CHAPTER I

GENERAL BACKGROUND

Introduction

In the last two decades, sustained release dosage forms have made significant progress in terms of clinical efficacy and patient compliance. (Merkus F.W.H.M., 1986)

Nowadays, The design of oral sustained release dosage forms utilized two main approaches.

a) Introduce a physical barrier to prevent direct contact of the drug with fluid of the digestive system. This reduces diffusion rate and the rate at which the drug is being leached out from the dosage form.
b) Add selected interactions to the formulation, such as ion exchange resin or complexants, which form weak chemical bonds with the drugs.

In the first approach, many different production technologies can be employed. The main ones are (a) coating technique (b) embedding the drug in a wax or polymer matrix.

Matrix system is one of the accepted methods for prolongation of drug release, most frequently used and easily obtained system to formulate the sustained release oral preparation in the form of capsule or tablets. (Theeuwes F. et al., 1991)

Drug reservoir in the matrix system was consisted of drug in solid particle form being mixed with the polymer or inert wax homogeneously. The release

rate in such a system may be controlled by the diffusion of the drug dissolved through the polymer network, capillary or channel in the pellet or tablet. Examples of the most common matrix forming agent are insoluble plastic (Pevicon®), hydrophilic polymer (hydroxy propylmethylcellulose), lipophilic material (Precirol®, Cutina®)

Fats or waxes, a natural, inert, non toxic, low cost materials, have been important adjuvants in the preparation of various types of pharmaceutical products for many years. It was found that waxes are good matrix forming agents that could be used in prolong release formulations. In addition, waxes have historically been used as lubricants, candles, polishes, and an important adjuvant in suppository and ointment formulations. Fats and waxes can also be used to coat drugs to achieve modified release characteristics (Banakar U. and Speake W., 1990).

The use of wax seems to have particular advantages due to wax chemical inertness against other materials. A rigid wax matrix can be made by simply heating. Drugs, however, are sometimes unstable under heating, so manufacturing machines and operational conditions have to be carefully specified to obtain wax matrix with the desired properties. Preparation of matrix systems has been discussed (Ghali E.S. et al., 1989; Folonier N. and Doellcer E.T., 1994; McTaggart C.M., 1984), but the process is not easy to specify in the case of high quality matrices. Furthermore, considering of gastric emptying time of pharmaceuticals, multiple unit formulation is suitable for sustained release dosage forms (Bechgaard H. and Nielsen G.H., 1978), but it is rather difficult to prepare small pellets or granules in the manufacturing process. Wax matrix granule or pellet would be valuable as convenient dosage form for controlling drug release if these problem could be solved by avoiding high temperature over wax's melting point during pellet or granule formation process.

Recently, Peh K.K.(1995) and Montousse (1999) reported that a wax matrix could easily be obtained using extrusion-spheronization. Matrix pellets obtained by this wax are of great interest because a subsequent release modifying

coating is theoretically not necessary to obtain slow release of drugs. Other studies reported that extended release materials were chitosan, ethylcellulose, or acrylic polymer, and polyethylene glycol. Microcrystalline cellulose was often used as the spheronizing aid.

Lipidic substances such as carnauba wax or hydrogenated castor oil could also be successfully spheronized to produced beads if the wetting fluid was ethanol instead of water. With Precirol® (glyceryl palmitostearate), wetting was achieved with water; however, a subsequent thermal treatment was needed to obtained extended release spheroids (Ghali E.S. et al., 1989). Beads could also be prepared with this wax excipient if the drug was previously dispersed in the melted material. However, the authors have not given any results concerning drug release. In addition, the drug using in these formulations possessed only low to moderate water solubility such as ibuprofen, and theophylline, respectively.

In former method sustained release matrix pellets are produced which can be further processed into single non-disintegrating unit dose forms by compressing into tablets. The ability to compress them into tablets confers on the matrix pellets which we described considerable advantages over alternative sustained release units such as microcapsules or coated pellets or granules. The outer wall or coating of these other units tends to rupture on compression thereby reducing their sustained release properties (McTaggart C.M. et al., 1984). Other advantage of this study is to investigate the release characteristic of pellet and tablet. The different in shape like sphere (pellet) and cylinder (tablet) form may have different release characteristic despite of the same matrix system.

In order to develop sustained or controlled release oral drug delivery systems. Development was faced the difficulties of restraining and localizing the system at targeted area of the gastrointestinal tract. Water soluble drugs are considered difficult to deliver in the form of sustained or controlled release preparation due to

their susceptibility to "dose dumping" phenomenon. Drugs like propranolol hydrochloride which was highly water soluble play leading role in its respective field of therapy. Consequently, propranolol hydrochloride has been made in sustained release preparation in order to attain those advantages as described.

Although there are a number of reports on the wax matrix pellets preparations, but only a little of reports concerning about wax matrix pellet prepared by extrusion and spheronization can be found especially with the highly water soluble drugs.

In the present study, propranolol hydrochloride was selected as a model drug. This work involved application of extrusion-spheronization technique on producing propranolol hydrochloride matrix pellets. The matrix pellets were compacted by using single hydraulic press machine, resulting the tablet.

In this study, two groups of waxy or lipidic materials (commonly used waxes and Gattefosse's waxes) in various concentrations were used as a matrix forming agent to control the release of drug.

Commonly used waxes
: beeswax, carnauba wax, glyceryl monostearate, Lubritab®
Gattefosse's waxes
: Compritol 888 ATO®, Precirol ATO 5®, Gelucire 50/02®

The suitable amount and types of waxy and lipidic materials in the manufacture of sustained release matrix pellet and tablet were investigated. The amount of drugs in the preparation were also evaluated. The drug release characteristics of sustained release products prepared by extrusion-spheronization and compaction was comparatively studied with a commercial product (Inderal® LA 160).

Objectives of the Study.

1. To study the application of extrusion-spheronization technique in preparation the pellets containing various waxes or glycerides as additives.
2. To evaluate the release characteristic of the wax pellets and the effect of type, amount of various waxes and glycerides including the pH of dissolution medium on the release of the drug from the pellets.
3. To investigate the release characteristic of compressed wax matrices prepared from wax pellets.
4. To evaluate the effects of loading dose of highly water soluble drug on drug release characteristics of wax pellets and compressed tablets.
5. To study release kinetic and mechanism of propranolol hydrochloride from the lipidic matrix.

Literature Review

1. Pelletization Technique.

Pellets are spheres of varying diameter. Pellets, manufactured in the pharmaceutical industry, are sized between 500 and 1500 μm (Ghibre-Sellassie I., 1989) and are commonly filled into hard gelatin capsule but can also be compressed to the tablets (Jalal I.M. et al., 1972)

Pellets can be produced in different ways: spraying a solution or a suspension of a binder and a drug onto an inert core, building the pellet layer after layer (Gamlen M.J., 1985); spraying a melt of fats and waxes from the top into a cold tower (spray congealing) forming pellets due to the hardening of the molten droplets (Ghibre-Sellassie I., 1989); spray drying a solution or a suspension of the drug forming pellets due to the evaporation of the fluid phase (Ghibre-Sellassie I., 1989); spraying a binder solution into the whirling powder using a fluidized bed; extrusion and spheronization technique; fluid bed rotogranulator or by the centrifugal granulator (Goodhart F.W., 1989)

1.1 Extrusion-Spheronization

Extrusion-spheronization as a pelletization technique was developed in the early 1960S and since then has been extensively researched. The technology is unique in that it is not only suitable for the manufacture of pellets with a high drug loading, but it can also be used to produce extended release pellets in the same step in certain situation, and hence obviate the need for subsequent film coating.

The extrusion-spheronization process is a multi step procedure, involving:

Dry Mixing and Wet Granulation

The first step of an extrusion-spheronization cycle consists of the preparation of the plastic mass. Different types of granulators are used to perform the mixing of the powder blend and the granulation liquid. The most commonly used granulator is a planetary mixer (Harrison P.J. et al., 1985b) although the use of high shear or sigma blade mixer has also been reported. Some research used a continuous granulator to prepare the wet powder mass.

During the granulation step the evaporation of the fluid phase should be restricted to a minimum. This could especially be a problem with the high shear mixers as they introduce a large amount of energy into the mass, which is partly transformed into heat. This rise in temperature will induce the evaporation of the granulation liquid (Baret L. et al., 1991), thus influencing the extrusion behavior of the wet mass. A special feature of the granulation step is the homogenous distribution of the liquid phase throughout the granulated mass.

Extrusion

The second step of the process is the shaping of the wet mass into long rods during extrusion. The extrusion process, used in pharmaceutical industry, can be performed using four main classes of extruders:

The screw extruder consisted one or two (twin screw) Archimedes screws feeding the plastic mass to an axial or radial extrusion screen. In the axial type, the screen is placed at the end of the screw, perpendicularly with the axis of the screw in contrast to the radial type where the die is placed around the screw, discharging the extrudate perpendicularly to the axis of the screw.

In the sieve and basket extruders, the granulate is fed by screw or by gravity into the extrusion chamber, where rotating or oscillating device pushes the plastic mass through the screen. A sieve extruder, the screen positioned at the bottom of the extrusion chamber, while in the case of basket type extruder the vertical walls of the extrusion chamber make up the extrusion screen.

Roll extruder: an extruder equipped with two contrarotating wheels of which one or both are perforated. Using this type of extruder the mass is fed between the two wheels and the extrudate is collected inside the extrusion wheels. The second type has perforated cylinder, which rotated around one or more rollers, discharging the material to the outside of the cylinder.

The principle of ram extruder is based on a piston, which pushes the wet mass through the screen situated at the end of the barrel.

Spheronization

During the third phase of the extrusion-spheronization process the cylinders are dumped onto the spinning plate of the spheronizer, called the friction plate, where the extrudate is broken up into smaller cylinders with a length equal to their diameter.

According to Rowe R.C., 1985. Those plastic cylinders are rounded due to frictional forces. In the spheronization process, different stages can be distinguished depending on the shape of the particles, i.e., starting from a cylinder over a cylinder with rounded edges, dumbbell and elliptical particles to eventually perfect spheres. (Figure 1A)

Baret and Remon (1993) suggested that another pellet forming mechanism might exist (Figure 1B). In this mechanism, a twisting of the cylinder occurs after the formation of the cylinders with rounded edges, finally resulting in the breaking of the cylinder into two distinct parts. Both parts have round and a flat side. Due to 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.

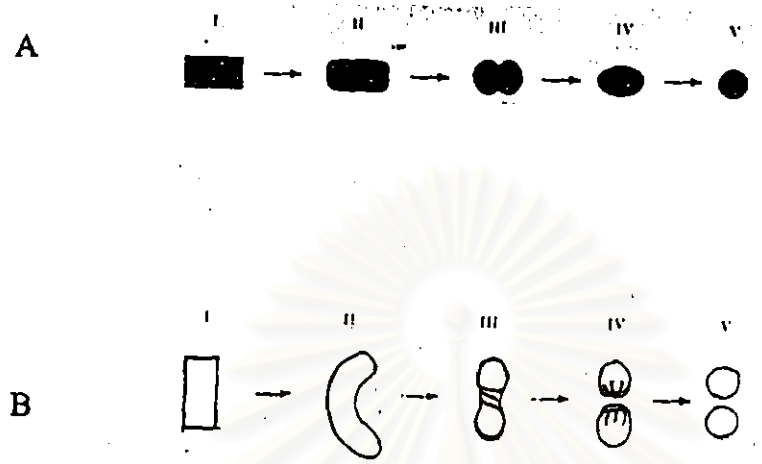


Figure 1 Pellet-forming mechanism according to: (A) Rowe: I, cylinder; II, cylinder with rounded edges; III, dumb-bell; IV, ellipsoid; V, sphere; (B) Baret: I, cylinder; II, rope; III, dumbbell; IV, sphere with a cavity outside; V, sphere.

The friction plate has a grooved surface to increase the frictional forces. Two types of geometry of the grooves exist (Rowe R.C., 1985), cross hatch geometry where the grooves form right angles and radial geometry where a radial pattern is used (Figure 2).

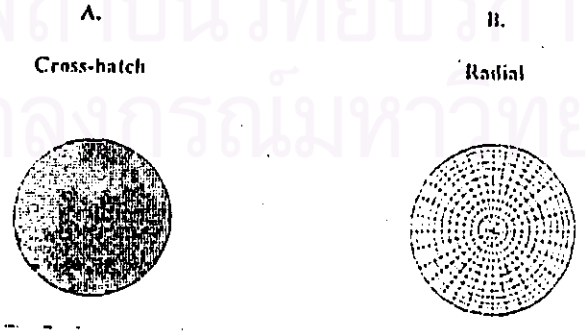


Figure 2 Geometry of the spheronization plate (A) Cross-hatch, (B) radial.

Drying

The final step of the process is the drying of the pellets. The pellets can be dried at room temperature or at elevated temperature in a fluidized bed or in an oven or in a microwave oven.

1.2 Formulation

In the extrusion-spheronization process, the excepients were incorporated in the formulation for a specific function, such as fillers, lubricants and pH modifiers, play a critical role to produce pellets with the desired attributes. The granulated mass should be plastic and sufficiently cohesive and self-lubricating during the extrusion step.

The extruded material should have characteristics, such as moisture content that are desirable for the spheronization step. The degree of the liquid saturation of the granulation is one of the most critical factors in the formulation, and must be just high enough to bring about the optimum surface plasticity required for spheronization. Very dry granulated material may generate extrudates that produce large quantities of fines during the spheronization step. Very wet 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. Therefore, the extrudate must have sufficient mechanical strength to form strands during the extrusion, but must also be easily broken into uniform rods during spheronization to provide pellets with a narrow particle size distribution.

Generally, the liquid content of the wet powder mixture is about 20 to 30 % (w/w). Solvents, such as ethanol or mixtures of water and ethanol, may be used as granulating liquids when pure water is not suitable, for instance, for stability and solubility reasons. However, the more volatile the granulation liquid is, the more difficult it is to control the spheronization process.

Excipients play a critical role during extrusion-spheronization (Harris M.R., and Ghebre Sellassie I., 1989). They impart strength and integrity to pellets following drying and govern final pellet formation. Microcrystalline cellulose is one of the most important and widely investigated excipients in the extrusion-spheronization. It is used as filler and a spheronization aid, regulating the water content and distribution in the granulation. In effect, it modifies the rheological properties of the formulation and imparts plasticity to the pellets. Lactose is another excipient that has been used occasionally to evaluate the mechnism and process of the pelletization by extrusion-spheronization.

In contrast to layering process, which are mainly utilized to produce pellets that are coated with a functional membrane to control the rate of the drug release, extrusion-spheronization can be used to manufacture pellets with sustained release characteristics wihtout membrane. For instance, matrix-type pellets can be produced with the help of microcystalline cellulose and sodium CMC (O'Conner R.E. et al., 1985; Ghali E.S. et al., 1989). Organic acid can be incorporated into the matrix pellet formulation to stabilize pH dependent sensitive drug substance (Bianchini R. et al., 1992). Not only water or other granulation media act as lubriating agents during the extrusion process, but also other libricants are sometimes incorporated to improve processing. (Mesiha M.S. and Valles J., 1993)

It is not surprised that the drugs substance itself plays an important role in the pelletization process, particularly at high drug loading. Physical properties such as particle size and polymorphism, and chemical properties such as pKa and solubility determine the amount of active ingredient which can be incorporated in the formulation and influence the quality of the final pellet with respect to shape and surface smoothness.

1.3 Some Factors Influencing the Formation of Matrix Pellets Prepared by Extrusion and Spheronization.

The Spheronization Speed.

The spheronizer speed affected the particle size of the pellets (Wan L.S.C. et al., 1993; Ku C.C. et al., 1993) A decreasing amount of fines and an increasing amount of large particles with increasing spheronization speed correlating with an increased mean diameter were also observed. According to Rowe R.C. (1985), the spheronization speed should be optimized to obtain the desired densification. He stated that a low spheronization speed would not provide sufficient densification to obtain perfect spheres, as opposed to a spheronization process at higher speed which could led the agglomeration of the individual pellets.

The Spheronization Time

The parameter on formulations containing mixtures of MCC: an increased diameter (Wan L.S.C. et al., 1993), an narrow particle size distribution (Bianchini R et al., 1992), higher sphericity (Wan L.S.C. et al., 1993), an change in bulk and tapped density and a change in the yield of a certain size range (Hasznos L. et al., 1992) were observed with extended sphernization time.

The Spheronizer Load.

The yield of pellets of a specific range decreased with increased spheronization speed at a low spheronizer load and increased with extended spheronization time at higher spheronization load (Chariot M. et al., 1987). Hasznos et al., (1992) demonstrated the influence of the spheronizer load on particle size distribution as the mean diameter increased with increasing spheronizer load.

The Extrusion Speed.

Harrison et al. (1985) showed that the surface impairment such as roughness and sharkskinning because more pronounced with increasing extrusion speed. These surface defects of the extrudate lead to pellet of lesser quality because the extrudate will break up unevenly during the initial stage of the spheronization process, resulting in a lot of fines and a wide particle size distribution.

The extrusion-spheronization is a very complex manufacturing process that depends on a number of formulation and processing factors shown in Table 1

Table 1 Critical factors in extrusion-spheronization. (Ref. Pelletization Tech.)

	Characteristic	Significance[a]
Drug substance	Particle size	+++
	Particle size distribution	++
	Particle shape	+++
	Solubility	++
Formulation	Water content	+++
	Water temperature	+
	Excipients type	+++
	Excipients concentration	++
	Excipients particle size	++
Extrusion	Extruder type	++
	Extruder speed	++
	Extrusion screen size	+++
	Thickness of the die plate	+
Spheronization	Spheronizer speed (rpm)	+++
	Spheronizer load	+
	Spheronization time	+++
	Friction plate design	+

[a]relative significance : +, low; ++, medium; +++, high.

2. Concept of Compaction

The principal physico-mechanical process involved in the compaction of particulate matter can be summarized as follows (Celik M. and Maganti L., 1994):

Initially, the particles undergo a rearrangement stage in which they flow with respect to each other until a "closer packing" arrangement is achieved. At this stage, as the upper punch penetrates into the die containing the powder bed, there are essentially only points of contact between the particles. Application of an external force to the bed results in forces being transmitted through these interparticulate points of contact, where the stress is developed, and where local deformation of the material occurs. The deformation will feature either one or a combination of the following: elastic, plastic, and/ or brittle fragmentation. The type of deformation depends upon the rate and magnitude of the applied force as well as the duration of the locally induced stress and physical properties of the materials.

When the particles are in sufficiently close proximity they can become permanently bonded to each other by several mechanism. The simplest type of bonding is termed "mechanical interlocking" which is facilitated by irregular particle shape and surface roughness. Particles can also be bonded as a result of a phase transition at the points of contact where the magnitude of the pressure is tremendously high and the temperature at those points may reach the melting points of the materials to liquefy the solid particles. Another mechanism of bonding is termed "intermolecular forces" which encompasses three known types of molecular bonding: Van der waals forces, Hydrogen bonding, and Ionic bonding.

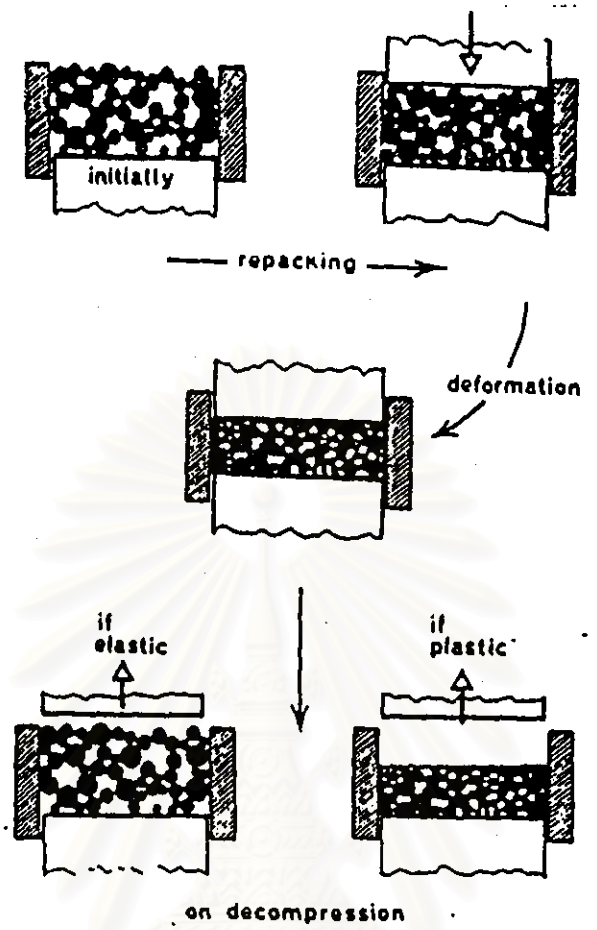


Figure 3 Diagrammatic representation of the stages of compaction.

Compaction Studies on the Multiparticulate Dosage Forms.

There is a small amount of literature available on the compaction characteristics of microsphere or microcapsules as can be seen on the following

Millili G.P. and Schwartz J.B., 1990 reported that the strength and physical properties of microsphere containing microcrystalline cellulose were affected by the granulating solvent. In this work, water granulated microcrystalline cellulose pellets were found to be strong, hard, and uniform in shape, where as the 95/5 ethanol/water granulating solvent resulted in microsphere with lower strength and less uniform shape. On the other hand, the former pellets exhibited poorer compactability than the

latter ones. This was attributed to the work bonding of the 95 % ethanol granulated pellets, which ruptured upon compaction, exposing more smooth surface to surface contacts for bonding. The water granulated pellets resisted rupturing due to their high bond strength and allow less surface to surface contacts for bonding to occur, thus producing weaker tablets.

Lloanusi N.O., and Schwartz J.B., 1998 observed the effect of wax on the deformation behavior and compression characteristics of microcrystalline cellulose and acetaminophen bead prepared using extrusion-spheronization

A waxy material was added from 10 to 70 % of total solid weight. Previous work characterized the compaction parameters of beads containing microcrystalline cellulose concluded that microcrystalline cellulose beads are relatively non compressible, but will form soft intact tablets (Schwartz J.B. et al., 1994). Beads made without wax (the control formulation) required greater compression forces to form cohesive tablets. To improve the compressibility of the beads, a waxy material was added to the bead formulation. As the amount of wax was increased, the beads become more plastic and harder tablets can be formed, without any external additives or additional lubrication.

3. Lipid in Pharmaceutical Dosage Forms

Fats and waxes have been important adjuvants in the pharmaceutical product for many years. Initially, they were simply used to enhance and improve the properties of dosage forms. By the late 1960's people realized the therapeutic value as nutritional supplement and started using them intravenously administered fat emulsion. At the same time it was found that waxes were very good matrix forming agents that could be used in prolonged release formulations.

3.1 Characterization

Lipids encompass a wide spectrum of organic compounds that vary considerably in their chemical and physical properties. The principle categories of materials are illustrated in Figure 4.

Fixed oil and fats are generally esters of glycerol and fatty acids. Fixed oils, which are solid at ordinary temperatures, are commonly called fats. So fats are mixtures of glyceryl esters of the so-called fatty acids. In particular those of higher molecular weight like palmitic, stearic, and oleic acids. The individual glyceryl esters themselves are preferred to as glycerides.

Fats are greasy to touch, lighter than water and insoluble in water. However, they soluble in ether, chloroform and some other water immiscible solvents. As they contain carotene, fats often have a yellowish color.

Waxes, like fats, are esters of higher molecular weight monohydric alcohol and high molecular weight fatty acids. The alcohols found in waxes are one of the higher even number monohydric alcohols from C_{16} to C_{36}, such as cetyl alcohol ($C_{16}H_{33}OH$), ceryl alchol ($C_{30}H_{61}OH$). While waxes often contain these alcohols and fatty acids C_{24} to C_{36} in the free state as the major components, some waxes obtained from plants contain paraffin hydrocarbons.

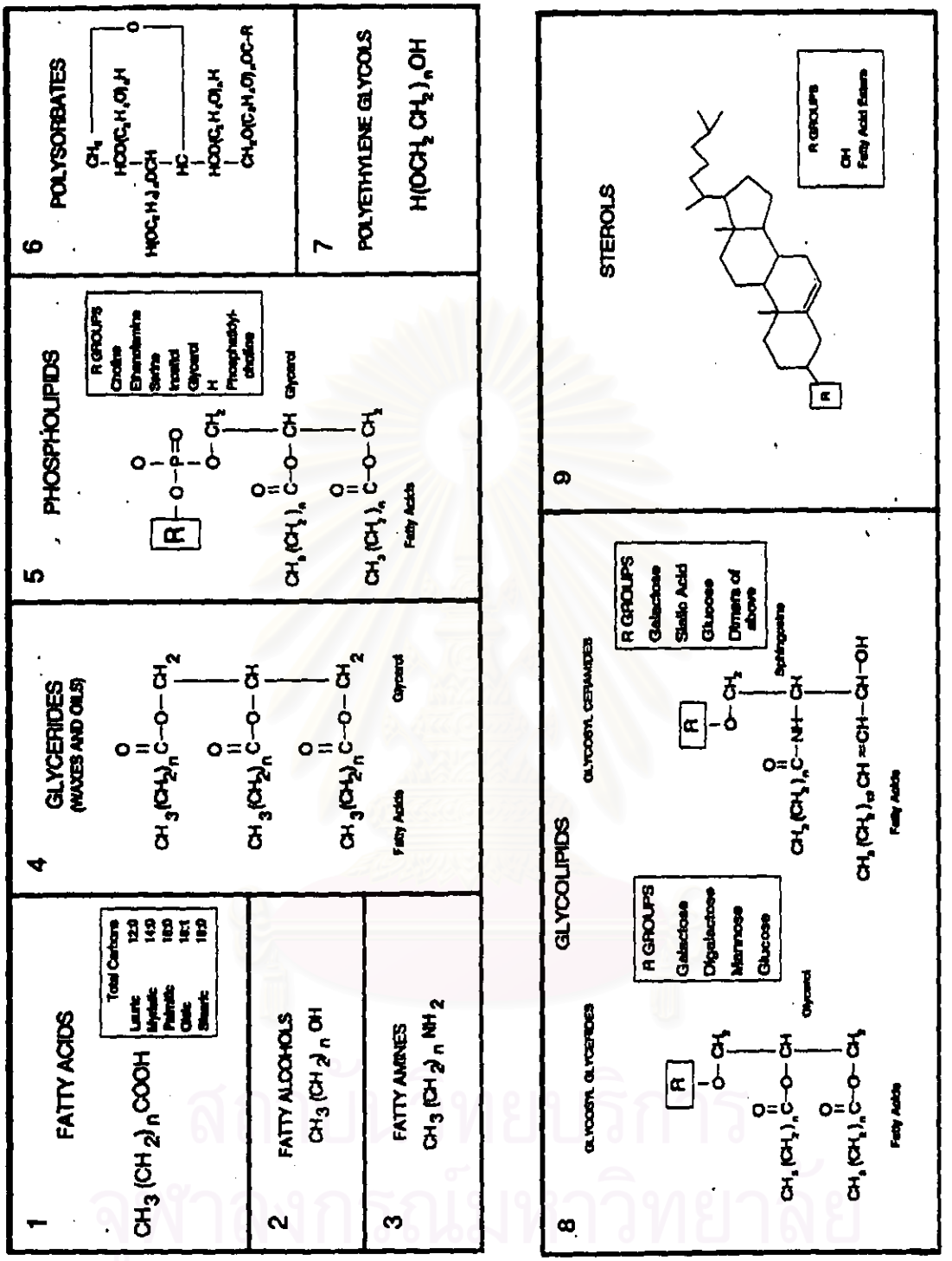


Figure 4 Lipid classification and structure.

The analytical factors of importance in identifying fats are the iodine value, the acid value and the saponification value. The iodine value is expressed as the number of grams of iodine absorbed by 100 g of a sample, the acid value is the number of mg of potassium hydroxide required for neutralize the free acids in 1 g of sample. The saponification value is the number of mg of potassium hydroxide required to neutralize the free acids and to saponify the esters in 1 g of sample. Specific gravity, color, odor and congealing point are also worth considering.

Waxes are more difficult to identify and there is little information in the literature. The esters in waxes are generally much more resistant to saponification than those of fats

3.2 **Lipid Uses in Pharmaceutical Dosage Forms.**

Overall prospective the uses of lipids in pharmaceutical dosage forms can be grouped into one of four categories:

1. an improvement in the processing or stability of the formulation in the preferred physical state,
2. enhancement or reduction in cellular or systemic absorption of the drug from the formulation,
3. more effective drug targeting to efficacy sites and away from toxicity sites
4. slower or more controlled delivery of drug from the formulation

3.2.1 Conventional dosage forms.

When used in emulsion, suspension and ointments, fats and waxes can give the product a dry formulation and suitable consistency or form.

Fats and waxes are also widely used as emulsifiers in the preparation of emulsions. Whether a substance is a good emulsifier depends on the value of its hydrophile-lipophile balance (HLB). This HLB value, which was developed by

Griffin, gives means of selecting the appropriate emulsifying agent. Compounds with HLB values of between 4 and 6 are shown to yield water-in-oil (W/O) emulsions while those with HLB values between 8 and 18 generally suitable for preparation of oil in water (O/W) emulsions

3.2.2 Modified release

There are many situations that require an alternative to the conventional rapid release formulations. Possibilities include sustained-, prolonged-, and controlled release items, which are generally obtained either by modifying the chemical structure of the active ingredient to alter its physicochemical properties or by careful selection of excipients.

In some formulations fats and waxes are used to interfere with the release of the medicament, causing it to deviate from the conventional rapid release characteristic to modified release behavior. This interference might involve producing a hydrophobic environment for drug release, coating drug particle to give an additional behavior for dissolution or providing a matrix type structural environment that entraps the drug. Coating and preparation of wax-matrix systems are both widely used.

3.3 Production of Sustained Release Products using Fats and Waxes.

Spray congealing (John P.M. and Becker C.H., 1968; Hamid I.S. and Becker C.H., 1970; Groves M.J. and Wiseman E.H. and Federici N.J., 1968; Galindez F.E., 1976). In this process, the drug is allowed to melt, disperse, or dissolve in hot melt of lipid substance. The mixture is then sprayed into an air chamber where the temperature is below the melting point of the formulation components. Depending on the physicochemical properties of the ingredients and the formulation, various pellets with immediate or controlled release behavior can be produced by this process. Products from this process come in the form of powder or pellets.

Spray drying (Asker A.F. and Becker C.H., 1966) The process is different from spray congealing in that the drug is dispersed in a solution of lipid dissolved in organic solvent. The resulting suspension is sprayed in an atmosphere of warm air, and the product is formed on evaporation of the solvent.

Fusion and congealation (Dakkuri A. et al., 1978; Kumar K. et al., 1975; Dave S.C. et al., 1974; Robinson I.C. and Becker C.H., 1968) the lipid substance, singly or mixture, is melted at the temperature close to the melting point which is then filled into capsule while hot. For incorporating an active ingredient, its size should be reduced to fine. Adjuvant is incorporated to the melt little by little under agitation. The agitation is maintained until the total mixture is congealed and they are granulated by sieving with suitable equipment.

In a novel way, Bodmeir R., et al. (1990) studied the sustained release wax matrices by filled the drug-wax powder blends in hard gelatin capsule. The waxes will melted within the capsules in a heated fluidized bed and formed solid drug-wax matrices upon cooling.

Aqueous dispersion (Draper E.B. and Becker C.H., 1966; Emori H. et al., 1984) The procedure of this method involves adding an active ingredient under agitation control into a molten lipid excipient. The mixture is then dispersed in the water, often containing dispersant, at the same temperature. After cooling this system to an optimum temperature, the drug lipid particles are filtered, washed and dried.

Factors influencing the physical aspects of the final products and on their drug release characteristics are as follows:

- Nature and amount of active ingredient and lipid excipient.
- Type (HLB valued) and concentration of dispersing agent.
- Initial temperature of two liquids.
- Degree of solidification.
- Speed and type of agitation.

Evaporation (Dakkuri A. et al., 1978) This method involves dispersing the powder into an organic solvent of lipid that is preheated. The solvent is evaporated under agitation, and the mass remaining is further treated according to the procedure of fusion and congealation method.

Wet granulation (Capan Y., 1989; Parab P.V. et al., 1987) In wet granulation, drug mixture of the lipid excipient and active ingredient is damped by water or organic solvent. The damped mass is then granulated in conventional manner, dried and sieved.

Coating of multiparticulates (Barthelemy P.H. et al.; Michael J.J. et al., 1990) Waxes are used in some formulations to coat granules or pellets, as to alter and control the rate of drug release.

Direct compression (Capan Y., 1989; Parab P.V. et al., 1987; Simoons J.R.A., 1962) The active ingredient is mixed with the pulverized lipid excipient and other adjuvant. The resulting mixture is then compressed at high pressure.

3.4 Most Popular Method for Preparing Wax Matrix Pellet or Granule.

3.4.1 Melt pelletization or melt granulation (Schaefer T. et al., 1993; Thomsen L.J. et al., 1994; Zhou F. et al., 1998)

Melt pelletization or melt granulation (thermoplastic granulation) is a process in which granulation is obtained through the addition of a binder which melt or soften at a relatively low temperature. After melting, the binder acts like a binding liquid. The binders normally used for melt pelletization are polyethylene glycol, different waxes, or stearic acid.

Melt pelletization process is advantageous compared with an ordinary wet granulation process, since the liquid addition phase as well as the drying phase of the process is eliminated. Consequently, melt pelletization requires less heat energy. Melt pelletization is an alternative to the use of solvents when granulating water sensitive materials. By selecting a melting binder which is insoluble in water, melt pelletization might be a way of producing sustained release pellet or multiparticulate. Solid dispersion can be prepared by dissolving a drug in the molten binder.

By melt pelletization in a high shear mixer the binder is added either in powder form to the starting materials at ambient temperature following by heating to above the melting point of the binder or in molten form to the heated material. The temperature of the mixture is increased by a heating jacket or by heat of friction solely. (Schaefer T. et al., 1990)

Heating by heating jacket is possible in a laboratory scale mixer but might be inconvenient in a production scale mixer. It is advantageous, therefore, to use a high shear mixer with a power input sufficiently high to generate the heat of friction required to melt the binder within a reasonably short time. In the Baker Perkins® high shear mixers the maximum impeller is very high. Flanders P. et al., (1987) examined a 10 liters, a 60 liters, and a 60 liters Baker Perkins mixer and found that melt pelletization by heat of friction wax possible in all of them. In the 60 liters mixer the temperature increased to about 100 ^{0}C during 15 minutes.

They mentioned that Fielder® and Diosna® high shear mixers are unsuitable for melt pelletization because of a long processing time. The shorter granulation time in the Baker Perkins® mixer is due to a larger relative swept volume of the impeller in that mixer. Spheroids produced by melt pelletization do not have to go through a drying stage. Melt pelletization has comparatively short process time. Contaminations problems can also be minimized by the contaminant of the whole spheroid formation process in the same equipment, i.e. in "one pot".

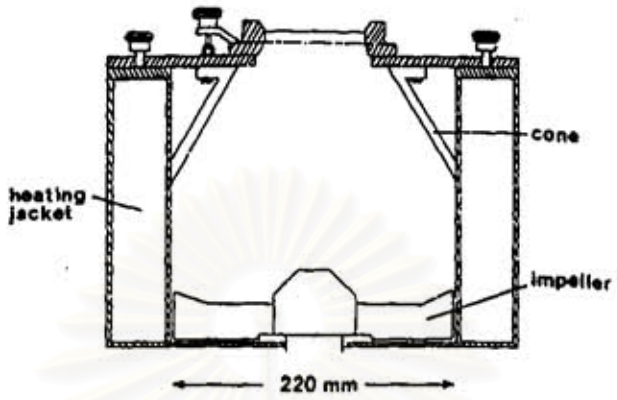


Figure 5 Out line of pellmix PL 1/8 high shear mixer

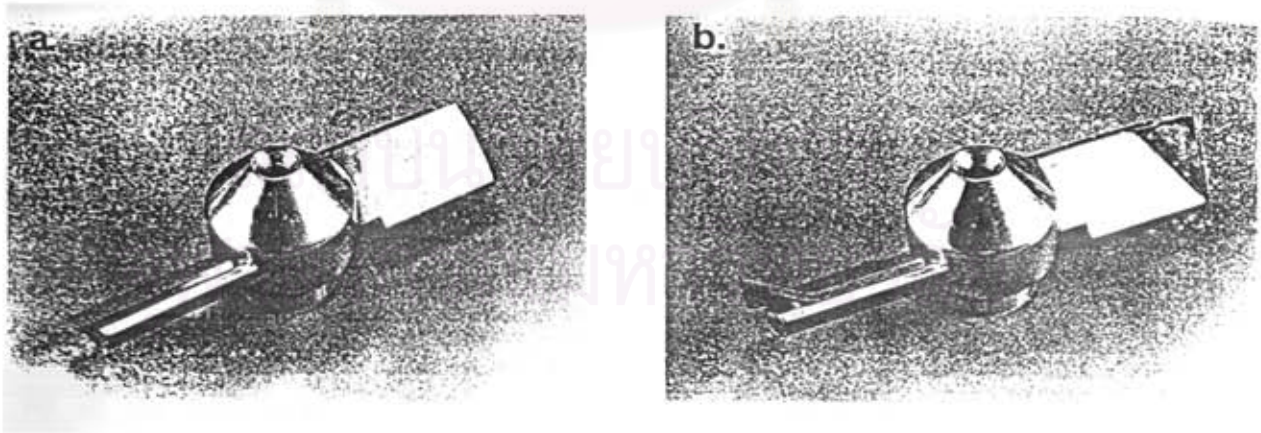


Figure 6 Impeller with changeable impeller blades.

Pellet Formation Mechanism in Melt Pelletization (Vonk P. et al., 1997; Schaefer T. and Mathiesen C., 1996).

Nucleation growth mechanism starts with one droplet. At the moment the droplet reaches the moving powder bed, a nucleus is formed. This nucleus is loose agglomerate and can be characterized by a high porosity and a low tensile strength. The primary nucleus grows due to layering. The size of primary nucleus is approximately 5 mm. Break up of the nuclei proceeds according to two mechanisms: attrition and fragmentation. The weak nuclei wear off due to nuclei/nuclei and nuclei/wall collisions (attrition), and break into fragments because of the action of the impeller and chopper (fragmentation). Both mechanisms cause the formation of the secondary nuclei. The secondary nuclei are the starting materials for the exponential growth. The exponential growth starts when the solid mass is sufficiently wetted and densification of the secondary nuclei occurs. Due to the densification stronger pellets are formed, which survive many collisions. Another consequence of the densification is that liquid is squeezed to the pellet surface, which increased the coalescence probability. During kneading, coalescence proceeds because densification still occurs. The growth rate decreases because no more liquid is applied, and break up becomes more and more important.

This mechanism is not a step-wise process, but a combination of all different sub mechanisms that occur at the same time.

Distribution of the molten binder on the surface of the solid particles will occur when the molten binder of the droplet are smaller than the solid particles or are of the same order of size. Subsequently, agglomerates will be formed by coalescence between the wetted particles. Immersion of the solid particles in the molten binder will occur when the molten binder droplets are larger than the solid particles.

Both mechanisms will be active simultaneously, because the binder droplets become comminuted by the high shearing forces. Normally, one of the mechanisms will be dominant. The distribution mechanism is promoted by a small particle size of the solid binder, by a low binder viscosity and by a high impeller speed. The immersion mechanism is promoted on the other hand by using the meltable binder as flakes, by a high binder viscosity and by low shearing forces during the processes.

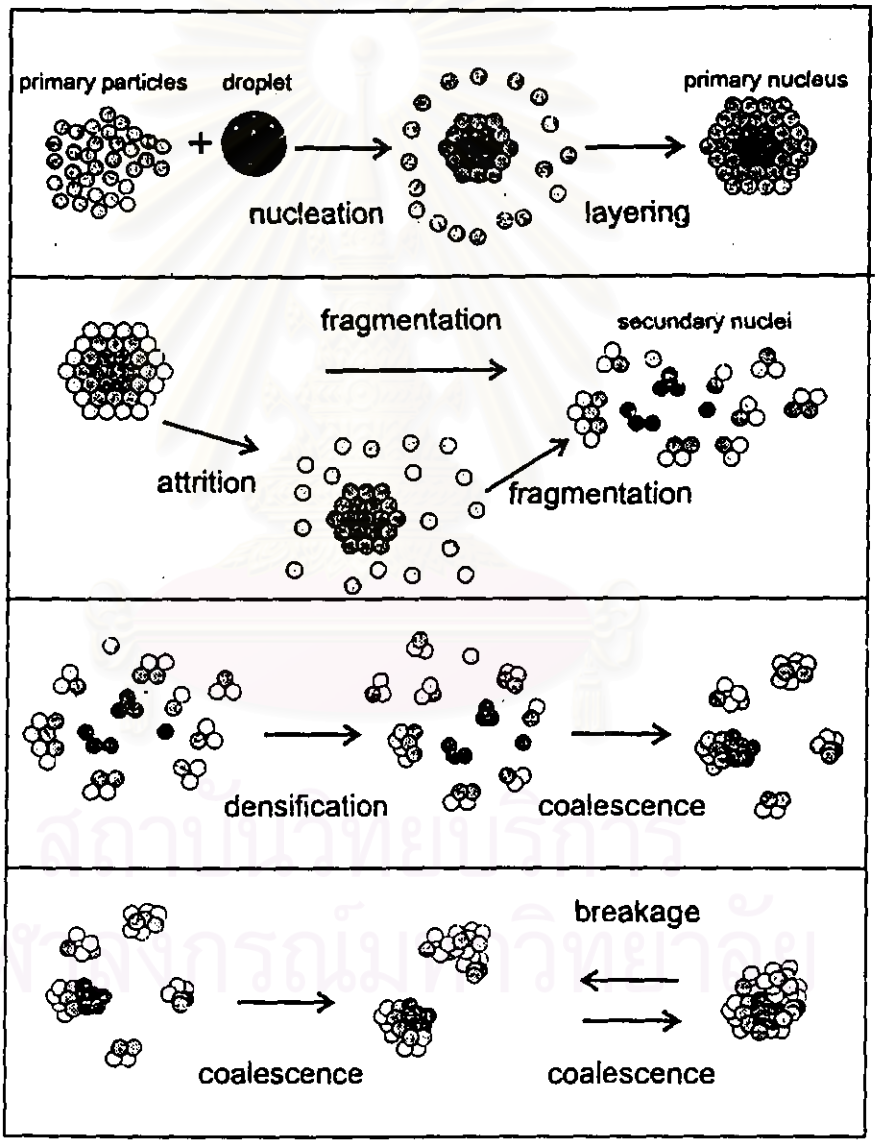


Figure 7 The destructive nucleation growth mechanism of high shear pelletization.

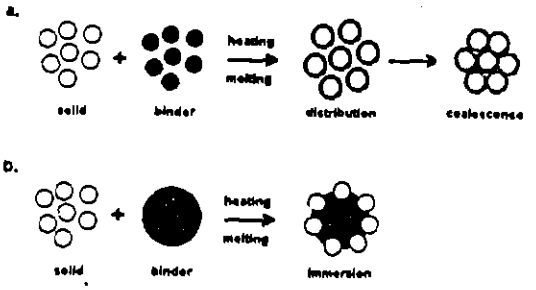


Figure 8 Granule formation mechanisms in melt agglomeration. a) Distribution mechanism. b) Immersion mechanism.

Factors Affecting to Melt Pelletization.

1. Process variable (Thomsen L.J. et al., 1993; Schafer T. et al., 1993)

The effect of jacket temperature, product temperature during massing, product load, impeller speed during massing, and massing time showed effect on the course of pelletization. In order to avoid deposits and large amounts of an over size particles, jacket temperature should be set at high temperature near the upper part of binder melting interval. Further more, it appeared to be advantageous if the product temperature declined into the binder-melting interval during massing. Since the movement of the mass, the optimum mixer load might depend on the physical properties of the starting materials. A high-power input is a prerequisite for making pellets. It is desirable, therefore, to measure the power consumption during the process. A high-energy input will speed up the pelletization to a certain extent, where after the process becomes uncontrollable. The two parameters controlling the energy input were impeller speed and massing time.

2. Apparatus variables (Schaefer T. et al., 1993)

The dimensions of the bowl of the mixer seem to be critical. If the bowl is too high, the vertical movement of the mass might be so high that the contact between the impeller and the mass is reduced. This will give rise to an insufficient power input to the material and will cause an irregular movement of the mass. The size and shape of the impeller blades must be such that the impeller gives rise to a high energy input to the material and causes a helix-like movement of the mass. An impeller with planes blade was found to be unsuitable for melt pelletization in the small mixer. The relative swept volume might possibly be used for evaluation of the applicability of an impeller in a larger mixer, but not in a laboratory scale mixer.

3. Product temperature (Schafer T. and Mathiesen C., 1996)

High temperature will decrease the viscosity of the molten binder and increase the volume of the binder liquid owing to thermal expansion. The lower viscosity will give rise to a higher deformability of the agglomerates and this promotes agglomerate growth by coalescence. The increase in the volume of binder liquid will cause a slight increase in the liquid saturation, which results in a slightly larger agglomerate size. The pellets were normally found to become smoother at a high product temperature because of a combined effect of a lower viscosity and a higher liquid saturation.

4. Binder viscosity, binder particle size (Schaefer T. and Mathiesen C., 1996)

A higher binder viscosity will increase the viscous contribution to the force of the dynamic pendular liquid bridges, and this will increase the potential of

agglomerate growth by coalescence. However, a higher viscosity will decrease the deformability of the agglomerates simultaneously, and this will reduce the potential between for growth. The effect of viscosity on agglomerate growth will depend on the balance between these counteracting effects. The subsequent agglomerate growth by coalescence is dependent on the binder particle size too. At low viscosity, a fine powder results in a lower agglomerate growth rate than coarse powder or flakes. These effects are assumed to be due to differences in the deformability of the agglomerates caused by an effect of the binder particle size on the intragranular distribution o f the binder.

3.4.2 Wax matrix granule prepared by twin screw extruder

A wax matrix could easily be obtained using a twin screw compounding extruder. A powder mixture consisting of the drug and wax was continuously fed into the extruder and discharged from the die to form a rigid wax matrix at ambient temperature. Formation occurred even at temperatures lower than wax melting point because of high-pressure condition created by two screws in the barrel of the extruder. The use of the twin screw compounding extruder therefore has several advantage such as ease of manufacturing, short manufacturing time, low temperature, ease of sharpening small granules, and the ability to produce quite homogenous matrices.

Miyagawa Y. et al., (1996) studied the wax matrix granule prepared by twin screw extruder. Powders were introduced into supply window of the extruder and extruded toward the die through a barrel consisting of four sections. These sections are called the first, second, third and fourth from the supply window. The powders were again mixed and exposed to high pressure between two screws in the barrel, but carnauba wax did not melt in the first and second sections, maintained at temperatures

of 30 and 50 ^{0}C, respectively. The screws in these two sections mainly mix the powders and extrude it toward the third and fourth sections. In the third section, carnauba wax was confirmed to be melted (the screws have a special structure enabling them to generate higher pressure here than in the other sections). Due to the extruded powder and screws, the high pressure could be maintained in the fourth sections, in which temperature was held at 70 ^{0}C. As a result of high pressure and this relatively high temperature, carnauba wax was kept in a molten state although the normal melting point of the wax is around 83 ^{0}C. The temperature of 70 ^{0}C was necessary to prevent the solidification and blockage of the discharge of molten wax matrix at the die. The wax matrix was cut into about 2 mm. diameter, 2 mm long monolithic wax matrix granule by a hot cutter after solidifying at ambient temperature.

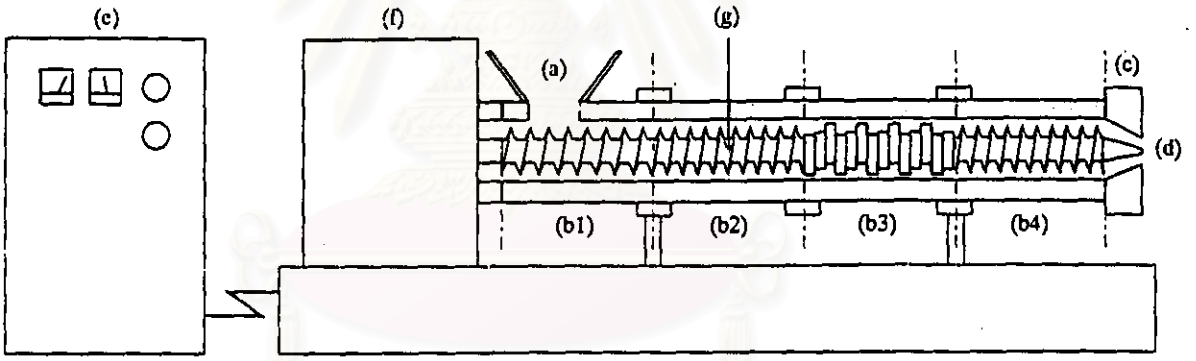


Figure 9 Schematic representation of a twin screw compounding extruder. a) the powder supply window; (b1-4) the barrel; c) the die with 2-mm diameter hole; d) the hole; e) the control panel; f) the driving section; g) the screw.

3.4.3 Tumbling melt granulation (Maejima T. et al., 1997)

The tumbling melt granulation (TMG) method, for preparing spherical beads without any use of the solvent, was developed. A mass of seed material was heated previously in the CF granulator (CF-360S) by blowing hot slit air. The

powdered mixture of meltable material and non meltable materials was gradually fed to the driving bed of the seed material. As illustrated in Figure 10, the meltable material was melted on the surface of the preheated seed material, and then the molten meltable material acting as a binder led the non-meltable material to adhere onto the seed material. By continuous tumbling and heating, the resultant melt granulation layer was gradually compacted and the surface of the outer layer becomes smooth. The bed temperature was kept constant during the granulation process. After feeding the designated amount of the powder mixture, the resultant beads were taken out of the CF granulator and cooled at room temperature.

In order to prepare spherical beads with a narrow particle size distribution and a smooth surface, it was concluded that the bed temperature during the processing should be maintained at least 5 ^{0}C higher than the melting point of the meltable material. Particle sizes of both the meltable and non meltable materials should be lowered below one-sixth of the diameter of the seed material; and the mixing ratio of the meltable material in the powdered mixture should be set at an optimum value.

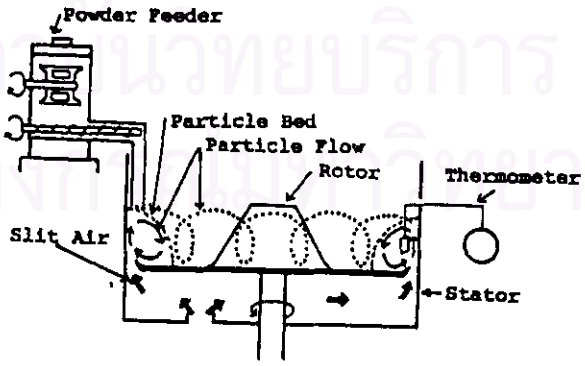


Figure 10 Scheme of CF granulator (CF-360S)

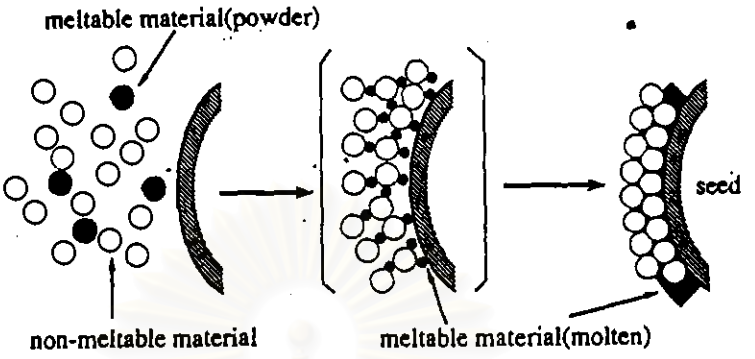


Figure 11 Schematic representation of principle of TMG method.

3.4.4 Extrusion and spheronization. (Blanque D. et al., 1995; Edimo A. et al., 1993; Montousse C. et al., 1999)

Matrix pellets obtained by extrusion and spheronization are of great interest because a subsequent release modifying coating is theoretically not necessary to obtain slow release of drugs. The extended release material were chitosan (Goskonda S.R. and Upadrashta S.M., 1993; Tapia C. et al., 1993), ethylcellulose or acrylic polymer (Neau S.H. et al., 1996; Goskonda S.R. et al., 1994) and polyethlene glycol or GMS (Blanque D. et al., 1995). Microcrystalline cellulose was often used as the spheronizing aid.

The machine, the process, and the step about formation of pellet are the same as normal pellet and the details are discussed in the prior part.

Lipidic substances such as carnauba wax or hydrogenated castor oil could also be successfully spheronized to produced beads if the wetting fluid was ethanol instead of water. Beads could also be prepared with this waxy excipient or

with gelucire 50/02 if the drug was previously dispersed in the melted material (Edimo A. et al., 1993). However, the authors have not given any results concerning drug release.

There were two ways for formation of optimum wet mass before extrusion and spheronization.

1. Wax was first dispersed in sufficient quantity of hot distilled water, followed by the addition of the drug with constant stirring until slurry was formed. The hot slurry was immediately mixed and blended with microcrystalline cellulose in mixer. The wet powder mass was then extruded and spheronized. (Peh K.K. and Yuen K.H., 1995)

2. Drug was incorporated into the melted wax at melting point + 10 ^{0}C using water bath and a stirrer. The resulting mixtures were cast in a layer of 1-cm. thickness on previously cooled plates and store overnight at between 0 – 4 ^{0}C. The congealed mixtures were milled using a screen. Other ingredients were added and the wetting was done in a planetary mixer. (Montousse C. et al., 1999)

4. <u>Matrix Systems</u>.

Matrix system is one of the popular controlled release systems. The drug to be released is dispersed uniformly throughout the rate controlling matrix medium. The release profile is then determined by the loading of dispersed agent, the nature of the component, and the geometry of the device. These spots, pinhole, and other similar defect, which can be serious problems with the reservoir systems, do not substantially alter the release from matrix devices. This, together with the ease with dispersion can be compounded, results in low fabrication costs. These advantages often out weigh the

less desirable feature of declining release rate with time that is characteristic of these systems.

Table 2 Material used as retardants in matrix tablet formulations.

Matrix characteristics	Material
Insoluble, inert	Polyethylene
	Polyvinyl chloride
	Methyl acrylate-methacrylate copolymer
	Ethylcellulose
Insoluble, erodible	Carnauba wax
	Stearyl alcohol
	Stearic acid
	Polyethylene glycol
	Castor wax
	Polyethylene glycol monostearate
	Triglycerides
Hydrophilic	Methylcellulose (400 cps, 4000 cps)
	Hydroxyethylcellulose
	Hydroxypropylmethylcellulose (60 HG, 90 HG, 25 cps, 4000 cps, 15000 cps)
	sodium carboxymethylcellulose
	carboxypolymethylene
	galactomannose
	sodium alginate

One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blends of drug, retardant material, and additive to form a tablet which drug is embedded in a matrix core of retardant. Alternatively, retardant drug blends may be granulated or pelleted prior to compression. Furthermore, from the advantage of the multiparticulate system, a novel matrix pellets system become more popular which can be prepared by extrusion-spheronization, melt pelletization and so on. Table 2 identifies examples of the three classes of retardant materials used to formulate matrix tablets, each class demonstrating approach to the matrix concept. The first class consists of retardants that form insoluble or "skeleton" matrices: the second class represents water insoluble materials that potentially erodible; and the third class consists of polymer that form hydrophilic matrices. Loading doses are best included as the second layer of a two-layer tablet or in coating applied to the matrix core.

5. Release of Active Ingredient.

5.1 **Drug release form wax matrices.** (Schwartz J.B. et al., 1968; Higuchi T.,1963)

Matrices composed of plastic polymers have been shown to exhibit release profiles, which are best described by the linear square root of time dependence indicating that a diffusion controlled mechanism is operative. Waxes, on the other hand, present a much more complicated system, due to various physico-chemical factors and property not present in the plastic systems.

The mechanism of release from wax matrices has not been as firmly established. But it would be highly described that the release rate from these systems also be quantitated by use of the diffusion model and the determination of the necessary controlling parameters made.

Theoretical treatment has shown that drug release from an insoluble, inert matrix is described by T. Higuchi equation if the rate determining process is diffusion, and this is given by

$$Q = \{(D\varepsilon/\tau).(2A-\varepsilon C_s).(C_s t)\}^{1/2} \quad 1)$$

where Q is the amount of drug released per unit area of the disk exposed to the solvent; D is the diffusion coefficient of the drug in the solvent; ε is the porosity of the matrix; A is the concentration of solid drug in the matrix; C_s is the solubility of the drug in the solvent; and t is the time.

A drug wax system is developed in which the drug release behavior is relatively complex over one range of drug wax composition the rate appears to be diffusion controlled through the aqueous pores, but the tortuosity values are extremely high. In the second range (high drug concentrations in tablet) the mechanism appears to change to one in which the rate is not solute diffusion.

If the matrix is composed of nearly spherical particles, such as one would have in a bed of sphere, the τ value should range between about 1.5 – 3. On the other hand, if the matrix material were less spherical, either because the initial particles are non-spherical or because during preparation of the particles become distorted, then greater τ values would be expected. However, even under extreme conditions, it is difficult to imagine τ values much greater than 10 or 20 when the sample concept underlying the meaning of tortuosity is used.

Apparent τ values greater than 1000 have been observed with compressed tablet made of drug wax combination. It is assumed that the drug particles are isolated in a sea of wax. This should be a reasonable approximation at low drug concentrations, since most waxes are extremely soft (plastic) and should flow around the drug particles during compression.

The important feature of this situation is that diffusion is most difficult in the waxes region connecting the pores (left behind after the drug is leached) rather than in the pores themselves as might be generally assumed. Thus the permeability of the drug is largely determined by the permeability characteristic of the wax matrix itself.

After ingestion of the dosage form composed of lipid matrix, the release of drug may be operative to the following mechanism.

1. Diffusion of drug to the dissolution medium along the pore or channels within the matrix by leaching of drug or other additives. The diffusion of drug across lipid matrix may not ensure the release of drug to aqueous medium sufficiently because it required high lipophilicity of drug.
2. Erosion of the matrix by lypolysis of pancreatin lipase enzyme or by simple hydrolysis or even by solubilization in digestive juice.

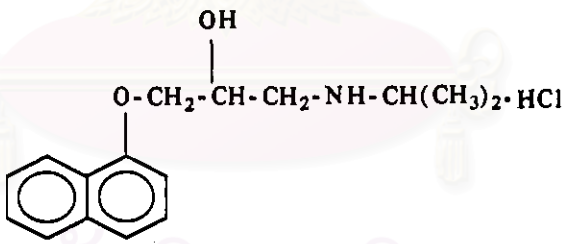
One or both of mechanisms just described may govern the release of drug from the lipid matrix, depending on the type of lipid material used. In the case that lipid materials are intact, not sensitive to the action of lipase or not solubilized by ionization, the release of drug is operative to diffusion controlled mechanism.

Ishino R. and Sunada H. (1993) elucidated individually the influence of five drugs having different solubilities and the matrix structure on the drug release rate from a wax matrix tablet, the intrinsic dissolution rates of drugs and release rates of several matrix tablets consisting of various proportions of drug and hydrogenated castor oil. From this study, therefore, it is clear that the boundary retreat rate constant, namely, the drug release rate constant from the matrix tablet, was inversely proportion to the square root of tortuosity. It was found that the tortuosity formed in the matrix tablets varied with the drug species, even though the porosity was the same. Furthermore, it was determined that the dependency of tortuosity on porosity could be controlled by the additions of other materials.

The dissolution, erosion, and swelling profiles of the drug dispersion were assessed by Sutananta W. et al., 1995. Gelucire 40/01® and 54/02® systems werer found to release the drug by a simple diffusion mechanism, with no evidence for erosion or swelling being noted. Gelucire 50/18®, however, showed a more complex mechanism involving both diffusion and erosion. On increasing the drug load within the matrices, the predominance of the erosion mechanism increased. Drug released from gelucire 50/13 matrices took place principally by erosion, although the process was dominated by swelling and subsequent disintegration of the matrix. Gelucire 50/02® matrices also exhibit swelling, although drug release occurred predominantly via diffusion. Gelucire® may release incorporated drugs by a number of mechanisms depending on the chemical composition of the base.

6. **Propranolol Hydrochloride**

Propranolol hydrochloride is a non-selective β adrenergic blocking agent. (AHFS drug information® 98). Its formula and molecular weight are presented below



Empirical formula $C_{16}H_{21}NO_2.HCl$ (MW = 295.8)

Propranolol hydrochloride occurs as white or off-white, crystalline powder; odorless, with a bitter taste. It absorbs less than 1 % of water at 25 ^{0} C at releative humidity up to 80 %. Propranolol hydrochloride melts in a range of 163 ^{0} to 166 ^{0} C. The pH of 1 % solution of propranolol HCl in water lies between 5 and 6. Dissociation constant (pKa) of propranolol HCl is 9.5 (24 ^{0} C) and the partition coefficient in octanol/phosphate buffer, pH 7.4, as 11.61 (Clarke F.H. and Cahoon N.M., 1987)

Propranolol hydrochloride is soluble 1 in 20 of water and 1 in 20 of ethanol; slightly soluble in chloroform and practically soluble in ether.

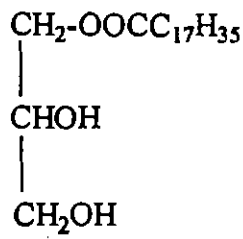
Propranolol HCl is affected by light and should be stored at room temperature (25 ^{0} C). The manufacturer recommends that propranolol HCl extended release capsules be stored in tight, light resistant containers and be protected from moisture, freezing, excessive heats. In aqueous solutions, it decomposes 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.

The excipients used in Inderal® 160 consist of brilliant blue FCF (133), erythrosine (E127), ethylcellulose, gelatin, hypromellose, iron oxide (E172), microcrystalline cellulose, povidone, talc, titanium dioxide (E171).

After oral administration of 160 mg propranolol (Inderal, ICI) and 160 mg long acting propranolol (ICI) to healthy volunteers, plasma concentration peaked at 2 hours and 10 hours, respectively were observed. (Nace G.S. and Wood A.J.J., 1987; Dunn J., 1987)

7. **Glyceryl Monostearate**

Glyceryl monostearate is used as a non-ionic emulsifier, stabilizer, emollient and plasticizer in a variety of food, pharmaceutical and cosmetic preparations. It acts as an effective stabilizer, i.e. as a mutual solvent for polar and non-polar compounds, which may form W/O or O/W emulsions (Eceleston G.M., 1992). It is also used as a lubricant and to sustained release of active ingredients in tablet formulations.



Glyceryl monostearate is a white to cream colored, wax like solid in the form of beads, flake or powder. It is waxy to touch and has a slight fatty odor and taste. It can be melted at 55 – 60 ^{0} C and its HLB value is 3.8. glyceryl monostearate can soluble in hot ethanol (95 %), ether, chloroform , hot acetone, mineral oil and fixed oils. Practically insoluble in water, but readily dispersible in hot water with the aid of anionic or cationic agent.

8. **Lubritab® (hydrogenated cotton seed oil)**

$$R_1COOCH_2\text{-}CH(OOCR_2)\text{-}CH_2OOCR_3$$

Where R_1, R_2 and R_3 are mainly C_{15} and C_{17}

Lubritab® is used as a lubricant in tablet or capsule from 1 – 6 % W/W. it is additionally used as the matrix forming material in lipophilic controlled release formulations (Wang P.Y., 1989; Ciftci K. et al., 1990; Watanabe Y. et al., 1990). It may also be used as coating aid in controlled release formulation.

Lubritab® is a mixture of triglyceride of fatty acids. It occurs in various forms, e.g. fine powder, flakes, and pellets. The material is white to yellowish-white with the powder grades appearing whiter colored than the croaser grades. It can be melted at 61 – 66 ^{0} C. Lubritab® can be soluble in chloroform, petroleum spirit, and hot propan- 2 – ol, practically insoluble in water.

9. **Carnauba Wax**

Carnauba wax is the hardest and highest melting point of the waxes and is used primarily as a 10 % W/W aqueous emulsion to polish sugar coated tablets. Carnauba wax (10 – 50 % W/W) has also been used alone or with stearyl alcohol to produce

sustained release dosage formulations (Wiseman E.H. and Federici N.J., 1968; Dave S.C. et al., 1974; Kumar K. et al., 1975)

Carnauba wax consists primarily of a complex mixture of esters of acids and hydroxyacids. It occurs as a light brown to pale yellow colored powder, flakes, or irregular lumps of a hard, brittle wax. It possesses a characteristic bland odor and practically no taste. It is free from rancidity. It can be melted at 81 – 86 ^{0} C and soluble in warm chloroform, and warm toluene; slightly soluble in boiling ethanol (95 %) practically insoluble in water.

10. **White Beeswax**

White wax is a chemically bleached form of yellow wax. It is used to increase the consistency of creams and ointments, and to stabilize W/O emulsions.

It consists of 70 – 75 % of a mixture of various esters of straight chain monohydric alcohol with even number carbon chain C_{24} – C_{36} esterified with straight chain acids which also have even number of carbon atoms up to C_{36} together with some C_{18} hydroxy acids. White wax consists of tasteless, white or slightly yellow colored sheets or fine granule with some translucense. It can be melted at 61 – 65 ^{0} C and soluble in organic solvent.

11. **Precirol® (glyceryl palmitostearate)**

Glyceryl palmitostearate is used as a lubricant and lipophilic matrix for sustained release tablet and capsule (Parab P.V. et al., 1986; Saraiya D. and Bolton S., 1990; Shaikh N.H. et al., 1991). Sustained release tablet formulations that contain glyceryl palmitostearate as the base may be prepared either by granulation or by a hot melt technique. Glyceryl palmitostearate may also be used to form microspheres, which may be used in capsule or compressed to form tablets.

Glyceryl palmitostearate, is a mixture of mono, di, triglycerides of C_{16} and C_{18} fatty acids, occurs as a fine white powder with a faint odor. It can be melted at 52 – 55 ^{0} C and freely soluble in chloroform and dichloromethane; practically in soluble in ethanol (95 %), mineral oil, and water.

12. Compritol® (glyceryl behenate)

Glyceryl behenate is used as a lubricant (use level 1 – 3 %), binding agent by direct tabletting, lipophilic matric for sustained release tablet or capsule (use level > 10 %)

it is a mixture of glycerides of fatty acids, mainly behenic acid. It can be soluble in chloroform, methylene chloride when heated and insoluble in ethanol, n-hexane, water, and mineral oils.

13. Gelucire 50/02®

Gelucire 50/02® is saturated polyglycolysed glycerides: specific mixture of mono, di, and triglycerides and polyethylene glycol mono and diesters.

It is used as excipient for hard gelatin capsules, bioavailability ragulator for sustained formulation with

- protective action against oxidation and hydrolysis
- handling of low density product or toxic or low dose active drug
- formulation of solid dosage form with liquid active

It can be freely soluble in chloroform, methylene chloride, insoluble in ethanol, and dispersible in water and mineral oil.