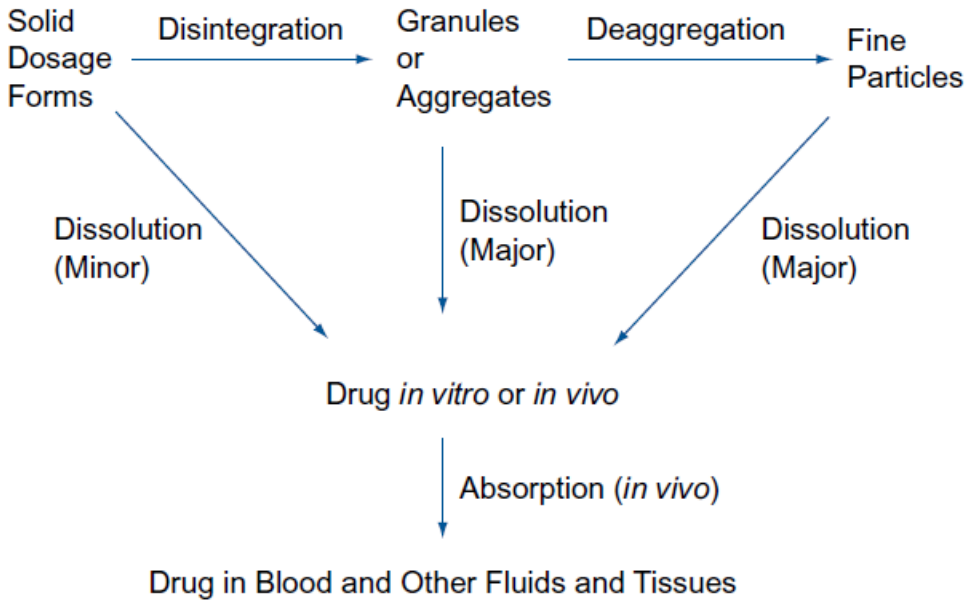
Dissolution

Dissolution is defined as the process by which solid substances enters in solvent to yield a solution. Stated simply, dissolution is the process by which a solid substance dissolves.
Fundamentally, it is controlled by the affinity between the solid substance and the solvent. The physical characteristics of the dosage form, the wettability of the dosage unit, the penetration ability of the dissolution medium, the swelling process, the disintegration, and the deaggregation of the dosage forms are a few of the factors that influence the dissolution characteristics of drugs, figure below show the processes involved in the dissolution of solid dosage forms.



A number of studies conducted, especially in the United States, confirmed the significance of dissolution- bioavailability relationship in the pharmaceutical product development.

Although considerable efforts were made to establish *in vitro/in vivo* correlations between release of drug from the formulation and drug absorption, the limited knowledge of the complex composition and hydrodynamics of the gastrointestinal fluids remains a real barrier.

In spite of the reported success of several *in vitro/in vivo* correlation studies, dissolution cannot be relied upon as a predictor of therapeutic efficiency. Rather, it is a qualitative tool that can provide valuable information about the biological availability of a drug, as well as batch-to-batch consistency. Another area of difficulty is the accuracy and precision of the testing procedure, which is dependent, to a large extent, on the strict observance of so many subtle parameters and detailed operational controls.

Dissolution is considered, today, as one of the most important quality control procedures performed on pharmaceutical dosage forms, and dissolution studies have become an essential part of drug applications to regulatory bodies worldwide. Whether or not it has been correlated with biological effectiveness, the standard dissolution test is a simple and inexpensive indicator of a product's physical consistency.
If one batch differs from the other in its dissolution characteristics or if the dissolution profiles of the production batches show a consistent trend upwards or downwards, it sounds a sure warning that some factor in the raw material, formulation, or process is out of control.
Additionally, dissolution data seems to be a useful tool in the early stages of drug development and molecular manipulation.

Carstensen proposed a scheme incorporating the following sequence:

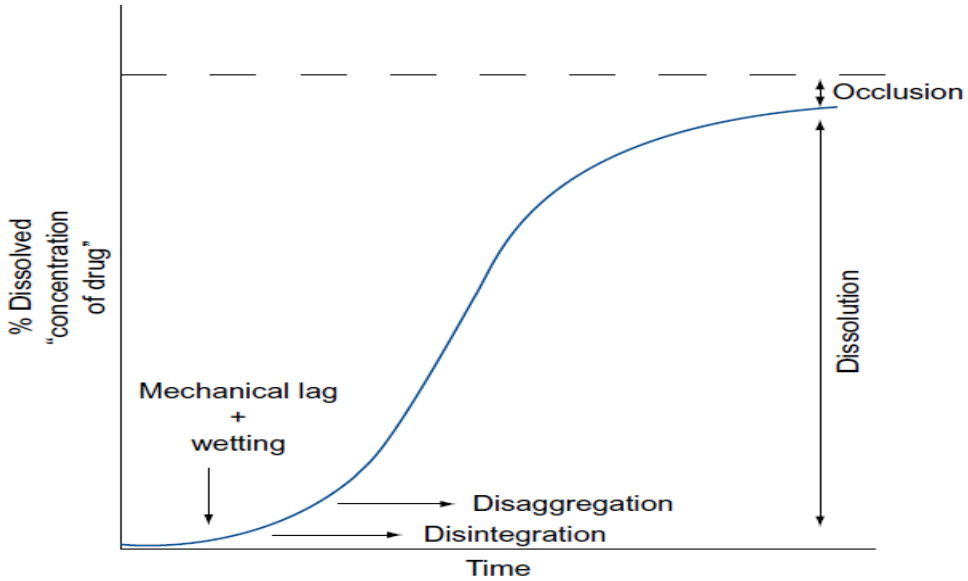
1. Initial mechanical lag.
2. Wetting of the dosage form.
3. Penetration of the dissolution medium into the dosage form.
4. Disintegration.
5. Deaggregation of the dosage form and dislodgement of the granules.
6. Dissolution and occlusion of some particles of the drug.

Carstensen explained that the wetting of the solid dosage form surface controls the liquid access to the solid surface and, many times, is the limiting factor in the dissolution process.
The speed of wetting directly depends on the surface tension at the interface (interfacial tension) and upon the contact angle between the solid surface and the liquid.

Generally, a contact angle of more than 90° indicates poor wettability. Incorporation of a surfactant, either in the formulation or in the dissolution medium, lowers the contact angle and enhances dissolution. Also, the presence of air in the dissolution medium causes the air bubbles to be entrapped in the tablet pores and act as a barrier at the interface. For capsules, the gelatin shell is extremely hydrophilic, and, therefore, no problems in wettability exist for the dosage itself, although it may exist for the powders inside.

After the solid dosage form disintegrates into granules or aggregates, penetration characteristics play a prime role in the deaggregation process. Hydrophobic lubricants, such as talc and magnesium stearate, commonly employed in tablet and capsule formulations, slow the penetration rate and, hence, the deaggregation process.

A large pore size facilitates the penetration but, if it is too large, it may inhibit penetration by decreasing the internal strain caused by the swelling of the disintegrant. After deaggregation and dislodgment occur, the drug particles become exposed to the dissolution medium and dissolution proceeds. This figure graphically presents the model proposed by Carstensen.



It is apparent from figure that the rate of dissolution of the drug can become a rate-limiting step before it appears in the blood. However, when the dosage form is placed into the gastrointestinal tract in solid form, there are two possibilities for the rate-limiting step.

The solid must first dissolve, and the drug in solution must then pass through the gastrointestinal (GI) membrane. Freely water-soluble drugs tend to dissolve rapidly, making the passive diffusion of the drug or the active transport of the drug rate-limiting step for absorption through the GI membrane. Conversely, the rate of absorption of poorly water-soluble drugs will be limited by the rate of dissolution of the undissolved drug or disintegration of dosage form.

The rate of dissolution of drug substance is determined by the rate at which solvent-solute forces of attraction overcome the cohesive forces present in the solid. This process is rate limiting, when the release of solute into solution is slow and the transport into the bulk solution is fast. In this case, the dissolution is said to be interfacially controlled.

Dissolution may also be diffusion controlled, where the solvent-solute interaction is fast, compared to transport of solute into the bulk solution. In diffusion-controlled process, a stationary layer of solute adjacent to the solid/liquid interface is postulated and is commonly referred to as the diffusion layer. The saturation concentration of solute develops at the interface and decreases with distance across the diffusion layer.

Mathematics of dissolution:

It has long been recognized that the release of the active drug from a drug product may be greatly influenced by the physicochemical properties of the drug, as well as the dosage form.

The availability of the drug is usually determined by the rate of release of the drug from the physical system (dosage form). The release of the drug from its dosage form is usually determined by the rate at which it dissolves in the surrounding medium. The rate of dissolution of a chemical or drug from the solid state is defined as the amount of drug substance that goes into solution per unit time under standardized condition of liquid/solid interface, temperature, and solvent composition.

In biopharmaceutics, rate of dissolution usually refers to the rate at which the drug dissolves from an intact dosage form or from fragments or particles from the dosage form during the test.

Intrinsic dissolution:

The rate of dissolution of a pure pharmaceutical active ingredient, when conditions, such as surface area, temperature, agitation or stirring speed, pH, and ionic strength of the dissolution medium is kept constant, is known as intrinsic dissolution rate. This parameter allows the screening of the drug candidates and aids in understanding their solution behavior under various bio-physiological conditions.

Intrinsic dissolution rate constants:

The rate at which a substance dissolves in a liquid to form a solution is governed by physical parameters, such as the surface area of the substance at a given time during the process of dissolution, the shape of the substance, the characteristics of the solid/ liquid interface, and the solubility of the substance in the liquid.

Hence, dissolution can be considered a specific type of certain heterogeneous reaction, which results in a mass transfer as a net effect between the escape and deposition of solute molecules at a solid surface. Mathematically, the process can be simply described as follows:

$$dM/dt = KA(C_s - C)$$

Where:

M is the mass of the substance remaining to be dissolved,

A is the surface area exposed to the dissolution medium,

Cs is the saturation concentration referred to as solubility in the dissolution medium,

C is the amount dissolved or the concentration of the drug in solution at time t,

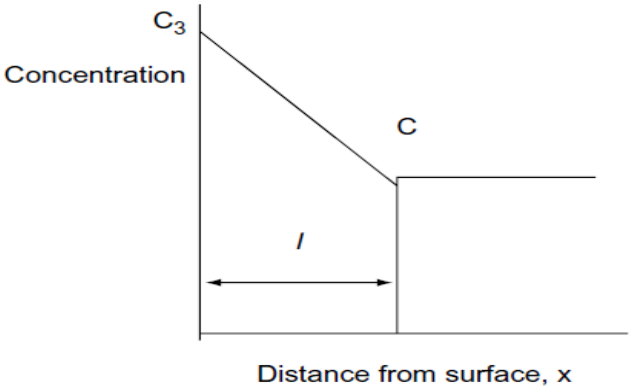
and K is the dissolution rate constant.

$$dM/dt = KAC_s$$

This equation is commonly referred to as a sink-condition equation, which implies that sink conditions exist during the process of dissolution.

When the process of dissolution takes place under sink conditions, a stagnant film of liquid (dissolution medium) is adsorbed onto the solid, the thickness of this film being l cm. The liquid in the film in direct contact with the solid is saturated with drug in solution. The concentration of the drug in solution then drops as the distance from the dissolving solid surface increases.

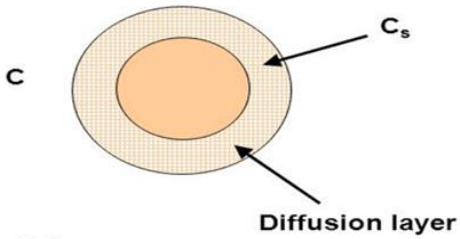
At the end of the film, l cm from the surface, the concentration in the film is the same as that in the bulk solution, Cb. The driving force behind the movement of solute molecules through the stagnant film is the concentration gradient that exists between the saturation concentration of the solute, Cs, in the stagnant layer at the surface of the solid and its concentration on the farthest side of the stagnant film, Cb.



Factors affecting dissolution and solubility:

Noyes-Whitney equation

$$\frac{dC}{dt} = \frac{D \cdot A(C_s - C)}{h}$$



dC/dt: the rate of dissolution of the drug particles

D: the diffusion coefficient of the drug in solution in the gastrointestinal fluids

A: the effective surface area of the drug particles in contact with the gastrointestinal fluids

h: the thickness of the diffusion layer around each drug particle

Cs: the saturation solubility of the drug in solution in the diffusion layer

C: the concentration of the drug in the gastrointestinal fluids

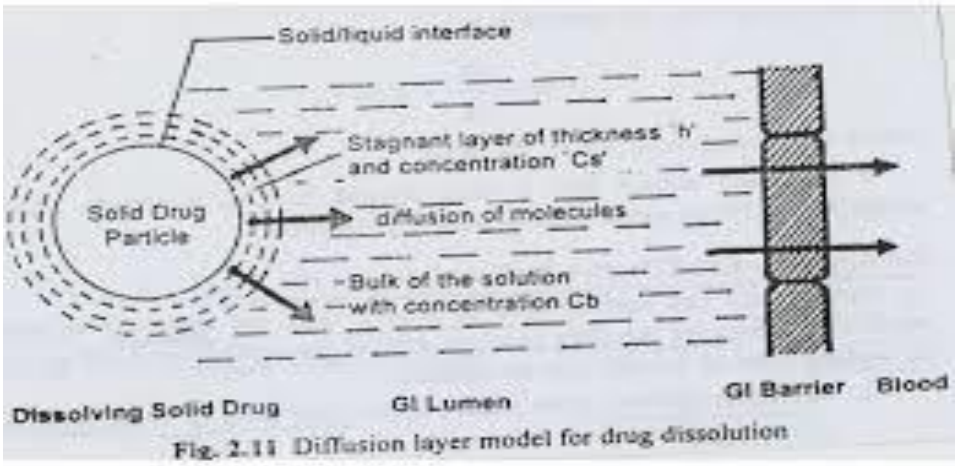


Fig. 2.11 Diffusion layer model for drug dissolution

Factors affecting the rate of dissolution:

The dissolution rate data can be meaningful, only if the results of successive test on the same dosage form are consistent within reason. The dissolution test should yield reproducible result, even when it is performed in different laboratories or with different personnel.

To achieve high reproducibility, all variables that influence the test should be clearly understood and possibly controlled.

Factors affecting the dissolution rate of drugs from a dosage form include:

1. Factors related to the physicochemical properties of the drug
2. Factors related to drug product formulation
3. Factors related to dissolution test parameters
4. Miscellaneous factors

Factors Related to the Physicochemical Properties of the Drug

Effect of solubility on dissolution

The physicochemical properties of the drug substance play a prime role in controlling its dissolution from the dosage form. The modified Noyes and Whitney equation shows that the aqueous solubility of the drug is the major factor determining its dissolution rate. Actually, some studies show that drug-solubility data could be used as a rough predictor of the possibility of any future problems with bioavailability, a factor that should be taken into consideration in the formulation design.

Effect of particle size on dissolution

The dissolution rate is directly proportional to the surface area of the drug. Since the surface area increases with the decreasing particle size, higher dissolution rates may be achieved through the reduction of the particle size.

It is important to recognize the fact that it is the effective surface area that has to be increased. The effective surface area is the surface area available to the dissolution fluid. If the drug is hydrophobic and the dissolution medium has poor wetting properties, reduction of particle size may lead to decreased effective surface area and, hence, a "slower" rate of dissolution.

Effect of solid phase characteristics of the drug on dissolution

Amorphicity and crystallinity, the two important solid phase characteristics of drugs affect their dissolution profile. Numerous studies have demonstrated that the amorphous form of a drug usually exhibits greater solubility and higher dissolution rates, as compared to that exhibited by the crystalline form.

Chloramphenicol palmitate is one example that exists in at least two polymorphs. The B form is apparently more bioavailable. The recommendation might be that manufacturers should use polymorph B for maximum absorption.

Effect of Polymorphism on Dissolution

Polymorphic forms of drugs have been shown to influence changes in solubilizing characteristics and, thus, the dissolution rate of the drug in question. Numerous reports have shown that polymorphism and the state of hydration, solvation, and/or complexation markedly influence the dissolution characteristics of the drug. The drugs that exhibit influence on the dissolution behavior include tolbutamide, chloramphenicol, and others.

Factors Related to Drug Product Formulation

It has been shown that the dissolution rate of a pure drug can be altered significantly when mixed with various excipients during the manufacturing process of solid dosage forms. These excipients are added to satisfy certain pharmaceutical functions, such as diluents (fillers), dyes, binders, granulating agents, disintegrants, and lubricants. Generically identical tablet and capsule products, manufactured by different pharmaceutical manufacturers, were found to exhibit significant differences in dissolution rates for their active ingredients.

Effect of Granulating Agents and Binders

Phenobarbital tablets, granulated with gelatin solution, provide faster dissolution rate in gastric fluid than those prepared using sodium carboxymethylcellulose or polyethylene glycol 6000 as a binder. This observation was attributed to the fact that gelatin imparts hydrophilic characteristics to the hydrophobic drug surface, whereas PEG 6000 forms complex with poor solubility, and sodium carboxymethylcellulose is converted to its less soluble acid form at low pH of the gastric fluid.

Effect of Disintegrants and Diluents

The type and amount of disintegrating agent employed in the formulation significantly controls the overall rate of dissolution of dosage form. The effect on the dissolution rate of tablets by the addition of disintegrants, before and after granulation, was assessed. When added before granulation, they will slow dissolution rate. However, when added after granulation, did not result in lowering the dissolution rate.

The effect of starch, the most commonly used diluent, on the rate of dissolution of salicylic acid tablets manufactured by the dry, double-compression process. Increasing the starch content from 5% to 20% resulted in a dramatic increase in the dissolution rate, almost three-fold. This was attributed to better and more thorough disintegration. It suggested that the hydrophobic drug crystals acquire a surface layer of fine starch particles that imparts a hydrophilic property to the granular formulation and, thereby, increases the effective surface area and, hence, the dissolution rate.

Effects of Lubricants

The nature, quality, and quantity of lubricants added can affect the dissolution rate. The effect of various lubricants on dissolution rate of salicylic acid was studied, and it was concluded that magnesium stearate, a hydrophobic lubricant, tends to retard the dissolution rate of salicylic acid tablets, whereas sodium lauryl sulfate enhances dissolution, due to its hydrophilic character combined with surface activity, which increases the microenvironment pH surrounding the weak acid and increases wetting, and better solvent penetration into the tablets.

Effect of lubricants on the dissolution rate of drugs from dosage form depends on properties of the granules, the lubricant itself, and the amount of lubricant used.

If granules are hydrophilic and fast disintegrating, a water-soluble surface-active lubricant will have an insignificant effect ovbn the dissolution.

Conversely, if the granules are hydrophobic, the surface-active lubricant will enhance dissolution. It was also found that hydrophobic lubricants, such as magnesium stearate, aluminum stearate, stearic acid, and talc, decrease the effective drug-solvent interfacial area by changing the surface characteristics of the tablets, which results in reducing its wettability, prolonging its disintegration time, and decreasing the area of the interface between the active ingredient and solvent.

Factors Related to the Dissolution Test Parameters

Method of Granulation

Wet granulation has been shown to improve the dissolution rates of poorly soluble drugs by imparting hydrophilic properties to the surface of the granules.

Additionally, the use of fillers and diluents, such as starch, spray dried lactose, and microcrystalline cellulose, tends to increase the hydrophilicity of the active ingredients and, thus, improve dissolution. Consequently, wet granulation was considered superior to a dry or double-compression procedure.

Effect of compression force on dissolution rate

The high compression may also inhibit the wettability of the tablet, due to the formation of a firmer and more effective sealing layer by the lubricant under the

high pressure and temperature that usually accompanies a strong compressive force.

Dissolution Medium

Selection of suitable fluid for dissolution testing depends largely on the solubility of the drug, as well as mere economics and practical reasons.

pH of the Dissolution Medium

Great effort was first placed on simulating in vivo conditions, especially pH, surface tension, viscosity, and sink condition. Most of the early studies were conducted in 0.1N HCl or buffered solutions with a pH close to that of the gastric juice (pH ~ 1.2). The acidic solution tends to disintegrate the tablets slightly faster than water and, thereby, may enhance the dissolution rate by increasing the effective surface area. However, due to the corroding action of the acid on dissolution equipment, currently, it is a general practice to use distilled water, unless investigative studies show a specific need for the acidic solution to generate meaningful dissolution data.

Another approach for avoiding the deleterious effects of hydrochloric acid is to replace it with acidic buffers, such as sodium acid phosphate, to maintain the required low pH.

Surface Tension of the Dissolution Medium

Surface tension has been shown to have a significant effect on the dissolution rate of drugs and their release rate from solid dosage forms. Surfactants and wetting agents lower the contact angle and, consequently, improve penetration by the dissolution medium. Low levels of surfactants were recommended to be included in the dissolution medium, as this seemed to give a better in vivo and in vitro correlation.

Viscosity of the Dissolution Medium

In case of diffusion-controlled dissolution processes, it would be expected that the dissolution rate decreases with an increase in viscosity. In the case of interfacial-controlled dissolution processes, however, viscosity should have little effect. The

Stokes-Einstein equation describes diffusion coefficient, D, as a function of viscosity.

Miscellaneous Factors

In addition to the factors discussed earlier, there are several other factors that can affect the dissolution characteristics of the drug product.

Adsorption

The adsorbent has an influence on the dissolution rate of a slightly soluble solid. It was also reported that the adsorbent is capable of increasing the dissolution rate observed in water under conditions of a decreased concentration gradient applying Nernst-Brunner film theory. Maximum dissolution rate can be obtained when a constant-concentration gradient is maintained.

Adsorption isotherms can be employed to calculate the approximate amount of adsorbent required to increase the slower dissolution rate.

Sorption

The effect of water sorption on disintegration and dissolution properties, among other physical properties, of tablets containing microcrystalline cellulose was examined. It was concluded that water sorption from the atmosphere into the tablet containing microcrystalline cellulose is a very rapid first-order process, resulting in substantial changes in the physical properties.

These changes are attributed to the breaking of the hydrogen bonds. The relative density of the tablets was found to decrease, resulting in increased disintegration time with increase in water sorption-rate constants. These changes were found irreversible.

Humidity

In relation to the dissolution rate of a drug substance, humidity is usually associated with storage effects. Moisture has shown to influence the dissolution rate of many drugs from solid dosage forms.

Types of dissolution apparatus

1.USP/NF Method 1 (Rotating Basket Method)

The USP/NF rotating basket method of dissolution testing essentially consists of a 25mm × 37mm high stainlesssteel 40-mesh wire basket, rotated at a constant speed ranging from 25 to 150 rpm. It is immersed in 900 ml of dissolution medium in a vessel of 1000 ml capacity. The medium in the vessel is maintained at a constant temperature of 37 °C by means of a suitable water bath.

The environment in which the apparatus is placed should not contribute significant motion, agitation, or vibration to the assembly. A fitted cover may be used to retard evaporation. The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly without any significant wobble.

In case of non-disintegrating dosage forms, this apparatus is superior to Apparatus 2, since it constrains the dosage form in steady state fluid flow. This method may seem inferior fortesting of dosage forms, which contain gums, due to the clogging of screen matrix. In case of floating dosage forms, this method performs well, but care should be taken that excipients do not clog the basket mesh.

2. USP/NF Method 2 (Rotating Paddle Method)

For all practical purposes, the compendial specifications outlined for this method are identical to method 1, except that the paddle is substituted for the rotating basket.

The metallic or suitably inert, rigid blade and shaft comprise a single entity. The paddle and blade shaft may be coated with suitable inert coating. The dosage form is allowed to sink to the bottom of the vessel before rotation of the blade is started. This apparatus is frequently used for both disintegrating and non disintegrating dosage form at 50 rpm.

3. USP/ NF Method 3 (Reciprocating Cylinder)
4. USP Apparatus 4 (Flow-Through Cell)
5. USP Apparatus 5 (Paddle Over Disk)
6. USP Apparatus 6 (Rotating Cylinder)
7. USP Apparatus 7 (Reciprocating Cylinder)

Biopharmaceutical classification system

For the drug approval process, it is essential to have the current knowledge about solubility, permeability, dissolution, and pharmacokinetics of a drug product.

Based on drug solubility and permeability, the following Biopharmaceutical Classification System (BCS) is recommended in the literature:

Class 1: High solubility-High permeability drugs

Class 2: Low solubility-High permeability drugs

Class 3: High solubility-Low permeability drugs

Class 4: Low solubility-Low permeability drugs

This classification can be used as a basis for setting in vitro dissolution specifications and in vivo/in vitro correlation (IVIVC). The BCS suggests that, for high solubility, high permeability (Class 1) drugs and, in some cases for high solubility, low permeability (Class 3) drugs, 85% dissolution in 0.1N HCl in 15 minutes can ensure that bioavailability is not limited by dissolution. In case of low solubility, high permeability drugs (Class 2), drug dissolution may be the rate-limiting step for drug absorption, and an IVIVC may be expected

Apparatus Classification in European Pharmacopoeia for different dosage forms

For solid dosage forms	Paddle apparatus Basket apparatus Flow-through apparatus
For transdermal patches	Disk assembly method Cell method Rotating cylinder method
For special dosage forms	Chewing apparatus (medicated Chewing gums) Flow-through apparatus