit S coating.

Table 12 shows the coated tablet properties in the simulated gastric fluid. The film coating disintegrates at 2.8 mg/cm^2 and up to a level of 5.1 mg/cm^2 of polymer application indicating poor film integrity at the lower coating levels. It can be seen from these results that at 2.8 mg/cm^2 polymer application the drug release is 25%, a coating thickness of 4.7 mg/cm^2 improves the film integrity and reduces the drug release until no drug was released at $\geq$ 5.6 mg/cm^2 applied polymer coating level. The film was intact at a coating thickness of 5.6 mg/cm^2 and beyond. Furthermore, no drug release into the simulated gastric fluid was detected from the tablets coated with $\geq$ 5.6 mg/cm^2 during the 2-hour gastric resistance test. Figure 6 shows the effect of amount of polymer coating on drug release. Drug release is significantly affected by the amount of polymer applied at the lower level until 5.6 mg/cm^2 application. As the polymer applied increases the drug release gradually decreases and no drug release was observed after 5.6 mg/cm^2 of polymer application. Thus, we can conclude that to produce a delayed release effect a minimum of 5.6 mg/cm^2 of polymer coating is required for adequate seal coating.

Table 12. Dissolution Results for Eudragit L Film Coated Tablets (T_{120})
Simulated Gastric Fluid

Coating Level (%)	Polymer Applied (mg/cm^2)	Disintegration Time (sec)	Albuterol Release (%)
3.0	2.8	140	25.0
3.5	3.3	175	22.5
4.0	3.7	180	20.3
4.5	4.2	205	20.5
5.0	4.7	207	15.5
5.5	5.1	220	8.0
6.0	5.6	Intact	0.0
6.5	6.1	Intact	0.0
7.0	6.5	Intact	0.0

Figure 6. Effect of Coating Film Thickness on Albuterol Release
Eudragit L 30 D-55 (Simulated Gastric Fluid)

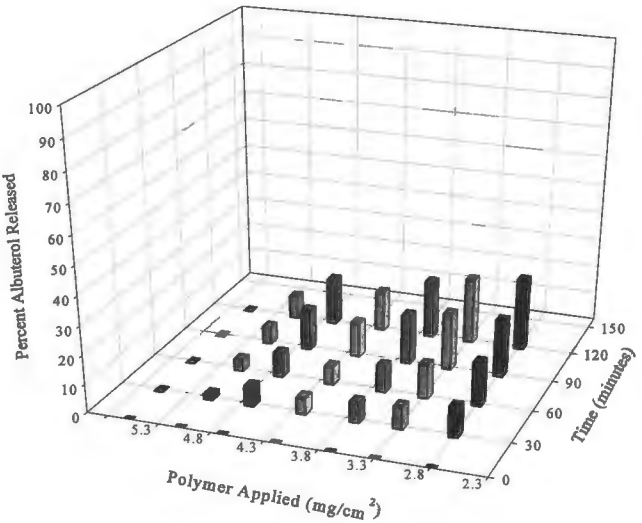


Table 13 shows the coated tablet properties for Eudragit L coated tablets for formulation II at both the pilot and large scale. Although 5.6 mg/cm^2 polymer application gave adequate gastric-protection, 7% (6.5 mg/cm^2) coating level was chosen as discussed earlier to accommodate any variability in the coating process during routine manufacture. Results indicate a good recovery and efficiency (99.8%) for the tablets coated using the large coating pan (Accela-Cota 48"). However, the coating process using the small coating pan used in the pilot study shows poor recovery (97.6%) and was not efficient when compared with the large coating pan. Although the pilot scale (24" pan) coating process for Eudragit L 30 D-55 is more efficient when compared with the Eudragit S coating process, the efficiency is still low. There is a clear indication that the large scale manufacturing process is efficient than the small scale independent of the formulation. Effect of moisture on drying temperature was studied to determine the optimum drying temperature for the coated tablets (Figure 7). Moisture loss measured as percent loss on drying was linear for a period of 480 minutes. After which the loss on drying was constant and no moisture loss observed. The maximum percent moisture loss observed was 3% w/w, which is similar to the loss on drying values obtained for the dry granulation and uncoated tablets, suggesting that the coating process did not impart any additional moisture to the tablet cores. Weight variation for the delayed release coated tablets was found to be comparable for the two different batch sizes, with reproducible LOD values.

Dissolution results for coated and uncoated tablets is presented in Figure (8). It can be seen from these comparisons that the uncoated tablets release drug faster than the coated tablets as expected. A polymer coating thickness of 5.6 mg/cm^2 produces a slower

Table 13. Summary of Tablet Properties for Eudragit L Coated Tablets

Batch Size	% Polymer coated		Efficiency	Tablet Weight		Assay	LOD
	Theoretical	Actual	%	mg	%RSD	%	%
Pilot Formula II	7.0	6.8	97.6	144.8	1.9	100.1	3.2
Scale-up Formula II	7.0	7.0	99.8	148.1	1.7	99.8	2.9

Figure 7. Moisture Determination for Eudragit L 30 D-55 Coating
Drying Temperature 50°C (n=100)

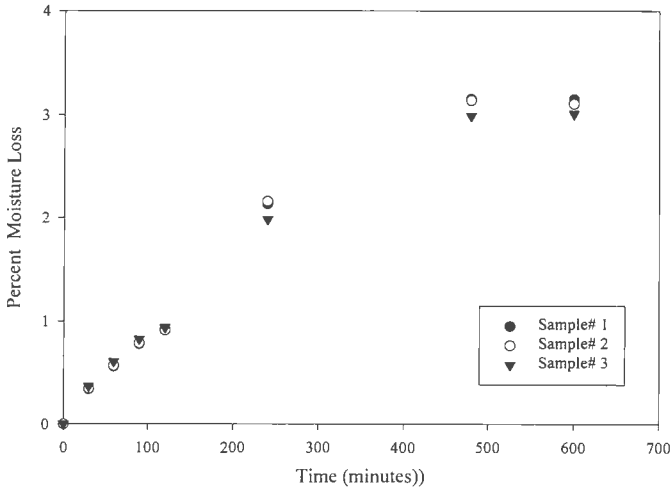
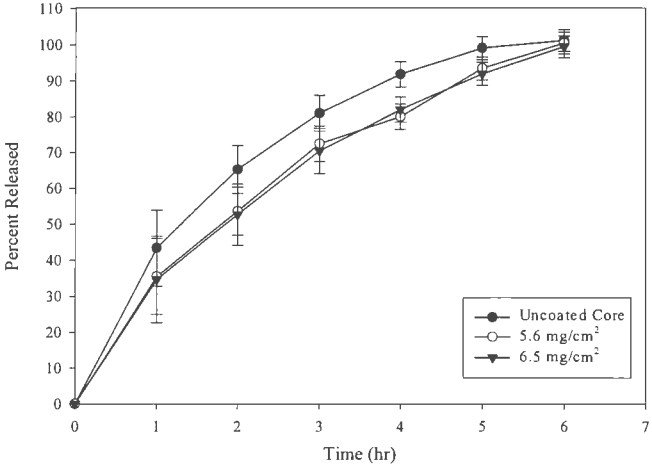


Figure 8. Effect of Eudragit L 30 D-55 Coating on Albuterol Release



drug release approximately 10-15 percent slower across all the time points compared with the uncoated tablets, and as the dissolution continues further almost all of the drug (100 percent) was released at the end of six hour. Tablets coated with 6.5 mg/cm^2 produced similar effect suggesting that the increased coating thickness beyond 5.6 mg/cm^2 did not have significant effect on the drug release.

5.0 Conclusions

Batches manufactured at two different scales exhibited similar granulation and tablet properties for the two formulations studied. Tablets produced using two different tablet presses exhibited similar tablet characteristics and dissolution profiles. A film thickness of 3.7 mg/cm^2 or greater was required to provided adequate seal coating and delayed release characteristics for the Eudragit® S 100 coating on a fast release core formulation. Furthermore, a film thickness of 5.6 mg/cm^2 was required for Eudragit® L 30 D-55 film to provide adequate delayed release for the slow release formulation. However both film coatings disintegrated within in a short period of time when exposed to simulated intestinal fluid. No difference in film disintegration time was observed between the two different coatings when treated at pH 7.4. The rate and extent of drug release was not affected within a reasonable increase in film thickness. Since the Eudragit L films are designed to dissolve at pH 5.5 and higher, a in-vivo evaluation may be necessary to identify potential impact of these property on the in-vivo drug release and absorption.

Tablets manufactured at small scale using small coating pan had larger variability in film thickness at lower coating level. It appears that the variability in coating uniformity is a function of batch size, larger equipment uses larger pan load increased number of spray guns and hence is more efficient and uniform coating. Thus we can conclude that the large coating pan is efficient compared to the small coating pan. Because of the size, shape and operating speeds of the coating pans differ for various types of coating pan, the parameters obtained from one size and type of equipment cannot be applied to the other even though the operating principles are same. In addition

identification and optimization of the coating parameters that influence the coating film thickness and uniformity would help reduce the variability observed in the coating. Furthermore, the tablets produced had satisfactory physical characteristics and was used for further coating studies to develop the immediate release coating of the second dose of the drug.

REFERENCES

1. Lehman, K., Acrylic lattices from redispersible powders for peroral and transdermal drug formulation. Drug Dev. and Ind. Pharm., 12 (3), 265-287 (1986).
2. Signarino C.A., Aqueous Enteric Coating, Pharmaceutical Technology, Supplement 24-26, (1999).
3. Specht. F, Saugestad. M, Waaler. T and Muller, B. W., The application of Shellac as an Acidic Polymer for Enteric Coating, Pharm. Technol., 23 (3), 146-154 (1999).
4. Mazer. T., Zein: The Versatile Reverse Enteric, Proceed. Int'l. Symp. Control. Rel. Bioact. Mater., 26, 267-268 (1999).
5. Palaniswamy, S., Modified Release Adrenergic Drug for Twice a Day Dosing, Masters Thesis, University of Rhode Island, Kingston, RI, USA, May (1994).
6. Khan, M. Z. I., Prebeg, Z and Kurjaković N., A pH-dependent colon targeted oral drug delivery system using methacrylic acid copolymers , I – Manipulation of drug release using Eudragit® L 100-55 and Eudragit® S 100 combinations, J. Controlled Release., 58, 215-222 (1999).
7. Bauer, H. K., Lehmann, K., Osterwald, P and Rothgang, G., *Coated Pharmaceutical Dosage Forms*, 1st Ed, CRC Press, Medpharm Scientific Publishers Stuttgart, GmbH Germany (1998).
8. The United States Pharmacopoeia 23 Rev., United States Pharmacopoeial Convention, Inc 12601, Twinbrook Parkway, Rockville, MD 20852 (1995).
9. Dangel, C., Kolter, K., Reich, H. B and Schepky, G., Aqueous Enteric Coatings with Methacrylic Acid Copolymer Type C: On Acidic and Basic Drugs in Tablets and

Pellets, Part I: Acetylsalicylic Acid Tablets and Crystals", Pharm. Technol., 24 (3), 64-70 (2000).

10. Dangel, C., Kolter, K., Reich, H. B and Schepky, G., Aqueous Enteric Coatings with Methacrylic Acid Copolymer Type C: On Acidic and Basic Drugs in Tablets and Pellets, Part II: Dosage Forms Containing Indomethacin and Diclofenac Sodium, Pharm. Technol., 24 (4), 36-42 (2000).

MANUSCRIPT III

DEVELOPMENT OF IMMEDIATE RELEASE DOSE FOR A PULSED-RELEASE TABLET

PART II

IMMEDIATE RELEASE COAT DEVELOPMENT

ABSTRACT

Aqueous film coating of solid dosage forms is a process that continues to grow in importance in the pharmaceutical industry. Aqueous film coating process can influence the quality of the final coated dosage form, such as surface characteristics, gloss, coating efficiency and coating uniformity. There is also a widespread interest in evaluating the uniformity of the film coatings. The reason for this interest is that the uniformity of the coating affects the quality of the tablet finish, accuracy of the dose delivered and functionality of the coating.

The aim of this study was to examine the influence of processing parameters on the uniformity of the coating applied to deliver low dose active ingredient in the immediate release portion of a pulsed release tablet dosage form containing immediate and delayed release of water soluble drug. The effect of mixing on coating suspension and the spray rate on coating uniformity was evaluated. A method for assessing the extent and uniformity of film-coat application by the determination of albuterol sulfate in the coating was used to determine the charge of tablets in the coating pan in the pilot scale and production scale.

Tablet characteristics such as weight variation, thickness, hardness and content uniformity were compared using statistical analysis to evaluate the reproducibility of the coating process and the final product at different scales. Dissolution testing of the coated tablets was performed using USP apparatus 3. Formulation stability was evaluated at various storage conditions to determine the robustness of the developed product. Coating solution mixing speed did not have an impact on the homogeneity of the suspension. Tablets coated using 24" coating pan produce larger variability in the coating and had

low process efficiency. On the other hand the larger coating pan showed better efficiency and uniformity of coating suggesting a better process choice for the application of active drug onto the tablets. Results indicate that longer processing time improved the coating uniformity. Perforated coating pan can be used to apply film coatings containing low dose active drug and coatings applied using two different coating equipment at different scales exhibited similar tablet properties.

1.0 Introduction

Pharmaceutical coatings are applied to compressed tablets for a variety of reasons, some as simple as improving the aesthetics of the tablet, color for marketing etc. Others relate to the performance of the product itself. There is a growing interest in incorporating soluble and insoluble active drugs into the coating of coated tablets. For this technique to be useful for delivering active drug via the coated film, the variation in coating between the tablets must be minimal. Application of active drug onto tablet cores using conventional spray coating processes is very challenging. Various coating techniques and processes for the application and delivery of active drug via a tablet dosage form have been studied in detail elsewhere (1). A number of process variables and additives in the coating affect the uniform application of the film forming material onto the tablet cores (2). Such variables affect the quality, appearance and performance of the final film. Coatings may be applied by spraying a solution or suspension containing dissolved or undissolved drug substance and/or pigment onto a large number of tablets tumbling in a rotating pan (1,3).

Aqueous film coating is a process that is routinely employed today as unit process in the preparation of pharmaceutical solid dosage forms (4,5,6). Uniform color on the color-coated tablets as perceived visually usually marks the end point of the coating process. However, when applying film coatings with colorless films or with colors similar to the tablet core, a visual color check may not be the appropriate method for determining the end point. One variable identified to more accurately determine the coating end point is the weight gain of the tablets during the coating process. Along with the weight gain measurements, assay of the coating material may be used to confirm the

coating end point and evaluate the uniformity of the coating film application. An alternative method for quantifying the amount of film-coat applied to a tablet incorporating marker compounds into the coating medium have been reported and materials such as potassium bromide (7), tartrazine (8), and FDC Blue #1 (9) have been considered for this purpose. In each case, the coat was removed from the tablet by dissolution in an aqueous medium and the marker detected using an appropriate analytical method.

The goal of the present study is to systematically evaluate the relevant processing parameters in both pilot scale (24") and production scale (48") coating pans. These investigations include the evaluation of coated tablet characteristics using two differently releasing tablet core formulations, fast and slow release, at the small scale and production scale to make recommendations for further optimization and modification to the coating process to obtain a uniform drug coating with reduced intra-batch variability.

2.0 Objective

The objective of the present study is to develop an immediate release coat for a seal coated controlled release matrix tablet in order to deliver a low dose immediate release of an initial dose of drug. To identify the coating parameters, characterize and compare the coated tablet attributes, such as weight variation, assay, coating uniformity and dissolution profiles of the formulations manufactured at two different scales (pilot and production scale).

3.0 Methods

3.1 Materials:

Albuterol Sulfate, USP (Propharmaco, Nobel Industries, Italy); Opadry® II White (Colorcon, West Point, PA); Seal coated matrix tablets containing 2 mg of albuterol previously prepared. All raw materials used complied with the current USP/NF grade specifications.

3.2 Equipment:

Accela-Cota 24" and 48" (Thomas Engineering, Hoffman Estates, IL); Peristaltic Pump, Masterflex Model 7520-10 (Cole Parmer, Chicago, IL); Moisture Analyzer, Computrac Max 50 (Arizona Instrument, Tempe, Arizona); Vector Tablet Hardness Tester (Vector Corp., Marion, IA); pH meter, Model 811, (Orion Research Inc., Cambridge, MA); Bio-Dis Tester (Vankel Industries Inc., Edison, NJ); Shimadzu LC-4A, High Performance Liquid Chromatograph (HPLC) Equipped with a Shimadzu SPD-2AS spectrophotometer detector (Shimadzu, Japan).

3.3 Tablet Coating:

3.3.1 Immediate Release Coating Suspension Preparation

Albuterol sulfate was dissolved in purified water; to this solution Opadry® II was added and mixed to obtain a homogeneous coating suspension. The immediate release coating suspension formulation is presented in Table 1. A coating suspension sample was collected at the end of the mixing process to determine the amount of albuterol sulfate in the final coating suspension. The coating mixture was continuously stirred during and until used for processing.

3.3.2 Determination of Moisture in the Coating material

It was necessary to determine the moisture level in the coating material because the coating end point was determined based on the amount of solids applied calculated on a dry film weight basis. The amount of moisture in the coating material (Opadry® II) was used to adjust the amount of moisture that would contribute to the final tablet weight gain as part of total solids. A thermal gravimetric and Karl fisher moisture analysis was performed to determine the amount of moisture.

3.3.3 Immediate Release Coating Procedure

Delayed release seal coated matrix tablets manufactured previously were used as substrate for the immediate release coating. Development, characterization and evaluation of seal coated tablets are discussed in detail in manuscript II part I. The delayed release seal coated tablets were loaded into the coating pan, pre-warmed for five minutes and the immediate release albuterol sulfate coating suspension was sprayed onto the

Table 1. Formula for Albuterol Sulfate Immediate Release Coating

Ingredient	Content	
	Percent w/w	mg/tablet
Albuterol Sulfate, USP	3.00	2.46
Opadry II® (Y-22-7719)[a]	8.00	6.54
Purified Water, USP	89.00	–
Total	100.00	9.00

[a] Proprietary blend of ready to use coating material consisting of film forming material, plastisizer and opacifier for film coating purposes.

tablets. The tablets were coated using the coating suspension formulation presented in Table 1 and the processing parameters listed in Table 2. The pilot scale coating was performed in 24" coating pan, at a pan speed of 12 rpm, airflow of 200 ft^3/min, pan pressure of –0.06 to–0.08in. water and a product/exhaust temperature of 38°C. A quantity of tablets equivalent to twelve kilograms was placed in the pan and preheated for 5 minutes at 40°C, the inlet and outlet temperatures were maintained at 59 ± 2°C and 40 ± 2°C. The pan was rotated at a speed of 12 rpm and the coating suspension was sprayed continuously using a peristaltic pump at an average spray rate of 25 grams/minute with a single spray gun (1-mm nozzle diameter). For the coating applied using the Accela Cota, C-48 a quantity of tablet equivalent to 120 kilograms was placed in the coating pan and prewarmed for 5 minutes at 40°C, the inlet and outlet temperatures were maintained at 60 ± 2°C and 40 ± 2°C with air volume of 1600 ft^3/min The pan was rotated at a speed of 4 rpm and the coating suspension was sprayed continuously using a peristaltic pump at an average spray rate ranging from 50 – 85 grams/minute/gun (1-mm nozzle diameter) using three spray guns. The spray to tablet bed distance was maintained at 10 inches for all coating trials. The coating suspension was stirred continuously throughout the coating process to maintain homogeneity. Average tablet weight gain of 6.7% solids was applied using both pans to deliver a quantity equivalent to 2 mg of albuterol per tablet on the coating.

Table 2. Coating Parameters for Accela-Cota Immediate Release Coating

Parameter	C–24	C–48
Drum Size (Inches)	24	48
Batch Size (kg)	12	120
Pan (rpm)	12	4
Number of Spray Guns	1	3
Spray Rate (g/min/gun)	25	50–85
Bed to Spray Distance (inch)	8	10
Atomizing Air Pressure (Bar)	1.	1.5
Inlet Air Temperature (°C)	58	60
Product Temperature (°C)	38	38
Drying Time (min)	30	30

3.3.4 Effect of Mixing on Coating Suspension Homogeneity

To evaluate the homogeneity of the coating suspension solids and identify the optimum mixing speed during the process, the coating suspension was mixed at various mixer speeds. Samples were collected from different location in the mixing tank at various mixing speeds to confirm a uniform dispersion of solids. Samples were also collected from the spraying end of the spray guns at various mixing speeds and at a constant spray rate of 85 g/min/gun. To evaluate the homogeneity of albuterol in the coating suspension, samples were assayed by HPLC to determine the amount of albuterol in the sample and in the coating suspension formulation.

3.3.5 Effect of Coating Suspension Spray Rate on Uniformity

To study the effect of spray rate on the coating uniformity, the coating suspension was sprayed at 50, 70 and 85 g/min/gun. The seal coated tablets were coated with the immediate release coating suspension formulation presented in Table 1. Tablet samples were collected at each spray rate after applying 30, 50, 75 and 100% of the theoretical solid weight gain. Tablet samples were evaluated for weight, thickness and were assayed for albuterol sulfate in the coating to determine the uniformity of coating applied at various spray rates.

3.4 Immediate Release Assay:

Ten tablets were chosen at random from the composite sample obtained from the coating pan at the end of the coating process. These tablets were transferred into a sample vial and approximately 20 mL of water was added. The sample was vortexed for 1 minute. The solution was decanted into 500 mL volumetric flask. Then, the vial was

rinsed nine times with 20mL water and the rinse solutions were decanted into the same 500 mL volumetric flask. The 500 mL flask was diluted to volume with water. 12.5 mL of this solution was transferred to 200 mL volumetric flask and diluted to volume with water. An aliquot of this solution was filtered through a 0.45μm PTFE filter, discarding the first 5 mL of the filtrate. This sample was injected onto the chromatographic system.

3.5 Drug Release Testing:

The pH's selected were 0.1 N hydrochloric acid pH 1.2, acetate buffer pH 4.7, and phosphate buffer pH 7.4 as recommended by USP 23. The dissolution study was performed using USP apparatus 3 (Reciprocating cylinder, Bio-Dis) (10). The temperature of the dissolution medium was maintained at 37 ± 0.5°C in all the studies. 250 ml of dissolution media was used in each cylinder and the stroke speed was set to 20/minute, sink conditions were maintained. Multipoint dissolution profiles were performed by collecting samples at specified intervals and assaying by HPLC to determine the amount of drug released. Tablet assay and content uniformity were determined using a validated HPLC procedure.

3.5.1 Assay Procedure

A reverse phase High Performance Liquid Chromatography (HPLC) assay was selected due to the advantage of direct analysis of aqueous samples, high sensitivity, and separation of excipients that may interfere with the assay. An aliquot of sample solution was filtered through a 0.45 μm PTFE filter, discarding the first 5 ml of the filtrate. A reverse phase column (Keystone ODS/H, 5μm 4.6x250 mm) in conjunction with a

variable wavelength UV detector was used. The injection volume was 30 μL with a flow rate of 1mL/minute and column temperature was maintained at 35°C.

4.0 Results and Discussion

Table 3 shows the coating suspension uniformity test results for the samples collected at various mixing speeds, from the solution tank and at three different spray guns. Although the coating suspension used for the study had an 8% w/w theoretical content of Opadry® II solid, only ~7.4% of the solids was recovered by gravimetric analysis which is equivalent to 92.5% of the theoretical amount of total solids used in the preparation of the coating suspension. The difference in the amount of solid recovered may be explained by the amount of moisture found in the raw material itself. Table 4 shows the moisture analysis data for the lots of Opadry® II raw material using various methods. These results show that there is approximately 7.5% moisture present in the material. These findings also suggest that there is not an actual loss of solids and that the low recovery of solids from the samples collected from the spray gun is due to the loss of moisture originally present in from the raw material.

The percent solids determination results obtained from the coating suspension sampled from the suspension tank ranged from 7.38 – 7.42%. The amount of solids recovered from the samples collected at the spraying end of each spray gun at the different mixing speeds for individual samples ranged from 7.29 – 7.42%. The average values range from 7.37 – 7.40% with an RSD value ≤ 0.78% These results suggest that the coating suspension solids delivered through each spray gun is fairly consistent, uniform and are similar to the results obtained from the samples tested from the tank. Furthermore, these results also indicate that the mixing speed did not have an adverse effect on the coating suspension homogeneity. The results also show low variability in

Table 3. Opadry® II Recovered from the Coating Suspension Using Gravimetry Analysis

Mixer Speed (rpm)	Percent Recovered				Average Solids (%)	RSD (%)
	Spray Gun			Tank		
	A	B	C			
500	7.39	7.42	7.42	7.38	7.40	0.28
1500	7.36	7.37	7.31	7.42	7.37	0.61
2000	7.42	7.36	7.29	7.40	7.37	0.78

Table 4. Moisture Content of Three Lots of Opadry® II

Lot#	Percent Moisture			
	LOD	Karl-Fisher	TGA	Gravimetry[a]
3948	6.5	7.2	7.0	7.4
5238	7.2	7.3	7.2	7.5
5328	7.1	7.5	6.8	7.6

[a] 8% w/w Opadry® II suspension, n=3 for all determination

the percent solids from the spray guns indicating that the suspension flow through the various parts of the spray system is consistent between the three spray guns. This is a critical property because inconsistencies in the coating suspension flow between spray guns may lead to uneven spray patterns ultimately affecting the uniformity of the deposited coating material on the tablets (11). Table 5 shows the assay and percent solids results recovered for the actual coating suspension. It can be seen from these results at all three mixing speeds the specific gravity values range from 1.023 – 1.028, suggesting that the solid particles are dispersed uniformly throughout the suspension. This is further supported by the fact that the observed assay values for these samples ranged from 2.93 – 3.09% of the theoretical amount of 3% w/w of albuterol sulfate. Furthermore, the variability in the amount of active drug recovered from all three mixing speed samples from the tank and the spray guns are minimal. A major concern would be non uniformity of the coating solids, that may affect the final film characteristics and uniform deposition of the coating material on the tablets (11,12). These results show that a uniform coating suspension can be delivered from each spray gun consistently independent of mixing speeds.

Coating solution spray rate may have a significant effect on the coating film uniformity (12). In order to evaluate the effect of coating suspension spray rate on the coating uniformity, tablets were coated using three different spray rates (50, 70 and 85 g/min/gun). Results are presented in Table 6. It can be seen from these results that at a spray rate of 50 g/min/gun the weight variation is highest at a RSD of 6.8% which indicates that the amount of coating material deposited on each tablet may not be uniform

Table 5. Mixing Study Results for Immediate Release Coating Suspension

Mixer Speed (rpm)	Sample[a]	Suspension Properties					
		Solids (%w/w)	RSD (%)	Specific gravity	RSD (%)	Assay (%)	RSD (%)
500	A	7.42	0.82	1.023	0.26	3.01	0.51
	B	7.36		1.024		2.98	
	C	7.30		1.028		2.99	
	Tank[b]	7.46	0.91	1.024	0.19	2.93	0.52
1400	A	7.40	1.71	1.025	0.14	2.98	1.39
	B	7.56		1.026		2.96	
	C	7.31		1.024		3.04	
	Tank[b]	7.31	0.56	1.025	0.21	3.05	0.47
2000	A	7.39	0.64	1.026	0.15	2.98	1.92
	B	7.41		1.023		3.09	
	C	7.32		1.025		3.07	
	Tank[b]	7.32	0.75	1.024	0.23	2.94	0.39

[a]A,B, and C are the 3 spray guns for the 48 inch coating pan
[b] n=3 for all determinations

Table 6. Tablet Characteristics as a Function of Spray Rate

Spray Rate (g/min/gun)	Solids Applied (%w/w)	Weight Variation		Tablet Thickness		Albuterol	
		Weight (mg)	RSD (%)	Thickness (mm)	RSD (%)	Assay (%)	RSD (%)
50	30	148.4	6.8	3.64	3.7	31.6	15.5
70	50	150.4	5.2	3.67	2.9	44.8	11.4
85	75	152.9	3.9	3.70	2.3	73.8	8.6
85	100	155.4	1.8	3.72	1.2	101.1	5.4

at this stage of the process. It should be noted that increasing the spray rate reduced the weight variation to 5.2% at 70 g/min/gun and to 1.8% at 85g/min/gun when 100% of the solid application is complete. Interestingly, the variation in tablet thickness is minimal across the various coating ranges. However, this parameter is difficult to compare between various samples, simply because the amount of material being deposited is small and the physical measurement is not sensitive enough to pick subtle differences. In contrast, the highly sensitive HPLC assay used to measure the content uniformity of the coatings shows high variability at the lower spray rate of 50g/min/gun. Also it can be seen from these results that increasing the spray rate, further along the process the coating uniformity is improved with minimal variability between the tablets. These findings are opposite of the results reported in an earlier study, that increasing the coating level does not reduce the variability of the coating (9). This may in fact be due to the prolonged exposure of the tablets to the coating zone as the number of coating cycles increases tablet residence time. At a spray rate of 85 g/min/gun and a level of 75% application of solids the calculated percent RSD value for the content uniformity is 8.6%. This variability was improved when spraying at 85 g/min/gun and increasing the duration of coating time to give a percent solid application of 100%. Nevertheless when coating was applied at a spray rate of 85 g/min/gun for the entire process there was a significant improvement in the uniformity of the coating which suggests that uniform coating may be obtained using higher spray rates and increasing the duration of coating.

Table 7 compares the physical characterization results for tablets that were uncoated, seal coated and immediate release coated at the different production scales. The results show a low variability of the cores in terms of weight, thickness, hardness and

diameter for the uncoated tablets for both batches of the pilot and scale-up levels of manufacture. Similar results were observed for the seal coated tablets for weight, thickness and diameter suggesting a uniform seal coating of the tablet core regardless of scale. As expected the seal coated and immediate release coated tablets show an increase in tablet weight that is reflected in increased tablet thickness. However, tablet hardness increased slightly for the immediate release coated tablets when compared with the seal coated tablets and is not significant. Figure 1 and 2 show the individual assay results of the immediate release coating of the tablets coated using the small and the large coating pans. It can be seen from Figure 1 that a majority of the tablet samples assayed had values that are further away from the target value of 50% of the intended 4 mg dose for the final tablet formulation. It is also evident from Figure 1 that the observed assay values are beyond the acceptable ± 95% of the calculated mean assay value. The average percent albuterol assayed was 49.8 and 50.5 with a standard deviation of 5.6 and 3.6 for small scale and large scale respectively. Statistical comparison of the average assay values for small and large scale did not show a significant difference in average assay for content uniformity. However, comparison of standard deviation shows there is a statistically significant difference between the variance. Table 8-9 Appendix II show a complete statistical evaluation of these results. This may be due to the lack of uniform application of the coating material, which in turn affects the uniform distribution of the active drug onto the tablets. Coating uniformity may be influenced by a number of parameters such as number of spray guns, pan speed, spray rate, tablet mixing and coating material concentration in the coating solution (6,9,12,13). A single spray gun was used for the small scale (24" pan) coating process. Figure 2 shows the individual assay results for

Table 7. Comparison of Tablet Properties

Batch Type	Weight (mg)/Tablet			Thickness (mm)			Hardness (kp)		
	Uncoated	Seal coated	IR coated	Uncoated	Seal coated	IR coated	Uncoated	Seal coated	IR coated
Pilot Formula I	135.4	147.4	153.6	3.50	3.57	3.66	8.1	14.5	15.6
Pilot Formula II	134.9	149.7	159.6	3.50	3.62	3.72	8.0	13.5	15.1
Scale-up Formula I	135.2	147.8	155.7	3.50	3.58	3.64	8.0	14.2	16.2
Scale-up Formula II	135.7	149.9	159.6	3.51	3.60	3.71	8.2	13.9	14.7

Figure 1. Immediate Release Coating Assay - For Pilot Scale Batch

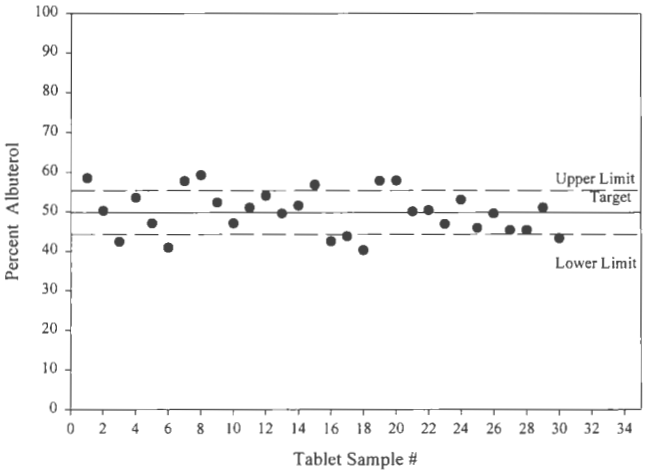
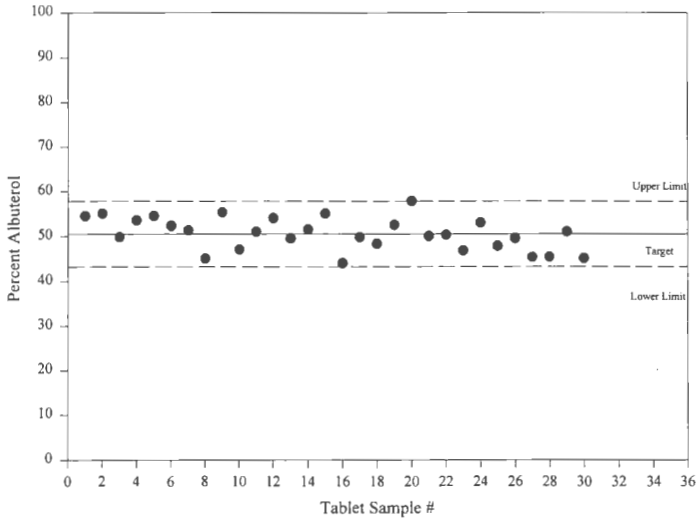


Figure 2. Immediate Release Coating Assay- For Large Scale Batch



immediate release coatings applied using 48" coating pan. Variability in the assay value for these batches were minimal as compared with the variability observed for the tablets coated using 24" coating pan. It may be postulated that improved coating uniformity from the small scale to the large scale may be due to the increased number of spray guns used to spray the coating suspension that results in a more uniform spray of coating material across the tablet bed. Secondly the coating pan speed, which may have significant effect on the coating uniformity, in this case 4 rpm vs. 12 rpm for the 48" and 24" respectively. It has been shown that slower pan speed improves the coating uniformity, primarily because the time tablets reside in the spray zone is longer at lower pan speeds, exposing the tablets to the spray zone for a longer period of time (6,12).

Percent RSD values for entire tablet content uniformity assay values are higher in both cases pilot and large scale (Table 10). The percent RSD values ranged from 5.3-9.7% indicating that the coating application is not uniform and variable between two different scales. Although the observed variability for the content uniformity measurements for the scale-up batches were small, it barely meets the USP content uniformity requirement of RSD < 6% for solid dosage forms. Since the variability is reasonably small for the tablets coated using the large scale equipment, identifying the influential parameters and optimizing these parameters may be beneficial in further reducing the variability in the coating.

Furthermore, statistical evaluations using ANOVA for the content uniformity results of the pilot scale and scale-up batches shown in Table 10 is included in Table 11-13 Appendix II. These results do not show a significant difference in the mean content uniformity values for the entire tablet. Also the observed P-values for the comparison of

standard deviation values are greater than 0.05 (0.2249 and 0.1757) for the whole tablet content uniformity values and there is not a statistically significant difference among the standard deviation values at the 5% level. Moreover, these results also suggest that the film coatings applied using large scale equipment is fairly uniform and reproducible. Clearly, there is a lack of uniform coating of the tablets coated using the 24" coating pan, suggesting that this may not be a suitable process to deliver precise amount of low dose active drug on the coating of the tablet that will meet the USP content uniformity requirement for solid dosage forms.

Table 14 shows the entire tablet assay and content uniformity results for both formulations coated using the 24" and 48" coating pan. Actual assay value for all the batches range from 95.3-99.3%, suggesting a good recovery of the coating material. However, the actual assay values for the tablets manufactured using the 24" coating pan is lower than the theoretical assay value, suggesting a lower coating efficiency at this scale. On the other hand actual assay values for the tablets manufactured using the 48" coating pan closely agree with the theoretical assay value, indicating the coating process is efficient. Furthermore, the immediate release coated (pulsed-release) tablets manufactured for both formulations at different scales showed nearly similar dissolution characteristics (Figure 3 and 4). These findings suggest that release of drug from these coatings are directly scalable and are independent of batch size. Furthermore, a statistical comparison of the mean drug release at t=0.5 hr and at t=8.0 hr was performed for both formulations manufactured at different scales and these results show no significant difference in drug release at these intervals. Complete ANOVA results for these comparisons are included in Appendix I. However, the variability in drug release between

Table 10. Tablet Content Uniformity for Pilot and Large Scale Batches

Tablet Sample#	Pilot		Scale-up	
	Formula-I	Formula-II	Formula-I	Formula-II
	Assay %			
1	85.2	95.1	91.7	101.9
2	83.6	87.6	104.8	107.6
3	98.5	95.8	100.3	90.9
4	107.5	79.5	96.7	97.9
5	92.1	97.9	107.5	95.4
6	109.5	99.6	101.2	94.2
7	96.5	107.8	94.6	98.5
8	95.7	97.8	93.7	99.3
9	89.1	98.3	98.0	104.9
10	107.4	85.1	93.8	102.1
Average	96.5	94.5	98.6	99.5
Range	83.6 – 109.5	79.5 – 107.8	90.9 – 107.6	91.7 – 107.5
RSD (%)	9.7	8.7	5.1	5.3

Table 14. Summary of Albuterol Sulfate Pulsed-Release Tablet Properties

Batch Size	Assay (%)		Content Uniformity[a]		F_2
	Theoretical	Actual	Assay (%)	RSD (%)	
Pilot Formula I	99.8	96.1	54.1	12.0	89.8
Pilot Formula II	98.9	95.3	52.1	11.7	66.9
Scale-up Formula I	99.8	99.3	50.5	7.2	89.8
Scale-up Formula II	99.5	98.9	50.3	6.8	66.9

[a] immediate release coating n=10 for all determinations

Figure 3. Effect of Scale-up on Drug Release
Formulation-I

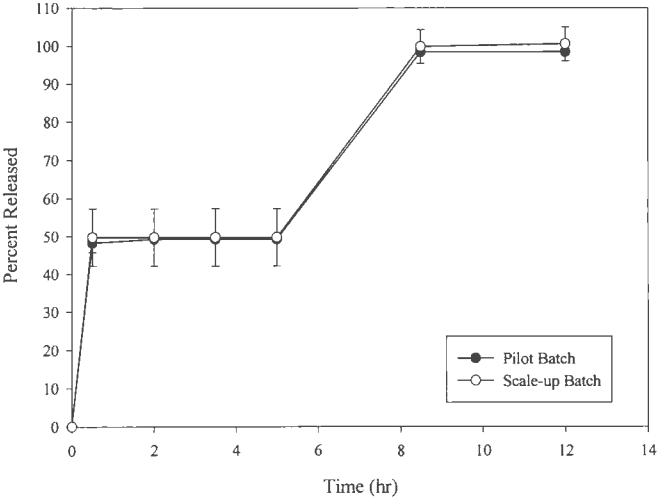
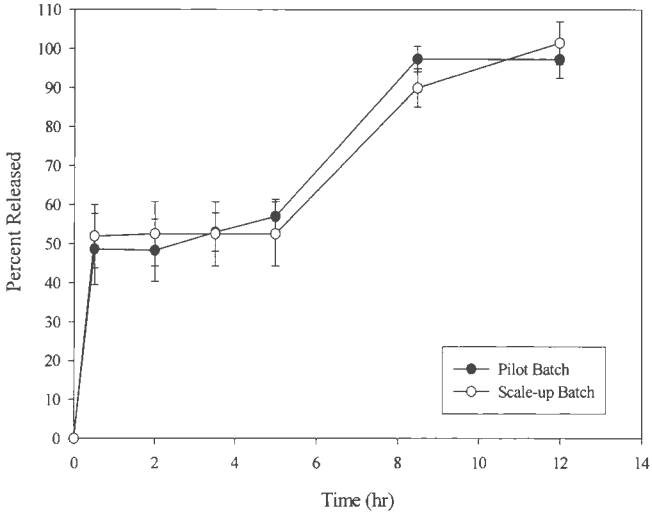


Figure 4. Effect of Scale-up on Drug Release
Formulation II



tablets as a measure of percent RSD values at each time point was larger at the early dissolution time points, suggesting that the variability is inherent and needs further optimization of the coating process. Moreover, this phenomenon was observed in both formulations and is limited to the immediate release portion of the tablet and the variability drops as the second dose starts releasing from the seal coated tablet core. These findings further suggest that the immediate release is the major contributor of the variability in drug release at the early time points.

The pair-wise comparisons of the dissolution results for two different scales of the formulations evaluated using F_2 metrics show a value of 89.8 and 66.9 for formulation I and II respectively. An F_2 value of 50 or greater indicates that dissolution profiles are similar according to the F_2 metrics established by SUPAC guidelines (14,15,16). F_2 analysis results for these comparisons are included in Table 15-16 Appendix II. In addition, tablets coated at two different scales using small and large coating pan were stored in HDPE bottles at two different storage conditions controlled room temperature (25°C/60% RH) and accelerated conditions (40°C/75% RH) for 6 months and showed no significant change in assay values (Figure 5 and 6). Observed assay values for stability samples showed no significant change in the amount of albuterol from the initial time point and until 6 months period. These results suggest that the formulation is stable, and the specified storage conditions does not seem to have any detrimental effect on the product. Figures 7 and 8 show the effect of storage condition on the drug release characteristics of both formulations at both scales of manufacture. It can be seen from these results that there is no change in the dissolution pattern at various test intervals when the products were stored at 25°C and 60% RH, suggesting that the room

Figure 5. Effect of Temperature and Humidity on Albuterol Assay
Storage Condition 25°C/60%RH

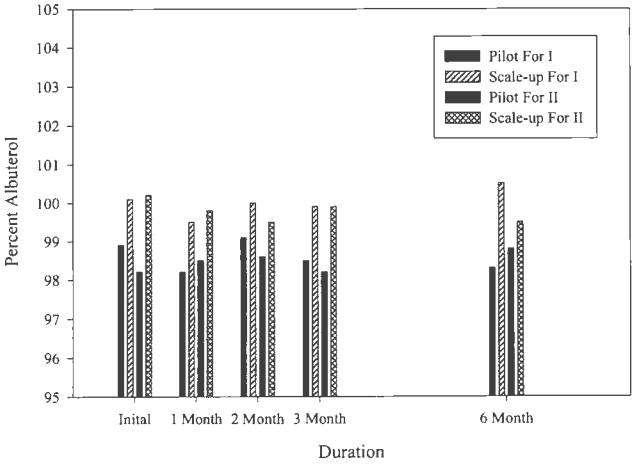


Figure 6. Effect of Temperature and Humidity on Albuterol Assay
Storage Conndition 40°C/75%RH

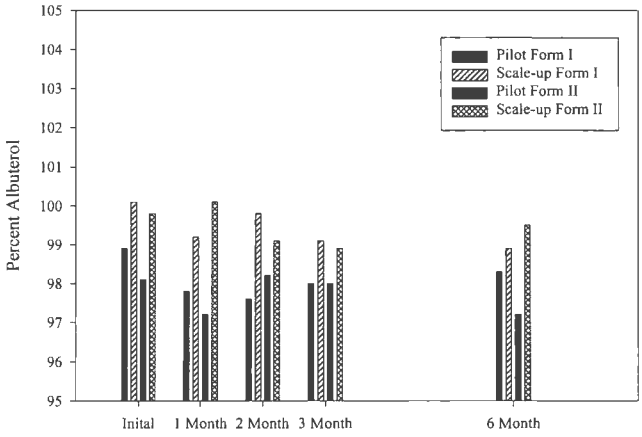


Figure 7. Effect of Temperature and Humidity on Albuterol Release
Storage Condition-25°C/60% RH (Formulation-I)

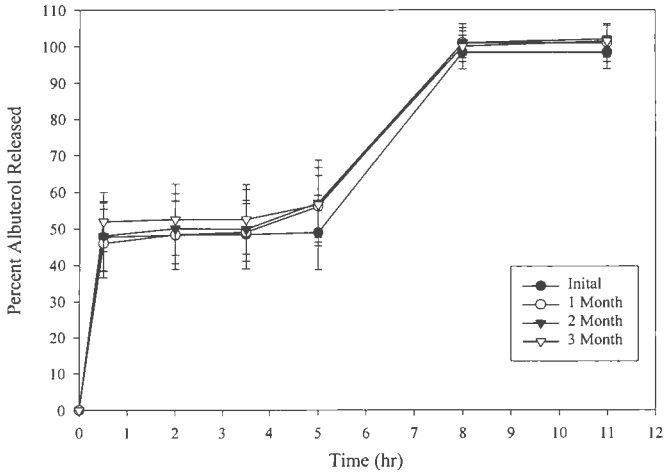
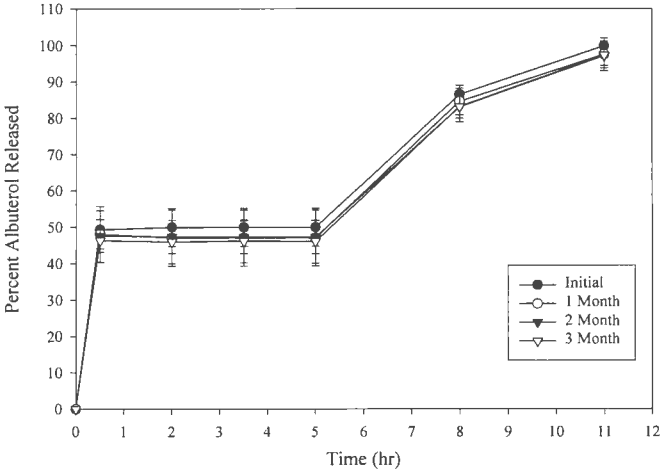


Figure 8. Effect of Temperature and Humidity on Albuterol Release
Storage Condition 25°C/60%RH (Formulation-II)



temperature storage condition is acceptable. Although there was variability in drug release between tablets, the overall drug release pattern for both the formulations were similar at various stability test intervals indicating that the storage conditions did not have a significant effect on the rate and extent of drug release.

5.0 Conclusions

Immediate release coating formulation and process was developed to incorporate water soluble drug in the coating to deliver as immediate release of the initial dose a pulsed-release tablet dosage form. The coating equipment used was geometrically similar in design for both small and large scale coating process. The most important factor should be considered during scaling up of the aqueous coating process include; coating solution spray rates, number of spray guns (to obtain a uniform spray on the entire surface of the tablet bed), adequate mixing of tablets, pan speed and adjusting the in-process air volume to provide adequate drying capacity.

Tablets coated using 24" coating pan produce larger variability in the coating and had low process efficiency. Thus we can conclude that using 24" coating pan may not be suitable for the application of active drug onto the tablets to deliver low dose. On the other hand the larger coating pan showed better efficiency and uniformity of coating suggesting a better process choice for the application of active drug onto the tablets. Film coatings applied using two different coating equipment at different scales exhibited similar tablet properties. Although the large scale process is efficient and uniform, it was challenging to meet the USP content uniformity requirements for solid dosage forms. However, it may be possible to meet this requirement, once the influential parameters are identified and optimized.

The statistical evaluation of the dissolution results further indicate that there is no statistically significant difference between the mean drug release at the 5% level for two different scales of coating. Furthermore, for both scales of manufacture, all the pair-wise comparisons of dissolution results for both formulations were similar based on SUPAC

F_2 criteria. Stability study results also suggest that development and direct scale-up of immediate release coating formulation of low dose water soluble drug is possible from the pilot to the production scale.

REFERENCES

1. Palaniswamy. S., Modified Release Adrenergic Drug for Twice a Day Dosing, Masters Thesis, University of Rhode Island, Kingston, RI, USA, May (1994).
2. Porter, S. C., The effect of additives on the properties of an aqueous film coating, Pharm. Technol., 4 (3), 67-75 (1980).
3. Porter, S. C., Aqueous film coating an overview, Pharm. Technol., 3 (9), 55-59 (1979).
4. Hogan, J. E., Aqueous versus Organic Solvent Film Coating, Int. J. Pharm. Tech. & Prod. Mfr., 3 (1), 17-20 (1982).
5. Pondell, R. E., From Solvent to Aqueous Coatings, Drug Dev. Ind. Pharm., 10 (2), 191-202 (1984).
6. Signarino, C. A and Forcellini, L. J., Evaluating the Uniformity of Aqueous Film Coating, Pharm. Technol., Yearbook, 48-53, (1996)
7. Meakin, B. J and May, G., 3rd International Conference on Pharmaceutical Technology., 145-153 (1983).
8. Prater, D. A., Ph. D. Thesis, University of Bath (1982).
9. Skultety, P. F., Rivera, D., Dunleavy, J and Lin, C. T., Quantitation of The Amount and Uniformity of Aqueous Film Coating Applied To Tablets in a 24" Accela-Cota, Drug Dev. Ind. Pharm. 14 (5), 617-631 (1988).
10. The United States Pharmacopoeia USP 23 Rev., United States Pharmacopoeial Convention, Inc 12601, Twinbrook Parkway, Rockville, MD 20852 (1995).

11. Vesey, C. F and Fegely, K. A., Determination of Critical Process Parameters on The Application of An Aqueous, High Gloss Film Coating System, PharmSci., 1 (1) 4, 750 (1999).

12. Mathur, L. K., Forbes, J and Yelvigi, M., Characterization techniques for the aqueous film coating process, Pharm. Technol., 8 (10), 43-53 (1984).

13. Fourman, G. L., Hines, C. W and Hritsok, R. S., Assessing the Uniformity of Aqueous Film Coatings Applied to Compressed Tablets, Pharm. Technol., 19 (3), 70-76 (1995).

14. FDA Guideline for Industry-immediate release solid oral dosage form/scale-up and post approval changes (SUPAC-IR): Chemistry, manufacturing, and controls. In vitro dissolution and in vivo bioequivalence documentation, Federal Register, Vol. 60, No. 230, 30 November 1995, pp. 61638-61643.

15. Moore, J. W and Flanner, H., Mathematical Comparison of Dissolution Profiles, Pharm. Technol., 20 (6), 64-75 (1996).

16. Augsburger, et al., An Approach Toward Establishing a Scientific Foundation for Interpreting Regulations and Workshop Reports on Scale-Up and Post Approval Changes, Pharm Res., 11 (10), S161 (1994).

MANUSCRIPT IV

AN INVESTIGATION OF UNIFORMITY OF AQUEOUS FILM COATING CONTAINING LOW DOSE ACTIVE DRUGS USING STATISTICAL DESIGN OF EXPERIMENTS

ABSTRACT

The film coating process can influence the quality of the final coated dosage form, such as surface characteristics, gloss, coating efficiency and coating uniformity. Aqueous film coating of solid dosage form is a process that continues to grow in importance in the pharmaceutical industry. There is also a widespread interest in evaluating the uniformity of the film coatings. The reason for this interest is that the uniformity of the coating affects the quality of the tablet finish, accuracy of the dose delivered and functionality of the coating. Coating uniformity can be improved when the critical parameters are understood and optimized. The aim of this study was to examine the influence of processing parameters on the uniformity of the coating applied to deliver low dose active drug in the immediate release portion (coating) of a pulse-release tablet dosage form containing immediate and delayed release of water soluble drug.

The application of statistical Design of Experiments (DOE) has the potential to allow rapid identification and optimization of the processing parameters. A factorial design was used to study the critical processing parameters that were known to influence film coating process. The parameters of interest are spray rate, coating pan speed and drug concentration in the coating solution. The responses measured were coating assay, coating uniformity, process efficiency and process duration. The results of analysis of variance was used to predict the effect of various processing parameters on the response. Results show that coating suspension spray rate and coating pan rotation speed significantly affect the coating uniformity. The content uniformity between tablets is significantly improved by using a low spray rate, low drug concentration in the coating solution and slower pan speed. However, lower spray rate and concentration significantly

increase process duration. Coating process efficiency is significantly affected by increased spray rate and pan speed. Production size batches manufactured with the selected coating parameters produced uniform coatings with a immediate release content uniformity assay of 90 – 110%, RSD < 7% and the entire tablet content uniformity met the requirements specified in the USP for solid dosage form.

1.0 Introduction

There is a growing interest in incorporating soluble and insoluble active drugs into the coating of coated tablets. For this technique to be useful for active drug application, the variation in coating between the tablets must be minimal. Application of active drug onto tablet cores using conventional spray coating processes is very challenging. Various coating techniques and processes for the application and delivery of active drug via a tablet dosage form have been studied in detail elsewhere (1,2,3). A number of process variables affect the uniform application of the film forming material onto the tablet cores as well as the quality, appearance and performance of the final film.

Coating may be applied by spraying a solution or suspension containing dissolved or undissolved drug substance and/or pigment onto a large number of tablets tumbling in a rotating pan (1,2). Under normal coating conditions, only the top portion of the tablet bed receives coating during each revolution and is limited by application time. Uniform color on the color-coated tablets as perceived visually concludes the end point of the coating process. This is achieved by increasing the coating time and the coating material applied on the core. Poor tablet movement in the drum can lead to differences in the amount of material applied to each tablet during the coating process (2). This can result in color variation, bridging of embossing on the tablets, and variability in drug release on diffusion barrier coated tablets. The problem of variation is seen in the tablet bed as light and dark cores during coating while applying a colored film over a light colored core (2). While color variation in the coated tablets may cause an elegance problem, variation in the coated drug may cause a therapeutic efficacy problem. Tablets that are coated with a

functional coating would exhibit a performance problem (e.g., enteric and sustained release coating). Many different tablet coating machines are on the market, each with different configuration and controllable parameter options (1,4). Various coating conditions and equipment configurations also have a profound effect on the development of a robust coating process with uniform coating of low dose active drugs. The variables that may influence coating uniformity include: mixing, pan rpm, concentration of the substrate in the coating solution, number of spray guns, spray pattern and coating time (3,5). A robust formulation is one that is insensitive to normal coating process variation. Normal variation includes the controllable process parameters and environmental factors (temperature and humidity) that affect the product quality and performance.

Generally, in developing and evaluating a coating process we learn through a series of activities in which we make conjectures about a process, perform experiments to generate data from the process, and then use the information from the experiments to establish new conjectures, which lead to new experiments (6). One strategy of experimentation that is widely used in practice is the one-factor-at-a-time approach. The major disadvantage of this strategy is that it fails to consider any possible interaction between the parameters. Interaction between factors is very common, and if occurring, the one-factor-at-a-time approach will produce poor results. An improved approach that addresses multiple parameters is the factorial experiment. This is an experimental strategy in which multiple parameters are varied together, instead of one at a time. Experimental design methods have found broad application in many disciplines, and is a critically important tool for improving the performance of both new and previously developed manufacturing processes. The application of experimental design techniques early in

process development can result in; improved process yields, process efficiency, reduced variability and overall savings in development cost. This article describes statistical design of experiment (DOE) studies that were conducted as part of the development, characterization and evaluation of a pulsed-release tablet dosage form for low dose water soluble drug.

2.0 Objective

To use a statistically designed set of experiments to evaluate the individual and interactive effects of process variables on the content uniformity of drug in the film coating and overall coating application process.

3.0 Methods

3.1 Materials:

Albuterol Sulfate, USP (Propharmaco, Nobel Industries, Italy); Microcrystalline Cellulose, USP (FMC Corp., Philadelphia, PA); Starch 1500, NF (Colorcon, West Point, PA); Lactose DT (Quest International, Hoffman Estates, IL); Magnesium Stearate, NF (Manllinckrot Inc., St. Louis, MO); Opadry® II (Colorcon, West Point, PA); Eudragit® S 100 (Rohm Pharma, GmbH, Germany); Aqueous Ammonia Solution, NF (Morflex Inc., Greensboro, NC); Triethylcitrate, NF (Morflex Inc., Greensboro, NC). All raw materials used complied with the current USP/NF grade specifications.

3.2 Equipment:

Sieve Shaker (Sweco, Florance, KY); V-blender (Patterson-Kelly, East Stroudsburg, PA); Micron Air Jet Sieve (Hosokawa Micron Powder Systems, Summit, NJ); Moisture Analyzer, Computrac Max 50 (Arizona Instrument, Tempe, AZ); Tablet Press, Kikusui Model Libra 836 KRCZ (Kikusui, Seisakusho Ltd., Kyoto, Japan); SMI Force Monitoring System (SMI Inc., Pittstown, NJ); Tooling 9/32" Standard Concave, (Natoli Engineering Co., Chesterfield, MO); Vector Tablet Tester (Vector Corp., Marion,

IA); Friability Tester (Erweka Instrument Corp., Milford, CT); Disintegration Apparatus Erweka ZT 3-4E (Erweka Instrument Corp., Milford, CT); Masterflex Peristaltic Pump, Model 7523-20 (Cole-Parmer Instrument Co., Barington, IL); High Speed Disperser, Model 89 (Premier Mill Corp., Reading, PA); Accela Cota 48" (Thomas Engineering, Hoffman Estates, IL); Shimadzu LC-4A, High Performance Liquid Chromatography (HPLC) Equipped with a Shimadzu SPD-2AS spectrophotometer detector (Shimadzu, Japan)

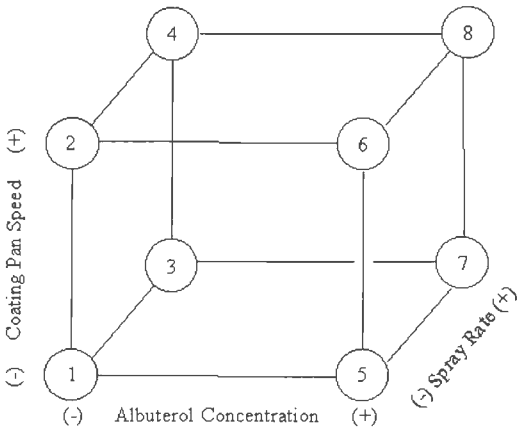
3.3 Experimental Design:

Based on the previous experimental work and available information from the literature it was clear that processing conditions significantly affect the uniformity and quality of coating (2,3,5,7). Processing parameters can interact both synergistically or antagonistically are not additive. Although successive approximation experiments can yield incremental improvement in coating quality and performance, the data from these experiments do not allow positive identification and quantification of interaction effects. Utilization of a factorial design during coating formulation and process development overcomes the information limitations of the successive approximation approach and more efficiently provides the kind of understanding and results that are needed (5,6). DOE is a multivariate approach in which two are more variables may be studied in one experiment. It is a most efficient method of experimentation that leads to a clear definition of variable effects that ultimately leads to process optimization. Even with DOE, the amount of work increases significantly as the number of study variables increase. Therefore, it was important to pre-screen the process parameters carefully to

select those critical parameters that would be expected to have an influence on the process. To determine the influence of the coating process variables on the uniformity of coating and to identify the relative importance of the estimated effects and any possible two-factor interactions, experimental designs were selected using Statgraphics® Plus version 3.1 (Manugestics Inc., Rockville MD). Figure I shows the 2^3 factorial (cube) design for evaluating the process variables.

The Statgraphics software generated an experimental design of 8 coating trials for the 2^3 factorial design. Ideally replication of the experiment is recommended for statistical analysis, as this would aid in obtaining an estimate of the experimental error if any. Due to limited resources; cost, time and the large quantity of raw material needed in scaling up on production size equipment replication is not often feasible. Therefore a replicate experiment was not performed to provide a true reading of actual conditions. Based on the product quality requirements the six response variables shown in Table 1 were selected for the study. Due to limited resources and time constraints, three critical processing variables that were believed to contribute for the most variation from a list of ten controllable process parameters that potentially affected the response variables were selected (8,9). The controllable variables were drug concentration in the coating solution, coating solution spray rate and coating pan rotation speed. These variables with their corresponding usage levels are presented in Table 2. Statistical analysis of the observed results for each response was analyzed to determine which of the three factors had the

Figure 1. Cube Design for Evaluating Spray Processing Variables



(+) High Level
(–) Low Level

Table 1. Response Variables in the Order of Importance

Response Variable	Units
Coating assay	%
Relative standard deviation (coating uniformity)	%
Coating process efficiency	%
Loss on drying	%
Process duration	hr
Pan exhaust temperature	°C

Table 2. Selected Process Variables Usage Levels

Experiment Variable	Level		Measurement (Units)
	Low	High	
Drug concentration in coating suspension	2.5	4.0	%
Spray rate	150	350	grams/min
Coating pan speed	4	8	rpm

most effect. Analysis was also performed to estimate how strongly each of the experimental factors affects the response. Analysis results were graphically presented as pareto charts and response surface graphs to represent the relative significance of the effects. A *P*-value of 0.05 was considered as the criteria for statistical significance. Analysis of variance (ANOVA) was used as an alternative tool to justify the estimated regression model. All coating trials in this experiment used 7-mm diameter, standard convex shaped placebo tablets weighing approximately 135 mg. Total batch weights of 135 kg of placebo tablet cores were used for each coating trial. Table 3 shows the placebo tablet core formulation used in this study. Placebo tablet cores were manufactured using a 36 station instrumented Kikusui rotary tablet press. These placebo tablet cores were then seal coated using the 48 inch Accela-Cota, by spraying the coating suspension formulation presented in Table 4 and using the fixed processing parameters shown in Table 5. These seal coated placebo tablets were used as substrate cores for the immediate release coating experimental trials.

3.4 Granulation Manufacture:

Excipients were pre screened (deagglomerated) using a Sweco sieve shaker fitted with a 20 mesh wire screen. Screened excipients were then placed in a 50 ft^3 V-blender and mixed for 20 minutes. Magnesium stearate was passed through a 30 mesh screen, screened material was added to the blender and mixed for 3 additional minutes. The granule properties examined include percent loss on drying, granule size distribution, bulk densities and percent compressibility (Carr index).

Table 3. Formula for Placebo Tablet Core

Ingredient	Content	
	Percent w/w	mg/tablet
Microcrystalline Cellulose, USP	30.0	40.5
Pregelatinized Starch, NF	24.3	32.8
Spray Dried Lactose, NF	45.0	60.7
Magnesium Stearate, NF	0.7	1.0
Total	100.0	135.0

Table 4. Formula for Seal Coating Tablet Cores

Ingredient	Content	
	Percent w/w	mg/tablet
Eudragit S® 100	12.0	6.75
Aqueous Ammonia Solution 1N	6.1	–
Triethylcitrate, NF	6.0	3.38
Talc, USP	4.0	2.25
Purified Water, USP	71.9	–
Total	100.0	12.38

Table 5. Coating Parameters for Seal Coating (Accela-Cota 48")

Operating parameter	Condition
Drum Size (inches)	48
Batch Size (kg)	135
Number of Spray Guns	3
Pan Speed (rpm)	4
Atomizing Air Pressure (bar)	1.5
Process drying air (cfm)	1600
Coating level (%)	6
Drying Time (min)	30

3.5 Tablet Manufacture:

The manufactured granulation was filled in the hopper of an instrumented Kikusui Libra tablet press (Kikusui Seisakusho Ltd., Kyoto, Japan). The tablet press was setup to compress thirty six 7 mm diameter shallow convex tablets per revolution. The target tablet weight was adjusted to 135 mg, and tablets were produced using pre compression and main compression force of 300 kg and 1000 kg respectively to produce a target tablet hardness of 7 kp for the entire batch. Tablet samples were collected and stored in tightly sealed containers for subsequent physical characterization. The uniformity in weight of the placebo tablet was determined using the weight variation test procedure <905> specified in the United States Pharmacopoeia (USP 23)(10). The weight, thickness, hardness was measured using vector automatic tablet tester (Vector Corp., Marion, IA) USP acceptance criteria were applied in the evaluation of the results. The tablet friability, resistance to abrasion during the handling and coating process, was measured using a Roche type friabilator (Erweka Instrument Corp., Milford, CT). Fifty tablets were randomly selected from the bulk sample for this test. The tablets were weighed and subjected to 100 rotations (25 rpm for 4 minutes) in the friabilator. The tablets were then dusted and reweighed to determine loss of abrasion. Friability is reported as percent weight loss.

3.6 Tablet Coating:

3.6.1 Seal Coating Suspension Preparation

The seal coating suspension formulation presented in Table 4 was used. Eudragit® S 100 powder was dispersed in purified water, added to the dispersion liquid ammonia

mixed for 60 minutes. Triethyl citrate was added to this mixture and mixed for an additional 60 minutes. Talc was dispersed separately in purified water; this dispersion was then added to the Eudragit dispersion to form the coating suspension. The coating mixture was continuously stirred during the suspension preparation process.

3.6.2 Immediate Release Coating Suspension Preparation

The immediate release coating suspension formulation is presented in Table 6. Albuterol sulfate was dissolved in purified water; to this solution Opadry® II white was added and mixed to obtain a homogeneous coating suspension. The coating suspension sample was collected at the end of the process to determine the amount of albuterol sulfate in the final coating suspension.

3.6.3 Seal Coating Procedure

A 48 inch Accela-Cota (Thomas Engineering, Hoffman Estates, IL) was loaded with 135 kg of compressed placebo tablets. The tablets were seal coated using the coating suspension prepared using the formulation presented in Table 4. The coating suspension was stirred continuously throughout the process to maintain homogeneity. The solution spray guns were calibrated by spraying the coating suspension for a specified amount of time and weighing the material sprayed through each spray gun. Spray to tablet bed distance was set at 10 inches for all coating trials. The Eudragit coating suspension was sprayed using three spray guns equipped with a 1 mm spray nozzle, pan speed ranging from 4-6 rpm, airflow of 2000ft^3/min, pan pressure of -0.05in. water, and a

Table 6. Formula for Albuterol Sulfate Immediate Release Coating

Ingredient	Percent w/w
Albuterol Sulfate, USP	2.5–4.0
Opadry® II White	8.5–7.0
Purified Water, USP	89.00
Total	100.00

product temperature of 32°C. A Masterflex peristaltic pump, equipped with silicon tubing was used to deliver the coating suspension. After coating, the tablets were allowed to dry in the coating pan for 30 minutes by tumbling at 40°C before cooling. Tablet samples were collected at the end of the coating process for physical characterization.

3.6.4 Immediate Release Coating Procedure

The seal coated tablets were loaded into a 48 inch Accela-Cota and the immediate release albuterol sulfate coating suspension presented in Table 6 was sprayed onto the tablets. The coating suspension was sprayed using three spray guns, with process airflow of 2000ft^3/min, pan pressure of -0.05 inch water, and a target product/exhaust temperature of 45°C. The inlet and outlet temperatures were maintained at 59 ± 2°C and 40 ± 2°C. The coating suspension was sprayed continuously using a peristaltic pump with spray guns equipped with 1 mm spray nozzle. An average tablet weight gain of 8% solid was applied which is equivalent to 2 mg of albuterol per tablet. The coating suspension was stirred continuously throughout the process to maintain homogeneity. Appropriate coating solution spray rate and pan speed were selected as per the randomized experimental run created by the design of experiment shown in Table 7 and fixed processing conditions shown in Table 8.

3.7 Coating Assay:

A reverse phase High Performance Liquid Chromatography (HPLC) assay was selected due to the advantage of direct analysis of aqueous samples, high sensitivity and separation of excipients that may interfere with the assay.

Table 7. Coating Experimental Trials from Design of Experiments

Experiment Run No.	Spray Rate (g/min)	Pan Speed (rpm)	Albuterol Conc. (%w/w)
1	350	8.0	4.0
2	350	4.0	4.0
3	350	8.0	2.5
4	150	4.0	4.0
5	150	4.0	2.5
6	150	8.0	4.0
7	150	8.0	2.5
8	350	4.0	2.5

Table 8. Fixed Processing Conditions for the Experimental Trials (Accela-Cota 48")

Operating parameter	Condition
Drum Size (inch)	48
Batch Size (kg)	130
Solution Spray Pump	Peristaltic
Number of Spray Gun	3
Spray Type	Continuous
Spray to Bed Distance (inch)	12
Atomizing Air Pressure (bar)	1.5
Process Air Volume (cfm)	2000
Coating level (%)	8
Drying Time (min)	30

Twenty tablets were selected at random; each tablet was placed in a separate volumetric flask containing 20 mL of water. The sample was sonicated and vortexed for one minute until all of the outer coating (immediate release portion) of the tablet was dissolved. The solution was decanted into 500 mL volumetric flask. The vial was rinsed with 20 mL water total of nine additional times, and the rinse solutions were decanted into the same 500 mL volumetric flask. The 500 mL flask was diluted to volume with water. 12.5 mL of this solution was transferred to 200 mL volumetric flask and diluted to volume with water.An aliquot of this solution was filtered through a 0.45 μm PTFE filter, discarding the first 5 mL of the filtrate. A reverse phase column (Keystone ODS/H, 5μm 4.6x250 mm) in conjunction with a variable wavelength UV detector was used. The injection volume was 30 μL with a flow rate of 1mL/minute and a column temperature of 35°C.

3.8 Relative Standard Deviation (Coating Uniformity):

Coating uniformity is generally defined as the variation in weight gain of coated tablets within a coating trial. In each experimental trial, 100 tablets were collected before and after coating. Twenty tablets were used for weight variation measurements and twenty tablets were individually assayed to determine drug content uniformity in the coating. For the purpose of this experiment, RSD will be expressed as the first standard deviation of the variation in percent assay and is calculated by (5, 11):

$$\% \text{ RSD} = \frac{\sqrt{\dfrac{\Sigma[(wt_a - wt_b) - \bar{x}]^2}{n-1}}}{\bar{x}}$$

Where wt_a and wt_b are the tablet weights after and before coating respectively. n is the number of tablets measured and x is the average weight gain of the n measured tablets from the coating trial. All measurements were corrected for moisture content. This method provided an effective means of determining the coating uniformity in each coating run thereby allowing the assessment of process changes on coating uniformity.

3.9 Coating Process Efficiency:

Coating process efficiency is generally defined as a measure of the determined actual coating applied expressed as a percentage of the theoretical amount of coating intended to be applied.

$$CPE = [wg_a/wg_t] \text{x } 100\%$$

Where wg_t is the theoretical percent weight gain and wg_a is the actual percent weight gain, which is computed as: $wg_a = [wt_a - wt_b / wt_b] \text{ x } 100\%$

Where wt_a and wt_b are the total batch weights before and after coating respectively. All measurements were corrected for moisture content.

3.10 Loss on Drying:

Percent loss on drying is a measure of the moisture content of the tablet. It can be extremely important to both tablet cores, coating end point determination and drug stability. Percent loss on drying is the moisture content of the coated tablet expressed as percent weight. Percent LOD is calculated as follows:

$$\% \text{ LOD} = [wt_a - wt_b / wt_b] \text{ x } 100\%$$

Where wt_a and wt_b are the coated tablets weights before and after drying, respectively. The tablets were weighed, dried at 50°C in a temperature-controlled oven for 24 hours then reweighed.

3.11 Product Bed Temperature:

Product bed temperature data was obtained from an average of the values recorded throughout the coating process. The inlet, outlet and the exhaust temperature were measured using a temperature probe integrated with an automatic data collection system.

4.0 Results and Discussion

4.1 Placebo Tablet Core Properties:

Friability is a term used to describe the resistance of tablets to mechanical wear as shown by the breakage, chipping, and abrasion witnessed during coating, high-speed packaging and transportation. Tablets were compressed at a target main compression force of 1000 kg, which produced a hardness of 7 kp. Ten tablets were collected at specified intervals (every fifteen minutes) through out the compression run and were tested for weight, thickness, hardness and friability as an in-process control check. Tablets produced were close to the target hardness and weight with minimal variation across the entire batch. Tablet friability was $\leq$ 0.1%. This yielded tablets that were suitable for the coating process. Table 9 shows the placebo tablet properties.

4.2 Seal Coated Tablet Properties:

Coating summary results for seal coated tablets are presented in Table 10. Results indicate a good recovery of the amount of solids applied as weight gain. The coating efficiency was calculated as a function of polymer weight gain based on the amount of solids applied and ranged from 97.6 to 99.8% for all eight batches, suggesting that the process is efficient and reproducible. Weight variation for the seal coated tablets was minimal with the average tablet weight ranging from 146.2 – 148.4 mg suggesting low inter-tablet variability. The observed variation RSD values ranged from 1.3 – 2.3%

Table 9. Summary of Tablet Properties (Placebo Core)

Properties	Weight (mg)	Thickness (in.)	Hardness (Kp)	Friability (%)	Disintegration (min)
Average	135.2	0.140	7.1	0.1	2.5
RSD (%)	0.95	0.45	1.7	–	2.8

Table 10. Summary Results for Seal Coating

Batch No.	% Polymer coated		Efficiency	Tablet Weight		Loss on Drying
	Theoretical	Actual	%	Avg. (mg)	%RSD	%
1	5.0	4.9	97.8	147.3	1.6	3.2
2	5.0	4.7	97.6	147.1	2.1	2.8
3	5.0	4.8	98.9	146.9	1.3	2.9
4	5.0	5.1	99.8	148.4	1.7	3.1
5	5.0	4.9	98.6	147.7	2.0	2.8
6	5.0	4.9	99.1	147.2	1.5	3.2
7	5.0	4.8	98.8	146.2	2.2	2.9
8	5.0	5.0	99.5	147.9	2.3	3.3

indicating that the coated tablets have minimal variability in weight and hence are suitable as a substrate for further coating. Loss on drying values were < 3.3%, and similar to the values obtained for the dry granulation. These results suggest that the seal coating process does not affect the original moisture level in the granulation.

A statistical evaluation of the results obtained from these experiments were analyzed to identify the influence of each of the three factors (spray rate, pan speed and drug concentration in the coating solution) on the coating uniformity, assay, coating process efficiency, loss on drying, product temperature and processing time in an attempt to select the optimum processing parameters for the large scale production. Analysis of variance along with various graphical evaluations of the response data was performed to identify the statistical significance of the influential factors.

4.3 Coating Assay:

Amount of active drug in the coating is of primary importance, especially since the film coating delivers the initial dose of 2 mg, which is 50% of the drug from the dosage form and should be readily available as immediate release. Coating drum speed, pan charge, amount of material applied and spray pattern were known to affect the amount of material deposited on the tablets (7, 12). Hence, it was necessary to explore the relationship between the amount of solids applied and the amount recovered. Any difference in solid deposition and recovery may affect the amount of active drug in the dosage form and potentially result in low assay values. The response results; average tablet weight, assay for albuterol, and percent efficiency along with RSD values for the tablet samples from the 8 experimental runs is presented in Table 11 (Appendix III). It is

immediately apparent from these results that experiments 1, 3 and 7 with higher pan speed (8 rpm) show low tablet weight and assay values suggesting a significant loss of solid material deposited on the tablet. The loss on drying values for tablet samples for all experiments range from 2.3–3.7% and the variability is minimal and are close to the loss on drying values of the seal coated tablet cores. These findings suggest that the coating process did not impart any additional moisture to the coated tablets that may invariably affect the tablet weight gain and assay values. Table 12 (Appendix III) shows the ANOVA results for percent assay response for all 8 experiments. In this case, three factors have P-value less than 0.05, indicating that they are significant. The order of significance pan speed–albuterol concentration interaction (BC) P=0.0381 followed by pan speed (B) P=0.0409 and spray rate (A) P=0.0489 is the least significant of all three that affect the amount of coating material deposited on the tablets. The R-Squared statistics indicates that the model explains 99.9% of the variability in coating assay response which is mostly contributed by these three effects. Figure 2 shows the standardized pareto chart for the percent albuterol assay, the results indicate that the coating pan speed (B), suspension spray rate (A) and combined pan speed–albuterol concentration (BC) were the most important factors that significantly affect the amount of albuterol in the tablet coating. These are significant effects because; their associated bars cross the vertical line, which represents a 95 percent test of significance. Figures 3-4 show the main effect and interaction effect for pan speed, albuterol concentration and coating suspension spray rate. It can be seen from the assay values (Figure 3) that the higher spray rate has a negative impact on the amount of drug coated. Also, it can be seen

Figure 2. Standardized Pareto Chart for Assay Response

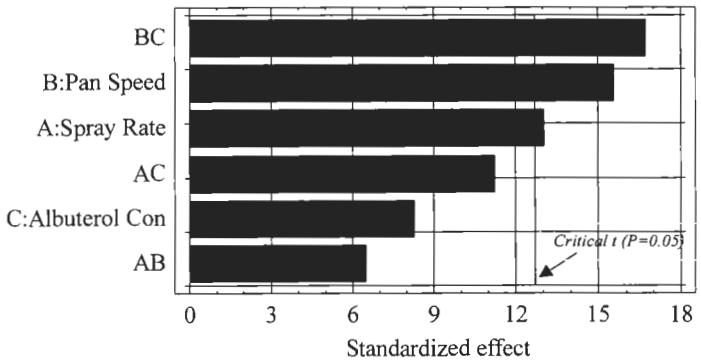


Figure 3. Main Effects Plot for Assay Response

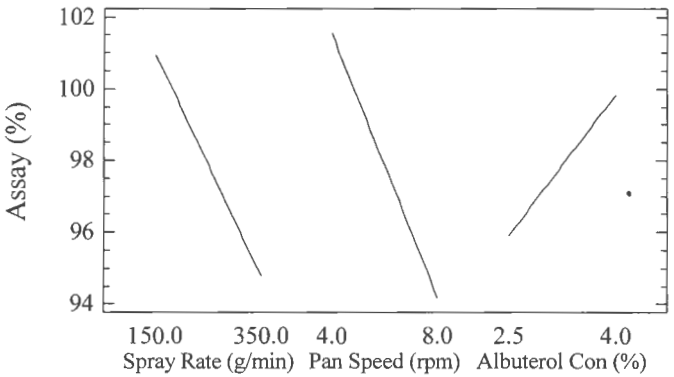
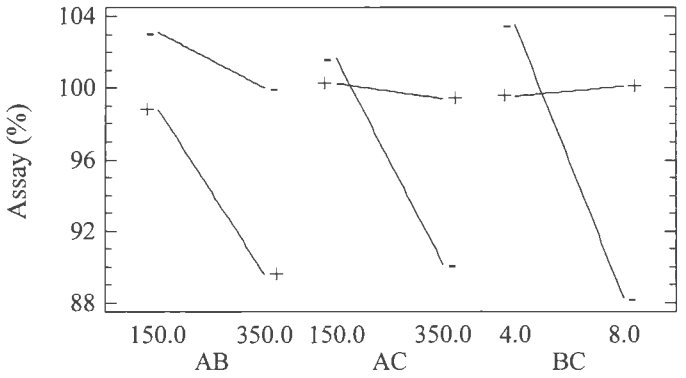
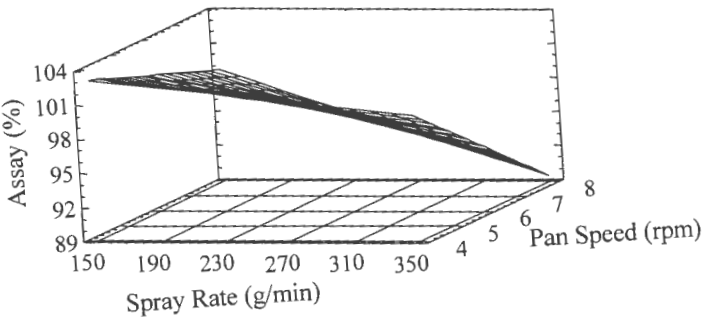


Figure 4. Interaction Plot for Assay Response



from these plots of assay results, the amount of drug in the tablet coating decreases when the coating pan speed and spray rate was increased simultaneously. However, increasing the albuterol concentration in the coating solution produces quite opposite effect. Increased albuterol concentration in the coating solution increases the assay values. Although there is interaction between albuterol concentration in the coating solution and spray rate, (Figure 4) it is not prominent. Furthermore, there is no spray rate–pan speed (AB) interaction effect that influence coating solids application. Therefore, it can be concluded that interaction effect pan speed–albuterol concentration (BC) significantly influences the amount of coating material applied on to the tablets. Hence, tablet assay values are affected. Similarly, the coatings are not affected by lower pan speed but higher pan speed and spray rate has negative impact on the assay. Figure 5 is a response surface graph showing the effects of both spray rate (x-axis) and pan speed (z-axis) on assay (y-axis) across the experiment ranges used. The linear, interaction and curvilinear effects of the experiment variables are best visualized using response surface graphs. It is clear from the figure that increasing the spray rate reduces the assay value. Figure 5 also shows the curvilinear effect of pan speed, which results in reduction in drug coated onto tablets with increasing pan speed. The reason for this seems to be, that although the tablets undergo large number of rotational cycles in a given time under the spray zone, the actual time over which the tablets are exposed under the coating zone is short. These results have important practical implications on the uniformity of film coating. In this case increasing the pan rotational speed may well be detrimental since, although improving mixing of the tablet bed, it may well result in increased coating material carryover,

Figure 5. Estimated Response Surface Plot for Assay

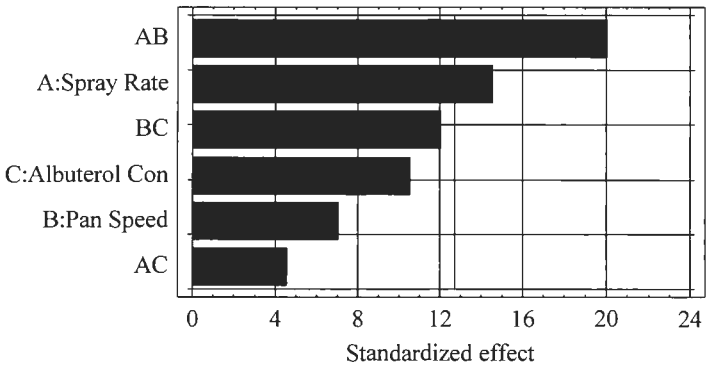


decreased solid deposition on the tablet core and thus a reduced amount of active drug on the coated tablets.

4.4 RSD (Coating Uniformity):

Coating uniformity is of primary importance, especially since the film coating delivers the first dose of 2 mg of albuterol for immediate release. A tablet that has received too little coating will have less active drug (leading to low loading dose), while the one that received too much coating will deliver an overdose leading to excessive therapeutic activity or possible side effects. It is evident from Table 11 (Appendix III) that experiment 2 and 8 both with high spray rate show larger RSD values for tablet weight (1.53 and 1.67%) and content uniformity (12.8 and 11.1%) suggesting lack of uniform application of the coating material and has the shortest process time. However, experiment 5 with low spray rate and longest coating time exhibits the smallest RSD value for both tablet weight (0.85%) and content uniformity assay (7.1%). Table 13 (Appendix III) shows the ANOVA results for percent RSD response. In this case, two effects have *P*-values less than 0.05, indicating that they are significant. Since, the *P*-value is 0.0438 for spray rate and interaction effect spray rate–pan speed 0.0318, we can conclude that there is a significant interaction between spray rate and pan speed. Furthermore, the main effect for spray rate is also significant. The R-Squared statistics indicates that the model explains 99.9% of the variability in percent RSD data of which 65.3% of the variability is contributed by the above mentioned two factors. Figure 6 presents a standardized pareto chart for percent relative standard deviation for drug

Figure 6. Standardized Pareto Chart for Percent RSD



content uniformity. The results show that interaction effect pan speed–spray rate (AB) and coating suspension spray rate (A) are the two significant factors affecting the percent relative standard deviation (their associated bars cross the vertical line, which represents the critical *t*-value at a *P*-value of 0.05).

It is obvious from the relative standard deviation values, higher the spray rate, larger the variability in the coating application resulting in poor coating uniformity. Also the combined effect of spray rate along with pan speed has an adverse effect on the coating uniformity. Figures 7-8 display the main effect and interaction effect of the three factors studied in graphic form. It can be seen from this figure that among the three factors pan speed seems to have the least effect on the percent relative standard deviation for coating uniformity. Both a higher spray rate and increased albuterol concentration in the coating solution increases the variability in coating as a result increased percent RSD value of the tablet content uniformity. As expected a uniform spray of drug coating onto the tablet cores produces less variability in drug content uniformity and smaller RSD values. The half-normal probability plot for these effects (Figure 9) shows that two factor interaction spray rate–pan speed located further away from the fitted line suggesting that they have significant effect on the uniformity of the film coating. Furthermore, the effect of spray rate on the coating uniformity is also significant. Figure 10 is the contour plot showing the effect of spray rate and pan speed on percent RSD. It can be seen from the plot that a lower RSD value is obtained towards the slower pan speed and spray rate. Figure 11 is a response surface graph that also shows the effects of both spray rate (x-axis) and pan speed (z-axis) on percent RSD (y-axis) across the experiment ranges used

Figure 7. Main Effects Plot for Percent RSD

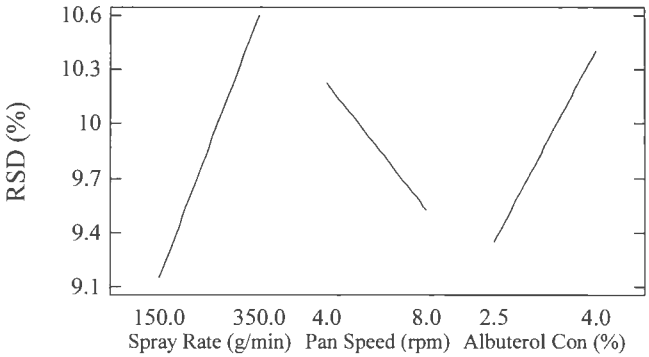


Figure 8. Interaction Plot for Percent RSD

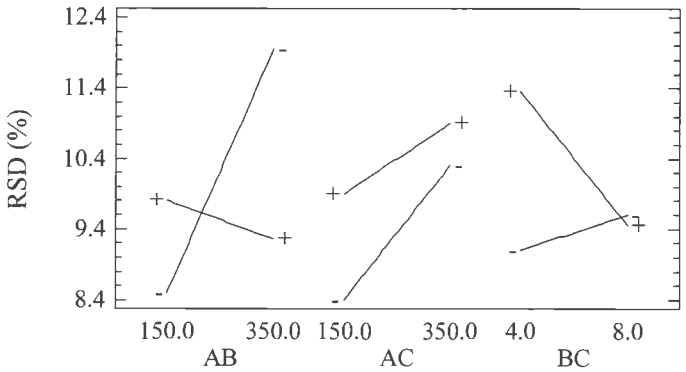


Figure 9. Half-Normal Probability Plot for Percent RSD

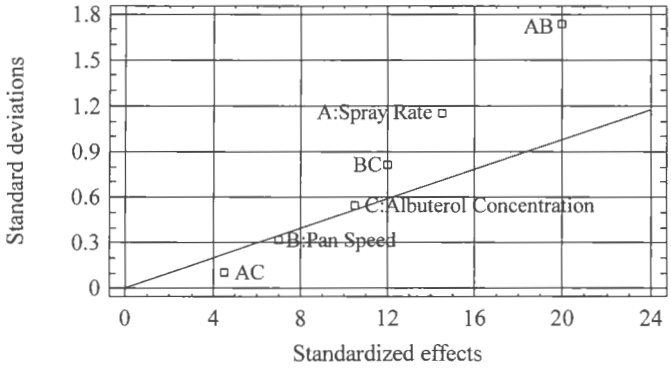


Figure 10. Contours of Estimated Response Surface for RSD

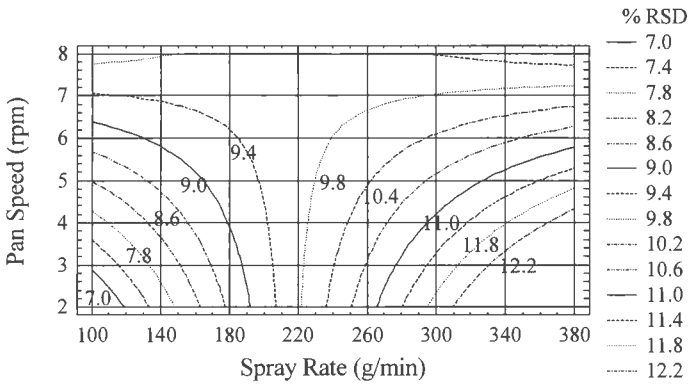
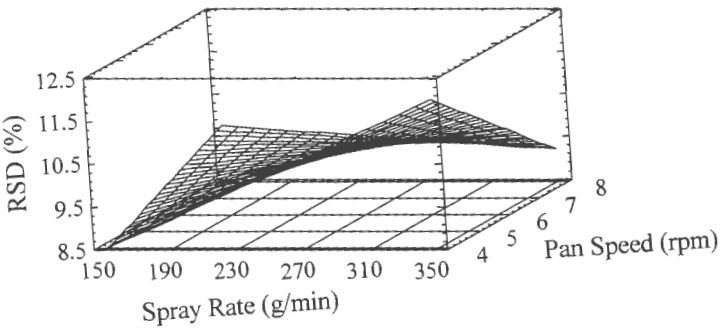


Figure 11. Estimated Response Surface Plot for Percent RSD



in this study. Lower RSD values for the tablet content uniformity were observed at low spray rate and pan speed.

The content uniformity between tablets is significantly improved by using a low spray rate and reduced pan speed. This is primarily due to longer exposure time of the tablets cores to the coating spray zone (increased number of revolutions). In contrast, increasing the pan speed and spray rate produce poor coating uniformity. This effect may be caused due to the turbulent motion of the tablets in the coating pan due to higher pan speed and abrasion of tablets resulting in lack of uniform coverage and loss of coating material from the tablet surface.

4.5 Coating Process Efficiency:

Pickard (1979) has defined process efficiency as the ratio of mean weight of coating found on the tablet to the mean weight of solids applied per tablet from the coating solution and often expressed as percent (14). Polymer film coating solution was sprayed onto the tablet bed by means of spray guns that are mounted in the coating drum. It is quite possible not all of the coating material applied to be deposited on to the tablets surface. There are number of reasons for this; spray drying of the coating material before reaching the tablet surface, abrasion of tablets-tablets, tablets to the pan surface and material carry over in the exhaust plenum (12,13,14). In an attempt to examine the relationship between the process efficiency with regard to solids deposition and process variables such as spray rate, pan speed and drug concentration a statistical evaluation was performed on the percent efficiency response results obtained from the experiments. In this study the coating process efficiency response ranged from 81.2% to 101.2%,

indicating a broad range; from inefficient (20% loss) to almost 100% recovery of the coated solids. Table 14 (Appendix III) shows the ANOVA results for coating process efficiency. Since, the *P*-values are 0.478 and 0.496, for spray rate and pan speed we can conclude that these main effects are significant. The R-Squared statistics indicates that the model explains 99.8% of the variability in coating process efficiency. Figure 12 presents a standardized pareto chart for coating process efficiency. The ranking also identifies spray rate followed by pan speed as the significant factor affecting the coating process efficiency at the 5% level. Figure 13-14 display the main effects and interaction effects of the three factors studied in graphic form. It can be seen from these results that among the three factors studied albuterol concentration in the coating suspension seem to have the least effect on the coating efficiency. Furthermore, both increased pan speed and spray rate reduce the coating efficiency.

The process efficiencies reported by Kara et al using a 24 inch coating pan to measure the material carry over through the exhaust plenum were slightly lower than the values obtained from these experiments (12). Earlier studies showed lower process efficiency due to lower pan charge along with increased spray rate and pan speed (12,13). Surprisingly that was not the case in our experiments. Our result indicate that a greater quantity of coating material applied is lost and that the efficiency of the process becomes progressively lower with increasing spray rate and pan speed while the pan charge was kept constant in all the experiments. The low process efficiency observed in these experiments may be due to the changes in airflow pattern through the tablet bed because of increased void spaces in the tumbling tablet bed.

Figure 12. Standardized Pareto Chart for Coating Process Efficiency

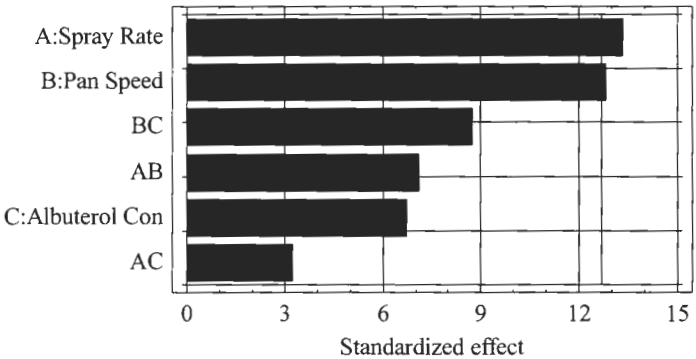


Figure 13. Main Effect Plot for Coating Process Efficiency

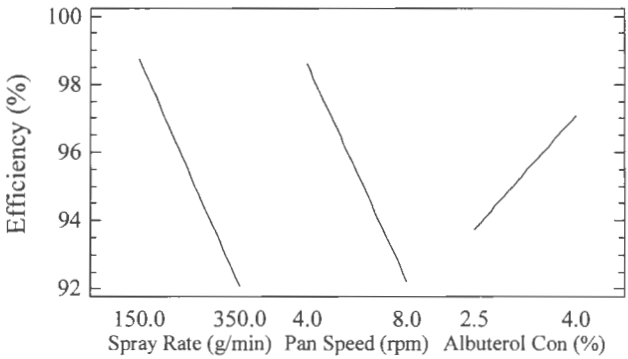


Figure 14. Interaction Plot for Coating Process Efficiency

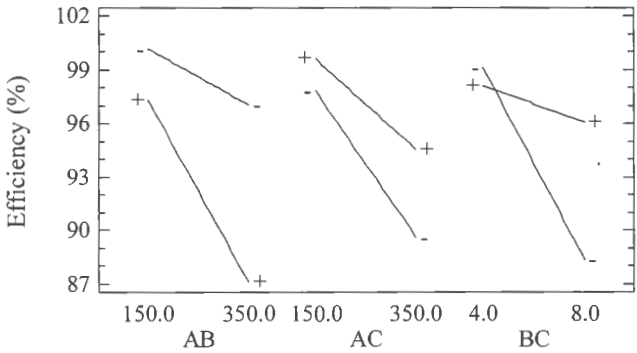


Figure 15 is a response graph showing the effects of both spray rate and pan speed on process efficiency across the experimental ranges used in this study. The direct and curvilinear effects of these two variables are responsible for all of the variation in the coating process efficiency. It can be seen from the graph that the process efficiency decreases as the spray rate and pan speed increases. Conversely, the process is efficient and almost 100% of the coating material applied were recovered at the lower spray rate and coating pan speed.

4.6 Loss on Drying:

Table 11 (Appendix III) shows the loss on drying measurements for all the experiments. The percent loss on drying values ranged from 2.4–3.7%. Figure 16 is a standardized pareto chart that graphically presents in rank order the factors responsible for the percent loss on drying response. This indicates that spray rate is the single most variable that had a substantial effect on this response. However, this effect is not significant at the level of alpha 5%. Figure 17-18 display the main effect and interaction effect of the three factors studied in graphic form. It can be seen that among the three factors, coating suspension spray rate has the most effect on loss on drying. It can therefore be considered as another indicator of overwetting or over drying of the coated tablets. Although there is interaction effect pan speed–albuterol concentration (BC) it is not apparent.

Coating process efficiency is a measure of the actual amount of coating applied to the tablets relative to the theoretical quantity of coating applied. Since, the coating end

Figure 15. Estimated Response Surface Plot for Process Efficiency

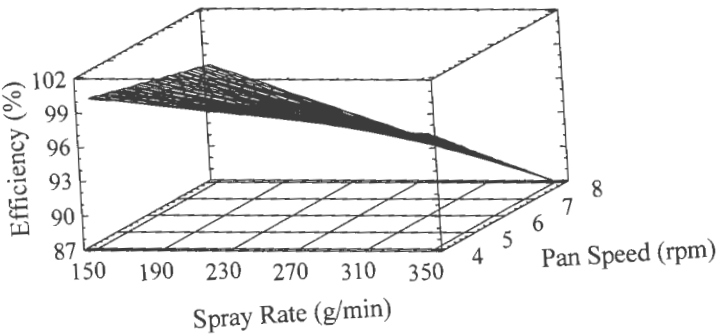


Figure 16. Standardized Pareto Chart for Loss on Drying

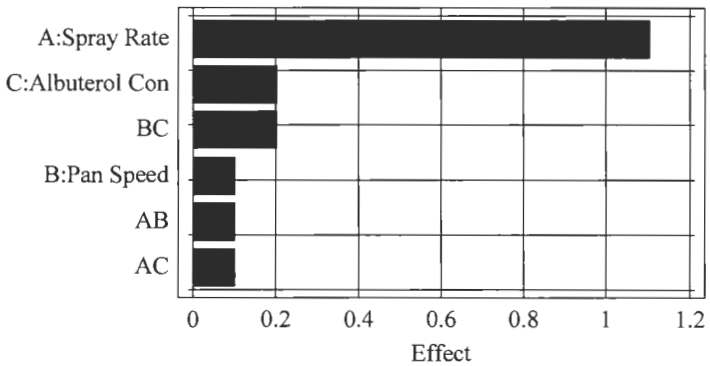


Figure 17. Main Effect Plot for Loss on Drying

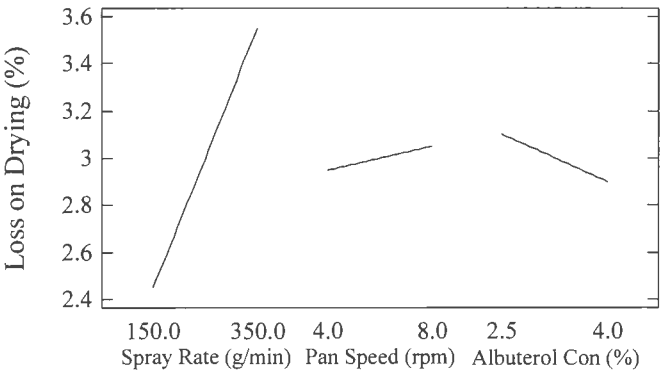
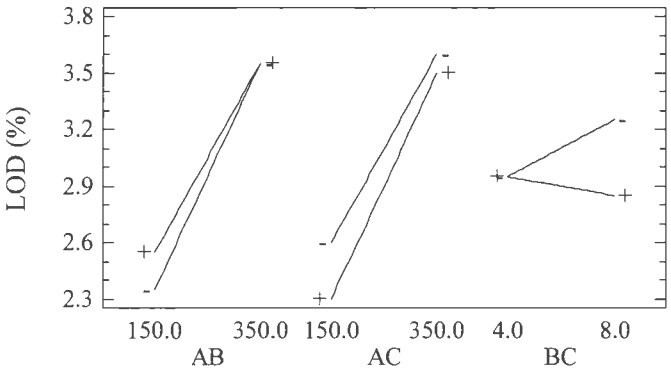


Figure 18. Interaction Plot for Loss on Drying Response

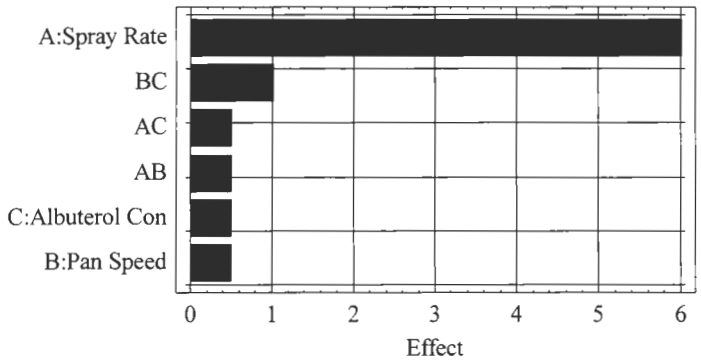


point was determined using the tablet weight gain, it was very important to maintain the moisture level closer to the actual starting level found in the granulation. Increased or decreased moisture level of the tablet cores along the process from the original levels could significantly affect the coating end point determination and the amount of solids applied (drug substance). This would eventually lead to variation in the amount of drug coated onto the tablets and inaccurate coating end point determination. Since, none of the factors have a significant effect on the percent loss on drying values, we can conclude that the moisture level in the coated tablet is not affected by the processing conditions and that the moisture level remains consistent at various processing stages.

4.7 *Exhaust Temperature:*

Exhaust air temperature was used as a measure of product temperature in this study, and ranged from 34–41°C. Inlet air temperature, process air volumes and spray rates accounted for the majority of the effects on product temperature. Increase in spray rate resulted in lower product temperature, as expected. Figure 19, standardized pareto chart, graphically presents the product temperature analysis results. Spray rate (A) is the only factor affecting the product and or exhaust temperature. Since, only the solution spray rate has an effect on the exhaust temperature it can be easily controlled without affecting the quality of the product. Moreover, there was no interaction effect of any of the factors on the product temperature.

Figure 19. Standardized Pareto Chart for Product/Exhaust Temperature



4.8 Processing Time:

Processing time was crucial for any given process. Shorter processing time obviously has a significant economical advantage over an extended process. Shorter processing reduces the active drug exposure time to the harsh coating environment, saves utility cost and labor associated with the process. Hence, it was important to evaluate the significance of these factors on the process time. In this study the processing time response ranged from 3 to 11 hours, indicating that spray rate is the single most variable that had a substantial effect on this response. Table 15 in (Appendix III) shows the ANOVA results for coating process duration. In this case, only spray rate has a *P*-value less than 0.05, indicating that is significant. The R-Squared statistics indicating that the model explains 99.8% of the variability in coating process duration of which spray rate contributes to 74%. A longer processing duration means that the tablet residence time in the spray zone is longer and going through a large number of passes under the spray zone. Figure 20 a standardized pareto chart, graphically presents the processing time analysis results. It is immediately evident that spray rate is the significant factor affecting the process time at the level of 5% alpha. Figure 21 is the half-normal probability plot of the effects on process duration. The spray rate and albuterol concentration are the two points that are located further away from the fitted line suggesting that two factors spray rate and albuterol concentration have significant effect on the process duration. Processing time increased almost 4 fold with lower spray rate and low albuterol concentration as expected. It is not surprising that the processing conditions that gave a better uniformity had the longest processing time. However, we cannot ignore the fact that the drug concentration in the coating solution also contributes to the extended process time.

Figure 20. Standardized Pareto Chart for Process Duration

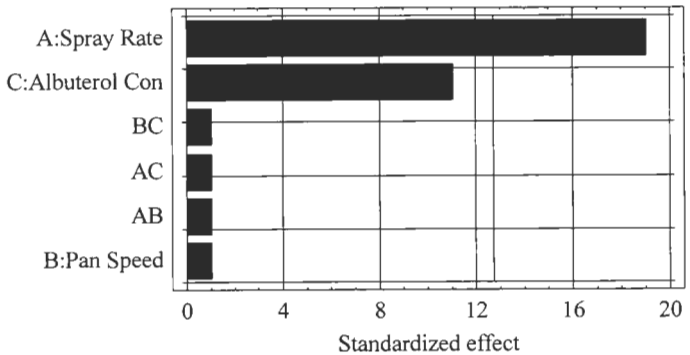
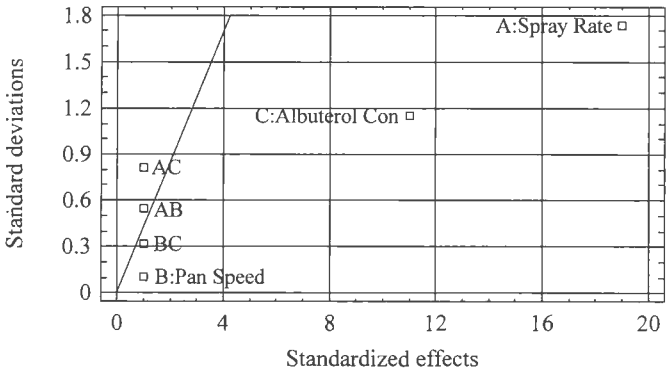


Figure 21. Half-Normal Probability Plot for Process Duration



5.0 Conclusions

The effect of coating pan rotation speed, coating suspension spray rate and active drug concentration in the coating suspension on film coating uniformity was studied through the use of statistical design of experiments and chemical testing. These studies show that coating suspension spray rate and coating pan rotation speed have a significant effect on the coating uniformity of the film which in turn affects the uniformity of the active drug delivered via this film coating system. It can be concluded that low spray rate and reduced drug concentration in the coating solution can significantly improve the content uniformity of the drug being coated onto the tablets. The best possible coating parameter with acceptable coating uniformity had low spray rate and slow pan speed. Of course, this comes with a price due to extended process time and increased utility cost in running the process.

The coating efficiency is also significantly affected by the spray rate and pan speed. Furthermore, the assay values were lower at higher spray rate and pan speed, indicating some material carryover through the exhaust plenum might occur during the coating process. Material carryover and the significance of various baffle positions in the coating pan to improve better mixing and uniformity of coating is debatable, but should be tested and is beyond the scope of this study.

The results of analysis of variance can be used to predict the effect of various processing parameters on the response. Preliminary experiments conducted for coating trials allowed to identify the critical processing parameters that influence the coating process. The use of statistically designed experiments aided in the selection of suitable processing parameters for the large scale coating process. Furthermore, the statistical

analysis of the measured response allowed to explore the relationship between the processing parameters and their optimum levels. Based on the findings appropriate coating parameters were chosen for the scale-up and production batches.

Finally, production size batches manufactured with the selected coating parameters met the immediate release coating content uniformity (RSD < 7%) and entire tablet content uniformity requirements for the developed product. These findings also suggest that it is possible to deliver low dose active drug in the tablet coating without compromising the product quality.

REFERENCES

1. Palaniswamy, S., "Modified Release Adrenergic Drug for Twice a Day Dosing", Masters Thesis, University of Rhode Island, Kingston, RI, USA, May (1994).
2. Signarino, C. A and Forcellini, L. J., "Evaluating the Uniformity of Aqueous Film Coating", *Pharm. Technol.* Yearbook, 48-53 (1996).
3. Fourman, G. L., Hines, C. W and Hritsok, R. S., "Assessing the Uniformity of Aqueous Film Coatings Applied to Compressed Tablets", *Pharm. Technol.* **19** (3), 70-76 (1995).
4. Porter, S. C., "Aqueous Film Coating: an Overview', *Pharm. Technol.* **3** (9), 55-59 (1979).
5. Porter, S. C., Verseput, R. P and Cunningham, C., "Process Optimization Using Design of Experiments", *Pharm. Technol.* **21** (10), 60-70 (1997).
6. Montgomery, D. C., *Design and Analysis of Experiments*, (John Wiley and Sons, New York, 2nd ed., 1990).
7. Skultety, P. F., Rivera, D., Dunleavy, J and Lin, C. T., "Quantitation of the Amount and Uniformity of Aqueous Film Coating Applied to Tablets in a 24 Accela-Cota", *Drug Dev. Ind. Pharm.* **14** (5), 617-631 (1988).
8. Mathur, L. K., Forbes, ST. J and Yelvigi, M., "Characterization Techniques for the Aqueous Film coating process", *Pharm. Technol.* **8** (10), 43-53 (1984).
9. Palaniswamy, S., Needham, T. E., Zia, H and Szymanski, D. J., "Optimization of Immediate Release Coating Portion of An Extended Release Dosage Form of a Water Soluble Drug", *PharmSci.* 1 (1), S-157 (1998).

10. The United States Pharmacopoeia 23 Rev., United States Pharmacopoeial Convention, Inc 12601, Twinbrook Parkway, Rockville, MD 20852 (1995).

11. Cornell, J. A., *Experiments With Mixtures*, (John Wiley and Sons, New York, 2nd ed., 1990).

12. Kara, M. A. K., Leaver, T. M and Rowe, R. C., "Material Carryover and Process Efficiency During Tablet Film Coating in Side-vented Perforated Drum (Accela-Cota)", *J. Pharm. Pharmacol.* **34**, 469-470 (1982).

13. Harrison, J. J., Lafferty, I., Moore W. D., Rawins, D. A., Rissen, N. R and Thwaites, P. M., "Titanium Determination as a Method of Quantifying Film-Coat Application on to Tablets", *Drug Dev. Ind. Pharm.* **17** (I), 149-155 (1991).

14. Pickard, J. F., Ph. D. Thesis, Council for National Academic Awards (1979).

SECTION III

Appendix I

Appendix II

Appendix III

Appendix I

Table 18. ANOVA Test Results for Blend Uniformity Comparison at Two Scales
Formulation I

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
Between groups	0.8	1	0.8	0.28	0.6042
Within groups	51.732	18	2.874		
Total (Corr.)	52.532	19			

Formulation II

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
Between groups	29.0405	1	29.0405	5.88	0.0260
Within groups	88.885	18	4.93806		
Total (Corr.)	117.925	19			

Table 19. ANOVA Test Results for Blend Uniformity Comparison of All Four Batches

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
Between groups	49.3008	3	16.4336	4.21	0.0119
Within groups	140.617	36	3.90603		
Total (Corr.)	189.918	39			

The ANOVA table decomposes the variance of the data into two components: a between-group component and a within-group component. The F-ratio, which in this case equals 4.20724, is a ratio of the between-group estimate to the within-group estimate. Since the P-value of the F-test is less than 0.05, there is a statistically significant difference between the means of the 4 variables at the 95.0% confidence level. To determine which means are significantly different from which others, Multiple Range Test was performed.

Table 20. Multiple Range Test (Fisher Least Significant Difference)

Multiple Range Tests

Method: 95.0 percent LSD

	Count	Mean	Homogeneous Groups
FormII10X	10	98.48	X
FormI10X	10	100.88	X
FormII1X	10	100.89	X
FormI1X	10	101.28	X

Contrast	Difference	+/- Limits
FormI10X - FormI1X	-0.4	1.79255
FormI10X - FormII10X	*2.4	1.79255
FormI10X - FormII1X	-0.01	1.79255
FormI1X - FormII10X	*2.8	1.79255
FormI1X - FormII1X	0.39	1.79255
FormII10X - FormII1X	*-2.41	1.79255

* denotes a statistically significant difference.

This table applies a multiple comparison procedure to determine which means are significantly different from which others. The bottom half of the output shows the estimated difference between each pair of means. An asterisk has been placed next to 3 pairs, indicating that these pairs show statistically significant differences at the 95.0% confidence level. At the top of the page, 2 homogenous groups are identified using columns of X's. Within each column, the levels containing X's form a group of means within which there are no statistically significant differences. The method currently being used to discriminate among the means is Fisher's least significant difference (LSD) procedure. With this method, there is a 5.0% risk of calling each pair of means significantly different when the actual difference equals 0.

Table 21. Comparison of Measured Hardness at 5kp Multiple Batches

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
Between groups	0.558	3	0.186	3.80	0.0183
Within groups	1.762	36	0.0489444		
Total (Corr.)	2.32	39			

Table 22. Comparison of Measured Hardness at 6kp Multiple Batches

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
Between groups	0.076	3	0.0253333	0.61	0.6141
Within groups	1.5	36	0.0416667		
Total (Corr.)	1.576	39			

Table 23. Comparison of Measured Hardness at 7kp Multiple Batches

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
Between groups	0.18675	3	0.06225	1.39	0.2617
Within groups	1.613	36	0.0448056		
Total (Corr.)	1.79975	39			

Table 24. Comparison of Measured Hardness at 8kp Multiple Batches

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
Between groups	0.009	3	0.003	0.06	0.9793
Within groups	1.73	36	0.0480556		
Total (Corr.)	1.739	39			

Table 25. Comparison of Measured Hardness 9kp Multiple Batches

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
Between groups	0.347	3	0.115667	2.50	0.0748
Within groups	1.664	36	0.0462222		
Total (Corr.)	2.011	39			

Table 26. Comparison of Measured Hardness 10kp Multiple Batches

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
Between groups	0.34275	3	0.11425	2.21	0.1032
Within groups	1.857	36	0.0515833		
Total (Corr.)	2.19975	39			

Table 27. ANOVA Test Results for Blend and Tablet Content Uniformity Assay

Formulation I (Batch Size 1X)

Analysis of Variance for Bld1XI - Type III Sums of Squares

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
MAIN EFFECTS					
A:Scale	0.747556	1	0.747556	0.31	0.5862
B:Stage	0.00355556	1	0.00355556	0.00	0.9699
RESIDUAL	41.2644	17	2.42732		
TOTAL (CORRECTED)	43.58	19			

All F-ratios are based on the residual mean square error.
The ANOVA table decomposes the variability of Bld1XI into
contributions due to various factors.The P-values test the statistical
significance of each of the factors. Since no P-values are less than 0.05,
none of the factors have a statistically significant effect on Bld1XI
at the 95.0% confidence level.

Table 28. ANOVA Test Results for Blend and Tablet Content Uniformity Assay

Formulation I (Batch Size 10X)

Analysis of Variance for Bld10XI - Type III Sums of Squares

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
MAIN EFFECTS					
A:Scale	0.4205	1	0.4205	0.25	0.6231
B:Stage	5.3045	1	5.3045	3.16	0.0933
RESIDUAL	28.5245	17	1.67791		
TOTAL (CORRECTED)	37.7895	19			

All F-ratios are based on the residual mean square error.
The P-values test the statistical significance of each of the factors.
Since no P-values are less than 0.05, none of the factors have a
statistically significant effect on Bld10XI at the 95.0% confidence
level.

Table 29. ANOVA Test Results for Blend and Tablet Content Uniformity Assay

Formulation II (Batch Size 1X)

Analysis of Variance for Bld1XII - Type III Sums of Squares

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
MAIN EFFECTS					
A:Scale	0.868056	1	0.868056	0.43	0.5185
B:Stage	2.56806	1	2.56806	1.29	0.2725
RESIDUAL	33.9489	17	1.997		
TOTAL (CORRECTED)	50.1295	19			

All F-ratios are based on the residual mean square error.
The P-values test the statistical significance of each of the factors.
Since no P-values are less than 0.05, none of the factors have a
statistically significant effect on Bld1XII at the 95.0% confidence
level.

Table 30. ANOVA Test Results for Blend and Tablet Content Uniformity Assay

Formulation II (Batch Size 10X)

Analysis of Variance for Bld10XII - Type III Sums of Squares

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
MAIN EFFECTS					
A:Scale	0.896056	1	0.896056	0.11	0.7416
B:Stage	1.44006	1	1.44006	0.18	0.6762
RESIDUAL	135.597	17	7.97629		
TOTAL (CORRECTED)	137.037	19			

All F-ratios are based on the residual mean square error.
The P-values test the statistical significance of each of the factors.
Since no P-values are less than 0.05, none of the factors have a
statistically significant effect on Bld10XII at the 95.0% confidence
level.

Table 31. ANOVA Test Results for Dissolution Comparison Tablet Hardness Study Time for 50% Release

Formulation I

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
Between groups	0.0	1	0.0	0.00	1.0000
Within groups	72.0	10	7.2		
Total (Corr.)	72.0	11			

Table 32. ANOVA Test Results for Dissolution Comparison Tablet Hardness Study Time for 75% Release

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
Between groups	5.33333	1	5.33333	0.22	0.6484
Within groups	241.333	10	24.1333		
Total (Corr.)	246.667	11			

Table 33. ANOVA Test Results for Dissolution Comparison Tablet Hardness Study Time for 50% Release

Formulation II

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
Between groups	0.0833333	1	0.0833333	0.02	0.8892
Within groups	40.8333	10	4.08333		
Total (Corr.)	40.9167	11			

Table 34. ANOVA Test Results for Dissolution Comparison Tablet Hardness Study Time for 75% Release

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
Between groups	280.333	1	280.333	2.71	0.1309
Within groups	1035.33	10	103.533		
Total (Corr.)	1315.67	11			

Table 35. F_2 Analysis for Dissolution Comparison
Controlled Release Tablets (Formulation-I)

Time Point	Batch Size 1X	Batch Size 10X	Difference	Calculations
				0
0	0	0	0	0
1	56.8	58.4	-1.6	2.56
2	88.4	89.6	-1.2	1.44
3	98.7	99.5	-0.8	0.64
4	98.7	99.4	-0.7	0.49
			0	0
				5.13
				1.732857143
				0.759658881
				75.96588812
			F_2 =	94.03093098

Table 36. F_2 Analysis for Dissolution Comparison
Controlled Release Tablets (Formulation-II)

Time Point	Batch Size 1X	Batch Size 10X	Difference	Calculations
0	0	0	0	0
1	46.3	43.4	2.9	8.41
2	68.2	65.3	2.9	8.41
3	83.7	81.1	2.6	6.76
4	92.3	91.9	0.4	0.16
5	99.3	99.1	0.2	0.04
6	100.3	101.2	-0.9	0.81
				24.59
				4.512857143
				0.470732525
				47.07325254
			F_2 =	83.63871035

Appendix II

Table 8. Comparison of Content Uniformity Assay for Pilot and Large Scale

Summary Statistics

	Pilot scale	Large scale
Count	30	30
Average	49.79	50.52
Variance	31.1078	13.2368
Standard deviation	5.57744	3.63825
Minimum	40.2	44.0
Maximum	59.2	57.8
Stnd. skewness	0.164067	-0.218458
Stnd. kurtosis	-1.07356	-0.887946
Sum	1493.7	1515.6

Table 9. Comparison of Standard Deviation Deviations for Coating Content Uniformity

	Pilot scale	Large scale
Standard deviation	5.57744	3.63825
Variance	31.1078	13.2368
Df	29	29

Ratio of Variances = 2.3501

95.0% Confidence Intervals
Standard deviation of Pilot scale: [4.44191,7.49783]
Standard deviation of Large scale: [2.89752,4.89095]
Ratio of Variances: [1.11856,4.93754]

F-tests to Compare Standard Deviations

Null hypothesis: sigma1 = sigma2

(1) Alt. hypothesis: sigma1 NE sigma2
F = 2.3501 P-value = 0.0245823

(2) Alt. hypothesis: sigma1 > sigma2
F = 2.3501 P-value = 0.0122912

This option runs an F-test to compare the variances of the two samples. It also constructs confidence intervals for each standard deviation and for the ratio of the variances. Of particular interest is The confidence interval for the ratio of the variances extends from 1.11856 to 4.93754. Since the interval does not contain the value 1.0, there is a statistically significant difference between the standard deviations of the two samples at the 95.0% confidence level. The F-tests shows a P-values below 0.05 indicate significant differences between the two standard deviations.

Table 11. ANOVA Test Results for Entire Tablet Content Uniformity

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
Between groups	133.555	3	44.5183	0.86	0.4685
Within groups	1854.24	36	51.5066		
Total (Corr.)	1987.79	39			

The ANOVA table decomposes the variance of the data into two components: a between-group component and a within-group component. The F-ratio, which in this case equals 0.864324, is a ratio of the between-group estimate to the within-group estimate. Since the P-value of the F-test is greater than or equal to 0.05, there is not a statistically significant difference between the means of the 4 content uniformity variables at the 95.0% confidence level.

Table 12. Multiple Range Comparison Results for Entire Tablet Content Uniformity

Method: 95.0 percent LSD

	Count	Mean	Homogeneous Groups
PilotIITab	10	94.45	X
Pilot ITab	10	96.51	X
ScaleupITab	10	98.23	X
ScaleupIITab	10	99.27	X

Contrast	Difference	+/- Limits
Pilot ITab - PilotIITab	2.06	6.50931
Pilot ITab - ScaleupIITab	-2.76	6.50931
Pilot ITab - ScaleupITab	-1.72	6.50931
PilotIITab - ScaleupIITab	-4.82	6.50931
PilotIITab - ScaleupITab	-3.78	6.50931
ScaleupIITab - ScaleupITab	1.04	6.50931

* denotes a statistically significant difference.

This table applies a multiple comparison procedure to determine which means are significantly different from which others. The bottom half of the output shows the estimated difference between each pair of means. There are no statistically significant differences between any pair of means at the 95.0% confidence level. At the top of the page, one homogenous group is identified by a column of X's. Within each column, the levels containing X's form a group of means within which there are no statistically significant differences. The method currently being used to discriminate among the means is Fisher's least significant difference (LSD) procedure.

Tablet 13. Hypothesis Testing for Standard Deviation Values of Immediate Release Coating

```
Cochran's C test: 0.421559    P-Value = 0.22489
Bartlett's test: 1.15462    P-Value = 0.175737
Hartley's test: 3.41011


The three statistics displayed in this table test the null
hypothesis that the standard deviations within each of the content
uniformity assay values for various batches are the same.
Of particular interest are the two P-values.  Since the smaller of
the P-values is greater than or equal to 0.05, there is not a
statistically significant difference amongst the standard deviations
at the 95.0% confidence level.
```

Table 15. F_2 Dissolution Comparisons for Formulation-I
(Pilot vs. Scale-up)

Time (hr)	Pilot Form I	Scale-up Form I	Difference	Calculations
0.5	48.3	49.8	-1.5	2.25
2	49.3	49.8	-0.5	0.25
3.5	49.3	49.8	-0.5	0.25
5	49.3	49.8	-0.5	0.25
8.5	98.4	99.8	-1.4	1.96
12	98.4	100.5	-2.1	4.41
				9.37
				2.561666667
				0.624796649
				62.47966488
			F2 =	89.78693457

Table 16. F_2 Dissolution Comparisons for Formulation-II
(Pilot vs. Scale-up)

Time (hr)	Pilot Form II	Scale-up Form II	Difference	Calculations
0.5	48.6	51.9	-3.3	10.89
2	48.3	52.5	-4.2	17.64
3.5	52.9	52.5	0.4	0.16
5	56.9	52.5	4.4	19.36
8.5	97.3	89.9	7.4	54.76
12	97.2	101.4	-4.2	17.64
				120.45
				21.075
				0.217829256
				21.78292561
			F2 =	66.90581042

Appendix III

Table 11. Summary of Response Result for Experiments

Experiment Run No.	Weight Variation (mg)	RSD (%)	Content Uniformity Assay (%)	RSD (%)	LOD (%)	Exhaust Temperature (°C)	Efficiency (%)	Process Time (hrs)
1	155.9	1.11	97.9	9.1	3.4	35	92.0	3
2	156.6	1.53	100.9	12.8	3.6	36	97.1	3
3	153.9	1.01	81.2	9.5	3.7	35	82.2	6
4	154.1	1.13	98.2	9.9	2.3	42	92.1	8
5	157.4	0.85	108.0	7.1	2.4	41	101.2	11
6	156.9	1.05	102.3	9.9	2.3	40	100.1	8
7	155.9	1.07	95.3	9.7	2.8	41	94.5	10
8	157.1	1.67	99.1	11.1	3.5	34	97.0	6

Table 12. Analysis of Variance Result for Coating Assay

Analysis of Variance for Assay - Immediate Release Optimization

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
A:Spray Rate	76.2612	1	76.2612	169.00	0.0489
B:Pan Speed	108.781	1	108.781	241.07	0.0409
C:Albuterol Con	30.8113	1	30.8113	68.28	0.0767
AB	18.9112	1	18.9112	41.91	0.0976
AC	56.7112	1	56.7112	125.68	0.0566
BC	125.611	1	125.611	278.36	0.0381
Total error	0.45125	1	0.45125		
Total (corr.)	417.539	7			

R-squared = 99.8919 percent
R-squared (adjusted for d.f.) = 99.2435 percent
Standard Error of Est. = 0.671751
Mean absolute error = 0.2375
Durbin-Watson statistic = 1.0

Assay = 176.965 - 0.100125*Spray Rate - 8.50729*Pan Speed -
22.1083*Albuterol Con - 0.0076875*Spray Rate*Pan Speed + 0.0355*Spray
Rate*Albuterol Con + 2.64167*Pan Speed*Albuterol Con

Table 13. Analysis of Variance Result for Coating Uniformity RSD

Analysis of Variance for RSD - Immediate Release Optimization

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
A:Spray Rate	4.205	1	4.205	210.25	0.0438
B:Pan Speed	0.98	1	0.98	49.00	0.0903
C:Albuterol Con	2.205	1	2.205	110.25	0.0604
AB	8.0	1	8.0	400.00	0.0318
AC	0.405	1	0.405	20.25	0.1392
BC	2.88	1	2.88	144.00	0.0529
Total error	0.02	1	0.02		
Total (corr.)	18.695	7			

R-squared = 99.893 percent
R-squared (adjusted for d.f.) = 99.2511 percent
Standard Error of Est. = 0.141421
Mean absolute error = 0.05
Durbin-Watson statistic = 1.0

RSD = -10.9 + 0.047*Spray Rate + 2.375*Pan Speed + 3.85*Albuterol Con
- 0.005*Spray Rate*Pan Speed - 0.003*Spray Rate*Albuterol Con -
0.4*Pan Speed*Albuterol Con

Table 14. Analysis of Variance Result for Coating Process

Analysis of Variance for Efficiency - Immediate Release Optimization

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
A:Spray Rate	88.445	1	88.445	176.89	0.0478
B:Pan Speed	81.92	1	81.92	163.84	0.0496
C:Albuterol Con	22.445	1	22.445	44.89	0.0943
AB	25.205	1	25.205	50.41	0.0891
AC	5.12	1	5.12	10.24	0.1928
BC	37.845	1	37.845	75.69	0.0729
Total error	0.5	1	0.5		
Total (corr.)	261.48	7			

R-squared = 99.8088 percent
R-squared (adjusted for d.f.) = 98.6615 percent
Standard Error of Est. = 0.707107
Mean absolute error = 0.25
Durbin-Watson statistic = 1.0

Efficiency = 129.683 - 0.0146667*Spray Rate - 4.09375*Pan Speed -
9.13333*Albuterol Con - 0.008875*Spray Rate*Pan Speed +
0.0106667*Spray Rate*Albuterol Con + 1.45*Pan Speed*Albuterol Con

Table 15. Analysis of Variance Result for Coating Process Duration

Analysis of Variance for Process Time - Immediate Release Optimization

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
A:Spray Rate	45.125	1	45.125	361.00	0.0335
B:Pan Speed	0.125	1	0.125	1.00	0.5000
C:Albuterol Con	15.125	1	15.125	121.00	0.0577
AB	0.125	1	0.125	1.00	0.5000
AC	0.125	1	0.125	1.00	0.5000
BC	0.125	1	0.125	1.00	0.5000
Total error	0.125	1	0.125		
Total (corr.)	60.875	7			

R-squared = 99.7947 percent
R-squared (adjusted for d.f.) = 98.5626 percent
Standard Error of Est. = 0.353553
Mean absolute error = 0.125
Durbin-Watson statistic = 1.0

Process Time = 20.3542 - 0.0220833*Spray Rate - 0.489583*Pan Speed -
1.91667*Albuterol Con + 0.000625*Spray Rate*Pan Speed -
0.00166667*Spray Rate*Albuterol Con + 0.0833333*Pan Speed*Albuterol Con

BIBLIOGRAPHY

Augsburger, L. et al., "An Approach Toward Establishing a Scientific Foundation for Interpreting Regulations and Workshop Reports on Scale-Up and Post Approval Changes", Pharmaceutical Research., 11 (10), S161 (1994).

Avallone, H. L., "Development and Scale-up of Pharmaceuticals", Pharmaceutical Engineering., 10 (4), 38-41 (1990).

Badaway, S. I. F and Menning, M. M., "Effect of Over-Lubrication on Disintegration and Dissolution Rates of A Tablet Dosage Form for A Low Dose Compound", PharmSci., 1 (4), 250 (1999).

Baken, J. A and Anderson, J. L., Microencapsulation, in The Theory and Practice of Industrial Pharmacy., (2nd Ed.), Lea & Febiger, Philadelphia, p. 420 (1976).

Baken, J. A and Powell, T. C., "Long Term Stability of controlled Release Pharmaceutical Microcapsules Prepared by Phase Separation Technique", 8th International Symposium on Controlled Release of Bioactive Materials., Ft. Lauderdale, p. 158 (1981).

Baker, R. W and Lonsdale, H. K., Controlled Release of Biologically Active Agents., Plenum Press, New York, p. 15 (1974).

Barkin, J. S., Harary, A. M., Shamblen, C. E and Lasseter K. C., "Potassium chloride and gastrointestinal injury", Annals of Internal Medicine., 98 (2), 261-262 (1983).

Bauer, H. K., Lehmann, K., Osterwald, P and Rothgang, G., Coated Pharmaceutical Dosage Forms., (1st Ed.), CRC Press, Medpharm Scientific Publishers Stuttgart, GmbH Germany (1998).

Baveja, S. K., Ranga Rao K.V., Singh, A and Gombar, V. K., "Release characteristics of some bronchodilators from compressed hydrophilic polymer matrices and their correlation with molecular geometry", International Journal of Pharmaceutics., 41 (1), 55-62 (1988).

Baveja, S. K., Ranga Rao, K. V and Devi, K. P., "Zero-order Release Hydrophilic Matrix Tablets of Beta-Adrenergic Blockers", International Journal of Pharmaceutics., 39 (2), 39-46 (1987).

Bhalla, H. L and Sanzgiri, Y. D., "Improvised controlled release tablet of salbutamol sulfate", Indian Journal of Pharmaceutical Sciences., 49, 22-25 (1986).

Blythe, R. H., U.S. Patent 2,783, 303 (1958).

Bungenberg de Jong, H. G., Colloid Science., (H. R. Kruyt 2nd Ed.), Elsevier, Amsterdam, p.244 (1949).

Carr, R. L., "Evaluating Flow Properties of Solids," Chemical Engineering., 72, 163-168 (1965).

Cass, L. J and Frederick, W. S., "Clinical comparison of a sustained and a regular-release asprin", Current Therapeutic Research., 7 (11), 673-682 (1965).

Center for Drug Evaluation and Research., Blend Uniformity Analysis, Guidance for Industry, August 3, 1999.

Chowhan, Z. T., "Aspects of Granulation Scale-up in High-Shear Mixers", Pharmaceutical Technology., 12 (2), 26-44 (1988).

Christenson, G. L and Dale, L. B., U.S. Patent 3,065,143 (1960).

Conte, U., Maggi, L., Torre, M. L., Giunchedi, P and La manna, A., "Press-coated Tablets for Timed-programmed Release of Drugs", Biomaterials., 14 (13), 1017-1023 (1993).

Cornell, J. A., Experiments With Mixtures., (2nd Ed.), John Wiley and Sons, New York, (1990).

Dangel, C., Kolter, K., Reich, H. B and Schepky, G., "Aqueous Enteric Coatings with Methacrylic Acid Copolymer Type C: On Acidic and Basic Drugs in Tablets and Pellets, Part I: Acetylsalicylic Acid Tablets and Crystals", Pharmaceutical Technology., 24 (3), 64-70 (2000).

Dangel, C., Kolter, K., Reich, H. B and Schepky, G., "Aqueous Enteric Coatings with Methacrylic Acid Copolymer Type C: On Acidic and Basic Drugs in Tablets and Pellets, Part II: Dosage Forms Containing Indomethacin and Diclofenac Sodium", Pharmaceutical Technology., 24 (4), 36-42 (2000).

Deasy, P. B., Brophy, M. R., Ecanow, B and Joy, M., "Effect of ethylcellulose grade and sealant treatments on the production and in vitro release of microencapsulated sodium salicylate", Journal of Pharmacy and Pharmacology., 32 (1), 15-20 (1980).

Farhadieh, B., Borodkin, S and Buddenhagen, J. D., "Drug release from methyl acrylate-methyl methacrylate polymer matrix -I Kinetics of release", Journal of Pharmaceutical Sciences., 60 (2), 209-212 (1971).

Farquharson-Roberts, M. A., Giddings, A. E and Nunn, A. J., "Perforation of small bowel due to slow release potassium chloride (Slow-K)", British Medical Journal., 26 (3), 206 (1975).

Fassihi, A. R., "Solid State Interaction of Bromazepam with Polyvinylpyrrolidone in the Presence of Moisture", International Journal of Pharmaceutics., 37, 167-170 (1987).

Fatome, M., Courteille, F., Laval, J. D and Roman, V., "Radioprotective activity of ethylcellulose microspheres containing WR 2721, after oral administration", International Journal of Radiation Biology and Related Studies in Physics, Chemistry, and Medicine., 52 (1), 21-29 (1987).

Food and Drug Administration Guideline for Industry-immediate release solid oral dosage form/scale-up and post approval changes (SUPAC-IR): Chemistry, manufacturing, and controls. In vitro dissolution and in vivo bioequivalence documentation, Federal Register., Vol. 60, No. 230, 30 November 1995, pp. 61638-61643.

Ford, J. L., Rubinstein, M. H and Hogan, J. E., "Formulation of sustained release promethazine hydrochloride tablets using hydroxypropyl methylcellulose matrices", International Journal of Pharmaceutics., 24, 327-338 (1985).

Fourman, G. L., Hines, C. W and Hritsok, R. S., "Assessing the Uniformity of Aqueous Film Coatings Applied to Compressed Tablets", Pharmaceutical Technology., 19 (3), 70-76 (1995).

Gazzaniga, A., Busetti, C., Moro, L., Sangalli, M. E and Giordano, F., "Time-dependent Oral Delivery system for Colon Targeting", S.T.P. Pharma Sciences., 5 (1), 83-88 (1996).

Gazzaniga, A., Sangalli, M. E and Giordano, F., "Oral Chronotrophic Drug Delivery Systems: Achievement of Time and/or Site Specificity", European Journal of Pharmacology and Biopharmaceutics., 40 (4), 246-250 (1994).

Geoghegan, E. J., Mulligan, S and Panoz, D., "Controlled Absorption Diltiazem Formulation for Once Daily Administration", U.S. Patent, 5,616,345 (1997).

Geoghegan, E. J., Mulligan, S and Panoz, D., "Diltiazem Formulation", U.S. Patent, 4,891,230 (1990).

Gerald, K. M., (Ed.) Drug Information., AHFS Published by ASHP, 617-619 (1988).

Gohel, M. C and Jogani, P. D., "An Investigation of the Direct-Compression Characteristics of Coprocessed Lactose-Microcrystalline Cellulose Using Statistical Design", Pharmaceutical Technology., (11), 54-62 (1999).

Goodhart, F. W., McCoy, R. H and Ninger, F. C., "Release of water-soluble drug from wax matrix timed-release tablet", Journal of Pharmaceutical Sciences., 63 (11), 1748-51 (1974).

Graham, H. V., "Antihypertensive Effects of Reserpine in Sustained-Release Form: A Comparative Study", Journal of American Geriatric Society., 6, 671-674 (1958).

Green, M. A., "One Year's Experience With Sustained Release Antihistamine Medication An Experimental and Clinical Study", Annals of Allergy., 12, 273-283 (1954).

Gunsel, W. C and Kanig, J. L., Tablets, in Theory and Practice of Industrial Pharmacy., (2nd Ed.), Lea & Feiber, Philadelphia, p.321 (1976).

Harrison, J. J., Lafferty, I., Moore, W. D., Rawins, D. A., Rissen, N. R and Thwaites, P. M., "Titanium Determination as a Method of Quantifying Film-Coat Application on to Tablets", Drug Development and Industrial Pharmacy., 17 (1), 149-155 (1991).

Hausberger, A., McDermott, T., Erhart, L., Freel, D and Kirkman, C., "Effect of Blender Scale, Blender Type and Sample Size on Blender/Granulation Homogeneity", PharmSci., 1 (1), S179 (1998).

Higuchi, T., "Mechanism of Sustained-Action Medication. Theoretical Analysis of Rate of Release of Solid Drugs Dispersed in Solid Matrices", Journal of Pharmaceutical Sciences., 52 (12), 1145-1149 (1963).

Higuchi, W. I., "Analysis of Data on the Medicament Release from Ointments", Journal of Pharmaceutical Sciences., 51 (8), 802-804 (1962).

Hogan, J. E., "Aqueous versus Organic Solvent Film Coating", International Journal of Pharmaceutical Technology and Product Manufacture., 3 (1), 17-20 (1982).

Holiday, W. M., Berdick, M., Bell, S. A and Kiritsis, G. C., U.S. Patent 3,488,418 (1960).

Hollister, L. E., "Studies of Prolonged-Action Medication II. Two Phenothiazine Taranquilizers (Thioridazine and Chlorpromazine) Administered as Coated Tablets and Prolonged-Action Preprations", Current Therapeutic Research., 4 (9), 471-479 (1962).

Huber, H. E and Christenson, G. L., "Utilization of hydrophilic gums for the control of drug substance release form tablet formulation II. Influence of tablet hardness and density on dissolution", Journal of Pharmaceutical Sciences., 57 (1), 164-167 (1968).

Huber, H. E., Dale, L. B and Christenson, G. L., "Utilization of Hydrophilic Gums for the Control of Drug Release from Tablet Formulations I. Disintegration and Dissolution Behaviour", Journal of Pharmaceutical Sciences., 55 (9), 974-976 (1966).

Ispen, J., "Mathametical Relationship of In Vitro Release Rates and Biological Availability of Controlled-Release Nitroglycerin (Nitrong®)", Current Therapeutic Research., 13 (3), 193-208 (1971).

Jambhekar, S. S., Makoid, M. C and Coby, J., "Relationship between planar and all-surface rate constants for drugs formulated in non disintegrating cylindrical slow-release tablets", Journal of Pharmaceutical Sciences., 76 (2), 146-148 (1987).

Kara, M. A. K., Leaver, T. M and Rowe, R. C., "Material Carryover and Process Efficiency During Tablet Film Coating in Side-vented Perforated Drum (Accela-Cota)", Journal of Pharmacy and Pharmacology., 34, 469-470 (1982).

Khan, M. Z. I., Prebeg, Z and Kurjaković, N., "A pH-dependent colon targeted oral drug delivery system using methacrylic acid copolymers, I – Manipulation of drug release using Eudragit® L 100-55 and Eudragit® S 100 combinations", Journal of Controlled Release., 58, 215-222 (1999).

Khanna, S. K., Gode, K. D and Jayaswal, S. B., "Sustained Release Solid Dosage Form of Propranolol Hydrochloride", Indian Drugs., 18 (3), 103-108 (1980).

Klaui, H. M., Hauseer, W and Huschke, G., Technological aspects of use of fat-soluble vitamins and carotenoids and of the development of stabilized marketable forms, in Fat-soluble Vitamins., (R. A. Mortan Ed.), Pergamon, London, p.133 (1970).

Lachman, L., Liberman, H. A and Kanig, J. L., The Theory and Practice of Industrial Pharmacy., (3rd Ed.) Lea & Febiger, Philadelphia, (1987).

Lapidus, H and Lordi, N. G., "Some Factors Affecting the Release of a Water-Soluble Drug from a Compressed Hydrophilic Matrix", Journal of Pharmaceutical Sciences., 55 (8), 840-843 (1966).

Lehman, K., "Acrylic lattices from redispersible powders for peroral and transdermal drug formulation", Drug Development and Industrial Pharmacy., 12 (3), 265-287 (1986).

Leuenberger, H., "Scale-up of granulation Process with Reference to Process Monitoring", Acta Pharmaceutica Technologica., 29 (4), 274-280 (1983).

Levin, M., "Equipment Characterization for Solid Dosage Process Scale-Up Using Dimensionless Numbers and Performance Indices", PharmaSci., 1 (4), 1261 (1999).

Lubbe, W. F., Cadogan, E. S and A. Kannemeyer, H. R., "Oesophageal ulceration due to slow-release potassium in the presence of left atrial enlargement", New Zeland Medical Journal., 90 (647), 377-379 (1979).

Luzzi, L. A and Palmieri, A., An overview of pharmaceutical applications in Biomediacal Application of Microencapsulation., CRC Press, Inc., Boco Raton, Florida, p.9 (1983).

Luzzi, L. A., "Microencapsulation" Journal of Pharmaceutical Sciences., 59 (10), 1367-1376 (1970).

Magee, K. R and Wasterberg, M. R., "Treatment of myasthenia gravis with prolonged-action Mestinon", Neurology., 9, 348-351 (1959).

Malahy, B., "The effect of instruction and labeling on the number of medication errors made by patients at home", American Journal of Hospital Pharmacy., 23 (6), 283-292 (1966).

Malamataris, S., Karidas, T and Goidas, P., "Effect of Particle Size and Sorbed Moisture on Compression Behavior of some Hydroxypropyl Methylcellulose Polymers", International Journal of Pharmaceutics., 103, 205-215 (1994).

Malamataris, S and Karidas, T., "Effect of Particle Size and Sorbed Moisture on the Tensile Strength of Some Tableted Hydroxypropyl Methylcellulose (HPMC) Polymers", International Journal of Pharmaceutics., 104, 115-123 (1994).

Mathur, L. K., Forbes, ST. J and Yelvigi, M., "Characterization Techniques for the Aqueous Film coating process", Pharmaceutical Technology., 8 (10), 43-53 (1984).

Mazer, T., "Zein: The Versatile Reverse Enteric", Proceedings of International Symposium on Controlled Release Bioactive Materials., 26, 267-268 (1999).

Meakin, B. J and May, G., 3rd International Conference on Pharmaceutical Technology., 3, 145-153 (1983).

Mellinger, T. J., "Serum Concentration of Thioridazine After Different Oral Medication Forms", American Journal of Psychiatry., 121, 1119-1122 (1965).

Mira, C., Garcia-Montoya, E., Perez-Lozanao, P., Garcia-Tobajas, A., Coderch, M., Gurrero, M., Minarro, M., Sune-Negre, J and Tico, J., "Comparative Study of the Technological Parameters for Direct Compression (DC) Excipients", PharmaSci., 1 (4), 1281 (1999).

Mitchell, et al., "Influence of concentration on the release of drugs from gels and matrices containing Methocel", International Journal of Pharmaceutics., 100 (8), 155-163 (1993).

Montgomery, D. C., Design and Analysis of Experiments., (2nd Ed.) John Wiley and Sons, New York, (1990).

Moore, J. W and Flanner, H., "Mathematical Comparison of Dissolution Profiles", Pharmaceutical Technology., 20 (6), 64-75 (1996).

Morse, L. D., U.S. Patent, 3,557,279 (1971).

Mosquera, M. J., Cu• a, M., Souto, C., Concherio, A., Martínez-Pacheco, R and Gómez-Amoza, J. L., "Effects of hydroxypropyl methylcellulose (HPMC) moisture content on hydrochlorothiazide release from HPMC-based tablets", International Journal of Pharmaceutics., 135, 147-149 (1996).

Nakkano, M., Ohmori, N., Ogata, A., Sugimoto, K., Tobino, Y., Iwaoku, R and Juni, K., "Sustained Release of Theophylline from Hydroxypropylcellulose Tablets", Journal of Pharmaceutical Sciences., 72 (4), 378-380 (1983).

Narisawa, S., Nagata, M., Ito, T., Yoshin, H., Hirakawa, Y and Noda, K., "Drug Release Behavior in Gastro intestinal Tract of Beagle dogs from Multiple Unit Type Rate-Controlled or Time-Controlled Release Preparations Coated with Insoluble Polymer-Based Film", Journal of Controlled Release., 31, 253-260 (1993).

Nixon, J. R., " In vitro and in vivo release of microencapsulated chlorothiazide", Journal of Pharmaceutical Sciences., 70 (4), 376-378 (1981).

Noda, K., Hirakawa, Y., Yoshin, H and Narisawa, S., "Controlled Release Succinic Acid Microcapsules coated with Aqueous Acrylics", U.S. Patent 5, 395,628 (1995).

Palaniswamy, S., "Modified Release Adrenergic Drug for Twice a Day Dosing", Masters Thesis., University of Rhode Island, Kingston RI, USA, May (1994).

Palaniswamy, S., Needham, T. E., Zia, H and Szymanski, D. J., "Optimization of Immediate Release Coating Portion of An Extended Release Dosage Form of a Water Soluble Drug", PharmSci., 1 (1), S-157 (1998).

Palmieri, A., "Dissolution of Prednisone microcapsules in conditions simulating the pH of the gastrointestinal tract", Canadian Journal of Pharmaceutical Sciences., 12 (10), 88-89 (1977).

Pang, J., Wu, L., Chen, J. G., Markovitz, D and Hussain, M. A., "Process Scale-up and Optimization for Low Strength DMP 543 Capsules", PharmSci., 1 (4), 1235 (1999).

Pichieri, A and Rohera, B. D., "Study of effect of Scaling-up on the Content Uniformity of A Model Drug", PharmSci., 1 (4), 1262 (1999).

Pickard, J. F., Ph. D. Thesis., Council for National Academic Awards, (1979).

Pondell, R. E., "From Solvent to Aqueous Coatings", Drug Development and Industrial Pharmacy., 10 (2), 191-202 (1984).

Porter, S. C., "Aqueous Film Coating: an Overview", Pharmaceutical Technology., 3 (9), 55-59 (1979).

Porter, S. C., "The effect of additives on the properties of an aqueous film coating", Pharmaceutical Technology., 4 (3), 67-75 (1980).

Porter, S. C., Verseput, R. P and Cunningham, C., "Process Optimization Using Design of Experiments", Pharmaceutical Technology., 21 (10), 60-70 (1997).

Pozzi, F., Furlani, P., Gazzangia, A., Davis, S. S and Wilding, I. R., "The Time Clock System: a new Oral Dosage form for fact and Complete Release of Drug After a Predetermined Lag Time", Journal of Controlled Release., 31, 99-108 (1994).

Prater, D. A., Ph. D. Thesis., University of Bath. (1982).

Price, J. C and Palmieri, A., "Microencapsulation of drugs suspended in oil, preparation and evaluation of prednisone and hydrocortisone microcapsules, in Microencapsulation New Techniques and applications., (T. Kondo Ed.), Techno Books, Tokyo, Japan, p.119 (1979).

Rogers, H. L., "Treatment of Allergic Conditions with Sustained Release Chlorprophenpyridamine Maleate", Annals of Allergy., 12, 266-272 (1954).

Rowe, R. C., "Some Fundamental Properties of Polymeric Materials and Their Application in Film Coating Formulations – A Review", International Journal of Pharmaceutical Technology & Product Manufacture., 3 (1), 3-8 (1982).

Rowley, F., "Common problems to avoid in aqueous coating", Pharmaceutical Technology., 15 (10), 68-72 (1991).

Russo, E. J., "Typical Scale-up Problems and Experiences", Pharmaceutical Technology., 8 (11), 46-56 (1984).

Salib, N. N., "Microencapsulation and Flocculation Techniques in Pharmaceutical Formulation. I. Evaluation of Some Microencapsulation and Flocculation Techniques", Pharmazeutische Industrie., 34 (9), 671-674 (1972).

Samuelov, Y., Donbrow, M and Friedman, M., "Sustained release drugs from ethylcellulose-polyethylene glycol films and kinetics of drug release", Journal of Pharmaceutical Sciences., 68 (3), 325-329 (1979).

Sawayanagi, Y., Nambu, N and Nagai., "Use of Chitosan for Sustained-release Preparations of Water-soluble drugs", Chemical Pharmaceutical Bulletin., 30 (11), 4213-4215 (1982).

Schaible, D. J., "Flow Characterization of Specialty Microcrystalline Cellulose Grades for Use in Direct Compression", PharmSci., (1), S-644 (1998).

Shah, A. C., "Therapeutic Formulations with Bimodal Release Characteristics, International Patent Application", WO8.700,044.

Signarino, C. A., "Aqueous Enteric Coating", Pharmaceutical Technology., Year Book, 24-26, (1999).

Signorino, C. A and Forcellini, L. J., "Evaluating the Uniformity of Aqueous Film Coating", Supplement to Pharmaceutical Technology., Year Book, 48-53 (1996).

Skultety, P. F., Rivera, D., Dunleavy, J and Lin, C. T., "Quantitation of The Amount and Uniformity of Aqueous Film Coating Applied To Tablets in a 24" Accela-Cota", Drug Development and Industrial Pharmacy., 14 (5), 617-631 (1988).

Specht, F., Saugestad, M., Waaler, T and Muller, B. W., "The application of Shellac as an Acidic Polymer for Enteric Coating", Pharmaceutical Technology., 23 (3), 146-154 (1999).

Sune-Negre, J., Tico, J., Minarro, M., Garcia-Montoya, E., Perez-Lozanao, P., Coderch, M., Gurrero, M., Garcia-Tobajas, A and Mira, C., "Comparative Study of the Technological Parameters for Direct Compression (DC) Excipients in A Simple DC Formulation For Ibuprofen Tablets", PharmaSci., 1 (4), 1316 (1999).

Talukdar, M and Kinget, R., "Comparative study on xanthum gum and hydroxypropyl methylcellulose as matrices for controlled release drug delivery. Part 2. Drug diffusion in hydrated matrices", International Journal of Pharmaceutics., 151, 99-107 (1997).

The United States Pharmacopoeia USP 23, United States Pharmacopoeial Convention Inc, 12601, Twinbrook Parkway, Rockville, MD 20852 (1995).

Venkatesh, G. M., Lamey, K. A., Levin, M and Murphy, S., "Correlations Between a Hydraulic Compaction Simulator Instrumented Manesty BetaPress and The Prester™", PharmaSci., 1 (4), 1297 (1999).

Vesey, C. F and Fegely, K. A., "Determination of Critical Process Parameters on The Application of An Aqueous, High Gloss Film Coating System", PharmSci., (1) 4, 750 (1999).

Vestre, D and Schiele, B. C., "An evaluation of slow-release and regular thioridazine and two medication schedules", Current Therapeutic Research., 8 (12), 585-591 (1966).

Walia, P. S., Jo Meyer Stout, P and Turton, R., "Preliminary Evaluation of an Aqueous Wax Emulsion for Controlled-release Coating", Pharmaceutical Development and Technology., 3 (1), 103-113 (1998).

Wells, J. I., Pharmaceutical Preformulation., (1st Ed.), Ellis Horwood Limited, Chichester, England, (1988).

Xu, X and Lee, P. I., "Programmable Drug Delivery from an Erodable Association Polymer System", Pharmaceutical Research., 10 (8), 1144-1152 (1993).