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Chapter 1...

Dissolution

1.1 INTRODUCTION

Dissolution is the process by which a solid or a liquid forms a homogeneous mixture with a solvent **(solution)**. This can be explained as a breakdown of the **crystal lattice** into individual ions, atoms or molecules and their transport into the solvent.

Dissolution tests have been used in pharmaceutical industry and they are official in the United States Pharmacopeia since the early 1960's. The dissolution test, reviewed primarily as a quality control tool, replaced the use of disintegration tests which had been official in the United States Pharmacopeia since 1950. Refinements in the dissolution test equipment and methodology have occurred over the years in order to enhance its relevance. The subcommittees of the USP Committee of Revision dealing with these issues have developed and refined compendial dissolution standards and policies for conventional solid-oral dosage forms and modified-release dosage forms. For drugs of limited water solubility, dissolution may be a more meaningful quality attribute than disintegration testing. The question arises as to why dissolution test is performed ? The reasons are :

1. To differentiate between formulations and to evaluate the potential effect of the formulation and other process variables on drug bioavailability.
2. To ensure bioequivalence from batch to batch.
3. To ensure that the preparation complies with product specification, as it is a requirement for regulatory approval of marketing for the registered product.
4. To predict the performance of the preparation under in vivo conditions. (It is possible to correlate dissolution rate of a drug with its bioavailability).

1.2 MECHANISM OF DISSOLUTION

The dissolution test determines the cumulative amount of the drug that goes into solution as a function of time. Dissolution of drug from a dosage form involves at least two consecutive steps : liberation of the solute or drug from the formulation matrix (disintegration), followed by dissolution of the drug (solubilization of the drug particles) in the liquid medium. The overall rate of dissolution depends on the slower of these two steps. The relative difference in rates should be carefully considered when designing the

dissolution method. The cohesive properties of the formulated drug play a key role in the first step of dissolution. For solid dosage forms, these properties include disintegration and erosion, whereas for semisolid or liquid formulations, the dispersion of lipids or partitioning of the drug from the lipid phase is the key factor. If the first step of dissolution is rate-limiting, then the rate of dissolution is considered to be *disintegration controlled*. Careful assessment of the intrinsic rate of dissolution and the effect of various aspects of the formulation (for example, release profiles from precompressed granules, impact of compression force, porosity, and lubrication) can reveal the relative contribution of the disintegration step to the overall dissolution of the drug. In the second step of dissolution—solubilization of the drug particles—the physicochemical properties of the drug such as its chemical form (for example, salt, free acid, free base) and physical form (for example, amorphous or polymorph, and primary particle size) play an important role. If this later step is rate limiting, then the rate of dissolution is *intrinsic dissolution controlled*. This is the case for most poorly soluble compounds in IR formulations. For poorly soluble compounds in solubilized formulations, *in vivo* precipitation also may need to be considered when developing a dissolution test method, in particular for establishing an IVIVR (in vitro in vivo relation) or IVIVC (in vitro in vivo correlation).

1.3 DISSOLUTION TEST DESIGN

Before human clinical studies are conducted, dissolution data usually must be generated without the benefit of comparative rankings between formulations or lots, estimated *in vivo* human absorption rates, or any other information that could guide the development of a discriminating dissolution test. When developing a dissolution test for poorly soluble compounds early in drug development, the process should focus on assessing relevant physical and chemical properties of the API and the drug product's dosage form design, because these will guide the choice of the dissolution medium and apparatus. This strategy for designing a dissolution test will change, however, in later stages of drug development, because of the evolving purpose of the dissolution test as well as the availability of additional data. For example, with the accumulation of both *in vivo* and *in vitro* experience during a product's development cycle, the early-phase dissolution test method should be critically re evaluated and potentially simplified for final QC testing. And in some cases, the data acquired will demonstrate the usefulness of alternative methods to replace dissolution testing. As the data become available for IR formulations that contain Class I drugs (For example, if the 85% of the drug dissolves in 15 min in pH 1.2, 4.5, and 6.8 buffers), a disintegration method can be justified and substituted for a dissolution test.

Media selection : The choice of medium will depend on the purpose of the dissolution test. For batch-to-batch quality testing, selection of the dissolution medium is based, in part, on the solubility data and the dose range of the drug product to ensure that sink conditions are met. The term *sink conditions* is defined as the volume of medium at least greater than three times that required to form a saturated solution of a drug substance. A medium that fails to provide sink conditions may be justifiable, however, if it is shown to be more discriminating or if it provides reliable data which otherwise can only be obtained with the addition of surfactants. On the other hand, when the dissolution test is used to indicate the biopharmaceutical properties of the dosage form, it is more important that the proposed biorelevant test closely simulate the environment in the gastrointestinal (GI) tract than necessarily produce sink conditions. The dissolution characteristics of oral formulations should first be evaluated using test media within the physiologic pH range of 1.2–6.8 (1.2–7.5 for modified-release formulations) because low-solubility drugs include those with adequate aqueous solubility at either acidic (For example, amines) or neutral (for example, organic acids) pH levels. During method development, it may be useful to measure the pH of the test medium before and after a run to see if the pH changes during the test. Selecting the most appropriate medium for routine QC testing is based on discriminatory capability, ruggedness, stability of the analyte in the test medium, and relevance to *in vivo* product performance wherever possible. Aqueous media without any surfactants are preferred, but aqueous media with surfactants may be used to increase the probability of establishing an *in vivo* relationship. For some low-solubility compounds, adequate dissolution cannot be obtained with aqueous solutions within physiologic pH ranges. For these compounds, an aqueous solution containing a surfactant may be used to enhance drug solubility. Commonly acceptable ionic or nonionic surfactants include sodium lauryl sulfate (SLS), polyoxyethylenesorbitan monolaurate (Tween), cetyltrimethyl-ammoniumbromide (CTAB), polyoxyl castor oil (Cremophor), hexadecyltrimethyl-ammonium bromide (HTAB), polyethylene glycol tert-octylphenyl ether (Triton), nonylphenol ethoxylate (Tergitol), cyclodextrins, and lecithin. In general, non-ionic detergents (for example, Tween) are considered more biologically relevant, and thus are often the first choice when considering the addition of a surfactant. A surfactant can be used as either a wetting agent or, when the critical micelle concentration (CMC) is reached, to solubilize the drug substance. The need for surfactants, as well as their type and concentration, should be justified. The amount of surfactant needed for adequate drug solubility depends on the surfactant's CMC and the degree to which the compound partitions into the surfactant micelles. The surfactant's CMC depends, in turn, on the surfactant itself and the ionic strength of the base medium. Because of the nature of the compound and micelle interaction, typically a linear dependence exists between

solubility and surfactant concentration above the CMC. If a compound is ionizable, surfactant concentration and pH may be varied simultaneously, and the combined effect can substantially change the solubility characteristics of the dissolution medium. Using an aqueous-organic solvent mixture as a dissolution medium is discouraged; however, if an IVIVR or IVIVC is demonstrated that cannot be accomplished with a purely aqueous medium, an aqueous-organic solvent may be considered. The acceptability of such an aqueous-organic solvent media based dissolution method should be discussed with regulatory agencies early in product development.

Apparatus Selection :

Physical and chemical properties of the API (for example, solubility and stability) as well as the formulation concept play a key role in selection of the dissolution test apparatus, especially for poorly soluble compounds. Dissolution testing is conducted on equipment that has demonstrated suitability, such as that described in the *United States Pharmacopeia* (*USP*) under the general chapters of Dissolution and Drug Release. The basket method (USP Apparatus 1) is routinely used for solid oral dosage forms such as capsules or tablets at an agitation speed of 50 to 100 r.p.m., although speeds of up to 150 r.p.m. have been used. The paddle method (USP Apparatus 2) also is used frequently for solid oral dosage forms such as tablets and capsules, but at 50 or 75 r.p.m. Both the paddle and the basket methods can accommodate media volumes ranging from 500 to 1000 ml with the standard vessel and 2000 to 4000 ml with larger vessels. Higher vessel volumes can be advantageous for low-solubility compounds. For highly potent, low dosage drugs, the use of 100 to 250 ml vessels should be considered. The reciprocating cylinder (USP Apparatus 3) and the flowthrough cell (USP Apparatus 4) also may offer advantages for some low-solubility dosage forms. Apparatus 3 can be used to estimate the drug release profile in the GI tract by using a series of different media in the vessels. Apparatus 4 may be more useful if certain ruggedness aspects can be improved by the vendors. By design, both the reciprocating cylinder and the flowthrough cell allows controlled pH and volume change of the dissolution medium throughout the test. However, USP Apparatus 3 and 4 or other modified configurations are most often limited for use in product development and characterization. Flexibility in the selection of the apparatus during development facilitates understanding of the dissolution mechanism. Once the dissolution mechanism is understood, attention is focused on developing a method that is compendially acceptable and that may demonstrate an IVIVR or IVIVC. The superiority of a new or modified apparatus design should be proven in comparison to the compendial apparatus. The effect of hydrodynamics such as speed, axial velocity, vessel contours, currents, eddies, surface area, positioning, paddle shape, cage, and sinkers, should be considered during method development.

1.4 DISSOLUTION TESTING APPARATUS

Dissolution test is performed in-process and on the final product. Dissolution test is a standard requirement for tablets and capsules. When dissolution test is prescribed, disintegration test may not be required. The USP gives standards for tablet dissolution. There are many apparatus available for drug release and drug dissolution for immediate release, extended release and enteric-coated tablets. Large numbers of different dissolution apparatus are described in the literature, but some of them withstand critical methodological examination. Two basic principles are applied in dissolution testing : stirred beaker method and flow through apparatus. **Table 1.1** shows the official dissolution test apparatus in IP, BP and USP. **Table 1.2** shows the dissolution test apparatus mentioned in United States Pharmacopoeia**.** Some other non-official dissolution test methods are used like tumbling method. In this method the dosage form is placed in tubes or bottles which are rotated using revolving drum. The rotating disk method measures the dissolution rate from constant surface area. This method is used to determine intrinsic dissolution rate, which gives useful information during preformulation studies regarding new chemical entity. Other apparatus includes rotating filter-stationary basket, magnetic basket apparatus and many more. These apparatus have automatic sampling and online attachment to the spectrophotometer.

The Sartorius apparatus utilizes in vivo simulative methods. The absorption simulators simulate passive drug transport processes across that occur in *vivo*, from the gastrointestinal tract to plasma across the lipoidal mucosal barrier. The solubility simulator simulates the drug dissolution and subsequent absorption from the gastrointestinal tract. The pH of the medium mimics the *in vivo* travel from the stomach to the intestine. Similarly the bio-predictor predicts the time course of *in vivo* drug response in the form of dissolution rate vs time profile.

Table 1.1 : Official Dissolution Test Apparatus

Apparatus No.	IP	BP	USP
1	Paddle	Basket	Rotating basket
2	Basket	Paddle	Paddle
3		Flow through cell	Reciprocating cylinder
4			Flow through cell
5			Paddle over disc
6			Rotating cylinder
7			Reciprocating disc

Table 1.2 : United States Pharmacopeia Official Dissolution test Apparatus

Apparatus No.	USP	Useful for
1	Rotating basket	Solids, floaters, beads, modified release dosage forms.
2	Paddle	Solids, modified release dosage forms, Transdermal patch, ointment, floaters, emulsion.
3	Reciprocating cylinder	pH profile, beads, sustained release dosage forms.
4	Flow through cell	Low solubility drugs, drugs undergoing degradation, media including pH change.
5	Paddle over disc	Transdermal patch, ointment, floaters, emulsion.
6	Rotating cylinder	Transdermal patch.
7	Reciprocating disc	Transdermal patch, solid dosage forms, pH profile, small volumes.

New wave in dissolution testing :

New approach in dissolution testing incorporate disintegration, solid transfer, and dissolution, changing pH/dissolution medium, absorption and clearance. It is capable of giving excellent IVIVC level A correlation. There is no necessity of mathematical models to predict the data. Results of dissolution testing gives the plasma concentration vs time profile. This can overcome the limitations of the other apparatus.

Equipment description :

It consists of three continuous, stirred cells connected in series. Simulated gastric fluid is pumped in to the first cell (the gastric cell), the effluent from the gastric cell is pumped into cell 2 (intestinal cell) together with simulated intestinal fluid and sodium hydroxide to neutralize the acid. The effluent from the second cell is fed into the third cell (systemic cell). All three cells are operated at a constant volume. The dosage form to be tested is added into the first cell. The extension of this method incorporates changes in the pH and composition of the fluid during the test to study the effect on the drug released in the intestinal tract, extended for non-disintegrating dosage forms, use of the biorelevant medias (surfactants, enzymes) and minibaskets to hold dosage forms. (The limitations of this method are that anything that affects absorption rate can not be studied and method does not address the first pass metabolism and first order clearance.

Dissolution Vessels : 250 ml, 1 litre, 2 litres, 4 litres, in clear glass or UV protected brown glass, with volume graduations.

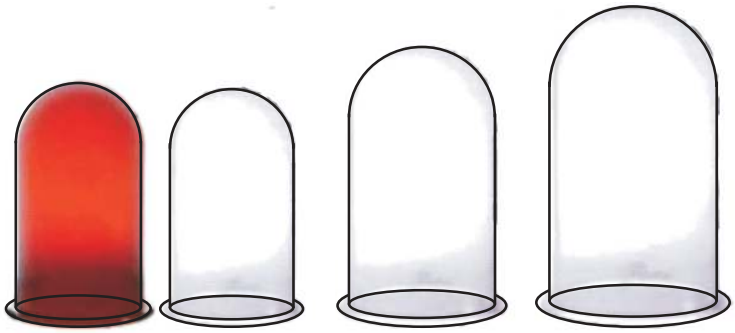
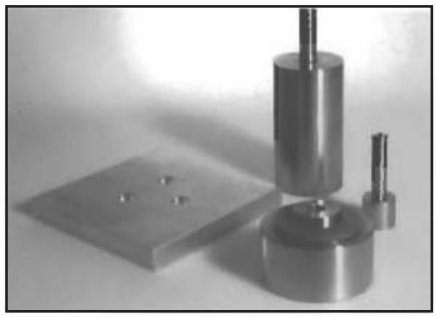
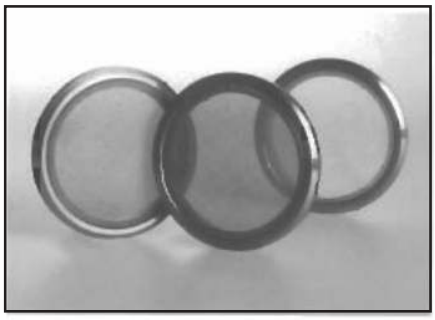


Fig. 1.1 : Different Capacity Dissolution Vessels

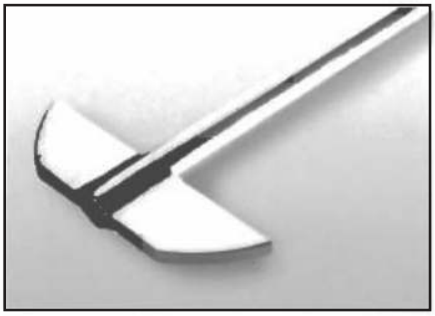
Dissolution Tools : Paddles (USP App. 2) in stainless steel, Teflon coated or gold plated. Baskets (USP App.I) in stainless steel or gold plated. Baskets supplied in 10, 40 or 100 mesh options. Mini paddles in stainless steel, paddle over disk (USP App. 5), rotating cylinders (USP App. 6), cream test cells, suppository dissolution cells, intrinsic dissolution accessory; all tool shafts are batch coded.



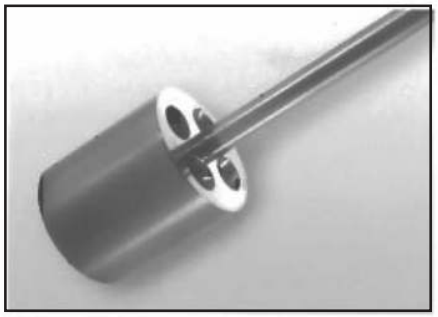
Intrinsic Dissolution Accessory



Paddle Over Disks



Paddles in Stainless Steel



Rotating Cylinders

Fig. 1.2

Baskets (Apparatus 1) Available in various mesh sizes, either in stainless or gold plated.

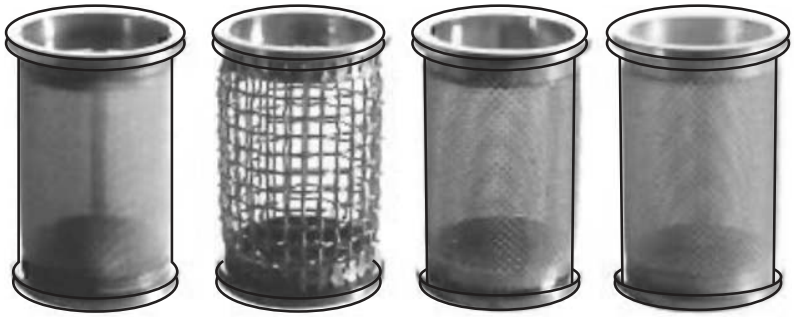


Fig. 1.3

Sinkers : Large variety of tablet and capsule sinkers in various forms and finishes are available. We have a range of paddle and basket depth gauges, manual sampling systems, in-line filters with 5 or 1 Dan pore sizes, water diffusers for even heating of water baths, flow through cells (USP Apparatus 4).

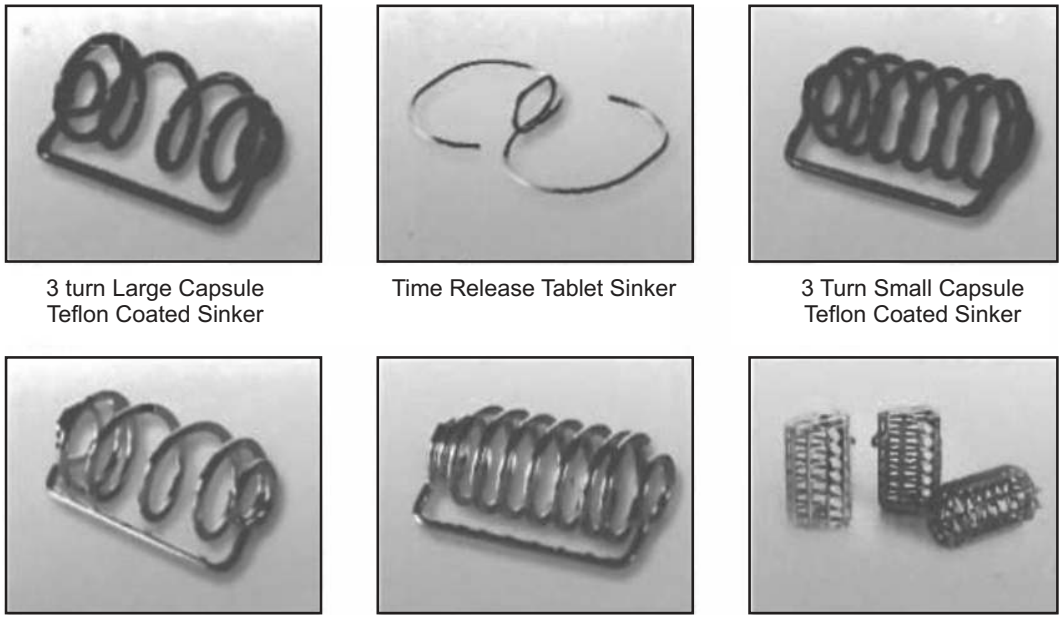


Fig. 1.4 : Dissolution Tools