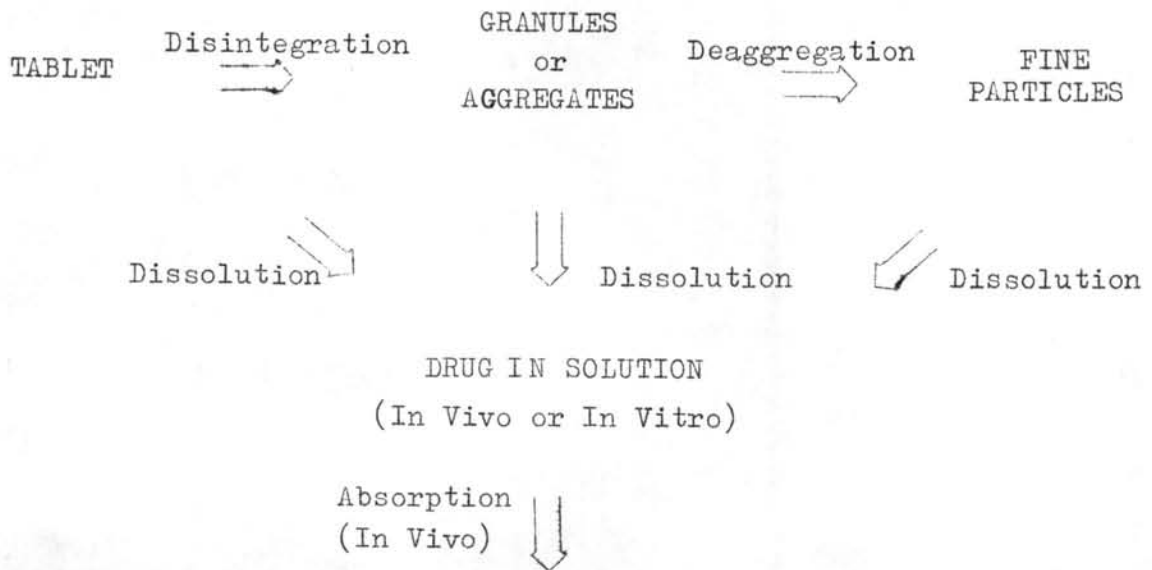# CHAPTER I

INTRODUCTION

Rationale

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.

TABLET →Disintegration→ GRANULES or AGGREGATES →Deaggregation→ FINE PARTICLES

Dissolution ↘   ⇓ Dissolution   ↗ Dissolution

DRUG IN SOLUTION
(In Vivo or In Vitro)

Absorption
(In Vivo) ⇓

DRUG IN BLOOD, OTHER FLUIDS & TISSUES

The scheme[1] as shown above 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 have 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 did not ensure 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 USP and NF have provided procedures for dissolution testing. Dissolution time of a given tablet formulation must meet the requirement as specified in the individual monograph[2,3] 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.

As it is obvious that additives have to be included as

part of tablet formulations in order to enhance the physical appearance, improved stability and aid in disintegration etc. They may be broadly classified according to their roles in compounding of tablet. The first group contains those which help to impart satisfactory compression characteristics to the formulation. These included diluents, binders, and lubricants. The second groups of added subtances helps to give additional desirable physical characteristics to the finished tablet. Included in this second group are disintegrants, colors, flavors, and sweetening agents.

As a result, care must be taken in the selection and evaluation of additives prior to use in order to ensure that physiological availability and therapeutic efficacy of the drugs will not be hindered. The variation of dissolution behaviors can exists when formulation and processing factors are altered. The dissolution rate of the same active ingredient from the solid dosage froms of several manufacturers may be significantly different mostly due to the differences of formulations.

There were many cases reported in the literatures concerning this subject, for example, the difference in dissolution rate of commercial phenobarbital tablets from 24 manufacturers was reported by Jacob and Plein[4]. Wagner at al.[5] indicated that the variation in dissolution rate and plasma concentration of digoxin tablets made by different manufacturers may

be due to the effects of nonactive compositions. Such variations were also found in different lots and in the same lot of the formulated product made by the same manufacturer[6]

In this connection, therefore the need for better understanding of the effect of additives, incorporated in the tablet formulation, on the availability of the tablet is deemed necessary. As it will be a base utilizable for further product development along this line.

Purposes of the Study

The scope of this research is to study the influences of various additives used in tablet formulation on the intrinsic dissolution rate of paracetamol. The effects of additives concentrations and compressional forces on dissolution rate of tablet will be investigated in order to elucidate the actual relationship.

The reason of selecting paracetamol as the model drug is due to the widespread use of paracetamol as an antipyretic and mild analgesic. Its popularity as an aspirin substitute has increased very rapidly mainly because of lesser untoward effects.

All the additives used in the experiments are commonly employed as a component of compressed tablet formulas. The amount of additives used in this studies are also varied in the practical range.

The present studies designed to cover only the initial evaluation of the effect of additives on dissolution rate of tablet. The objective is to encourage and facilitate the local tablet producers in order to make a decision in choosing the proper additives for tablet formulation.

The results of this study is not yet conclusive and further research seemed to be necessary for the total development of paracetamol tablet. In those instances, the other related factors such as compression behavior, hardness, friability, weight, disintegration time, and chemical stability may have to be carefully considered as well.

Literature Reviews

1. General

The effect of formulation and processing factors on dissolution rate of the active ingredients of compressed tablet has been the subjects of a number of reports and it could be seen that dissolution studies had been almost carried out by total dissolution techniques.

Hirschorn and Kornblum[7] studied the effects of excipients dilution and force of compression on dissolution of directly compacted quinazolinone compound tablets. They found that the greater the quantity of diluent, the higher was dissolution rate and a linear relationship was obtained when plotting

$t_{50 \%}$ versus tablet weight. But an increase of the compressional force provided divergent results, the larger the tablet size, the less effect compressional force had on the dissolution rate. They concluded that when formulation a tablet of a poorly water soluble drug, the following should be considered : optimum tablet size, hydrophilic nature of diluents and optimum force of compression.

Morlowe and Shangraw[8] demonstrated that sodium salicylate tablet prepared by direct compression with spray dried lactose exhibited faster dissolution rate than tablet prepared by wet granulation. And they concluded that dissolution of an active ingredient from a tablet is generally not depend selely on the effect of a single component or production specification but is the result of the interaction of many variables.

Shah et al.[9] reported that digoxin tablet prepared from triturations by ball milling or muller milling digoxin with a 20-fold excess of lactose, sucrose, calcium phosphate dibasic, or microcrystalline cellulose significantly enhance dissolution rate of digoxin. It was shown that the application of dispersion method markly improve dissolution rate.

Jacob and Plein[10] studied the effect of various binders such as gelatin, acacia, ethylcellulose, hydroxyethylcellulose. They found that increase in binder concentration and hardness of tablet resulted in a decreased in the dissolution

rates of phenobarbital tablet. Selection of binder, its concentration, and hardness at which tablets are compressed, are important factors which should be properly controlled.

Sakr and Elsabbagh[11] formulate tablet of nicotinic acid by using acacia and sodium alginate as the binder. In this work, it was found that acacia had little or no effect on dissolution time of nicotinic acid tablet while sodium alginate had a marked delaying effect on the dissolution rate. As the amount of sodium alginate was increased in the formula the rate of dissolution decreased.

The effects of binder concentration, compressional force, granule size on release of erythrosine from lactose compacts was reported by Shubair and Dingwall.[12] They found that the rate of in vitro release of erythrosine from compacts of lactose granulated with starch mucilage was reduced by increasing binder concentration and by increasing compressional force. But it was virtually unaffected by granule sizes. Effects produced by interaction of all three factors in combination were found to be non-significant.

Numerous reports have shown the effect of polyvinylpyrrolidone(PVP) on intrinsic dissolution rate of solid from nondisintegrating disk. Gibaldi and Weintraub[13] indicate that the presence of PVP in the diffusion layer would, therefore, tend to decrease the dissolution of salicylic acid from salicylic acid -

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

In a latter paper, Collett and Kesteven[14] reported that the presence of PVP in compressed disks composed of PVP and allopurinol did not affected dissolution rate even when present up to 40 % w/w of the disk. The conclusions of the reports above is in the paper published by Florence and Rahman[15]. They indicated that a poorly water soluble drug would be little affected by the presence of relatively soluble polymer such as PVP, the more soluble the drug the more likely it is to be affected by the presence of PVP.

Solvang and Finholt[16] investigated the effect of granulation, the rate of release of phenobarbital, phenacetin, and prednisolone from the granule and tablets prepared with galatin as binder was faster than the rate of dissolution of the pure drugs.

They compared the effect of different granulating agent on dissolution rate of phenobarbital tablets. Tablets prepared with gelatin were found to dissolved much faster in human gastric juice than tablets prepared with sodium carboxymethylcellulose or polyethylene glycol 6000 as binder, probably because gelatin makes the originally hydrophobic surface of drug particles hydrophilic where sodium carboxymethylcellulose at the pH of dissolu-

tion medium is converted into the less hydrophilic free acid and polyethylene glycol 6000 forms a complex of reduced solubility with phenobarbital.

Levy and Gumtow[17] investigated the effect of tablet lubricants on the dissolution rate of salicylic acid tablet. They found that a hydrophobic tablet lubricant (magnesium stearate) retarded dissolution rate.

Morlowe and Shangraw[8] compared the effect of water soluble lubricant(composed of 1:1:2 ratio mixture of DL-leucine, calcium benzoate, and polyethylene glycol 4000) and water insoluble lubricant (magnesium stearate). The dissolution pattern showed the only slight difference.

2. Factors Affecting Dissolution of the Solid Drugs

There are numerous physico-chemical factors which affect dissolution rate of pure drugs. They may be environmental factor during dissolution tests or may be the properties of the solid drugs.

Intensity of agitation affects the dissolution rate of solid materials. High degree of agitation increase dissolution rate.[18]

Influence of fluid motion on dissolution was also reported. Bisaillon and Tawashi[19] showed the difference between dissolution rates determined under laminar flow and

turbulent flow.

Temperature dependence on dissolution rate constant were shown by Nogami et al.[18] An increase in temperature of dissolution medium causes a significant increase in dissolution rate.

Properties of the dissolution medium of course affects dissolution. Piccolo and Tawashi[20] have shown that the presence of water soluble dyes in the dissolution medium reduces the dissolution rate of crystalline drugs and compressed disks of the pure drugs. They suggest the dye molecules adsorbed at the surface of solid particles and gave a marked inhibition of the dissolution rate.

Inhibitory action also depend on the chemical group of dyes, cationic dyes are more reactive in reducing dissolution rate than anionic dyes[21].

The effect of ionic strength in dissolution medium on dissolution rates were reported by Block and Patel[22] They found that dissolution rate of triamcinolone acetonide were markedly lower in potassium chloride solution in comparison with the water.

The solubility of a weak electrolyte usually varies considerably as a function of pH. Hence, difference are expected in the dissolution rate of a weak acid and a weak base at different pH. Dissolution rate of weak acid drugs increased with

increasing pH. The dissolution rate of weak base drugs would be optimal at low pH.[23]

Florence et al.[24] reported the influence of solution viscosity on dissolution rate. They have studied the effect of polyoxyethylene glycol 6000, polyvinylpyrrolidone and cetomacrogol 1000 in retarding the dissolution rate of sodium chloride and potassium chloride. Dissolution rate constants decrease with increasing bulk solution viscosity.

There are numerous reports showed the effect of surfactants in dissolution medium, enhance dissolution rate of hydrophobic drugs. The addition of polysorbate 80 to the dissolving fluids increase dissolution rate of benzoic acid,[25] benzocain,[26] phenacetin, and phenobarbital[27] This effect was mainly due to its ability to decrease the interfacial tension between drug particles and dissolution fluid. Finholt and Solvang[27] found that the rate of dissolution of phenobarbital and phenacetin in dilute gastric juice is higher than the rate of dissolution in 0.1 N HCl, since the dilute gastric juice has a much lower surface tension than hydrochloric acid solution. They suggest hydrochloric acid solution adjusted to a surface tension of $40 - 50$ dynes cm^{-1} is a better dissolution medium for an in vitro test than an hydrochloric acid solution with no surfactant added.

Many drugs can exists in more than one crystalline form

a property known as polymorphism. Although the drug is chemically identical in each form, polymorphs differ significantly with respect to a number of properties such as density, melting point, solubility and dissolution rate. At any one temperature and pressure only one crystal form of a drug will be stable other polymorphs will convert to stable form. It the conversion rate is so slow, the polymorph is said to be metastable. The metastable form has a higher dissolution rate than stable form because of higher **solubility**.

The influence of polymorphism both on in vitro dissolution rate and on in vivo bioavailability were investigated. Dissolution rate of three polymorphic forms of prednisolone were determined by Wurstur and Taylor,[28] they exhibit different results. Tawashi[29] studied the different dissolution behavior of two polymorphic forms of aspirin and found that one form dissolved 50 % faster than the other. The different dissolution rate behavior of two polymorphic forms of sulphathiazole and methyl-prednisolone was also reported.[30]

Aguiar[31] et al. studied the effect of polymorphism on the availability of chloramphenicol from polymorps A and B of Chloramphenicol palmitate. They found that peak blood level of chloramphenicol increase proportionality as the increase of percent concentration of polymorph B(metastable form) in the suspension dosage forms.

In addition to the polymorphic forms in which a compound may exist, a drug also may occur in a crystalline or amorphous form. The amorphous form of a compound is always more soluble than the crystalline form. An example of this effect can be found in a report concerning various forms of the antibiotic novobiocin. Crystalline novobiocin was found to dissolve exceedingly slowly in contrast to the amorphous form of the drug.[32]

Significant difference in the dissolution rate of anhydrous and hydrated form of caffeine, theophylline and glutethimide have been observed.[33] In each case the anhydrous forms dissolved more rapidly.

The effect of salt formation of compound on dissolution rate have been studied. Nelson[34] found that marked differences existed between dissolution rates of several weak acids and their sodium salts. The sodium salts always dissolved much more rapidly than the free acid.

In was evident that dissolution rate is directly proportional to the surface area of the drug, since the surface area increases with decreasing particle size, Higher dissolution may be achieved through reduction of particle size. However, the dissolution rate decreased with decreasing particle sizes,[27,35] since the powder drugs may resists wetting by dissolving fluid and it occur especially with hydrophobic drugs.

But it appears that the effect of particle sizes on

dissolution rate of materials from constant surface area is negligible. Milosovich[36] determined dissolution rate of sulpha-thiazole compressed disk made from differnet particle sizes, no size effect was observed.

Theoretical Concept

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".

Noyes and Whitney[37] studied dissolution behavior of benzoic acid and lead chloride in water, the surface area of dissolving solid remained essentially constant during their studies. They derived the equation as the following :

$$\frac{dc}{dt} = K \cdot (C_s - C_b) \qquad (Eq. 1)$$

where :

K = the rate constant,

C_s = the concentration of the saturated solution of the solute,

C_b = the concentration of solute in the dissolution medium at time t.

Later, Nernst and Brunner[38] introduced the film theory by extending the concept of Noyes and Whitney. The model, as shown in Fig.1[39,40] assumed that there is a "stagnant" layer between the solid and the solution at the solid solution inter-
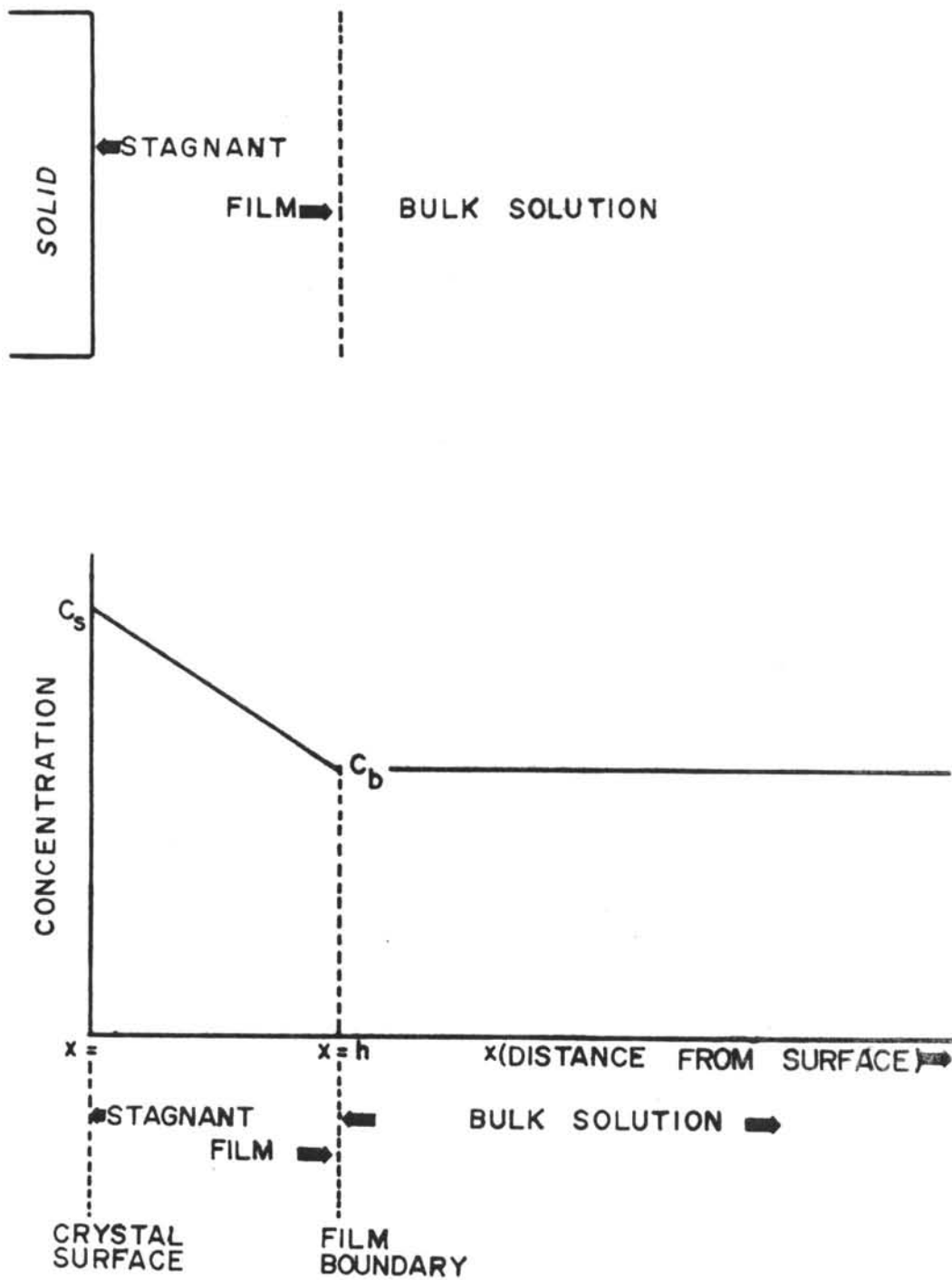
Figure 1. Top: Schematic representation of the stagnant film.
Bottom: Concentration gradient in film.

face. 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 buld 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 diffussion-controlled phenomenon under laminar flow conditions. The dissolution rate is expressed as the following equation :

$$\frac{V.dc}{dt} = \frac{dm}{dt} = \frac{D.O.(C_s - C_b)}{h}$$

$$= k.O.(C_s - C_b) \qquad (Eq. 2)$$

Where :

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 the solute in the dissolution medium,

h = the thickness of diffusion layer,

$$k = \text{the dissolution rate constant.}$$

Eq. 2. may be integrated to:

$$\ln (1-m/m_\alpha) = \ln(1-C_b/C_s) = -\frac{D.O.t}{h.V}$$

$$= -\frac{k.O.t}{V} \qquad (Eq. 3)$$

where :

$m_\alpha = $ the amount of solid dissolved in saturated solution.

or

$$\log (C_s - C_b) = -\frac{k.O.t}{2.3V} + \log C_s \qquad (Eq. 4)$$

For situation, as the solid initially dissolved, where the bulk concentration, C_b is much smaller than the concentration of saturated solution, C_s . So that Eq. 2 becomes

$$C_b = \frac{D.O.C_s.t}{h.V} = \frac{k.O.C_s.t}{V} \qquad (Eq. 5)$$

The situation when $C_b \ll C_s$ is denoted sink condition. The dissolution profiles under sink condition and non-sink condition are illustrated in Fig. 2.[39] Fig. 2-A are plotted according to Eq. 3 and Fig. 2-B curve are plotted according to Eq. 5. Fig. 2-A shows that at the early time period the slope of non-sink and sink condition are the same.

Sink conditions is said to be satisfied by the dissolution of solid dosage forms in digestive tracts.[41] Sink condition in vitro dissolution studies can be maintained if the bulk concentration do not exceed 10 to 15 % of concentration of saturated
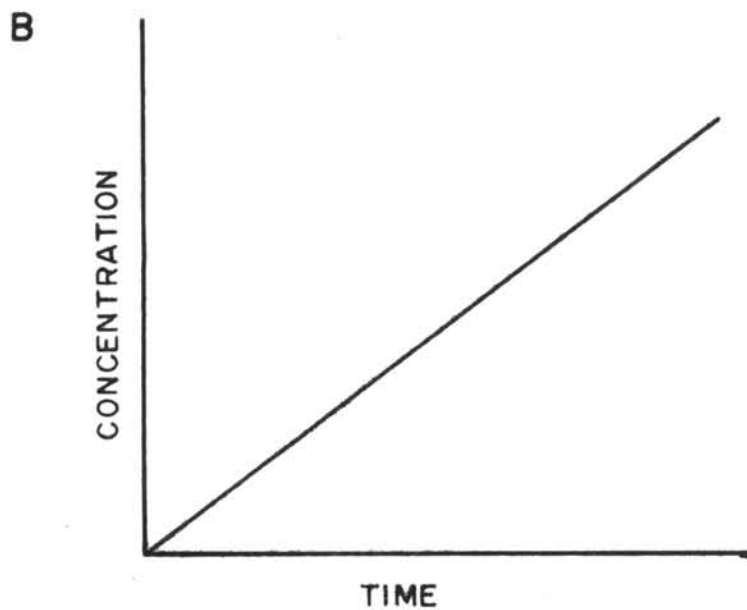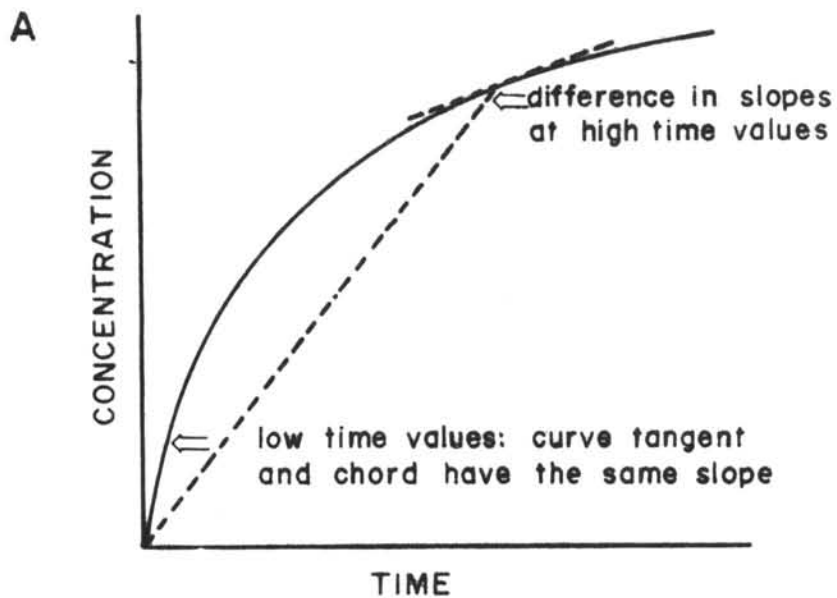
Figure 2. A. Dissolution profile under non-sink condition.
B. Dissolution profile under sink condition.

solutions.[40,42]

Eq. 5 may be rewritten :

$$V.C_b = k.O.C_s.t$$
$$m = K'.t \qquad\qquad (Eq. 6)$$

where K' is the rate constant, it can be obtained from the slope of plotting the amount dissolved versus time. Intrinsic dissolution rate in the unit of mass $area^{-1}$ $time^{-1}$ can be calculated from the rate constant(K') divide by the surface area of the dissolving solid.

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.[42,43]

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(nonsink and sink condition). Thus, the types of dissolution apparatus have been developed in many ways such as beaker method,[44] hanging pellet method,[34] rotating disk method,[45] basket

method,[46] rotating flask method,[47] etc.

During development of a dosage form, intrinsic dissolu-
tion rate can be a useful parameter for subsequent dissolution
evaluation. In the measurement of intrinsic dissolution rate, the
surface area of dissoved solid must kept constant all the time as
dissolution progresses. Rotating disk method is considered to be
superior for obtaining the values of intrinsic dissolution rate.
This method originally purposed by Levy and Sahli[45] in which a
flat faced tablet was mounted into an acrylic holder with the aid
of paraffin wax so that the only bottom face was exposed to the
dissolution medium. Later, Wood, Syarto, and Letterman[48]
described compression die assembly for used in rotational disk
dissolution studies. The drug to be studied is compressed in the
die hole. The assembly, served as the tablet holder is then
mounted in any desired rotational motor assembly and immersed in
the fluid in which dissolution is to be studied. For the initial
portions of the dissolution, the planar surface is still intact
and not subject to any erosive tendency.