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IN VITRO DRUG DISSOLUTION AND DISSOLUTION TESTING APPROACHES: AN REVIEW

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ABSTRACT

The contrasting views of dissolution testing taken by pharmaceutical scientists and regulators lead to constant development and review of the technology. The industrial drive is to improve the IVIVC, so speeding up the identification and development of new therapeutic products, whilst the regulatory focus is on the use of dissolution testing as a quality control tool to confirm product safety and efficacy. In vitro dissolution testing of solid dosage forms is the most frequently used biopharmaceutical test method in formulation development. It is used from the start of dosage form development and in all subsequent phases. Investigation of drug release mechanisms, especially for ER formulations obtaining a predefined target release profile and robust formulation properties regarding influences of physiological factors (e.g., pH and food) on the drug release. Generation of supportive data to bioavailability studies as an aid in interpretation of in vivo results. Validation of manufacturing processes. Investigation of effects of different storage conditions. Batch quality control (QC). A surrogate for bioequivalence studies. Drug release is determined by formulation factors such as disintegration/dissolution of formulation excipients or drug diffusion through the formulation. In vitro dissolution testing should thus provide predictions of both the drug release and the dissolution processes in vivo.

KEYWORDS: Dissolution, Solubility, Paddle method, Basket method, Noyes Whitney eqn.

INTRODUCTION

Dissolution tests are one of the most commonly used tests in the characterization of drugs and in the quality control of certain dosage forms. Dissolution tests are used to confirm compliance with compendial specifications and are therefore needed as part of a marketing authorization. Additionally they are used during product development and stability testing as part of the development specification for the product. Critically, from an R&D perspective, there is the potential to correlate in vitro dissolution data with in vivo bioavailability, which would greatly facilitate product development. Whether the solution process takes place in the laboratory or *in vivo*, there is one law which defines the rate of solution of solids when the process is diffusion-controlled and involves no chemical reaction.

Dissolution mechanisms

The dissolution of a solid in a liquid may be regarded as being composed of two consecutive stages.

1. First is an interfacial reaction that results in the liberation of solute molecules from the solid phase. This involves a phase change, so that molecules of solid become molecules of solute in the solvent in which the crystal is dissolving. The solution in contact with the solid will be saturated (because it is in direct contact with un dissolved solid). Its concentration will be Cs, a saturated solution.

2. After this, the solute molecules must migrate through the boundary layers surrounding the crystal to the bulk of the solution, at which time its concentration will be C. This step involves the transport of these molecules away from the solid-liquid interface into the bulk of the liquid phase under the influence of diffusion or convection. Boundary layers are static or slow moving layers of liquid that surround all wetted solid surfaces .

3. Mass transfer takes place more slowly through these static or slow-moving layers, which inhibit the movement of solute molecules from the surface of the solid to the bulk of the solution. The concentration of the solution in the boundary layers changes therefore from being saturated (Cs) at the crystal surface to being equal to that of the bulk of the solution (C) at its outermost limit.

To describe the dissolution process of a particle: **dw/dt = D/h. S (Cs-Ct)**

- where dW/dt is the rate at which a material dissolves across a surface S at a time t; Cs -Ct is the concentration gradient between the concentration of solute in the stagnant layer (thickness h and immediately adjacent to the dissolving surface) surrounding the dissolving particles, and is assumed to be equal to the difference between the saturated solubility of the drug (Cs) and the concentration of the solute in the surrounding medium at time t (Ct). The parameter D is a function of the diffusion coefficient of the solute molecules.
- Maximum dissolution rates are predicted when Ct = 0. Consequently, as C_t increases, the dissolution rate decreases. The parameter D is also dependent on, Cs -Ct. Such conditions, where dissolution is followed by absorption of the drug, as in the in vivo situation, are described as sink conditions.

The parameters of the dissolution equation can be changed to increase (+) or decrease (-) the rate of solution

Equation parameter	Comments	Effect on rate of solution
D(diffusion coefficient of drug)	May be decreased in presence of substances which increase viscosity of the medium	-
S (area exposed to solvent)	Increased by micronisation and in 'amorphous' drugs	+
h thickness of diffusion layer	Decreased by increased agitation in gut or flask	+
$\mathbf{c_s}$(solubility diffusion layer)	That of weak electrolytes altered by change in pH, by use of appropriate drug salt or buffer ingredient	-,+
$\mathbf{c_t}$ (concentration in bulk)	Decreased by intake of fluid in stomach, by removal of drug by partition or absorption	+

- In vitro systems should ideally maintain a sink condition and the dissolving solid should be tested in fresh solvent, where there is no build-up of dissolved drug in the dissolution medium. Such a situation is only actually achieved in flow-through type apparatus e.g., USP Apparatus 4, whilst in USP Apparatus 1 and 2 there is a gradual increase in C_t during the test.
- The parameter D is temperature dependent. Consequently, both the temperature of the dissolution fluid and its viscosity (which is also temperature dependent) should be carefully controlled. In addition, the presence of electrolytes and changes in pH may influence the diffusing species by altering their ionization. Such factors imply that dissolution fluids should be as simple as possible. However, this is in contrast with the

need for complex, biorelevant media to be used if any attempt is to be made to use a product's in vitro dissolution to make useful estimates of its likely in vivo activity.

- It is therefore apparent that before a drug substance can be successfully formulated into a dosage form many factors must be considered. These can be broadly grouped into three categories:

1. Biopharmaceutical considerations, including factors affecting the absorption of the drug substance from different administration routes
2. Drug factors, such as the physical and chemical properties of the drug substance
3. Therapeutic considerations, including consideration of the clinical indication to be treated and patient factors.

Measurement of dissolution rates

- Many methods have been described in the literature, particularly in relation to the determination of the rate of release of drugs into solution from tablet and capsule formulations, because such release may have an important effect on the therapeutic efficiency of these dosage forms.
- Having identified some of the important criteria and models for dissolution, let us examine some of the apparatus used to measure dissolution rates.

The ideal features of a dissolution apparatus are:

1. The apparatus must be simply designed, easy to operate, and useable under a variety of conditions.
2. The fabrication, dimensions and, positioning of all components must be precisely specified and reproducible, run to run.
3. The apparatus must be sensitive enough to reveal process changes and formulation differences but still yield repeatable results under identical conditions.
4. The apparatus, in most cases, should permit a controlled, but variable intensity of mild, uniform, non-turbulent liquid agitation. Uniform flow is essential because changes in hydrodynamic flow will modify dissolution.
5. Nearly perfect sink conditions should be maintained.
6. The apparatus should provide an easy means of introducing the dosage form into the dissolution medium and holding it, once immersed, in a regular and reliable fashion.

7. The apparatus should provide minimum mechanical abrasion to the dosage form (with exceptions) during the test period to avoid disruption of the microenvironment surrounding the dissolving form.
8. Evaporation of the solvent medium must be eliminated and the medium must be maintained at a fixed temperature within a specified narrow range. Most apparati are thermostatically controlled at around 37°C.
9. Samples should be easily withdrawn for automatic or manual analysis without interrupting the flow characteristics of the liquid. In the latter case, efficient filtering should be achieved.
10. The apparatus should be capable of allowing the evaluation of disintegrating, non-disintegrating, dense or floating tablets, or capsules and finely powdered drugs.
11. The apparatus should allow good inter laboratory agreement.

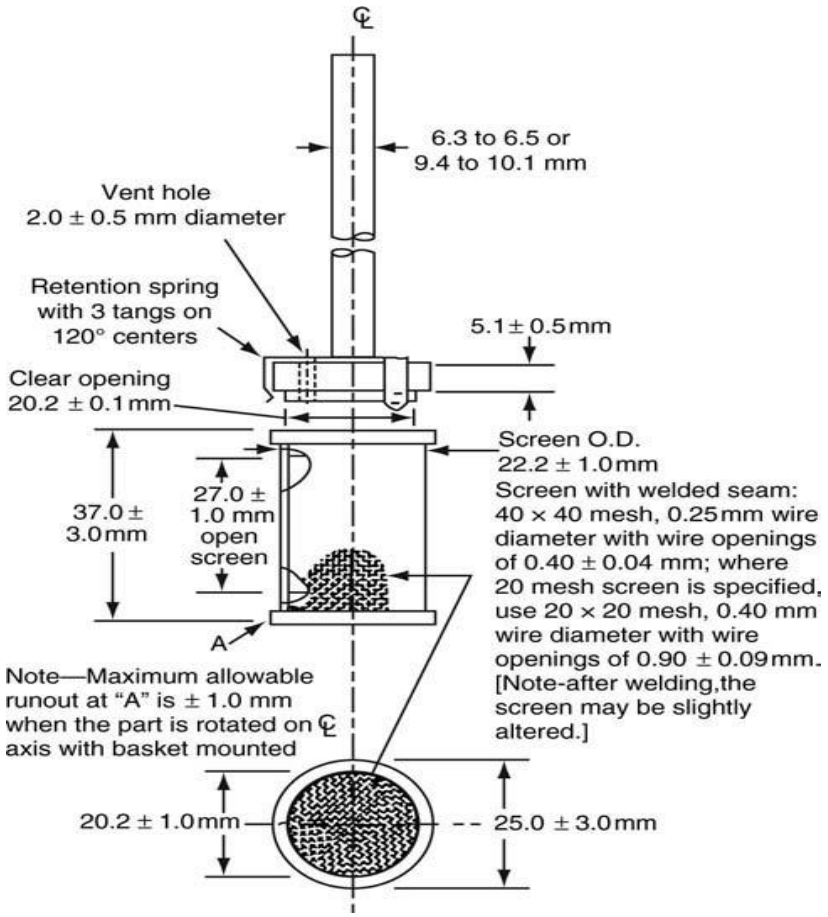
- The general principle of dissolution tests is that the powder or solid dosage form is tested under uniform agitation, which is accomplished by either passing the medium over the sample or by rotating the sample in the medium. Two general methods are currently included in the USP 28 and the British Pharmacopoeia (BP) 2004 to measure dissolution from immediate release oral tablets and capsules whilst there are several variants used in the testing or modified-release oral dosage forms and other, non-oral types of dosage form.

1. Basket Apparatus (USP Apparatus 1)

The apparatus consists of a motor, a metallic drive shaft, a cylindrical basket, and a covered vessel made of glass or other inert transparent material. The latter should be made of materials that do not sorb or react with the sample tested. The contents are held at 37± 0.5°C. There should be no significant motion, agitation, or vibration caused by anything other than the smoothly rotating stirring element.

Ideally, the apparatus should provide observation of the stirring element and sample. The vessel is cylindrical with a hemispherical bottom and sides that are flanged at the top. It is 160–175mm high and has an inside diameter of 98–106 mm, and a nominal capacity of 1000 ml. A fitted cover may be used to retard evaporation but should provide sufficient openings to allow ready insertion of a thermometer and allow withdrawal of samples for analysis. The shaft is so positioned that its axis is no more than 2mm at any point from the vertical axis of the vessel and should rotate smoothly, without significant wobble. The shaft rotation speed should be maintained within ±4% of the rate specified in the individual monograph. The shaft

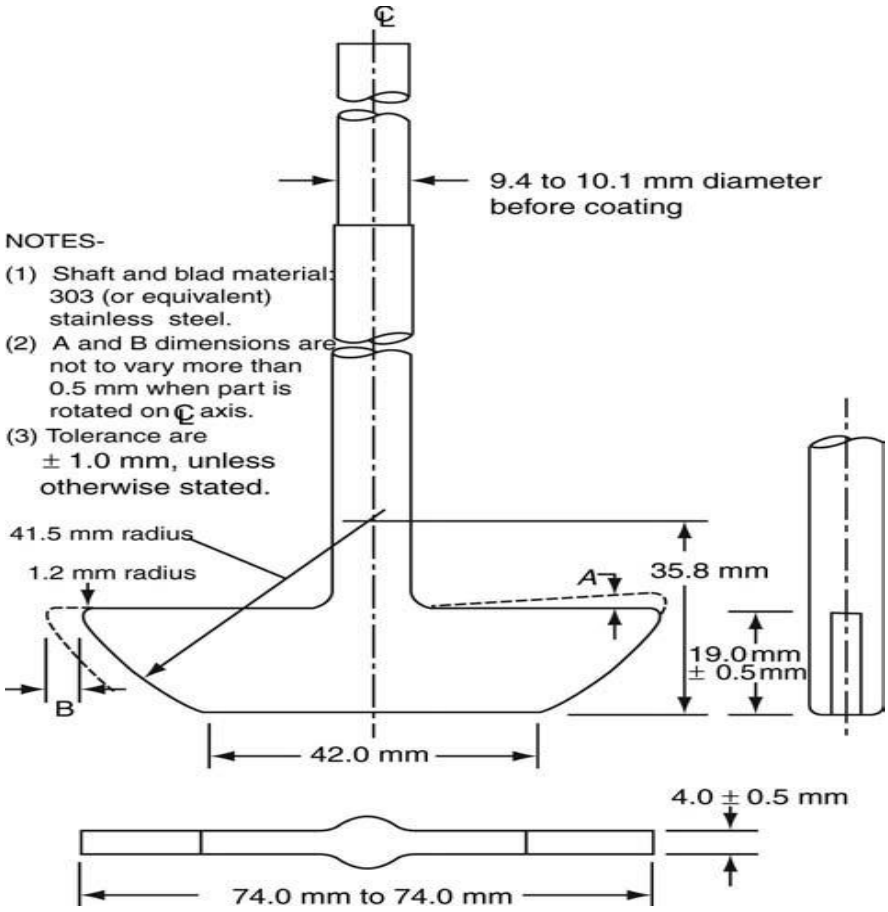
has a vent and three spring clips or other suitable means to fit the basket into position. Each should be fabricated of stainless steel, type 316 or equivalent. Welded seam, stainless steel cloth (40 mesh or 425 *m*m) is used, unless an alternative is specified. A 2.5 *m*m thick gold coating on the basket may be used for acidic media. For testing, a dosage unit is placed in a dry basket at the beginning of each test. The distance between the inside bottom of the vessel and the basket is 25 ± 2 mm.



2. Paddle Apparatus (USP Apparatus 2)

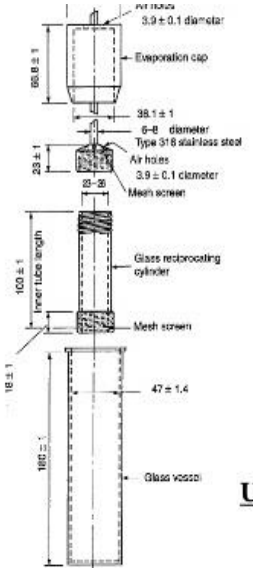
In the Apparatus 2,—the paddle apparatus method—a paddle replaces the basket as the source of agitation. As with the basket apparatus, the shaft should position no more than 2mm at any point from the vertical axis of the vessel and rotate without significant wobble. A distance of 25± 2mm between the blade and the inside bottom of the vessel is maintained during the test. The metallic blade and shaft comprise a single entity that may be coated with a suitable inert coating to prevent corrosion. The dosage form is allowed to sink to the bottom of the flask before rotation of the blade commences. In the case of hard-gelatin capsules and other floating dosage forms, a ‘‘sinker’’ is required to weight the sample down until it

disintegrates and releases its contents at the bottom of the vessel. The sinker has to hold the capsule in a reproducible and stable position directly below the paddle, but it needs to be constructed in such a fashion that it doesn't significantly affect hydrodynamic flow within the vessel nor should it appreciably reduce the surface area of the capsule available to the dissolution medium.



3. Reciprocating Cylinder Apparatus (USP Apparatus 3)

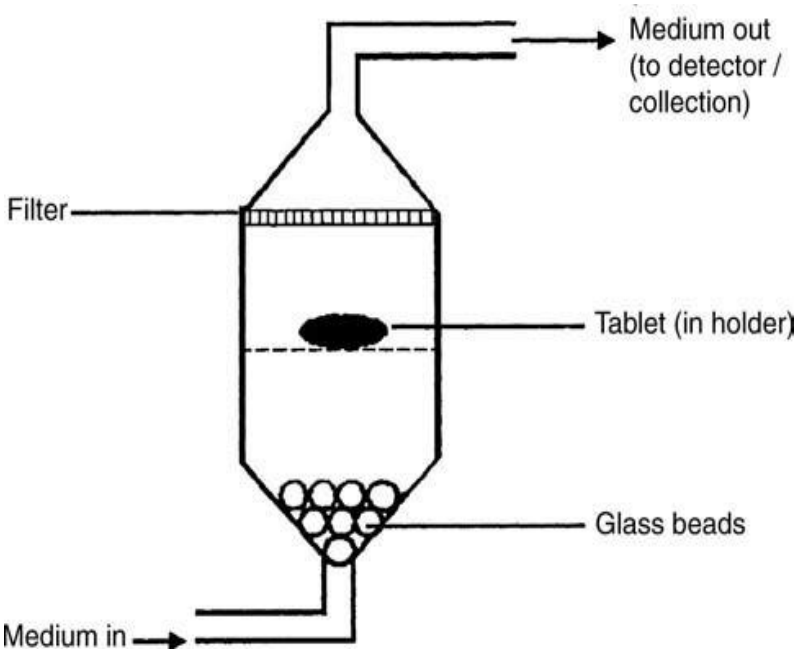
which allows tubes containing the sample to be plunged up and down in a small vessel containing the dissolution medium It has been designed to allow the tubes to be dipped sequentially in up to six different media vessels, using programs that vary the speed and duration of immersion. It allows automated testing for up to six days and the manufacturers advocate its use in the testing of extended-release dosage forms.



USP TYPE III : RECIPROCATING CYLINDER

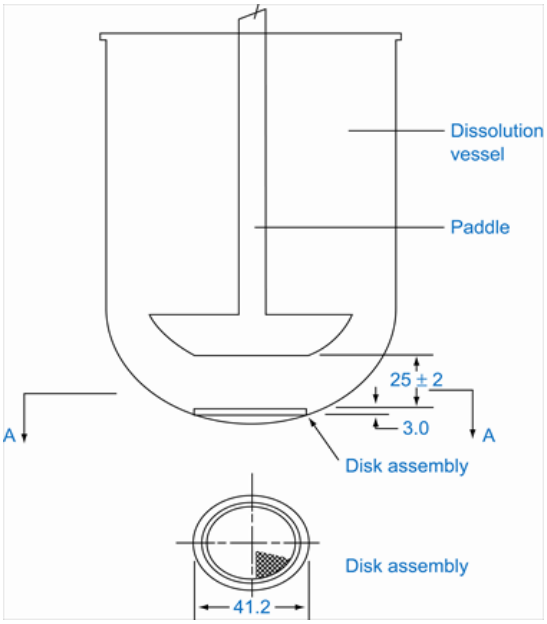
4. Flow-Through Cell Apparatus (USP Apparatus 4)

Limited-volume apparatus with a finite volume of dissolution fluid suffer from the problem that they operate under non-sink conditions, which results in limitations when poorly soluble drugs are considered.



A flow-through system and reservoir may be used to provide sink conditions by continually removing solvent and replacing it with fresh solvent. Alternatively, continuous recirculation may be used when sink conditions are not required. The drawbacks of nonflow- through apparatus include: (i) lack of flexibility; (ii) lack of homogeneity; (iii) the establishment of concentration gradients; (iv) their semi quantitative agitation; (v) the obscuring of details of the dissolution processes; and (vi) their variable shear.

5. Paddle-over-Disk Apparatus



Usually a transdermal delivery system, being attached to a stainless steel disk, which is then placed on the bottom of the vessel, directly under the paddle.

6. Cylinder Apparatus (USP Apparatus 6)

This is a modification of the basket apparatus (USP Apparatus 1) with the basket being replaced by a stainless steel cylinder. The sample is again usually a transdermal delivery system attached to the outside of the cylinder.

7. Reciprocating Holder Apparatus (USP Apparatus 7)

The sample holder may take the form of a disk, cylinder, or a spring on the end of a stainless steel or acrylic rod, or it may simply be the rod alone. The sample is attached to the outside of the sample holder either by virtue of being selfadhesive (e.g., transdermal delivery system) or is glued in place using a suitable adhesive.

This apparatus may be used for transdermal products, coated drug delivery systems, or other suitable products (e.g., osmotic pump devices).

DATA PRESENTATION

The data collected during dissolution tests will, especially at the developmental stage, be presented as dissolution profiles whereby the amount released is plotted as a function of time. It is common practice to monitor drug release at several points or where possible

continuously until 100% of the dose is dissolved and dissolution profiles showing drug release against time can be produced. Values equivalent to the times for 10%, 50%, 70%, or 90% drug release are often cited as $t_{10\%}$, $t_{50\%}$, $t_{70\%}$, or $t_{90\%}$.

The USP 28 assesses dissolution in a three-stage series of tests with the amount of drug dissolved after a specified time being expressed as a percentage of the nominal content of the dosage form. The time at which the sample is to be tested is specified in the monograph, as is the so-called Q-value, the minimum percenatage dissolved at that time. In the first stage (S_1), six units are tested and the pass criteria are that the amount of drug dissolved from each unit at the specified time should be no less than Q + 5%. Failure at S_1 requires a second stage test (S_2) to be performed on an additional six units. To pass the test at this stage, the average content dissolved from the combined two stages (i.e., 12 units) should be equal to or greater than Q with no unit being less than Q - 15%. Failure leads to stage 3 where a further 12 units are tested. These results are combined with the results from the previous stages. The average of the total of the 24 units thus tested should be equal to or greater than Q. No more than two units should be less than Q - 15% and no unit should be less than Q -25%.

OPERATIONAL FACTORS - AFFECT THE DISSOLUTION TEST

a. Stirrer Shaft

Many problems associated with variations in the dissolution rate are caused by misalignment. Limits should be set on shaft eccentricity, although bending of the stirring rod has been reduced by increasing the acceptable diameter from 6.0–6.5mm to approximately 10 mm. Minor changes in physical alignment of the paddle may produce large variations in results.

b. Sampling Procedures

Flow-through facilities usually allow UV analysis of drug dissolved or collection of samples for subsequent analysis. Filtering must be accomplished before analysis to prevent insoluble excipients or undissolved drug particles from passing through the beam. Filters remove solid particles prior to assay at the stage of sample removal, reduce turbidity problems caused by undissolved drug and excipients, and help eliminate spurious results caused by particles dissolving following removal.

c. Temperature Control

The USP directs that the thermometer should be removed before the test and that the temperature should be checked periodically. The dissolution fluids should be maintained at

37±0.5°C as even slight temperature variations may have a significant effect on tablet dissolution. It is essential, therefore, to prevent evaporation of the medium both to reduce heat loss and maintain the volume of the liquid for dissolution. This is achieved with tight-fitting plastic lids or film across the opening of the vessels.

d. Variation in Speed of Agitation

Agitation speed must be uniform throughout the test. Some motor drives result in a satisfactory mean speed but during the test will periodically slow down or speed up. Consequently, speed should be checked at the start and end of each run using a suitable, calibrated tachometer or other means.

CONCLUSIONS

The increasing importance of dissolution testing in the development and routine commercial production of pharmaceuticals has become acknowledged within the industrial, academic, and regulatory communities. Improvements in dissolution testing instrumentation and an awareness of the importance of correlating in vitro data with in vivo performance have offered the possibility of more rapidly developing safer and more efficacious drugs Industrial and academic laboratories have focused on developing suitable test procedures for more sophisticated dosage forms and governmental regulatory agencies have entered into debate as to the most appropriate specifications for products at various stages of their development lifecycle. In particular, developments in the field of biopharmaceutics and regulatory changes in the wake of the ICH process have stimulated recent changes.

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