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FORMULATION OF AN ORAL MODIFIED RELEASEDOSAGE FORM OF AN ADRENERGIC DRUG

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FORMULATION OF AN ORAL MODIFIED RELEASE

DOSAGE FORM OF AN ADRENERGIC DRUG

BY

SURESH PALANISWAMY

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE

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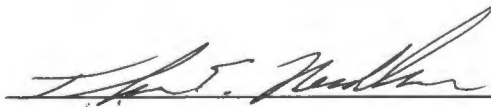
MASTER OF SCIENCE

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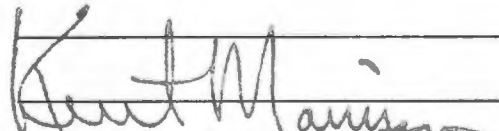MASTER OF SCIENCE THESIS

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    Thesis committee
    Major professor

DEAN OF GRADUATE SCHOOL

UNIVERSITY OF RHODE ISLAND

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ABSTRACT

Albuterol, a sympathomimetic amine is a potent selective Beta adrenergic agonist. As a result it is used as a bronchodilator to treat chronic obstructive airway diseases in adults and childrens. The drug has a short half-life of 3-4 hours and must be administered 3-4 times daily to maintain a therapeutic concentration.

This investigation was undertaken to study the in-vitro drug release characteristics of the marketed product under conditions that mimic in-vivo dissolution behavior. It was determined that the original marketed product released the initial dose in first half an hour and then the second dose after a period of 5-6 hours. High variability in drug release profiles were observed between various lots. It was decided to investigate the applicability of several new polymers and modern formulation techniques to provide similar but more reproducible release. To reproduce the extended release portion of the tablets, various concentrations of polymer and tabletting excipients were evaluated and an optimum formulation that provided near zero order release was determined. The formulation developed in the laboratory was scaled up to a production size batch. Various physical characteristics of the tablets were evaluated as specified in the USP XXII.

Two different types of coating processes, the Accela-cota and fluidized bed coating apparatus (Aeromatic STREA I), were used to coat the tablets with an aqueous polymer latex dispersion to retard drug release from tablet cores for a period of 5-6 hours. These tablets were further coated with 2 mg of albuterol per tablet to provide the immediate

release dose. Optimum coating parameters were determined for the seal coating and the immediate release coating.

A High Performance Liquid Chromatography and UV spectrophotometric assay method were used to determine drug release from the dissolution samples. The USP Apparatus I (Basket) and III (Reciprocating cylinder) dissolution testing methods were used for evaluating drug release from the marketed and the developed products. A statistical evaluation using ANOVA was performed on all the dissolution tests to compare the difference in mean drug release between different batches of the developed product and the marketed product. A significant difference in mean drug release was observed between different lots of tablets at various time points in the marketed product. The in-vitro dissolution data shows that the drug release profile of the developed product is less variable than the marketed product.

ACKNOWLEDGMENTS

"To my family"

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

I INTRODUCTION

Over the past three decades, significant advances have been made in the development of new and improved drug delivery systems[1]. Due to the modern technology, processing methods, and the availability of variety of polymers, oral drug delivery systems are now able to achieve predictable and reproducible release rates for an extended period of time[2]. Greater utilization of controlled release drug delivery has been possible due to various factors such as the discovery of novel polymers, a better understanding of formulations, the expiration of existing patents, the high cost of developing new drug entities, improvement in processing technology and the elimination of organic solvents that cause environmental and health hazards[3].

Controlled-release delivery systems are designed to meet a specific biopharmaceutical requirement of an active drug producing steady-state plasma drug levels for a prolonged time[4]. Drugs suitable for inclusion into modified release drug delivery systems usually have a short half life or a narrow therapeutic index. Another aspect to consider is the significant improvement in patient compliance often seen with these products during the therapy[3]. Conversely, conventional solid dosage forms often lead to fluctuations in plasma levels that may exceed the maximum and minimum therapeutic levels as well as requiring multiple dosing intervals that lead to reduced patient compliance.

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[5]. As a

result, it is used as a bronchodilator to treat chronic obstructive airwaydiseases in adults and children. Albuterol may be administered in a variety of dosage forms. Albuterol 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 conventional release and 4 mg repeat action tablets. The repeat action tablets were designed to deliver 2 mg immediately which is coated on the outer most layer and 2 mg slowly from the core for a period of several hours[5]. 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 in the US market is Proventil Repetabs and the market potential of this dosage form is significant.

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 and about 50 % of the orally administered drug is excreted within 3-4 hours. Maximum plasma albuterol concentration of about 18 ng/ml are achived within 2 hours after administration of 4 mg as syrup[5]. The peak plasma concentration of albuterol and the metabolites are reported as 5.1-11.7 µg percent at 2.5 to 3 hours after an oral dose of 4 mg[5,6].

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 pre term labor[6,8].

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[5,6]. Unfortunately, this requires careful observance of the treatment regimen which ultimately interferes with the ability to achieve full therapeutic benefit from the treatment. The main objective of a modified release dosage form development is to reduce the number of doses from four to two per day.

An extended release formulation of albuterol is marketed but the detailed technology is not reported. However first marketed in the 1950's using old technology, there has been no further modifications in the design and processing methods of these dosage forms. Contents as reported in the labeling of the marketed products of this type show use of excipients that are derived from natural origin. These excipients show variability in content, drug release and often give less than reproducible results.

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

This investigation was undertaken to study the in-vitro drug release of the marketed product under conditions that mimic the in-vivo process; and then to develop a new modified release dosage form with consistent drug release based on the combined 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

3

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.

1. Physicochemical Properties of Albuterol

$$\left[\begin{array}{c} \text{HOCH}_2 \\ \text{HO} - \bigcirc - \text{CHCH}_2\text{NHC(CH}_3)_3 \\ | \\ \text{OH} \end{array} \right]_2 \bullet \ \text{H}_2\text{SO}_4$$
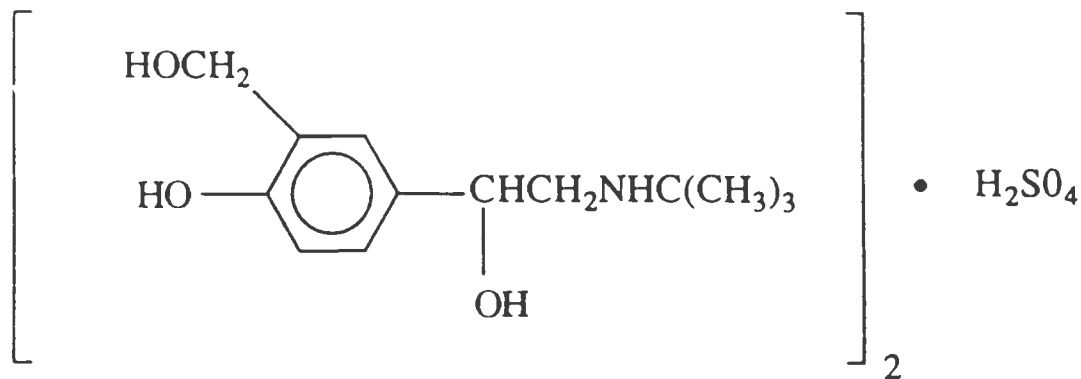
Molecular Weight:		239.31
Chemical name	:	N-tert-butyl-2-(4-hydroxy-3-hydroxymethyl phenyl)-2-hydroxyl amine.
Generic names	:	Albuterol, Salbutamol
Appearance	:	White crystalline powder odorless and tasteless
Melting point	:	151-152$^\text{O}$C
Solubility	:	1 in 70 of water
		1 in 25 of ethanol
pKa	:	9.3 and 10.3
UV Absorbance	:	Maxima at 226 and 276
Therapeutic Category	:	Sympathomimetic amine used as a bronchodilator
Precautions	:	Stored in a light resistant container.

5

2. Controlled Release Dosage Forms

The term "Controlled release" has become associated with those systems from which therapeutic agents may be automatically delivered at a predetermined rate over a long period of time[9]. Products of this type have been formulated for oral, injectable, topical use and also include inserts for placement into body cavities[9,10].

In general, controlled release delivery attempts to[9]:

1. Sustain drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of the undesirable side effects often associated with the saw tooth plasma levels of single repeated dosage forms.

2. Localize drug action by spatial placement of the controlled release dosage form adjacent to or in the diseased tissue or organ.

3. Target drug action by using carriers or chemical derivatization to deliver drugs to a particular "target" cell type.

In practice, a very few if any of the applied systems embrace all of these activities. For the most part, these products focus on maintaining a constant drug level in the plasma. Theoretically, in a controlled release system, the rate of absorption should equal the rate of elimination. However, this is possible only by the use of an intravenous infusion. Thus, in practice alternative noninvasive routes such as oral, nasal and transdermal routes are preferred in attaining the therapeutic objectives of controlled release.

2.1. Oral Controlled Release Systems

Oral controlled release systems are popular because of convenient administration and reduced design constraints[8]. Ideally,

6

an oral controlled release preparation should immediately provide part of the dose at the absorption site to achieve a rapid therapeutic response. The remaining drug should be available at a rate sufficient to maintain the desired pharmacological activity[9].

The Design of an oral controlled release system is subject to a number of variables among these are the location of the target site which maximizes absorption, the physicochemical properties of the drug, the desired dose and extent of therapy, disease and patient variables.

Over the past five decades a number of technologies have been developed and employed to sustain the delivery of oral medications to the systemic circulation. These systems are largely based on the principles of diffusion, dissolution, ion exchange and recently on the principle of osmosis (GITS). A variety of methods have been used to retard drug release. The following is the summary of the methods given by Lee et al[9].

1. Capsules of polymeric material filled with a solid or liquid drug or with a suspension of drug in a fluid, such that drug release is controlled by diffusion through the capsule wall

2. A heterogeneous dispersion of drug particles in a solid matrix which can be either biodegradable or non biodegradable and which controls drug release by diffusion through the matrix, by erosion of the matrix, or by a combination of both diffusion and erosion

3. A laminate of therapeutic agent and polymeric material made by coating a film of biodegradable or non biodegradable material with solid drug and then forming the film into a sealed "sandwich" or

"jelly roll", in which drug release is by diffusion

4. A heterogeneous dispersion or solution of drug in a water swellable hydrogel matrix, which controls drug release by slow surface-to-center swelling of the matrix by water and subsequently diffusion of the drug from the water-swollen part of the matrix

5. Liquid-liquid encapsulation of drug in a viscous solution of polymer, which controls drug release by slow diffusion via dilution of the media

6. Pumps that either mechanically or chemically (osmotic pressure) provide drug in a controlled manner

7. Drug coated micropellets which have an apparent density lower than that of the gastric juice. Thus, the final product floats in gastric juice and remains in the stomach for an extended period, while slowly releasing drug

8. Drug-containing bioadhesive polymer that adheres to the mucin coating of the gastrointestinal tract and which is retained on the surface epithelium to extend GI transit time of the drug. Drug is released at a controlled rate from the bioadhesive polymer for subsequent absorption

9. Chemical bonding of a drug to a polymer backbone by pendent amide or ester linkages in which hydrolysis controls drug release.

10. Formation of macromolecular structures of the drug via ionic or covalent linkages, which controls drug release by hydrolysis, thermodynamic dissociation, or microbial degradation

2.2. Diffusion Controlled Release

Drug release is controlled by a combination of several physical processes such as penetration of water, leaching of drug from the

matrix, and erosion of matrix material. Alternatively, drug is dissolved in the matrix material and released by diffusion through the matrix material. In this latter case, the drug release is controlled by dissolution and diffusion. These type of dosage forms are the simplest to prepare. They are usually prepared by dispersing the drug particles in a polymeric matrix or by coating the drug particles or the granules with varying thickness of a retardant polymeric material. The basic principle of drug release from a polymer matrix is as follows: The drug dissolves in the polymer matrix and diffuses out from the surface of the matrix. As the drug is released, the distance for diffusion of the drug from the marix to the saturated solution increases. The drug is leached out from the interconnecting pores and or capillaries. The release kinetics of such dosage forms are given by Higuchi[9].

$$dm_t/dt = A/2 \, (2DC_sC_0/t)^{1/2}$$

Where A is the area, D is the diffusion coeffecient, C_s is the solubility of active drug in the matrix, C_0 is the total concentration in the matrix m_t is the total amount of drug released at time t.

2.2.1. Repeat Action Tablets

A repeat-action tablet is one that provides the usual single dose of the drug immediately after administration and delivers the next single dose after a period of time. Repeat-action 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. In this type of dosage forms the core

serves as the base to which the initial dose is applied by usual coating techniques.

This type of dosage forms is prepared either by coating the immediate release portion of the drug over an enteric coated core tablet or by presscoating the initial dose over the core which has been coated with an enteric material. Figure 1. shows the schematic representation of dissolution process of a repeat-action tablets.

2.2.2. Albuterol Extended Release Tablets

Albuterol sulfate has been studied extensively and formulated into various types of dosage forms[10,11,12,13]. To date, the only controlled release oral dosage form available in the US market is albuterol sulfate repetabs[7]. The other oral dosage forms available in the market are conventional tablets, syrups and oral inhalations. These dosage forms are designed to deliver two or four mg orally or 90 µg per actuation for inhalation in a metered dose[7].

3. General Aspects of Coating

The process and techniques employed in the coating of tablets were inherited from the pill coating technique[15] and have been surrounded by secrecy. Tablet coating is a unit operation in which a layer of designed thickness of a suitable material sugar or film is cast around a compressed tablet core[13].

There are a number of various reasons for coating tablets[13,14]:

1. Improve the appearance of the tablet

2. Mask the odor and taste of the drug in the core

3. Protect the drug from its surrounding environment (air, light, and

10

Repeat-action Tablets

Layer Containing
First Dose

*Dissolution Of
Immediate Release Portion*

Time Increasing

Seal or Enteric
Coat

Intact Core Containing Second Dose

DRUG IN
SOLUTION

*Diffusion And Erosion
Controlled Release*

Slowly Dissolving and Eroding Core
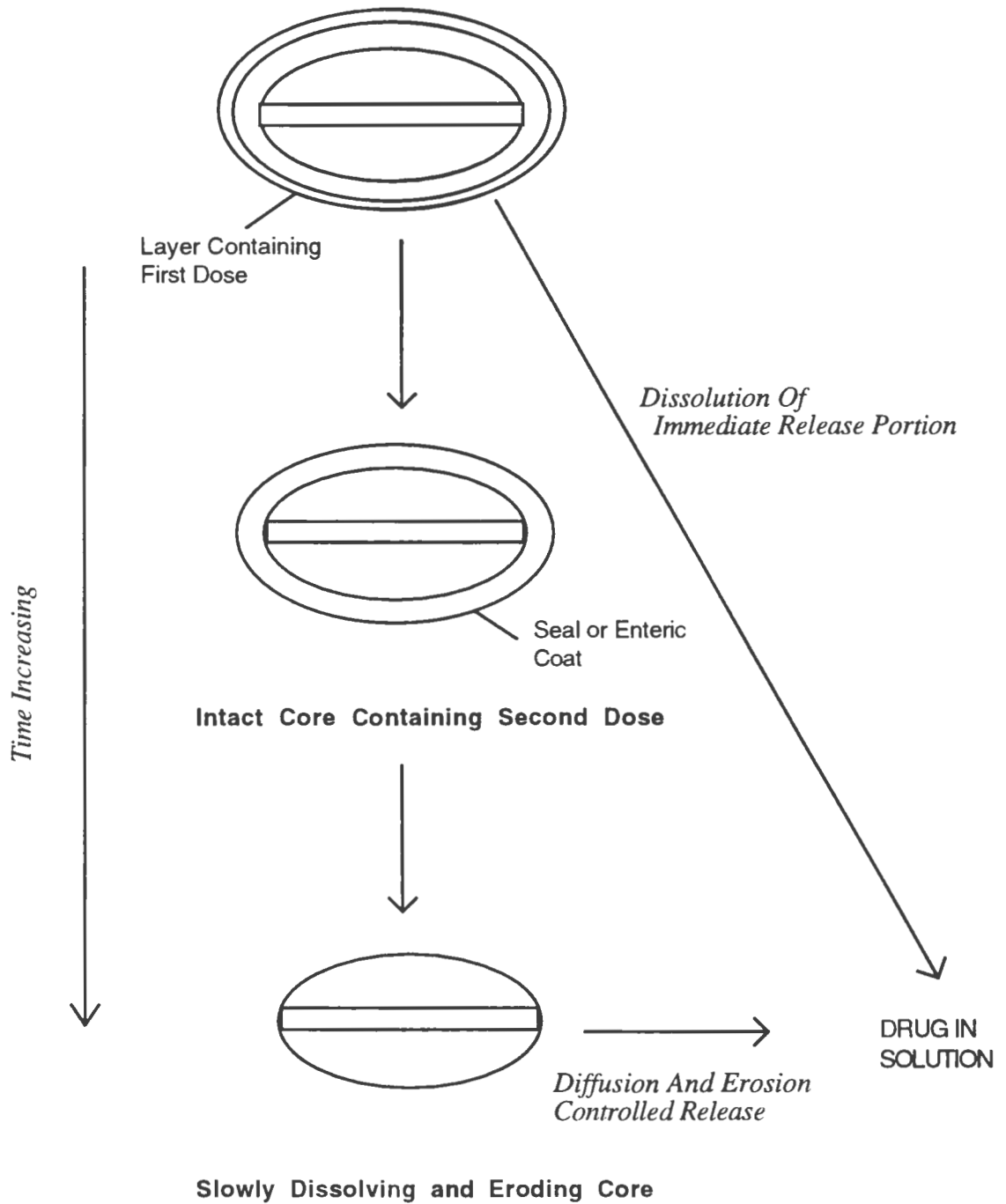
Figure 1. Design And Mode Of Drug Release From a
Repeat-action Tablet

moisture) and improve stability

4. Program the release of the medicament at a certain rate over a given period of time

5. Improve the product mechanical integrity

6. Reduce or eliminate incompatibility of two or more drugs

7. Improve the product identity from manufacturing to patient

3.1. Sugar Coating

In the recent past sugar was the most widely used material for coating tablets[15,16,17]. Gelatin and sugar are used as main coating materials since they are readily soluble and proven safe for domestic use[15]. Sugar coating is essentially a multiple process where success is still measured in terms of the elegance of the final product. This type of coating is still largely dependent on the use of skilled manpower.

The basic procedure of sugar coating can be broken into four distinct operations. Sealing, subcoating, smoothing, coloring and polishing. While a detailed description of this topic is out of scope of this thesis. Figure 2. briefly illustrates the various steps involved in the sugar coating process[17]. A seal coat is applied to the tablet core to prevent the moisture penetration, usually employing a sealant such as shellac. Subcoating or the foundation is applied to round out the sharp edges and build up the tablets to a desired size and shape. Smoothing is achieved by applying several coats of plain syrup. When the tablets become perfectly smooth, a subsequent syrup coating that contains a suitable color is applied. Finally the tablets are polished in a canvas-lined pan to give the desired luster.

Core

Sealing

Subcoating,
Grossing
& Smoothing

Color
Coating

Polishing.

Based on
initial core
weight,
50-100%
weight gain
achieved
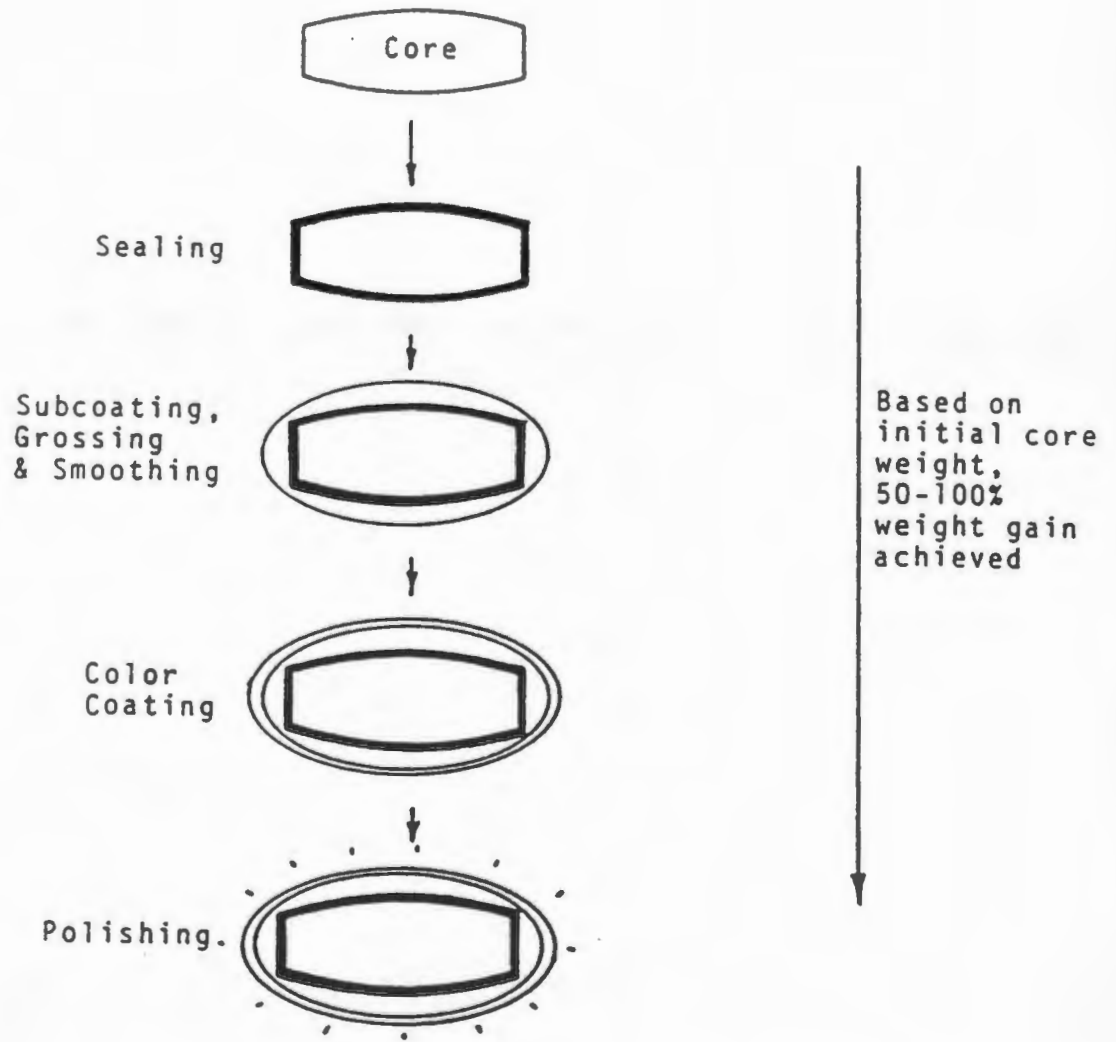
Figure 2. Steps Involved In the Sugar Coating Process for Tablets

13

3.2. Film Coating

Utilization of some kind of coating process to modify the characteristics of a dosage form has long been practiced in the pharmaceutical industry. Film coating in the pharmaceutical industry was introduced by Abbott laboratories with the first commercial film coated product introduced into the market in 1953[17].

Film coating affords greater flexibility, faster processing time and an overall increase in manufacturing efficiency. The process involves deposition of a thin (20-150 µm), polymer-based coating material onto the surface of a pharmaceutical substrate. The film coating process is mainly accomplished by the spray application of polymer solutions using volatile solvents. The film-forming process involves two major steps, deposition of the polymer particles as fine droplets onto the tablet surface and coalescence of the droplets to form a thin film which is accompanied by continuous drying. Figure 3. shows a schematic representation of the film coating process.

The quality of film coating is influenced by the formulation and the process used. Several formulation and manufacturing problems are related to coating formulations[18]. The viscosity of this coating liquid influences delivery, atomization and spreading of the polymer solution. Poor uniformity in film thickness, results from uneven spraying of the film forming polymer. Drug release properties from the core may be altered due to porosity or thickness of the polymer film[20,21].

3.2.1. Film Coating Materials

Since its introduction in the 1950's, film coating has undergone some radical change, both with respect to the equipment used for

14

DROPLET   FORMATION

IMPINGEMENT

DRYING IS CONTINUOUS THROUGHOUT

COALESCENCE
ADHESION
&
AUTOHESION (COHESION)

WETTING   SPREADING
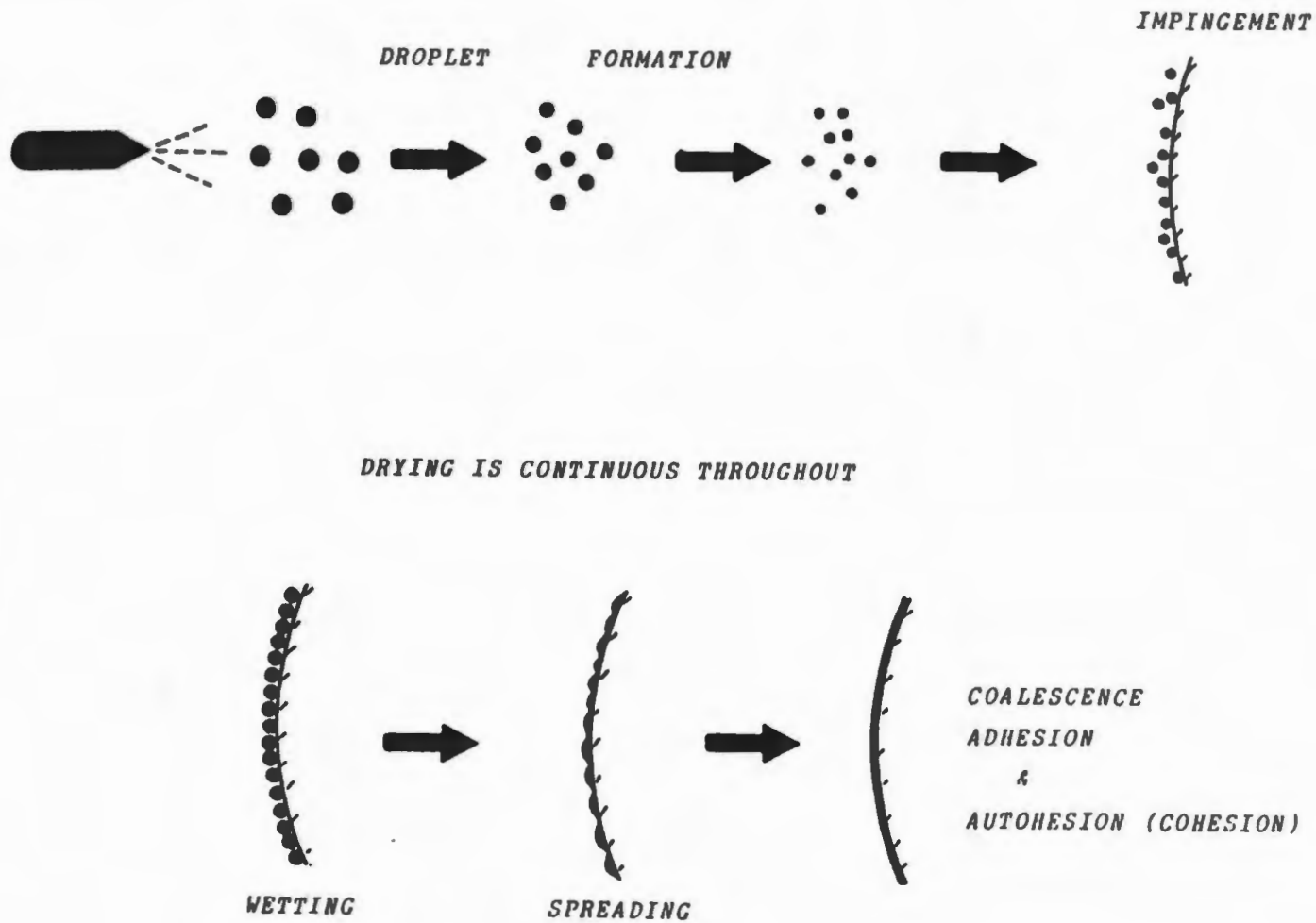
Figure 3. Schematic Representation of Film Coating Processes

15

processing and coating formulations used[23,24]. The major change, of course is represented by the transition from non-aqueous film coating to aqueous film coating. If we follow the progress of pharmaceutical coating technology, we will see that it has essentially gone full circle. Figure 4. shows the evolution of the film coating processes. The coating process that began predominantly with the use of water based suspensions to provide sugar coating ultimately became essentially non aqueous to provide polymer films. Initially film coating used organic solvents due to the advantages of shorter processing time and reduced effect of heat and moisture on the stability of the drug. Finally the trend has resulted in preference being shown for an aqueous process[25]. This change has occurred as the result of a desire to eliminate certain disadvantages associated with the use of organic solvents. Namely the hazards concerned with using flammable materials, concerns over the use of toxic materials, the environmental issues surrounding atmospheric pollution by gaseous effluents used in the coating process and lastly the continued increase in solvent cost.

Thus, aqueous film coating has become more acceptable and produced major benefits with respect to safety and cost. One potential drawback, however, when using aqueous coating is the relatively high latent heat of vaporization of water[26]. Thus one should anticipate that greater difficulty will be experienced in removing water from an applied film coating than that found with the previously used organic solvents. Concerns related to this issue are the potential for increased processing time, greater risk of temperature and moisture affecting drug stability, and opportunities for changes in drug release characteristics[27,28]. In order to minimize these concerns, aqueous

Aqueous Processes   **Non-Aqueous Processes**

Sugar coating

Film Coating

Film Coating
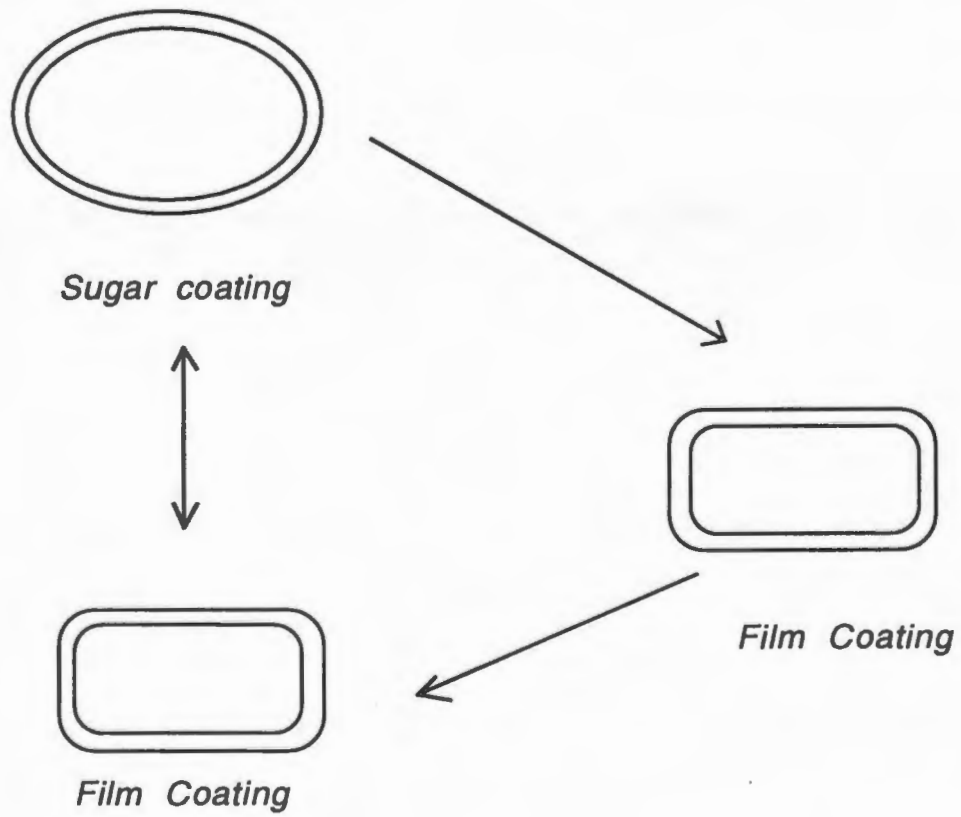
Figure 4. Evolution Of Pharmaceutical Coating Processes

coating solutions containing a higher percent of solids than found in organic solvent based coating solutions are used[27]. This approach minimizes both the total amount of coating solutions applied and thus the amount of water that has to be removed. As a result, a compromise has to be made between coating solid load, process time, product stability and the desired release characteristics[28].

3.2.2. Issues Related to Aqueous Film Coating

Aqueous film coating deals with two predominantly different types of coating systems, namely: Solutions of polymers in water and dispersions (latex) of polymers in water. Aqueous polymer solutions are typically used when conventional water soluble coatings are required[29]. While a latex dispersion is used to produce a more highly functional film coating. When solutions of polymer in water are used, the viscous liquid is converted into a viscoelastic solid during the film formation process. The various stages of this process are, rapid surface evaporation of solvents which causes an increase in polymer concentration and a decrease in the overall area from which the solvent can evaporate. Continued loss of solvent, proceeds at a slower rate largely determined by solvent diffusion through the polymer matrix to the surface. "Solidification" of the film results from immobilization of the polymer molecules. Continued solvent loss continues at an extremely low rate with concurrent formation of shrinkage stresses within the film as a result of constraints imposed by the immobility of polymer molecules and adhesion of coating to the substrate. As solvent loss occurs, the glass transition temperature of polymer/solvent mixture is continually raised, and free volume

(intermolecular space) is diminished. Ultimately free volume may decrease to such a low level that it is impossible to effectively remove the last trace of solvent from the film[28].

Formation of a film from an aqueous polymeric dispersion follows a different and more complex procedure. In the liquid state, the polymer is in the form of discrete particles dispersed in an aqueous vehicle. To form a continuous film, these polymeric particles must be consolidated, deformed, and ultimately fused together[28,29].

The complexity of the film forming process with in latex dispersions has given rise to several competing theories[30]. Generally, during film formation sufficient pressure must be developed to cause the polymeric particles to deform and coalesce. This coalescence is facilitated by the interparticulate capillary forces that are generated as water evaporates. However complete coalescence can only occur as a result of viscous flow which eliminates the boundaries between the adjacent polymer particles. Thus "diffusion" of polymer chains across the boundaries must occur which is possible only if sufficient free volume exists in the bulk polymer to accommodate the diffusion process. Thus the formation of these polymeric dispersion is critical for successful film coating. Processing conditions such as spray rate, atomizing air pressure, droplet size, droplet distribution, drying conditions (air flow, temperature and humidity) spreading and coalescence are equally important[31].

3.3. Processing Equipment

The choice of proper equipment and creation of a suitable processing environment is as essential to achieving a good film coating

as selecting an appropriate coating formulation[29]. This is particularly true for aqueous film coating. Film coating requires a delicately balanced environment. The coating material must contain sufficient solvent to adhere properly and coalesce as it reaches the surface of the substrate, yet it also must dry rapidly and not be transferred from one tablet or particle to another. To create the necessary environment for this process to occur, specialized coating equipment is required.

3.4. Coating Pan

Over the past several decades, the design of coating pans have undergone major changes due to advances in coating technology and an increased demand for compliance with GMP's[31]. Originally, pharmaceutical coating pans evolved from designs used in confectionery pan coating. However, it was obvious that aqueous film coating placed significant demand on the drying capabilities of the coating equipment. Designers of such equipment have made a variety of modifications to increase the interaction between the product being coated and the air responsible for removing solvent from that product. In this regard fluid-bed equipment is considered as most effective[31,32].

However, in spite of the advantages of the fluid-bed coating equipment, the so-called side vented pan has surfaced as the design of choice in most film coating applications. While a multitude of side vented pan designs exist, the basic principles are similar. The air is introduced into the interior of the pan, drawn through the product being coated, and exhausted to the exterior. Several of the approaches to air flow in the various types of side vented pans are shown in Figure 5.

Style #1

1 = inlet

2 = outlet

Style #2

1 = inlet

2 = outlet

Style #3

1 = inlet

2 = outlet

Style #4

1 = inlet or outlet

2 = inlet or outlet

3 = outlet

Style #5

1 = inlet or outlet

2 = inlet or outlet

3 = inlet or outlet

Style #6

1 = inlet

2 = outlet

Style #7

1 = inlet

2 = inlet or outlet

3 = inlet or outlet
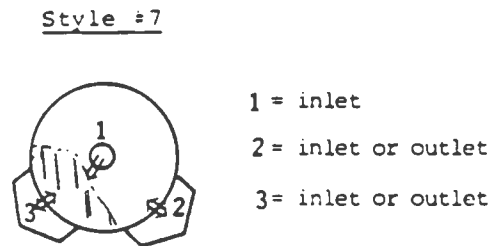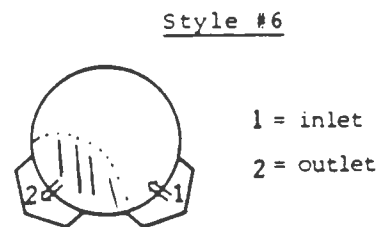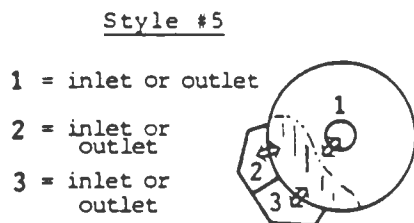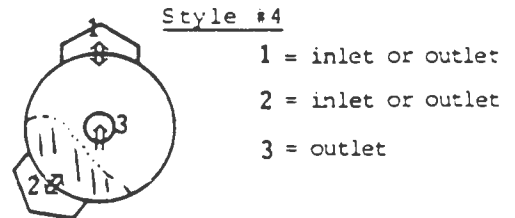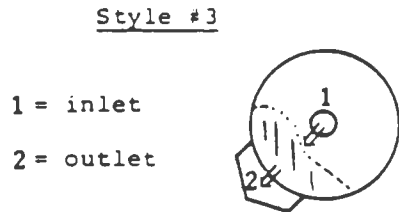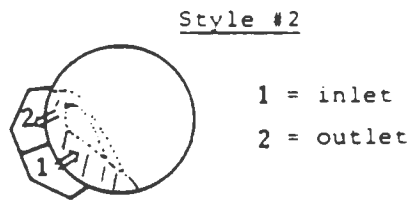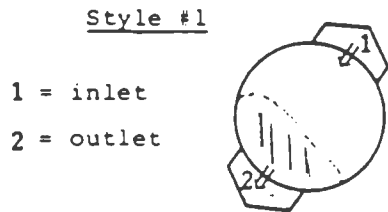
Figure 5. Air Flow Patterns In Side Vented Pans

21

3.4.1. Accela-cota

The Accela-cota equipment introduced in 1960's (by Thomas Engineering), is based on a design patented by Eli Lilly who was the pioneer in the design of side-vented pans[18]. Equipment of this type consists of a perforated drum that is rotated on its horizontal axis in an enclosed housing. The coating solution is applied to the surface of the rotating tablet bed via spray nozzles that are positioned within the drum. Figure 6. shows a schematic representation of the Accela-cota. This equipment has undergone various modifications since being introduced. Air flow through the pan and the product is facilitated by more fully perforating the cylindrical portion of the pan. Air is introduced by a plenum in contact with the top of the pan and is drawn through the pan and tablets. The air is then exhausted through a plenum located on the exterior of the pan in a position immediately below the cascading bed of tablets. The air flow pattern of Accela-cota is similar to that shown in style #1 of figure 5. There are various alternative coating equipment available in the market include Hi-coater, Dicoater and Glatt pan-coating equipment. All of those designs differ slightly in air flow patterns and vent.

3.5. Fluid-bed Coating Equipment

The fluid-bed or air suspension process has long been used in the coating of pharmaceutical solids. Equipment for this process was originally patented in the 1950's by Wurster[32]. A schematic diagram of the Wurster fluid-bed coating process is shown in Figure 7.

During normal operation, fludizing air causes the product being coated to accelerate rapidly up through the inner partition which
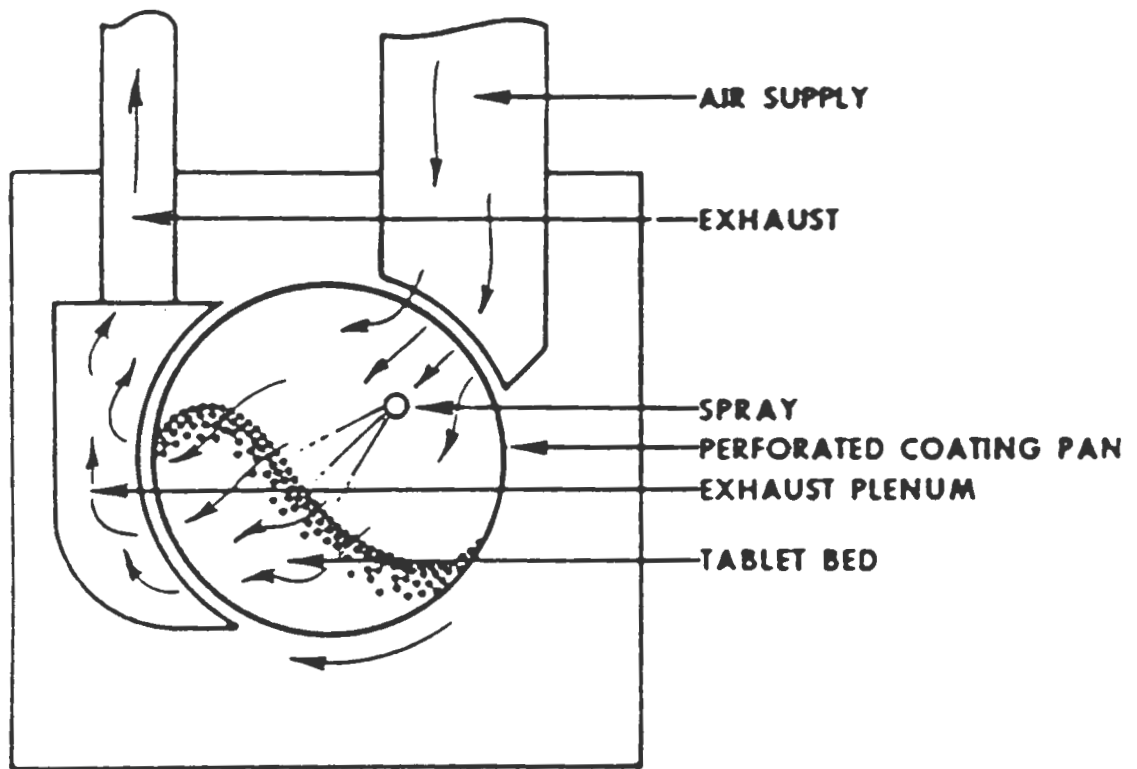
Figure 6. Schematic Representation Of Accela-cota

AIR SUPPLY

EXHAUST

SPRAY

PERFORATED COATING PAN

EXHAUST PLENUM

TABLET BED
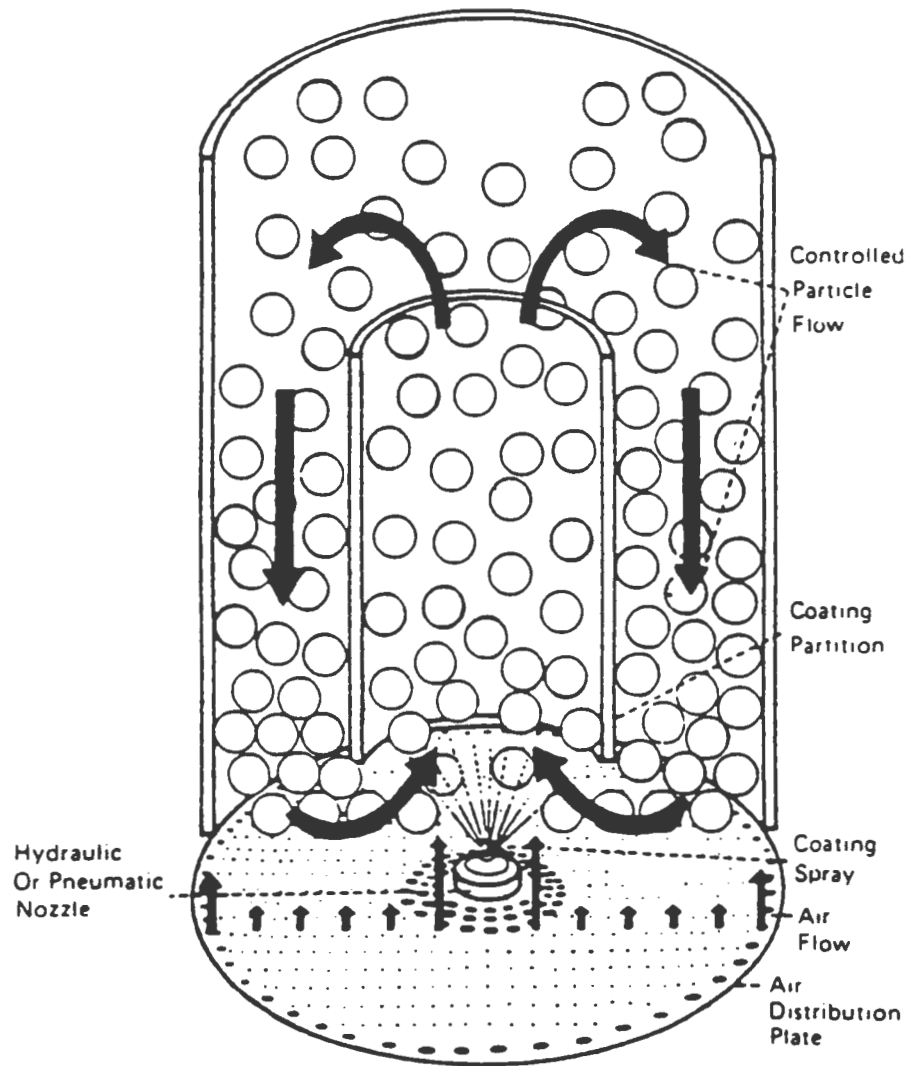
Figure 7. Schematic Representation Of Wurster Fluid-bed
Coating Process

The figure is labeled with the following text:

Controlled Particle Flow

Coating Partition

Coating Spray

Air Flow

Air Distribution Plate

Hydraulic Or Pneumatic Nozzle

defines the spray zone. Deceleration occurs in the region of the top expansion chamber, causing the product to drop back into the coating chamber as confined by the walls of the chamber and the insert. The product moves quickly down to the bottom of the coating chamber where the cycle begins again. In the heyday of organic-solvent based film coating, the wurster process proved to be very popular for coating tablets[33]. The product coated in the wurster process is typically characterized by uniform coating and the process itself exhibits excellent drying characteristics. Since the aqueous process would benefit from these outstanding drying capabilities, there is a growing interest in this type of equipment for aqueous film coating of tablets[33]. The Aeromatic fluid-bed coating equipment designs are versatile which operate on the same principles as the wurster process. This type of coating equipment has many added features and is designed to accommodate a variety of modular inserts such as dryer, spray granulator, aero-coater for bottom spray coating and ultra coater, bottom/tangential spray for tablet coating. Since these film coatings need to be highly functional, the benefits of the fluid-bed process, with its capabilities for applying coating uniformly with minimized particle agglomeration are readily evident and outweighs the side vented pan coating equipment in this regard.

4. Methods For Testing Drug Release

Setting up a dissolution method for evaluation of drug release during the development of a new dosage form is of critical importance. It has been well established that different operating parameters of the various dissolution methods can yield different

results[40,41]. In the compendia, stirring rate, volume and mesh may vary for individual drug monographs. The USP further specifies special criteria for monitoring the dissolution of controlled release dosage forms and also recommends that drug release be monitored at various pH's to mimic the in-vivo dissolution behavior.

A number of dissolution methods have been developed, but only a few are officially recognized by the USP. The Tumbling method was developed in 1930 followed by various methods such as Beaker method, Rotating disc, Magnetic basket and Rotating bottle. The rotating bottle was not the method of choice due to the limitations in media volume and lack of automation[41]. The USP basket was introduced in 1969 and USP paddle was introduced in 1978[42].

4.1 USP Apparatus I

The USP basket method or apparatus I is the primary *in-vitro* dissolution testing equipment for conventional release dosage forms. It was adopted as the first official method by the USP XVIII in 1969[43]. The basket apparatus described in USP XXII, is simple, robust and adequately standardized because of this advantage it is recommended by the USP for the in-vitro dissolution testing of controlled release preparations. This apparatus consists of a 40 mesh, stainless steel wire basket, 1000 ml capacity dissolution flask. A water bath which maintains the temperature of the dissolution medium at $37^{\circ}\pm0.5^{\circ}$C. The basket is rotated at varying speeds from 25 to 150 RPM. However, because of the 'single container' nature of the basket apparatus it is difficult to change the test media partially during the test especially if the dissolution of the drug should be studied in various pH. Thus the

USP apparatus III (Reciprocating Cylinder) and apparatus IV (Flow through cell) has distinct advantage over the basket apparatus preferably for testing controlled release dosage forms. Figure 8. shows the specification of the basket apparatus[43].

4.2. USP Apparatus III (Reciprocating Cylinder)

In-vitro dissolution of a dosage form under appropriate conditions allows the prediction of in-vivo behavior: this is true for sustained and controlled release dosage forms which have to be studied under various pH conditions and in the presence of media resembling those likely to be present in the GI tract during the transit of the dosage from.

When the USP apparatus I and II were recognized as official instruments for in-vitro dissolution testing. Various researchers have observed difficulties in using this instruments to evaluate controlled release dosage forms[44,45,46]. Especially when the pH of the media has to be changed and the sink conditions has to be maintained during the dissolution process. For more than a decade there was no appropriate dissolution testing apparatus suitable for testing controlled release preparations at various pH's, until the USP apparatus III, the reciprocating cylinder and the flow through apparatus IV, was recognized officially in 1993[15,53].

Beckett et al[48] proposed a novel device, the "Bio-Dis", that can be automated, thereby saving handling time and can be used to determine drug release at various pH's. Which is now recognized officially as USP apparatus III (USP XXII supplement VI 1993) or the reciprocating cylinder. This apparatus is recommended by USP for

27

General

- Water bath temperature 36.5°C–37.5°C
- Media as in monograph, but otherwise 900 ml in USP/NF and 1000 ml in BP. BP specifies deaeration. USP/NF states dissolved gases must not interfere
- Samples required: USP/NF 6 + 6 + 12 sequenced until specification is met. BP 5 + 5 sequenced for 100% of 5

Speed (rpm) as specified in monograph
25–150 rpm (± 4% USP/NF ± 5% BP)

Shaft
USP/NF — 6–10.5-mm diameter;
BP — approximately 6-mm diameter;
2-mm vent in drive disc

Centering (or tilt)
± 2 mm at all points

Eccentricity
USP/NF — no significant wobble;
BP — no perceptible wobble

Sampling Point
USP/NF — midway from top of basket to top of fluid and no closer than 1 cm to side of flask
BP — halfway between basket and side at middle of basket

Flask
USP/NF — cylindrical with spherical bottom, 16–17.5-cm high, inside diameter 10–10.5 cm, plastic or glass
BP — cylindrical, flat bottomed, glass

Basket

Basket Position
USP/NF — 2.5 ± 0.2 cm
BP — 2.0 ± 0.2 cm

Figure 8. Specifications for USP Basket Apparatus I

28

testing drug release from controlled release dosage forms. This equipment has the advantage that the medium pH can be changed with out interrupting the test. Figure 9. shows the specification of reciprocating cylinder USP apparatus III[53].
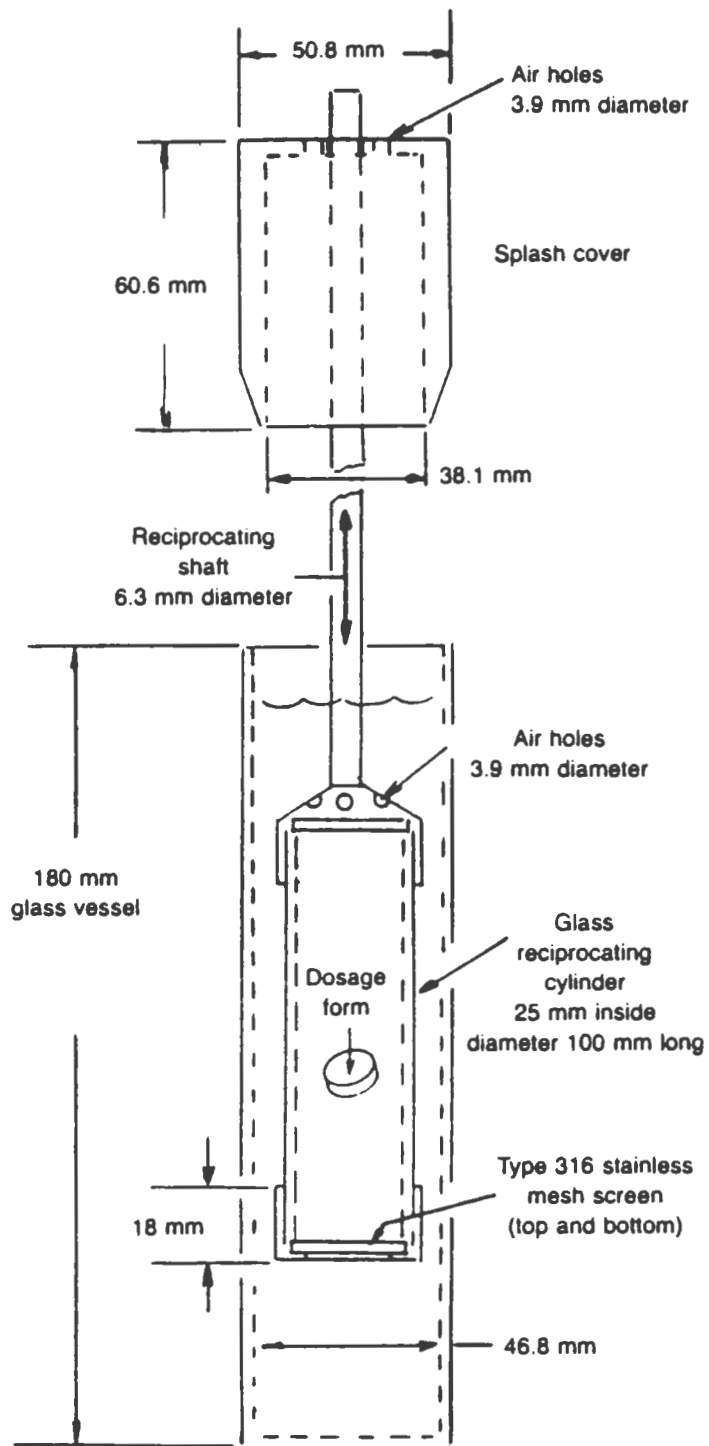
Figure 9. Specifications for USP Apparatus III (Reciprocating cylinder)

II PURPOSE OF STUDY

Describing that number of products on the market for a long period containing many natural ingredients which often show variability in the content uniformity and drug release; Over the past years greater number of new excipients introduced in pharmaceutical formulation, which have specific components that are well defined, improved shelf-life and cost effective processing techniques that are environmentally safe. Hence it would be desirable to formulate a dosage form using the novel technique, and variety of synthetic polymers, this approach will exclude the variability's in the drug release imparted by the raw materials obtained form the natural source. It was my intention to use the simple aqueous film coating technique to deliver the initial dose for immediate release and aqueous polymer latex coating to retard the release of second dose for a period of 5-6 hours.

The rationale for using cellulose polymers for tablet matrix is that it has been widely used in the formulation of controlled release dosage forms and also approved by the FDA as 'GRAS' materials. Eudragit was selected as a retardant film forming material because it was reported in the literature in various ways to be used in the controlled release dosage from preparation by coating tablets, forming beads, granulating with polymer and direct blending of drug polymer and excipients[33,34,35,36].It is effective in low concentration and is soluble in higher pH which is a property similar to zein[15,70].

The purpose of this study was to formulate a modified release dosage form that would eliminate the use of hazardous organic solvent coating, also to eliminate the variability in drug release induced by the raw materials obtained from natural source used for retardant release

31

6. To evaluate two different types of processing equipment for their efficiency, reproducibility, and consistency.

7. To perform in-vitro dissolution tests to evaluate the release rate of albuterol from the marketed product and the developed tablet dosage form.

8. To compare the dissolution profile obtained from the two different dissolution apparatus specified in the USP XXII (Apparatus I and Apparatus III).

III Experimental

1. Materials

A. Chemicals

1. Acetic acid, Glacial Reagent A.S.C.[1]

2. Acrylic acid copolymer, Rohm Pharma, GmBH, Germany.

3. Ammonium hydroxide solution A.S.C.[1]

4. Diethyl citrate, Sigma chemical company, St. Louis, Missouri.

5. Hydrochloric acid[1]

6. Lactose Directly compressible

7. Methanol HPLC grade[1]

8. Magnesium stearate, Mallinkrodt Company, New York.

9. Phosphoric acid HPLC grade[1]

10. Polyethylene glycol 400 , Union Carbide

11. Potassium phosphate dibasic[1]

12. Sodium hydroxide[1]

13. Sodium phosphate dibasic[1]

14. Sodium phosphate monobasic[1]

15. Sodium acetate[1]

16. Starch 1500, Colorcon, West Point, Pennsylvania.

17. Syloid brand of colloidal silica, Division Chemical, Baltimore, Maryland.

18. Talc, Amenda Drug and Chemical Co., Irvington, New Jersy.

19. Various cellulose polymers, The Dow Chemical Company, Midland, Michigan.

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[1] Fisher Scientific Company, Fair lawn, New Jersy.

34

B. Model drug

Albuterol sulfate (Lot# 180712), Propharmaco, Nobel Industries.

2. Equipment

Accela Cota 24", Thomas Engineering, Hoffman Estates, Illinois.

Bio-Dis Tester, Vankel Industries, Inc., Edision New Jersy.

Carver Laboratory Press, Model C, Fred S. Carver INC., WIS.

Diode Array Spectrophotometer Model 8451 A Hewlett Packard, Atlanta, Georgia.

Dissolution System, Six spindle basket apparatus, Model 2100, Dis-Teck Inc., New Jersy.

Electric Balance, Model H8 Mettler, Will Scientific Inc., Rochester, New York.

Electronic Analytical Balance, Sartorus GmBH, Germany.

Electronic Balance , Mettler, Will Scientific Inc., Rochester, New York.

Fluid Bed Apparatus, Model Strea I, Niro-aeromatic Columbia, Maryland.

Friability Tester, Erweka, GmBH, Germany.

Granule Blender, Turbula Mixer, Switzerland.

Hardness Tester, Digital Model 4M, Schleuniger, Solothurn, Switzerland.

High Speed Disperser, Model 89, Premier Mill Corporation, Reading, Pennsylvania.

Juliet Particle Size Analyzer, interfaced with image analyzer and Olympus Optical Microscope Model BHT 232430, Japan.

Peristaltic Pump, Master flex Model 7520-10, Cole Parmer, Chicago, Illinois.

pH meter, Model 811, Orion Research Inc., Cambridge, Massachusetts.

The flow rate was 1.5 ml per minute, the UV detector set at 276 nm and the injection volume was 25 µl (Using WISP). A plot of peak area vs. concentration was obtained using standard solutions of albuterol sulfate with concentration ranging from 0-20 µg/ml. The relationship thus obtained was linear and used for determining the concentration of albuterol sulfate in the dissolution sample.

The mobile phase with 70 percent methanol and glacial acetic acid in deionised, degassed distilled water provided the best resolution and was used through out these studies. The retention time for albuterol was found to be 4.733 minutes. A typical assay chromatogram is shown in Figure 10. The concentration of albuterol in the sample was calculated by the following equation.

$$\text{Concentration of Albuterol (mg/ml)} = AUC - 1.480/\ 17.487$$

The amount of albuterol, Xa (mg) was calculated by using the formula

$$Xa = C\ 2(239.31/576.70)\ (ru/rs)$$

C = Concentration of albuterol in mg/ml

ru = peak response for albuterol in assay preparation

rs = peak response of albuterol in standard preparation.

A linear relationship was observed between the peak area and albuterol concentration. A standard curve was generated during each run and the concentration of albuterol in the samples were determined from the corresponding relationship between peak area and concentration of standard solution. Figure. 11 shows the calibration curve for albuterol from 0-20 µg/ml.
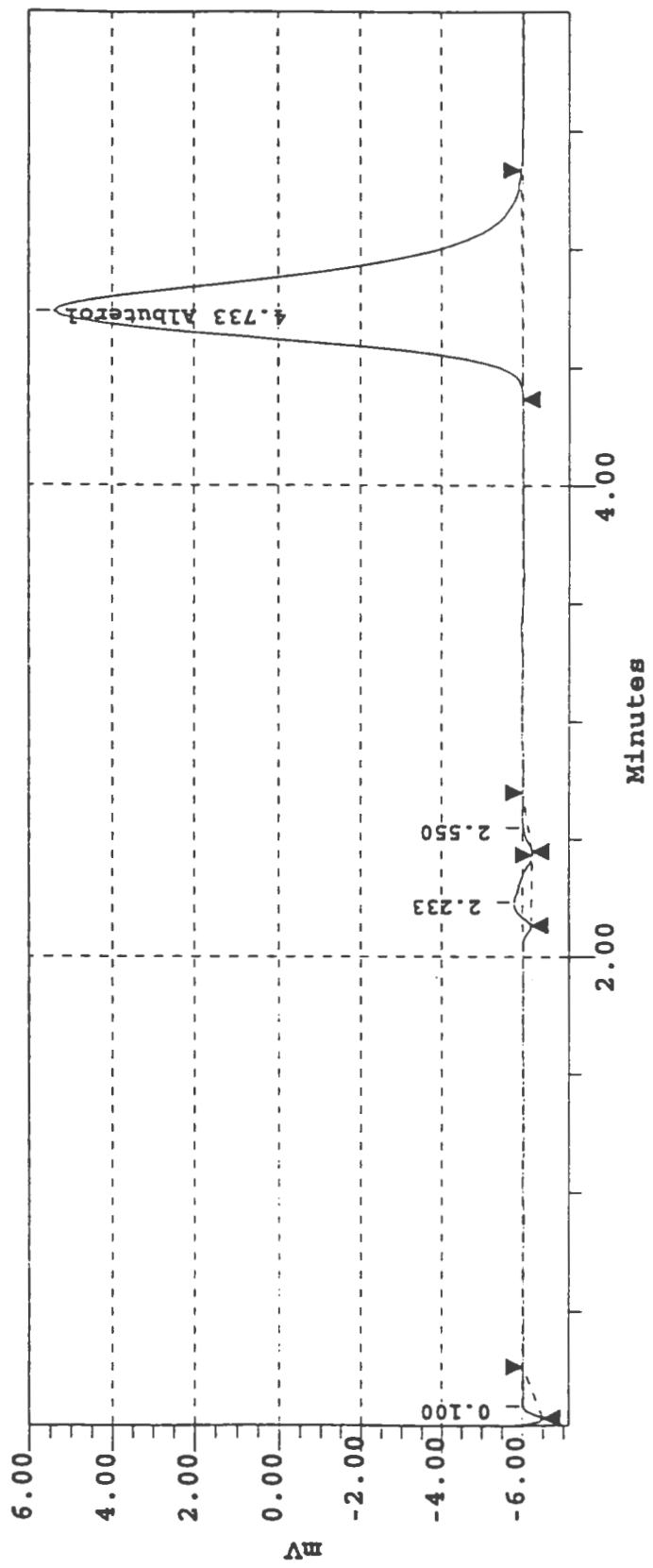
Figure 10. Assay Chromatogram for Albuterol sulfate

38

Figure 11. HPLC Calibration Curve for Albuterol Sulfate in Deionised water

$y = 1.4800 + 17.487x \quad R^2 = 1.000$
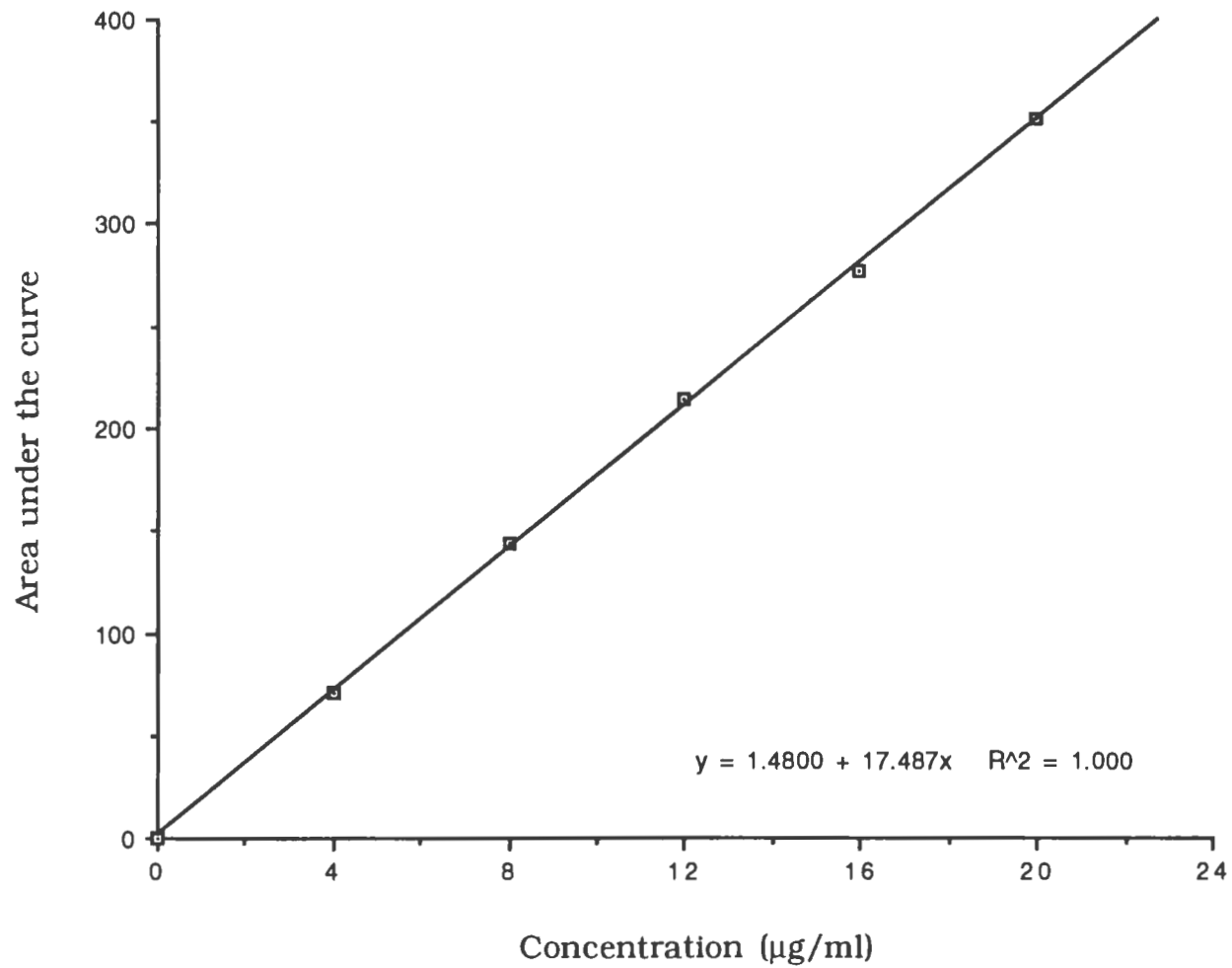
Actual percent of albuterol in each formulation was calculated using the following equation

$$P = 100 \ Xa/4 \ (wt/wa)$$

wt is the theoretical weight in mg, wa is the actual weight of tablet composite used for the assay preparation.

3.1.2. UV Detection

Since the above described High Performance Liquid Chromatography method was time consuming and required only for the analysis of Proventil tablets. Due to the interference of the tabletting excipients. The UV spectroscopic method was used for fast and simple analysis of dissolution samples of the experimental formulations. This method at a wavelength of 226 nm provided a simple, reliable, and sensitive assay which was reproducible.

For quantitative analysis of albuterol sulfate in the developed product an ultraviolet (UV) spectrophotometer was used. The resulting absorbance scan of 8 μg/ ml solution of albuterol sulfate is shown in Figure.12. From the resulting scan it was evident that albuterol exhibits 2 maximas one at 226 nm and second at 276 nm . The absorbance value at 226 was greater than that found at 276nm. Hence a shorter wavelength with higher absorbance value was selected for analysis. A standard curve for albuterol was obtained at this wave length for concentrations between 0 to 20 μg/ml. No buffer and excipient interference was found for the pH values selected for the in-vitro dissolution studies. There was no significant difference in absorbance value measurements. Detection was linear in the range of concentration

```
Sample  Name  : Albuterol Sul        Function          : Absorbance
Solvent Name  : 0.1 M Hcl             Wavelength Range : 200 to 350 nanometers
Concentration.:   0.0080              Integration Time : 1 seconds
Units         : 99.80                 Std Deviation    : OFF
```
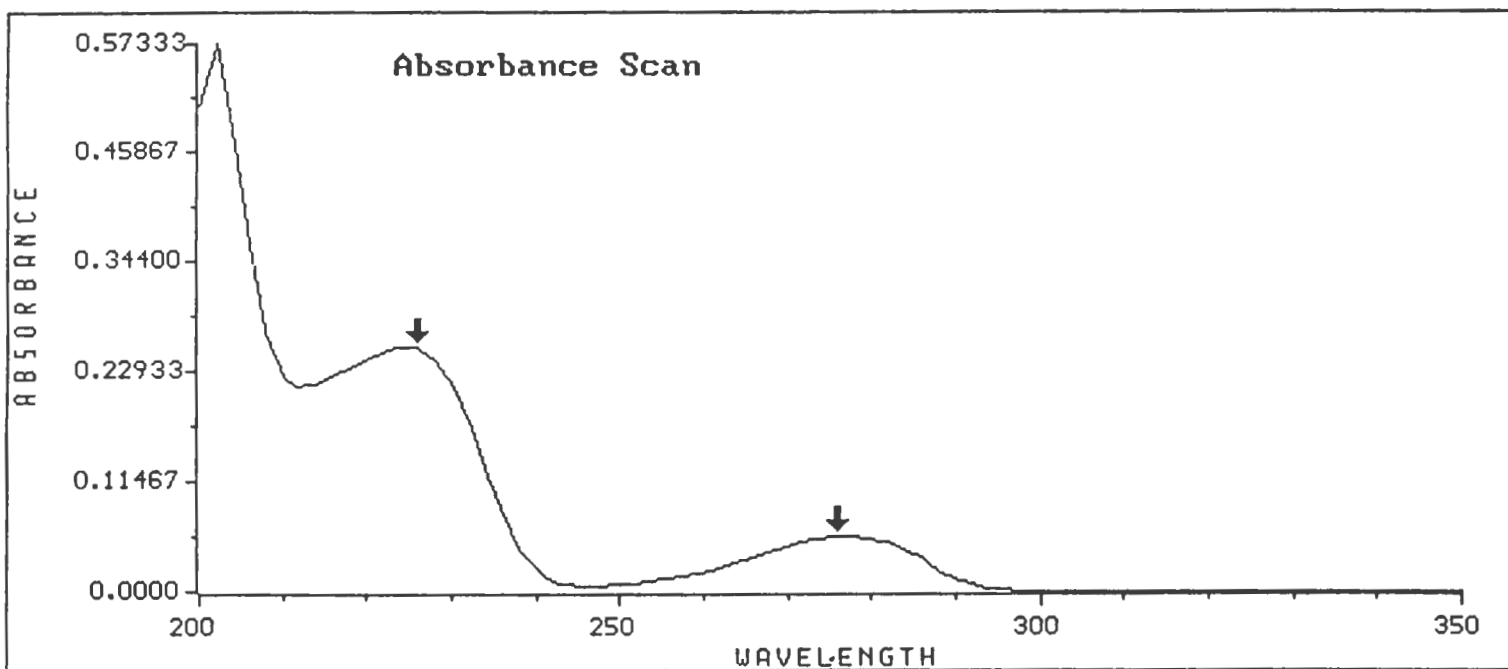


```
Annotated Wavelengths:
  1 : Wavelength =   226    Result =    0.254898
  2 : Wavelength =   276    Result =    0.056396
```

Figure 12. UV Absorbance Scan for Albuterol Sulfate

(0-20µg/ml) selected for the calibration curve. The concentration of albuterol was calculated by using the following equation.

$$\text{Concentration} = \text{Absorbance} - 0.0073/27.61$$

A typical standard curve for albuterol is shown in Figure 13. The results obtained from the two assay methods were compared and the difference was not significant. Hence the UV assay can be used for routine quality control measurements for the developed product.

4. Drug Release Studies of Marketed Product

In-vitro drug release from several lots of the marketed product was studied in various pH mediums 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 XXII. The dissolution study was completed by using two different dissolution apparatus as specified in the USP XXII as: USP apparatus I (Basket), and apparatus III (Reciprocating cylinder, Bio-Dis). The temperature of the dissolution medium was maintained at 37°C ± 0.5°C in all the studies. The media volume was 500 ml in case of apparatus I and the basket was rotated at 50 RPM. In apparatus III, 250 ml of dissolution media was used in each cylinder and the stroke speed was set to 20 per minute. Samples were collected at specified intervals and assayed by HPLC to determine the amount of drug released. Sink conditions were maintained in both methods. UV spectrophotometric assay was not possible for Proventil-Repetabs due to the interference of the tablet excipients. Table I. shows the excipients in Proventil-Repetabs as specified in the labeling.

42

Figure 13. UV Calibration Curve for Albuterol Sulfate

$y = -1.7304e\text{-}3 + 2.7612e\text{-}2x$ $R^2 = 1.000$
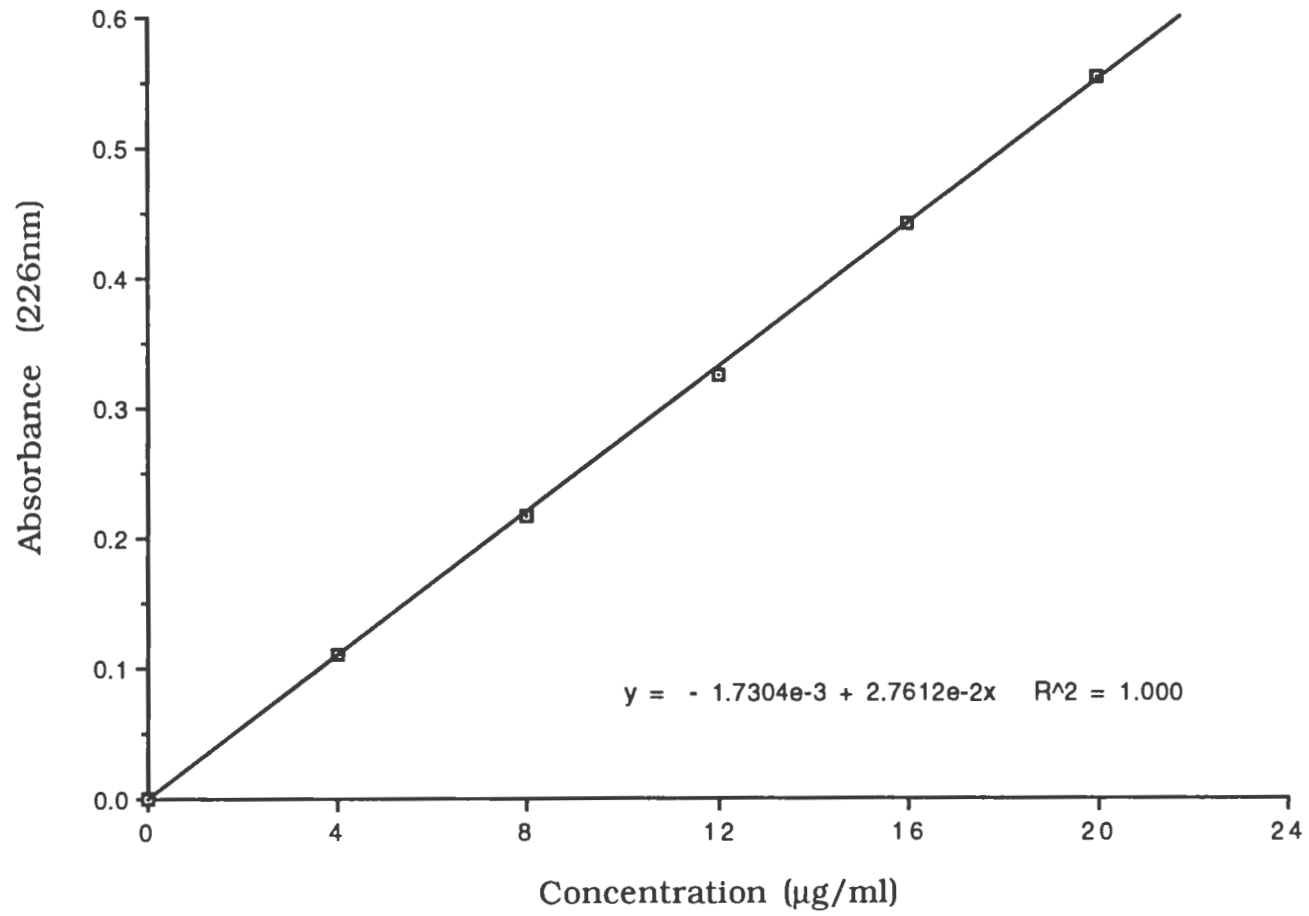
Table I. Ingredients of Proventil Extended Release Tablets*

Albuterol Sulfate 4.8 mg/Tab	Calcium Sulfate
Lactose	Calcium Phosphate
Acacia	Neutral Soap
Corn Starch	White wax
Carnauba Wax	Oleic acid
Butyl Paraben	Rosin
Zein	Titanium di oxide
Sucrose	Mg Stearate
Talc	

---

* As specified in the product label

5. SCALE UP OF TABLET MANUFACTURE

5.1. Laboratory Scale Manufacture

Various formulations of albuterol sulfate tablets were prepared in the laboratory by blending the drug, polymer and excipients in a specified order for a total time of 25 minutes using a turbula mixture.These blends were compressed using a carver laboratory press model-C to determine the initial parameters, such as formulation component concentration, blending time, hardness, tablet weight and drug release. The initial formulation components of three different formulations are shown in Table II.

The final formulation selected was scaled up to a batch size of one kilogram (~7000) tablets using a stokes single punch F1 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 of 7-8 kilo pascals.

5.2. Particle Size Determination

Particle size of the ingredients used in hydrophilic matrix formulation can have significant impact on the performance and drug release characteristic[56,57]. In light of this logic, it was necessary to determine the particle size of the drug and the excipients used in the formulation. The particle size was characterized for albuterol sulfate and all other tabletting excipients used in the study. For this purpose a Juliet particle size and image analyzer interfaced with an Olympus optical microscope under plane polarized light was used. A suspension containing 5µg/ml of albuterol sulfate in mineral oil was used for

Table II. Ingredients for Modified Release Albuterol Tablet Cores

Ingredients	%W/W
Albuterol Sulfate	1.77
Starch 1500	16.74
Lactose DT	53.00
Magnesium Stearate	0.74
Silicon di oxide	0.74
HPMC	27.00

albuterol. Figure 14. shows the particle size distribution histogram for albuterol sulfate. The particle size ranged from 2 to 7 microns with a mean particle size of 3 microns. About 40 percent of the particles lie in the range of 2 to 5 microns which is fairly uniform. Figure 15. shows the particle size distribution histograms for HPMC. A majority of the particles lie in the size range of 3 to 4.5 microns and complies with the data reported in the literature[28]. Figure 16 and 17 show the particle size distribution data for direct compression lactose and starch 1500 respectively. The particle size distribution for lactose ranged from 9 to 14 microns giving an approximate bell shaped distribution. Since the particle size of all the excipients were fairly uniform, an effective powder flow and direct compression was possible. Photographs of the particles were taken using a Polaroid instant photographic camera fitted to the Olympus optical microscope to study the surface morphology of the particles. (see figure 18 and 19).

5.3. Blending

Since the blending equipment used in the laboratory was not applicable for the large scale manufacture it was necessary to re-determine the optimum blending time using the half cubic foot V-Blender. In order to optimize the blending time five different lots were made by varying the total blending time from 30 minutes to 75 minutes. Drug and excipients were added in specified order similar to that of laboratory scale manufacture, finally magnesium stearate was added as a lubricant and blended.
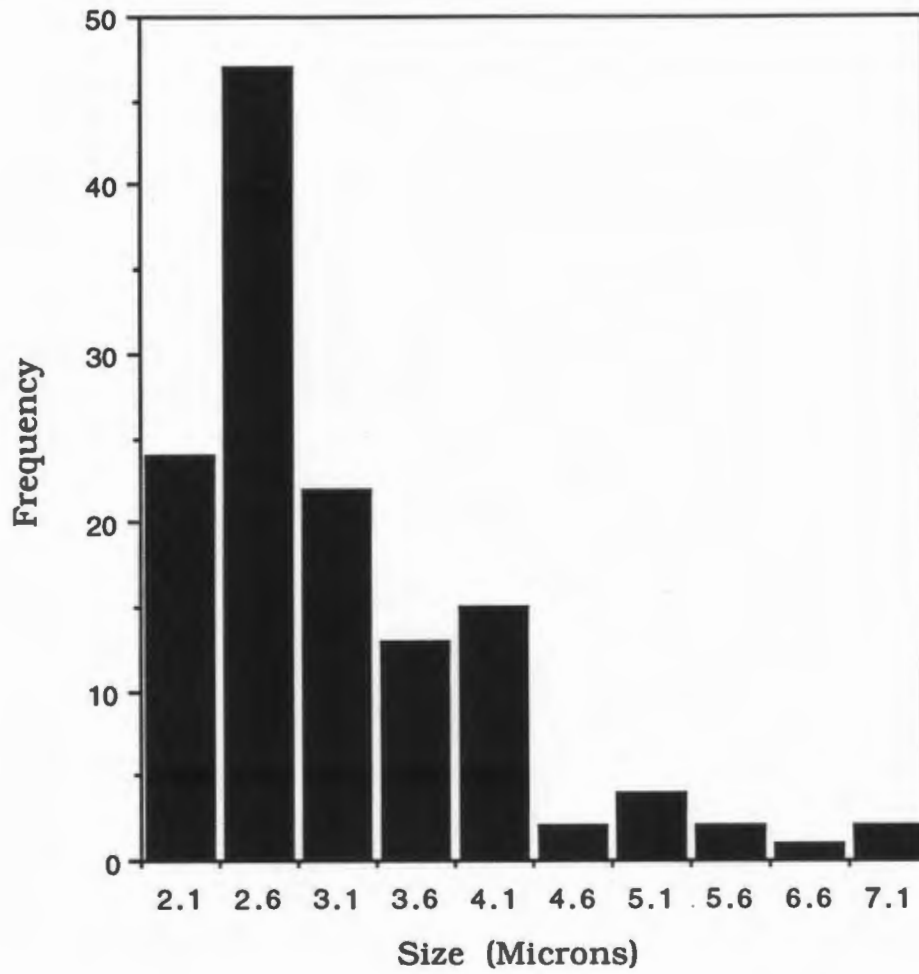
Figure 14. Particle Size Histogram for Albuterol Sulfate
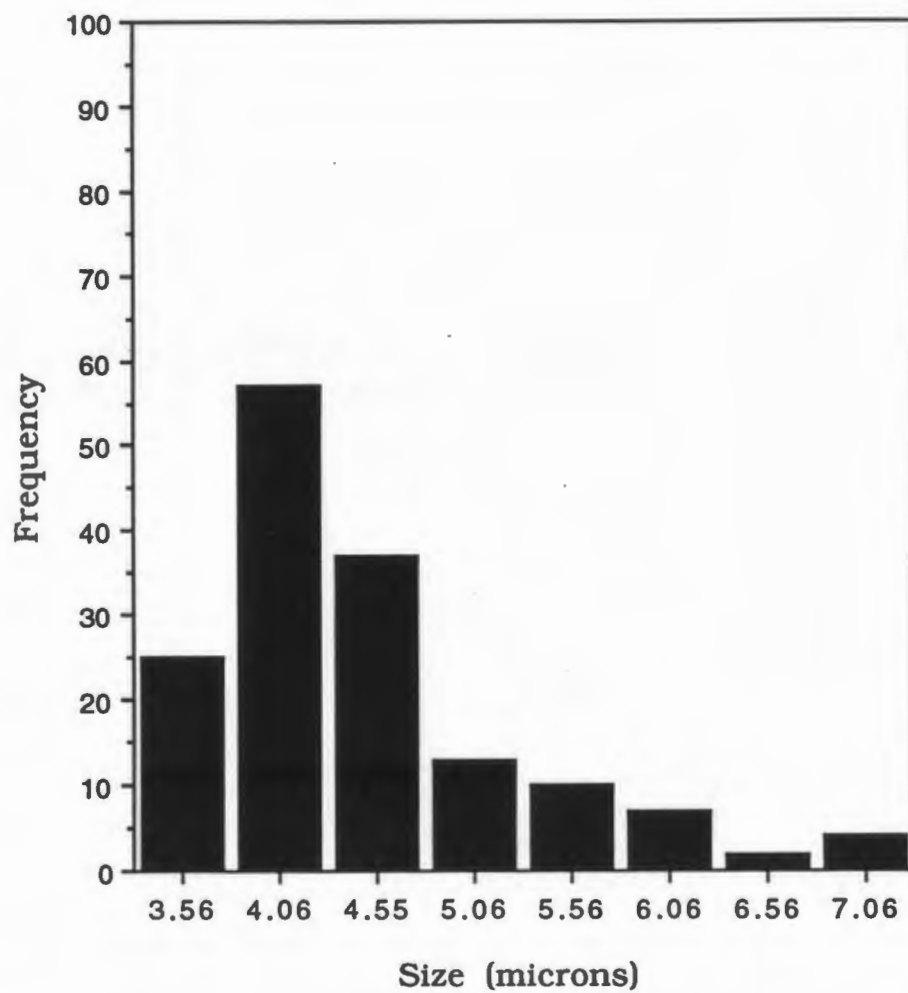
Figure 15. Particle Size Distribution Histogram of HPMC
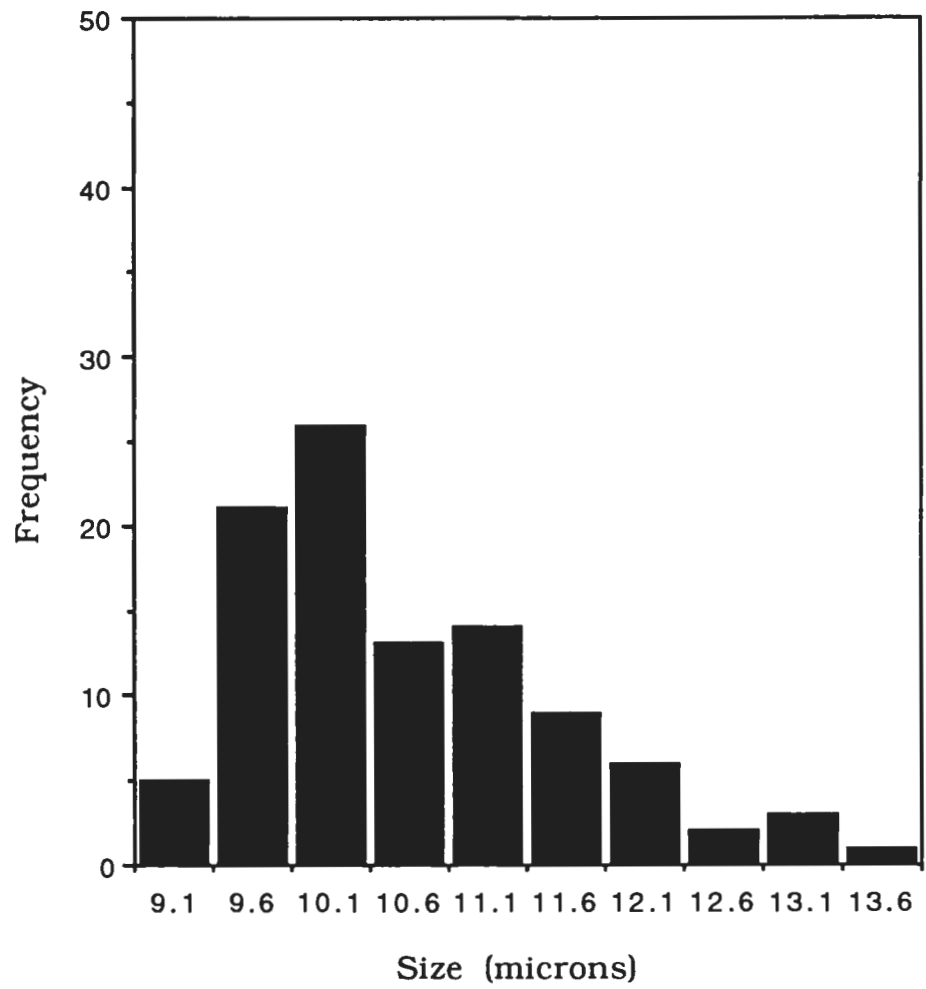
Figure 16. Particle Size Distribution Histogram for Lactose
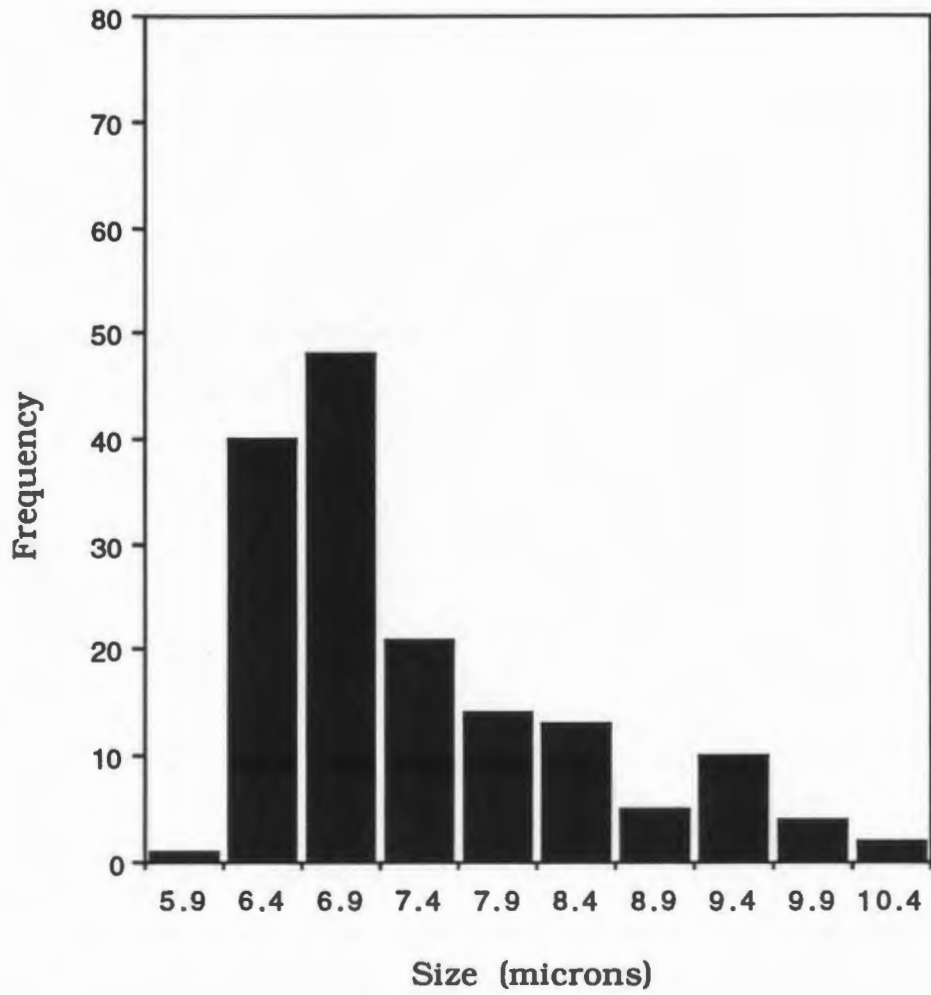
Figure 17. Particle Size Distribution Histogram for Starch 1500
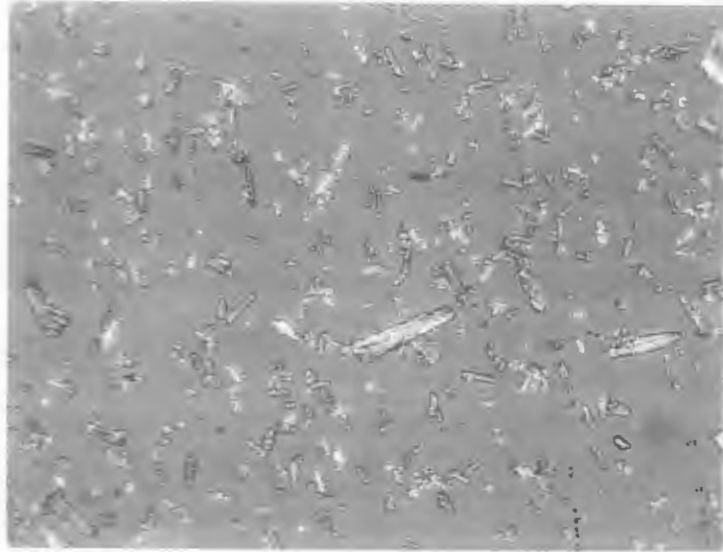
Figure 18. Albuterol Sulfate Dispersed in Mineral Oil
Plane Polarized Light (100 X).

Figure 19. HPMC Dispersed in Mineral Oil
Plane Polarized Light (100 X)

52

5.4. Bulk Density and Flow Properties

The bulk density of all the formulation components, and the tabletting blend was studied. A weighed amount of powder was placed in a 100 ml graduated cylinder and the volume occupied by the powder was determined. A preweighed quantity of powder was placed in a 100 ml graduated cylinder which was then tapped using a tap density apparatus (J. Engelsmann A.G, GmBH, Germany) at a constant rate of ~500 taps and the final volume was noted as tapped density. These data together with the initial poured bulk and tapped densities were used to calculate flowability and the indices of compressibility derived by Hausner (1967) and Carr (1970)[56]. The drug excipient blend was placed in a powder funnel with a one centimeter diameter opening that was supported using a retard stand such that the bottom of the orifice was 10 centimeters from the bench surface. The powder was allowed to flow with the help of gravitational force and the angle of repose which is the angle(Θ) obtained between the free standing powder heap and the horizontal plane was measured.

6. PRODUCTION SCALE MANUFACTURE

6.1. Tabletting

The formulation developed in the laboratory was scaled up to a production size batch of 100,000 tablets. The drug, polymer and excipient blend was directly compressed into tablets using 9/32" standard concave tooling fitted in a Stokes 16 station instrumented rotary tablet press. The tablet weight and hardness was adjusted to 135 mg and ~7 kilo pascals respectively. These tablets were later used for coating. The physical properties of the tablets were studied in accordance

with the methods specified in the USP XXII. Various parameters such as blending time, powder flow properties, weight variation, hardness and drug release was determined in an attempt to compare the reproducibility of the process during large scale manufacture.

7. TABLET COATING

7.1 Preparation of Seal Coating Suspension

The Eudragit-S was dispersed in distilled water and a specified concentration of ammonium hydroxide solution was added to the Eudragit dispersion with constant stirring to effect the partial neutralization of the polymer[55]. A dispersion of talc in distilled water was prepared separately using a high speed dispersator. The talc dispersion was slowly added to the polymer latex suspension with constant stirring, plastisizer was added and the latex dispersion was thoroughly mixed. Table III and IV. show the coating solution formulation components for seal coating and immediate release coating respectively.

7.2 Preparation of Immediate Release Coating Solution

The coating solution for immediate release portion was prepared as follows. Hydroxypropylmethyl cellulose was dispersed in distilled water that had been preheated to 75-80°C. The polymer solution thus formed was cooled to room temperature and a cold aqueous solution of albuterol sulfate was added and mixed thoroughly, finally plastisizer was added to this solution and mixed to obtain a homogeneous coating solution.

Table III. Coating Formula for Retarding Drug Release

Ingredients	%W/W
Eudragit S	12.00
Aqueous Ammonia Solution	6.10
Triethyl Citrate	6.00
Talc	4.00
Distilled Water qs	100.00

Total solids 22 %

Table IV. Coating Formula for Immediate Release Portion

Ingredients	%W/W
Albuterol Sulfate	1.54
HPMC E 5M	6.44
Polyethylene Glycol 400	2.76
Distilled Water Qs	100

Total solids 10.74%

7.3 Coating Procedure

A quantity equivalent to one kilogram (~ 7400 tablets) of tablet cores was placed in the conical coating vessel of the fluidized bed apparatus and preheated for 3 minutes at 40°C, the fluidizing air pressure was set to 10 in a scale of 11. The coating suspension was sprayed continuously at a rate of 15 grams per minute using a peristaltic pump.

For the coating applied using the Accela Cota, a quantity equivalent to seven kilograms of tablet cores(~ 51,000 tablets) was placed in the pan and preheated for 5 minutes at 40° C, the inlet and outlet temperatures were maintained at 55 ± 2°C and 35 ± 2°C. The pan was rotated at a speed of 12 RPM and coating suspension was sprayed continuously using a peristaltic pump at a rate of 36 grams per minute. The tablets were further coated with an immediate release portion containing 2 mg of albuterol per tablet. The tablets were dried for 30 minutes at 40°C at the end of the run in both the process.

8. Drug Release Studies for Developed Product

Drug release was studied using USP apparatus I and USP apparatus III. Six tablets were tested from each lot. The temperature of the dissolution medium was maintained at 37°C ± 0.5°C in all the dissolution experiments. For USP apparatus I were withdrawn automatically at appropriate interval samples with the help of a tris pump auto sampling unit. The quantity of albuterol dissolved was determined using a UV spectrophotometer at 226 nm[7]. Similarly, the USP apparatus III was programmed such that the tablets were allowed to dissolve for a specified time at the specified pH in each row for a total

period of twelve hours. At the end of the dissolution period a 5 ml sample was collected from each dissolution vessel with the help of a glass syringe fitted with 0.22 µm membrane filter and samples analyzed in HPLC.

IV RESULTS AND DISCUSSION

This section contains an evaluation of the experimental protocol and assay techniques used in this study and results thus obtained as well as a critical discussion and interpretation of these results. This section is divided into the following sections for easy reference by the reader.

A. Variability in the Marketed Albuterol Tablets

B. Evaluation of Various Formulations at Laboratory Scale

C. Scale-up of Core Formulation to Full Scale production

D. Evaluation of Coating Manufacturing Methods

E. Dissolution Studies

A. Variability in the Marketed Albuterol Tablets

Various physical characteristics of the Proventil tablets were studied in an attempt to determine the consistency in tablet weight, and content uniformity. It can be seen from the results in Table V that lot RDR-44 has the lowest coefficient of variation for average tablet weight. The variability in weight may be due to the uneven thickness of sugar coat which is less consistent than the film coating[54,55]. The in-vitro dissolution of these lots of Proventil tablets were studied at various pH's in order to determine the amount of drug released in the specified time interval. The results for the two USP apparatus are presented in Table VI and VII and in Figure 20-21 for USP apparatus I and III respectively. The results show that the drug release from the tablet core is faster in USP apparatus III after 5 hours and slower in apparatus I. The faster drug

Table V. Content Uniformity and Weight Variation Data for
Several Lots of Proventil Tablets

Lot #	RDR-244	RDR-44	RDR-254
% Albuterol recovered	99.90	102.3	103.5
Coefficient of variation	3.4	3.9	4.0
Avg wt	318.77	317.03	319.04
Coefficient of variation	5.0	4.5	6.26

Table VI. Dissolution for Various Lots of Proventil Tablets Using USP Apparatus I [a]

Medium pH	Time (min)	RDR-44	RDR-254	RDR-244
1.2	30	46.65 ± 3.72	53.52 ± 2.81	49.55 ± 3.53
	120	47.03 ± 3.07	54.93 ± 2.53	51.71 ± 3.74
4.7	210	48.54 ± 4.60	56.41 ± 1.90	55.83 ± 4.91
	300	48.54 ± 0.00	58.02 ± 4.11	60.20 ± 5.20
7.4	420	63.60 ± 14.46	83.60 ± 7.32	79.13 ± 9.87
	600	93.96 ± 10.23	99.11 ± 13.90	98.71 ± 15.32
	720	94.28 ± 9.24	105.42 ± 15.52	102.52 ± 10.75

[a] values indicate average percent release ± standard deviation (n=6)

Table VII. Dissolution for Various Lots of Proventil Tablets Using USP Apparatus III [a]

Medium pH	Time (min)	RDR-44	RDR-254	RDR-244
1.2	30	54.58 ± 2.40	50.35 ± 0.90	51.12 ± 4.10
	120	55.31 ± 2.53	50.98 ± 1.00	52.44 ± 4.50
4.7	240	55.31 ± 2.53	52.50 ± 3.71	55.41 ± 4.50
	360	62.34 ± 16.30	77.35 ± 25.17	86.88 ± 22.85
7.4	540	107.00 ± 2.92	102.60 ± 2.70	105.59 ± 3.40
	720	108.00 ± 2.72	102.95 ± 3.75	106.95 ± 2.78

[a] values indicate average percent released ± standard deviation (n=6)

Figure 20. Dissolution for Various Lots of Proventil Tablets USP Apparatus I
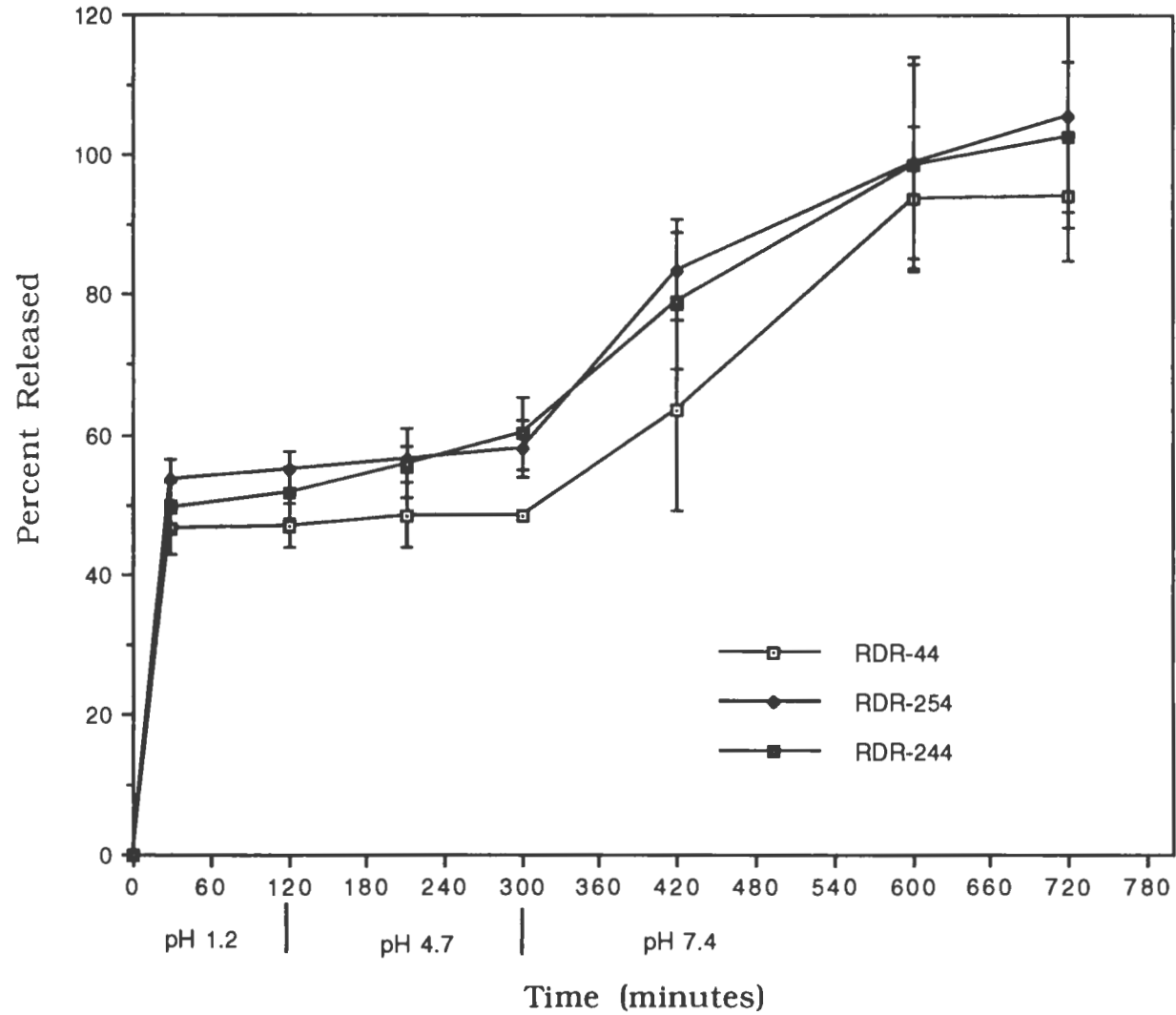
Figure 21. Dissolution for Various lots of Proventil Tablets USP apparatus III

pH 1.2   pH 4.7   pH 7.4

Time (minutes)

Percent Released

RDR-44
RDR-254
RDR-244
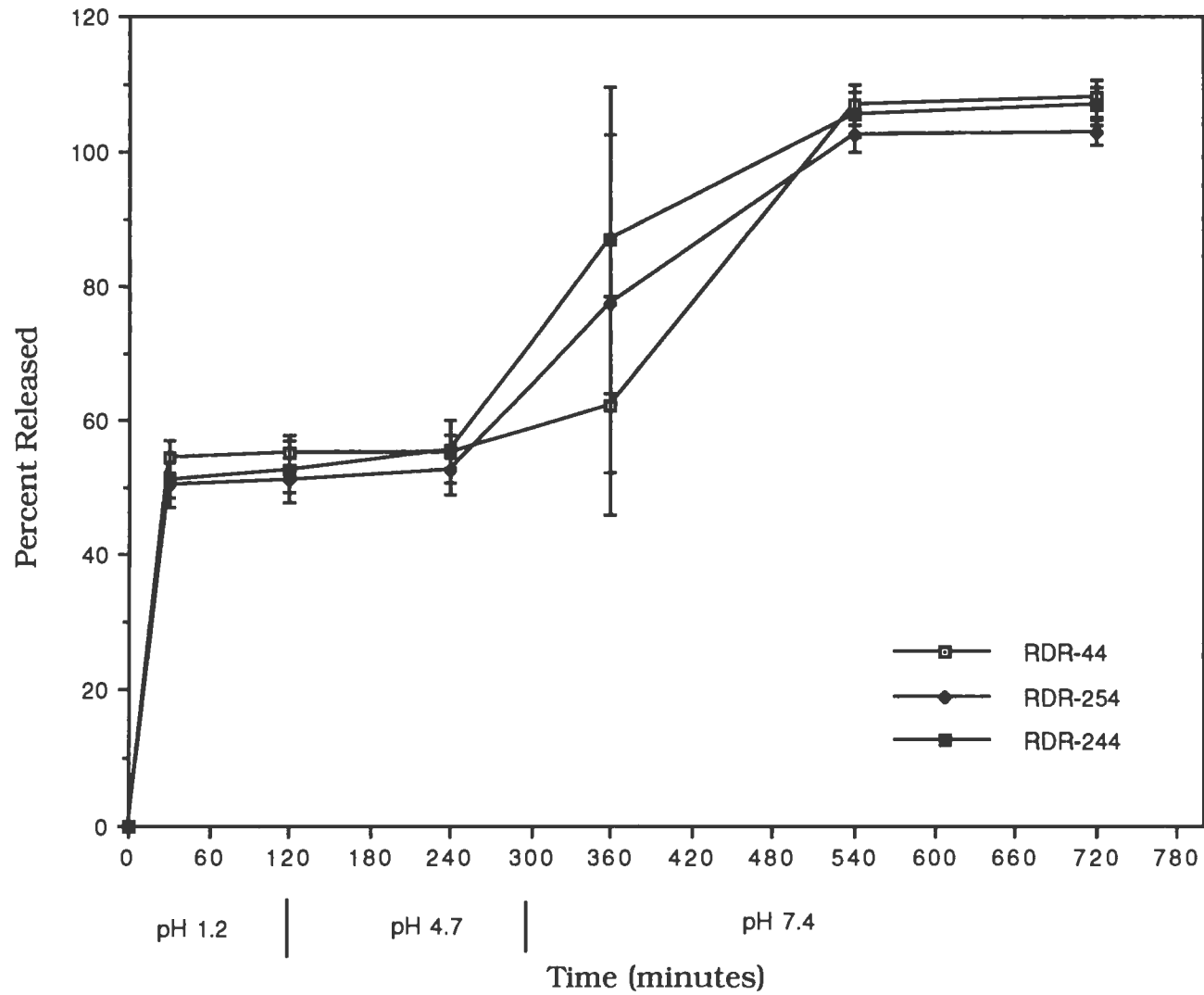
release may be due to the higher agitation rate in the apparatus III[53]. A significant difference in average percent release was observed between various lots of Proventil tablets independent of the dissolution method used for testing. Table VIII shows the ANOVA test results for various lots of Proventil tablets. A significant difference in the mean drug release of the immediate release portion was observed at 30 minutes and also difference in mean drug release was observed in the extended release portion at 360 minutes between RDR-44, RDR-254 and RDR-244. The variability in the drug release from a coated core tablet can be attributed to various factors such as coating thickness[44,47], solubility of coating material, diffusion of drug through the coating layer and aging of the coating material[55,56]. In this formulation the variability may be due to the coating thickness and the aging of the retardant coating material.

B. Evaluation of Various Formulations at Laboratory Scale

1. Design of Core Tablets

Based upon the above findings, a synthetic polymer with well defined release characteristics, which is soluble at pH higher than 6.8 was selected to seal coat the core tablets of the experimental formulation. An aqueous film coating technique was used to coat both core and the immediate release portion.

In an attempt to match the drug release observed in the extended release portion of Proventil repetabs, various core formulations were made by directly compressing powder blends with different proportions of starch, lactose and hydroxypropylmethylcellulose plus albuterol sulfate (see Table IX),

65

Table VIII. ANOVA Test Results for Average Percent Release at Various Sampling time for Proventil Tablets [a]

Time (min)	RDR-44	RDR-244	RDR-254
30	+	+	+
360	+	+	+
720			

+ indicates a significant difference in the mean percent release between lots

The observed F value is compared to the theoretical F at a 95% confidence

df = 2 for treatments and 18 for error at all time points

[a]USP Apparatus III

Table IX. Formulation Component Concentrations for 2 mg Albuterol Tablet Cores

Ingredients	Lot of Tablet Core (mg)		
	46A	46B	46C
Starch 1500	22.60	22.60	13.50
Lactose DT	67.50	71.55	80.65
HPMC	45.00	36.45	36.45

Each formulation contains Albuterol Sulfate 2.4 mg.
Magnesium stearate and silicon dioxide 1 mg each.

to obtain a tablet core that would exibit a near zero order releases for a period of 5 to 6 hours.

The effect of the soluble components on the drug release was studied to determine the optimum concentration of these excipients necessary to obtain the desired drug release profile. The dissolution results obtained from various formulations are shown in Table X and Figure 22. It can be seen that drug release from formulation 46A with the highest concentration of hydroxypropylmethylcellulose and a low concentration of soluble excipients is fastest. Conversely, formulation 46C with a higher concentration of the soluble excipients and lower concentration of polymer shows slower drug release. Formulation 46B was found to release about 25 percent in the first 30 minutes followed by approximately 15 percent every hour with 100 percent of the drug is released in 5-6 hours.

Therefore, it can be seen that drug release was significantly altered by varying the concentration of lactose in a formulation containing hydroxypropylmethycellulose. The formulation containing 48 percent lactose releases the drug faster and one with 59 percent releases slower. This difference in release is due to the fact that polymer hydration is effected by increasing the concentration of soluble excipients[57,59].

The physical characteristics of the tablets were evaluated for all the formulations. The bulk density data in Table XI show that formulation 46B has better consolidation and flow compare to 46A and 46C. Though formulation 46C has bulk properties similar to that of 46B, it was not selected because of its slower drug release. The friability of formulation 46B was slightly less (< 0.005 percent) compared to the other two formulations and the hardness ranged from 7-8 kilopascals. Thus

Table X. Dissolution of Various Core Tablet Formulations Using the USP Apparatus I [a]

Time (min)	46 A	46 B	46 C
30	26.05 ± 1.90	26.75 ± 0.60	23.81 ± 0.63
120	65.50 ± 2.01	55.93 ± 1.10	50.99 ± 0.80
180	82.03 ± 2.00	69.72 ± 1.20	65.08 ± 1.30
240	92.30 ± 2.10	81.21 ± 1.30	77.77 ± 0.70
360	102.10 ± 1.70	98.01 ± 1.30	92.84 ± 0.90
480	103.10 ± 1.73	102.20 ± 1.50	99.98 ± 1.00

[a] n=6, values indicate average percent release ± standard deviation.

**Figure 22. Effect of Formulation Component Concentration on
Drug Release Using USP Apparatus I**
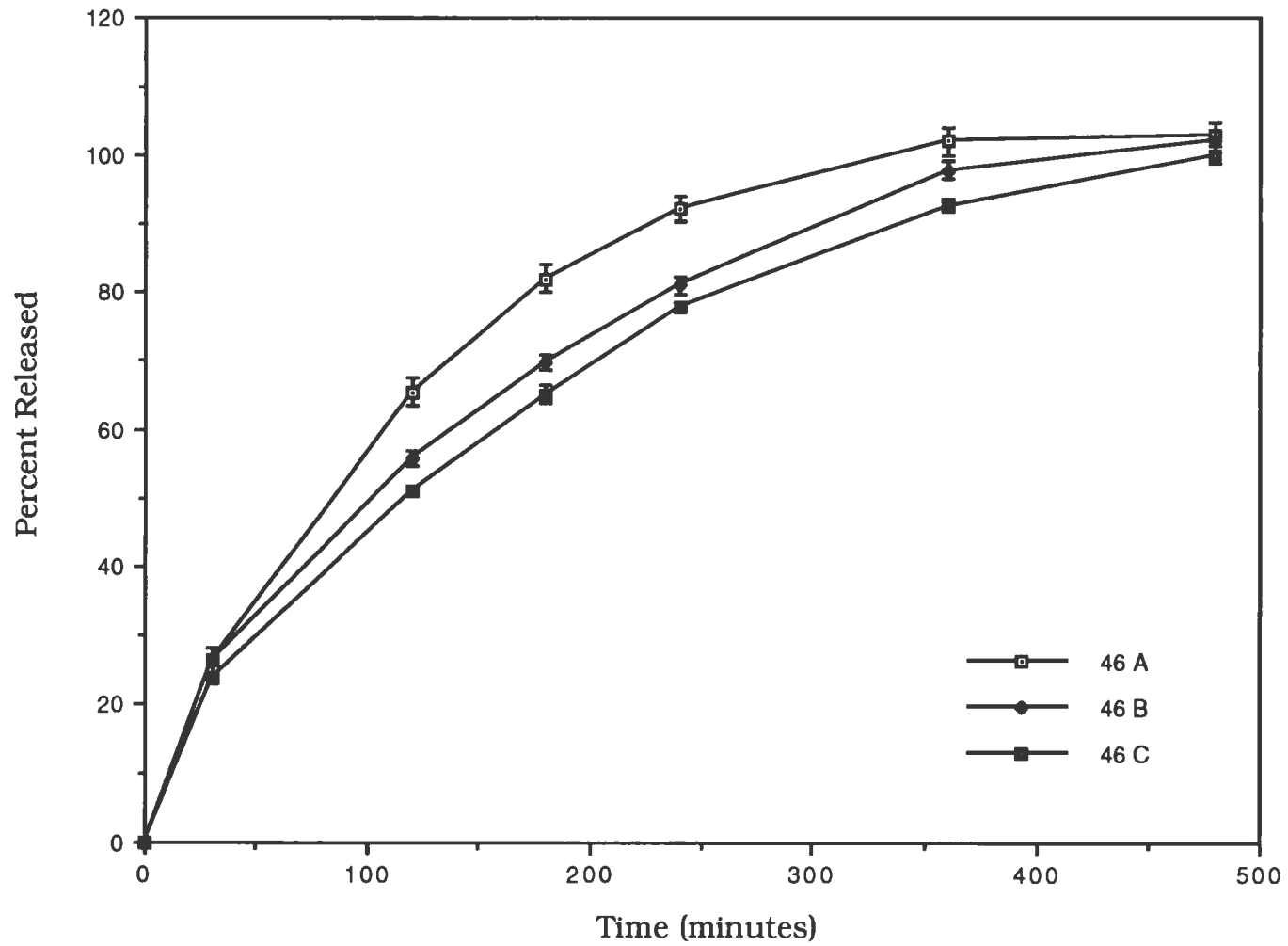
Table XI. Bulk Density Data for Various Lot of Core Tablet
Formulation Blends

| Bulk Density (gm/cm^3) | Lot # | | |
	46A	46B	46C
Bulk Density Poured	0.663	0.598	0.614
Bulk Density Tapped	0.819	0.722	0.737
Compressibility	19.01	17.17	16.68
Hausner Ratio	1.23	1.20	1.19
Repose Angle (Θ)	32$^{\text{o}}$	28$^{\text{o}}$	28$^{\text{o}}$

formulation 46B was selected as the final formulation for further experiments and scale-up.

2. Evaluation of Physical Characteristics of Core Tablets

Parameters such as weight variation, hardness, thickness and friability must lie within an acceptable range for the tablets to be useful in providing the desired drug release and product characteristics. In addition, since these tablets would be coated for protection and to control drug release; it is important that the tablets withstand the physical stress encountered during the coating process[39,42,45]. Therefore, it is necessary to evaluate the physical characteristics of randomly selected tablets cores from each batch. After selecting formulation 46B as the final formulation a series of tablet lots (100,000 tablets) were made to evaluate the physical characteristics of these tablets under production conditions. Table XII shows the results obtained from these lots. The hardness falls within the expected range of 7 to 8 kpa for all the lots. Friability was found to be less than 0.005 percent. All of the test batches passed the official testing for physical characterization of tablets as described in USP XXII.

C. Scale-up of Core Formulation to Full Scale Production

After selection of 46B as final core formulation for scale-up, a series of formulations were made while varying the total blending time to re-determine the optimum blending time needed for the large scale production. The results obtained for physical characterization and content uniformity of these formulations are shown in Table XIII. It is quite evident from the results of physical characterization of tablet that

Table XII. Physical Characteristics of Various Lots of Formulation 46 B Tablet Cores

Lot#	Weight (mg) ± sd	Thickness(in) ± sd	Hardness (kpa) ± sd	Friability %*
79A	136.2 ± 1.6	0.1366 ± 0.0005	8.35 ± 0.31	0.005
79B	134.9 ± 0.5	0.1374 ± 0.0003	7.83 ± 0.45	0.000
130 A	135.2 ± 0.5	0.1367 ± 0.0001	7.50 ± 0.32	0.003
130 B	134.9 ± 0.7	0.1389 ± 0.0001	7.79 ± 0.50	0.001

* n=20, 25 RPM for 4 minutes.

Table XIII. Evaluation of Blending Time for Formulation 46 B Using the V-blender [a]

Lot#	32 A	32 B	32 C	32 D	32 E
Mix Time (min)	30	45	55	65	75
Albuterol % Rec	98.99	99.98	99.50	100.95	99.97
Coeffecient of variation	4.9	2.5	1.6	1.9	1.7
Avg wt mg	133.8 ± 6.5	134.2 ± 3.4	134.1 ± 2.5	134.0 ± 2.7	134.1 ± 2.7
Hardness (kpa)	7.20 ± 2.05	8.30 ± 1.34	7.72 ± 1.04	8.5 ± 1.59	8.9 ± 1.61
Thickness (in)	0.1394 ± 0.0024	0.1363 ± 0.0012	0.1362 ± 0.0011	0.1363 ± 0.0012	0.1362 ± 0.0013
Friability %	2.13	1.5	0.005	0.001	0.003

[a] values indicated are average of ten determinations ± standard deviation

the blending time has a significant effect on the content uniformity and weight variation of the tablets. Tablets made with a total blending time of 30 minutes are softer, and friability was greater than 2 percent. Variability in weight and uniformity in drug content between tablets was found to be larger with drug release (see Table XIII) faster than the other lots with increased blending time. By increasing the total blending time the variability in content uniformity and weight was reduced and consistent drug release was observed. However, tablets made with a blending time above 55 minutes showed no significant improvement in content uniformity or weight variation than those lots with longer blending times. The friability of these tablets were less than 0.05 percent which signifies that they can withstand the physical stress applied during the coating processes. Thus the optimum blending time was selected as 55 minutes.

The final large scale production batch was made with a total blending time of fifty five minutes and a hardness of 7 to 8 kpa. No significant difference in mean drug release was observed between tablets made on a laboratory scale and production scale when tested using USP apparatus I and III. This shows that the formulation and the processing method developed was reproducible. The dissolution results of the various formulations produced in the large scale production with a total blending time of 55 minutes are presented in Table XIV and Figure 23.

D. Evaluation of Coating Methods
Seal Coating

Tables XV and XVI show the weight variation and percent solid recovery results obtained for various lots of tablet cores coated in

Table XIV. Dissolution for Various Lots of Albuterol Tablet Cores Using USP Apparatus III [a]

Time (min)	079 A	079 B	130 A	130 B
60	37.55 ± 0.07	36.12 ± 0.27	35.90 ± 1.00	36.10 ± 0.68
120	56.96 ± 0.29	55.77 ± 0.35	54.71 ± 0.56	54.58 ± 0.62
180	72.36 ± 0.50	70.92 ± 0.16	69.50 ± 0.21	69.47 ± 0.59
240	83.64 ± 0.37	82.33 ± 0.17	81.00 ± 0.34	80.66 ± 0.40
300	91.09 ± 0.90	89.91 ± 0.31	88.69 ± 0.69	88.38 ± 0.40
360	95.83 ± 0.50	94.26 ± 0.29	93.05 ± 0.85	93.16 ± 1.00

[a] Each tablet contains 2 mg of albuterol (n=6) values indicate average
percent release ± standard deviation

Figure 23. Dissolution Profiles for Final Formulation of Albuterol Core Tablets
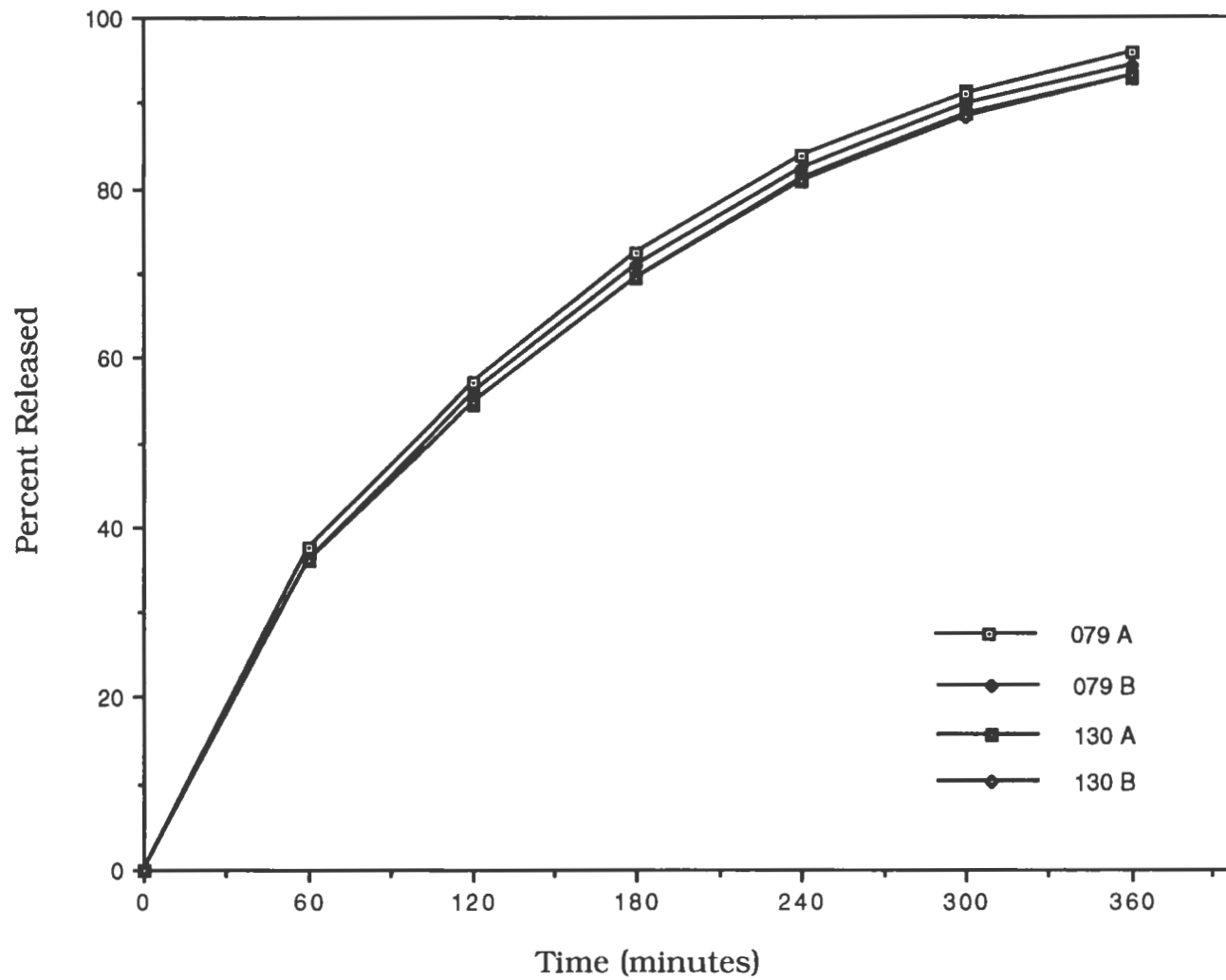
Table XV. Evaluation of Coating Efficiency of the Eudragit-S Coating
Using the Accela-cota

Lot #	Weight (mg)	Coefficient of variation	Percent solid coated	Percent recovered
79 A	147.10	1.00	7.60	90.93
79 B	145.78	1.25	8.00	90.62
130 A	150.40	1.13	10.90	87.75
130 B	152.70	1.37	12.50	89.35

n=10 for all determinations

Table XVI. Evaluation of Coating Efficiency for the Immediate release
Coating Using the Accela-cota

Lot #	Weight (mg)	Coefficient of variation	Percent solid coated	Percent recovered
79 A	154.50	1.00	4.80	66.00
79 B	152.03	1.04	4.30	68.00
130 A	159.80	1.50	5.63	61.00
130 B	161.50	1.09	5.85	62.00

n=10 for all determinations

Accela-cota for both the Eudragit-S seal coating and the Immediate release coating. A series of different flow rates were tested and an optimum flow rate with uniform spray was found to be 36 grams per minute for the seal coating and 20 grams per minute for the immediate release coating. A 0.8 mm spray nozzle was used initially for spraying the seal coating suspension. However, a potential problem of clogging of the spray nozzle was observed during the coating process. This problem was eliminated by replacing the 0.8 mm spray nozzle with 1 mm spray nozzle. It can be seen from the results in Table XV that the average weight of the tablets coated with the aqueous latex dispersion of Eudragit-S are uniform and consistent with a small and insignificant coefficient of variation (1 to 1.5 percent). The low variability in the average tablet weight between lots is due to the difference in the coating thickness of the polymer applied for seal coating. In addition Table XVI shows that the variability in average tablet weight for immediate release coating is also very small. Since 2 mg of drug is coated onto each tablet, high variability in the uniformity of coating would have a significant effect on the dose of drug delivered for immediate release. The efficiency of the coating process was determined by calculating the percent recovery of the total solids coated onto the tablet cores. Table XV shows that about 88 to 90 percent of the solids sprayed were recovered. It has been reported that percent recovery can be increased by adjusting parameters such as air pressure, spray nozzle size and decreasing the spray to bed distance[39,40]. The processing parameters used for applying the seal coat using the Accela-cota is presented in Table XVII. After these processing parameters were determined the optimum coating thickness necessary to seal the core tablets and retard drug release for a period of 4 to 5 hours was

Table XVII. Processing Parameters for Accela-cota 24" for Seal Coating and Immediate Release Coating

Pan Speed	12 RPM
Pan Charge	9 Kg
Pump	Peristaltic
Avg. weight of Tablet	134.6 mg
Flow rate[‡]	35 gms/min.
Inlet Temperature[*]	$53^{o} \pm 2^{o}C$
Out let Temperature[†]	$36^{o} \pm 2^{o}C$
Nozzle Opening	0.8 mm
Atomizing air pressure	25 psi
Spray Type	Continuous
Inlet air opening	70%

Immediate Release coating
[‡] 20 grams /min
[*] $62 \pm 2^{o}C$
[†] $42 \pm 2^{o}C$

determined by coating selected lots of tablet cores with three different concentration of Eudragit-S latex dispersion. Table XVIII and Figure 24. show the dissolution results for these three different formulations. The tablets coated with 4 percent polymer releases the second dose earlier than the 6 and 8 percent level of coating. However, no significant difference in retarding drug release was observed by increasing the concentration of polymer from 6 to 8 percent. It is evident from the results that the retardation of drug release from the extended release portion can be changed by varying the coating thickness. The results show that the concentration of polymer required to delay the drug release from 5-6 hours requires at least a 6 percent of polymer coating.

Immediate Release Coating

The uniformity and consistency of the coating for immediate release portion is critical. Since only 2 mg of the active drug is coated over each tablet core, a slight deviation in the applied coating may cause significant variability in the dose delivered. For this reason many authors have suggested using air-less atomization for applying low dose coating solutions[60,61] due to minimum loss of coating solids during this type of spray process. The resultant drug release obtained from tablets coated using the Accela-cota shows that a uniform coating could be achieved using air atomized spray coating. It was determined that as low as 2 mg of active drug per tablet could be delivered consistently. However, if we compare the percent recovery results obtained for the Eudragit-S seal coating which is approximately 90 percent followed by the immediate release coating (68 percent), the efficiency of immediate release coating is low. This may be due to the low concentration of solids in the immediate

Table XVIII. Dissolution for Various Concentration of Eudragit-S coating [a]

pH of medium	Time (min)	Concentration of Eudragit-S Coating		
		4% polymer	6% polymer	8% polymer
1.2	30	49.06 ± 2.52	51.68 ± 2.21	51.47 ± 3.19
	120	52.73 ± 1.81	52.00 ± 1.13	51.99± 2.14
4.7	240	64.33 ± 1.93	52.00 ± 0.00	51.99± 0.00
	360	79.37 ± 1.40	52.00 ± 0.00	51.99± 0.00
7.4	540	101.49 ± 1.82	82.62 ± 2.23	82.11 ± 1.08
	720	103.89 ± 1.70	100.69 ± 1.56	99.01 ± 2.63

[a] Equipment - Accela-cota, values represent average percent release
± standard deviation (n=6)

Figure 24. Effect of Various Concentrations of Eudragit-S Coating on Drug Release Using USP Apparatus III
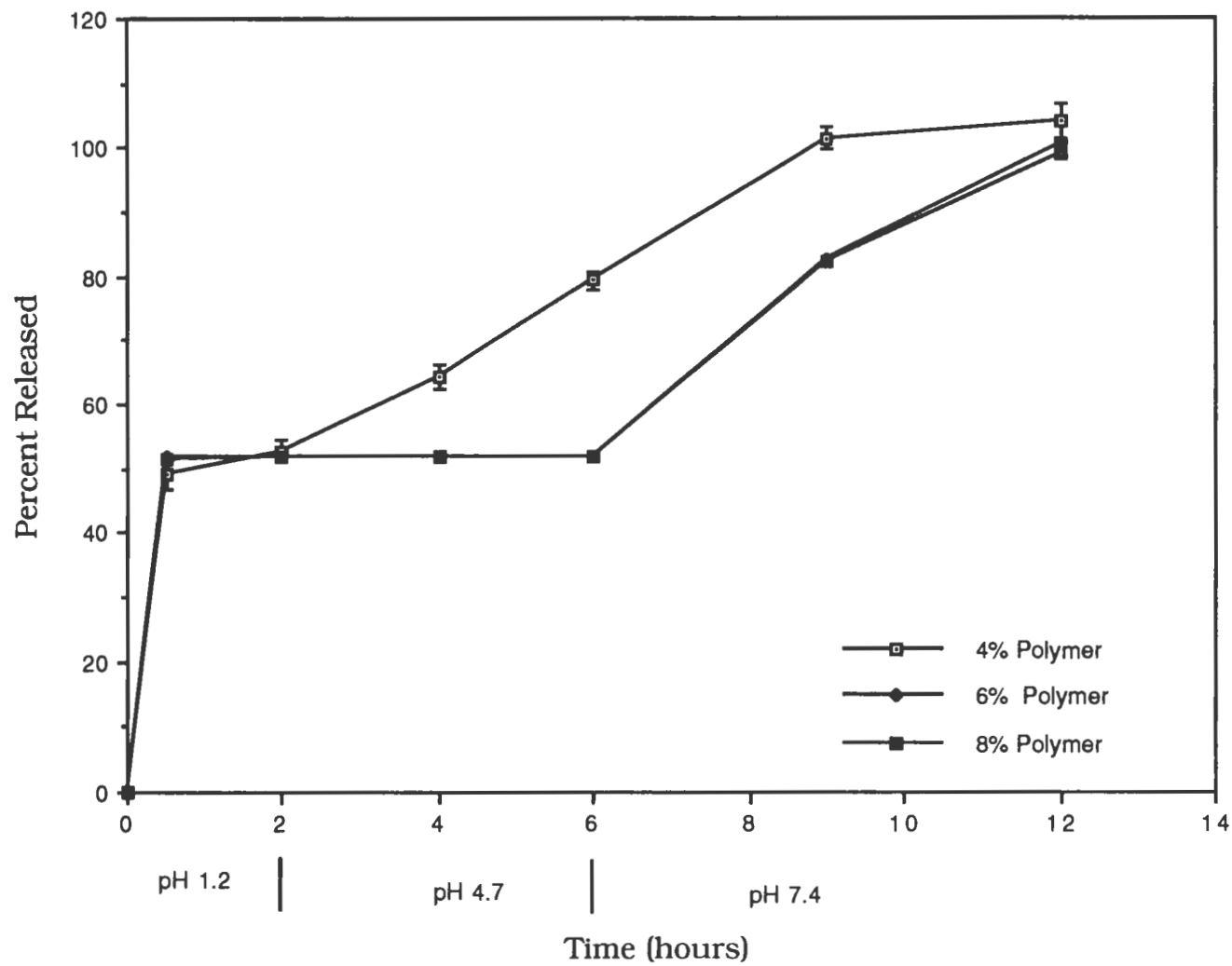
release coating solution. The literature suggests that the percent recovery may be increased by adding inert solids to the coating solution and by reducing the atomization air pressure[61,62]. This approach seems reasonable and was tried in fluidized bed coating which is discussed below. The Accela-cota was not tested for this process due to time constraints

The results obtained from coating tablets using the fluidized bed coating apparatus (Aeromatic STREA I) for Eudragit-S seal coat and immediate release portion are presented in Table XIX and XX respectively. While literature generally considers the fluidized coating process to be efficient and consistent in coating granules and tablets[41,42], our results and observations show that this equipment is less efficient than Accela-cota in providing a uniform coating for tablets. The coefficient of variation of the average tablet weight for immediate release coating using fluidized bed coating was high (2 to 3 percent) compare to the Accela-cota (1 to 1.5 percent). The efficiency of immediate release coating was also found to be poor using fluid bed process with only about 45 percent of the solids recovered and the processing time extending to twice that of the Accela-cota. Addition of three percent talc to the coating solution increased the percent recovery to approximately 75 percent. However, further studies on improving the coating efficiency were not conducted due to time constraints. Hence it was not possible to evaluate this process completely. The optimum coating parameters for the Aeromatic STREA I is shown in Table XXI.

Table XIX. Coating Efficiency ot the Eudragit-S Coating Using the
Aeromatic Apparatus

Lot #	Weight (mg)	Coefficient of variation	Percent solid coated	Percent recovered
46 A	151.50	1.32	7.80	91.59
46 B	150.88	3.04	7.41	90.38
46 C	152.70	2.00	7.56	89.92

n=10 for all determinations

Table XX. Evaluation of Coating Efficiency for the Immediate Release Coating Using the Aeromatic Apparatus

Lot #	Weight (mg)	Coefficient of variation	Percent solid coated	Percent recovered
46 A	165.90	2.27	10.16	46.15
46 B	162.29	2.26	9.46	45.13
46 C	167.13	2.77	9.79	74.02

n=10 for all determinations

Table XXI. Processing Parameters for Fluidized Bed Coating
(Aeromatic STREA I)

Pump	Peristaltic
Spray rate[‡]	25 grams/min
Quantity Coated	1 Kg
Wurster size	9 inch
Atomizing air	27 psi
Drying Temperature[*]	$50^{o}C$
Outlet Temperature[†]	$35^{o}C$
Nozzle Opening	1 mm
Spray method	Continuous
Bottom Plate Opening	4%
Fan Speed	11 in a 11 scale
Exhaust	100%
Blow back Pressure	15 Psi
Blow back cycle	15 sec

Processing Conditions for Immediate Release Coating

[‡] 15 grams/ min

[*] $60^{o} \pm 1^{o}C$

[†] $40^{o} \pm 1^{o}C$

E. Dissolution Studies

The Accela-cota was used to apply the seal coat and the immediate release coating. Tables XXII-XXIII and Figure 25 show the dissolution results for the final coated formulations as determined using USP apparatus I and III respectively. Since the total drug concentration was well below the saturation solubility, it was possible to maintain sink conditions for both of the dissolution apparatuses. The number of sampling intervals were limited in case of USP apparatus III due to the limited capacity of that instrument. The drug release is uniform and consistent for all the experimental formulations tested in both of the dissolution apparatuses. While drug release was slightly faster in USP apparatus III than that found in apparatus I, the difference was not significant at $P<0.05$ level. Interestingly, data presented earlier in this thesis showed significant differences in the mean percent released between various lots of Proventil tablets using USP apparatus I and III (see Figure 20-21).

The in-vitro drug release of the marketed product is highly variable, this in turn may be expected to have a significant effect on the in-vivo bioavailability. The drug release from the experimental tablets was found to be consistent with rapid release of the initial 2 mg of drug followed by a near zero order release of the second dose of 2 mg for period of 5-6 hours that was seen for the Proventil tablets. This second interval of drug release indicates that a steady state plasma level should be maintained. While the in-vitro drug release profiles of the experimental tablets are comparable to the marketed product and exhibit significantly less variability in drug release further clinical investigation

Table XXII. Dissolution of Albuterol Tablets Using USP Apparatus I [a]

pH of medium	Time (minutes)	Experimental Lots			
		79A	79B	130A	130B
1.2	30	49.8 ± 2.00	49.45 ± 1.90	46.59 ± 3.71	46.30 ± 2.70
	120	52.7 ± 2.00	49.76 ± 1.90	49.42 ± 2.16	47. 01 ± 2.15
4.7	180	53.8 ± 1.53	49.76 ± 1.90	49.42 ± 0.16	47. 01 ± 2.15
	240	60.7 ± 1.72	49.76 ± 1.90	49.42 ± 0.16	47. 01 ± 2.15
7.4	300	74.0 ± 2.07	64.42 ± 2.01	63.07 ± 2.25	63.05 ± 1.87
	480	84.9 ± 2.59	72.59 ± 1.13	71.45 ± 1.17	70.57 ± 1.35
	600	91.8 ± 2.01	90. 86 ± 1.02	88.32 ± 2.25	86.13 ± 2.30
	720	97.0 ± 1.5	103.36 ± 1.5	94.48 ± 2.50	92.93 ± 1.97

[a] Average percent release of six tablets ± standard deviation

Table XXIII. Dissolution of Albuterol Tablets Using USP Apparatus III [a]

pH of medium	Time (min)	Experimental Lots			
		79 A	79 B	130 A	130 B
1.2	30	47.71 ± 1.38	51.26 ± 2.00	51.09 ± 3.71	51.48 ± 3.72
	120	51.42 ± 2.05	51.26 ± 2.00	51.10 ± 4.00	52.00 ± 3.76
4.7	210	62.72 ± 3.65	51.26 ± 2.00	51.10 ± 0.00	52.00 ± 0.76
	300	77.38 ± 4.45	51.26 ± 2.00	51.10 ± 0.00	52.00 ± 0.76
7.4	510	98.96 ± 2.18	84.12 ± 1.53	80. 32 ± 2.72	82.13 ± 2.50
	720	101.68 ± 2.08	100.00 ± 1.32	98.40 ± 1.53	98.75 ± 1.71

[a] Average percent release of six tablets ± standard deviation

Figure 25. Comparision of Dissolution Profiles for Different Lots of Albuterol Tablets Using USP Apparatus I and III
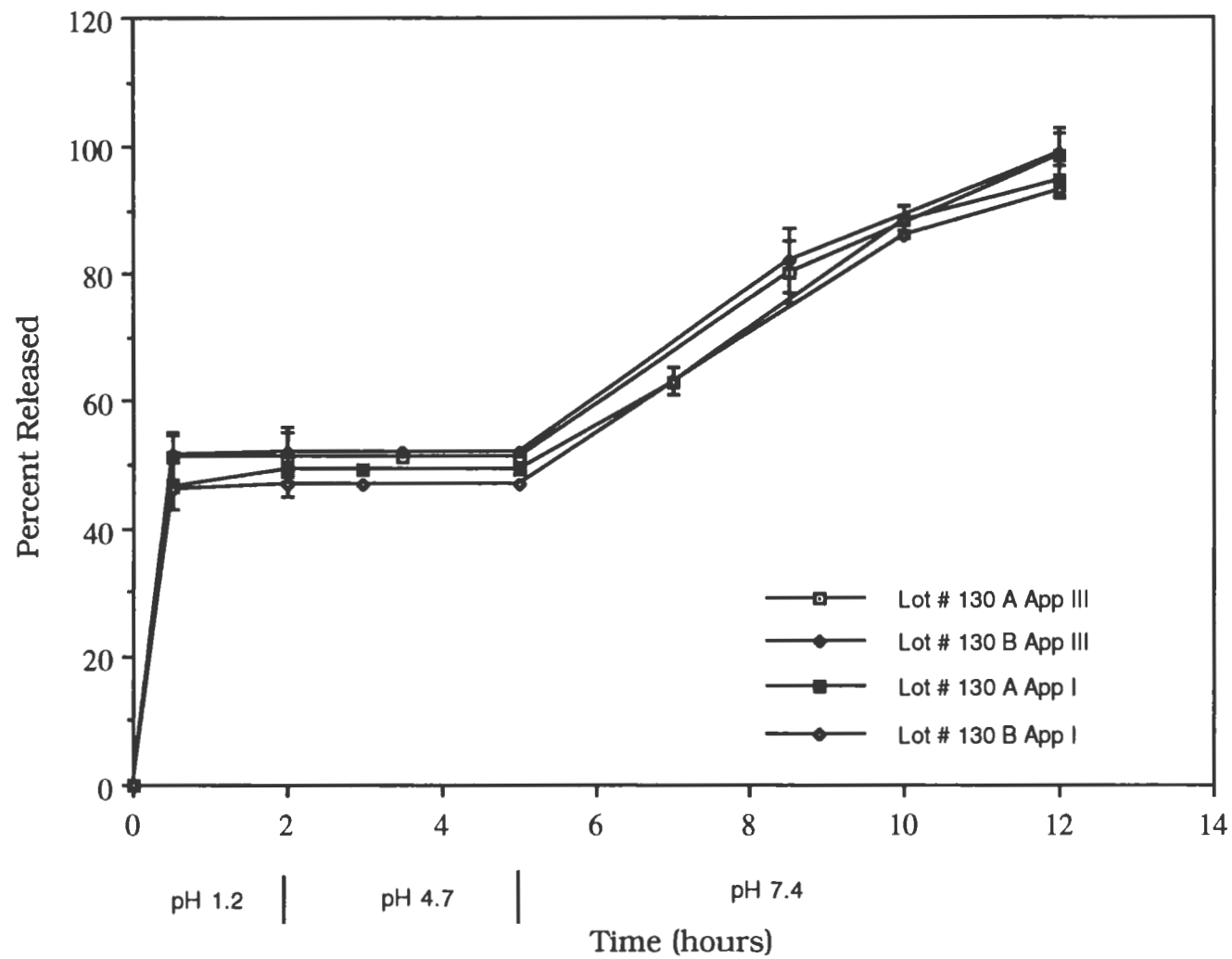
of the in-vivo drug release are needed before a final comparision of bioequivalence can be determined.

V CONCLUSIONS

1. In-vitro dissolution studies of the marketed repeat-action product showed significant differences in mean drug release between various lots.

2. A sensitive, reliable and reproducible UV assay method was developed for quantitation of albuterol. Comparison of this UV method to a stability indicating HPLC assay method shows both assays to be equivalent for the experimental formulations and allowed use of the less labor intensive UV method throughout this study.

3. A core tablet formulation was developed in the laboratory and successfully scaled-up to the production size batch level. The optimum blending time to prepare uniform distribution of drug and weight for large scale production was determined. Optimum concentrations of the tablet excipients necessary to obtain the desired drug release profile were determined.

4. The optimum concentration of a safe aqueous solvated polymer which provided a seal coating and retarded drug release for a period of 5 to 6 hours was determined.

5. The optimum coating parameters for the immediate release coating using an aqueous polymer solution was determined. Two different manufacturing methods, the Accela-cota and the Areomatic fluid bed coating, were compared and their coating efficiency evaluated. The Accela-cota was found to be more efficient than the fluid bed coating

process for applying the immediate release portion. However, the seal coat can be applied either of the two apparatus, But the Accela-cota is preferred due to its larger production capacity.

6. The dissolution profiles obtained for the experimental formulations using the USP apparatuses I and III were found to be comparable. The drug release profiles for the experimental formulations were not significantly affected by the different dissolution methods and found to be uniform, consistent and reproducible.

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