CHAPTER II

LITERATURE REVIEW

1.   Extrusion and spheronization technology

Multiple unit dosage form

The concept of the multiple unit dosage form was initially introduced in the early 1950s. These forms play a major role in the design of solid dosage form processes because of their unique properties and the flexibility found in their manufacture. These forms can be defined as oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. Together, these characteristic units provide the overall desired controlled release (CR) of the dose. The multiple units are also referred to as pellets, spherical granules of spheroids. Pellets or spherical granules are produced by agglomerating fine powders with a binder solution. These pellets usually range in size from 0.5-1.5 mm and in some applications may be large as 3.0 mm.

The use of pellets as a vehicle for drug delivery at a controlled rate has recently received significant attention. Applications are found not only in the pharmaceutical industry but also in the agribusiness (such as fertilizer and fish food) and in the polymer industry (Vervaet et al., 1995). There are numerous advantages offered by multiple unit dosage forms.

- Pellets disperse freely in the gastrointestinal (GI) tract, and so they invariably maximize drug absorption, reduce peak plasma fluctuation and minimize potential side effects without appreciably lowering drug bioavailability.

- Pellets also reduce variations in gastric emptying rate and overall transit times. Thus inter-and intra-subject variability of plasma profiles, which is common with single unit regimens, is minimized.

- High local concentration of bioactive agents, which may inherently be irritative or anesthetic, can be avoided.

- When formulated as modified-release dosage forms, pellets are less susceptible to dose dumping than the reservoir-type, single unit formulations. (Ghebre-Sellassie, 1989)

- Better flow properties, narrow particle size distribution, less friable dosage form and uniform packing.

- The pellets offer advantages to the manufacturer because they provide an ideal shape (low surface area to volume ratio) for the application of film coating. They can also be made attractive because of the various shades of color that can be easily impaired to them during the manufacturing process, thus enhancing the product elegance and organoleptic properties (Ghebre-Sellassie, 1989).

- Pellets also offer the advantage of flexibility for further modifications, such as compressing to form tablets or coating to achieve the desired dosage-form characteristics (Bechard et al., 1992).

Methods of pellets preparation

Pellets are spheres of varying diameter and they may be manufactured by using different methods according to the application and the choice of producer.

In a spray-drying process, aqueous solution of core materials and hot solution of polymer is atomized into hot air, the water then evaporates and the dry solid is separated in the form of pellets, usually by air suspension. In general, a spray-drying process produces hollow pellets if the liquid evaporates at a rate faster than the diffusion of the dissolved substances back into the droplet interior out the liquid to the droplet surface, leaving behind a void (Ghebre-Sellassie, 1989).

In spray congealing a slurry of drug material that is insoluble in a molten mass is spray congealed to obtain discrete particles of the insoluble materials coated with congealed substances. A critical requirement for this process is that the substance should have well-defined melting point or small melting zone.

In fluidized bed technology a dry drug form is suspended in a stream of hot air to form a constantly agitated fluidized bed. An amount of binder or granulating liquid is then introduced in a finely dispersed form to cause a momentary reaction prior to vaporization. This causes the ingredients to react to a limited extent, thereby forming

pellets of active components. Using this process by some researchers prepared and characterized pellets of Salbutamol and Chlorpheniramine maleate, respectively.

In the rotary processor (rotogranulator) the whole cycle is performed in a closed system. The binder solution and powder mix are added at a fixed rate in the plate of the spheronizer so that the particles are struck together and spheronized at the same time. Using this process prepared acetaminophen pellets and, in a comparison with extrusion-spheronization, they demonstrated that acceptable, immediate release pellets could be produced.

A novel method involving the use of a rotary shaker pelletizer has been developed for making pharmaceutical spheres. It is essentially based on a laboratory shaker in which a cylindrical bowl is attached to the platform of a rotary shaker. Spiral particle motion combined with a high degree of particle bowl bottom friction and interparticulate collision in the bowl (feed with plastic extruders) results in plastic deformation of extrudate and the granule surface to form the spheres (Jaiswal et al., 1995.)

A further technique used to prepare pellets is the layer building method, in which a solution or suspension of binder and a drug is sprayed onto an inert core and the pellets are built layer after layer. However, use of this technique is limited because of the smaller drug loading that can be layered effective onto the core material, thus making this technique unsuitable for drugs with large doses (Chambliss, 1989).

Extrusion and spheronization

Extrusion and spheronization is currently one of the technique used to produce pharmaceutical pellets. With each production technique, pellets with specific characteristics are obtained. The preparation of spherical granules or pellets by extrusion and spheronization is now a more established method because of its advantage over the other methods, and are presented in Table 1.
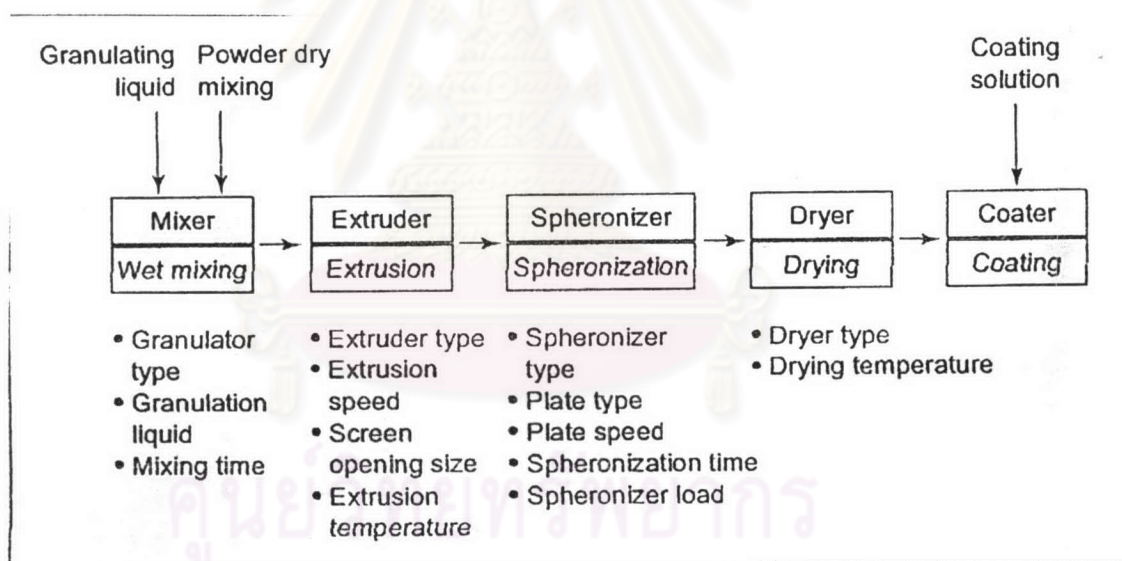
Process and equipment

In basic terms, the extrusion and spheronization process involves four steps:

- Granulation - preparation of the wet mass
- Extrusion - shaping the wet mass into cylinder
- Spheronization- breaking up the extrudate and rounding
- Drying - drying of the pellets

Table 1   Advantages of the extrusion and spheronization process (Gandhi et al., 1999).

Ease of operation
High throughput with low wastage
Narrower particle size distribution
Production of pellets with low friability
Production of pellets that are suited for film coating
More sustained and better controlled drug-release profile when compared with other techniques

Different steps, parameters and equipment used in the process are summarized in Figure 1.

Figure 1   Flow diagram showing different steps, process parameters and equipment involved in extrusion and spheronization to produce spherical controlled release pellets (Gandhi et al., 1999).

The first step of the extrusion and spheronization cycle consists of the preparation of the wet mass. Different types of granulators are used to perform the mixing of the powder blend and the granulation liquid. There are three types of processors used to mix different constituents of the powder blend. The most commonly used granulator is a planetary mixer, although in various cases use of a high shear mixer, sigma blade mixer and a continuous granulator (Hellen et al., 1993a) has also been reported. However, it is important to note that high shear mixers introduce a large amount of heat into the mass during granulation, which may cause evaporation of the granulation liquid because of a rise in temperature, thereby influencing the extrusion behavior of the wet mass. This may be avoided by cooling the granulation bowl.

Extrusion

Extrusion is the second step of the process and consists of shaping the wet mass into long rods, which are more commonly termed 'extrudate'. The extrusion process is used not only in the pharmaceutical industry but also in the food, ceramic and polymer industries. The extrusion process is currently used as an alternative method for the manufacture of complete water-soluble tablets.

Types of extrusion devices have been grouped into four main classes; that is, screw, sieve and basket, roll and ram extruders. A screw extruder, as the name implies, utilizes a screw to develop the necessary pressure to force the material to flow through the uniform openings, producing uniform extrudates. In the sieve and basket extruders the granulate is fed by a screw or by gravity into the extrusion chamber in which a rotating or oscillating device processes the plastic mass through the screen. The basket type extruder is similar to the sieve extruder except that the sieve or screen is part of a vertical, cylindrical wall. The third class of extruders are the roll extruders and these are also known as 'pellet mills'. Two types of roll extruders are available (Hicks et al., 1989). One extruder is equipped with two contrarotating wheels, of which one or both are perforated, and the second type of roll extruder has a perforated cylinder that rotates around one or more rollers that discharge the materials to the outside of the cylinder. The final type of extruder is an experimental device called the ram extruder. The ram extruder is believed to be the oldest type of extruder and features a piston riding inside a cylinder or channel that is

used to compress material and force it through an orifice on the forward stroke. Some researcher compared the extrusion and spheronization behavior of wet mass processed by a ram extruder and a cylinder extruder and concluded that they are not always equivalent.

Spheronization

The third step of the extrusion and spheronization process involves the dumping of the cylinders onto the spheronizer's spinning plate, known as the friction plate, upon which the extrudate is broken up into smaller cylinders with a length equal to their diameter. A spheronizer is a device that consists of a vertical hollow cylinder (bowl) with a horizontal rotating disk (friction plate) located inside. The friction plate has a grooved surface to increase the frictional forces. Two types of geometry of the grooves exist; more common is the cross-hatch geometry in which the grooves intersect each other at 90° angles, whereas the other pattern is radial geometry in which grooves emanate from the centre like the spokes of a bicycle wheel. The spheronization of a product usually takes 2-10 minutes, and a rotational speed of between 200-400 rpm for the friction plate is satisfactory to obtain highly spherical pellets. A special type of spheronizer, designed by NICA systems, features a lip around the rim of the friction plate that is claimed to reduce the milling effect of the plate in order to produce a smaller amount of fines. The fourth and final step of the process is the drying of the pellets. The pellets can be dried at room temperature or at an elevated temperature in the fluidized-bed drier, in an oven, in a forced circulation oven or in microwave oven. Pellet quality is dependent on the type of dryer used. Oven drying provides less porous and harder minigranules and a more homogeneous surface than those dried by microwave oven. Dryer et al. (1994) prepared ibuprofen pellets that were dried either by tray drying or fluidized–bed drying, and they showed that the drying technique has a quantifiable effect on the diameter crushing strength and elasticity of the pellets, their in vitro release, and a qualitative effect on the surface characteristics of ibuprofen pellets.

Pellet formation

Numerous mechanisms of pellet formation have been suggested. The overall process of spheronization can be divided into various stages in terms of the changes in the shape of the extrudate. Extruded plastic cylinders are rounded in the form of pellets because of frictional forces. Cylinders transform into cylinders with rounded edges then to dumbbells and elliptical particles and eventually to perfect spheres. Some researchers suggested that another pellet forming mechanism might also exist that is based on frictional forces as well as rotational forces. In this mechanism a twisting of the cylinder occurs after the formation of a cylinder with rounded edges, finally resulting in the breaking of the cylinder into two distinct parts with both parts featuring a round and a flat side. Because of the rotational and the frictional 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 2 shows both pellet-forming mechanisms (Erkoboni, 2003)
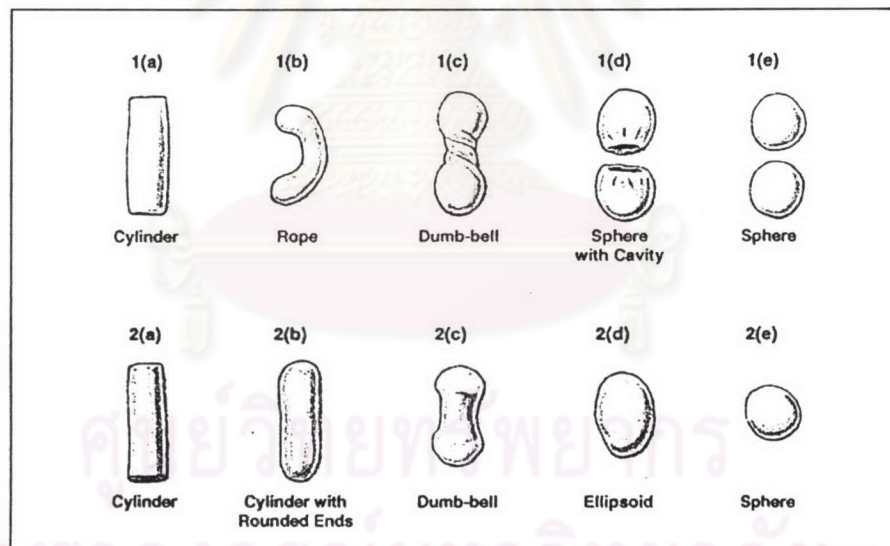
Figure 2   A graphic representation of the two models proposed to describe the mechanism of spheronization. The model proposed by Rowe describes a transition from cylindrical particle (2a) into cylindrical particles with rounded edges (2b), dumbbells (2c), ellipsoids (2d), and spheres (2e). The model proposed by Baert describes a transition from initial cylindrical particle (1a) into a bent rope (1b), dumbbell (1c), two spherical particles with a hollow cavity (1d), and spheres (1e) (Erkoboni, 2003).

The process of extrusion and spheronization is a multi-step process that involves a number of parameters that have a final bearing on the characteristics of the obtained pellets. Moisture content is an extremely important parameter in the extrusion and spheronization process. It is necessary to give the powder mass its plasticity so that it can be extruded and shaped afterwards. It was shown that there is a certain limit of moisture content at which pellets of an acceptable quality are produced. If the moisture content is less than a certain lower limit, a lot of dust will be introduced during spheronization, which will result in a large yield of fines. If moisture content is more than a certain upper limit then an overweighed mass and agglomeration of individual pellets during spheronization are caused because of an excess of water at the surface of pellet. The extent of moisture content also influences the mechanical strength, friability, internal porosity and the particle size distribution of pellets.

Ostuka et al. (1994) reported that the internal porosity of spherical granules decreases with increasing water concentration, weight loss after the friability test increases with a decreasing amount of water and the quantity of water influences the mechanical strength of granules. Moisture content also affects the shape and size of granules. Gazzaniga et al. (1998) found differences in the friability and particle size of pellets when the powder mass was wetted with different quantities of water.

Starting material

The physical nature of the starting material influences the particle size, hardness, and sphericity as well as the release rate of the included drug. There is not only the obvious difference in pellet quality produced from different compositions but also the difference when different types of the same product are used. The use of similar products but from different suppliers has also been found to change the characteristics of the pellet. Pellets prepared with three types of microcrystalline cellulose (MCC)-Avicel® PH 101, Emcocel®, Unimac®-MG from different manufacturers featured differences in size and roundness when processed under the same conditions. The physical properties of two types of commercial MCC, Avicel® PH 101 and Microcel MC show differences during the step of moistening, thereby affecting the particle size and hardness of the pellets obtained. The difference in

release rate in different types of dissolution medium has been observed between pellets containing only MCC and those containing MCC with sodium carboxymethyl cellulose (NaCMC). This difference is because a gel-like structure was formed in water through the presence of NaCMC with MCC, whereas the pellets containing only MCC remain unchanged in aqueous medium resulting in a greater rate of release.

Granulation liquid

The use of different amounts of water as a granulation liquid alone or in combination with alcohol affects the hardness and particle size distribution of the final pellets. The most commonly used granulating liquid is water, although in some cases the use of alcohol or a water-alcohol mixture has also been reported. The effect of the alcohol content in a water-alcohol mixture has been extensively studied by Millili et al. (1990). Binary mixtures of theophylline and Avicel® PH-101 (10:90 w/w) were found to form pellets when granulated with 90% ethylalcohol in water-alcohol mixture. Differences in friability and dissolution were observed between water granulated and 95% ethylalcohol in water-alcohol mixture-granulated pellets. Increasing the water content in the granulation liquid leads to an increase in the hardness of the pellets. The increase in the hardness was correlated with a slower in vitro release rate of theophylline. Gazzaniga et al. (1998) reported that when β-Cyclodextrin (β-CD) was used to form pellets using water as the granulating liquid, the poor quality of the extrudates, in terms of plasticity and sticking, invariably lead to irregularly shaped pellets and agglomerates with broad size distribution. In this respect, preliminary promising results were obtained by lowering the solubility of β-CD in the wetting liquid through the use of water-alcohol mixtures. This probably improves the plasticity of the wetted mass and thus the feasibility of the overall process.

Extruders

Several studies appear in the literature regarding the influence of the type of extruder on the size distribution, sphericity and density of pellets. The studies have shown that pellets obtained from two types of extruder had differed in sphericity and

in particle size distribution because of a shift in the optimal amount of granulation liquid needed with each extruder or because of the difference in the length-to-radius ratio of the extrusion screen used. An axial screw extruder produces a more dense material compared with the radial screw extruder; the latter has a higher output but also produces a greater rise in the temperature of the mass during processing.

Extrusion screen properties

Pellet quality is dependent on the extrusion screen, which 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 and hence the pellets. Some authors reported the difference in extrudate quality when they were obtained by extrusion with different screen thickness. The screen with low thickness formed a rough and loosely bound extrudate, whereas the screen with high thickness formed smooth and well-bound extrudate because of the higher densification of the wet mass in the screen with the greatest thickness. Similarly, the diameter of the perforations determines the size of pellets, and a larger diameter in the perforations will produce pellets with a larger diameter when processed under the same conditions. An increase in the extruder screen opening size was found to result in an increase in the hardness of the tablets made from these pellets.

Extrusion speed

The total output of the extruder is mainly governed by the extrusion speed. The output should be as high as possible for economical reasons, but several authors state that an increase in the extrusion speed can influence the size and surface proper-ties of the final pellets. Several studies show that the surface impairments, such as roughness and shark skinning, become more pronounced with increasing speed. The surface effects of extrudate lead to pellets of lower quality because the extrudate will break up unevenly during the initial stages of the spheronization process, resulting in a number of fines and a wide particle-size distribution.

Extrusion temperature

Extrusion temperature influences the pellet quality by affecting the moisture content. The rise in temperature during the extrusion cycle could dramatically alter the moisture content of granules because of evaporation of the granulation liquid. This may lead to a difference in the quality of the extrudate produced at the beginning of the batch and at the end of the batch. Evaporation of water during extrusion is possible because most of the water is available as free water. Extrusion temperature control becomes an important parameter when a formulation with a thermolabile drug is processed. To avoid a rise in the temperature during an extrusion cycle, use of screw extruder with a cooling jacket around the barrel to keep the temperature of the given formulation between predetermined limit has been reported.

Spheronizer specifications

Pellet quality is also dependent on spheronizer load. It mainly affects the particle size distribution, bulk and tap density of the final pellets. The yield of pellets of a specific range decreases with an increase in the spheronizer speed and at a low spheronizer load, and increases with extended spheronization time at a higher spheronizer loads. Some authors reported that an increasing spheronizer load decreased the roundness and increased the hardness of pellets, whereas yield in the majority size range remained unchanged. Hellen et al. (1993b) reported that the bulk and tap density increased and the size of the pellets decreased with an increasing spheronizer load.

The spheronization speed affects the particle size of pellets. In the initial stages of the spheronization process, an increase in the smaller fractions is seen, probably because of the greater degree of fragmentation. In contrast, a decreasing amount of fines and a higher amount of particles with faster spheronization speed correlating with an increased mean diameter was also observed. The hardness, roundness, bulk and tapped density, porosity, friability, flow rate and surface structure of pellets are also affected by a change in the spheronization speed.

Spheronization time mainly affects the particle size distribution and bulk and tap density of pellets. A wide range of results has been witnessed when assessing the importance of this parameter in formulations containing mixtures of MCC. These

results include an observed increase in diameter, a narrower particle size distribution, a change in the bulk and tap density and a change in the yield of a certain size range with an extended spheronization time.

2.   Modified pellets (Chopra et al., 2001)

Pellets of different shapes were produced by modifying the processing parameters of a standardized pellet formulation. Any change in formulation or processing parameters could produce changes in both morphology and total structure of the pellets. Thus, the internal porosity could change, as could the surface roughness and the overall size. So, methods to study these properties have their pitfalls and should be chosen carefully. The variable parameters incorporated into the system were:

a.   The solid to water ratio

b.   The length of time on the spheronizer plate

c.   The wet mass passed through an oscillating granulator fitted with a 1 mm^2 aperture mesh (granulation/spheronization)

d.   The wet mass processed directly from a planetary mixer (direct spheronization)

Each batch of pellets was sieved to obtain a 1-1.4 mm size fraction. Summary of the manufacturing conditions of the eight batches of pellets are presented in Table 2. The pellet shape was initially determined from visual inspection and examples of each type of pellet are shown in Figure 3.

The results of pellet shape and size show that although the pellets are obtained as one sieve fraction, there are variations in all dimensions when assessed by an accurate procedure. The biggest pellets are the ones made with ethanol/water-hence the solvent influences the packing of particles during processing and drying. The smallest pellets were obtained when extrusion was replaced by granulation. Presumely, the granules can break more easily into smaller fragments resulting in smaller pellets. The pellets produced with less fluid or spheronized for shorter time are clearly elongated, but their breadth and thickness values are not very different.

Determination of different **surface roughness** parameters (laser profilometry) resulted mostly in a similar ranking of the pellets in terms of surface roughness. Batches which had been subjected to extrusion prior to spheronization process (SP,

OV, DU, LD) provided pellets with lower surface roughness except for ethanol/water as liquid (AL). A shorter spheronization time resulted in rougher pellet surfaces (CY). The pellets prepared by granulation/spheronization (GR) or direct spheronization (DS) are least subjected to force during their processing, which obviously results in rougher surfaces.

The results for **bulk density**, if pellets have an extreme shape such as cylindrical batch, the bulk density values are significantly lower than for the roundish pellets.

Table 2   Summary of the manufacturing conditions of the eight batches of pellets (Chopra et al., 2001).

Batch	Solid to liquid ratio	Visual shape	Processes	Spheronization time	Liquid
SP	1:1.2	Spherical	Extrusion/spheronization	10 min	Water
OV	1:1.0	Oval	Extrusion/spheronization	10 min	Water
DU	1:0.8	Dumbbells	Extrusion/spheronization	10 min	Water
LD	1:0.7	Long dumbbells	Extrusion/spheronization	10 min	Water
CY	1:1.2	Cylindrical	Extrusion/spheronization	10 min	Water
AL	1:1.1	Spherical	Extrusion/spheronization	10 min	Ethanol/Water (70 v/v%)
GR	1:1.15	Spherical	Granulation/spheronization	10 min	Water
DS	1:1.1	Spherical	Spheronization	10 min	Water
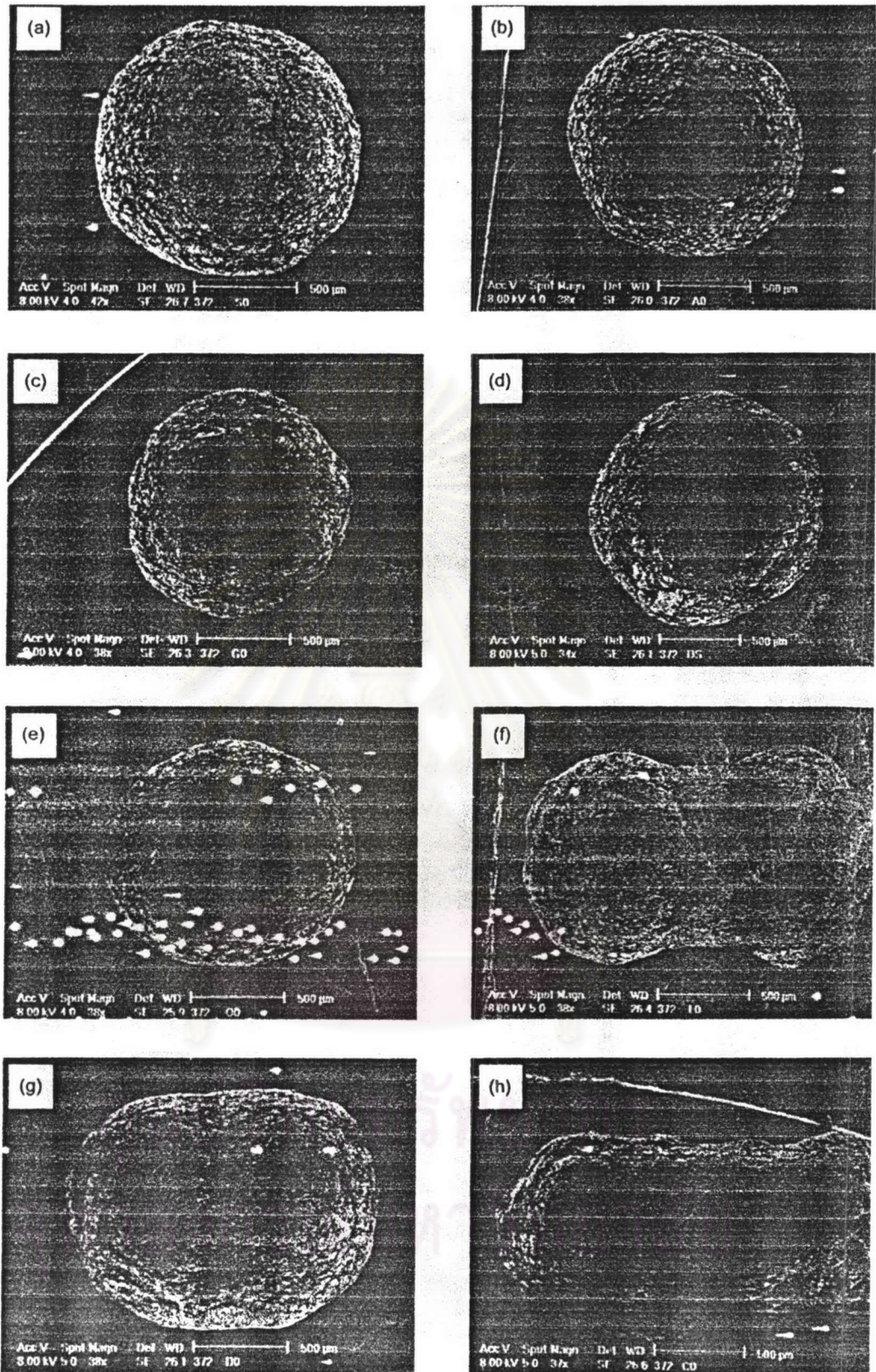
Figure 3 Scanning electron micrographs for different pellet batch: (a) SP, (b) AL, (c) GR, (d) DS, (e) OV, (f) DU, (g) LD, (h) CY (Chopra et al., 2001).

3. The sphericity and surface roughness parameters

The sphericity parameters

The spherical shape is of special interest in extrusion/spheronization and other pelletisation techniques. Therefore, several studies have investigated the possibility to describe the deviations from being a sphere using the two-dimensional particle outline obtained form photography, microscopy or image analysis. Up to 20 different shape factors have been devised and compared without presentation of a satisfactory solution. Most popular are the aspect ratio and elongation. Aspect ratio is the ratio between the longest distance of a particle and its perpendicular dimension (or defined as the longest Feret diameter over the Feret diameter perpendicular to the longest (Eriksson et al., 1997). And the elongation ratio is the ratio between the smallest Feret diameter and its perpendicular Feret diameter. In principle, these two descriptors provide different numbers for irregular shaped particles. Some authors were only concerned with the assessment of shape of spherical particles, and hence came to the conclusion that aspect and elongation ratios are mathematically equivalent. However, the process of extrusion/spheronization can lead to irregular as well as spherical particles, and hence a clear definition is essential if comparisons are to be made. Some authors compared the information content of several shape factors and concluded that aspect and elongation ratios do not reflect truly the shape of a particle. Hence, they should be avoided. Another popular shape factor for spherical particles is called circularity. But the circularity is unable to differentiate between symmetrical figures such as squares or circles providing in both cases the numerical value of 1 (Podczeck et al., 1995).

One of the most important characteristics of a pellet is its roundness. The main claim of benefit, which the process gives, is spherical shape with uniform sized, better flow properties, uniform packing and smooth minimum surface area for efficient film coating to provide uniform control of drug release.

Pellets can be divided into six shape groups (I-VI) by visual inspection (Figure 4), the shape varied from long, cylindrical rods through dog-bones and ellipsoids to almost spherical pellets.
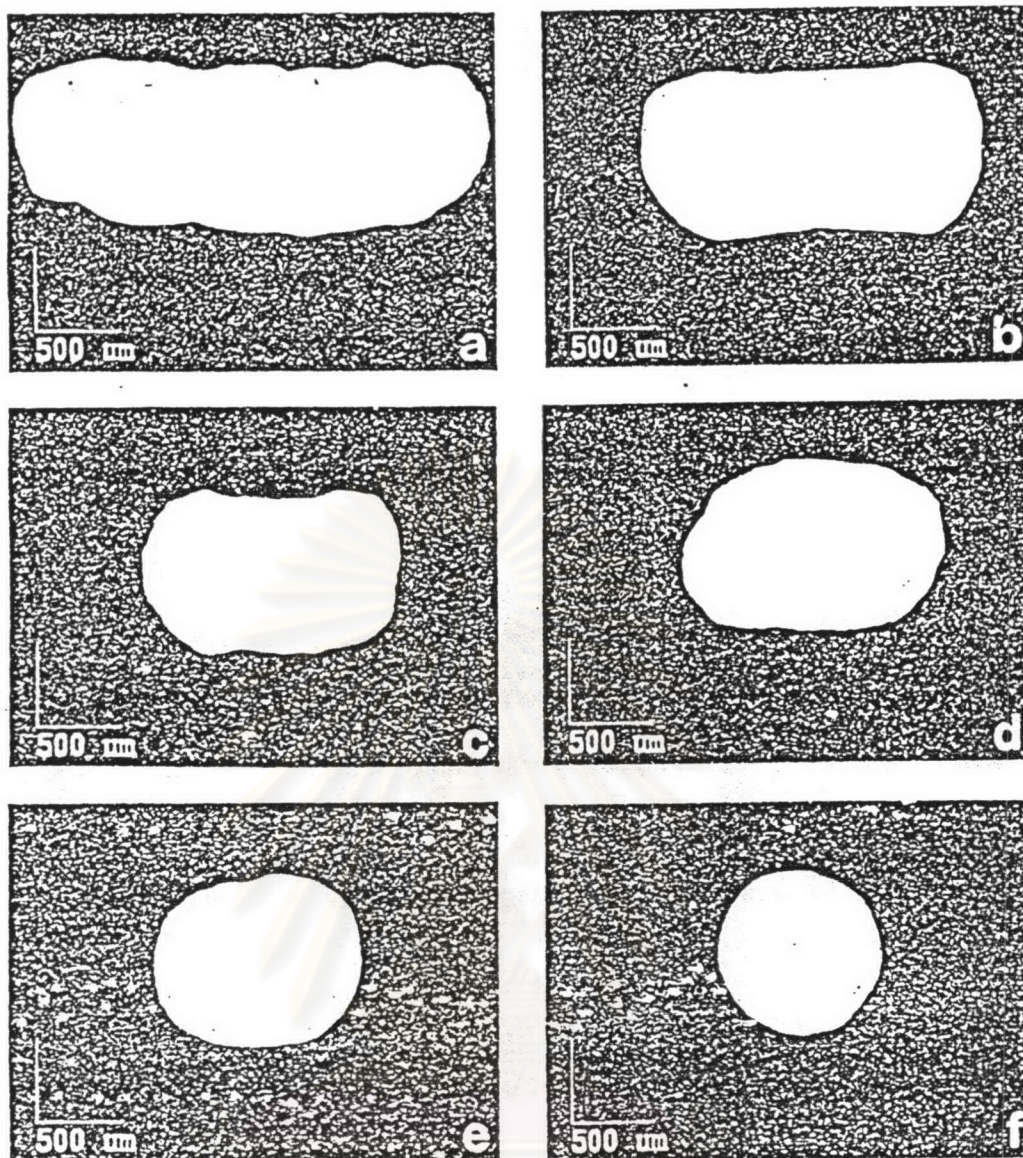
Figure 4   Pellets representing shape groups I-VI that varied from long, cylindrical rod, dog-bone, ellipsoid, almost spherical and spherical, respectively (Hellen et al., 1993b).
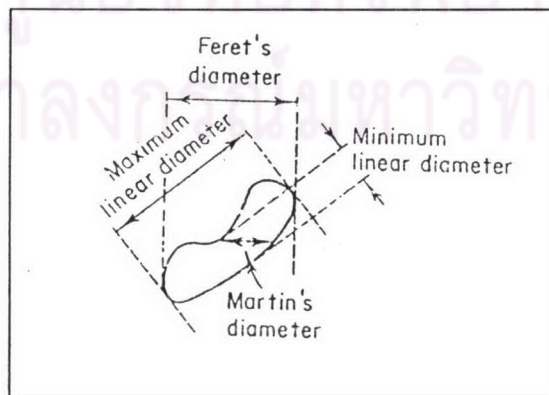
Figure 5   Various dimension of an irregular particle (Chemical Engineering)

There are seven tested parameters (Equation 1-7) indicating shapes were derived from size data measured by OPT/IA (optical microscopy/image analysis). The purpose of these parameters was to emphasis the degree of sphericity of the pellets. The value close to 1, which calculated from each parameter model represented the most spherical, pellets (Hellen et al., 1993c). These parameters were as follows:

$$\text{Circularity} = \frac{4 \times \pi \times A}{(perim)^2} \quad \dots\dots\dots\dots (1)$$

$$\text{Roundness} = \frac{A}{\pi \times (d_{max}/2)^2} \quad \dots\dots\dots\dots (2)$$

$$\text{Elongation} = \frac{d_{max}}{d_{min}} \quad \dots\dots\dots\dots (3)$$

$$\text{Pellips} = \frac{perim}{\pi \times d_{max}} \quad \dots\dots\dots\dots (4)$$

$$\text{Rectang} = \frac{A}{d_{max} \times d_{min}} \quad \dots\dots\dots\dots (5)$$

$$\text{Modelx} = \frac{perim \times d_{max}}{4 \times A} \quad \dots\dots\dots\dots (6)$$

$$\text{Roughness} = \frac{perim}{cperim} \quad \dots\dots\dots\dots (7)$$

Where A, $perim$, $cperim$, d_{max} and d_{min} are two-dimensional area of the projection of the pellets (mm^2), perimeter of the project which is the length of the outline of the projection (mm), convex perimeter of the object which is the length of a regular polygon with 64 corners stretched around the object, maximum Feret's diameter and minimum Feret's diameter, respectively. (Feret's diameter is the perpendicular projection, on to a fixed direction, of the tangents to the extremities of the particles profile (Figure 5).

The calculated shape parameters for the six shape groups of pellets I-VI (VI refer to roundest pellet) are evaluated (Hellen et al., 1993c). **The circularity parameter** seemed to be limited in the evaluation of the shape of pellets this parameter could not distinguish the difference between the three roundest pellets shape groups IV-VI. **The roundness parameter** was more sensitive and could

classify the pellets clearly according to visual observation. The roundness parameter increased as pellets shape became more spherical and the value was close to 1.0. The roundness of the batches studied behaved mainly like the circularity parameter, but even more effectively especially in the case of the roundest pellet batches. **The pellips parameter** increased as the shape of pellets became more spherical like circulartiy and roundness parameter. **The elongation and modelx parameters** behaved very similarly. The numerical value of both these parameters decreased systematically as the pellets became rounder and the value was close to 1.0. It quite difficult to say which one of the two parameters is more useful. The calculation of elongation is, however, easier, which supports the use of this parameter. **The rectang parameter** was somewhat limited because it was able to classify these six pellets only in two categories. Shape groups I-III had slightly higher rectang values than shape groups IV-VI because the first group really had a more rectangular shape on the basis of the pictures presented earlier. **The roughness parameter** could not distinguish the different shapes or surface structures from each other. Hence, due to its insensitively, the roughness parameter cannot be used as an indicator of shape or surface structure in the case of pellets.

Different shape factors and shape assessment techniques are clearly different in their sensitivity to small variations in particle shape (Podczeck et al., 1994; Eriksson et al., 1997). Although pellets are three-dimensional, roundish objects, but their image is captured as a two-dimensional particle outline. It is impossible to focus precisely on the particle equator, because the equator is halfway down the pellet body. Therefore, authors have adopted different opinions on the usefulness of shape factors. For example, Podczeck et al. (1994 and 1995) developed a shape factor (e_R) for two- or three-dimensional pellets shape assessment, which was shown to significantly more sensitive to deviations from the ideal round shape and to surface irregularities than the standard shape factors used. However, its use, in particular the three-dimensional version of the shape factor, shows the assessment procedure down, and the raw data, which can principally be obtained on any image analysis system, needs to be processed further (Podczeck et al., 1999).

In general, the ability of the shape factors e_R and e_{R3} to distinguish between pellet batches in a statistical manner is much more pronounced that for aspect ratio, whereby the three-dimensional shape factor (e_{R3}) is clearly the most sensitive. The Heywood surface factor f ranks the pellet batches in the same order as the three-

dimensional shape factor e_{R3} confirming that the third dimension is an important issue in assessing the pellet shape. Hence, from the data obtained it appears as though the three-dimensional shape factor (e_{R3}) and the heywood surface factor (f) are the most suitable shape assessors (Chopra et al., 2001).

The surface roughness parameters

In the pharmaceutical field, fractal geometry has mainly been used in the study of the surface smoothness of powders, either excipients or drugs. Since it has been revealed that powder or granule characteristics, like flow and packing properties, are also related to the smoothness of the particle surface knowledge about the smoothness of the pellet surface is important (Vertommen et al., 1997).

Taking into account the degrees of surface irregularity and roughness, it can be possible to predict their effects on the dissolution rate of drugs and, therefore, on the biopharmaceutical behavior of the elaborated formulations. The mathematical tool used to quantify the surface properties is fractal geometry. The basic approach of this theory is to describe quantitatively a complex geometry of an object if the object is symmetric to transformation of scale.

The fractal concept describes the surface of particles in terms of the "fractal surface", with a characteristic parameter called the fractal dimension (D). Fractal analysis relies on the fact that perimeter of a silhouette edge is dependent on the step length with which we measure it. Thus, the smaller the step length, the larger is the perimeter measured, since more details of the structure are taken into account. So, the fractal dimension of particle contours is used to characterize the surface roughness (Holgado et al., 1995).

An ideal fractal structure should yield a linear plot, at all resolutions, when log L_n is plotted against log δ, where L_n is the perimeter and δ is the step length. The length-estimated L_n tends to increase without limit as the step size, δ, decreases. The slope is this straight line is S, where $S = 1 - D$, and D is the fractal dimension. By this approach, the degree of irregularity is given by D, so that $1 \leq D < 2$ for lines and $2 \leq D < 3$ for surfaces. The more irregular and wiggly an object is, the higher the value of D. Therefore, a particle contour with $D = 1.2$ will have a less rugged, smoother boundary than particle with $D = 1.5$ (Thibert et al., 1988).

Definition of selected parameter in Image Pro Plus[®]

Area : Reports the are of each of each object (minus any holes). The area comprised of pixels having intensity values within the selected range is reported unless the Fill holes option has been enabled. If Fill Holes is enabled, all pixels within the object perimeter are included in the area measurement.

Aspect : Reports the ratio between the major axis and the minor axis of the ellipse equivalent to the object (i.e. and ellipse with the same area, first and second degree moments), as determined by Major Axis/Minor Axis. Aspect is always ≥ 1.

Diameter (mean) : Reports the average length of the diameters measured at two degree intervals joining two outline points and passing through the centroid.

Feret (max) : Reports the longest caliper (feret) length.

Feret (min) : Reports the shortest caliper (feret) length.

Fractal dimension : Reports the fractal dimension of the object's outline.

Perimeter : Report the length of the outline of each object. When holes are outlined, the perimeters of the holes re added to the perimeter of the object.

4. Polymeric solution coating (Lehmann, 1994)

Organic solvents were the preferred media for natural waxes or polymers that were available to make the membranes. Due to the relatively small consumption of organic solvents for this special application, broader selections of such solvents were acceptable. But increasing problems of air pollution from industrial processes let to severe restrictions from the governments of highly industrialized countries.

The solvent system required to deposit the film-forming polymer on the tablet surface and produce a perfect film plays an important role in the coating process.

Mechanism of film formation (Bauer et al., 1998)

Film formation from solutions is relatively simple process. The droplets of the spray fluids must, however, be able to spread on the surface and coalesce to a liquid film and should, therefore, be sprayed with care.

For this reason, evaporation of solvent in the spray must be limited to prevent any major viscosity increase in the droplets or even spray drying of some of the smaller ones.

Spreading of the droplets depends on the interfacial tension between tablet surface and coating fluid and can be controlled via measurement of the contact angle. The contact angle is the acute angle that forms between drop of liquid and the solid surface to which it is applied. The drop may either stay at a defined angle or spread over the entire surface, in which case the angle approaches zero.

The smaller the contact angle, the better the droplets will spread on the surface and the better the distribution of the coating around the core. The interfacial tension between tablet and coating fluid, however, only matters at the very beginning of the coating process. After a very short time the tablet is covered with a thin polymer membrane, and what matters thereafter is that the film surface is properly wetted and the droplets coalesce well on it. Once the droplets have spread, the remainder of the solvent in which the polymer is dissolved evaporates, the film becomes stronger and shrinks at the same time.

During the drying process, the solvent evaporates from the solution in which the polymers initially exist in the form of isolated coils. Colloidal solutions of polymers convert into even more concentrated solutions. If the solvent evaporates

slowly, the coil moves closer together until they penetrate each other at a specific concentration.

The conditions of film formation are fulfilled when the individual droplets coalesce, giving the macromolecules opportunity to penetrate each other during the drying process. To this end it is also necessary that at least some segments of the chains remain flexible, i.e. the polymer chains must have exceeded their glass transition temperature (Tg). At this point, however, the solvents that are still present exert a strong influence, usually acting as plasticizers and lowering the glass transition temperature.

5. Polymeric dispersion coating

Aqueous dispersions are disperse systems in the dispersing medium water. When the dispersed phase is built up by polymers, they are referred to as polymer dispersions. The dispersed phase can be solid, liquid or any intermediate state, since the transition of polymers from solid to liquid takes place over a wide temperature range.

The term "latex" is used for colloidal polymer dispersions and derives from the natural rubber latex. Synthetic latexes are dispersion obtained by emulsion polymerization, whereas artificial latexes are obtained by direct dispersion. The term pseudolatex is used for systems prepared by emulsification of organic polymer solutions in water with subsequent removal of the solvents.

Water-based systems have been developed for pharmaceutical dosage forms instead of organic solvent-based polymeric solution because of their environmental and economic advantages. Because water has a high heat of vaporization, aqueous systems that might require lengthy processing times seemed initially to have serious economic disadvantage despite their environment advantages. However, in addition to the progress of fluidized-bed technology, the aqueous polymeric latexes and pseudolatexes that have been developed since the 1970s have overcome the disadvantage by their low viscosities and high polymer content.

Mechanism of film formation

The coating is achieved by a spraying and drying process of the dispersions, where the system is composed of three phase: environment gas phase, aqueous solution and polymeric particles. Water is evaporated, leaving the polymeric solid. The subject to be discussed here is how the residual solid, which is originally composed of discrete particles, becomes a homogeneous film.

The process of film formation of an acrylic latex film can be divided into six stages and are presented in Figure 6 (Tent et al., 2000).

These first four stages describe the process of flocculation and coalesce and the last two stages that autohesion.

(I)   Evaporation of water from the bulk; this causes uniform shrinkage of the interparticle distance.

(II)   Percolation of water between the flocculated particles nears the air/latex interface and eventually evaporation of water at the air/latex surface.

(III)   Dense packing of particles.

(IV)   Evaporation of water from the interstices that are present between the densely packed immobile particles; this causes the particles to deform into a polyhedric structure, due to interfacial forces.

(V)   Diffusion of water through the closed polymer film and autohesion of polymer particles (the particles lose there identity).

(VI)   Homogeneous polymer film formation

The first four parts of the film formation process take place on the order of 5 to 10 min, whereas for the last two stages much more time is needed: time scales of days and even months have been reported.

The mechanisms of film formation from aqueous polymeric dispersions have been discussed for along time and many theories have been proposed (Yang and Ghebre-Sellassie, 1990, Fukumori, 1994 and Wheatley and steuernagel, 1997). Fusion and film formation of polymeric particles during the coating process can be explained by the wet sintering theory for particles suspended in water, the capillary pressure theory for particle layers containing water in various degrees of saturation, and the dry sintering theory for the dry particle layers.

A.   Wet sintering theory

When two particles are in contact, as shown in Figure 7, the pressure difference at the neck in the contact region can occur. And because r_1 can be very small, especially at the beginning of deformation, it is possible for very high pressure difference to be induced on the contact region. Consequently, the pressure gradient is induced within the polymeric particle.

The polymer is forced to flow by the pressure gradient, leading to expansion of the contact region if it will yield mechanically. The pressure gradient is decreased with increase in the curvature r_1 and r_2 during deformation. The two particles should finally be fused into a sphere if the polymer continues to yield.

When particle fusion at this stage can proceed easily, dispersion stability is lost by particle coalescence or aggregation. To facilitate film formation in subsequent processes, the polymeric particles usually have to be made deformable. Therefore, the polymeric phases are prevented from direct contact by adding surfactants or by other procedures.

B.   Capillary pressure theory

By water evaporation from droplets of a dispersion sprayed on and adhering to core particles, the dispersion is condensed and the polymeric particles are closely packed on the surfaces of core particles. When the surface layer of polymeric particles is exposed to air, the air-water surface tension generates capillary pressure on the surface of a water-saturated layer of polymeric particles (Figure 8). The capillary pressure compresses the polymeric particles, the compression acting to squeeze out the water. Since the curvatures of the capillary surface are thus enlarged, capillary pressures are decreased. This process is repeated until water resides only among the interparticulate contact points. Then the polymeric particles can be fused by capillary pressure. When water is located only at interparticulate contact points, capillary pressure is exerted in the contact regions of polymeric particles (Figure 9). Although precise prediction is difficult, the capillary pressure is qualitatively increased with water-air surface tension and is inversely proportional to the polymeric particle radius.

How far particle fusion can proceed at this stage depends on the rate of disappearance of the aqueous phase in addition to the surface tension and mechanical

properties of the polymeric of the polymeric phase. The aqueous phase can disappear through evaporation and by permeation of the water into the core or underlying layer. The evaporation rate depends on the temperature, humidity and flow rate of air. When coating is done under high humidity conditions, the capillary pressure can act over a much longer period, leading to enhance film formation. When the underlying surface is water absorbable or porous, the aqueous phase will be shorter and there will not be enough time for film formation to be completed.

It is useful in film formation that particles be under capillary pressure for a long period. But, polymeric particles can have the best chance to act as a adhesive among core particles. This can lead to the agglomeration of core particles, which is not preferable in multiparticulate dosage forms.

C.   Dry sintering theory

After the water is completely evaporated, the pressures caused by replacing the water-polymer interfacial tension by air-polymer surface tension are exerted on the polymeric particles. By the induced pressure gradient, dry sintering can proceeded if the polymer is deformable and the fusion of polymeric particles is not completed.

If dry sintering proceeds at significantly high rate during the coating process, agglomeration of core particles cannot be avoided. However, the rate of dry sintering is usually low; therefore, further gradual coalescence can proceed for a long period after coating. During that time, membrane properties such as drug permeability continue to change. This should cause serious problems. To complete film formation, the products are usually cured by heating (aging) at temperatures higher than the softening temperature of the membrane material; then, to avoid aggregation of the particles with softened membrane, powder is dusted on the particle surface.
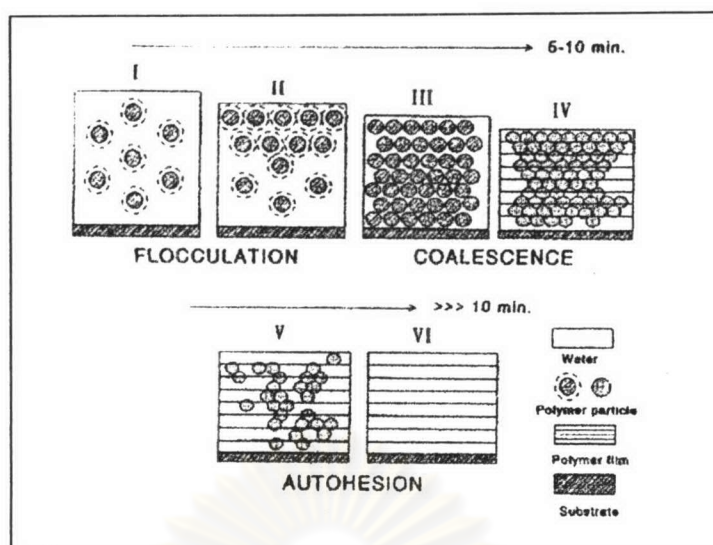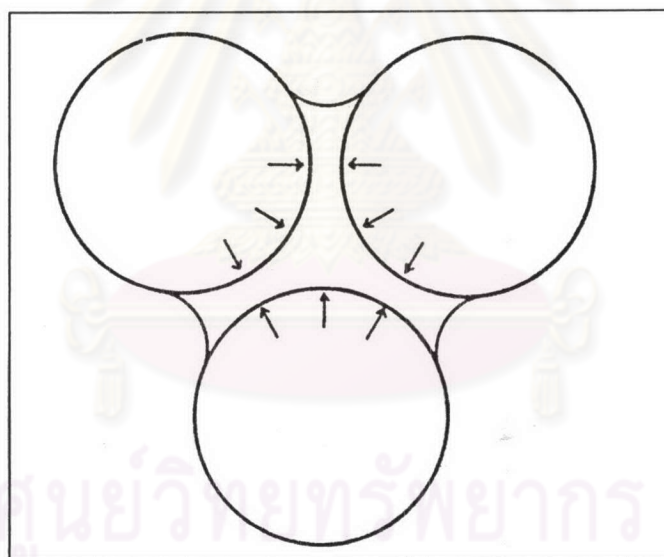
Figure 6   Typical film formation behavior of drying acrylic latices (Tent et al., 2000)
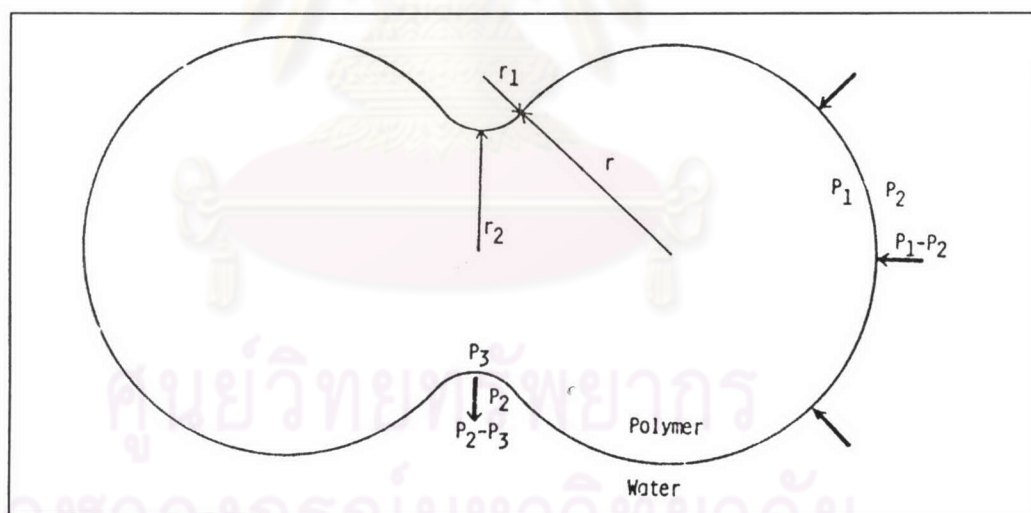
Figure 7   Fusion of polymeric particles (Bauer et al., 1998)
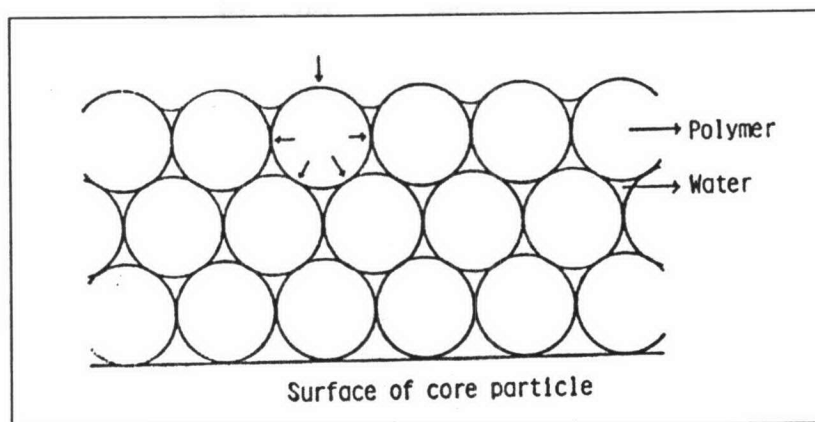
Figure 8   Capillary pressure acting on the layer of polymeric particles saturated with water (Bauer et al., 1998).

Figure 9   Capillary pressure acting on polymeric particles holding interparticulate bridge water (Bauer et al., 1998).

6.   **Dry powder coating**

A.   **Dry powder coating in pharmaceutical science.**

In pharmaceutical science, dry powder coating is an alternative technology, whereby the dosage forms are coated directly with micronized polymer powder (Obara et al., 1999). They investigated the practically of this technique for both bead and tablets coating using Hydroxypropyl methylcellulose acetate succinate (HPMCAS, commercial cellulosic enteric coating agent). Coating experiments were performed using a centrifugal granulator, fluidized bed and tablet coating machine. But small amount of water is an essential factor for the final curing process to achieve film formation. Because they speculated that the evaporation of water provides a driving force to fuse the polymeric particles together, as in the film formation mechanism proposed for aqueous latex system. Water might act as a trigger or inducer of film formation.

Secondly, Pearnchob N. and Bodmeier R. has developed dry powder coating technique by using shelleac (Pearnchob et al., 2003a), Eudragit RS (Pearnchob et al., 2003b) and Ethylcellulose (Pearnchob et al., 2003c). Pellets were coated with polymer powder by using fluidized bed coater. Formulations for the coating pellets were consisted of two parts, powder and liquids. The powders (polymer plus talc) and an emulsion of liquid material (plasticizer plus 10 % w/w HPMC solution) were fed/sprayed separated onto drug-loaded pellets as in Figure 10. And the coated pellets were oven-cured with humidity (100 % RH) at different temperatures and times.

Finally in this technique high concentrations of plasticizer (40 % based on the polymer) and small amount of water still were necessary to achieve complete film formation.
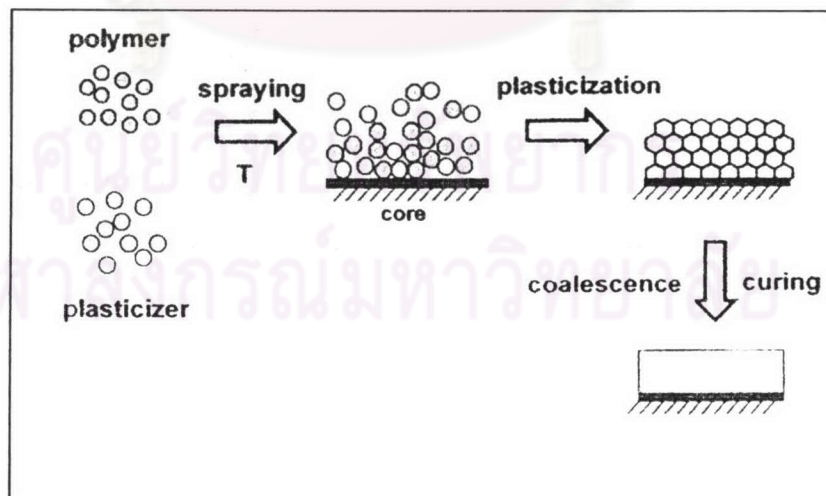
Mechanism of film formation

The film formations from polymer powders occurred via several steps and are shown in Figure 11. First, polymer particles had to adhere to the surface of the heated pellets. This adhesion was achieved by spraying simultaneously to the powder feeding as aqueous HPMC solution containing the plasticizer. The polymer particles and the pellet surface were wetted thus promoting adhesion of the particles to the surface and

cohesion of subsequently fed particles to the already adhering particles. The process was also performed at elevated temperatures, which resulted in the softening of the polymer particles and plasticizer uptake and sticking of the particles to each other on the pellet surface. However, the particles did not coalesce into a homogeneous film during the coating process. Like with aqueous colloidal polymer dispersions. A thermal after-treatment (curing) at elevated temperatures was necessary for the coalescence of the plasticized polymer particles and good film formation.
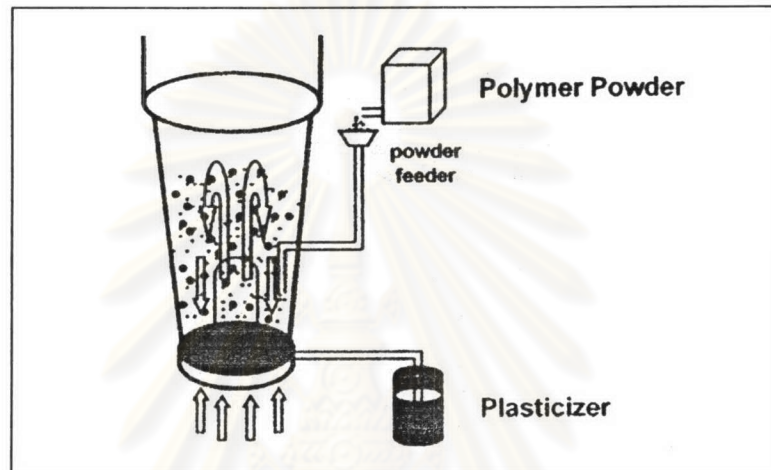
Figure 10   Schematic illustration of dry powder coating with a fluidized bed (Obara et al., 1999).

Figure 11   Mechanism of film formation of dry powder coating (Pearnchob et al., 2003a, b and c)

B.   Dry powder coating in other application (Richart, 1995)

Powder coating is the generic designation for a variety of processes for applying a coating to a substrate utilizing solid resinous or polymeric powders. Since the individual powder particles at some stage must be melted to flow out and form a continuous coating, powder coating methods are frequently referred to as fusion coating processes. While most coating powders are used for decorative and protective coating, usually on a metallic substrate, heavier coating can also be applied for functional purposes such as electrical insulation, corrosion protection, abrasion resistance, friction and wear characteristics, etc. Both thermoplastic and thermosetting coating powders are available, although thermoplastic powders are used primarily in the fluidized bed and flame spraying processes and thermosetting powders in flocking and electrostatic spray methods. The first powder coating produced were based on thermoplastic polymers, which melt at the application temperature and solidify upon cooling. But the weakness such as high temperature of fusion, low pigmentation level, poor solvent resistance and bad adhesion on metal surfaces necessitating the use of a primer can be listed. These problems inherent to the thermoplastic powder coatings were successfully overcome later on by the thermosetting powders, which very quickly took the largest part of the market. The term "powder coating" is used frequently to describe both the materials and the process.

Because of their different nature compared to liquid coating, powder coatings are applied on the object to be coated by techniques that have little in common with the well-known methods of application of conventional solvent borne coating.

Four different powder coating processes have been developed during the last thirty years: electrostatic spraying, fluidized bed, electrostatic fluidized bed and flame spray, the last one being developed recently and not yet widely used.

Powder coating methods

A. Electrostatic spraying technique

Electrostatic spraying is the most common process used for application of powder coatings in metal finishing. The basic principle of the process concerns propulsion of the dry powder by means of compressed air through a spray gun, in

which it becomes electrically charged. The movement of the particles between the charged gun and the substrate to which the powder is applied is governed by combination of electrical and mechanical forces. The electrical forces are the result of interaction between the charged powder particles and the electric field between the substrate and gun, while the mechanical forces are derived from the air that blows the powder through the gun.

B. Fluidized bed process

This is the simplest method of powder coating. In this process the preheated workpiece enters the space where by means of the air stream the powder particles are kept in fluidized bed. Powder particles coming in contact with the preheated surface melt and adhere to the substrate. Depending in the temperature, the heat capacity of the workpiece and its residence time in the fluidized bed, coating layers with various thicknesses can be applied. Postheating is usually not necessary in the case of the thermoplastic powder coating, especially when workpiece is a massive object with a large heat capacity. When thermosetting powder coatings are used, additional postheating follows the application step in order to complete the curing of the coating.

The fluidized bed process is a very attractive application technique in many respects. The powder is confined to an enclosure and therefore is much easier to handle without the need to recycle and reblend the overspray. Due to the absence of recycling and reblending equipment, fluidized bed installations are in principle very compact compared to the spray sun/booth combinations

Film thickness depends on the temperature to which the part is preheated and on the Tg of the powder. Thin film cannot be applied in the fashion. Most commonly, the method is used for applying thermoplastic coating materials.

C. Electrostatic fluidized bed

Electrostatic fluidized beds are similar the fluidized bed process, but electrodes are added to generate ions in the air before the object passes through the powder. The object to be coated is grounded. Powder is attracted to the object by electrostatic force, as in electrostatic spray.

D. Flame-spray technique

Flame spray is another technology for applying thermoplastic powder coatings. In a flame spray gun, the powder is propelled through a flame, remaining there just long enough to melt. The molten powder particles are then directed at the object to be coated. The flame heats and melts the polymer and heats the substrate above the melting temperature of the polymer so that the coating can flow into irregularities in the surface to provide an anchor for adhesion.

Powder coating materials

Table 3   General comparison of resins used in coating powders

Thermoplastic resins	Thermosetting resins
High molecular mass	Low molecular mass
High degree of crystallinity	Amorphous
Tough, difficult to grind requires cryogenic condition	Friable, easy to grind only air cooling required
High melt viscosity	Low melt viscosity
Higher application temperature	Lower application temperature
Stable, nonsintering	Stable, nonsintering

1.   Thermoplastic coating powders

Many thermoplastic resin have been evaluated as coating powder over the years but only relatively few have the necessary combination of melting temperature range, melt viscosity and thermal stability that allows them to be used successfully in fusion coating processes.

2.   Thermosetting coating powders

Thermosetting coating powders are room-temperature stable mixtures of thermosetting resins, a curing agent (hardener) and frequently a catalyst. Coating

powders also contain a flow-control additive to reduce cratering and promote film formation as well as pigments or colorants, inert fillers or extenders and other additives to modify gloss, texture, mar resistance, hardness, heat and color stability, ultraviolet resistance and other characteristics.

General requirements for coating powders

- Non sintering on storage up to 120 °F
- Exhibit low melt viscosity at low rates of shear
- Exhibit a wide temperature range between melting and degradation
- Possess good dry flow characteristics
- Possess good storage stability; flow and application characteristics should not change significantly after storage at least six months at normal temperatures.
- Should not be moisture sensitive
- Must be uniform in color, application characteristics and properties from lot to lot
- In the case of thermosetting materials, cure rapidly at elevated temperatures
- Do not give off volatiles during curing

7.   The glass transition temperature

The glass transition temperature (Tg) is found in all amorphous polymers and in amorphous regions of partially crystalline polymers. The Tg of the latter is independent of the degree of crystallization but the magnitude of the transition decreases with an increase in crystallinity with the result that the transition becomes difficult to detect in highly crystalline polymers (Ford and Timmins., 1989).

At low enough temperatures, all amorphous polymer exist in a glassy state where no large-scale molecule motion can take place, and while in **the glassy state, polymers are characterized by their hardness, stiffness and brittleness. As the temperature is raised, polymers undergo a transition, known as the glass transition temperature, Tg, where they change from glass to a rubbery elastomer**

or flexible plastic. This transition takes place over a narrow temperature range and corresponds to the onset of segmental motion of long segments of the polymer chain, which is brought about by the availability of sufficient thermal energy to overcome intermolecular interactions.

As a consequence of this transition, the polymer undergoes an abrupt change in properties. Among these are coefficients of expansion, permeability, heated content, refractive index, and hardness. Thus, in designing a controlled-release device, it must be known whether at use, the polymer will be above or below its glass transition temperature.

The glass transition temperature also knows as the second-order transition, is a characteristic of a particular polymer structure, and its value is closely related to intermolecular forces and chain stiffness. Thus, because above the Tg segmental motions of polymer chains take place, it follows that very flexible polymer, where free rotation about bonds along the polymer chains is possible, will in general have low Tg values. For this reason, poly (dinethyl siloxane), in which virtually unrestricted rotation takes place between the silicon-oxygen bond, has one of the lowest Tg values known (-123 °C).

Clearly, the onset of segmental motion of polymer chains will also depend on the magnitude of intermolecular forces because no motion of polymer chains can take place until enough thermal energy is available to overcome those forces. Consequently, polymer with strong intermolecular interactions will tend have high Tg values (Heller, 1987).

Changes in the Tg of one polymer usually affect different film properties. Adding plasticizer can generally lower Tg because plasticizer enhances segmental mobility of polymer. In another way, adding pigment can generally reduce polymer chain mobility, which manifests as an increase in Tg. Moreover, modification to the polymer that increase the presence of polar groups, hydrogen bonds, and other factors that enhance the intermolecular forces tend to raise Tg.

Properties of glass transition temperature on coating properties (Misev, 1991)

A.   Tg and powder stability

Assume now a layer of powder coating particles exposed to a certain pressure derived from the weight of the powder particles above. If the **Tg of the powder is higher than the storage temperature**, because of the absence of segmental mobility there is no diffusion of the material on a segmental of molecular scale between different particles. In the case of having **Tg lower than the storage temperature,** the segmental mobility is high enough to produce, in the long term, a considerable degree of inter penetration of the molecular chains between different powder particles, resulting in blocking of the same. This phenomenon as known as physical instability of the powder coating. Therefore a high Tg value of the powder coating is a prerequisite for good physical stability.

B.   Tg and the melt viscosity

According to the free volume theory, Tg is related to the unoccupied volume by the polymer segments of molecules. The latter is directly proportional to the difference between the Tg and the temperature at which the viscosity of the polymer is monitored. The occupied volume facilitates the flow of the material or, with viscosity of the polymer defined, as a resistance to flow, should be directly dependent on Tg.

The Tg of the powder coating resins is much higher than the Tg of the resins for solvent borne coatings, for reasons related to the physical and chemical stability of the coatings. Consequently, the melt viscosities of the powder coating are several hundred times higher than those solvent borne coating at the curing temperature. The fact that there is no solvent present to reduce the viscosity during the film formation emphasizes this difference even more. This has an adverse effect on the flow and the levelling characteristics of powder coating.

C.   Tg and the thermal stress development

The internal stress development in cured coating is not a characteristic typical only of powder coatings. This phenomenon exists in almost all types of coating. The dimensional changes in the coating during film formation are the main reason for the stress formation. The shrinkage of the coating during crosslinking is very noticeable in the case of the radiation curing coatings, where the stress can be a reason for development of microcracks in the cured film or in extreme cases can cause even a detachment of the coating from the surface.

When the exploitation temperature of the coating is above Tg, the internal stress is completely relieved due to the fact relaxing processes. Below Tg the relaxation processes are very slow, and the coating layer cannot follow the dimensional changes of the substrate. Therefore a certain stress will build up, proportional to the difference between the Tg of the cured film and the temperature to which the coating layer is cooled down after the curing.

D.   Molecular weight and Tg

Tg is dependent on molecular weight of polymer. Some authors founded that Tg increased from 27 $^{\circ}$C for the molecular weight of Poly DL-lactic acid of 3,500 (PLA) to 54 $^{\circ}$C for the highest molecular weight PLA of 553,000. However, the differences in Tg became progressively less significant as the molecular weight increased from 92,000 to 553,000, reaching a plateau at 57-58 $^{\circ}$C. As the polymer molecular weight increased, there were fewer chain ends, which had less free volume than the same number of atoms in the middle of the chair. The decrease in free volume gradually reached a limit as the molecular weight increased because of chain entanglements. In the same manner, the energy required to produce the excess free volume, as reflected by the Tg, also reached a limiting value.

E.   Chemical structure and Tg

The influence of the chemical structure on Tg is not fully elucidated, although some general rules are well established. Since the Tg is related to the cooperative

motion of the groups or atoms making up the polymer chain, any molecular parameter affecting the chain mobility will influence the Tg. More precisely, any group or structure that reduces the chain mobility will increase Tg.

In system without solvents, like the powder coating, one could expect that the intermolecular attraction forces between the binders and the pigments and fillers should increase the Tg. But some author found that the fillers can increase or decrease the Tg, or have no remarkable effect.

F.   Tg of polymer blends

Polymer-polymer compatibility may also be evaluated from Tg data. If the two polymers in a binary film system are compatible, one Tg, lying between the Tg's of the individual polymers in the blend, is observed. For partially compatible polymers, two Tg's are detectable if the compatibility limit is exceeded: one for the blend and the other for the polymer which is in excess. Moreover, the glass transition spread or width for partially compatible polymer blends increases as the content of the second polymer is raised until just before incompatibility sets in.

7.   **Propranolol Hydrochloride**

Chemical name   :   * (±) 1-Isopropylamino-3- (1-naphthyloxy) propan-2-ol

                                                 o r   * 1 - [(1 - m e t h y l e t h y) a m i n o] - 3 - (1 - naphthalenyoxy)-2-propanol

Empirical formula   : $C_{16}H_{21}NO_2.HCl$

Structural formula :
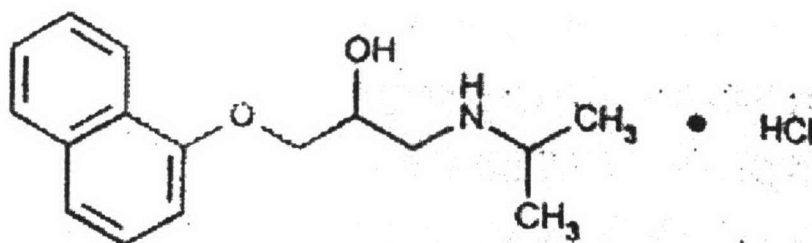
Figure 12 Chemical structure of propranolol hydrochloride (Lund W., 1994).

Molecular weight : 295.80

Description : white to off-white, odorless or almost odorless, crystalline powder with bitter taste. It absorbs less than 1 % of water at 25 °C at relative humidity up to 80 %.

Dissolution constant : pKa 9.5 (24 °C)

Melting point : melts in the range 163 to 166 °C.

Partition coefficients : in octnol/aqueous buffer pH7.4 is 1.2

Solubility : 1 in 20 ml of water and of alcohol, slightly soluble in chloroform and practically insoluble in ether.

Stability : Propranolol hydrochloride is affected by light. In aqueous solutions, it decomposes with oxidation of the isopropylamine side chain, accompanied by reduction in the pH and discoloration of the solution. Solutions are most stable at pH 3.0 and decompose rapidly under alkaline conditions.

Propranolol hydrochloride is a nonselective β-adrenergic blocking agent, which can inhibit responses to adrenergic stimuli by competitively blocking at the β-adrenergic receptors within myocardium, bronchial and vascular smooth muscle.

Propranolol hydrochloride is almost completely adsorbed from a GI tract and appears in plasma within 30 min, and peak plasma concentrations are reached about 60-90 min after oral administration.

Propranolol hydrochloride is widely distributed into body tissues including lungs, liver, kidney, heart and readily crosses the blood-brain barrier or placenta. The apparent volume of distribution at steady state widely varies in proportion to the fraction of unbound drug in whole blood. Propranolol hydrochloride is more than 90 % bound to plasma proteins over a wide range of blood concentrations. Both free and protein-bound drugs are metabolized. Increased plasma protein binding of the drug increases its metabolism and decreases its volume of distribution, resulting in a shorter terminal half-life.

Propranolol hydrochloride is almost completely metabolized in the liver and at least 8 metabolites have been identified in urine. Only 1-4 % of an oral dose of drug appears in feces as unchanged drug and metabolites.

Elimination or propranolol hydrochloride appears to follow first-order kinetics and seems to be independent of plasma concentration or the dose administered, at least with oral doses of 160-320 mg/day.

8.   Eudragit® E 100 and Eudragit® E PO

"Butylmethacrylat-   (2-Dimethylaminoethyl)   methylacrylat-Methylmethacrylat-Copolymer (1:2:1)" DAB

"Aminoalkylmethacrylate Copolymer E" JPE
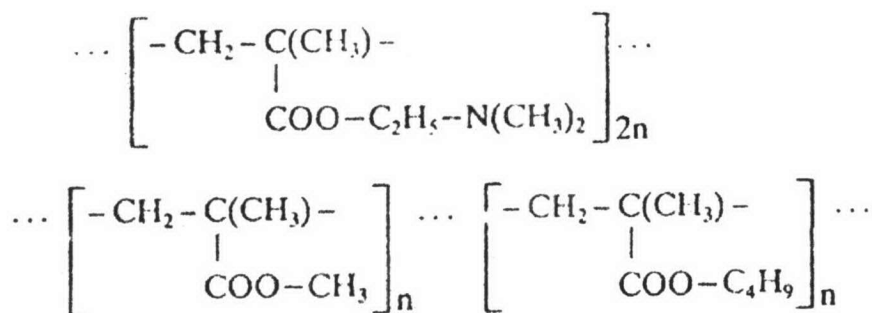
A. Commercial form

Eudragit® E 100   :   Solid substance (granules)

Eudragit® E PO   :   Solid substance obtained from Eudragit® E 100.

B. Chemical structure

Eudragit® E 100 is a cationic copolymer based on dimethylaminoethyl methacrylate and neutral methacrylic esters. The average molecular weight is approximately 150,000.

$$\cdots \begin{bmatrix} -CH_2 - C(CH_3) - \\ | \\ COO-C_2H_5-N(CH_3)_2 \end{bmatrix}_{2n} \cdots$$

$$\cdots \begin{bmatrix} -CH_2 - C(CH_3) - \\ | \\ COO-CH_3 \end{bmatrix}_{n} \cdots \begin{bmatrix} -CH_2 - C(CH_3) - \\ | \\ COO-C_4H_9 \end{bmatrix}_{n} \cdots$$

Figure 13   Chemical structure of Eudragit® E PO (Bauer, 1998)

C. Characters

Description   :   Eudragit® E 100; colorless to yellow tinged granules with a characteristic amine-like odor.

Eudragit® E PO; white powder with a characteristic amine-like odor.

Solubility   :   1 gm of solid substance (granules, powder or film) dissolves in 7 gm methanol, ethanol, isopropyl alcohol, acetone, ethyl acetate, methylene chloride or 1 N hydrochloric acid to give clear to slightly cloudy solutions.

The solid substance is practically insoluble in petroleum ether and water.

D. Tests

Test solution   :   12.5 % (w/w) dry substance is dissolved in mixture of 60 % (w/w) isopropyl alcohol and 40 % (w/w) acetone.

Particle size   :   Eudragit® E PO; at least 90 % <0.315 mm

Film formation   :   When the test solution is poured onto a glass plate, a clear film forms upon evaporation of the solvents.

Loss on drying   :   Max 2.0 %

E. Storage

Protect from warm temperatures and moisture. Eudragit® E 100 and Eudragit® E PO tend to form lumps at warm temperatures. This has no influence on the quality. The lumps are easily broken up again. Temperatures above 25 °C will cause caking of Eudragit® E PO. The product must therefore be stored well closed at or below room temperature

F. Applications

Eudragit® E is adequate for ordinary protective functions such as taste masking and satisfactory storage stability in moderate climates. A coating of this type is, moreover, sufficiently abrasion-resistant and disintegrates rapidly in gastric fluid, as well as in water at neutral pH by swelling of cores with some slight disintegrating action

Lin and co-workers have investigated the mechanical properties, adhesion strength, drug-polymer interaction and drug release from a self-adhesive drug-loaded Eudragit® E film for transdermal application (Lin et al., 1991).

Eudragit® E was found successful in preventing crystallization in drug-in-adhesive transdermal system of estradiol (Kotiyan et al., 2001).

Solid dispersions of itraconazole prepared with pH-dependent hydrophilic polymers, AEA® and Eudragit® E, resulted in greater increases in drug solubility over those prepared with pH-independent hydrophilic polymers, PEG 20,000, PVP, Poloxamer® 188 and HPMC. Tablets containing the solid dispersion particles prepared by spray drying showed enhanced dissolution profiles of itraconazole over the marketed product (Jung et al., 1999).

9.   **Eudragit® RD 100**

A. Commercial form

Solid substance in the form of a fine white powder with a faint, amine-like odor.

B. Chemical structure

Eudragit® RD 100 is a powder combination of 91 parts dry substance of Eudragit® RL 100 and 9 parts sodium carboxymethylcellulose for the manufacture of rapidly disintegrating coating. When stirred into water, Eudragit® RD 100 forms a dispersion that can be processed in the usual manner it is pH independent and fast disintegrating for aqueous taste and odor masking formulations.

C. Dispersibility

100 gm of water was filled into a 250 ml beaker and dissolved 3 mg of polysorbate 80 therein, using a magnetic stirrer. Then 15 g of Eudragit® RD 100 was added slowly stirring and continues for another 30 min. The dispersion was passed thus was obtained through a steel wire cloth with mesh size of 0.4 mm and rinse the cloth with water until the filtrate is clear. There should be no major residues.

Table 4   Processing properties of Eudragit® RD 100

Processing properties	Data
Minimum film-forming temperature	<10 °C with 20 % polysorbate 80
Glass transition temperature	Approximately 26 °C with 20 % polysorbate 80
Decomposition temperature	>130 °C

D. Storage conditions and stability

Eudragit® RD 100 should be protected against moisture and stored below 25 °C

E. Application

Rapidly disintegrating coating on tablets and active particles in coating pns and fluidized bed equipment.

For medium-sized tablets, a polymer weight of 1 mg/cm2 is usually sufficient for a coherent coating. In special cases, e.g. for effective taste masking, higher quantities may be required. Owing to the excellent pigment-binding capacity, even very dark cores can be provided with light-colored coating at low polymer requirement. Surface textures, e.g. engraving, are reproduced and recognizable after coating.

Tablets and particles can be coated in conventional equipment according to known techniques. The process parameters to be selected are the same as for working with aqueous dispersions. Polysorbate 80 serves as a plasticizer and reduces the minimum film-formation temperature.
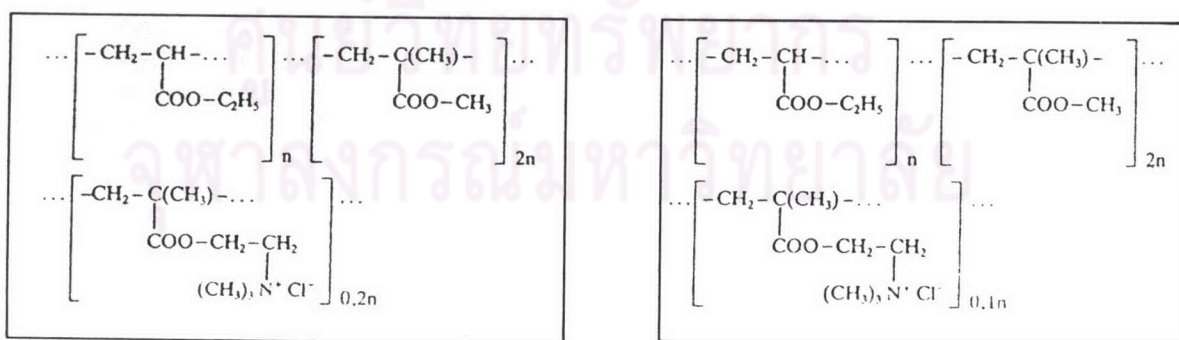
9. Eudragit® RL PO and Eudragit® RS PO

"Ammonio Methacrylate Copolymer, Type A and B" USP/NF

A. Commercial form

Solid substances obtained from Eudragit® RL 100 or Eudragit® RS 100.

B. Chemical structure

Eudragit® RL PO and Eudragit® RS PO are copolymer of acrylic and methacrylic acid esters with a low content in quaternary ammonium groups. The ammonium groups are present as salts and make the polymers permeable. The average molecular weight is approximately 150,000.

A.   B.

Figure 14   Chemical structure of (A) Eudragit® RL PO and (B) Eudragit® RS PO (Bauer, 1998).

C. Characters

Description   :   White powders with a faint amine-like odor.

Solubility   :   1 gm of Eudragit® RL PO or Eudragit® RS PO dissolves in 7gm aqueous methanol, ethanol and isopropyl alcohol (containing approximately 3 % water), as well as in acetone, ethyl acetate and methylene chloride to give clear to cloudy solutions.

Eudragit® RL PO and Eudragit® RS PO are practically insoluble in petroleum ether, 1 N sodium hydroxide and water.

D. Testes

Test solution   :   12.5 % (w/w) dry substance is dissolved in mixture of 60 % (w/w) isopropyl alcohol and 40 % (w/w) acetone.

Particle size   :   at least 90 % <0.315 mm

Film formation :   When the test solution is poured onto a glass plate, a clear film forms upon evaporation of the solvents.

Loss on drying :   Max 3.0 %

E. Storage

Protect from warm temperature and moisture.

F. Applications

Eudragit® RL 100 / Eudragit® RS 100 are copolymers synthesized from acrylic and methacrylic acid esters with hydrophilic quaternary ammonium groups s functional units in the polymer chain. They can be used without other release-controlling excipients as permeable membranes. The permeability depends directly on the content of the hydrophilic units (trimethylammonioethyl methacrylate chloride). Eudragit® RL 100 contains 10 % w/w of this unit, resulting in very permeable film that tend to disintegrate quickly in water; therefore, this type is used for fast

disintegrating cores. On the other hand, Eudragit® RS 100 contains only 5 % w/w hydrophilic units and exhibits very low permeability. With increasing film thickness up to about 100 micron, the release rate can be dropped down to very low rates, to give sustained release over 24 hour or even more.

Because of the outstanding characteristic of Eudragit® RL and Eudragit® RS many utilization have been presented. Many applications are applied to the controlled drug delivery system. Changing polymer types, polymer ratio, coating level and pH range will affect the characteristics to the drug release. Such implementations are followed:

Binchini prepared a multiple units dosage form in order to control the release of alpha-indobrufen. The system consists of cores containing the active substance coated with a diffusive film. Polymer chosen for the film formulation were ethylcellulose and copolymers of acrylic ester with differing permeability characteristics. Film composition and film thickness are reconfirmed as parameters that extremely influence drug release profile.

Chang prepared theophylline pellets coated with Eudragit® RL and Eudragit® RS 100 in a fluidized bed. The effect of polymer type and coating level, plasticizer concentration and pH of the dissolution medium on drug release Eudragit® RS films retarded theophylline release over a wide pH range. Release of the drug was found to be a function of the polymer coating level, plasticizer concentration and dependent on pH of the dissolution medium.