CHAPTER I

INTRODUCTION

Introduction

Sustained release preparations have become a suitable way of solving some problems connected with classical oral pharmaceutical dosage forms. Certain drugs-principally those with a short half-life are of more benefit when administered daily in a form, which maintains the drug blood level over the minimum effective level.

Among the various methods that have been proposed, pellets, due to their particular properties seem to be an attractive method in the design and development of these kind of preparations. In fact, pellets or beads have the minimum surface/volume ratio and are an ideal shape for coating. These properties offer a practical method to control the site and rate of drug dissolution in the gastro-intestinal tract. Moreover, the lower level of gastric irritation, the fewer dose-dumping accidents and the possibility of building up different barriers for different drugs are a few of the advantages which confirm the success of this particular dosage form. In addition, pellets are highly preferred over tablets in developing sustained release dosage forms because of their greater predictability and reproducibility of therapeutic effects.

One of the most successful processes to obtain pellets is extrusion/spheronization, which came increasingly into use during the late 1970s. Since the various works have been published pointing out the interacting factors of the whole process: the formulation factors (Hasznos et al., 1992); the extrusion conditions (Bataille et al., 1993); the type and amount of glycerides (Thomsen et al., 1994); the solubility and concentration of drug (Zhou et al., 1996; Gupta et al., 2001); effect of particle size of pellets (Millili and Schwartz, 1990; Shaikh et al., 1991); and the relationship with the quality of the spheres (Vervaeat et al., 1994) are some of these studies.

Several attempts have been made to modify drug release from multi-particulate oral dosage forms without the necessity of extending the process of production with a second step of film coating. Several authors have tried to achieve retardation by incorporating various hydrophobic materials into a basic formulation for pellets (Ghali et al., 1989). Such systems retard the penetration of aqueous fluids into the formulation and hence slow the rate of drug release. Glycerides are a group of materials derived from natural products, which have a wide variety of applications within pharmaceutical formulation. In particular, glycerides, which are solid or semi-solid at room temperature, are used as suppository bases and, more recently, as controlled release matrices (Howard and Gould, 1987).

Several researchers have been investigated the effect of glycerides concentration on the release of drug from the preparation such as Brossard et al. (1999) depicted that drug release is found to be increased as the melting point of glycerides decreased and drug solubility rose. Thomsen et al. (1994) also studied effect of 12 meltable substances on the ability to form prolonged release of pellets. It was found that few substances were able to pelletize a formulation. Whereas pellets prepared with combinations of glyceryl monostearate (GMS) and microcrystalline wax demonstrated the slower release. The release of drug could be varied within wide limits by varying the composition of binder phase. Peh et al. (1995) have found that the effect of wax concentration play an important roles on the release of theophylline from matrix pellets produced by extrusion/spheronization. Zhou et al. (1996); Miyagawa et al. (1999); Bodmeier et al. (1990); and Brabander et al. (2000) explored the effect of wax concentration on the release of drug in the form of pellet matrix, granule matrix, semi-solid matrix capsule, and tablets, respectively. They have been indicated that as the concentration of wax increased, the release of drug from matrix decreased with the time.

Other workers have attempted to enhance release by the inclusion of polyethylene glycols and surfactants into the pellets (Vervaet et al., 1994a). Serajuddin et al.(1990), and Kenneth et al. (1992) reported that the dissolution of a poorly soluble drug is improved by incorporating PEG 1450 and Tween® 80 in the formulation by solid dispersion technique. The processing of the dosage form was

simplified by encapsulating the formulation directly into hard gelatin capsules as molten solution. At room temperature, the dispersion solidified to form plugs inside capsules. Large scale manufacturing of such a dosage form is feasibility.

Glycerides such as hydrogenated castor oil could also be successful spheronized to produce beads if the wetting fluid was ethanol instead of water. With Precirol®, wetting was achieved with water, however, a subsequent thermal treatment was needed to obtain extended release spheroids (Ghali 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 used in these formulations possessed only low to moderate water solubility such as ibuprofen, and theophylline, respectively.

Although, there are many reported on the release of drug from matrix preparation, but only a few reports concerning matrix prepared by extrusion/spheronization with highly and poorly water soluble drug (propranolol hydrochloride and diclofenac sodium, respectively). And the effects of thermal treatment on the release of highly water-soluble drug (propranolol hydrochloride) from glycerides matrix.

The purpose of this study was to determine the application of extrusion/spheronization technique for producing propranolol hydrochloride and diclofenac sodium matrix pellets by using GMS, Lubritab®, and Compritol® ATO 888 as a matrix-forming agent in various concentrations. And exploring the effect of additive and thermal treatment on the release of matrix pellets.

Objective of the Study

1. To evaluate the release characteristics of highly water-soluble drug (propranolol hydrochloride) and poorly water-soluble drug (diclofenac sodium) and effect of type and amount of glycerides on the release of the drugs from matrix pellets.
2. To investigate the amount of additives on the release characteristics of drugs from matrix pellets.
3. To compare the release characteristics of pellets having different surface area on the release of drugs from matrix pellets.
4. To elucidate the effect of pH of dissolution medium on the release of drugs from matrix pellets.
5. To study release kinetic and mechanism of propranolol hydrochloride and diclofenac sodium from glycerides matrix pellets.

Literature Review

1. Pelletization

Pellets are spheres of varying diameter depending on the application and the wish of the producer. Historically, the pellets has been used by a number of industries to describe a variety of agglomerates produced from divers raw materials, utilizing different pieces of manufacturing equipment. These agglomerates include fertilizers, animals feeds, iron ores, polymer and pharmaceutical dosage forms, and hence do not only differ in composition but also encompass different sizes and shapes. Therefore, pellets mean different things for different industries.

In the pharmaceutical industry, pellets can be defined as small, free flowing, spherical particulate manufactured by the agglomeration of fine powders or granules of drug substance and excipients using appropriate processing equipment. Pellets are sized between 0.5-1.5 mm (Ghebre-Sellassie, 1989) and are commonly filled into hard gelatin capsules but can also be compressed to tablets (Bechard and Leroux, 1992; Millili and Schwartz, 1990).

The reasons that pellet are of great interest for the pharmaceutical industry because they not only offer flexibility in dosage form design and development, but also utilized to improve the safety and efficacy of bioactive agent.

Pellets can be produced in variety techniques such as spraying a solution or a suspension of a binder and a drug onto an inert core, building the pellet layer after layer (Li et al., 1989); 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 (Ghebre-Sellassie, 1989); spraying a binder solution into the whirling powder using a fluidized bed (Olsen, 1989). The most popular method of producing pellets is by the extrusion-spheronization technique. The most recent method for production of pharmaceutical pellets is by mean of the fluid-bed rotor granulator or by the centrifugal granulator (Maejima et al., 1992; Bechard and Leroux, 1992) performing the whole cycle in one closed system. For example, pellets formed by extrusion-

spheronization show a slower release profile compared to those made by the layer building technique (Zhang et al., 1990, 1991).

2. Extrusion-Spheronization Process

The extrusion-spheronization process involves five unit operations. These are dry mixing, wet granulation, extrusion, spheronization, drying and (if necessary) screening (Figure 1).

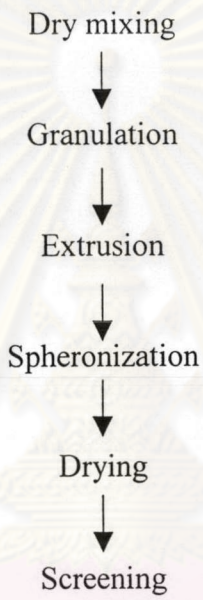


Figure 1 Flow chart of a typical extrusion-spheronization process.

Dry Mixing and Granulation

The first step is dry mixing of the drug and excipients in suitable mixers followed by wet granulation, which converts the powder into a plastic mass that can be easily extruded. The most commonly used granulator is a planetary mixer (O'Connor et al., 1985; Fielden et al., 1989; Zhang et al., 1990, 1991; Yuen et al., 1993; Blanque et al., 1995; Peh et al., 1995; Sousa et al., 1996) although the use of high shear (Ku et al., 1993; Zhou et al., 1996, 1997, 1998; Schaefer et al., 1992, 1993a, 1993b, 1996a, 1996b, 1996c, 1996d) or sigma blade (Woodruff and Nuessle, 1972) mixers has also been reported.

Extrusion Operator

In the extrusion step, the wet mass is passed through the extruder to form rods, similar to short strands of spaghetti. These extruded strands are called extrudate. The extrudate length may vary, depending on the physical characteristics of material to be extruded, the method of extrusion, and how the particles are manipulated after extrusion. Various type of extruders can be performed using four main classes, i.e, screw, sieve and basket, roll, and ram extruder (Hick and Frecse, 1989).

A. Screw Extruder

This type of extruder is the only strictly continuous devices as a result of extrudate can exit in a smooth continuous flow. As the name involves, screw extruder utilizes one or two (twin-screw) screw to develop pressure forcing the mass through opening. Two fundamentally different mechanisms for screw extrusion are possible (Figure 2).

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.

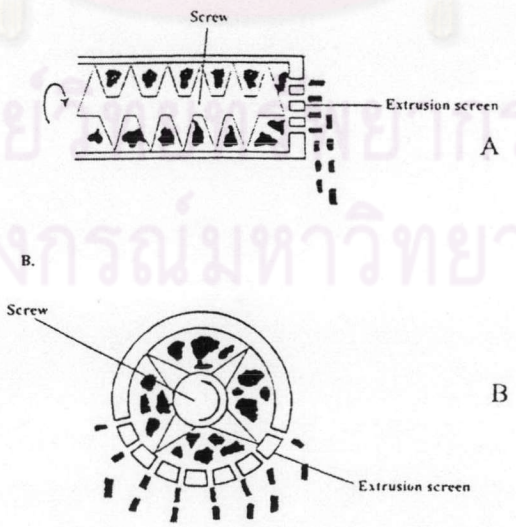


Figure 2 Schematic view of a screw extruder : A) Axial type; B) Radial type

B. Sieve and Basket Extruders

In the sieve and basket extruders (Figure 3), the granulator is fed by a screw or by gravity into the extrusion chamber and pressed through the screen by rotating or oscillating device. The different between the sieve and basket extruders is similar to that between the radial and axial screw extruders. In a sieve extruder the screen is 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.

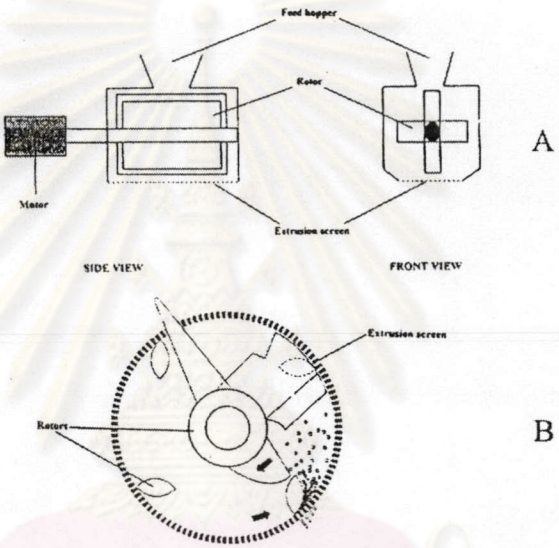


Figure 3 Schematic view of a sieve extruder (A); a basket extruder (B)

C. Roll Extruder

In this type, the mass is fed and pressed between roller and perforated plate. Two different types can be described: the first type equipped with two contrarotating rollers which one or both are perforated and the extrudate is collected inside the extrusion rollers (Figure 4 A and B). The second type of roll extruder has a perforated cylinder rotates around one or more rollers installed inside that cylindrical chamber and discharging the material out ward (Figure 4C).

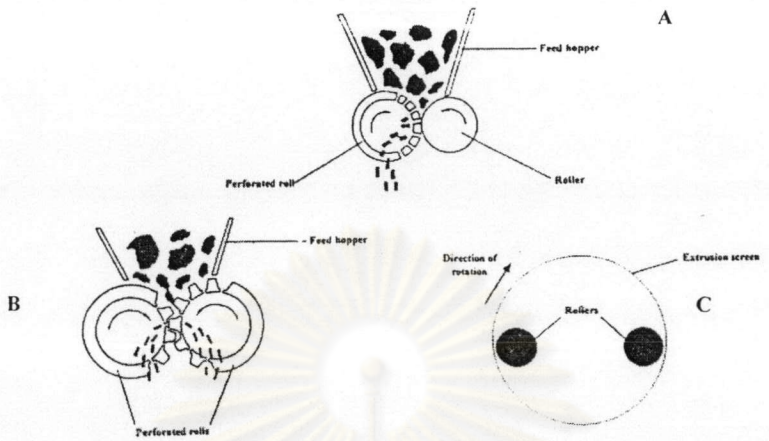


Figure 4 Schematic of roll extruder with one perforated roll (A); with two perforated roll (B); with the extrusion screen rotating around roller (C).

D. Ram Extruder

Ram extruder (Fielden et al., 1989; 1992; Tapia et al., 1993; Blandque et al., 1995), probably the oldest type of extruders. The principle of this extruder is based on a piston that pushes the wet mass through the screen situated at the end of the barrel (Figure 5).

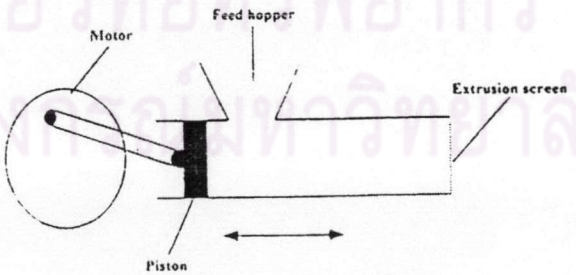


Figure 5 Schematic of ram extruder

Spheronization Operation

In this case, the extrudates 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. The static cylinder can be jacketed for temperature control. The friction plate, a rotating disk with a characteristically grooved surface, is the most important component of the equipment. A standard friction plate with a crosshatch pattern, where the grooves intersect at a 90° angle is the most popular type. Another type of friction plate is radial geometry where a radial pattern is used (Figure 6).

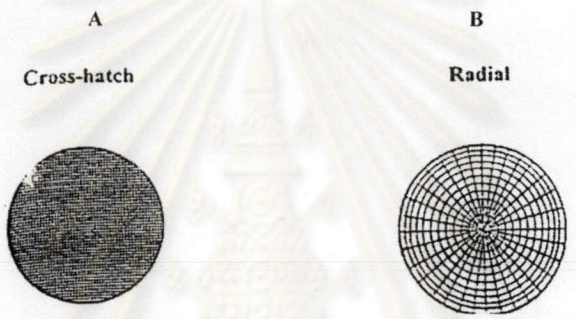


Figure 6 Geometry of the spheronization plate cross-hatch (A); radial (B).

According to Rowe (1985) those plastic cylinders are rounded due to frictional forces. In the spheronization process different stages can be disguised depending on the shape of the particle, i.e. starting from a cylinder over a cylinder with rounded edges, dumb-bell and elliptical particles to eventually perfect spheres (Figure 7A). Baert and Ramon (1993) suggested that another pellet forming mechanism might exist (Figure 7B). In this mechanism, a twisting of the cylinder occurs after the formation of cylinders with rounded edges, finally resulting in the breaking of the cylinder into two distinct parts. Both parts have a 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.

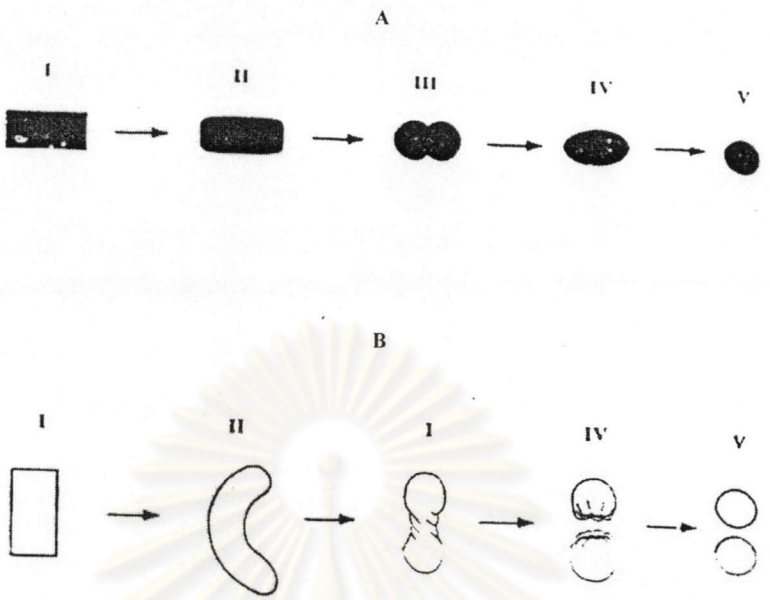


Figure 7 Pellet-forming mechanism according to (A) Rowe: I, cylinder; II, cylinder with rounded edges; III, dumb-bell; IV, ellipse; V, sphere; (B) Baert: I, cylinder; II, rope; III, dumb-bell; IV, sphere with a cavity outside; V, sphere.

Drying

The resulting pellet can be dried at room temperature (Hellen and Yliruusi, 1993) or at elevated temperature in a fluid-bed (Baert and Ramon, 1993; Ku et al., 1993), a hot air oven (Woodruff and Nuessle, 1972; O'Connor and Schwartz, 1985; Zhang et al., 1990) or a microwave oven (Bataille et al., 1993).

3. Parameter Influencing the Final Pellets Prepared by Extrusion and Spheronization

There are various process and formulation parameters that effect on the qualities of pellets. These parameters can be described as follows:

3.1 Formulation

3.1.1 The Moisture Content in Granulated Mass

The moisture content plays a critical role in the extrusion-spheronization process. Many research presented the effect of moisture content on the characteristics of final pellet (Baert and Ramon, 1993; Ku et al., 1993; Pinto et al., 1993). If the moisture content is less than the lower limit, a lot of dust will be formed during spheronization resulting in a large yield of fines. Exceeding the range of the moisture content leads to an overwetted mass and agglomeration of the individual pellets during spheronization due to the excess of water at the surface of the pellets. Furthermore, mean diameter, size distribution, sphericity, hardness and drug release rate may be increased. The increasing of hardness due to the decreasing of porosity and friability of pellet.

Generally, the liquid content of the wet powder mixture is about 20-30% 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 or solubility reasons.

3.1.2 The Physical Properties of Starting Materials

There is not only the obvious difference in pellet quality stating from different compositions but also a difference when different types of the same product are used.

O'Connor and Schwartz (1985) demonstrated the effect of Avicel® type on the quality of the pellets (pellet size, sphericity as well as release rate of an included drug). The RC and CL type showed the release rate of drugs because a gel-like structure was formed in water due to the presence of sodium carboxymethylcellulose whereas the pellets containing Avicel® PH 101 remained in the aqueous dissolution medium, resulting in a greating release rate.

Herman et al. (1988) demonstrated that using various types of microcrystalline cellulose (Avicel® PH 101 and Avicel® RC-581; microcrystalline cellulose blend with carboxymethyl cellulose) provided the pellets with different release rate in different types of dissolution fluids.

The use of similar products but from different suppliers could change the characteristics of the pellets (Heng and Staniforth, 1988).

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

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

3.2 Extrusion Process

3.2.1 The Type of Extruder

Several research have investigated the effect of extruder type on the pellet characteristics (Rowe, 1985; Fielden et al., 1992). Fielden et al., (1992) compared some behaviors of extrudate using ram and cylinder or roll extruder. The finding showed that the pellets obtained from the two type of extruder differed in sphericity and particle size distribution. The uncontrolled agglomeration occurred when ram extruder was used and this behavior depended on the particle size of starting material. This observation was due to differences in shear rate or shear stress between these two types of extruder. Furthermore, the different in particle size distribution owed to distinction in the length-to-radius ratio (L/R ratio) of the extrusion screen the different types of extruder was used.

3.2.2 The Extrusion Speed

Harrison et al. (1985) reported that increasing in extrusion speed (high through put rate) affected the extrudate quality including surface impairments such as roughness and sharkskinning. These defects lead to pellets of lesser quality because the extrudate will break up unevenly during the initial stages of the spheronization process, resulting in a lot of fines and a wide particle size distribution.

3.2.3 The Properties of the Extrusion Screen Size

The extrusion screen size is characterized by the thickness of the screen and the diameter of the perforations. The diameter of the perforations determines the size of the pellets, a larger diameter of the perforations will produce pellets with a larger diameter when processed under the same conditions.

Baert et al. (1993a) described the difference in extrudate quality between an extruder equipped with a screen of a length-to-radius ratio (L/R ratio) of 1.8 and one of L/R ratio formed a rough and loosely bound extrudate while the screen with an L/R ratio of 4 formed a smooth and well-bound extrudate. This observation can be explained by the higher densification of the wet mass in the screen with the greatest thickness.

3.3 Spheronization Process

3.3.1 The Spheronization Speed

Several researches indicated the effect of spheronization speed (speed of friction plate) on the characteristics of pellets (Ku et al., 1993; Wan et al., 1993). An increase in the yield of the smaller fractions was seen, probably due to a greater degree of fragmentation during the initial stages of the spheronization process. In contrast, a decreasing amount of fines and increasing amount of large particles with increasing spheronizing speed correlating with an increased mean diameter were also observed. The hardness, roundness, porosity, bulk and tapped densities, friability, flow rate and surface structure of the pellets were also influenced by a change in the

spheronization speed (Woodruff and Nussle, 1972). According to Rowe (1985) the spheronization speed should be optimized to obtain perfect spheres, as opposed to a spheronization process at higher speed, which could lead to agglomeration of individual pellets.

3.3.2 The Spheronization Time

A wide variety was witnessed when assessing the importance of this parameter on formulations containing mixtures of microcrystalline cellulose: an increased diameter, a narrower particle size distribution, a change in the bulk and tapped densities and a change in the yield of a certain size range were observed with extended spheronization time. Baert et al. (1993) also found an increased of the sphericity of the pellets when a formulation containing only Avicel® pH 101 was processed. In contrast, they found that no influence on the granulometry, the hardness and the friability when formulations containing on Avicel® pH 101 were spheronized for different periods of times.

3.3.3 The Spheronizer Load

The importance of the spheronizer load was determined by means of an experimental design. 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 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. In addition, the size of the pellets decreased and their bulk and tapped densities increased with an increasing spheronizer load.

3.4 The Drying Method

Drying is the final step to eliminate the excess of the solvent used in granulation liquid. The pellets can be dried at room temperature or at elevated temperature in a fluidized bed, a hot air oven or a microwave oven. Comparing a

formulation dried in a microwave and ordinary oven, the pellets dried with microwave differed from those dried in the oven as their surface was rougher, more porous and lesser hardness (Betaille et al., 1993).

4. Wax Matrix Pellets System

The matrix system is commonly used for manufacturing sustained release dosage forms because it makes such manufacturing easy. In this system, the drug in the form of fine powder and a matrix-forming component are mixed and the mixture is then shaped in an appropriate mold. Non-bioerodible polymer and wax are commonly used as matrix-forming components. The use of wax seems to have a particular advantage due to wax's 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 matrices with the desired properties. Preparation of matrix systems has been discussed, but the process is not easy to specify in the case of preparation of high-quality matrices. Furthermore, considering of gastric emptying time of pharmaceuticals, multiple unit formulation is suitable for sustained release dosage forms, but it is rather difficult to prepare small pellets or granules with the wax matrix system because of the aggregation of granules in the manufacturing process. Wax matrix granule would be valuable as convenient dosage form for controlling drug release if these problems could be solved.

Several attempts have been made to modify drug release from multi-particulate oral dosage forms without the necessity of extending the process of production with a second step of film coating. Several authors have tried to achieve retardation by incorporating various hydrophobic materials into a basic formulation for pellets (Ghali et al., 1989). Such systems retard the penetration of aqueous fluids into the formulation and hence slow the rate of drug release.

Other workers have attempted to enhance release by the inclusion of polyethylene glycol and surfactants (Vervaet et al., 1994). Such systems, however, would only function if the presence of modifying agent did not interfere with the

production process. The preparation of pellets by extrusion/spheronization is not a process, which can be used for all formulations. Hence, it is importance to evaluate the factor, which could affect both the ability to make spheres and the influence such factors, would have on the drug release performance.

Controlled Parameters of the Matrix System

Technological factors influencing release from controlled release pellets can be states following parameters:

A. Type and Amount of Drug Incorporated in Matrix

The influence of the type and amount of drug incorporated in matrix is interesting and of practical importance in the field of controlled release. Fessi et al. (1982) have shown that several systems of loading type obeyed the Higuchi square root equation, such that the slope is approximately proportional to the initial drug loading.

Foster et al. (1990a, 1990b) showed the release of ephedrine hydrochloride and procaine hydrochloride from hydrogenated castor oil matrix tablet. The effect of drug revealed that the release profiles at 25 °C in terms of cumulative amount release per unit area versus square root of time are linear. The release increased with are increase in concentration of drug. A similar result are happened when change to other drug.

O'Connor and Schwartz (1993) determined the effect of drug on the release of drug from matrix pellets. The result showed that an increase in aqueous solubility was found to be corresponding to an increase in the amount of drug dissolved at any time. This study indicated that the release rate of drug as follows; hydrochlorothiazide > quinidine sulfate > theophylline > chlorpheniramine maleate, respectively. They also studied the dissolution rate of pellets containing various concentrations of theophylline. An increase in the concentrations of drug in the matrix resulted in an increase in the amount of drug release at any time t. It must be noted that a change in

concentration of drug will affect the porosity and may possibly affect the tortuosity of the matrix.

Ishino et al. (1993) observed the release rate of five drugs having different solubility. The result exhibited that release rate decreased with increasing hydrogenated castor oil content. Similarly to the suggestion of Blanque et al. (1995), the drug release from the pellets is also delayed by decreasing the solubility of the drug.

Adeyeye and Price (1994) studied the effect of drug loading on the dissolution of ibuprofen from ceresine wax-stearyl alcohol microspheres. The result indicated that increased drug loading from 9 to 17% could significantly increase the release rate of drug from microspheres.

Otsuka and Matsuda (1995) investigated the release of pentoxifliine from a dry coat wax matrix tablet contains behenic acid as wax matrix. The result shown that increased drug load will increase the release of drug. Not all the wax matrix tablets disintegrated during the dissolution test.

In addition, Sprockel et al. (1997) compared the release of the three drugs, chlorpheniramine maleate had the fastest release rate and theophylline had the slowest release rate, with salicylic acid in between. The solubility determined for the three drugs are relative because no effort was made to maintain the pH constant in the saturated solutions. The extremely high solubility of chlorpheniramine maleate compared to the other two drugs provided a very large concentration gradient for diffusion. The solubility of chlorpheniramine maleate was approximately 60 times greater than that for theophylline and 100 times greater than that salicylic acid.

B. Type and Amount of Matrix Material

The matrix material should be met the selection criteria in Table 1 (Phillai et al., 1988).

Emori et al. (1984) reported that the increase in the release rate occur with increasing amount of polymer in phenacetin wax matrix. Because of an increase in the diffusion rate of drug molecules through channels that resulted from leaching of the polymer and also by a shortening of this channel length due to matrix disintegration.

Table 1 The criteria in selection polymers for matrix development.

1.	Molecular weight, glass-transition temperature, and chemical functionality of the polymer must allow the proper diffusion and release of the specific active agent.
2.	Polymer functional group should not react chemically with to active agent.
3.	The polymer and its degradation product must be non-toxic.
4.	The polymer must not decompose during the entire shelf-life.
5.	The polymer must be easily manufactured or fabricated into a desired product.
6.	The cost of polymer should not be expensive as to make controlled drug release device very expensive.
7.	It should be readily available.

Mctaggart et al. (1984) reported that both wax content and wax type had an effect on the release rate of drug from matrix granules. Reducing wax content the time and temperature at which the end point of granulation occurs will tend to increase due to the dilution of wax by the drug particles. Granules produced with low wax contents will have a more porous structure and thus be more friable, giving rise to the dissolution rate. On the type of wax, when increasing melting point of powdered wax, the time taken to achieve granulation remains constant, the dissolution rate will decrease. The decrease in the dissolution parameters with increasing melting point of the wax could be related to the increasing melting range of the powdered waxes as their melting point increase.

Flanders et al. (1987) found that the release of potassium chloride from wax matrix tablets was dependent on the wax level. There is a general increase in dissolution rate as wax level falls although the lowest level of wax still produces a significant slowing of dissolution.

Adeyeye and Price (1994) studied the effect of different waxes (ceresine, ozokerite, and microcrystalline wax microspheres) on the dissolution rate of ibuprofen microspheres 17% drug loading. The result showed only slight differences in their 50% dissolution times. The 50% dissolution time for ceresine and ozokerite was about 4.3 hr, while for microcrystalline wax it was 4.5 hr. There were some differences, however, in the total amount release after 12 hr for the three waxes: 80 and 77% for ceresine and ozokerite microspheres, respectively, and 66% for microcrystalline wax microspheres. The amount released after 12 hr showed some correlation with the melting points of the three waxes, which are 74, 84, and 93 ° C, respectively. The higher of melting point show the less cumulative amount release after 12 hrs.

Sprokel et al. (1997) investigated the release profiles of theophylline from matrix disks prepared with polycaprolaction (PC), polyethylene (PP), polyvinyl acetate (PVA), and cellulose acetate butyrate (CAB) at 50% drug load. The results depicted that the slowest release was seen with CAB and the fastest release was seen with PVA. Since the effect of polymer type is attributed to the difference in chemical properties of the surfaces between the disks. For example, different contact angles between the media and the disk surface may cause dissimilar rate of media influx into the pore network, resulting in different release rate. The presence of pores does not guarantee release of drug, and that the chemical nature of the surface (i.e. hydrophilic or hydrophobic) influences wetting and, therefore, drug release. At extremely low total soluble fraction polymer characteristics will influence diffusion through the polymer phase.

C. Matrix Additive

It is well known that the poor bioavailability of some drugs is related to their low dissolution rate. Several method have been described in order to increase the in vitro release rate and the bioability of poorly water-soluble drugs such as reduction of the particle size, the use of modified starch, and of solid dispersions of high molecular weight polyethylene glycol (Chiba et al., 1991; Law et al., 1992). The addition of phosophatidylcholine, egg albumin, water-soluble gelatin, hydroxypropyl cellulose,

polyvinylpyrrolidone, bile salt, and tensioactives also proved to enhance the dissolution rate of poorly soluble-drugs.

Al-Shora et al., (1980) reported that sustained release theophylline tablets constituting carnauba wax (matrix) and polyethylene glycol (channeling agent) were prepared using fusion or solvent evaporation techniques for blending the drug, the matrix and the channeling agent. The channeling agent increased the release rate according to its concentration and molecular weight.

Dakkuri et al. (1978a) found that surfactants increased the dissolution rate of tripelnnamine hydrochloride from tablets of carnauba wax matrix, and that the release followed zero-order process over the first 4 hrs. Furthermore, Dakkuri et al. (1978b) found that povidone increased the release of tripelnnamine hydrochloride from the wax matrix; between 0.5 and 8 hrs the drug released by zero-order process. The authors explained the effect of surfactants and povidone as being due to formation of channels formed inside wax matrix and reached a conclusion that while it was possible to design a sustained release from using 10% of channeling agent, total drug release might, however, be difficult to achieve.

Emori et al. (1984) showed that the release of phenacetin from a wax matrix was improved by the addition of an acrylic acid polymer. Increasing the amount of polymer increased the release rate of phenacetin due to the formation of pores and channels in the matrix resulting from leaching of the polymer. Parab et al. (1986) shown that the addition of mannitol or hydroxypropylmethyl cellulose into the wax matrix can improved the release rate of theophylline. The release rate of hydrochlorothiazide from Avicel® PH 101 pellets was enhanced by the incorporated of polyethylene glycol 400 (PEG-400) and PEG-40 hydrogenated castor oil (Cremophor® RH 40) into the formulation (Vevacet et al., 1994).

Shanawany (1993) evaluated the effect of the channeling agents on the release of nitrofurantoin wax matrix. The result revealed that the channeling agent appear to give a marked effect on the drug release. The release of drug was significantly increased with increase in the concentration of channeling agent.

In addition, Sato et al. (1997) reported that hydroxypropyl cellulose (HPC-SL) was increased the release rate of diclofenac sodium wax matrix granules by swelling ability and solubility of HPC-SL. It can observe from cracking on the surface of wax matrix granules. Compared to use sodium chloride, indicated that no cracking was observed on the surface of sodium chloride containing wax matrix granules.

D. Influence of Size of Pellets

The mechanism for drug release from different particle size fractions of solid dispersions is very complex. It has been reported that there were no differences in the sulfathiazole dissolution from its 5% or 10% sulfathiazole-urea solid dispersions between the 840-2000 μm particle size fractions (Chiou and Niazi, 1971). That smaller sieve fraction gave faster dissolution was observed with dissolution of solid dispersions of sodium salicylate in PEG 3000 (Sjokvist and Nystrom, 1988). However, the faster dissolution rates from 25% nifedipine-PVP solid dispersions was obtained from particles of 48-60 mesh size rather than from 12-16 mesh size or < 145 mesh size (Sugimoto et al., 1980). That such an optimal size range existed for maximum dissolution rates was also observed with dissolution of different size fractions of indomethacin-PEG 6000 solid dispersion (Ford and Elliott, 1985).

Lin et al. (1996) proposed that smaller particles possessed higher dissolution rates than larger particles due to the former possessing a greater available surface area of drug generated may control the release of drug from solid dispersions.

Shanawany (1993) reported that the effect of granule size on the release of nitrofurantoin from matrix is reduced as the granule size increases. This effect is mainly due to the reduction in surface area of granules exposed to the dissolution medium. Consequently, granules of 125-200 μm showed the highest drug release 80% (w/w), while granules of 300-450 μm showed the lowest release 52% (w/w) after 6 hrs.

Wang et al. (1997) reported that the diclofenac sodium release rate of pellets is significantly higher in small-size pellets (30-35 mesh) than in large-size pellets (25-30

mesh). This may be due to the higher diclofenac sodium loading capacity in small-size pellets. This would result in an increased ratio of diclofenac sodium to polymer.

5. The Analysis of Dissolution Data of Controlled Release System

5.1 The Release Pattern of Controlled Release System

The pattern of delivery achieves by a controlled release system can vary over a wide range, but most release profiles categorized into three types.

1. Zero-order release pattern.
2. Square-root time release pattern.
3. First-order release pattern.

5.1.1 Zero-Order Model

An ideal controlled release device is one, which can deliver the drug at a constant rate, until the device is exhausted of active agent. Mathematically, the release rate from this device is given as:

$$\frac{dM_t}{dt} = k \qquad (1)$$

where k = zero-order constant

t = time

M_t = the mass of active agent released

5.1.2 Square-Root of Time Model (Higuchi Model)

The second common release pattern frequently referred to as square root of time or $t^{1/2}$ release, provided compound release that was linear with the reciprocal of the square root of time. The release rates then give as:

$$\frac{dM_t}{dt} = \frac{k}{\sqrt{t}} \qquad (2)$$

The release pattern of this type can be described by Higuchi equation (Higuchi, 1963).

$$Q = \frac{[D\epsilon (2A-\epsilon C_s) C_s t]^{1/2}}{\tau} \qquad (3)$$

where Q = the amount of drug released per unit surface area

D = the diffusion coefficient of the drug in the release medium

ϵ = the porosity of the matrix

τ = the tortuosity of the matrix

A = the total amount of drug present in the matrix per unit volume

C_s = the solubility of drug in the release medium

t = time

The assumptions made derived equation (3) are as follows:

1. The system is in perfectly sink condition.
2. A pseudo-steady state is maintained during release.
3. Drug particles are quite small than those in matrix.
4. Drug particles are uniformly distributed in the matrix.
5. A is greater than C_s, i.e., excess solute is present.
6. The diffusion coefficient remains constant.

In general Higuchi's equation is usually desired and used as in equation

$$Q = kt^{1/2} \qquad (4)$$

where k = Higuchi constant

Therefore the plot of amount of drug released from matrix versus square root of time should be increased linearity if drug release from the matrix is diffusion controlled.

5.1.3 First-Order Release Pattern

The release rate in first order model was proportional to active agent contained with device. The rate was then given as:

$$\frac{dQ_t}{dt} = k(Q_0-Q_t) \qquad (5)$$

where, Q_0 = initial amount of drug
Q_t = amount of drug release
k = first-order rate constant

First-order pattern can be predicted by equation (6) by plotting the log of the drug left against time (Schwartz et al., 1968). The initial curvature can be attributed to the presence of surface drug and can be ignored.

$$\log Q = \frac{kt}{2.303} + \log Q_0 \qquad (6)$$

where, Q = amount of drug left
Q_0 = initial amount of drug
k = first order constant
t = time

Since both first-order and square root of time plots are acceptably linear, a more stringent test was developed to distinguish between the mechanisms. The use of the predicted rate equations corresponding to equation (3) and (6) can be used for this purpose as shown by the following treatment (Schwartz et al., 1968).

Equation (3) square-root of time can be reduced to

$$Q' = kSt^{1/2} \qquad (7)$$

where, Q' = amount release = Q*S

S = surface area

$$K = \left[\frac{D\epsilon}{\tau}(2A-\epsilon C_s)C_s\right]^{1/2} \qquad (8)$$

By differentiation of the above reduced equation and appropriate substitution, Equation (9) can be obtained.

$$\frac{dQ'}{dt} = \text{rate} = \frac{K^2S^2}{2Q'} \qquad (9)$$

This indicates that the rate will be inversely proportional to the amount of drug release, Q. The rate predicted by first order kinetics, however, is given by the following relationship:

$$\frac{dQ'}{dt} = \text{rate} = kQ_0 - kQ' \qquad (10)$$

The plots of rate release versus $1/Q'$ were linear, indicating that the release was fitted with Higuchi model. If the plots of rates of release versus Q' were linear, indicating that first-order model was obtained.

5.2 Release Mechanism of Controlled Release System

A simple semiempirical equation (11) can be used to analyze data of controlled release of drug under perfect sink conditions. The general form of this equation is given by Peppas (1985).

$$\frac{M_t}{M_\infty} = kt^n \qquad (11)$$

where, $\frac{M_t}{M_\infty}$ = the fractional release of drug up to time t

t = the release time

k = a constant incorporating structure and geometric characteristics of the controlled release device

n = the release exponent, indicative of the mechanism of drug release

The determination of the exponent n is valid for the first 60% of the total released drug ($M_t/M_\infty \leq 0.6$), which also applied only to the early times of release.

Clearly, at desirable mechanism for many applications is that which leaded to n equals 1, which characterized zero-order release behavior. Table 2 summarized the general dependence of n on the diffusional mechanism (Peppas, 1985).

Table 2 Interpretation of diffusional release mechanisms from drug release data from thin polymer film.

Release exponent (n)	Drug transport mechanism	Rate as a function
0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1.0	Anomalous (non-Fickian) transport	t^{n-1}
1.0	Case-II transport	Zero-order (time-independent) release
n>1.0	Super-Case-II transport	t^{n-1}

The empirical equation (11) could be modified for application to non-planar geometric. The relationship between the diffusional exponent n and the corresponding release mechanism is clearly dependent upon the geometry employed as shown in Table 3 (Rittger and Peppas, 1987a).

Table 3 Diffusional exponent and mechanisms of diffusional release from various non-swellable controlled release system.

Diffusional Exponent, n			Drug Release
Thin Film	Cylindrical Sample	Spherical Sample	Mechanism
0.5	0.45	0.43	Fickian Diffusion
0.5<n<1.00	0.45<n<1.00	0.43<n<1.00	Anomalous (non-Fickian) transport
1.0	1.0	1.0	Zero-order release

In non-swellable matrices, the values of n are 0.45 and 1.00 for Fickian and Case-II transport, respectively. Case-II transport is a special case readily identified and characterized by the constant velocity of the moving solvent front and the resulting linear weight gain with time. However, its characteristics are not as well understood, nor are they as fundamental in origin as those of Fickian diffusion. When the value of n is > 0.45 and < 1.00, the release was said to be non-Fickian (Ritger and Peppas, 1987a). A value of n=1, however, mean that the drug release is independent of time, regardless of the geometry. Thus, zero-order release can exist for any geometry.

In swellable controlled release systems, Case-II (Fickian diffusion) and Case-II solute release behaviors are unique in that each can be described in terms of a single porometer. Case-I transport is described by a diffusion coefficient, while Case-II transport was described by a characteristic relaxation constant. Non-Fickian behavior, by comparison, required two or more parameters to describe the coupling of diffusion and relaxation phenomena.

In swellable matrices, when the system did not swell more than 25% of its original volume, the values of n are 0.45 and 0.89 for Fickian and Case-II transport, respectively. When the value of n is > 0.45 and < 0.89, the release was said to be non-Fickian (Ritger and Peppas, 1987b). When the value of n was greater than that of the Case-II transport, the release was said to be Super-Case-II transport. Table 4 summarized the range of values of diffusional exponent n, and the released transport mechanism for each geometry (Ritger and Peppas, 1987b). A value of n=1, mean that

the drug release can exist for any geometry; only for slabs did this release coincide with Case-II transport.

Table 4 Diffusional exponent and mechanisms of drug from various swellable controlled release system.

Diffusional Exponent, n			Drug Release Mechanism
Thin Film	Cylindrical Sample	Spherical Sample	
0.5	0.45	0.43	Fickian Diffusion
0.5<n<1.00	0.45<n<0.89	0.43<n<0.85	Anomalous (non-Fickian) transport
1.0	0.89	0.85	Case-II transport

6. Propranolol Hydrochloride

Propranolol hydrochloride is a non-selective β-adrenergic blocking agent.

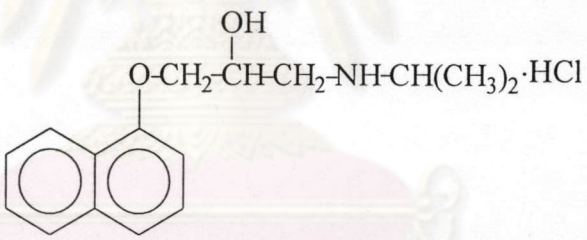


Figure 8 The structural formula of propranolol hydrochloride

Empirical Formula $C_{16}H_{21}NO_2HCl$

Molecular Weight 295.8

Chemical Name (1)(±)1-Isopropylamino-3-(1-naphthyloxy)propan-2-ol

(2)1-[(1-methylethy)amino]-3-(1-naphthalenyoxy)-2-propanol

Proprietary Name Angilol; Apsolol; Avlocardyl; Bedranol; Berkolol; Beta-Neg; Cardinol; Dociton; Frekven; Inderal; Inderalici; Sloprolol; Tonum

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

Melting Point melts in the range 163° to 166°C

Dissolution Constant pKa 9.5 (24°C)

Partition Coefficients in octanol/aqueous buffer pH 7.4 is 1.2

Solubility

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

Stability

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

Use and Administration

Propranolol hydrochloride has pharmacological action similar to those of other β-blocker for treatment hypertension, cardiac arrhythmias, angina pectoris, prophylaxis after recovery from myocardial infraction, treatment symptomatic condition from hyperthyroidism and prophylaxis the headache from migraine.

Propranolol hydrochloride is almost completely absorbed after oral administration. Dosage is 20 mg to 2 gm daily in divided doses. Peak plasma concentration is achieved at approximately two hours in fasting patient. It is highly bound to plasma proteins about 85-95% but it has short plasma half-life 3-4 hours and rapidly hepatic metabolism after oral administration, therefore; it needs several times (3-4 times) by oral regimen.

Adverse Effect

Propranolol hydrochloride has narrow therapeutic range at constant condition in plasma 20-50 μg/ml. The apparent volumes of distribution 182 liters are larger than volume of total water in body (52 liters) (approximately 50 liters in 70 kg body weight), it means drug is highly deposit or bound to tissue. The clearance is 637 mL/min result in rapidly excretion.

7. Diclofenac Sodium

Diclofenac sodium is a synthetic, non-steroidal anti-inflammatory and analgesic compound. It is widely used for relief of pain and inflammation.

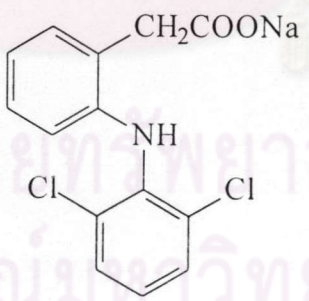


Figure 9 The structural formula of diclofenac sodium

Empirical Formula $C_{14}H_{10}C_{12}NO_2Na$

Molecular Weight 318.13

Chemical Name (1) 2-[2,6-Dichloropheny)amino]benzeneacetic acid monosodium salt

(2) [O-(2,6-dichloroanilino)pheny]acetic sodium salt

(3)Sodium[O-[(2,6-dichlorophenyl)amino]phenyl]acetate

Description odorless, white to off-white crystalline, slightly hygroscopic powder.

Melting Point diclofenac sodium melts at 283 to 285°C.

Dissociation Constant (pKa) and Partition Coefficient

The pKa of diclofenac sodium in water is 4 and the partition coefficient in n-octanol/aqueous buffer pH is 13.4.

Solubility

The aqueous solubility of diclofenac sodium is dependent on pH; solubility is poor at low values of pH but when the pH rises above the pKa, rapid increases in solubility occur (Maitani et al., 1991; Herzfeldt and Kummel, 1983).

The presence of cations (sodium ions or potassium ions) markedly affects the solubility of diclofenac sodium. The addition of sodium or potassium chloride to the dissolution decreased the solubility of diclofenac sodium and showed the dissolution rate, with the effect of sodium chloride being greater.

The equilibrium solubility performed in various solvents at the room temperature (RT) is shown in Table 5.

Stability

Diclofenac sodium tablets film coated with polymers like acrylic and hydroxypropyl cellulose were reported to be stable after storage for one week at 30 °C

in 80% relative humidity. Suppository formulation was also analyzed for stability using thin layer chromatography and ultraviolet spectroscopy. The formulation was stable for 24 months at room temperature. Stability in biological fluid (serum) was determined and the results demonstrated that diclofenac sodium could be frozen for at least two weeks without degradation.

Buffered solution (pH 7.4) that contained diclofenac sodium dissolved in either β-cyclodextrin (β-CD) or hydroxypropyl-β-cyclodextrin (HP-β-CD) were prepared either in presence or absence of oxygen and stored in the dark. Solution from which oxygen had been removed was claimed to be more stable than those with oxygen. Although precipitation was observed in solutions without β-CD or HP-β-CD during a short storage time at 21° C, no loss of diclofenac sodium was reported after 520 days. At 71° C, in solutions (without oxygen) that contained diclofenac sodium alone, or with β-CD or with HP-β-CD, 24.7%, 30.4%, and 34.6% diclofenac sodium remained, respectively, after 207 days.

Table 5 The solubility of diclofenac sodium

Solvent	Temperature	Solubility (mg/ml)
Deionized water (pH5.2)	RT	>9
Methanol	RT	>24
Acetone	RT	6
Acetronitrile	RT	<1
Cyclohexine	RT	<1
PH 1.1	RT	<1
PH 7.2 (phosphate buffer)	RT	6

Use and Administration (Reynolds et al., 1993)

Diclofenac has analgesic, antipyretic, and anti-inflammatory properties; it is an inhibitor of cyclooxygenase.

Diclofenac is used mainly as the sodium salt for the relief of pain and inflammation in conditions such as rheumatoid arthritis, osteoarthritis, ankylosing

spondylitis, renal colic, acute gout, and following some surgical procedures. The usual dose by mouth is 75 to 150 mg of diclofenac sodium daily in divided doses. It may also be given rectally as a suppository in a usual dose of 100 mg each evening. Diclofenac sodium may also be given by intramuscular injection in a dose of 75 mg once daily or, if required in severe conditions, 75 mg twice daily. It is also used intramuscularly in renal colic in a dose of 75 mg repeated once after 30 minutes if necessary. In children the suggested dose by mouth or rectally for invenile chronic arthritis is 1 to 3 mg per kg body-weight daily in divided doses.

Adverse Effects (Reynolds et al., 1993; Adeyeye and Li., 1990)

Due to the activity of inhibit cyclooxygenase, the most frequent adverse effects occurring with diclofenac sodium are gastro-intestinal disturbances; reactions range from abdominal discomfort, nausea and vomiting, and abdominal pain to serious gastro-intestinal bleeding or activation of peptic ulcer. Cyclooxygenase, PGF_2 has a cytoprotective effect on the gastric mucosa by inhibiting gastric acid secretion and by helping to maintain the gastric mucosa barrier. Other adverse effects include CNS-related side effect; headache, dizziness, nervousness, tinnitus, depression, drowsiness and insomnia. Hypersensitivity reaction may occur occasionally and include fever and rashes.

8. Glyceryl monostearate

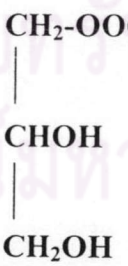


Figure 10 The structural formula of glyceryl monostearate

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. 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° 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.

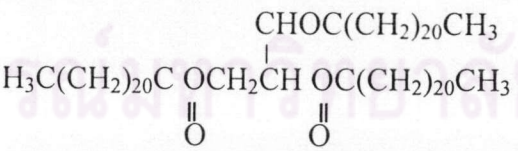
9. Lubritab® (Hydrogenated Cottonseed Oil)

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

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

Lubritab® is 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 ° C. Lubritab® can soluble in chloroform, petroleum spirit, and hot propan-2-ol, practically insoluble in water.

10. Compritol® (Glyceryl Behenate)



It is a mixture of glycerides of fatty acids, mainly behenic acid. It can soluble in chloroform, methylene chloride when heated and insoluble in ethanol, N-hexane, water, and mineral oils. It can melted at 70 °C and its HLB value is 20.

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