CHAPTER I

INTRODUCTION

Nowadays, sustained release systems are introduced to provide prolonged therapeutic action for various ailments. They are systems that drugs arrive rapidly at the site of action in the optimum concentration, remain for the desire time, be excluded from other site, and be rapidly removed from the site when indicated.

The advantages of administrating a sustained release product, are multifold. The first is to decrease the frequency with which the patient has to take the dosage from to obtain the desired effect and the second is to extent the drug's activity throughout the night so that the patient can sleep undisturbed until morning. Other advantages are, for hospitalized patients, a decrease in the number of doses administered can result in a time saving for nurses and pharmacists as well as a saving in drug storage space. Patient acceptance of the product when compared to conventional dosage forms can sometimes be an important advantage of prolonged action dosage forms. The severity of frequency of untoward side effects sometimes may be reduced by the administration of the medication in a prolonged action dosage form. And a prolonged action release mechanism may produce a more constant blood level of drug than repeated doses of a regular release ingredient administered per day (1).

Aspirin is commonly used as antipyretic, mild analgesic and anti-inflammatory. Its popularity as a paracetamol substitute

has increased very rapidly mainly because of lesser untoward effects.

Aspirin is also the drug of choice for the treatment of the rheumatic disease and may be administered high doses over prolonged periods of time. To maintain therapeutic blood levels, a total dose of about 100 mg per kilogram per day is devided into 4 or 6 doses. A sustained release aspirin preparation might be desirable in order to decrease the frequency of administration and to provide nighttime and early morning relief for patients with rheumatic arthritis.

Various aspirin prolonged release products are marketed such as Aspirin Relay Tablets® which 50% of the aspirin is quickly available and 50% is in sustained release form (2). Measurin® is aspirin tablet containing drug microencapsulated by the National Cash Register process. It was reported that Measurin® contains aspirin particles 600 mg coated with a thin, uniform, continuous film of inert polymer, creating Ca 6,000 microcapsules in each tablet (3), about half of the drug was available for immediate absorption and half showed prolonged release (4).

Polymers are widely used in pharmaceutical system as adjuvants, suspending and emulsifying agents, adhesives, coating agents and rate retarding agents. They can be divided into those that are water-soluble and those that are water-insoluble. This division, while not regid, is useful in that it separates the two main areas of use which form the basis of this account (5).

Several workers (6,7,8) have studied polymers as rate retarding agents. Example of polymers that they studied were polyvinylpyrrolidone (P.V.P.) and cellulose derivatives. Among

cellulose derivatives there are methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose etc.

Various methods are used to achieve sustained release products such as

1. Capsules of polymeric material filled with a solid or liquid agent or with a suspension or solution of agent in a fluid, in which the release of agent is controlled by diffusion through the capsule walls.

2. A heterogenous dispersion of particles of agent in a solid matrix, which can be either biodegradable or nonbiodegradable and which controls the release of agent by diffusion through the matrix, by erosion of the matrix, or by a combination of both diffusion and erosion.

3. A laminate of agent and polymeric material made by coating a film of biodegradable or nonbiodegradable material with solid agent and then forming the film into a sealed "sandwich" or "jelly-roll", which controls release of agent by diffusion, by erosion, or by both.

4. A heterogenous dispersion or solution of agent in a water-swellable hydrogel matrix, which controls release of the agent by slow surface-to-center swelling of the matrix by water and consequent diffusion of the agent from the water-swollen part of the matrix.

5. Liquid-liquid encapsulation of the agent in a viscous solution (syrup) of polymer, which controls release of agent by slow diffusion through or dilution of the media.

6. Chemical bonding of the agent to a polymeric backbone, as by pendant amide or ester linkages, which controls release of the agent by hydrolysis.

7. Formulation of macromolecular structures of the agent via ionic or covalent linkages, which controls release of the agent by hydrolysis, thermodynamic dissociation, or microbial degradation (9).

Of all these methods, a heterogeneous dispersion in a matrix seems to be easy, convinence and cost-saving. There are various dispersion matrices such as cellulose derivatives: carboxymethylcellulose methylcellulose, hydroxypropylmethylcellulose; plastic matrices; polyethylene, polyvinylacetate, polyvinylchloride, soft gelatin; shellac-P.E.G; polyvinylacetate-P.E.G..

Purposes of the Study

1. To formulate aspirin controlled release tablets containing methylcellulose as a rate retarding agent.

2. To study the influence of molecular weight of Methocel A (methylcellulose) on the dissolution of the drug.

3. To investigate the effect of content of P.V.P. K-30 on the release rate.

4. To study the effect of content of Methocel A on the release rate.

5. To study the mechanism of aspirin released from Methocel A matrix.

Literature Reviews

1. Aspirin (Acetylsalicylic acid)

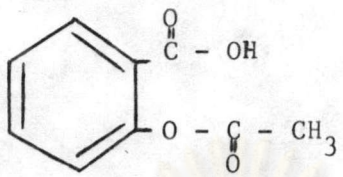


Figure 1 : Chemical structure of aspirin.

Aspirin may be called 2-(acetyloxy) benzoic acid or salicylic acid acetate. The formular is $C_9H_8O_4$. It's molecular weight is 180.15, containing of 60.0% of carbon, 4.48% of hydrogen and 35.53% of oxygen. The chemical structure of aspirin is shown in figure 1. It is usually prepared by acetylation of salicylic acid with acetic anhydride using a small amount of sulfuric acid as catalyst.

Aspirin is mostly monoclinic crystal usually elongated, but orthorhombic, and triclinic crystals are encountered at times.

It's density is 1.35. The melting point is 135°C. upon rapid heating and the melt solidifies at 118°C. It is odourless, but in moist air it is gradually hydrolyzed into salicylic acid and acetic acid and acquires the odour of acetic acid. It is stable in dry air. The rate constant, K at 25°C is 3.27×10^{-4}.

One gram of the drug dissolves in 300 ml of water at 25°C. in 100 ml water at 37°C, in 5 ml alcohol, 17 ml chloroform and 10-15 ml ether. It is less soluble in anhydrous ether. Aspirin is decomposed

by boiling water or when dissolved in solution of alkaline hydroxides and carbonates (10).

Aspirin has been a well known drug for almost 100 years because of its effectiveness, low price and low side effect. It is probably still the most extensively employed analgesic-antipyretic and anti-inflammatory agent, and it is the standard for comparison and evaluation of the others. It's therapeutic uses and doses are tabulated in table 1 (11).

Table 1: Therapeutic uses and doses of aspirin.

Therapeutic uses	dose
Antipyretic	adult: 325 mg - 1 g orally every 3 - 4 hr children: 10 - 20 mg/kg every 6 hr , not to exceed a total daily dose of 3.6 g.
Analgesic	relief pains of headache, arthritis, dysmenorrhea, neuralgia dose like antipyretic
Acute rheumatic fever	adult: total daily dose 5 - 8 g, in 1 g divided doses. children: 100 - 125 mg per kg per day divided doses every 4 - 6 hr.
Rheumatoid arthritis	dose in the range 4 - 6 g per day divided doses.
Pain of osteoarthritis	2 - 5 g per day in four divided doses.

Various aspirin prolonged release products are commercially marketed. They are produced as tablets, coated tablets, and capsules. Many studies of these products were reported for their effectiveness compared to conventional tablet.

Cass et al (12) studied clinical comparison of a sustained and regular release aspirin. They stated that a single dose of the sustained release aspirin provided pain relief as effective over an 8 hours period, as did two doses of immediate-release aspirin at 4 hours intervals at the same total dosage level.

Gotoff et al (3) reported the study of a sustained release aspirin preparation in children with acute rheumatic fever and suggested that sustained release aspirin tablets given every 8 hours were effective in suppressing symptoms in juvenile rheumatoid arthritis and that the drug was well tolerated.

Wiseman and Federici (13) designed sustained release aspirin tablet which was double layers in composition, with aspirin incorporated into a restraining matrix in one layer, and aspirin and a cornstarch binder in the second layer. The restraining matrix consisted of a vegetable wax, insoluble extenders, a water-soluble binder, and a fatty acid salt lubricant, for example; lactose, sucrose, carnauba wax and polyvinylpyrrolidone. It was found that the in-vitro rate of aspirin release into acid media shown excellent correlation with the observed in-vivo sustained characteristics.

A pilot trial of a new preparation of layered tablets of aspirin B.P. and sustained release aspirin (Bi-prin®) was conducted by Dick-Smith (14). He found that the preparation of sustained release aspirin was able to produce a very satisfactory clinical response, and

adequate serum levels of salicylate, central nervous system side effects were similar to those obtained with other forms of salicylate in adequate dosage and gastric intolerance was minor.

Of the clinical evaluations reported, microencapsulated aspirin has received considerable attention. Bell et al (4) compared sustained release aspirin with regular aspirin administered as a single dose and in divided dose and analyzed the blood levels as aspirin provided by each dosage form or regimen. When total salicylate blood levels were measured, all salicylates presumable producing and contributing to the antiinflammatory effect of aspirin, the sustained release product still gave demonstrably better results.

Rotstein et al (15) examined sustained release aspirin for use in the management of rheumatoid arthritis and osteoarthritis. In short-term double blind crossover studies the doses employed were large enough so that the patients received relief from both regular and sustained release aspirin, and observable differences between the two were obscured. However, in long-term usage studies, all the patients who had been on sustained release formulation showed better relief since it reduced the frequency of dosage and supplied more medication during the night, thus relieving morning aches and pains of arthritis. In both studies the incidence of side effects was significantly lower with sustained release therapy.

Various studies reported (16,17,18) that gastrointestinal blood loss can occur with different dosage form of prolonged action aspirin. However, significally less gastric bleeding occurred with prolonged action aspirin formulations compared to conventional aspirin preparations (17,18).

2. Methylcellulose (Methocel A)

Methylcellulose is a methyl ether of cellulose containing not less than 27.5 percent and not more than 31.5 percent of methoxy (OCH_3) groups, calculated on the dried basis. It's chemical structure is shown in figure 2. Methylcellulose obtained from cotton linter or wood pulp, is treated with caustic solution to produce alkalicellulose which in turn is treated with methyl chloride, yielding the methyl ether of cellulose. The fibrous reaction is purified and ground to a fine, uniform powder of granule. Properties of methylcellulose are tubulated in table 2.

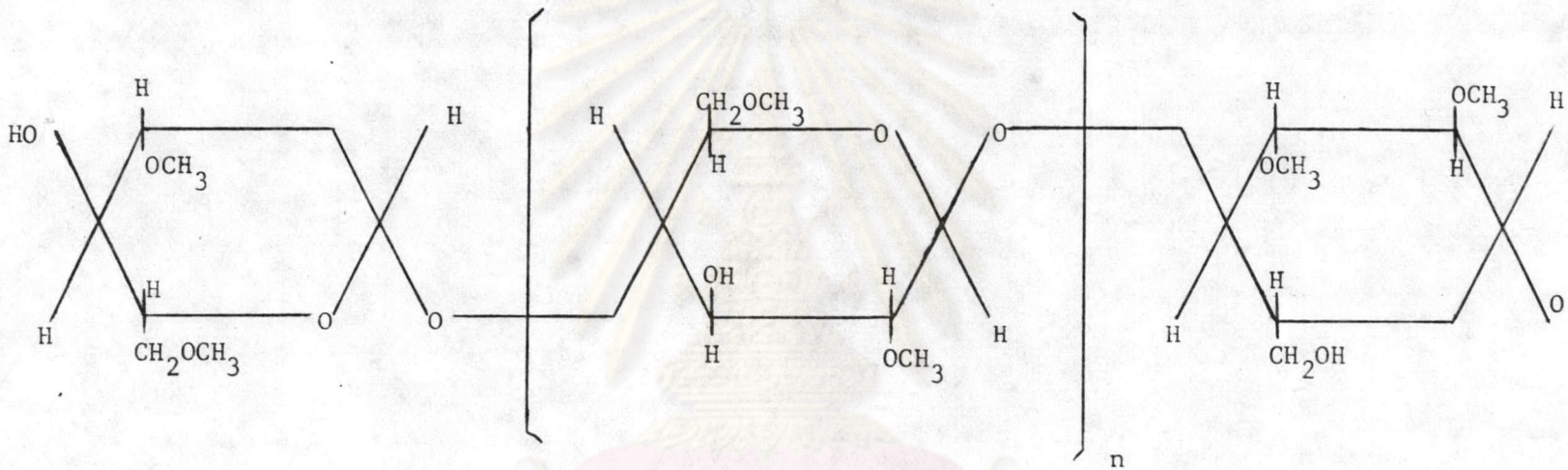
Methylcellulose can be completely recovered from the intestinal tract after ingestion. It is for all practical purposes proof that it is stable to a wide range of bio-chemical and enzyme systems.

Methylcellulose (Methocel A) has an exceptional and valuable combination of physical and chemical properties. These include.

a. Water solubility : It dissolves in water in all proportions; the maximum concentration is limited only by viscosity.

b. Organic solubility : Certain type and grades are soluble in a number of binary organic and organic-water solvent systems; these provide a unique combination of organic and water solubility.

c. Ionic charge : It has no ionic charge and is not polyelectrolytes; therefore it will not complex with metallic salts and ionic organics to form insoluble precipitates.



n = number of monomer

= 1,2,3----------

Figure 2: Chemical structure of methylcellulose

Table 2: properties of methylcellulose (Methocel A)

Physical appearance	white to slightly off - white, essentially odourless and tasteless powders
Apparent density (g/ml)	0.25 - 0.70
Browning temperature	190°- 200°C (374°- 392°F)
Relative flammability in a furnace at 700°C (1292°F)	+ 90
Specific gravity	1.39
Weight/gallon, pounds	11.6

Methylcellulose also has a number of note worthly performance properties making it useful as:

d. Thickener : It thickens both aqueous and non-aqueous systems. The degree of thickening is related to specific product viscosity and chemical type.

e. Film former : It forms clear, tough, flexible films that are excellent barriers to oil and greases.

f. Binder : It has excellent functionality as binder for pigments, tobacco product, paper in both coating and adhesive end-uses.

g. Lubricant : It reduces friction in rubber, asbestos, cement, ceramic extrusion and improves pumpability of concrete slurries.

i. Emulsifier : It stabilizes emulsion both by reducing surface and interfacial tension and by thickening the water phase.

Table 3 tubulates various grades and viscosity ranges of commercial Methocel A (19). Degree of substitution and typical weight percent of Methocel A are also listed in table 4 (19).

Coletta and Rubin (20) and Wood and Syarto (21) reported on the use of methylcellulose and ethylcellulose film to coat aspirin particles using the Wurster air-suspension coating technique. In this case, the methylcellulose dissolved out of the film leaving small channels in the film through which drug can diffused. The ethylcellulose barrier left on the particle served as a restraining barrier to maintain constant diffusional area and constant diffusional pathlength. The results of this study, the authours attempted to correlate the in-vitro availability rate with in vivo absorption rate. High ethylcellulose content provided good correlation.

Table 3: Various grades and viscosity ranges of Methocel A

Methocel A (grade)	Viscosity range (cps)
15 LV	13 - 19
4 C	350 - 500
15 C	1,200 - 1,800
4 M	3,500 - 5,000

Table 4: Degree of subsitution* and typical weight percent of Methocel A.

Premium and Standard grade	Methoxy degree of substitution	Methoxyl percent
Methocel A	1.6.- 1.9	27.5 - 31.5

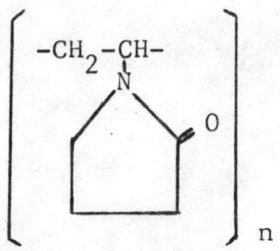
* The degree of substitution refers to the average number of methoxy groups that are substituted per anhydroglucose unit.

Water-soluble drugs dispersed in hydrophilic matrices were studied by Lapidus and Lordi (22). The results, using chlorpheniramine maleate dispersed in methylcellulose, showed that the release rate was controlled mostly by drug diffusion rather than polymeric dissolution. Thus, even when drugs are placed in a water-soluble matrix which will be subject to erosion, the rate-limiting step is diffusion of drug out of the matrix. Huber et al (23) employed hydrophilic gums as the matrix material and showed that drug diffusion from a gel barrier, at the periphery of the tablet, was rate limiting.

Some studies involved methylcellulose, function as barrier coated hydrophilic matrix (9) in prolonged-action dosage form preparation. The mechanism to release drugs was believed by (a) diffusion of drugs through hydrated gelatinous layer, or (b) the dissolution of gum, or (c) diffusion of water, or caused by the combination of three mechanisms. The main factors of these mechanisms are rate of diffusion of water through polymer, the diffusivity of drugs through polymer membrane and the thickness of diffusion path (24).

Sarisuta and Parrott (25) investigated the influence of viscosity on the dissolution rate of benzoic acid in aqueous solution of methylcellulose, hydroxypropylcellulose and guar gum. Using Stokes-Einstein equation, they demonstrated the relationship of the dissolution rate to viscosity. An equation is presented relating the dissolution rate of benzoic acid to solubility, diffusion coefficient and viscosity for these nonionic viscosity-enhancing agents.

3. Povidone (1-Vinyl-2-pyrrolidone polymer)



n = 1,2,3-------

Figure 3 : The chemical structure of povidone.

Povidone may be 2-pyrrolidinone, 1-ethyl-, homopolymer, polyvinylpyrrolidone (P.V.P.). The chemical structure of povidone is shown in figure 3.

U.S.P. XXI stated that povidone is a synthetic polymer consisting of linear 1-vinyl-2-pyrrolidinone groups, the degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a K-value, ranging from 10 to 95. The K value of povidone having a nominal K-value of 15 or less is not less than 85.0 percent and not more than 115.0 percent of the nominal K-value, and the K-value of povidone having a nominal K-value, or nominal K-value range with an average of more than 15 is not less than 90.0 percent and not more than 108.0 percent of the nominal K-value or average of the nominal K-value range (26).

Povidone is white to creamy white, odourless powder, It is hygroscopic, pH of 1 in 20 solution between 3 and 7. It is soluble in water, alcohol and chloroform, insoluble in ether (27).

Povidone is used in pharmacy as suspending and dispersing agent usually in a concentration of 0.01 to 10.0%. It is also used as tablet binding and granulating agent, usually in a concentration

of 0.5 to 5% but a higher proportion may be nescessary for some granules. It is particularly useful in the preparation of effervescent tablets and other tablets which are highly sensitive to water since it can be incorporated as a solution in an organic solvent such as alcohol or isopropyl alcohol.

It is also useful in the preparation of heat sensitive tablets since granules prepared with a solution of povidone in an organic solvents of low boiling point can be dried in air at ordinary temperatures. It is employed as dispersing agent for dyes in coloured tablet and as a stabilising agent in vitamin, enzyme and salicylate preparations (28).

In comparative study of povidone solution with the common tablet binding agent; acacia mucilage, syrup and starch paste, in tablet formulation of 5 drugs (ascorbic acid, aspirin, magnesium carbonate, sodium bicarbonate and sodium salicylate), povidone was an effective and stable binding agent and was comparable to or better than the other binding agents (29).

Florence and Rahman (30) studied the influcnce of P.V.P. on the dissolution rates of compounds of varying aqueous solubilities. They concluded that a poorly soluble drug would be little affected by the presence of relatively soluble polymer such as P.V.P., on the dissolution rate of drug. The more soluble the drug, the more likely it is to be affected by the presence of P.V.P.

Numerous reports have shown the effect of P.V.P. on intrinsic dissolution rate of solid from nondisintegrating disk. Gibaldi and Weintraub (31) indicated that the presence of P.V.P. in the diffusion layer would, therefore, tend to decrease the dissolution of salicylic

acid from salicylic acid-P.V.P. compressed mixtures. By forming a film of a high molecule P.V.P.-salicylic acid complex may form at the interface and depress dissolution rate.

In a latter paper, Collett and Kesteven (32) reported that the presence of P.V.P. in compressed disks composed of P.V.P. and allopurinol did not affected dissolution rate even when present up to 40% w/w of the disk. The conclusion of the above reports is in the paper published by Florence and Rahman (30).

4. Stearic acid (Octodecanic acid)

Stearic acid is white, odourless or almost odourless, almost tasteless, greasy, flaky crystals or hard masses. It may be powdered by sprinkling with alcohol during trituration. It's melting point is not below 54°C.

It is insoluble in water, soluble in 50 parts of alcohol, 2 parts of chloroform and 3 parts of ether.

The pure acid ($C_{17}H_{35}CO_2H$) has molecular weight = 284.5. It used as a lubricant in making compressed tablet and as an enteric coating for pills and tablet. When partly neutralised with alkaline or triethanolamine it forms a creamy basis with 5 to 15 times its weight of aqueous liquid and this sometimes used as the basis of vanishing creams. Free stearic acid in such creams may produce a pearly appearance on standing. After being neutralised and dissolved by heat in glycerol or alcohol, stearic acid will solidify when cold with at least 10 times its weight of liquid (33).

For the experimental use of stearic acid as coating agent

basis for sustained release tablet (34).

Kornblum and Zoglio (35) studied hydrolysis of aspirin in combination with tablet lubricants;talcum, stearic acid, hydrogenated vegetable oil, calcium stearate, magnesium stearate, and aluminium stearate, in an aqueous suspension. They suggested that by using the kinetic data obtained from the suspension study, an attempt was made to predict aspirin stability in a solid dosage form. There was evidence presented to support the concept that stearic acid would serve as a medium for aspirin degradation at temperature a slightly above room temperature.

5. Dissolution test

Dissolution of the active component as an index of drug availability for solid dosage forms is widely accepted. Since it is axiomatic that the drug must be in dissolved state before being absorbed into blood stream.

Figure 4 (36) indicates the processes involved when a tablet is exposed to dissolution fluid, it is evident that dissolution of the drug occurs not only from the fine particles of the drug ultimately produced but also to a small degree from the intact dosage form before its disintegration and from the fragments and agglomerates produced after disintegration. It concluded that the dissolution rate of a drug can be a rate-determining step in the absorption process. Thus, for sparingly water soluble drugs, dissolution rate must has greater effect on the rate of drug absorption. Consequently, dissolution rate may affect the onset, intensity, and duration of biological response.

On the otherhand, rapid disintegration of tablet does not ensure

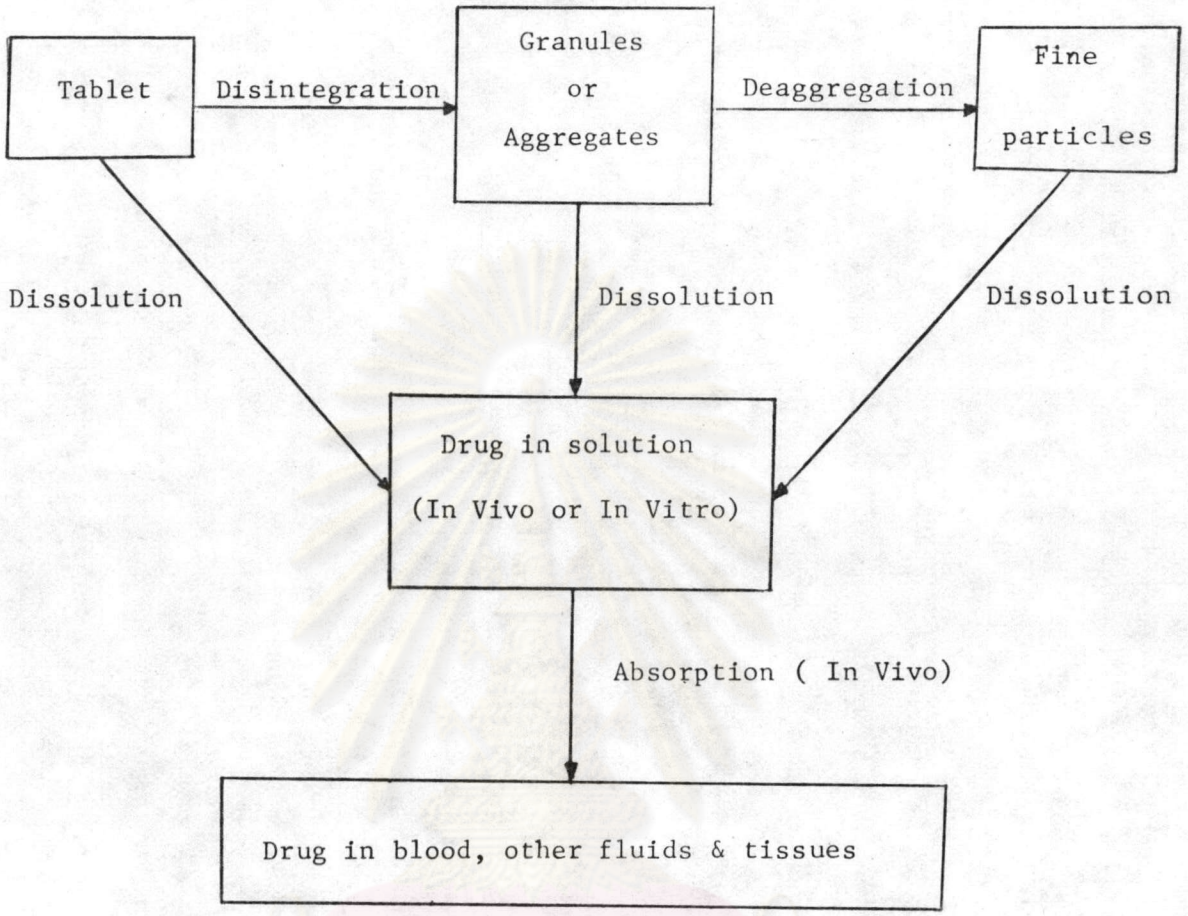


Figure 4: Process of dissolution of the drug

the rapid dissolution rate of the drug, since the discrete particles may be covered with the additives and inhibitory effect on dissolution may be produced. Therefore, since 1970 U.S.P. and N.F. have provided procedures for dissolution testing. Dissolution time of a given tablet formulation must meet the requirement as specified in the individnal monograph (37,38). Dissolution test is more capable of detecting difference between products and different lots of the same product than is the traditional tablet disintegration test. However, most of the local pharmaceutical manufacturers at the moment are still rely on tablet disintegration test as an indicator of drug availability of the newly developed formula.

Dissolution test is provided to determine compliance with the limits on "Dissolution" where stated in the individual monograph for tablet of capsule dosage form. It affords an objective means of determining the dissolution characteristic of a solid dosage form. Since drug absorption and physiological availability are largely dependent upon having the drug in the dissolved state, suitable dissolution characteristics are an important property of a satisfactory drug product.

Dissolution Methodology :

There are a number of methods available for the determination of in vitro dissolution behaviors of the solid drugs and there is no correlation between the results obtained from each procedures. Dissolution methodology may be classified according to a variety of factors (39,40).

They may be classified into two techniques, the suspension method or the constant surface method. The degree of agitation offers another alternatives for classification, they may be due to fluid motion (laminar flow or turbulent flow). Classification may be made on the basis of concentration gradient (non-sink and sink condition). Thus, the types of dissolution apparatus have been developed in many ways such as beaker method (41) hanging pellet method (42), rotating disk method (43), basket method (44), rotating flask method (45) etc.

There are several reports in the literature (46) on the in vitro dissolution rates which show a correlation with in vivo absorption or urinary excretion. There is not any universal in vitro method which can predict the absorption rate of the drug from the gastrointestinal tract. The physiological factors, such as gastric emptying time, p.H. of the gastrointestinal fluids, volume of the gastrointestinal fluid, sex and age, do effect the absorption of the drug from the gastrointestinal fluid.

Shah modified Levy's method and studied the correlation between in vitro dissolution and urinary excretion of salicylate. The release rate of the salicylic acid from various controlled release tablet formulation was determined in simulated gastric fluid for 3 hours

and then in simulated intestinal fluid at 37°C using U.S.P. dissolution apparatus. The results indicated that there existed a definite correlation between the in vitro dissolution and urinary excretion of salicylate from the controlled release formulation (47).

Mechanism of Drug Release :

It is very difficult to consider systems which rely on diffusion or dissolution as the principal mechanism for sustained release. Even though we have created clear-cut divisional lines for diffusion and dissolution, we should be aware that in practice it is common to see both mechanisms operative in a given dosage form, although one mechanism will usually predominant over the other. This can present problems in vitro evaluation of these types of products, and for those systems where both mechanisms appear equally active, the formulator is often guided by empirical observations.

1. Methods using diffusion

Diffusion entails the movement of drug molecules from a region of higher concentration to one of a lower concentration. Diffusion control of drug release by solid drug dispersed in an insoluble matrix and the rate of release of drug is dependent on the rate of drug diffusion and not on the note of solid dissolution. The appropriate equation describing drug release from this system has been derived by Higuchi (48).

$$Q = \frac{DE}{\mathcal{T}} (2A - ECs) Cst^{\frac{1}{2}} \qquad (eq \frac{n}{-} 2)$$

Q = amount of drug release per unit area of tablet surface

t = time

D = diffusion coefficient of the drug in the release medium

Cs= the solubility of drug in the medium

E = the porosity of the matrix

$\mathcal{T}$ = the tortuosity of the matrix

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

For purposes of data treatment Eq (2) is usually reduce to

$$Q = kt^{\frac{1}{2}} \qquad (eq^{n}\ 3)$$

where k is a constant

Methods using dissolution

Sustained oral products employing dissolution as the rate-limiting step are in principle the simplest to prepare. A drug with a slow dissolution rate is inherently sustained, and for those drugs with high water-solubility one can decrease solubility through appropriate salt or deviation formulation.

There are several theories of dissolution for explaining the occurence when the drugs dissolved into a dissolving mediums. The simplest and least complex theory is the "film theory"

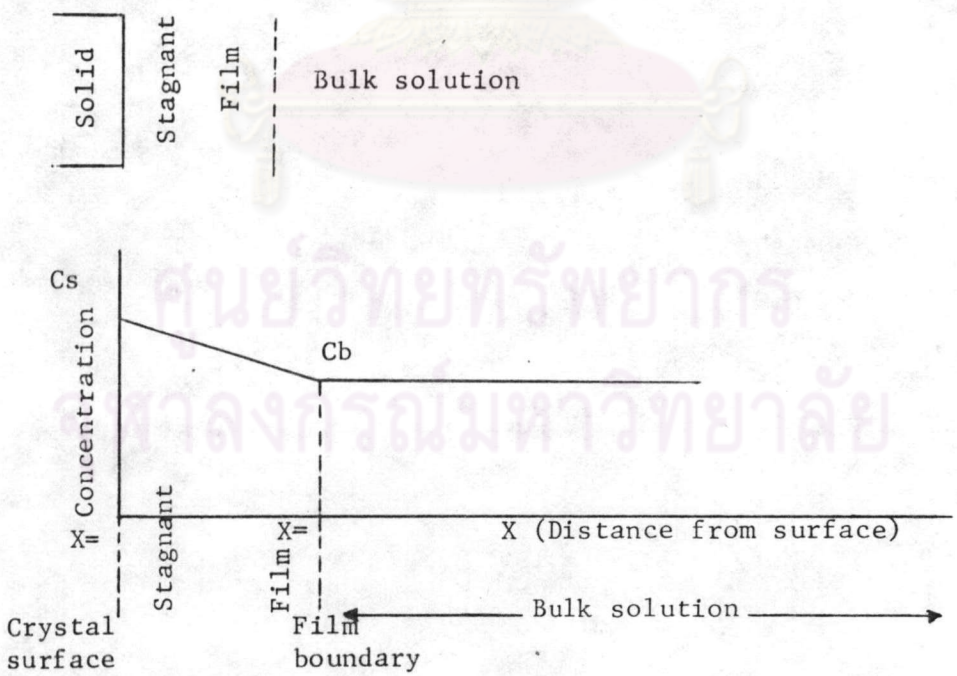


Figure 5 : Top : Schematic representation of the stagnant film.

Bottom : Concentration gradient in film.

The model as shown in Fig 5 (49, 50) assumes that there is a "stagnant" layer between the solid and the solution at the solid solution interface. The concentration of this diffusion layer is assumed to be equaled to the saturated concentration at the solid surface, and the concentration then decreases as the distance from the solid surface increases. At the end of diffusion layer, the concentration in the film is equal to the bulk solution. Therefore, the dissolution rate is controlled by the diffusion of the solute across this layer. When Fick's law of diffusion is applied to this diffusion-controlled phenomenon under laminar flow conditions. The dissolution rate is expressed as the following equation :

$$\frac{V.\,dc}{dt} = \frac{dm}{dt} = \frac{D.O.\,(Cs - Cb)}{h}$$

$$= k.O.\,(Cs - Cb) \qquad (eq^{n}\ 4)$$

m = the amount of solid dissolved into solution at time t.

V = the volume of the dissolution medium.

O = The surface area of solid exposed to the dissolution medium.

D = the diffusion coefficient of solute in the dissolution medium.

h = the thickness of dissolution layer.

k = the dissolution rate constant