CHAPTER I
INTRODUCTION

With the growing epidemic of Acquired Immune Deficiency Syndrome (AIDS) in developing countries, it is essential that low-cost, disease-combative, drug-formulations are made available to HIV-infected patients. Stavudine is one nucleoside reverse transcriptase inhibitors (NRTIs) which is effective for treatment against HIV. However, since mono-therapy with NRTIs results in rapid development of resistant HIV strains, co-administration of other anti-retroviral drugs is necessary (Zheng et al., 2001).

Concerning infected patients must take combination of anti-retroviral drugs for a long time and at present stavudine is only in the dosage form of immediate release, therefore the development of oral stavudine controlled-release was aimed to reduce dosing frequency, reduce amount of tablets or capsules taken each time, thereby improving patient compliance and therapeutic efficacy. In addition, the reproducibility of the drug blood level, unlike in conventional dosage form, leads to a minimization of drug related side effects. (Bechgard and Hegermann Nielsen, 1978; Eskilson, 1985)

The controlled-release dosage forms have been developed and categorized into single unit dosage forms and multiple unit dosage forms. Multiple unit dosage form referred to as pellet offers not only therapeutic advantages such as less irritation of the gastro-intestinal tract and a lowered risk of side effects due to dose dumping (Bechgaard and Hegermann Nielsen, 1978), but also technological advantages, for example, better flow properties, less friable dosage form, narrow particle size distribution, ease of coating and uniform packing (Reynold, 1970).

Although the pellets can be manufactured by many techniques, in this study, the stavudine pellets were prepared by the extrusion and spheronization process because of its ease of operation, low wastage and narrower particle size distribution (Rajesh Gandhi et al., 1999). This study also investigated the effect of spheronizer speed and spheronization time on the appearance and physical properties of pellets. The best formulation and preparing conditions to obtained satisfied pellets were chosen to produce controlled release pellets.

One of the most widely used water-insoluble polymer in pharmaceutical film coating is ethylcellulose, due to its convenient film formability, good physiochemical properties, flexible coating, minimum toxicity (Porter, 1989 ; Iyer et al., 1993) While ethylcellulose was initially used in organic solvent-based solutions, the application of water-based dispersions of ethylcellulose is common place in pharmaceutical industry and is the method of choice for film coating. In this study, polymer mixtures of ethylcellulose aqueous dispersion (Surelease®) and water-soluble polymer as hydroxypropyl methylcellulose (HPMC E15LV), were used to modify drug release. Core pellets were coated with various ratios of Surelease® and HPMC E15LV. The ratio of ethylcellulose to HPMC in coating solution, release rate and mechanism of drug release were investigated. The formulation of coated pellets showing good dissolution release profile would be selected to study in animals.

According to stavudine controlled release dosage form (Zerit® XR) is a new drug and it is still under clinical trial studies, therefore Zerit® XR 100 mg cannot be found in the market. This experiment compared the plasma pharmacokinetics profiles in rabbits given Zerit® IR and stavudine pellets in the same dose of 100 mg. The open, randomized, crossover, two treatments study was performed in twelve white New Zealand rabbits under fasting conditions with at least two weeks of drug free washout period between the two treatments. The pharmacokinetic parameters were evaluated and compared with the previous studies.

Since the suitable analytical methods are important for quality control and determination of product, therefore, this study described the development and validation of HPLC analytical methods both in vitro and in vivo studies. Zerit® IR and stavudine pellets were also placed in the stability test to ensure that both products could keep quality all along the storage period.

The results from this experiment were expected to provide a useful database for the future research, as well as, insight into the application of this research to develop product controlled release and study pharmacokinetic parameters in human.

OBJECTIVES

The objectives of this research were ;

1. To prepare stavudine pellets using extrusion and spheronization process.

2. To study the influence of spheronizer speed, spheronization time on the appearance and physical properties of stavudine pellets using extrusion and spheronization process.

3. To study the influence of amount of ethylcellulose aqueous dispersion and hydroxypropylmethylcellulose in the film coat solution on drug release from film coated pellets.

4. To determine the optimal ratio of ethylcellulose and HPMC in coating solution which exhibits a satisfactory in vitro release pattern.

5. To compare pharmacokinetic parameters of stavudine obtained from Zerit® IR and stavudine pellets in the rabbits.

Literature Reviews

Control-Release Single-Unit and Multi-Unit dosage forms

The single-unit dosage forms with controlled release have usually been known as tablets, either matrix tablets or coated tablets, which do not disintegrate in the gastro-intestinal tract. The solid oral dosage forms which consist of many mimi-depots e.g. pellets or microencapsulated crystals contained in a capsule or a tablet are called as the multi-unit dosage forms. Multi-unit dosage forms can disintegrate or disperse into a large number of subunits and spread through the gastro-intestinal tract. They show several highly important advantages as compared to single-unit dosage forms. The small particles are mixed with the contents of the stomach and intestine and distributed over a larger area. Thus high local concentrations of the drug are avoided and the risk of undesired side effects is reduced (Lehmann, 1994). The particles should be smaller than approximately 2 mm to be transported continuously together with the food contents through the digestive tract so that the quality, amount and timing of food in take as well as movement and relaxation time of the body is of minor influence on the drug release. They also can maximize drug absorption and can prevent dose-dumping, which may be more likely to occur when a single-unit controlled release system is used (Rekhi, 1989 ; Ghebre-Sellassie, 1985). Therefore, inter- and intra-individual variations of bioavailability are reduced and more constant blood levels of the drug can be achieved (Lehmann, 1994 ; Flament, 1994).

The summary of definitions, characteristics and examples of single-unit and multi-unit dosage forms was shown in Table 1.

Table 1 The summary of single-unit and multi-units dosage forms (Bechgarrd, 1978)

SINGLE-UNIT DOSAGE FORMS	MULTI-UNIT DOSAGE FORMS
Definitions	
• Oral pharmaceutical formulation consisting of one undisintegrated through the stomach.	• Oral pharmaceutical formulation consisting of a unit which disintegrates in the stomach into a large number of sub-units.
Characteristics	
• Transport dependent on gastric emptying. • Transport strongly influenced by intestinal motility and transit time of food. - Varying rate and extent of bioavailability. - Risk of accumulation of doses. - Risk of high local drug concentrations. - Risk of local irritation. • Tablets were non-dividable	• Transport virtually independent of gastric emptying. • Transport only moderately affected by intestinal motility and transit time of food. - Reproducible bioavailability - No risk of accumulation of doses and its consequences. • Tablets were dividable
Examples	
• Enteric-coated tablets passing undisintegrated through the stomach • Timed-release coated tablets, matrix tablets, etc. passing through the entire alimentary canal.	• Capsules containing hundreds of pellets or thousands of crystals individually coated (enteric or timed-release) being dispersed upon disintegration. • Tablets containing thousands of individually coated crystals being dispersed upon disintegration

Pelletization Technology

Pelletization is an agglomeration process that produces small, free flowing, spherical or semi-spherical units from fine powders or granules of bulk drug and excipients, referred to as pellets. Pellets typically range in size between 0.5-1.5 mm (Ghebre Sellassie, 1989) The classification of pelletization processes was shown in Figure 1. However, the most widely used process for producing pellets is the extrusion-spheronization technique.

Process used to prepare pellets include :

1. Balling is the process in which finely divided particles are converted to spherical particles by continuous rolling or tumbling motion.

2. Compression is the process in which mixtures or blends of active ingredients and excipients are compacted under pressure to generate pellets of defined shape and size. In fact, pellets produced by compression are nothing but small tablets that are approximately spheroidal in shape.

3. Extrusion and spheronization is the most wildly use process and will discussed in detail later.

4. Powder layering is the process which involved layering a drug powder and excipients onto nonpareils using syrup as the adhesive solution. The process is the first technique for developing a sustained release dosage form in the coating pan.

5. Solution and suspension layering is the process in which layering a suspension or solution of drug onto a seed material. The process result in pellet that are uniform in size distribution and very good surface morphology.

6. Spray drying is the process in which drugs and excipients in solution or suspension form are spray into a hot air stream to generate dry and highly spherical particles.

7. Spray congealing is the process in which a drug is melted, dispersed or dissolved in hot melts of gums, waxes, fatty acids, etc., and is sprayed into an air chamber where the temperature is below the melting points of the formulation components, to provide, under appropriate processing conditions, spherical congealed pellets.

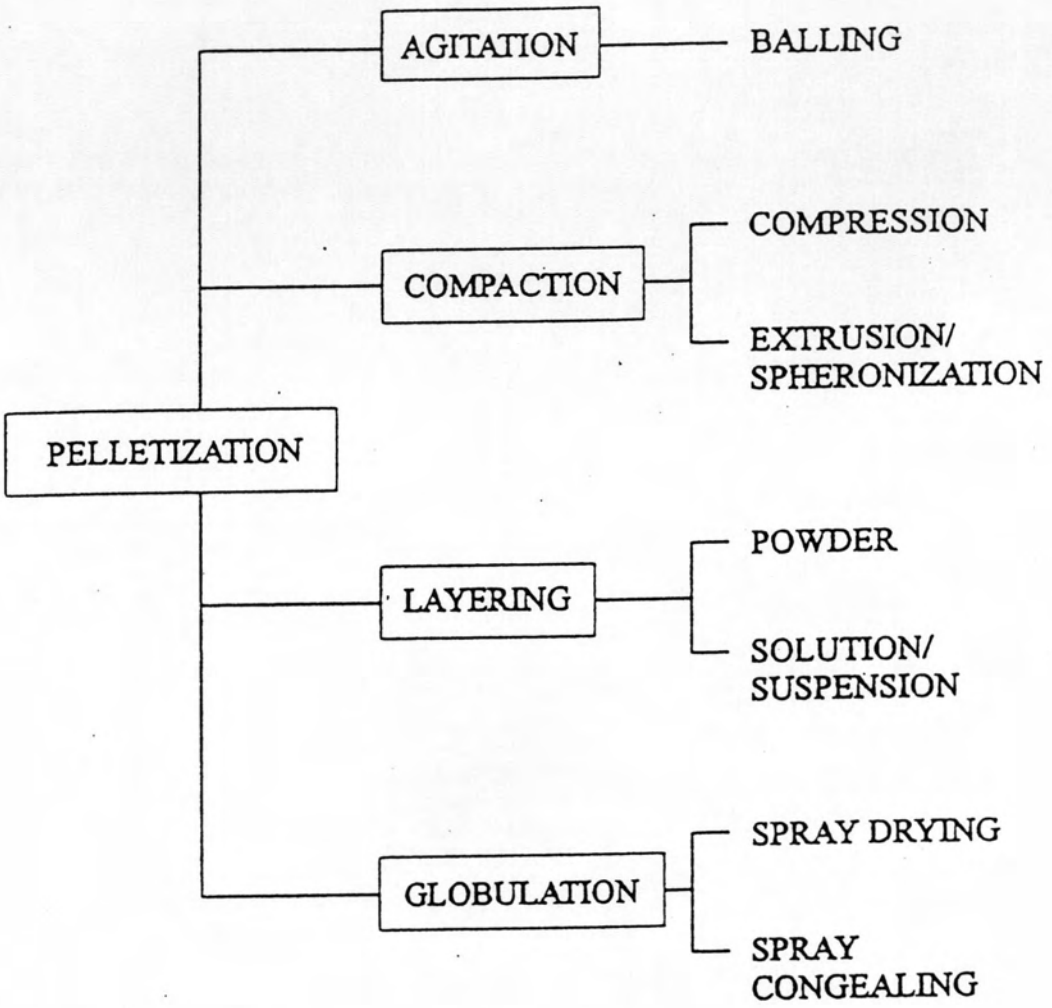

Figure 1. The classification of pelletization processes

Extrution and Spheronization Technique

Advantage of pellets produced by extrusion and spheronization process

1. Pellet produced by the process are not required seed core.
2. Pellet produced by the process have spherical particles.
3. Extrusion and spheronization process gives a very uniform size of pellets. Other method of spheronization produce random sized spheres which have to be carefully classified to obtain uniformity.
4. Pellets produced by the process have extremely low friability resulting in few fines and little associated waste.
5. Hardness measured in term of compressive force necessary to fracture a particle is greater for pellets produced by the process than for traditional granulations of similar size and formula.
6. The process is flexible in respect of sphere size which can be produced and is capable of high throughput and easy operation.
7. Spherical particles have good flow characteristic. These improved flow properties may be utilized in automated processes, and all tecnique requiring exact metering of solids, as in tableting, capsule filling, powder packaging.
8. The more spherical the particle, the easier it becomes to apply a uniform layer. Thus, if the particle is a smooth sphere, economy in coating material is achieved, as less is required to fill irrigularities in the surface.
9. High dose of active ingredients can be used by the process.
10. The application of the process is in the pharmaceutical, food, confectionery, agricultural and chemical products.

The extrusion-spheronization process consists of five unit operations. These are blending, granulation, extrusion, spheronization and drying.

Granulation

Granulation is the first step consisting of the preparation of the plastic mass by mixing of the powder blend and the granulation liquid. The most commonly used is a planetary mixer although the use of high shear or sigma blade has been also reported. (Baert et al., 1991; Elber et al., 1992; Hellen et al. (1992, 1993a, 1993b)

During the granulation step the evaporation of the fluid phase should be restricted to a minimum. This could especially be a problem with the high shear mixers as they introduce a large amount of energy into the mass which is partly transformed into heat. This rise in temperature will induce the evaporation of the granulation liquid (Baert et al., 1991) , thus influencing the extrusion behavior of the wet mass. Cooling of the granulation bowl might avoid this problem. A special feature of the granulation step is the homogeneous distribution of the liquid phase throughout the granulated mass. Some authors assumed that the water would equilibrate throughout the complete mass when the wet mass was left for 12 hours in a sealed polyethylene bag (Fielden et al., 1993; Bains et al., 1991; Pinto et al., 1993). Thus far, no comparative study has been performed examining the possible effect of the type of granulator on the final quality of the pellets.

Extrusion

Extrusion is an operation which a plastic deformable mass is forced through small openings under pressure. The pressure is created by a screw/conveyer, which produces a steady material flow. The wet mass is shaped into long rods during this step.

In recent years, more attention has been paid to the instrumentation of the extruder. Due to these modifications of the standard equipment, the authors were able to gain a better insight into the extrusion process. Baert et al. (1991) reported on the instrumentation of a roll extruder with two perforated cylinders, where it was possible to measure the forces during extrusion. This kind of instrumentation allowed an in-process control as the extrusion forces recorded could be correlated to the final quality of the pellets.

Harrison et al. (1987) measured the force applied on the piston of a ram extruder necessary to maintain the set extrusion speed. Other types of instrumentation are the measurement of the pressure at the extrusion screen using screw extruder (Elbers et al., 1992; Kleinebudde and Lindner, 1993) or the recording of the power consumption of the motor driving the extruder (Mesiha and Valles, 1993).

Spheronization

In the spheronization, the extrudates are initially broken down into short equal lengths. These are transported by centrifugal forces to the edge of the spinning plate, called the friction plate, where this spinning motion causes them to rise up the vertical wall and then fall as there momemtum is lost. This movement along with the angular velocity causes the moving mass to form a toroidal rope like shape. The friction plate has a grooved surface to increase the friction forces. Two types of geometry of the grooves exist, cross-hatch geometry where the grooves from right angles and radial geometry where a radial pattern is used.

The pellet-forming mechanism may be divided into two types. The different stages can be disinguished depending on the shape of the particles. The first mechanism, according to Baert and Remon (1993) a twisting of the cylinder occurs after the forming of cylinders with round edges, finally resulting in the breaking of the cylinder into two distinct parts. Both parts have around and flat side. Due to the rotational and the friction forces involved in the spheronization process the edges of the flat side fold together like a flower forming the cavity observed in certain pellets (Figure 2a). The overall process usually takes less than 15 minutes. Rowe (1985) suggested that another mechanism might exist. The mechanism starts from a cylinder over a cylinder with rounded edges, dumbbells and elliptical particles to eventually perfect spheres (Figure 2b)

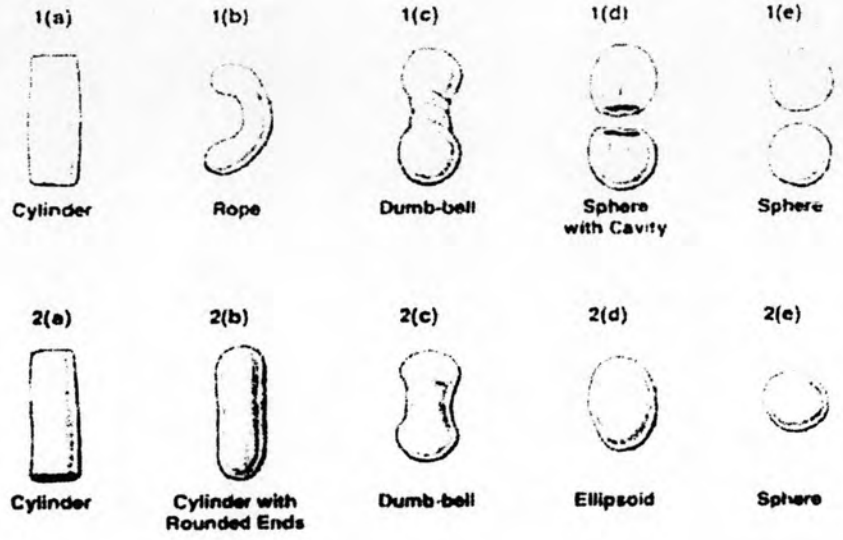

Figure 2. Pellet-forming mechanism according to :

a. Baert : I, cylinder ; II, rope ; III, dumb-bell ; IV, sphere with a cavity outside ; V, sphere

b. Rowe : I, cylinder ; II, cylinder with rounded edges; III, dumb-bell ; IV, ellipse ; V, sphere

Drying

Drying is the final step to eliminate the excess of the solvent used in granulation liquid. The pellets can be dried at room temperature or at elevated temperature in a fluidized bed, a hot air oven or a microwave oven. Comparing a formulation dried in a microwave and ordinary oven, the pellets dried with microwave differed from those dried in the oven as their surface was rougher, more porous and lesser hardness (Bataille et al., 1993)

Parameters influencing the final pellet quality

1. The moisture content of the granulated mass

The moisture, necessary to give the powder mass its plasticity so that it can be extruded and shaped afterwards, is an extremely important parameter in the extrusion-spheronization process.

If the moisture content is too low, a lot of dust will be formed during spheronization resulting in a large yield of fines. Exceeding the range of the moisture content leads to an overwetted mass and agglomeration of the individual pellets during spheronization due to excess of water at the surface of the pellets.

Harrison et al. (1987) showed that the rheological characteristics of the wet mass are important for achieving good properties for the extrusion process. Elbers et al. (1992) proved that by measuring the plasticity of a mixture after granulation at different moisture contents the optimal moisture content for a specific composition could be determined.

2. The type of granulation liquid

In most cases water is used as the granulating liquid although the use of alcohol or water/alcohol mixtures has also been reported.

The effect of this parameter was shown by Millili and Schwartz (1990); a minimum of 5% of the granulation liquid had to be water in order to produce pellets when processing a formulation of Avicel® PH101 and theophylline (90 : 10 ; w/w). Increasing the water content in the granulation liquid lead to an increase in the hardness of the pellets and correlated with a slower in vitro release rate of theopylline.

3. The physical properties of the starting material

O'Connor and Schwartz (1985) demonstrated the effect of the Avicel® type on the quality of the pellets. The RC and CL types slowed the release rate of drugs because a gel-like structure was formed in water due to the presence of sodium carboxymethylcellulose whereas the pellets containing Avicel® PH101 remained unchanged in the aqueous dissolution medium, resulting in a greater release rate.

The use of similar products but from different supplier could change the characteristics of the pellets. Pellets prepared with Avicel® PH101, Emcocel® and Unimac® had differences in size and in roundness when processed under the same condition (Newton et al., 1992)

The particle size of the starting material has a profound influence on the extrusion characteristics of the wet mass and on the size and the roundness of the resulting pellets. (Fielden et al., 1989, 1992a, 1993; Newton et al., 1992)

The solubility of the products in the granulation liquid has a dramatic influence on the amount of granulation liquid needed to obtain the proper plasticity. A soluble drug will dissolve in the granulation liquid increasing the volume of the liquid phase. This could lead to an overwetting of the system in contrast with a formulation containing a non-soluble drug (Baert et al., 1991)

4. The type of extruder

According to Reynolds (1970) and Rowe (1985), an axial screw extruder produced a more dense material compared to a radial screw extruder which had a higher output but also a greater temperature rise of the mass during processing.

Bart and coworkers compared a gravity feed with two perforated rolls versus a screw extruder and ram extruder. They showed that the pellets obtained from the two types of extruders differed in sphericity and in particle size distribution. These observations were due to a shift of the optimal amount of granulation liquid needed with each extruder or to differences in the length-to-radius ratio of the extrusion screen used or to differences in shear rate or shear stress (Fielden et al., 1992b)

5. The extrusion speed

Several authors stated that an increase in extrusion speed influenced the final pellet quality.

According to Harrison et al. (1985), the surface impairments such as roughness and sharkskinning became more pronounced with increasing extrusion speed. These surface defects of the extrudate lead to pellets of lesser quality because the extrudate will brake up unevenly during the initial stages of the spheronization process, resulting in a lot of fines and a wide particle size distribution.

However, some research reports, stated no influence of the extrusion speed on the size of the pellets was detected (Chariot et al., 1987; Hasznos et al., 1992; Hellen et al., 1993a)

6. The properties of the extrusion screen

The extrusion screen is characterized by two parameters, the thickness of the screen and the diameter of the perforations. Changing one of these two parameters influences the quality of the extrudate hence of the pellets. The diameter of the perforations determines the size of the pellets, a larger diameter of the perforations will produce pellets with a larger diameter when processed under the same conditions.

Baert at al. (1993) found that the screen with the lowest of a length-to-radius ratio (L/R ratio) formed a rough and loosely bound extrudate while screen with more L/R ratio formed a smooth and well-bound extrudate. This observation can be explained by the higher densification of the wet mass in the screen with the greatest thickness. Hellen et al.(1992) also observed that the surface of the extrudate was much rougher when the granulate was extruded by means of an extrusion screen with a low thickness.

Goodhart et al. (1973) observed an increase of the bulk density when the total area of the screen perforations increased related to the total area of the screen. The bulk density of the pellets increased when a screen with more perforations was used.

7. The extrusion temperature

A rise in temperature during the extrusion cycle could dramatically alter the moisture content of the granulate due to evaporation of the granulation liquid. This could lead to a difference in the quality of the extrudate produced at the beginning of a batch and at the end of a batch. The evaporation of water during extrusion of formulations containing Avicel® PH101 is possible because most of the water is available as free water (Fielden et al., 1988)

In order to gain an idea about the temperature increase during extrusion some authors built in a temperature probe (Baert et al.,1991; Mesiha and Valles. 1993). Other researchers used a screw extruder with a cooling jacket around the barrel in order to keep the temperature of a given formulation between predetermined limits. (Kleinebudde and Lindner, 1993)

8. The spheronization speed

The spheronization speed affected the particle size of the pellets. An increase of the yield of the smaller fractions was seen, probably due to a greater degree of fragmentation during the initial stages of the spheronization process. In contrast, a decreasing amount of fines and an increasing spheronization speed correlating with an increased mean diameter were also observed. The hardness, roundness, porosity, bulk and tapped densities, friability, flow rate and surface structure of the pellets were also influenced by a change in the spheronization speed.

According to Rowe (1985), the spheronization speed should be optimized to obtain the desired densification. He stated that a low spheronization speed would not provide sufficient densification to obtain perfect spheres, as opposed to a spheronization process at higher speed which could lead to agglomeration of the individual pellets.

9. The spheronization time

A wide variety of effects was witnessed when assessing the importance of this parameter on formulations containing mixtures of microcrystalline cellulose : an increased diameter (O'connor et al., 1984 ; Wan et al., 1993) , a narrow particle size distribution, higher sphericity (Wan et al., 1993) , a change in the bulk and tapped densities and a change in the yield of a certain size range (Malinowski and Smith, 1975) were observed with extended spheronization time. Baert et al. (1993) also found an increase of the sphericity of the pellets when a formulation containing only Avicel® PH101 was processed. In contrast, Bataille et al (1990) fond no influence on the granulometry, the hardness and the friability when formulations containing only Avicel® PH101 were spheronised for different periods of time.

10. The spheronizer load

Hasznos et al. (1992) demonstrated the influence of the spheronizer load on particle size distribution as the mean diameter increased with increasing spheronizer load.

Chariot et al. (1987) found that the yield of pellets of a specific range decreased with increased spheronization speed at a low spheronizer load and increased with extended spheronization time at higher spheronizer load.

According to Hellen and coworkers, the size of the pellets decreased and their bulk and tap density increased with an increasing spheronizer load. (Hellen et al., 1993)

Barrau et al. (1993) found that an increasing spheronizer load increased the hardness and decreased the roundness of the pellets whereas the yield in the majority size range remained unchanged.

11. Drying method

Comparing pellets containing Avicel® PH101 and lactose dried in a microwave and ordinary oven, the pellets dried with microwave differed from those dried in the oven as their surface was rougher, more porous and lesser hardness (Bataille et al., 1993)

Fluidized bed coating

The fluidized bed coating is well known for its drying efficiency, as it has been used for drying and granulating for many years. It has been recently given increased interested owing to its ability to apply virtually any type of coating system (solution, suspension, emulsion, latex and hot melt) to a wide range of particle sizes. Equipment of this type has proven to be particularly suitable for coating pellets. Coatings can be applied to fluidized particles by a variety of techniques, including spraying from the top, from the bottom, or tangentially. The tree fluidized bed equipment types, top spray, tangential spray and bottom spray (Wurster type) method are illustrated in the Figure 3, 4 and 5 respectively. The basic features of these techniques and their relative advantages and disadvantages are described in Table 2 In rationalizing the suitability of any one type of coating process compared to another, many factors may well have to be considered during the selection process. When considering the performance of the final coated product, the quality of the coating that is to be deposited will be a major key to success. The influence of various types of coating process on the quality of applied modified-release film coatings can be arranged from good to bad quality as follows : Wurster ≈ Tangential spray > Side-vent pan >> Conventional pan (Mehta et al., 1985)

There is no doubt that the fluidized bed process posses the best drying characteristics and that the proximity of the spray nozzle to the product being coated when using the Wurster or Tangential spray process helps to control deposition of the coating fluid and evaporation of the solvent/vehicle in that fluid and thus maximize quality of the final coating.

When comparing two fluidized-bed processes used in the application of organic solvent-based polymer solutions. The Wurster process claimed to be more efficient (in term of actual amount of coating deposited) than the top spray process. (Li et al., 1989).

The three fluidized bed process offer different advantages and disadvantages as shown in Table 2.

Table 2 Characteristics of three fluidized beds coating process

Processing method	Advantages	Disadvantages	Applications
Top-spray coating (Convention mode)	Accommodates large batch sizes, is simple to set up, and allows easy access to nozzle	Limited in its application	Hotmelt coating and aqueos enteric coatings Not recommended for sustained-release products
Bottom-spray coating (Wurster)	Accommodates moderate batch sizes, produces uniform and reproducible film characteristics, and allows for widest application range	Tedious to set up, does not allow access to nozzles during processing, and is the tallest fluid-bed machine for coating fine particles.	Sustained-release, enteric release and layering Poor for hotmelt coating
Tangential-spray coating (Rotary mode)	Simple to set up, allows access to the nozzles during processing, permits higher spray rates, and is the shortest fluid-bed machine for coating fine particles	Put mechanical stress on the product	Very good for layering, sustained-release, and enteric-coated products Hotmelt coating possible Not recommended for friable products

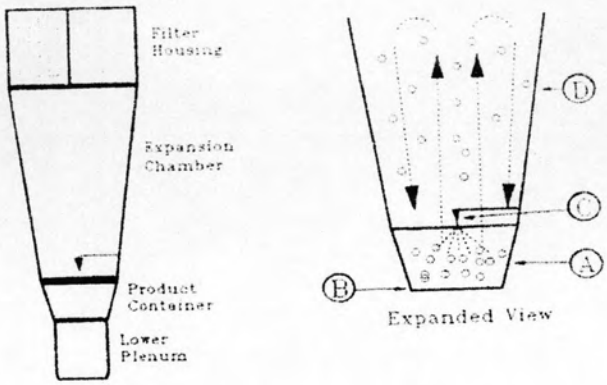

Figure 3. Schematic representation of top spray coater.

key : A, Product container

B, Air distribution plate

C, Spray nozzle

D, Expansion chamber

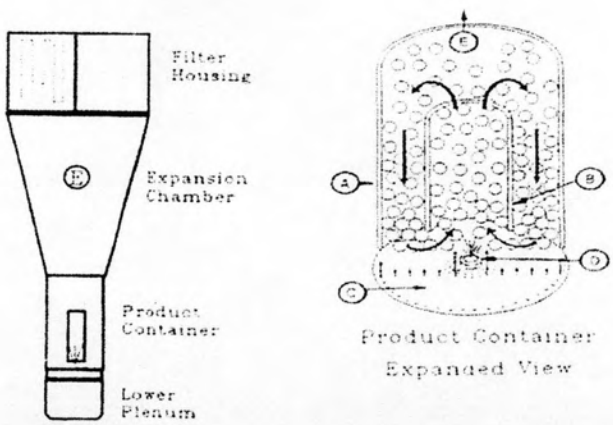

Figure 4. Schematic representation of Wurster bottom spray coater.

key : A, Coating chamber

B, Partition

C, Air distribution plate

D, Spray nozzle

E, Expansion chamber

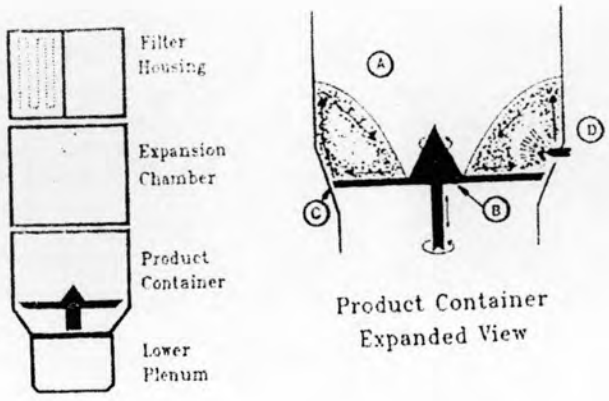

Figure 5. Schematic representation of tangential spray coater

key : A, Production chamber

B, Variable-speed disc

C, Disc gap or slit

D, Spray nozzle

Aqueous ethylcellulose dispersion

A film-forming polymer latex is deposited from an aqueous colloidal dispersion of discrete polymer spheres. Individual submicrometer-size sphere, each containing hundreds of polymer chains, coalesces into continuous film as the aqueous phase evaporates.

Figure 6 to 7 represents a latex dispersion consisting of spheres that are suspended and separated by electrostatic repulsion. As water evaporate, interfacial tension between water and polymer pushes particles into point of contact in a close-packed ordered array. A strong driving force which is necessary to overcome repulsive forces, deform the particles, and cause the sphere to fuse, resulting in complete coalescence. Capillary caused by the high interfacial surface tension of water provides the driving force to fuse the particles, and plasticizer inclusion in the dispersion swells and soften the polymer sphere, facilitating coalescence and reducing minimum film-formation temperature.

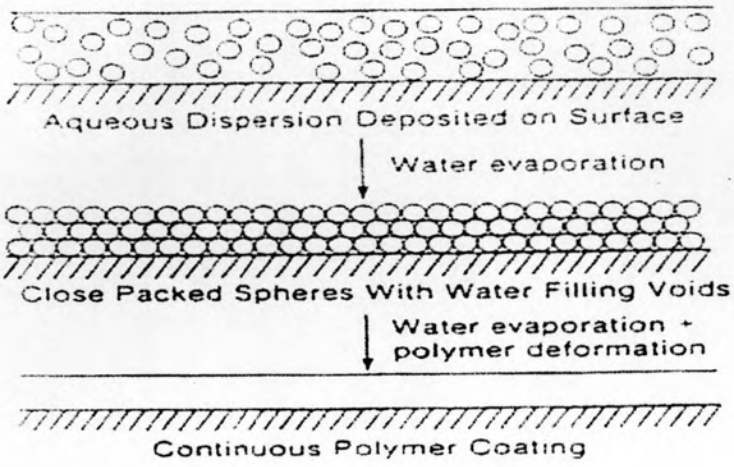

Figure 6 Film formation from pseudolatex

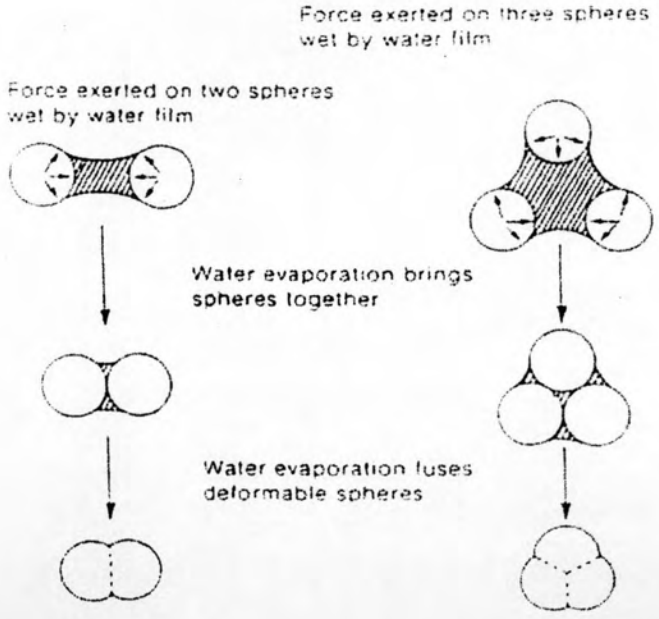

Figure 7 Particle coalescence during the evaporative phase

Mechanism of release from film coated pellets.

The major mechanism by which the drug is released from a pellet dosage form will naturally depend on the type of coating and the method by which it is applied. An important determinant of kinetics of release is the solubility behavior of the coating material under GI conditions. Behavior may be wildly classified according to three general types :

1. The coating is insoluble under all physiologically relevant conditions.
2. The solubility changes dramatically at some point of GI tract.
3. The coating is slowly erodible under GI conditions.

There are several possible mechanisms by which release from pellets dosage forms with GI-insoluble polymer may occur :

A. Solution/Diffusion through the continuous plasticized polymer phase

This mechanism assumes that the polymer forms a continuous phase in which the plasticizer and other additives are homogeneously dispersed. The diffusion of a solute molecule within an amorphous polymer phase is an activated process involving the cooperative movements of the penetrant (drug) and the polymer chain segments around it. In effect, thermal fluctuations of chain segments allow sufficient local separation of adjacent chains to permit the passage of a penetrant, then hindered molecular diffusion occurs. Another, less likely mechanism of release is the movement of the drug on the polymer chain, known as configurational diffusion.

The release rate for such a model can be described by :

$$J = \frac{Pm}{h} \times (Cs - Cb) \qquad (1)$$

Where J is the flux (release rate per unit surface area of coating), Cs and Cb are the concentration of drug at the drug-coating interface and the bulk, respectively, and h is the thickness of the film.

The permeability coefficient (*Pm*) of the coating polymer can be written as

$$Pm = \frac{D \times V \times k}{\tau \times \beta} \qquad (2)$$

Where *D* is the molecular diffusivity of the drug, *k* is the distribution coefficient of the drug between the polymer membrane and fluid in the core (imbibed water), *V* is the volume fraction of the chain opening, β is a chain immobilization factor, and τ is the tortuosity factor.

The solution/diffusion mechanism has been demonstrated for many polymer films prepared from organic solvents, which tend to form complete films. In general, it will be dominant only in those cases where the film is continuous (lacks pores) and flexile, and where the drug has a high affinity for the polymer relative to water.

B. Solution/Diffusion through plasticized channels

When the plasticizer is not uniformly distributed in the coating polymer, and when the plasticizer content is high, the plasticizer could conceivably take the form of continuous phase in the form of patched channels. If the solubility of the drug in the plasticizer is higher than that in water, it is possible that the drug would be preferentially transported through such plasticizer channels.

The release rate for this model can be descibed by equation 1, but with the permeability coefficient, *Pp* represented as

$$Pp = \frac{Dp \times Vp \times kp}{\tau p} \qquad (3)$$

In this case, *kp* is the distribution coefficient of the drug between plasticizer and the core fluid (imbibed water), *Vp* is the volume fraction of plasticizer channels and τp is the tortuosity of the plasticizer channels

C. **Diffusion through aqueous pores**

In this model, the coating is not homogeneous and continuous, but punctuated with pores. These pores fill with solution when the dosage form comes in contact with an aqueous medium, and thereby facilitate the diffusion of the drug. This mechanism is more likely to be operative for coating formed from aqueous dispersions of pseudolatexes than when the coating is applied from an organic solvent. During the coating and curing processes, the pseudolatex particles often do not fuse completely, thereby creating pores in the coating. These pores may be on the order of 1 μm . The transport mechanism in these pores can range from pure molecular diffusion to convection, depending on the pore size. For diffusion through aqueous pores, the permeability coefficient, Pa is given by :

$$Pa = \frac{Da \times Va}{\tau a} \qquad (4)$$

Where *Da* is the aqueous diffusivity of the drug, *Va* is the volume fraction of aqueous channels and τa is the tortuosity of the aqueous channels. The partition coefficient, *K* will be unity, as there is no partitioning between the channels and the aqueous environment in the bulk.

This mechanism is often accompanied by other mechanisms. The most usual combination is diffusion through the continuous polymer phase in parallel with diffusion through aqueous channels. Assuming that two mechanisms operate independently, the resultant permeability is given by equation 5.

$$Pt = Pm + Pa = \frac{D \times V \times k}{\tau \times \beta} + \frac{Da \times Va}{\tau a} \qquad (5)$$

Where *Pm* and *Pa* are the permeabilities in the polymer and the aqueous phase, respectively.

D. **Osmotically driven release**

When the coating is porous, there is also the possibility of release being driven by an osmotic pressure difference between the core materials and the release environment. Sources of osmotic pressure in the core formulation include low molecular weight excipients and the drug. For the drug to contribute significantly to the osmotic pressure, it should be highly water soluble, be low molecular weight, and be present in a substantial dose (capable of achieving saturation concentration in the core).

When pellets come into contact with an aqueous environment, water is imbibed through the coating, creating a solution in the core. The excipients and/or drug dissolve in the imbibed water, generating the interior osmotic pressure. The osmotic pressure difference between the core and the eternal medium then provides the driving force for efflux through pores in the coating. The release for this process can be described by equation 6.

$$J = \frac{Lp}{h} \times (\sigma \times \Delta\pi - \Delta P) \times (Ci - Cm) \qquad (6)$$

Where Lp is the filtration coefficient, σ is the reflection coefficient of the coating, $\Delta\pi$ is the osmotic pressure difference across the coating, ΔP is the hydrostatic pressure difference, $Ci - Cm$ are the interior and media drug concentrations, respectively.

The choice of core material will influence the degree of osmotic pressure generated. Because of their high sugar content, use of Nu-Pareil seeds is more likely to result in osmotically driven release than are granules in which the drug is spheronized with high-molecular-weight materials such as Avicel®. The usual method to check for osmotically driven release is to add various amount of urea to the dissolution media and observe whether the release rate is inhibited. Sodium chloride is less preferable, as in this case both osmotic pressure and ionic strength effects can contribute to change in the release profile. One should also check that the drug solubility is not affected by the presence of large concentrations of the osmotic agent used.

Stavudine

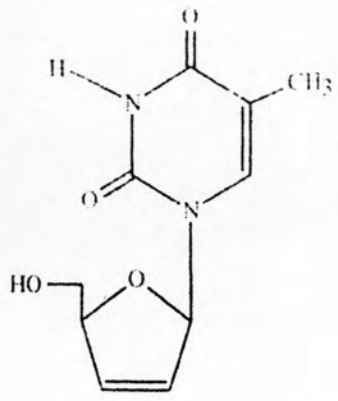

Figure 8 Chemical structural of stavudine

Chemical Composition : 2′, 3′ – didehydro – 3′ – deoxythymidine

Molecular Formular : $C_{10}H_{12}N_2O_4$

Molecular Weight : 224.2

Appearance : white to off-white crystalline solid

Physicochemical property :

The solubility of stavudine at 23^0 C is approximately 83 mg/ml in water and 30 mg/ml in propylene glycol. The n-octanol/water partition coefficient of stavudine at 23^0 C is 0.144.

The hydrolytic degradation of stavudine has also caused some concerns, as it is the main degradation pathway during the synthesis, purification, formulation and product shelf-life.

Table 3 *Stavudine marketed products*

Trade name	Dosage form	Dose*	Manufacturer
ZERIT® IR	Capsule	15, 20, 30, 40 mg bid	Bristol-Myers Squibb
ZERIT® XR	Capsule	75,100 mg once per day	Bristol-Myers Squibb
ZERIT®	Powder for oral solution	1 mg/ml	Bristol-Myers Squibb

Note : IR = Intermediate Release

XR = Extend Release

ZERIT® XR is a new once-daily version that was approved by the FDA in late 2002 (Richard 2002). However, this product are under clinical trial studies.

* The dose of Stavudine is based on patient weight and creatinine clearance as presented in Table 4.

Normal dose in adult

The recommended starting dose of stavudine in patient with Human Immunodeficiency Virus-I Infection (HIV) is 40 mg every 12 hours for patients 60 kg or greater and 30 mg every 12 hours for patients less than 60 kg.

However, it has been suggested that an initial dose of 0.5 to 1 mg/kg/day is effective. Dose greater than 1 mg/kg/day have shown a greater incidence of peripheral neuropathy.

For Stavudine XR, a 100-mg capsule once a day is recommended for patients who weight at least 60 kg, while a 75-mg capsule is recommended for patients who weight less than 60 kg.

Table 4 The dosing schedule is recommend in patients with renal impairment and is based on patient weight and creatinine clearance.

Creatinine clearance (ml/min)	Weight 60 kg or greater	Weight less than 60 kg
Stavudine Intermediate Release		
greater than 50	40 mg every 12 hours	30 mg every 12 hours
26-50	20 mg every 12 hours	15 mg every 12 hours
10-25	20 mg every 24 hours	15 mg every 24 hours
Stavudine Extended Release		
greater than 50	100 mg every 24 hours	75 mg every 24 hours

Pharmacology

Mechanism of action

Stavudine, a nucleoside analogue of thymidine, in vitro exhibits an-retroviral activity against both HIV-1 and HIV-2. Stavudine is phosphorylated by cellular kinases to the active metabolite stavudine triphosphate. Stavudine triphosphate inhibits HIV replication by the two following mechanisms :

1) It inhibits HIV reverse transcriptase (RT) by competing with the natural substrate, deoxthymidine triphosphate

2) It inhibits viral DNA synthesis by causing DNA chain termination because stavudine lacks the 3-hydroxyl group necessary for DNA elongation.

In addition, stavudine triphosphate may inhibit cellular DNA polymerase, particularly mitochondrial DNA polymerase γ.

Pharmacokinetics

The pharmacokinetics of stavudine have been evaluated in HIV-infected adult and pediatric patients (Cyntia, 1995 ; Kaul, 2002, Pollard, 2002; Rana, 1997). Peak plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) increased in proportion to dose after both single and multiple doses ranging from 0.03-4 mg/kg. There was no significant accumulation of stavudine with repeated administration every 6, 8, or 12 hours.

1. Absorption

In adult, Stavudine is absorbed rapidly following oral administration with a reported bioavailability of about 86 $\pm$ 18% (mean $\pm$ S.D.) and in pediatric patient, oral bioavailability is 77%

Peak concentrations in plasma (C_{max}) increased in a dose-relates manner and occured within 1 hour after dosing. Area under the plasma concentration-time curve from 0 hour to infinity ($AUC_{0-\infty}$) also increased in proportion to dose. The systemic exposure to stavudine is not significant different following oral administration either capsules or solution.

An oral administration with food would delays elimination but does not reduce absorption.

2. Distribution

The apparent volume of distribution of stavudine at steady state is 55-66 %, oral and IV. Stavudine has been shown to be distributed into the cerebrospinal fluid (CSF) producing a CSF : plasma ratio of about 0.4 after 4 hours.

Binding of stavudine to serum proteins was negligible over the concentration range 0.01-11.4 μg/ml

3. Metabolism

The metabolic fate of stavudine has not been characterized in humans. In addition to hepatic metabolism, some investigators suggested that degradation and salvage of stavudine by other pyrimidine pathway in liver might contribute to elimination.

Stavudine is metabolised intracellularly to the active antiviral triphosphate.

4. Excretion

Breast milk

HIV-infected women should not breast feed to avoid postnatal transmission of HIV-infection. Studies in rats have demonstrated that stavudine is readily excreted in breast milk; however, studies in human are not observed.

Kidney

Stavudine is mainly eliminated through the kidney. About 40% of the administered does is excreted unchanged in the urine between 6 and 24 hours after administration. Renal clearance is 0.21 l/hour/kg. The mean renal clearance is about twice the average endogenous creatinine clearance, indicating active tubular secretion in addition to glomerulat filtration.

Stavudine is removed by haemodialysis.

In adult and pediatric patient with HIV infection, the mean total body clearance after intravenous infusion was 8.3 ml/min/kg and 247 ml/min/m , respectively.

5. Half – life

The half life after a single 40 mg dose of stavudine significantly increased with decreasing renal function.

The elimination half-life is reported to be about 1 to 1.5 hours following single dose.

The terminal elimination half-life was 3.5 hours and 4.6 hours in patients with a creatinine clearance of 26 to 50 ml/min and 9 to 25 ml/min in patient after a single 40 mg oral dose of stavudine.

The terminal elimination half-life was 5.4 hours in patients on hemodialysis after a single 40 mg oral dose of stavudine.

Stavudine triphosphate has an intracellular half-life of 3 to 3.5 hours which may enable dosing at longer intervals than predicted by the plasma elimination half-life.