CHAPTER II

LITERATURE REVIEWS

Sustained release drug delivery systems

The sustained release dosage forms are developed for variety reasons such as they may improve patient compliance, reduce unexpected toxic effect due to high peak concentration and improve efficiency in treatment because of the less fluctuation in drug level. Sustained-release drug administration means not only prolonged duration of drug delivery, as in controlled-release and prolonged release, but also implies predictability and reproducibility of drug release kinetics (Chein, 1983).

In the exploration of oral sustained drug administration, one encounter two areas of potential challenge:

1. Drug delivery system: development of the drug delivery system, which is capable of administering a therapeutic agent at a schedule for duration required for an optimal treatment.

2. Gastrointestinal transit time: prolongation of the gastrointestinal residence time, so the drug delivery system developed can reside at the proper of absorption site for sufficient long period of time to deliver all the drug loading dose.

The majority of oral sustained - release dosage forms widely used in the present are the filmed-coated tablet, the matrix type tablet and especially pellets. The sustained – release dosage forms are relied on dissolution, diffusion, or a combination of both mechanisms to generate a slow release of drug to the gastrointestinal maliu (Hui, Robinson, and Lee, 1987).

Although, the pellets are widely used as sustained release dosage forms but the pellet productions have many drawbacks, which give undesirable pellets for the sustained release dosage forms such as broad size distribution, irregular shape and porous structure. Therefore, these disadvantages are overcome by microtablets.

1. The comparison of pellets and the microtablets

In general, the sustained release dosage forms are desirable to have a product, which posses a very uniform particle size with regular shape, the high weight uniformity, and low porous product. These properties are suitable to control the steady release of active compound per unit time. Although, the pellets are most widely used to be sustained-release dosage form but their production have many drawbacks that give undesirable properties of the obtained pellets because it have many equipment and processes. Therefore, it cannot control the various factors in processes of pellet production. Moreover, the cost of production may be higher than the other sustained release dosage forms. These disadvantages are overcome by microtablet. The microtablet is a tablet, which has a diameter of 1 – 3 mm, preferably 1.5 – 2.5 mm. Its shape is nearly spherical or cylindrical. It can be seen that its size and shape are not much different from the pellets. But the characteristics of microtablets are better than that of pellets. Moreover, the microtablets can produce by the conventional techniques, which are direct compression and wet granulation. The equipment for the microtablet production is similar to those of the plain tablet, except the microtabletting machine. Because it must use special punches that contain many small punches per one punch holder. Therefore, the requirements of the tabletting machine with special punches and dies are precision of the tabletting press, and good properties of the materials in the formulation, especially the flow properties (Kolter et al., 1997; Pich et al., 1989; Arati A., 1997).

Munday D.L. (1994) reported that the comparison of microtablets and granules, which were developed to be sustained-release dosage forms by coating technique. The effect of surface, shape, and porosity were studied. It was found that the granules had very irregular surface and shape similarly to pellets but the microtablets had smooth surface and uniform shape. Therefore, the requirement of coating materials for granules was 2.5-3 times

more than that for microtablets at the same surface area. Because the coating materials were filled into the rough irregular surface of granules that tend to make the granule smoother and more oven. Moreover, the release rates of drug from microtablets were more consistent than from granules.

Flemming and Mielck (1995) prepared microtablets with various excipients and by direct compression techniques. Moreover, the microtabletting process used various diameters of punches and dies that were 1.0, 1.2, 1.5, and 2.0 mm. These narrow diameters of the punches and dies required excellent flowability of powder as well as a strict limit for the maximum particle size, in order to avoid blocking of the die opening by coarser particles. Therefore, the powder mixtures were evaluated with respect to density, shape, size, particle size distribution, and flow rate. They observed that the characteristics of powder mixtures were uniform size with regular shape, narrow size distribution, and high flow rate. Their characteristics indicated excellent flowability that were suitable for producing the good properties of microtablets.

2. Drug available in sustained-release dosage form

Drugs with long biological half-life or requiring large dose should not be formulated as prolonged action products. Drugs used for chronic condition, with medium-duration half-life, small doses are chosen to be the candidates for such formulations. Diclofenac sodium is one of the drug candidates to be prepared in sustained – release dosage form. Because it has several advantages compared with conventional dosage forms. The main advantage is reduction in fluctuation of drug blood level concentrations and non-patient compliance, which could result in continuous protection of the patient against attack of pain of various diseases.

2.1) Formular, name, formular weight (Reynold et al., 1989, Budavari, 1989, Adeyeye and Li, 1990)

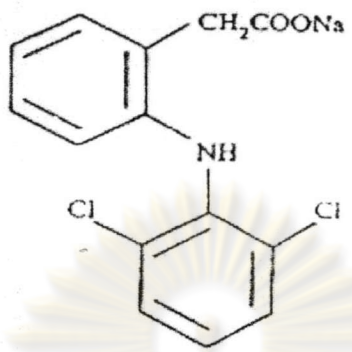


Figure 1 Diclofenac sodium ($C_{14}H_{10}Cl_2NnaO_2$), formular weight 318.3

Diclofenac sodium is also described under the following chemical names:

1. 2-[(2,6 - Dichlorophenyl)amino] benzeneacetic acid monosodium salt
2. [0 - (2,6 - dichloroanilino)phennyl] acetic acid sodium salt
3. Sodium [0 – [(2,6 – dichlorophenyl) aminophenyl] acetate
4. Sodium [2 – (2,6 – dichloroanilino) phenyl] acetate

2.2) Melting point: Diclofenac sodium melts at 283-285°C

2.3) Appearance, color and odor

Diclofenac sodium is white to off-white, odorless, crystalline powder with a bitter taste. It is slightly hygroscopic powder (Adeyeye and Li, 1990).

2.4) Solubility

The equilibrium solubility performed in various solvent at room temperature are shown in Table 1 (Adeyeye and Li, 1990).

Table 1 Solubility of diclofenac sodium.

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

2.5) Dissociation constant (pKa) and partition coefficient

The dissociation constant (pKa) of diclofenac sodium is 4.0 and the partition coefficient in n-octanol/aqueous buffer pH is 13.4 (Adeyeye and Li, 1990).

2.6) Stability

Diclofenac sodium tablets film coated with polymers such as acrylate and hydroxypropylcellulose 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 (Adeyeye and Li, 1990).

Buffer 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 with or without oxygen and stored in the dark (Backensfeld. et al., 1991). Solution from which oxygen had beer. removed was claimed to be more stable than those with oxygen. Although precipitation was observed in solution 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.

2.7) 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 juvenile chronic arthritis is 1 to 3 mg per kg body – weight daily in divided doses.

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

Due to the activity of inhibit cyclooxygenase, the most frequent adverse effects of diclofenac sodium are gastro-intestinal disturbances; reaction range from abdominal discomfort, nausea and vomiting, and abdominal pain to serious gastro-intestinal bleeding or activation of peptic ulcer. Cyclooxygenase, PEG_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.

3. Commercial product of sustained-release diclofenac sodium

In Thailand, several diclofenac sodium sustained – release dosage forms are widely margeted. Voltaren SR® tablet (Novartis) is one of these products, which is certainly the most successful of all the sustained-release diclofenac sodium products. It shows relatively uniform release pattern for 24 hours period of time. Its characteristic is film-coated tablet of two levels of dose. These products have 75 mg per tablet and 100 mg per tablet.

4. Microtablet or minitablet

Such new product is designed to sustained - release dosage form in various kinds, which are capsules by filling directly or coated microtablets by coating techniques. The microtablets are the tablets with a diameter equal to or smaller than 1 – 3 mm, preferably 1.5-2.5 mm. Their shapes are nearly spherical and cylindrical with a flat or convex upper side and lower side. It has definite advantages over the single unit dosage forms. These advantages are less risk of dose dumping, less inter- and intra- subject variability, and high degree of dispersion in the digestive tract that reduced the risks of high local drug concentrations. Therefore, microtablets also offer an alternative for pellets because of their uniform size with smooth surface and low porosity structure. It must use the special punches and dies that require high precision and mechanical stability. Because the punch station is equipped with a punch holder that contain many small concave punches, for example, 6 punches per punch holder (Kolter et al., 1997; Pich et al., 1989; Mielck et al., 1998; Rey et al., 2000).

Brabander et al. (2000) prepared ibuprofen matrix tablets that contained with combination of the different microcrystalline waxes with various melting range and starch derivatives, and by melt extrusion and standard compression techniques. The granules from melt extrusion technique were compressed by an eccentric tabletting machine that equipped with a standard filling shoe. And punch holders were equipped with flat punches 2 mm in

diameter. The mean compaction pressure was 156 ± 16 MPa for each microtablet. With an increase in the wax concentration, there was a corresponding reduction in drug release rate. The drug release was depended on a melting range of microcrystallinecellulose waxes. They observed that the slowest drug release was obtained with a melting range between 68° and 72°C. Moreover, the drug release profiles were also modified by addition of starches and mixture of starches. The ibuprofen concentration affected the release rate. It was observed that increasing the ibuprofen concentration to 70% w/w resulted in a faster drug release rate.

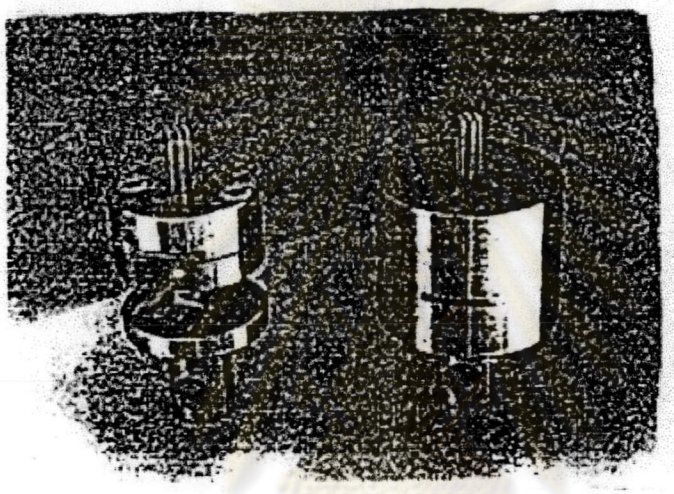


Figure 2 Concept for the construction of a multiple lower punch holder

The special punches and dies have many punches per punch holder, which are narrow diameters. Therefore, these tooling require excellent flowability that is important factor necessary for producing microtablets because it affects the uniformity of weight and content of the microtablets. (Flemming and Mielck, 1995; Pich et al. , 1989)

Rey et al. (2000) prepared sustained – release theophylline microtablets with wet granulation technique that using by a fluidized bed granulator. This process was carried out using a solution of Eudragit RS 30D, as a binder, a solution of Eudragit RS PO, as a matrix – forming polymer, and triethyl citrate as a plasticizer. The microtablets were compressed on rotary tabletting machine that using force feeder and 17 punch station. The punch station was equipped with a punch holder containing 19 small concave punch, each with a diameter of 2 mm. The speed was kept constant at 26 rpm. The compaction pressure of 200 MPa or 250 MPa was employed. The influence of the pressure, the plasticizer contents, the amount of theophylline, and the addition of magnesium stearate on the drug release were investigated. The compaction pressure and the plasticizer content affected the drug release whereas theophylline content did not. In addition, increasing the concentration of magnesium stearate decreased the dissolution rate.

Lennartz and Mielck (1989) examined the mechanical strength and the tendency of capping of paracetamol microtablets that compared with the normal–size of parcetamol tablets. The paracetamol microtablets were prepared by direct compression technique. The powder mixtures of paracetmol, spray–dried lactose and lubricant were continuously tabletted on an eccentric tabletting machine into convex–faced tablet with diameters ranging from 1.5 to 5 mm. They observed that the mechanical strength of paracetamol microtablets were higher than that of normal–size tablets. Moreover, the capping tendency of paracetamol microtablets was reduced. These results are predominant, especially in ranges smaller than 3 mm diameter of the tablet.

5. The techniques of microtablet production

Methods used to produce microtablet are similar to plain tablet production such as the direct compression method which is very easy to produce. Following this method, the active ingredient is mixed with other additives such as diluent and lubricant until homogeneously. Then the powder mixtures are compressed with the rotary tabletting machine that contained special punches and dies. The wet granulation method is more complicated than direct compression method. The active ingredient is mixed with diluent or filler until homogeneously. Then binder is added into the powder mixtures and are mixed

continuously until obtaining damp mass. The mass is passed through the sieve #8 or #10 by oscillating granulator. The granules are dried with conventional equipment such as air drying or oven drying that are controlled with temperature and time. The dried granules are passed through the sieve again by oscillating granulator and are mixed with the lubricant until homogeneously. The final granules are compressed with the rotary tabletting machine that contained the special punches and dies.

Sujja-areevath et al. (1996) prepared diclofenac sodium microtablets contained various types and amounts of natural gum, and by wet granulation method. The single punch tablettting machine contained flat-faced punches with a diameter of 3, 4.5, and 5 mm. The compression force used to compress the microtablets was 21.2 ± 0.6 kN. The effect of amount of gum on the drug release was studied. The effect of volume of matrix and types of excipient were investigated. They observed that the drug release rate decreased with increasing the gum content. Therefore, the amount of gum present appeared to play the dominant role in determining the drug release rate. The type of natural gum affected the drug release and release behavior. An increase in matrix volume could account for the slower drug release because of increasing the proportion of gum in these formulations. The solubility differences between excipients did not affect the release rate. However, increasing proportions of each excipient produced a faster or slower release that depended on their release mechanisms.

Saettone et al. (1995) prepared sustained release timolol maleate microtablets by direct compression and coated with Eudragit RS and Eudragit RL. The microtablets were pressed by a single punch tabletting machine that contained concave punches and dies with a diameter of 3.5 mm. They observed that an adequate control of the drug release from this microtablets could be obtained by adjusting the amount of acrylic polymer coating.

6. The Additives for Microtablet Production

6.1) Diluent / filler

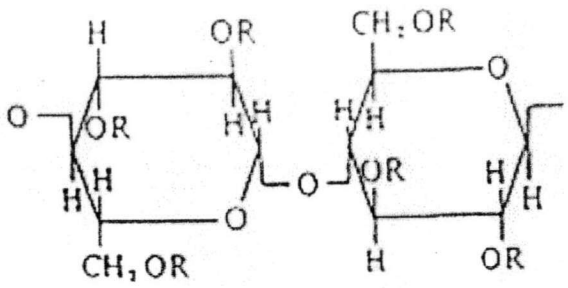
There are many kinds of dilients that are used to produce microtablet. They are similar to produce the plain tablet, which are Ludipress®, lactose, and corn starch. Their characteristics should be safety, inert, and compatibility with active ingredient. Therefore, the suitable diluents for producing the microtablet are depended on the characteristics of active ingredient and the techniques of microtablet production.

6.2) Sustained-release materials

The cellulose derivatives used as the both of diluent and sustained release materials. Therefore, they are widely used to be the additives in the formulations because they are the most abundant of all organic materials. It is a naturally occurring substance that has always been an importance part of the diet of the human being. Moreover, the cellulose derivatives have many difference types and several properties, such as hydroxypropylmethylcellulose, ethylcellulose.

- **hydroxypropylmethylcellulose**

An application of hydroxypropylmethylcellulose (HPMC) for film coating have become popular, taking the place of the classic sugar coating of tablets, since they give a superior appearance, act as protective coatings foe fragile tablets and can mask color and pleasant taste. The main reason that HPMC is preferred as a film coating in the initial stage is that its dissolves both organic solvents and water over the entire biological pH range. This means that film coating can be done using an organic solvent system and the film formed is expected to dissolve in the digestive juices, leading to complete release of the active ingredients.



R = H- , CH_3- or $CH_3CH(OH)CH_2$-

Figure 3 Chemical structure of hydroxypropylmethylcellulose

The chemical structure of HPMC is shown in Figure 3. HPMC is classified according to its substituent groups, composition and viscosity. HPMC of lower viscosity (less that 15 cps) is commonly used in film coating and is produced by depolymerization of higher viscosity HPMC. Commercially available brands of HPMC for film coating widely used throughout the world are pharmacoat 615, 606 and 603 (Shin-Etsu Chemical Co., Ltd., Japan), and Methocel E 15, E 5 and E 3 (Dow Chemical Co., Ltd., USA).

HPMC is cellulose ethers, which may be used as the basis for hydrophilic matrices of controlled release oral delivery. HPMC is an odorless, tasteless white or creamy-white fibrous or granular powder. It is soluble in cold water, forming a viscous a colloidal solution, insoluble in alcohol ether and chloroform but soluble in mixture of methylalcohol and methylene chloride. HPMC is very stable in dry conditions. Solutions are stable at pH 3.0-11.0. It is unstable in extreme pH conditions and incompatible with oxidizing materials. Human and animal feeding studies have shown to be safe. HPMC can be used as film former, thickening agent, protective colloid, emulsifier, suspending agent, and stabilizer. High viscosity grades are used to retard the release of water soluble drugs.

Lapidus and Lordi (1966, 1968) investigated drug release from compressed hydrophilic matrix of HPMC 15,000 cps. Water-soluble drugs (chlopheniramine, sodium salicylate) and water-insoluble drugs (benzoic acid, benzocaine) were used as model drugs. The dissolution profiles when plotted against square root of time were linear. In addition,

the effect of temperature added diluent and type of polymer on release patterns measured from plane surfaces and whole tablets were also reported.

Dissolution studies of indomethacin controlled release tablets showed that for a poorly water soluble drug, not only was the polymer to drug ratio important in controlling the release, but both viscosity grade of HPMC and particle size of the drug were to be recognized more eritically than the water soluble drugs. Furthermore, erosion of HPMC matrix was suggested to be the only mechanism by which poorly soluble drug were released from HPMC matrix (Ford, Rubinstein and Hogan, 1985a).

For a formulation containing cetperazine as active drug, aerosil 200, CMC and HPMC in the ratio of 1: 0.7: 4.4 gave a linear release for about 12 hours, both in vitro and in vivo studies. The release of drug from this formulation was found to be independent of hardness of tablet and pH of the dissolution medium (Beveja and Rao, 1986).

HPMC was used to produce hydrophilic matrix of propanolol hydrochloride, aminophylline and promthazine hydrochloride. It was found that a plot of percentage drug dissolved against square root of time produced a straight line. In addition, the major factor controlling drug release was the drug : HPMC ratio (Ford, Rubinstein and Hogan, 1985b, 1985c).

Sheu et al. (1992) studied the effect of parameters on the dissolution of diclofenac sodium from Voltaren SR and HPMC based matrix tablets. The result indicated that addition of sodium or potassium chloride to the dissolution medium decreased the solubility of the drug and slowed the dissolution rate, with the effect of sodium chloride being greater. Dissolution of the drug was studied in a medium, which simulated the changing pH of the pathway followed by the drug as it passes from the stomach to the intestine. Dissolution was found to be inversely related to the rate at which the pH was changed. This may be caused by the deposition of an insoluble drug layer when contact is made with an acid medium. When higher viscosity grades of HPMC were used, slower release rate result. Drug release from Voltaren SR was best described as non-Fickian in an aqueous medium irrespective of whether salt was added; however, a zero-order dependence became evident in pH changing media. The release of diclofenac sodium from the hydrophilic matrices followed a non-Fickian transport in all media.

❖ **ethylcellulose**

Ethylcellulose (EC) is the ethyl ether of cellulose and can contain 44.0 and 51.0 percent of ethoxy groups. Ethylcellulose is resistant to alkali, both dilute and concentrated, and also to salt solutions. It is subject to oxidative degradation in the present of sunlight or UV light at elevated temperatures. Ethylcellulose is incompatible with paraffin wax and microcrystlline wax. It is presented as a non-toxic substance, free flowing, white to light tan colored powder. EC can be used as tablet binder, coating material, film former and thickening agent. EC is insoluble in water glycerine and propylene glycol, but soluble in varying degrees in certain organic solvents, depending upon the ethoxy content. Its release mechanism is diffusion and erosion (Donbrow and Friedman, 1974).

EC used in combination with HPMC and corn starch produced a sustained release granule of nifedipine, and a linear relationship up to above 40% release is obtained based on the Higuchi equation (Kohri et al., 1987).

Gilligan and Po (1991) prepared sustained release pellets of dextromethophan. The system consisted of drug coated sugar spheres which were then overcoated with the rate controlling membrane. The membrane was produced by spray coating with an aqueous dispersion of EC containing HPMC. It was shown that adequate post-coating conditioning was important to ensure consistency of release rate. Drug release could be made pH-independent by a choice of proper formulation.

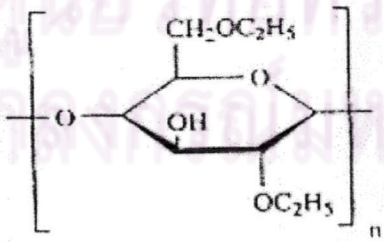


Figure 4 Chemical structure of ethylcellulose

6.3) Binder

Binder's properties should be non - toxic, inexpensive, readily available, and compatibility with the active agent. The characteristics of binder can bind the active ingredient with the other additives that used in the wet granulation method such as polyvinylpyrrolidone, corn starch paste. The percentage of granulating used and concentration used in formula are presented in Table 2.

Table 2 The concentration used of binder in the formula

Material	% of Granulating System normally used	Concentration Used (% of formula)
Acacia	10-20	2-5
Cellulose derivative	5-10	1-5
Gelatin	10-20	1-5
Gelatin-Acacia	10-20	2-5
Glucose	25-50	2-25
Polyvinylpyrrolidone	3-15	2-5
Starch paste	5-10	1-5
Sucrose	50-85	2-25
Pregelatinized starch	2-5	1-5
Tragacanth	3-10	1-4

6.4) Lubricant

Lubricant's characteristics should be non-toxic, inexpensive, readily available, and should not react chemically with the active agent. It uses for reducing the friction of tablet with punches and dies. Moreover, It improves the flow properties of the powders and granules such as stearic acid, magnesium stearate, and talcum. The concentration used of lubricants in the formula are presented in Table 3

Table 3 The concentration used of lubricant in the formula

Material	Usual range (%)
Stearate (magnesium, calcium, sodium)	1 / 4 - 2
Stearic acid	1 / 4 - 2
Waxes	1-5
Talcum	1-5
Sodium benzoate & sodium acetate	1-5
Sodium chloride	1-5
Sodium lauryl sulfate	1-5
Aerosil	0.1-0.5

7) Evaluation the flowability of powder of the microtablet production

The flowability of powder is also determined by various parameters:

7.1) The angle of repose (Gordon et al., 1990)

The common procedure of determining the angle of repose is displayed in Figure 5. In the fixed-funnel and free-standing cone method, a funnel is secured with its tip a given height, H, above a flat horizontal surface to which graph paper is attached. Powder or granules is carefully poured through the funnel until the apex of the conical pile just touches of tip of the funnel; thus,

$$\alpha = \arctan(h/R) \quad ; \alpha \text{ is the angle of reposes} \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

The value for angle of repose $\leq 30°$ generally indicated a free-flowing material, and angle $\geq 40°$ suggested a poorly flowing material.

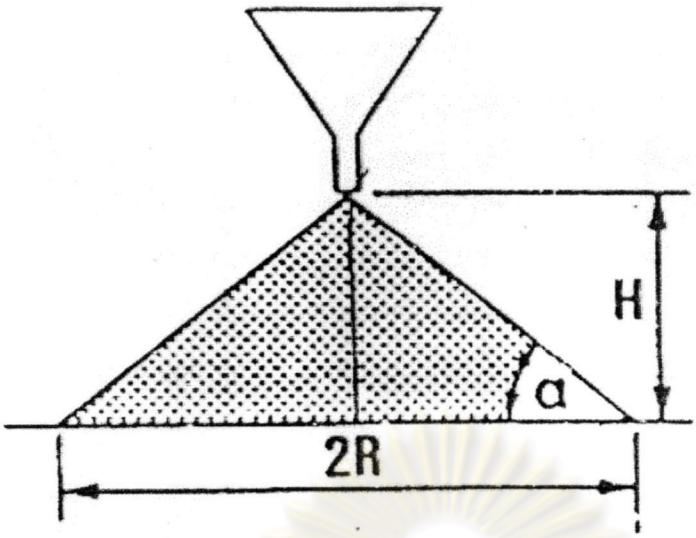


Figure 5 The method utilized in measuring the angle of repose

Tan and Newton (1990) examined the powder flowability that was an indication of capsule filling performance. Because a successful capsule filling operation and the production of capsules with uniform fill weights. It was essential that the powder had optimal flow and packing properties. In their work, the flowability of 5 excipients that were Starch 1500, Avicel pH101, calcium carbonate, and maize starch were studied. The parameters indicated the flow properties, such as angle of repose, the flow parameter of compressibility's index and Hausner's ratio were investigated. They observed that the angles of repose were less than 50° indicated free-flowing powder. Whereas the angles of repose were more than 60° indicated cohesive powder. And, the value of Hausner's ratio was less than 1.2 that indicated goo flowability. Moreover, flowability was depended on particle size. morphology, and bulk density of powder.

7.2) The bulk density and tapped density

The procedure of determining the bulk and tapped density is displayed in Figure 6. The bulk density was determined from the weight of powders or granules (accurate weight recorded), carefully transferred into a 100 ml graduated cylinder and the bulk volume was recorded. Division of weight by bulk volume yields bulk density. After

that, the motor is rotated effect to the vibration of graduated cylinder until the bulk volume is constant. The second bulk volume was recorded. Division of weight by the second bulk volume yields tapped density.

The derived parameters from the bulk and tapped density are indicated the flowability of powder such as:

The CARR's compressibility index is the difference of the tap density and the bulk density, time 100 over the tap density in percent

% Carr's index = {(tapped density – bulk density)/tapped density}×100}.....*(2)*

The value of % Carr's compressibility below 15% usually indicated good flowability

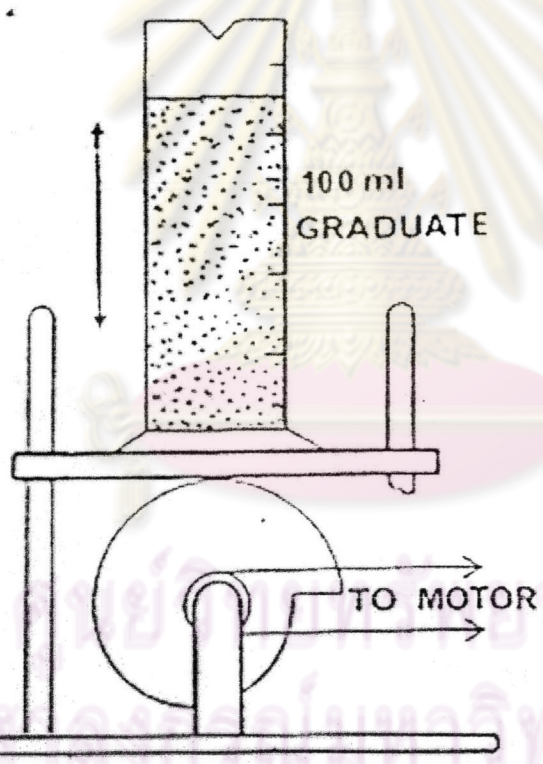


Figure 6 The measurement of bulk and tapped density by cylindrical method

Sienkiewicz et al. (1997) prepared theophylline pellets contained with various grades of microcrystallinecellulose, and by a fluidized-bed rotogranulation technique. The effect of various types and amounts of theophylline loading of characteristics on pellets were investigated. The characteristics of pellets were studied by size, shape, drug content, and

flowability. They observed that the potential of spheronization of binary system using anhydrous theophylline and microcrystalline cellulose depended on the choice of theophylline and the level of drug loading. Sphericity declined when drug loading exceeded 70%. Micronized theophylline was much more difficult to produce pellets but the large-sized particle grades of both drug and excipient materials worked best. The flowability was estimated with the Car's compressibility index. The value of the Car's compressibility index below 15% indicated good flowability. In this study, the obtained pellets showed similarities in flowability because all nine combinations of drug and excipients formed spheres. On the contrary, the other properties showed significant differences.

7.3) The flowability

The procedure of determining the flow rate is illustrated in Figure 7. In funnel method, the flowability of powders or granules are determined by directly measuring the amount of powders or granules masses flowing from funnel include interchangeable orifices (**) onto balances or blending bar with time, it can detect by sensor. The result shows in g/sec. The high flow rate generally indicated a free-flowing material.

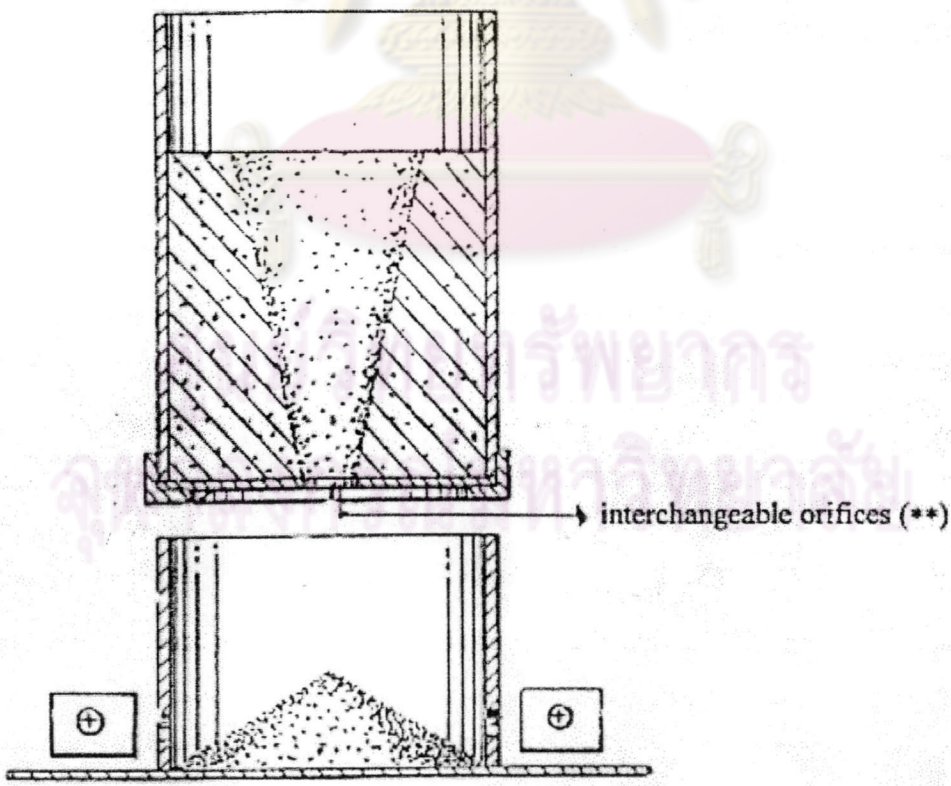


Figure 7 The measurement of flowability by funnel method

Flemming and Mielck (1995) prepared microtablets with eleven excipients, and by direct compression technique. The powder technological parameters, namely particle size distribution, density, and especially flow rate were determined. Therefore, the flowability of powders was necessary factor for rotary tabletting machine with narrow diameter of punches and dies. The flow rate was estimated by the funnel method with interchangeable orifices that varied the diameter. The mass of powder had flown from the funnel was recorded by sensor. In this investigation, the end masses and end time were taken for calculating the flow rates. They observed that the flow rate of free-flowing materials was higher than cohesive materials in the same orifice.

Valesco et al. (1995) studied the flow properties of bulk solid that had been carried out on various types of maltodextrin for direct compression, such as Maltrin M150, Maltrin M510, Maltrin QDM 500, and Maltrin QDM 550. Rheological properties of excipients like parameters form % compressibility, flow rate, and dynamic angles of repose were investigated. The percentage of compressibility was determined from the calculation of bulk density and tapped density. The materials that exhibited the value of percentage compressibility greater than 20% indicated cohesive material. The flow rate was measured by flowmeter that contained a stainless steel cylinder with different hole sizes, such as 6, 9, 12, 20, and 25 mm. A software program for data acquisition, graphic, and calculation were used. Moreover, the angle of repose was measure according to the revolving to cylinder method. The value of angle of repose $\geq 45°$ indicated cohesive powder. They observed that a different behavior between the Maltrin M 150 and the other excipients under study in flowmeter, being Maltrin M150 the only excipient, which did not flow through any orifices of the flowmeter. In addition, the values of percentage of compressibility and angle of repose were above limits. Therefore, the flowability of Maltrin M150 was better than the other excipients.

Fassihi and Kanfer (1986) investigated the effect of compressibility and powder flow properties on tablet weight variation. The flowability of powders, such as Emdex, Emcompress, magnesium oxide and three components powder mixture were assessed for flow rate, angle of repose, particle size and compressibility index. The compressibility index was greater than 20% indicated cohesive material. The value of angle of repose was greater

than 60° showed cohesive material whereas the value was less than 30° indicated free flowing material. A three-dimensional plot was constructed to illustrate the influence of flow rate, angle of repose, compressibility index on the coefficient of tablet weight variation. The data obtained during this study also indicated that when the compressibility index exceeded a value of about 20% a significant increase in tablet weight variation resulted irrespective of the powder flow rate. Moreover, the value of angle of repose indicated poor flowing or cohesive material that affected the weight variation.

8. The release pattern of matrix system

8.1) Matrix system

The literature about the matrix system was well reviewed by Baker (1987). A matrix system, as the name implies, consists of drug distributed homogeneously throughout a polymer matrix. When the term "matrix device" is used without qualification, it typically means that the containing polymers dose not chemically disintegrate. If the polymer does erode, the device – although actually a type of matrix device is referred to as an erodible, bioerodible, or biodegradable system.

Matrix systems have the advantage of generally being easier and less expensive to produce than reservoir systems. In addition, because they do not have a polymer covering that can suddenly break, there is no danger of an abrupt release of a large amount of drug.

There are two principal categories of matrix devices. If the active agent is dissolved in the polymer medium, the device is called a matrix solution. A device of this kind is often used when the active agent is a liquid, some polymer can easily dissolve up to 20% or more these liquids. If the active agent had a more limited solubility in the polymer medium and the remainder is dispersed as small particles throughout the polymer. A device of this type is called a matrix dispersion.

8.2) The release pattern of matrix system

The pattern of delivery achieves by a sustained release system can vary over a wide range but release profiles can be categorized into three types; zero – order release pattern, square-root-time release pattern, and first-order release pattern.

1) Zero – order release pattern

Such a ideal sustained release device is one which can deliver the drug at a constant rate until the device is exhausted of active ingredient. Mathematically, the release rate form this device is given as

$$dM_t/dt = k \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

where k is a constant, t is time, and the mass of active agent release is M_t. This pattern of release is called zero-order release model

2. Square-root-time model (Higuchi model)

The second common release pattern, frequently referrs to as square-root-of-time or $t^{1/2}$ release, provides compound release that is linear with the reciprocal of the square root of time. The release rate is then given as

$$dM_t/dt = k / t^{1/2} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (4)$$

3. First-order model

The first- order pattern is the third common type of the release model. The release rate in this case is proportional to the mass of active agent contained within the device. The release rate is then given as

$$dM_t/dt = k (M_0 - M_t) \quad \ldots\ldots\ldots\ldots\ldots\ldots (5)$$

where M_0 is the mass of active agent in the device at t=0. So, it can rearrangement as :

$$dM_t/dt = kM_0 \exp^{-kt} \quad \ldots\ldots\ldots\ldots\ldots\ldots (6)$$

In first - order model, therefore, the release rate declined exponentially with time, approaching a release rate of zero as the device approached exhaustion.

So that the exposed surface area of device decreased exponential with time, Wagner (1969) suggested that the drug release from most controlled–release matrices could be described by first order kinetics, thus:

$$A_t = A_0 e^{-k1t} \ldots\ldots\ldots\ldots\ldots\ldots (7)$$

where k_1 = first order release constant

A_0 = initial amount of drug

A_t = amount of drug remaining in the device at time t

Simplifying and taking the logarithm of Equation 5 yielded

$$\log A_t = \log A_0 - (k_1 t/2.303) \ldots\ldots (8)$$

First order model could be predicted by plotting the logarithm of the percent of drug remaining against time. If first order model, linear relationship was obtained.

If both the Higuchi model and first order model plots were linear, as indicated by correlation coefficient, it was necessary to distinguish between the models. The treatment was based upon use the differential forms of the first order and Higuchi equations (Schwartz, Simonelli, and Higuchi, 1968).

For Higuchi model, the rate would be inversely proportional to the total amount of drug release in accordance with equation (Sa, Bandyopadyay, and Gupta, 1990)

$$dQ/dt = (k_H^2 S^2)/2Q \ldots\ldots\ldots\ldots\ldots (9)$$

For First - model, this indicated that rate will be proportional to Q. This rate of release was determined by measuring the slopes at different points on the percent of drug release versus times curves.

$$dQ/dt = kA_0 - kQ \ldots\ldots\ldots\ldots\ldots\ldots (10)$$

The plots of rates of 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 operative.

The release pattern for each classes of device is illustrated in Figure 8 (Baker , 1987). The release patterns of zero-order, square-root time and first-order are depicted (Equation 3, 4, and 5) respectively

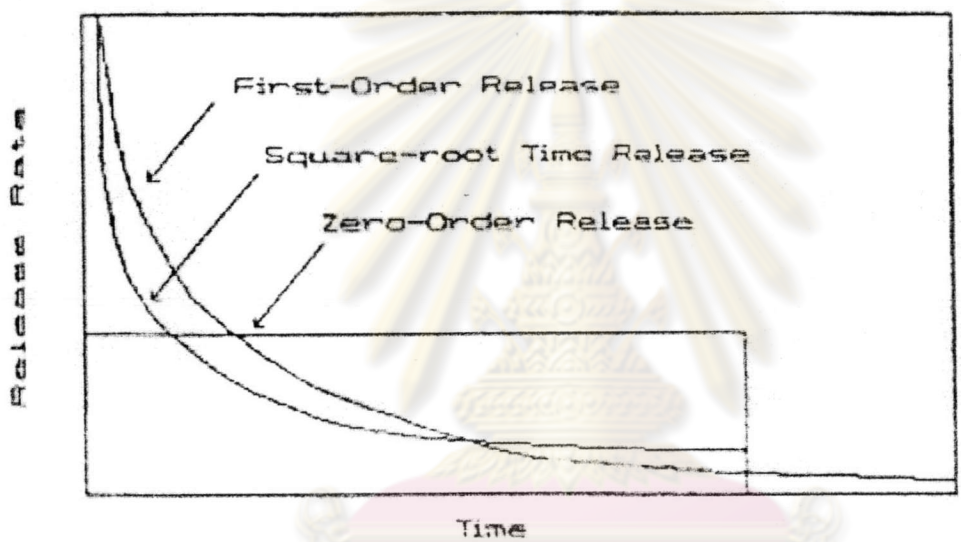


Figure 8 Zero-order, First-order, and Square-root time release pattern from devices containing the same initial active agent content