Chapter IV

Bioavailability and Dissolution
4. Bioavailability and Dissolution

Bioavailability is a concept of pharmacology. It refers to the quantification of the rate or the extent to which a drug or the active ingredient/metabolite reaches at the site of action. In other words it is the fraction of an administered dosage that finally reaches the systemic circulation and accesses the site of action. It is one of the principal pharmacokinetic properties of drugs. By definition, when a particular medication is intravenously administered, its bioavailability is quantified as 100%. However, when a prescription is delivered by any of the other routes (such as orally), its bioavailability generally decreases (due to factors like incomplete absorption, first-pass metabolism, etc.).

For a drug, the bioavailability can be greatly affected and altered by properties of the dosage form, which could be influenced to an extent by its design and manufacture process\textsuperscript{1,2}.

4.1 Bioavailability

Absolute bioavailability refers to the bioavailability of the active ingredient in systemic circulation after non-intravenous administration (i.e., after oral, rectal, transdermal, subcutaneous, or sublingual administration), with the bioavailability of the same drug following intravenous administration. Thus, it is the fraction of the drug absorbed through non-intravenous administration compared with the corresponding intravenous administration of the same drug. The comparison must be dose normalized (e.g., account for different doses or varying weights of the subjects); consequently, the amount absorbed is corrected by dividing the corresponding dose administered.

In pharmacology, in order to determine absolute bioavailability of a drug, a pharmacokinetic study must be done to obtain a plasma drug concentration vs time plot for the drug after both intravenous (iv) and extravascular (non-intravenous, i.e., oral) administration. The absolute bioavailability is the dose-corrected area under curve (AUC) non-intravenous divided by AUC intravenous.

Relative bioavailability is a ratio of areas under the curves. IV, intravenous; PO, oral route. Relative bioavailability compares the bioavailability of the active drug in systemic circulation following non-intravenous administration (i.e., after oral, rectal, transdermal, subcutaneous, or sublingual administration), with the bioavailability of the same drug following intravenous administration. It is the fraction of the drug absorbed through non-intravenous administration
compared with the corresponding intravenous administration of the same drug. The comparison must be dose normalized (e.g., account for different doses or varying weights of the subjects); consequently, the amount absorbed is corrected by dividing the corresponding dose administered.

Figure 4-1: Calculation of Bioavailability

Therefore, a drug given by the intravenous route will have an absolute bioavailability of 100% ($f = 1$), whereas drugs given by other routes usually have the bioavailability of less than one. If we
compare the two different dosage forms having same active ingredients and compare the two drug bioavailability is called comparative bioavailability.

4.2 Bioequivalence

Differences in bioavailability of a given drug for different formulations do have clinical significance. Thus, whether different formulations of the same drug are equivalent or not is an essential parameter to be assessed. Chemical equivalence refers to the situation where the drug products possess the same active ingredient, in the same amount, while meeting the set official standards; however, the inactive excipients in drug products may vary. Bioequivalence, on the other hand, indicates that the drug products, when administered to the same patient, in the same dosage schedule, result in equivalent concentrations of the delivered drug in blood plasma and tissues. Therapeutic equivalence indicates that drug products, when given to the same patient in the same dosage regimen, have the same therapeutic as well as adverse effects.

The bioavailability (estimated as the AUC) of a formulation (A) of a certain drug when compared with another formulation (B) of the same drug, usually an established standard, or through administration via a different route to know if the formulation can be exchanged. Such a study is done to assess bioequivalence (BE) between two drug products. For FDA approval, a generic manufacturer must demonstrate that the 90% confidence interval for the ratio of the mean responses (usually of AUC and the maximum concentration, Cmax) of its product to that of the "Brand Name drug" is within the limits of 80% to 125%. While AUC refers to the extent of bioavailability, Cmax refers to the rate of bioavailability. When Tmax is given, it refers to the time it takes for a drug to reach Cmax.

4.3 Factors that influence bioavailability

The bioavailability of a drug, when administered by an extravascular route, is usually less than one (i.e., F <100%). Various physiological factors reduce the availability of drugs prior to their entry into the systemic circulation. Whether a drug is taken with or without food will also affect absorption, other drugs taken concurrently may alter absorption and first-pass metabolism, intestinal motility alters the dissolution of the drug and may affect the degree of chemical
degradation of the drug by intestinal microflora. Disease states affecting liver metabolism or gastrointestinal function will also have an effect.

4.3.1 *Route of administration*

Drugs given by intravenous route have 100% bioavailability. Exception includes prostaglandins, which are inactivated/metabolized in the lungs, therefore, their bioavailability may be zero after I/V injection. Those given by intramuscular route have bioavailability less than I/V route but more than subcutaneous route, while subcutaneous route has bioavailability more than the oral route. Only 10% of the dose of digoxin reaches systemic circulation after oral administration because of lack of absorption and bacterial metabolism within intestines. Even some of the drugs given by oral route may have 100% bioavailability but this is rare. By rectal route, half of the drug undergoes first pass metabolism.4

Factors affecting absorption may be classified as those related to the drug and those related to the body. They have been discussed separately. If absorbance is decreased, bioavailability is decreased and vice versa. For a drug to be readily absorbed, it must be hydrophobic yet have some solubility in aqueous solution.

4.3.2 *First pass metabolism*

Pre systemic metabolism en-route from the route of administration to the site of action is known as the first pass metabolism. Most common site of first pass metabolism is the liver because after absorption the drug administered by oral route enters the portal circulation to reach the liver. First pass metabolism may also occur in the intestines, lungs adrenals or any other organ. Drug undergoing first pass metabolism has low bioavailability, the dose must be adjusted keeping this in mind. If a person is undergoing a liver disease, bioavailability may be increased, because most drugs then enter systemic circulation in unchanged form. The dose must be decreased otherwise toxic effects might result.

4.3.3 *Chemical Instability*
Drug may be destroyed by the HCl or enzymes present in the GIT. Benzyl penicillin is not given orally because it is destroyed by HCl. Parenteral route is generally preferred.

4.3.4 *Food effect*

Food can change the BA of a drug and can influence the BE between test and reference products. Food effects on BA can have clinically significant consequences. Food can alter BA by various means, including

- Delay gastric emptying
- Stimulate bile flow
- Change gastrointestinal (GI) pH
- Increase splanchnic blood flow
- Change luminal metabolism of a drug substance
- Physically or chemically interact with a dosage form or a drug substance

Food effects on BA are generally greatest when the drug product is administered shortly after a meal is ingested. The nutrient and caloric contents of the meal, the meal volume, and the meal temperature can cause physiological changes in the GI tract in a way that affects drug product transit time, luminal dissolution, drug permeability, and systemic availability. In general, meals that are high in total calories and fat content are more likely to affect the GI physiology and thereby result in a larger effect on the BA of a drug substance or drug product. We recommend use of high-calorie and high-fat meals during food-effect BA and fed BE studies.

Food Effects on Drug Products Administration of a drug product with food may change the BA by affecting either the drug substance or the drug product. In practice, it is difficult to determine the exact mechanism by which food changes the BA of a drug product without performing specific mechanistic studies. Important food effects on BA are least likely to occur with many rapidly dissolving, immediate release drug products containing highly soluble and highly permeable drug substances (BCS Class I) because absorption of the drug substances in Class I is usually pH- and site-independent and thus insensitive to differences in dissolution.
4.4 Causes of low bioavailability

Orally administered drugs must pass through the intestinal wall and then the portal circulation to the liver; both are common sites of first-pass metabolism (metabolism that occurs before a drug reaches systemic circulation). Thus, many drugs may be metabolized before adequate plasma concentrations are reached. Low bioavailability is most common with oral dosage forms of poorly water-soluble, slowly absorbed drugs. Insufficient time for absorption in the GI tract is a common cause of low bioavailability. If the drug does not dissolve readily or cannot penetrate the epithelial membrane (eg, if it is highly ionized and polar), time at the absorption site may be insufficient. In such cases, bioavailability tends to be highly variable as well as low.

Chemical reactions that reduce absorption can decrease bioavailability. They include formation of a complex (eg, between tetracycline and polyvalent metal ions), hydrolysis by gastric acid or digestive enzymes (eg, penicillin and chloramphenicol palmitate hydrolysis), conjugation in the intestinal wall (eg, sulfoconjugation of isoproterenol), adsorption to other drugs (eg, digoxin to cholestyramine), and metabolism by luminal microflora. Low bioavailability is most common with oral dosage forms of poorly water-soluble, slowly absorbed drugs. Solid drugs need to dissolve before they are exposed to be absorbed. If the drug does not dissolve readily or cannot penetrate the epithelial membrane (eg, if it is highly ionized and polar), time at the absorption site may be insufficient. In such cases, bioavailability tends to be highly variable as well as low. Age, sex, physical activity, genetic phenotype, stress, disorders (eg, achlorhydria, malabsorption syndromes), or previous GI surgery (eg, bariatric surgery) can also affect drug bioavailability.
4.5 Improvement of Bioavailability

Improvement of bioavailability of poorly water soluble drug remains one of the most challenging aspects of drug development. By many estimates up to 40% of new chemical entities discovered by the pharmaceutical industry today are poorly water soluble compounds. Together with the permeability, the solubility behavior of a drug is a key determinant of its bioavailability. There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Examples are griseofulvin, digoxin, sulphathiazole etc. With the recent arrival of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble compounds for delivery now presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry.

A fundamental step in the solubilization of drug compound is the selection of an appropriate salt form, or for liquid drugs, adjustment of pH of the solution. Traditional approaches to drug solubilization include either chemical or mechanical modification of the drug molecule, or physically altering the macromolecular characteristics of aggregated drug particles. Improvement of bioavailability can be obtained by following measures:

- Addition of solubilizing excipients
- Inclusion complexes
- Polymorphism
- Lipid-based emulsion systems
- Salt form
- Solid dispersions
- Particle size reduction etc.

4.6 Importance of Solubility

Solubility also plays a major role for other dosage forms like parenteral formulations as well. Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response. Poorly water soluble drugs often
require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations. Most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility.

Poorly water soluble drugs having slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. For orally administered drugs solubility is the most important one rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Problem of solubility is a major challenge for formulation scientist.

The improvement of drug solubility thereby its oral bio-availability remains one of the most challenging aspects of drug development process especially for oral-drug delivery system. There are numerous approaches available and reported in literature to enhance the solubility of poorly water-soluble drugs. The techniques are chosen on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be selected, and nature of intended dosage form.

As for BCS class II drugs rate limiting step is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so increasing the solubility in turn increases the bioavailability for BCS class II drugs.

The negative effect of compounds with low solubility include poor absorption and bioavailability, insufficient solubility for IV dosing, development challenges leading to increasing the development cost and time, burden shifted to patient (frequent high-dose administration).

3. Techniques for Solubility Enhancement

Solubility improvement techniques can be categorized into physical modification, chemical modifications of the drug substance, and other techniques.
**Physical Modifications**

Particle size reduction like micronization and nanosuspension, modification of the crystal habit like polymorphs, amorphous form and cocrystallization, drug dispersion in carriers like eutectic mixtures, solid dispersions, solid solutions and cryogenic techniques.

**Chemical Modifications**

Change of pH, use of buffer, derivatization, complexation, and salt formation.

**Miscellaneous Methods**

Supercritical fluid process, use of adjuvant like surfactant, solubilizers, cosolvency, hydrotrophy, and novel excipients

**Particle Size Reduction**

The solubility of drug is often intrinsically related to drug particle size; as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows greater interaction with the solvent which causes an increase in solubility. 6. Dissolution

**4.7 Dissolution**

The dissolution rate was first modeled using Fick’s second law of diffusion and the concentration gradient of the solute. This led to the following Noyes Whitney first-order equation:

\[
\frac{dc}{dt} = k(C_s - C_T)
\]

where \( \frac{dc}{dt} \) refers to the dissolution rate of the substance in terms of concentration, and \( k \) is a dissolution constant.

Most of the drugs are administered to the patient in the solid state, e.g., in the form of compressed tablets containing crystalline drug. Upon contact with aqueous based media in the body, the drugs have to dissolve in them, cross various membrane barriers that exist in the living organism finally reach out to the target sites of action. Significantly, the diffusional mass transport plays a predominant role for overcoming major obstacles, e.g., the mucosa in the gastrointestinal tract. Fick was the first to quantify diffusional mass transport. It is a phenomenon of fundamental importance for several processes in the human body and in nature in
Diffusion refers to the spontaneous transport of constituents from regions of higher concentration to regions of lower concentration. The basic driving force for this phenomenon is thermal agitation of the molecules of the solvent. Only dissolved (individualized) particles (molecules/ions/atoms) can diffuse (but not micro/macro-sized drug crystals or amorphous particles). Thus, if a drug exhibits very low solubility in water and/or if its dissolution rate at the site of administration is very low, only minor amounts of drug become available for diffusion. This might result in insufficient drug concentrations at the site of action (e.g. a receptor in the brain) and the failure of the treatment in vivo, despite a potentially ideal chemical structure of the drug to interact with its target site. A better understanding of the physico-chemical reasons for poor aqueous solubility and/or very low dissolution rates can be very helpful in such cases to overcome crucial hurdles. Thus, quantitative and mechanistically realistic mathematical modeling of the process of drug dissolution can be highly beneficial.

Figure 4-2: Flow Chart highlighting the role of dissolution and permeability for the bioavailability of solid drug particles.
In the most common situation, an oral dosage form is ingested and passes through the esophagus to the stomach. The rate of dissolution is a key target for controlling the duration of a drug’s effect, and as such, several dosage forms that contain the same active ingredient may be available, differing only in the rate of dissolution. If a drug is supplied in a form that is not readily dissolved, the drug may be released more gradually over time with a longer duration of action. Having a longer duration of action may improve compliance since the medication will not have to be taken as often. Additionally, slow-release dosage forms may maintain concentrations within an acceptable therapeutic range over a long period of time, as opposed is quick-release dosage forms which may result in sharper peaks and troughs in serum concentrations.

As can be inferred by the Noyes-Whitney equation, the rate of dissolution may be modified primarily by altering the surface area of the solid. The surface area may be adjusted by altering the particle size (e.g. micronization). For many drugs, reducing the particle size leads to a reduction in the dose that is required to achieve the same therapeutic effect. However, it should be noted that although the reduction of particle size increases the specific surface area and the dissolution rate, it does not affect solubility.

The rate of dissolution may also be altered by choosing a suitable polymorph of a compound. Different polymorphs exhibit different solubility and dissolution rate characteristics. Specifically, crystalline forms dissolve slower than amorphous forms, since crystalline forms require more energy to leave lattice during dissolution. The most stable crystalline polymorph has the lowest dissolution rate. Dissolution is also different for anhydrous and hydrous forms of a drug. Anhydrous often dissolve faster than hydrated; however, anhydrous forms sometimes exhibit lower solubility.
The term “dissolution” describes the mixing of the two phases, resulting in the formation of a new homogeneous phase: the “solution. In the case of a solid drug particle, which dissolves in an aqueous body fluid, one of the phases is the drug (e.g. in the form of crystal or amorphous particle), and the other phase is an aqueous.

During this process of mixing (“drug dissolution”) different physical phenomena occur, generally the following 5 major steps:

(a) The surface of the drug particle is wetted with water.

(b) Solid state bonds in the drug particle are broken down (e.g. attractive electrostatic forces in a drug crystal consisting of cations and anions).

(c) Individualized drug molecules/ions/atoms are surrounded by a shell of water molecules (“solvation”).

(d) The individualized drug molecules/ions/atoms diffuse from the surface of the drug particle through the liquid, unstirred boundary layer surrounding the system into the well-stirred bulk fluid. It has to be pointed out that even in thoroughly stirred aqueous liquids thin unstirred boundary layers exist directly at the surfaces of the drug particles (due to adhesional forces). The thickness of these boundary layers is a function of the degree of agitation.
(e) If the surrounding bulk fluid is well-stirred, the drug molecules/ions/atoms are transported by convection in the liquid, which is not part of the unstirred boundary layer: The mass flow created by stirring assures rapid movement of water and drug molecules. This type of mass transport is fundamentally different from the diffusional mass transport mentioned above:

Diffusion occurs also in non-agitated fluids and results from the thermal agitation of the solvent molecules (here water). It has to be pointed out that these processes occur in a series.

Thus, if one of these steps is much slower than all the other steps, the rapid processes can be neglected for the quantification of the overall process rate (here drug dissolution rate). The mathematical treatment can be restricted to the slowest mass transport step only. This can lead to very simple mathematical equations allowing to accurately quantify a rather complex phenomenon.

The “dissolution rate” of a drug in a liquid is generally defined as the change in the concentration of dissolved drug (individualized drug molecules/ions/atoms), $dc$, in the time interval $dt$: dissolution rate $= \frac{dc}{dt}$

Dissolution rate of a solid can be defined as the rate at which the solute is broken down to individual ions, atoms or molecules to finally form a homogenous phase with the solvent. It is described by the Noyes-Whitney equation as:

$$\frac{dm}{dt} = A \frac{D}{\delta} (C_s - C_{bulk}) \quad (1)$$

$m$ – Mass of the drug

$A$ – Surface area of the interface between the dissolving substance and the solvent, $m^2$;

$D$ – Diffusion coefficient, $m^2/s$;

$\delta$ - Thickness of the boundary layer of the solvent at the surface of the dissolving substance, $m$;

$C_s$ – Solubility, $kg/m^3$

$C_{bulk}$ – concentration of the substance in the bulk of the solvent, $kg/m^3$
Often ‘\(AD/\delta\)’ in the equation (1) is defined as the ‘dissolution constant’ (\(k\)). The surface area (‘\(A\’) in the equation) is directly related to \(k\). The rate of the solvent that freshly comes in contact with surface area of the solid depends on factors like particle size and shape of the solid, and density of the medium. A common observation consistent with experiments with many pharmaceutical preparations is that as the particle size of the solid decreases the dissolution increases. By encapsulating the drug particles in hydrophilic polymeric nanoparticles, apart from preventing the particles from agglomeration, we would also be increasing the surface area of interphase between the dissolving surface and the medium (\(A\) in the equation 1), and Solubility (\(C_s\)) since drug is incorporated in the hydrophilic polymer.

According to the Prandtl boundary layer equation\(^{22}\) for flow passing a flat surface, the hydrodynamic boundary layer thickness (\(h_H\)) can be expressed as follows:

\[
h_H = k \sqrt{\frac{L}{V}} \tag{2}
\]

where \(L\) is the length of the surface in the direction of flow, \(k\) denotes a constant and \(V\) is the relative velocity of the flowing liquid against the flat surface.

It was established\(^{16}\) that the diameter of the particle affects the parameter \(L\) in the above equation. Generally, for solid particles dispersed in a liquid by an agitating force, a decrease in particle size leads to a decrease in both \(L\) and \(V\). So, though the two parameters (\(L\) and \(V\)) counteract each other, it was realized\(^{16}\) that the net effect was the thinning of the hydrodynamic layer associated with the solid particles and a consequent increase in the dissolution rate. This effect becomes more prominent for substances with a mean particle size less than 5 \(\mu m\)\(^{22}\). It can be, thus, hypothesized that reduction in particle size to nanoscale dimensions can render the boundary layer still thinner and hence the dissolution rate would be enhanced. Hence, particle size reduction also results in an increase of the dissolution rate of a sparingly soluble material by decreasing the thickness of the diffusion layer around each particle.

Dissolution of a crystalline solid has been established as an energy-driven\(^{23,24}\) process in contrast to a passive one. Each step in dissolution requires a particular amount of energy for completion.
The ultimate aim of all drug solubilization procedures is to by and large minimize the overall energy required to completely dissolve the drug. The chemical nature and microstructure of the solute and solvent along with the system conditions determine the overall kinetics of the dissolution process. Therefore, increase in surface area was not the only reason for increase in dissolution with reduction in particle size. There were other consequences like increase in the surface energy of the particles as well.

The dissolution rate of a normal crystalline drug (solid) in a dissolution medium can be increased by reducing the particles to nanostructures characterized by nanoscale (short range) periodicity. However, in that highly disordered phase, the drug is metastable and spontaneously re-crystallizes. The corresponding and in fact, more critical issue of drug solubilization is that these unstable (metastable) drug phases must be “frozen” in a physically and chemically time-stable dosage form.

Looking at the equation 1, it becomes obvious that the possible strategies to be charted out to increase the dissolution rate of a drug (e.g. to increase the oral bioavailability in case of poor aqueous solubility), are:

(1) The surface area accessible for dissolution ought to be amplified. This can be achieved by decreasing the particle size.

(2) The drug solubility should be increased, e.g. by dispersing the drug in a high energy form with reduced crystallinity and long term stability or by addition of surfactants and/or hydrophilic/surface active carriers.

(3) The concentration of dissolved drug in the bulk of the dissolution fluid should be kept low, e.g. by enabling the consequent drug transport away from its site of dissolution.

(4) The thickness of the liquid, unstirred boundary layer should be decreased, e.g. by increasing the degree of agitation of the surrounding bulk fluid. However, in practice this is generally not possible in the human body.

(5) The diffusion coefficient of the drug in the liquid unstirred boundary layer should be increased, e.g. by decreasing the viscosity of the surrounding bulk fluid. However, again, in practice this is generally not possible in the human body.
### 4.8 Factors Influencing Dissolution

1. The solubility of the drug will influence the rate of dissolution by determining the magnitude of the drug’s concentration gradient ($C_s - C_t$).

2. Crystal morphology dictates the rate of dissolution along the different crystallographic axes. This dissolution anisotropy can be found in all but cubic crystals, which are isotropic.

3. Crystal defects and imperfections influence the crystal lattice energy. These defects, including dislocations, give rise to increased surface energy and may be a major factor in improving dissolution performance of poorly water-soluble, crystalline substances.

4. Polymorphism, where solute molecules crystallize in more than one form, with the polymorphs possessing different energies, will most likely give rise to different dissolution and solubility profiles. Polymorphs that have greater thermodynamic activity will dissolve faster than more stable ones, and this property has been exploited in the pharmaceutical industry in an attempt to increase therapeutic blood levels of insoluble or sparingly soluble drugs. In some instances, new polymorphs have been observed following size reduction processes.

5. Impurities (including surfactants, hydrates, solvates, complexes, and reactive additives) can greatly influence the rate of dissolution by modifying the crystal habit or by interfering with the interfacial transport of solute from the crystal to the bulk solution.

6. Physicochemical properties, such as density, viscosity, and wettability, influence ensemble properties (flocculation and agglomeration), which in turn influence dissolution by perturbing the effective specific surface area.

The hydrophilic polymers are easily wetted by water\textsuperscript{26} and thus they could be quickly dissolved exposing the drug particles. The drug particles, in the polymer nanoparticles, would be in high energy nanocrystalline state and hence can easily and quickly be released into the medium and subsequently dissolved. Another factor influencing the release rate of the drug is the swelling ability of the polymer in presence of the aqueous medium. As the polymer matrix swells in the medium, the solvent (here water) gushes into the matrix and the drug could get released into the aqueous medium. Polymeric gels for drug delivery are being employed based on this swelling ability of polymers\textsuperscript{27}. 
4.9 Bioavailability Enhancement

During last 20 years a new technology, reducing drug particle size, has been developed to increase drug dissolution rate. According to Noyes–Whitney equation, drugs with smaller particle size have enlarged surface areas which lead to increase dissolution velocity. Higher the dissolution rate together with the resulting higher concentration gradient between gastrointestinal lumen and systemic circulation could further increase oral bioavailability of drugs.11 Nanoformualtions refer a submicron sized dispersion of drug particles which may be stabilized by carriers/surfactants.

In nanosuspension technology, the drug is maintained in the required crystalline state with reduced particle size, leading to an increased dissolution rate and therefore improved bioavailability. An increase in the dissolution rate of micronized particles (particle size < 10 μm) is related to an increase in the surface area and consequently the dissolution velocity.

Nanosized particles can increase solution velocity and saturation solubility because of the vapor pressure effect. In addition; the diffusional distance on the surface of drug nanoparticles is decreased, thus leading to an increased concentration gradient. Increase in surface area as well as concentration gradient lead to a much more pronounced increase in the dissolution velocity as compared to a micronized product. Another possible explanation for the increased saturation solubility is the creation of high energy surfaces when disrupting the more or less ideal drug microcrystals to nanoparticles.

Increased efforts from academic and industrial researchers have pushed the understanding of drug-polymer interaction in aqueous media. The general solubilization mechanism of nanoformulations is the so called “spring and parachute” concept. The drug first dissolves along with the soluble polymer matrix to generate a supersaturated solution (spring) followed by decline in drug concentration in the media due to either absorption or precipitation (parachute) as shown in Figure 4-4.
4.10 Release Kinetics Modeling

Model dependent methods are based on different mathematical functions, which describe the dissolution profile. Once a suitable function has been selected, the dissolution profiles are evaluated depending on the derived model parameters. In order to determine the suitable drug release kinetic model describing the dissolution profile in non-linear regression analysis the Quasi-Newton and Simplex methods minimized the least squares. The model dependent approaches included zero order, first order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas, regression models.

Zero-order model

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:
\[ Q_0 - Q_t = K_0 t \]  
(3)

Rearrangement of equation (3) yields:

\[ Q_0 + Q_t = K_0 t \]  
(4)

where \( Q_t \) is the amount of drug dissolved in time \( t \), \( Q_0 \) is the initial amount of drug in the solution (most times, \( Q_0 = 0 \)) and \( K_0 \) is the zero order release constant expressed in units of concentration/time. To study the release kinetics, data obtained from \textit{in vitro} drug release studies were plotted as cumulative amount of drug released \textit{versus} time \(^{12,31}\).

Application: This relationship can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low soluble drugs in coated forms, osmotic systems, etc. (26, 27).

**First order model**

This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis. The release of the drug which followed first order kinetics can be expressed by the equation:

\[ \frac{dC}{dT} = -Kc \]  
(5)

where \( K \) is first order rate constant expressed in units of time \(^{-1}\).

Equation (5) can be expressed as:

\[ \log C = \log C_0 - Kt/2.303 \]  
(6)

where \( C_0 \) is the initial concentration of drug, \( K \) is the first order rate constant, and \( t \) is the time. The data obtained are plotted as log cumulative percentage of drug remaining vs. time which would yield a straight line with a slope of \(-K/2.303\).

Application: This relationship can be used to describe the drug dissolution in pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices\(^{32,33}\).
**Higuchi model**

The first example of a mathematical model aimed to describe drug release from a matrix system was proposed by Higuchi in 1961. Initially conceived for planar systems, it was then extended to different geometrics and porous systems. This model is based on the hypotheses that (i) initial drug concentration in the matrix is much higher than drug solubility; (ii) drug diffusion takes place only in one dimension (edge effect must be negligible); (iii) drug particles are much smaller than system thickness; (iv) matrix swelling and dissolution are negligible; (v) drug diffusivity is constant; and (vi) perfect sink conditions are always attained in the release environment. Accordingly, model expression is given by the equation:

\[ F_t = Q = A \sqrt{D(2C - C_s)C_s t} \quad (7) \]

where \( Q \) is the amount of drug released in time \( t \) per unit area \( A \), \( C \) is the drug initial concentration, \( C_s \) is the drug solubility in the matrix media and \( D \) is the diffusivity of the drug molecules (diffusion coefficient) in the matrix substance. This relation is valid during all the time, except when the total depletion of the drug in the therapeutic system is achieved.

**Korsmeyer-Peppas model**

Korsmeyer et al. derived a simple relationship which described drug release from a polymeric system equation. To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer-Peppas model.

\[ M_t - M_\infty = K t^n \quad (8) \]

where \( M_t \) / \( M_\infty \) is a fraction of drug released at time \( t \), \( k \) is the release rate constant and \( n \) is the release exponent. The \( n \) value is used to characterize different release for cylindrical shaped matrices. In this model, the value of \( n \) characterizes the release mechanism of drug as described in Table 1. For the case of cylindrical tablets, \( 0.45 \leq n \) corresponds to a Fickian diffusion mechanism, \( 0.45 < n < 0.89 \) to non-Fickian transport, \( n = 0.89 \) to Case II (relaxational) transport, and \( n > 0.89 \)
to super case II transport\textsuperscript{36,33,37}. To find out the exponent of $n$ the portion of the release curve, where $M_t / M_\infty < 0.6$ should only be used\textsuperscript{38}. To study the release kinetics, data obtained from \textit{in vitro} drug release studies were plotted as log cumulative percentage drug release versus log time.

### 4.11 References


23. Joshi, V. Y. & Sawant, M. R. Study on Dissolution Rate Enhancement of Poorly Water


