CHAPTER II
LITERATURE REVIEW

1. Fluidization

Fluidization is a process in which a bed of small solid particles is suspended and agitated by a rising stream of gas which enables a thorough gas-solid contact throughout the bed (Yang et al., 1992). The technology has been used in a number of industries for diversified application, ranging from limestone calcinations, preparation of synthetic gasoline, petrochemicals and even the design of nuclear reactors (Zenz, 1980). Fluid bed technology has been increasingly utilized by the pharmaceutical industry in various unit operations, including drying, granulation, pelletization and coating. It is well known for its drying efficiency, having been used for drying and granulating for many years. The use of fluid bed equipment in applying coating systems has increased greatly due to (1) improved drying efficiency, (2) improved design and (3) increased experience (Mehta, 1997).

1.1 Stage of fluidization

The successive stages of fluidization are shown in Figure 1. Fluidization is usually carried out in a cylindrical container or column holding the powder, which is supported when at rest on a porous plate. As the upward flow of fluidizing gas is increased through the stationary powder bed (stage A), the particles are lifted upward and the bed expands (stage B). Suddenly, there is a break in the heretofore uniform relation between the pressure applied and the flow rate produced, and the bed quickly changes over from static to mobile (stage C). Further small increases in pressure cause large increases in flow, and the bed expands considerably with an increase of voidage and usually the formation of bubbles (stage D). Eventually, the lifting force of the upward gas flow causes particles to be blown out of the bed altogether and pneumatic transport occurs (stage E). It is generally desirable that the air velocity be controlled at the minimum fluidization level (Mathur, 1992). Thus the upward lifting force on the bed of particles is just equal to their weight and the bed is just fluidized.

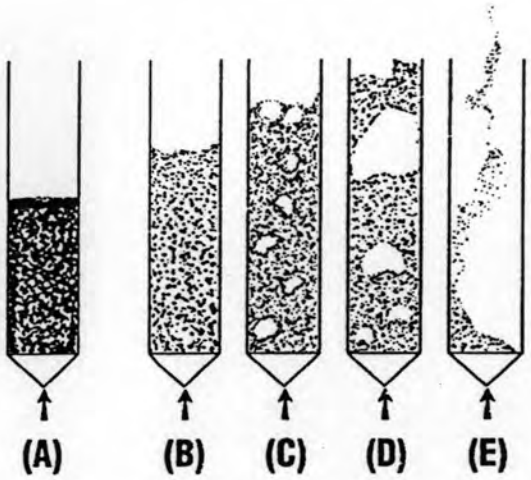

Figure 1 Stages of fluidization: (A) Static bed; (B) Expanded bed; (C) Mobile bed; (D) Bubble formation; (E) Pneumatic transport (Mathur, 1992).

1.2 The Geldart Classification of Particles

A full classification of powder according to their behavior in fluidization is complex depending on particle properties. Geldart and co-worker have identified two parameters to classify powder for fluidization i.e. the particle size, the particle density. Geldart's classification is clear and easy to use (Kunii and Levenspiel, 1991) and is readily displayed in Figure 2 for air fluidization at ambient conditions.

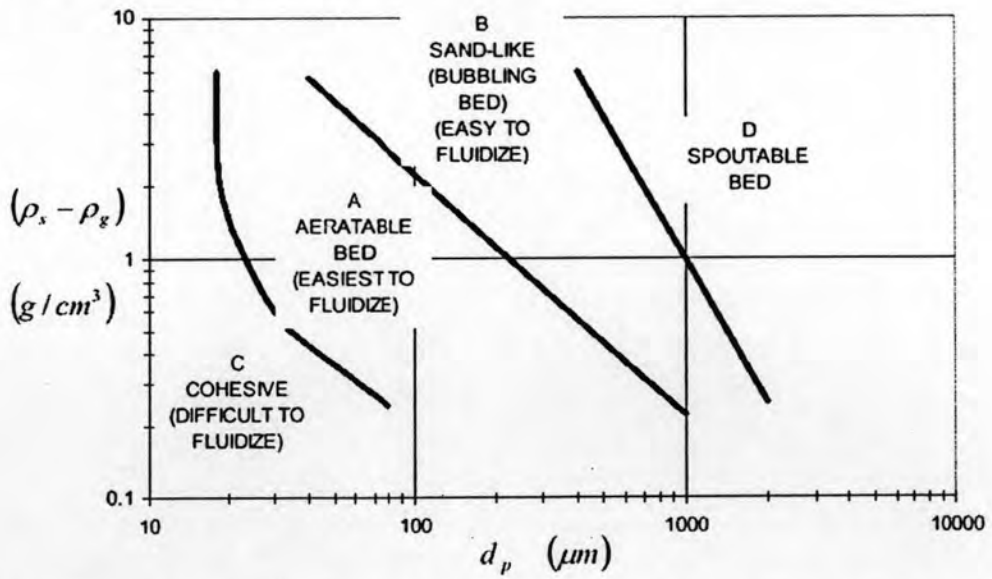

Figure 2 The Geldart classification of particles for air at ambient conditions (Phoonphetmongkon, 2004)

Group A: aeratable, or materials having a small mean particle size (range 50 to 200 microns) and/or low particle density. This particles exhibit large bed expansion after minimum fluidization and before start of bubbling; the bubble size is limited.

Group B: sandlike or most particles of size 40 to 500 microns and density 1.4 to 4 g/cm^3 e.g. sand, pellets and granules. These solids fluidize well with vigorous bubbling action and bubbles that grow large.

Group C: cohesive or very fine powder (size range less than 20 microns). This group is difficult to fluidize at all, they exhibit a tendency to form channeling. The denser and larger crystal are behave like group D.

Group D: spoutable or large and/or dense particles. Deep beds of these solids are difficult to fluidize. The bed expansion is minimal, even less than for the group B. They behave erratically, giving large exploding bubbles or severe channeling, or spouting behavior if the gas distribution is very uneven.

The key fluidization properties of solids from the different group appears in Table 1

Table 1 Summary of group properties (Phoonphetmongkon, 2004)

	A	B	D
Most obvious Characteristic	Bubble-free range of fluidization	Start bubbling at minimum fluidization velocity	Coarse solids
Typical Pharmaceutical substrates	Microparticles	Pellets; granules; Light, small crystals	Tablets; capsules; Heavy, large crystals
1. Bed expansion	High	Moderate	Low
2. Deaeration rate	Slow, linear	Fast	Fast

3. Bubble properties	Splitting / recoalescence predominate Maximum size exists Large wake	No limit on size	No know upper Size Small wake
4. Solids mixing	High	Moderate	Low
5. Slug properties	Axisymmetric	Axisymmetric; Asymmetric	Horizontal voids, Solids slug, wall Slugs
6. Spouting	Not except in very shallow beds	Shallow beds only	Even in deep beds

1.3 Fluid bed coater (Mathur, 1992; Yang et al., 1992; Mehta, 1997)

In fluid bed coating, a liquid feed is sprayed onto a bed of solid particles either for film deposition on each particle or for the growth of particle size. The liquid feed can be applied by using one of the three spray modes, top spray, bottom spray or tangential spray.

1.3.1 Top spray coating

The top spray mode may be used for granulating or coating. The geometry of a granulator is very similar to that of a top spray coater. Each consists of a product container and an expansion chamber. The most significant characteristics of the top spray method is that the nozzle sprays countercurrently or down into the fluidizing particles as shown in Figure 3.

The fluidization pattern is random and unrestricted. As a result, controlling the distance of the droplets travel before contacting the substance is impossible. The only difference in the geometry of a granulator and a top spray coater lies in the shape of the expansion chambers. In a top spray coater, the expansion chamber is longer to allow higher fluidization, and has a conical shape instead of a cylindrical shape, as in a granulator, to reduce the velocity of particles as they reach the section near the filter. The high velocity and efficient heat transfer allow aqueous coating of small particles with little or no agglomeration. It has the largest batch capacity, 0.5 kg to approximately 1000 kg, and downtime between batches can be only minutes. The films formed in this process are not as uniform, but for releases that

are not dependent on membrane thickness or perfection, such as taste masking, it is viable and simple approach.

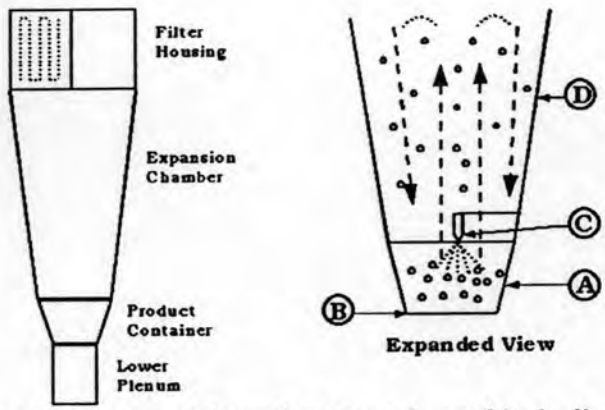

Figure 3 Top spray coater: (a) product container; (b) air distribution plate (c) spray nozzle; (d) expansion chamber (Mehta, 1997).

1.3.2. Bottom spray coating (Wurster process)

In the bottom spray mode, the nozzle is placed in the center of the gas distributor plate and liquid is sprayed concurrently with the fluidization air. The majority of the air is diverted through the partition, causing fluidization and upward travel of the cores. The process chamber for laboratory size equipment has a narrow diameter in the product-containing area which facilitates well organized particle motion, and therefore, reproducible coating results can be obtained. However, as the chamber becomes larger, particle motion loses its regular and circulatory pattern and becomes disorganized. As a result, a Wurster chamber (US patent 5,236,503) is commonly used for bottom spraying to produce an organized flow of particles similar to that observed in a spouted bed; more pronounced upward motion in the center and downward motion near the perimeter.

With a Wurster chamber (Figure 4), a cylindrical partition is mounted in the center and slightly above the gas distributor plate. The design of the plate is such that more air enters the partition than the surrounding area to generate a circulatory motion of particles. The fluidized particles enter the partition, travel upward through the spray zone and into the expansion chamber. Then, the particles decelerate and fall into the area outside the partition, from where they are driven horizontally back into the bottom of the partition to start the next circulatory cycle.

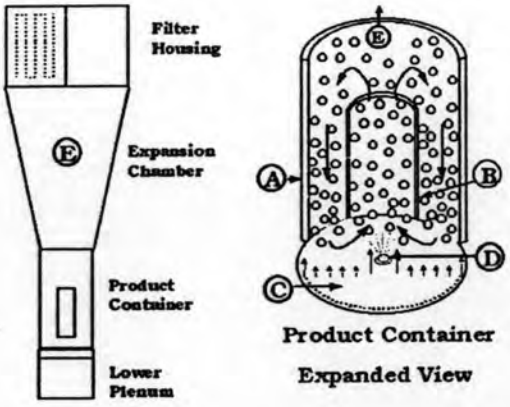

Figure 4 Wurster bottom spray coater: (a) coating chamber; (b) partition; (c) air distribution plate; (d) spray nozzle; (e) expansion chamber (Mehta, 1997).

The Wurster system has the widest application range of both water and organic solvents. The certain disadvantages of this system are that it is somewhat complicated and tallest machine among of the three types of fluidized bed machines. Also, the nozzles are inaccessible during the processing. In addition, it has minimum volume limitation, and shows difficulty of loading and unloading (Parikh and Mogavero, 2005).

1.3.3. Tangential spray coating

The basic design (Figure 5) employs a rotating disk in the product container. The disk can be moved up or down to create a variable slit opening between the outer perimeter of the disk and the side wall of the container. This allows independent control of air velocity over air volume. Air is drawn into the product container through the slit under negative pressure. This fluidizes the material along the circumferential surface of product chamber. At the same time the disk rotates at varying speeds and moves the product by centrifugal force to the outer portions where it is lifted by the fluidizing air stream into the expansion chamber. As the material decelerates, it descends to the center of the disk and repeats the sequence (Mathur, 1992). The motion of the fluidized material is thus controlled by the forces of fluidization, centrifugal force, and gravity. The magnitude of each of these forces

depends upon the fluidization air volume, the slit width and the rotating speed of the disk (Yang et al., 1992)

Different from the Wurster system, the rotary tangential spraying system has a relatively wide application range. It is the shortest machine in height of the three, and allows nozzle accessible during processing. It has capability of producing high dose pellets and applying coating for all types of release. Its primary disadvantage is that it exerts the greatest mechanical stress of the three methods and, thus, is discouraged for use with friable substrates.

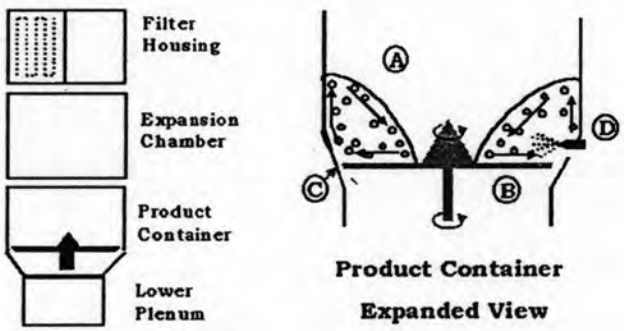

Figure 5 Tangential spray coater: (a) produce chamber; (b) variable speed disc (c) disc gap or slit; (d) spray nozzle (Mehta, 1997).

Since the spray mode determines not only the spray pattern of the coating formulation, but also how the sprayed droplets impinge and spread on the substrates, it is expected to have a significant impact on the film structure (Mehta and Jones, 1985).

Wesdyk et al. (1993) examined the effect of spray mode and process variation on the variation of film thickness for fixed particle size range and distribution. It was observed that unlike batches coated in the bottom spray (Wurster) mode, the batch coated in the top and tangential spray modes exhibited no trend in film thickness. The result also indicated that for the bottom spray mode, a reduction in the atomizing air pressure, while substantially reducing differences in fluidization patterns, had only a marginal effect in reducing the differences in film thickness.

2. Coating

The first coated pharmaceutical dosage forms were medication with sugar coatings for the purpose of masking unpleasant tastes and imparting a more elegant appearance. For a long time lasting gloss was therefore the major prerequisite. Nowadays the purpose of coating as the following categories (Radebaugh, 1992):

- Protection of drugs from environment factors such as light, moisture and air. In order to improve chemical and physical stability.
- Increased mechanical stability during manufacture, packing and shipment.
- Modification of product appearance to enhance marketability or hide undesirable color changes of the substrate.
- Masking of unpleasant taste, texture or odor.
- Increasing drug safety by better identification.
- Controlled or modified release of drugs.
- A mechanical barrier to avoidance of side effects or the interaction of incompatible ingredients.

The significant ingredients used in film coating are polymers, plasticizers and additives such as colorants, flavors or sweeteners, surfactants, antioxidants and antimicrobial agents.

2.1 Types of coating

Coating materials usually consist of a mixture of substances. The matrix formers are responsible for the stability of the coating structure, and they also determine the coating process. Depending on the type of matrix former or binder used, four coating categories can be distinguished.

2.1.1. Coating with sucrose and other sugar

It permits application of large amount of mass to the core and is widely used in the manufacture of pharmaceuticals and confectionery. Coating pans are the preferred type of equipment, belt coaters being the exception.

2.1.2. Hot melt coating

They are mainly used for confectionery. The most important raw materials are fats, mostly cocoa fat and the sugar/ alcohol mixture xylitol/ sorbitol. Process is conducted in pan or on belts.

2.1.3. Film coating

They require less material, forming thin membranes that largely follow the contours of the substrate, e.g. score and engravings. The film formers may affect the partly on pH-dependent solubility and selective permeability of coatings. Coating pans and fluidized bed equipment are generally used for processing.

2.1.4 Powder coating

Dosage forms are coated directly with micronized polymer powder. The curing after coating at elevated temperatures was necessary for the coalescence of the plasticized polymer particles and film formation. Coating was performed using a centrifugal granulator, fluid bed and coating pans.

There is an inherent conservatism expressed by pharmaceutical manufacturers towards accepting major changes in raw materials and processing technologies. Thus, change tends to be evolutionary rather than revolutionary (Rudnic and Schwartz, 2006). Some interesting events have occurred over the last decade.

One advance is the continuous coating processes, usually reserved for large volume products where desired applied coating levels are in the range 3-4% (based on the tablet core weight).

A more revolutionary approach to film coating, also based on a continuous process, involves the electrostatic deposition of powder coating system to the surface of the tablets and fusing the coating through application of heat using principles that are based on electrophotography (photocopying). In this process described by Staniforth et al. (1998) and illustrated in Figure 6, tablets are coat individually one side at a time. The advantages of this type of process are: no solvent are used; the coating deposits onto the tablets in a much more precise manner than conventional

coating process; novel imaging can be achieved and tablets can be only partially coated, thus facilitating applications involving novel drug delivery.

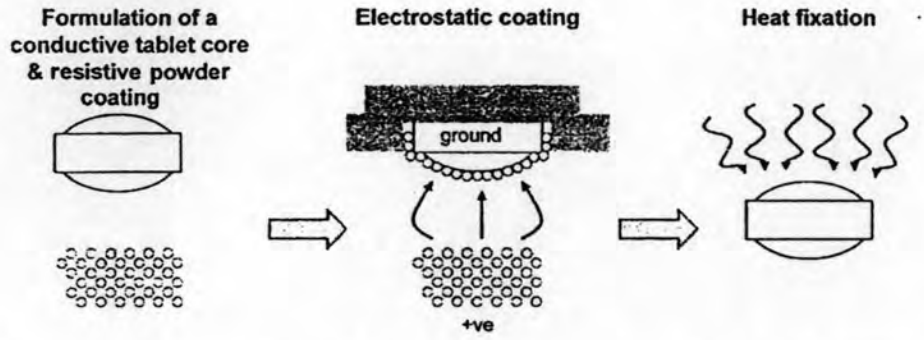

Figure 6 Electrostatic powder coating process (Staniforth et al., 1998)

In addition, the growing interest in Process Analytical Technology has resulted in bringing many analytical procedures out of the laboratory and closer to manufacturing process. The desire here is to introduce, ideally as on-line control function, specific analytical techniques that can be used to enhance the quality of the final coated products.

2.2 Film coating

Film coating are an integral part of the dosage form development process. The process of film coating involves the application of a thin film onto the surface of a solid substrate. The substrate can be tablets, capsules, pellets, granules or particles. Typically, the coating is approximately 25 to 100 μm in thickness and is applied to improve the physical and chemical properties of the substrate (non-functional film coating) or modified film coating, controlled release coating (functional film coating).

2.2.1 Core or substrate for film coating (Bauer, 1998)

The various core or substrate can be used in film coating. Whether or not a core is suitable for coating depends on the following common properties:

Hardness

Coating process requires core of adequate strength or abrasion-resistant substrate that is less susceptible to impact stress, because the formation of a

coherent film coating takes some time. However, the coated cores must also disintegrate rapidly enough in digestive fluids to ensure good bioavailability.

Shape

Slightly curved tablet cores are preferred for film coating. Small cores like pellets, crystals and granules show pronounced fluctuation in size, shape and surface. A narrow particle size distribution can be obtained by screening, which then avoids batch to batch fluctuations in material consumption and irreproducible results.

Surface

The surface has a major influence on the buildup of the first few coating layers. Film coating requires smooth and dust-free surfaces because they are relatively small thickness. Surface which are poorly wettable make it difficult to achieve adhesion between layers.

Size

Typically, coating technique serves for cores from about 0.2 mm diameter upwards. If the core are in the diameter range of 0.2 to 2 mm, they relatively large surface and small mass. The adhesion between the particles then has adverse influence on coating process, since they tend to stick together. The envisaged application dictates the upper limit of the core size .The pharmaceutical dosage form must still be swallowable and occasionally chewable.

Heat sensitivity

The process heat can have an adverse effect on sensitive drugs or excipients in the core. If the heat in the process is not properly controlled or critical temperature is exceeded, this may result in drug decomposition and changes in drug release or dissolution profile, in some cases even from batch to batch.

Interaction between core and coating

Excess of moisture residue in the core that migrates into the coating during the storage may cause cracks, crevices and reduced the stability of the active

ingredient. Hydrophilic swelling substances, which are normally incorporated as disintegrants, cause the core to swell under the influence of moisture. Swelling of the core during administration is, however, desired because some film coats resist dissolution, dissolve with difficulty or forming gel.

Substances migrating from the core into the coating may impair the aesthetic appeal of the coated product by mottling, discoloration or fading and blooming. Blooming means that substances migrate to the surface by sublimation or diffusion.

2.2.2 Polymeric solutions and Polymeric dispersions

Film coatings consist mainly of polymers, which are applied to the cores in the form of solution or dispersion in which the excipients are dissolved or suspended. After drying of the solvents or dispersing agents, the polymer and other excipients remain on the cores as a coherent, uniform film. The other excipients may account for up to 60% of the coating layer, depending on the pigment-binding capacity of the polymers (Bauer et al., 1998). Pharmaceutical film coating formulations including organic solutions and aqueous dispersions. Organic solution produces good results but suffers from serious drawnbacks such as pollution, fire and safety hazards. However, the technique is still widely used particularly when specialized polymers are used for coating. With the advent and successful use of aqueous film coating over several years, many initial difficulties and preconceptions have disappeared and a most useful pharmaceutical production process has resulted (Hogan, 1982).

2.2.3 Mechanism of film formation

Film structure is a key factor in determining the performance of any polymeric coating. Consequently, understanding the process of film formation with any polymeric system can help provide insight into how the final coating will behave.

Polymeric solution

Generally, film formation from an aqueous or organic solvent solution of polymer involves conversion of a viscous liquid into a viscoelastic solid.

Based on the solvation process itself, the particles involved are individual polymer molecules, extended as long chains and separated from each other only by molecular distances in the solvent. As solvent rapidly evaporates, the coating liquid will increase in concentration and contrast in volume and hence increment in the viscosity. Further loss of solvent at a slower rate is now controlled by the diffusion rate of solvent through the polymer matrix. Then, concentration of the polymer in coating increases to the point where the extended polymer chains ultimately become immobilized, so-called solidification point. As the remaining solvent is gradually lost, beyond the solidification point, resulting from the slow diffusion of residual solvent through the "dry" coating, the gelled solution forms a continuous film and produces a three-dimentional dried gel or xerogel network (Banker and Peck, 1981; Porter, 1989; Porter and Bruno, 1990).

From a structural standpoint, the quality of the final dried coating is very much determined by the initial interaction between the polymer and the solvent, and the volatility of the solvent system used. Maximum interaction between the polymer and the solvent often determined by cohesive energy densities, or solubility parameters, typically results in maximum chains in the resultant dried coating will also be high, yielding a film with good mechanical properties. Volatibility of the solvent will play a large part in determining the tendency of the polymer solution to partially "spray dry" during application, resulting in the formation of a very porous coating (Porter, 1989)

Aqueous polymeric dispersions

Films are formed from aqueous polymeric dispersions (or pseudolatex) by a completely different mechanism to those obtained from polymeric solution. In the liquid stage, the polymer is present as discrete particles in aqueous suspension. To form a continuous film, these polymeric particles must come closely together, deform and ultimately fuse together. At the same time, the vehicle, water, must be removed (Porter, 1989)

The actual mechanism is quite complex and many competing theories exist to explain the process. 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 dry particle layers (Fukumori, 1994).

In simplification, as latex dries and water rapidly evaporates, the latex particles are forced nearer and nearer together until they begin to contact one another closely. The water film surrounding the latex particles shrinks, thus providing a high surface tension that drives the particles still closer together. Strong driving forces must be present to overcome the inherent hardness of the polymer spheres, causing the polymeric particles to deform and coalesce; and overcoming electrostatic repulsive charges. Figure 7 represents a latex dispersion consistence of spheres that are suspended and separated by electrostatic repulsion.

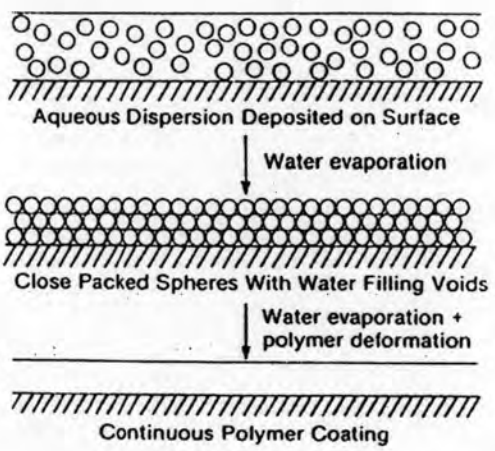

Figure 7 Film formation from pseudolatex (Wheatley and Steuernagel, 1997)

As water evaporates, the capillary force between particles resulting from high interfacial tension between the polymer and water and from the surface tension between water and air provides the main force for overcoming the electrostatic repulsion. The forces exerted on spherical particles as evaporation proceeds as shown in Figure 8. Film formation then occurs by coalescence as the boundaries between the adjacent latex particles disappear and movement of polymer molecules across the interfaces between particles occurs (Banker and Peck, 1981; Porter, 1989; Porter and Bruno, 1990; Wheatley and Steuernagel, 1997).

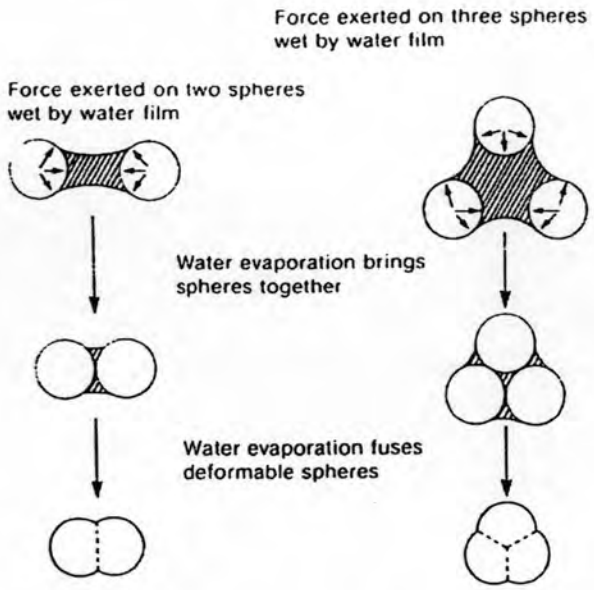

Figure 8 Particle coalescence during the evaporative phase.
(Wheatley and Steuernagel, 1997)

Coalescence of latex particles may be facilitated by the addition of appropriate plasticizer, one that should be capable of diffusing itself into latex beads. This will soften the beads and reduce their melting or transition temperature, thereby, reducing their resistance to deformation. The plasticizer has to be compatible with the polymer to promote polymer chain mobility and flexibility. Such plasticizer should not separate during film formation and should tend to become a permanent component of the film. The resulting structure helps the pseudolatex to produce denser, less-permeable films, higher-gloss films and films of higher mechanical strength (Banker and Peck, 1981; Fukumori, 1994).

3. Electrostatics

Electrostatics is that class of phenomena which is recognized by the presence of electrical charges, either stationary or moving. The interaction of these charges, this interaction being solely by reason of the charges themselves and their position and not by reason of their motion.

3.1 Electric charge

All substances are made up of atoms and molecules. Each atom has a positively charged central core, called the *nucleus*, which is surrounded by a cloud of negatively charged *electrons*. The nucleus consists of a number of *protons*, each with a single unit of positive charge, and, except for hydrogen, one or more *neutrons*. As the name suggests, a neutron is a neutral particle.

Normally, an atom of matter is in a neutral or uncharged state because it contains the same number of protons in its nucleus as there are electrons surrounding the nucleus. A schematic diagram of the neon atom is shown in the Figure 9. If, for some reasons, a neutral atom loses one or more of its outer electrons, the atom has a net positive charge and is referred to as a positive *ion*. A negative ion is an atom that has gained one or more additional electron (Tippens, 2007).

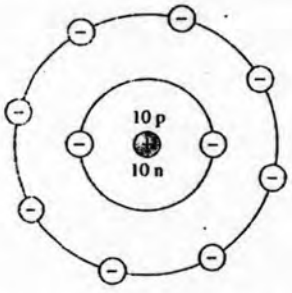

Figure 9 The neon atom consists of a tightly packed nucleus containing 10 protons (p) and 10 neutrons (n). The atom is electrically neutral because it is surrounded by 10 electrons.

When two particular materials are brought in close contact, some of loosely held electrons may be transferred from one material to the other. For example, when a hard-rubber rod is rubbed against fur, electrons are transferred from the fur to the rod, leaving an excess of electrons on the rod, negatively charged, and a deficiency of electrons on the fur, positively charged, (Tippens, 2007). It should be noted that for many materials it is easier to produce negative ions and for others positive ions are more readily produced. Many other substances form positive or negative ions with about equal ease.

The term ion a from its usage in electrochemistry, where it denotes the carriers of electrical current, moving charge particles, in conductive solutions. Here we make a distinction between ions and large charged particles-raindrops, for example. An ion is defined to be charged particle, either positive or negative, of atomic or molecular size. The ions may exist either in a liquid or in a gas and occasionally in a solid.

3.2 Law of electrostatics

If a glass or ebonite rod is charged by rubbing, some of that charge may be transferred to another object, such as a light pith ball, a light sphere of wood pith painted with metallic paint, by physical contact. By this procedure, one can, in a series of simple experiments diagrammed in Figure 10, demonstrate that:

1. Like charge repel each other.
2. Unlike charge attract each other.

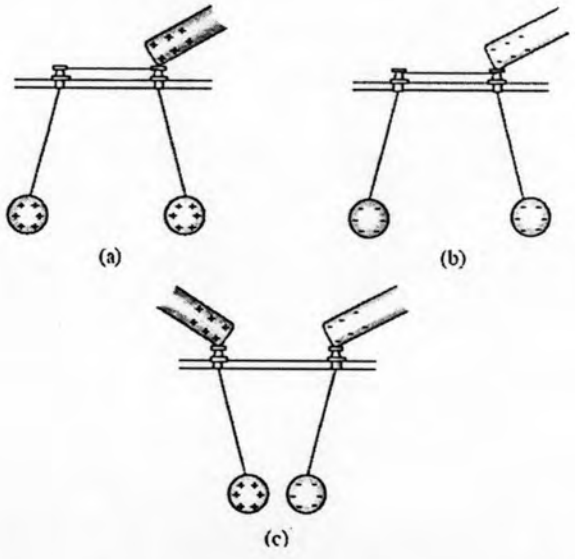

Figure 10 Two pith balls that have painted with aluminum paint are suspended by a metallic supports bar (Phoonphetmongkon, 2004).

(a) and (b) Like charge

(c) Unlike charge

Another important characteristics of electrical charge is that the net charge in an isolated system is always conserved. When two initially neutral objects are charged by being rubbed together, charge is not created in the process. The objects

become charged because electrons are transfer from one object to other. One object gains some amount of negative charge from the electron transferred to it while the other loses an equal amount of negative charge and hence is left with a positive charge. For the isolated system of two objects, no transfer of charge occurs across the boundary of the system (Jewett and Serway, 2006).

An uncharged object contains an enormous number of electrons. For every negative electron, however, a positively charge proton is also present; hence, an uncharged object has no net charge of either sign. Total charge on an object is quantized as integral multiples of the elementary charge (e= 1.60 x 10^{-19}) because the charge on an object must be due to an integral number of excess electrons or a deficiency of an integral multiples of the electrons.

3.3 Charging mechanism

The three mechanisms that are generally involved in charging materials are corona charging, induction charging and tribocharging(White,1963).

3.3.1 Corona charging

The charging of particles by ions from a corona discharge was investigated in the 19th century and led to the development of the electrostatic precipitator. Corona discharges are relatively low-power electrical discharges that take place at or near atmospheric pressure (Cross, 1987). The corona is invariably generated by strong electric fields associated with small diameter wires and sharp edges of electrodes. Ions from a corona discharge can be used to charge particles or surfaces. Any particles moving through such an ion-rich region perturb the local field, effectively intensifying the field at the particles surface, in proportion to the permittivity of the particle. Ions are directed by this intensified field to the particle surface and thus charge it. Random ionic motion may be ignored under many field-charging conditions. Field charging is considerably more efficient than charging by ion diffusion alone.

In powder coating or electrostatic precipitator applications, it is necessary to have a strong electric field near the collecting electrodes for efficient

deposition of charged particles. In the corona charging process, particles larger than 2 μm in diameter are charged by field charging (White, 1951) and particles smaller than 0.2 μm are charged primarily by diffusion charging (Cross, 1987). The particles in the intermediate range are charged by both diffusion and field charging.

3.3.2 Induction Charging

Charging an object by induction requires no contact with the object inducing the charge (Jewett and Serway, 2006). Charge can be conducted to ground or from ground onto a conductor. For instance, the situation shown in the sequence of Figure 11 (a), (b), and (c), when the positively charged glass rod is brought close to the metal sphere, which has been connected to ground by a conducting wire, negative charge electrons are attracted toward the positively charged glass and flow from ground to the surface of the sphere. If the wire is connected from the sphere without moving the glass rod, whatever charge has been drawn to the sphere from ground is trapped and will remain on the sphere even after the glass rod has been withdrawn.

This method of charging a conducting object is called charging by induction. The charge is induced on the conductor by the proximity of another charged object, not transferred to it directly as in charging by conduction. It is to benoted that when a conductor is charged by induction, its charge is of a sign opposite to that on the charging object. Also the convenience of charging by induction are: the charging objected of its charge; and the process can be repeated innumerable times without the need of renewed electrification by friction, that is, rubbing with silk cloth (Phoonphetmongkon, 2004).

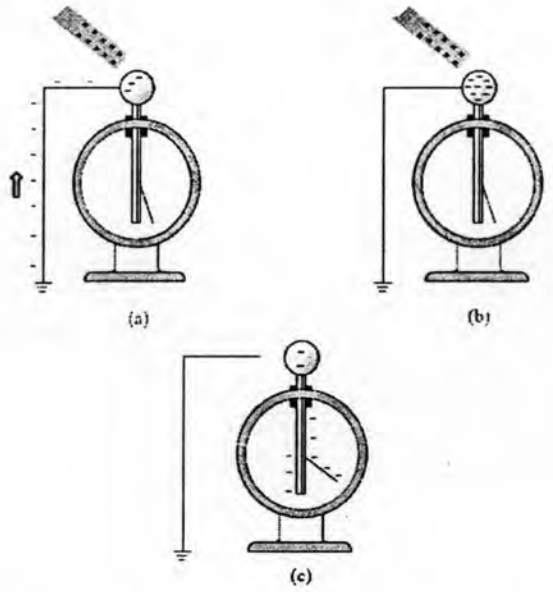

Figure 11 Charging by induction (Phoonphetmongkon, 2004)

(a) The electroscope is connected to ground. As the glass rod is brought near the metal sphere, negative charges are attracted to the sphere from the ground.
(b) The ground connection is removed while the glass rod is kept in position.
(c) If the glass rod is then withdrawn, the negative charge on the electroscope, which redistributes itself over this region, causes a deflection of the gold leaf, showing that there is a net charge on the instrument.

In an electrospray process, the droplets are charged by induction charging. If the droplets consist of a liquid which evaporate rapidly, then the charged droplets will evaporate until the maximum charge limit (Rayliegh limit) is reached (Cross, 1987; Cross et al., 1998; Hendricks and Schnieder,1963). The droplets then disrupt to smaller droplets. The process produces a fine mist of highly charged droplets. For a suspension undergoing the electrospray, the evaporation and electrostatic atomization result in a cloud of fine particles. For example, induction charging is used in continuous ink-jet printing, where ink droplets are charged and deposited in the printing process.

3.3.3 Tribocharging

Tribocharging occurs through two mechanisms: (1) contact charging, and (2) friction charging. When two dissimilar particles rub against each other, there

is a transfer of electrons, charges, from the surface of one particle to the other until the potentials of the metals are aligned. This results in one of the particles being positively charged and the other being negatively charged. The amount of triboelectric charge exchanged between two contacting surfaces depends upon their relative speed, the difference in work function, and the pressure between the surfaces in contact. As the pressure increases, the area or the number of contact points increases. The surface charge density achieved by this process can be very high (Mazumder et al., 2006).

Many researchers working in the field of triboelectricity have set up a "triboelectric series" similar to the "electrochemical potential series" for the metals. There is some agreement on the locations of some materials, but most of the series are very dissimilar, even when the same materials are used. The data on individual material used are apparently not reproducible. This is undoubtedly owing to the complexity of the surfaces of the materials themselves and also to the treatment of the surfaces in the many processes necessary for manufacture and handling. A typical triboelectric series, presented in Table 2 (Phoonphetmongkon, 2004), serves only as an example.

Table 2 A typical triboelectric series

Rabbit's fur	Cotton
Lucite	Wood
Bakelite	Amber
Cellulose acetate	Resins
Glass	Metals
Quartz	Polystryrene
Mica	Polyethylene
Wool	Teflon
Cat's fur	Cellulose nitrate
Silk	

It is certain that this series order will only be reproducible in rare instance. Conditions such as cleanliness and humidity affect the series drastically. The materials at the top of the list are positive with respect to those lower in the list.

3.4 Application of electrostatics

Many industrial and biomedical processes involve powders and droplets; the electrostatic charges in these powders and droplets often play an important role in the process involved. The fundamentals of electrostatic charging, charge control, neutralization, deposition of charge particles, charge decay, charge measurements and control discussed in literature (White,1963; Hughes,1985; Cross,1987; Schein,1988; Chang,1995; Mazumder,1998) provide information on the role of electrostatics in many industrial and biomedical processes including (1) electrostatic precipitator, (2) powder coating, (3) ink jet devices, (4) laser printer and copying machines in electrophotography, (5) application of plasma discharge devices, (6) electrophoresis, (7) cell sorting, and (8) electrospray and proteomics.

Mountain et al. (2001) explored the triboelectric charging of two acrylic-based polymer powders in fluidization and transport processes. Steady mass flow and dispersion of powder at a desired rate are necessary for controlling thickness and uniformity of deposited powder layer on the workpiece in electrostatic spray painting.

Influence of process parameters in electrostatic fluid bed powder coating of carbon steel was studied by Barletta and Tagliaferri (2006). Exposure time, applied corona voltage, and air flow rate were found to influence the performance of the coating process significantly.

Lenggoro et al. (2006) investigated electrical charging characteristics of particles produced by electrospray and patterned area created by contact charging of the electrical conductor with non- or semi-conductors. Locations where nanoparticles were deposited depend on voltage polarity applied to the spraying colloidal droplet and the substrate, and the existence of additional ions such as those from stabilizer.

Moreover, the attractive electric forces are responsible for the behavior of a wide variety of commercial products. For example, the plastic in many contact lenses, *etafilcon* ®, is made up of molecules that electrically attracted to the protein molecule in human tears (Jewett and Serway, 2006). These protein molecules are absorbed and held by the plastic so that the lens ends up being primarily composed of

the wearer's tears. Therefore, the lens does not behave as a foreign object to the wearer's eye and can be worn comfortably.

Many cosmetics also take the advantage of electrostatic forces by incorporating materials that are electrically attracted to skin or hair, causing the pigments or other chemicals to stay put once they are applied.

Phoonphetmongkon (2004) developed a top spray fluid bed enhanced by electricity for coating glass beads with aqueous solution containing hydroxypropylmethylcellulose (HPMC). The efficiency of coating process was significantly depended on fluidizing air velocity, flow rate of coating agent, size of core particles and electricity potential applied to a spraying nozzle.

Electrostatic powder deposition is being used to develop novel dosage forms and drug delivery systems such as Accudep® process (Friend, 2002). Drug powder is charged and deposited onto thin, water-soluble films. The depositions are covered, sealed, and cut into Accudep cores. These cores are further processed into tablets, capsules, controlled release systems, or novel formulations such as overwraps.

4. Evaluation of coating film

4.1 Coating efficiency

Coating efficiency can be measure in different ways depending on the application of coating process (Kage, et.al, 1996; Tobiska and Kleinedudde, 2003; Espinaco and Freitas, 2004). In this study, one of the most commonly used methods was used to evaluate the efficiency of electrostatic fluidized bed coating technique. Coating efficiency was defined by the ratio of the deposited coating mass onto the cores, weight gained, and mass of coating agent used in the process. Higher percent coating efficiency indicated that higher weight gained and lower amount of losing coating agent.

4.2 Film thickness

Film thickness is another parameters used to evaluate coated products, especially in pharmaceuticals. For modified or sustained release dosage forms, film

thickness applied significantly affected on the release rate of the active drug. The different methods such as scanning electron microscope (Wesdyk et al., 1990), fluorescence microscopy and image analysis (Andersson et al., 2000) have been used to determine of film thickness. The most common one is image analysis which could enable a direct measurement of film thickness and have been reported to be the optimal method for narrow size distribution (Andersson et al., 2000). In this study, image analysis was used to determine the film thickness of coated pellets due to its advantage of non-invasive method and lack of sample preparation requirement.

4.3 Confocal Laser Scanning Microscopy (CLSM)

The application of confocal laser scanning microscopy (CLSM) to physicochemical characterization of pharmaceutical system is not yet widespread as it is commonly applied in the filed of cell biology (Pygall et al., 2007).

However, the method has been developed to exploit the imaging capabilities of CLSM to study a wide range of pharmaceutical systems, including phase separated polymers (Zhu et al.,1998), colloidal systems (Clegg et al., 1996; Chestnut, 1997; Lacasse et al., 1998), microspheres (Lamprecht et al., 2000; Determan et al., 2004), pellets (Guo et al., 2002), tablets (Peltonen, 1997; Guo et al., 1999), film coatings (Ruotsalainen, 2003), hydrophilic matrices (Jayan et al., 1999), and chromatographic stationary phases. Additionally, the method is used to measure diffusion in gels, bioadhesives, and for monitoring microenvironmental pH change within dosage forms have been utilized (Shenderova et al., 1999). Its advantages over conventional microscopy are as the following : (Pygall et al., 2007)

- Reduced blurring of the image from light scattering.
- Increased resolution and electronically adjusted magnification.
- Improved signal to noise ratio.
- Usually clear observation of thick and light scattering objects.
- The potential for horizontal (x, y) and vertical imaging (x, z and y, z).
- Quantitative studies of the optical properties of the specimen.

In this study, CLSM was utilized as a tool to characterize film distribution on the surface of pellets because of its non-invasive nature and ability to visualize the

internal structure of film coating. Fluorescence material (6-carboxyfluorescein) was developed in coating agent for investigation of film formation.

5. Pelletization

In pharmaceutical industry, pellets can be defined as small, free-flowing, spherical particulates manufactured by the agglomeration of fine powders or granules of drug substances and excipients with binder solution, using appropriate processing equipment (Swarbrick and Boylan, 1989). They usually range in size from 0.5-1.5 mm, possessing high density and narrow particle size distribution. Pellets have several advantages over the single unit dosage forms (Follonier and Doelkar, 1992). These include reduced risk of systemic toxicity due to dose dumping, minimized local irritation of mucosa and predictable gastric emptying. Moreover, they can be divided into desired dose strengths without formulation or process changes and can also be blended to deliver incompatible bioactive agents simultaneously or particles with different release profiles at the same site or at different sites within the gastrointestinal tract (Swarbrick and Boylan, 1989).

Compaction and drug layering are the most widely used pelletization techniques in pharmaceutical industry. Of the compaction techniques, extrusion and spheronization is the most popular method. Recently, however, melt pelletization has been used frequently in making compaction pellets using a different type of equipment, e.g. a high-shear mixer (Ghali et al., 1990, Schaefer and Mathiesen, 1996, Zhou et al., 1996). Other pelletization methods, such as globulation, balling and compression are also used in the development of pharmaceutical pellets although in a limited scale (Ghebre-Sellassie, 1989).

5.1 Extrusion-spheronization

Extrusion-spheronization is a multiple-step process of preparation of spherical particles, which are commonly referred to as spheres or pellets. The spheres are of interest due to good flow, low dusting, uniform size distribution, low friability, high hardness, ease of coating, and reproducible packing (Erkoboni, 2003).

Extrusion-spheronization is a process requiring at least five units of operation including dry mixing, wet granulation, extrusion, spheronization and drying, with an optional sixth step-screening to achieve a target size distribution. The process flow diagram and critical variables associated with each of the process step is shown in Figure12.

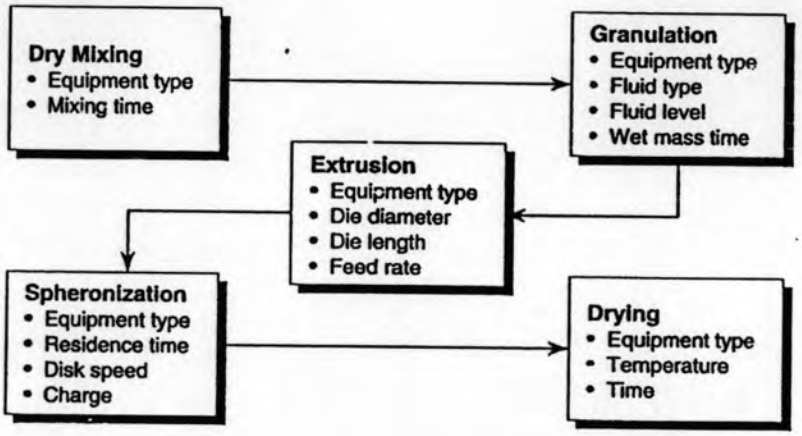

Figure 12 Process flow chart of the extrusion-spheronization process showing the process variables for each individual step (Erkoboni, 2003).

Many types of equipment are utilized in the extrusion-spheronization process. The most unique and critical processing equipment are extruder and spheronizer (Hicks and Freese, 1989, Swarbrick and Boylan, 1989).

5.1.1 Extruders

Extruders come in many varieties, but can generally be divided into three classes based on their feed mechanism. They include those that rely on a screw, gravity and ram or a piston to feed the wet mass into the extrusion zone. Examples of extruders each class is shown in Figure13.

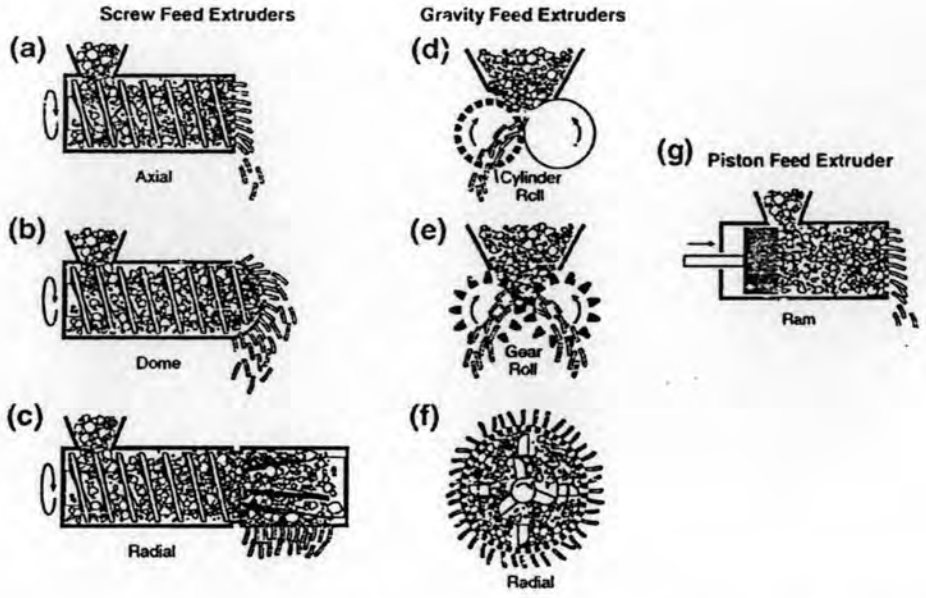

Figure 13 Schematic diagrams of extruder types used in extrusion-spheronization (Erkoboni, 2003).

Screw-fed extruders include the (a) axial or end plate, (b) dome, and (c) radial types, while gravity-fed extruders include the (d) cylinder, (e) gear, and (f) radial types. The screw and gravity fed types are used for development and manufacturing, with the radial varieties being the most popular for pharmaceutical applications. The piston-fed or ram extruder is primarily used in research as an analytical tool.

5.1.2 Spheronizers

A spheronizer consists of a static cylinder or stator and rotating friction plate at the base. The rounding of the extrudate into spheres or pellets is dependent on friction forces. The friction forces are generated by particle-particle and particle-equipment interactions. For this reason, the friction plate generally have a grooved surface that increases the forces generated as particles move across its surface. Disk having two geometrical patterns are typically produce as shown in Figure 14, a cross-hatch pattern with the grooves intersect at a 90° angle and a radial pattern with the grooves running radially from the center.

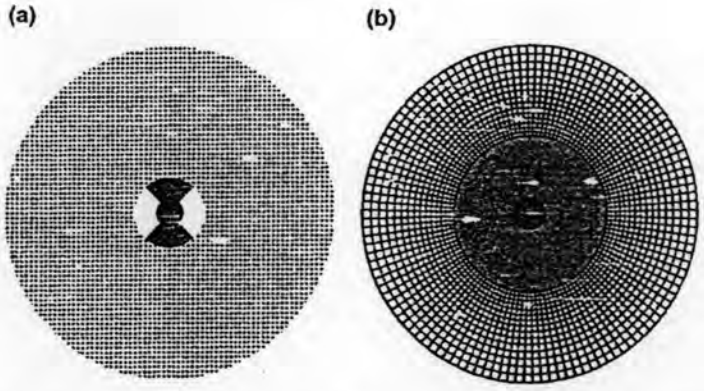

Figure 14 Spheronizer disks having two geometric pattern: (a) a cross-hatched pattern with the intersect at a 90° angle, and (b) a radial pattern with the grooves running radially from the center (Erkoboni, 2003).

The transformation from cylinder-shaped extrudate to a sphere occurs in various stages. Two models have been proposed to describe the mechanism and are shown graphically in Figure 15. The model proposed by Baert et al. (1993) suggested that the initial cylindrical particles (Fig 15-1a) are deform into a bent rope-shaped particle (Fig 15-1b), and then form a dumbbell with a twisted middle (Fig 15-1c). The twisting action eventually causes the dumbbell to break into two spherical particles with a flat side having a hollow cavity (Fig 15-1d). Continued action in the spheronizer causes the particles to round off into spheres (Fig 15-1e). When the sphere is fractured, a hollow particle is revealed (Baert and Remon, 1993).

The second model proposed by Rowe (1985) describes a transition whereby the cylindrical particles edges (Fig 15-2a) are first rounded off into cylindrical particles with round edges (Fig 15-2b), then form dumbbell-shape particles (Fig 15-2c), ellipsoids (Fig 15-2d), and finally spheres (Fig 15-2e). The exact mechanism is likely composition-dependent.

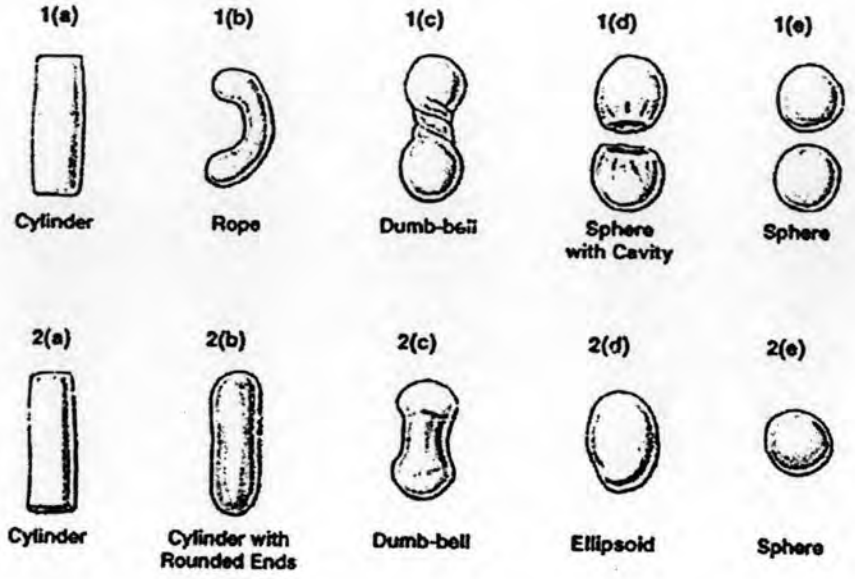

Figure 15 A graphical presentation of the two models proposed to describe the mechanism of spheronization.

5.1.3 Formulation variables

In the extrusion-spheronization process, the composition of the wet mass play a critical role to produce pellets with desired attributes. During the granulation step, a plastic mass is produced. The materials must form a sufficiently plastic mass, deform when extruded, and break off to from uniformly sized cylindrical particles. The degree of liquid saturation of the granulation is the one of the most critical factors in the formulation. Dry granulated material may generate extrudates that produce large quantities of fines during the spheronization step. Overwetted granulated material results in extrudates that may adhere to each other and form bundles of strands that cannot be processed further. Even if the extrudates remain separate following the extrusion step, they tend to form agglomerates readily during spheronization. Generally, the liquid content of the wet powder mixture is about 20 to 30 % (w/w) (Swarbrick and Boylan, 1989). Solvent, such as ethanol or mixtures of water and ethanol, may be used as granulating liquids when pure water is not suitable.

The importance of using excipients was early raised on. Conine and Hardley (1970) cited the necessity of using microcrystalline cellulose (MCC). Since then, more researches have been conducted in attempt to understand the significance

of material properties. MCC is one of the most important and widely investigated excipients in extrusion-spheronization. It is used as a filler and spheronization aid, regulating the water content and distribution in the granulation (Swarbrick and Boylan, 1989).

O'Connor et al. (1984) studied the behavior of some common excipients in extrusion-spheronization. Of the materials tested, only MCC and MCC with sodium carboxymethylcellulose (Na-CMC) were capable of being processed. Other excipients, including dicalcium phosphate, lactose, starch, and modify starch did not process adequately.

Moreover, the effects of drug substance and varying drug to excipient ratios were investigated. At low drug levels, the spheronizing excipient played the most significant role in determining sphere properties. MCC was the best excipient in low dose application because it formed the most spherical particles. At moderate drug loading (50%), MCC and MCC coprocessed with Na-CMC, resulting in acceptable pellets. At higher loading levels, however, the MCC did not yield acceptable pellets and the coprocessed materials did (O'Connor et al., 1984).

In addition, they found dissolution to be dependent on the type of excipient used, the solubility, and the concentration of the actives. An increase in drug load or drug solubility resulted in an increased release rate (O'Connor and Schwartz, 1985).

6. Drugs and excipients used in pelletization and film coating

Propranolol hydrochloride (Basic drug)

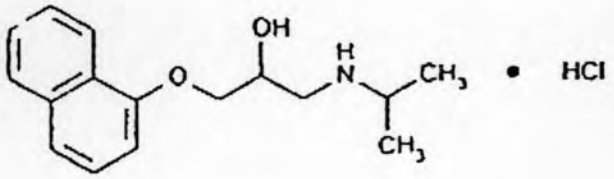

Figure 16 Structure formula of propranolol hydrochloride (O'Neil, 2006)

Propranolol hydrochloride is a nonselective β-adrenergic blocking agent. It is commonly used in treatment of hypertension and to improve the tolerance to exercise in patient with angina pectoris Available preparations are tablets, capsules and injection.

Its empirical formula is $C_{16}H_{21}NO_2HCl$ and chemical name is (±)-1 isopropylamino-3-(1-naphtyloxy) propan-2-ol hydrochloride, with molecular weight of 295.80. It appears in white to off-white, odourless or almost odourless, crystalline powder with bitter taste. It absorbs less than 1% of water at 25°C at relative humidity up to 80%. It has dissociation constant (pK_a) of 5-6 and melting point of 163-164 °C (O'Neil,2006).

Propranolol hydrochloride is soluble 1 in 20 of water and alcohol, slightly soluble in chloroform and practically insoluble in ether, benzene and ethylacetate. It is affected by light and should be preserved in well closed-light protection container at room temperature (about 25°C). 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.

Diclofenac Sodium (Acidic Drug)

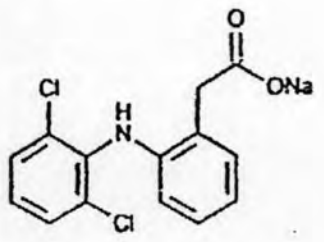

Figure 17 Structure formula of diclofenac sodium (O'Neil, 2006)

Diclofenac sodium is a prototypical non-steriodal anti-inflammatory drug (NSAID) that also exhibits analgesic and antipyretic activity. It can inhibit cyclooxygenase enzyme in the inflammation process of the diseases such as rheumatoid arthritis, osteoarthritis and acute gout. In general, diclofenac is used in sodium salt form and available in various preparations, tablet, suppository and intramuscular injection

Its empirical formula is $C_{14}H_{10}C_{l2}NNaO_2$ and it has many chemical name such as 2-[(2,6-dichlorophenyl)amino] benzeneacetic acid monosodium salt. Its molecular weight is 318.13. It appears in odorless, white to off-white crystalline, slightly hygroscopic powder. Crystal from water has melting point in range of 283-285 °C and dissociation constant (pK_a) of 4 in water. Partition coefficient is 13.4 in n-octanol/aqueous buffer. Its solubility is shown in Table 3.

Table 3 Solubility of diclofenac sodium in various solvent at 25 °C.

Solvent	Solubility (mg/ml)
Deionized water (pH 5.2)	> 9
Methanol	>24
Acetone	6
Acetonitrile	<1
Cyclohexane	<1
pH 1.1	<1
pH 7.2 (phosphate buffer)	6

Diclofenac sodium decomposed and/or undergoes a cyclization reaction before reaching its melting point depending on the environmental atmospheric condition under the thermal process is carried out (Tudja et al.,2001). Apparently, the decomposition process is a complex one and the extent of decomposition or conversion to 1-(2,6-dichlorophenyl)-indolin-2-one largely depend on the rate of heating of the substance.

Microcrystalline cellulose

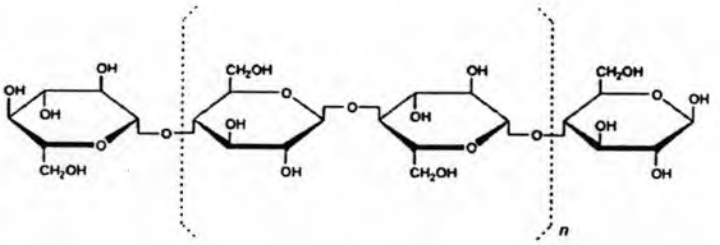

Figure 18 Structure formula of microcrystalline cellulose (Rowe et al.,2003)

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. In this study, It is used as spheronization aid.

Its empirical formula is $(C_6H_{10}O_5)_n$ where n $\approx$220. Density is 0.32 g/cm^3 for Avicel PH 101.Typical mean particle size is 20 – 200 μm. It appears in odorless, tasteless, white porous crystalline powder. Size and moisture depended on the quality of manufacturing and objective to use.

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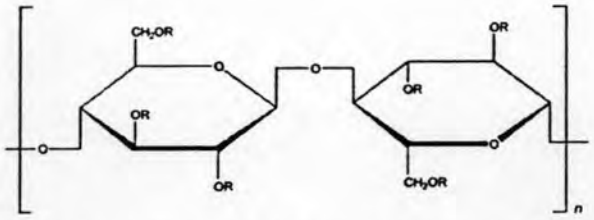
Hydroxypropyl methylcellulose (HPMC)



n = degree of polymerization, where R is H, CH_3, or $[CH_3CH(OH)CH_2]$

Figure19 Structure formula of HPMC (Rowe et al.,2003)

HPMC in pharmaceutical products is primarily used as a tablet binder and coating agent in film coating or as a rate-controlling polymer for sustained release tablet matrix. Depending upon the viscosity grade, concentrations of 2-20 %w/w are used for film-forming solutions.

It appears in odorless, tasteless, white or creamy-white fibrous or granular powder. It has glass transition temperature of 170 – 180 °C. HPMC is soluble in cold water, forming a viscous colloidal solution, practically insoluble in chloroform, ethanol (95%) and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane and mixtures of water and alcohol.

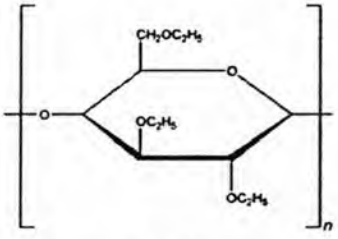
To prepare an aqueous solution, it is recommend that HPMC dispersed and thoroughly hydrated in about 20-30% of the required amount of water. The water should be vigorously stirred and heated to 80-90 °C, then the remaining HPMC added. Cold water should then be added to produce the required volume.

HPMC is incompatible with some oxidizing agents. Since it is nonionic, HPMC will not complex with metallic salts or ionic organics to form in soluble precipitates.

Mehta and Yeayer (1986), and Seitz (1988) suggested that film prepared with HPMC generally will need another polymer or plasticizers to improve their binding to tablet surfaces and avoid the problem of bridging or filling of tablet engraving.

Banker et al. (1981) evaluated HPMC as pharmaceutical film coating from completely water based systems. The coating results, applied in the Wurster tower, were excellent. Unpigmented coatings generally had shorter disintegration time than pigmented coated tablets and were much less prone to undergo increasing in disintegration time upon storage. But the pigment formulations clearly had a tendency to the lower moisture uptake, as compared to the coated tablets containing no pigment. They are also observed no change in hardness and color intensity with any coating after aging.

Ethylcellulose (EC)



n = degree of polymerization

Figure 20 Structure formula of ethylcellulose (Rowe et al.,2003)

Ethylcellulose (EC) is primarily used in oral formulation as a hydrophobic coating agent for tablets and granules (1-3% in concentration). EC coating are used to modify the release of a drug (3-20% in concentration), to mask an unpleasant taste or to improve the stability of a formulation; for example, where granules are coated with ethylcellulose to inhibit oxidation. Ethylcellulose, dissolved in an organic solvent or solvent mixture can be used on its own to produce water-insoluble films. Glass transition temperature of EC is 129 -133 °C

An aqueous polymeric dispersion (pseudolatex dispersion) of ethylcellulose such as Aquacoat ECD® and Surelease® may also be used to produce ethylcellulose film without the need for organic solvent. Aqueous polymeric dispersion has many

advantages over other polymeric solution systems, the most important of which may be it high solid content and low viscosity (Wheatley and Steuernagel, 1997). Other advantage in uses is that less energy is required to remove water during coating, simply because water is only a dispersion medium and does not solvate the polymeric beads (Fukumori, 1994). Therefore, the core tablets or granules are exposed to less heat during coating and less time is required for coating.

Aquacoat ECD® ethycellulose aqueous dispersion is a pseudolatex of ethylcellulose prepared mechanically by emulsification. This product designed for use by pharmaceutical industry for aqueous film coating of solid dosage form; beads, granules and tablets. Aquacoat consists primarily of ethylcellulose. In addition, cetyl alcohol, sodium lauryl sulfate and anti-foaming (dimethylpolysiloxane and silicagel) are also present. The first two ingredient serve as emulifiers and stabilizer during the latter stage of production. The composition of Aquacoat is as follow:

Solids content	30 %
Moisture content	70 %

The composition of non aqueous fraction is

Ethyl cellulose	87.1 %
Cetyl alcohol	8.7 %
Sodium lauryl sulfate	4.2 %

Aquacoat ECD should be stored at room temperature (20-25 °C) and is stable for two years at those conditions.

The pH-dependent drug release from EC pseudolatex (Aquacoat®) beads was caused by the presence of anionic surfactant, sodium lauryl sulfate (SLS) and a co-surfactant, cetyl alcohol. Drug release increased with increasing concentration of SLS while an increase in the amount of cetyl alcohol resulted in a significant decrease in drug release Bodmeier and Paeratakul (1990).

Besides the plasticizer, the surfactant system may have a significant influence on the coalescence of the polymer particles. Although a surfactant is needed to stabilize the pseudolatex, SLS may interfere with the coalescence during the coating

process. The surfactant was located at the particle surface and in the aqueous phase and repulsive forces had to be overcome during fusion of latex particles. They clearly concluded that the presence of anionic surfactant, SLS, in the coating caused the pH-dependent drug release from EC pseudolatex coated beads, and not the polymer (Bodmeier and Paeratakul, 1991)

Hutchings and Sakn (1994) studied six potential plasticizers for EC pseudolatex coating system (Aquacoat®). Three levels (25, 30 and 35%) of plasticizer were evaluated to study the influence of these additives on the release of a model compound, propranolol hydrochloride, from pellets in two different media, dilute HCl and phosphate buffer pH 7.4. The result showed that the release rate decreased when larger amounts of plasticizer were incorporated into the coating.

In addition, Wesseling and Bodmeier (2001) studied the influence of plasticization time, curing conditions, storage time, and core properties on the drug release from Aquacoat-coated pellets. It was found that the plasticization time did not affect the drug release, when the water-soluble, triethyl citrate, was used. Curing reduced the drug release and resulted in stable drug release profiles. The structure of the pellet core strongly affected the drug release.

Polyethylene Glycol (PEG)

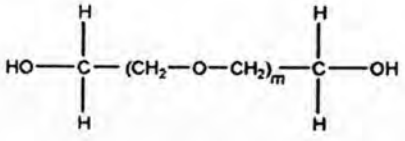


Figure 21 Structure formula of polyethylene glycol (Rowe et al.,2003)

In film coatings, solid grades of PEG can be used alone for the film coating of tablets or can be use hydrophilic polishing materials. Also, widely used as plasticizer in conjunction with film forming polymers. PEG grade 6000 and above can be used as lubricants, particularly for soluble tablets. Grades of PEG 6000 and above are available as free-flowing milled powders.

The melting point of PEG 6000 is 55-63 °C. Its density is 1.15-1.21 g/cm^3 Solid grade soluble in water (PEG 6000 = 1,900 g/ml at 25 °C), acetone, dichloromethane, ethanol and methanol. Slightly soluble in aliphatic hydrocarbons and ether but insoluble in fats, fixed oils and mineral oil.

Triethyl citrate (TEC)

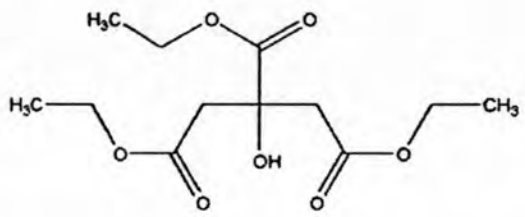


Figure 22 Structure formula of triethyl citrate (Rowe et al.,2003)

TEC is used to plasticize polymers in formulated pharmaceutical coatings. It appears in a clear, odorless, practically colorless, oily liquid. It is soluble 1 in 125 of peanut oil, 1 in 15 of water and miscible with ethanol (95%), acetone and propan-2-ol.

Sunset yellow

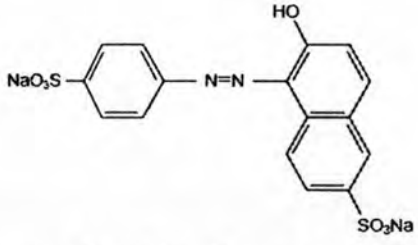


Figure 23 Structure formula of sunset yellow (Bauer, 1998)

Sunset yellow is generally used as coloring agent for foods and drugs. The synonym is FD&C Yellow No.6 and Yellow No.5 (Japan). It appears in reddish yellow powder. Aqueous solutions are bright orange colored.

It is poorly compatible with citric acid, saccharose solutions and saturated sodium bicarbonate solutions, incompatible with ascorbic acid, gelatin and glucose.

6-Carboxyfluorescein

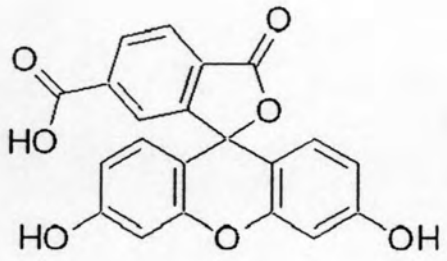


Figure 24 Structure formula of 6-carboxyfluorescein (Sigma-Aldrich, 2008)

6-Carboxyfluorescein is generally used as fluorescent dye. Its synonym is 6-FAM and FLUOS. It appears in greenish yellow-colored powder and solution. It is soluble in DMSO and water pH ≥ 5. Fluorescence λ_{ex} and λ_{em} of 6-carboxyfluorescein in 0.1 M Tris pH 8.0 is 492 nm and 517 nm, respectively. The absorbance maximum (λ_{max}) is 492 nm in 0.1N NaOH.