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Dissolution Study of pharmaceutical preparations

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ABSTRACT

Dissolution testing is a vital tool for characterizing the performance of oral solid dose forms. Its significance relies on the very fact that for a drug to be effective, it should 1st be released from the product and dissolve within the gastrointestinal fluids before absorption into the blood will happen. In other words, the speed and extent of drug absorption are determined by its dissolution from the dose type. A dissolution test measures the quantity of drug that goes into resolution over a amount of your time beneath standardized conditions. Factors that have an effect on the dissolution of a drug product embody the intrinsic properties of the api (e.g., solubility, wettability, particle size, surface area, morphology, polymorphs), the formulation composition and characteristics (e.g., excipients, hardness, producing process), and therefore the dissolution technique used for its assessment (e.g., apparatus, medium, test conditions, sampling, and sample analysis). This text deals with the various dissolution testing

Keywords: Wetting, Dissociation Constant

Introduction

Dissolution is pharmaceutically outlined because the rate of mass transfer from a solid surface into the dissolution medium or solvent below standardized conditions of liquid/solid interface, temperature and solvent composition. it is a dynamic property that changes with time and explains the method by that the same mixture of a solid or a liquid may be obtained in a very solvent. It happens to chemically occur by the crystal break down into individual ions, atoms or molecules and their transport into the solvent.

Objectives of Invitro Dissolution study

In vitro dissolution test is performed with the following objectives

• it's an important demand for the approval of promoting of the product that ar registered with the FDA and different drug regulation authorities.

• to produce a correlation between the product in vivo performance.

• It helps in ascertaining the standard of the product at an early stage.

• To assess batch to batch bioavailability and clinical potency of the merchandise.

• It is a guiding tool within the formulation and development of a product having the specified in vivo performance. (Jennifer J,2005)

Dissolution testing for pharmaceuticals

Dissolution testing could be a crucial preformulation solubility analysis research tool in the method of drug discovery that entails measuring the soundness of the investigational product, achieving uniformity in production lots and crucial its in vivo availableness. Thus, this Dissolution testing is a vital demand for the event, establishment of in vitro dissolution and in vivo performance (IVIVR), registration and quality control of different dose forms.

Mechanisms of dissolution

Several theories to clarify drug dissolution are planned. Diffusion layer model (Film Theory); Penetration or surface renewal theory (Danckwerts model); surface barrier model (double barrier mechanism or limited solvation theory).

Diffusion layer model (Film Theory This is the best and commonest theory for dissolution. Here, the method of dissolution of solid particles during a liquid, within the absence of reactive or chemical forces, consists of 2 consecutive steps. resolution of the solid to make a thin film or

layer at the solid/liquid interface referred to as because the stagnant film or diffusion layer that is saturated with the drug, this step is typically fast. Diffusion of the soluble solute from the stagnant layer to the majority of the solution, this step is slower and is so the speed determining step in drug dissolution. The earliest equation to explain the rate of dissolution once the method is diffusion controlled and involves no chemical change was given by Noyes and Whitney.

$$dC/dt = k(Cs - Cb) \rightarrow 1$$

Where dc/dt, is the dissolution rate of the drug

K - Dissolution rate constant

Cs - Concentration of drug in the stagnant layer

C - Concentration of drug in the bulk of the solution at time t

Equation was based on Ficks second law of diffusion. Burner incorporated Ficks first law of diffusion and modified the Noyes-Whitneys equation to

$$\frac{dc}{dt} = \frac{DAKw/o(Cs - Cb)}{Vh} \rightarrow 2$$

Where D - Diffusion coefficient of the drug

A - Surface area of the dissolving solid.

Kw/o - Water/Oil partition coefficient of the drug considering the fact that dissolution body fluids are aqueous. Since the rapidity with which a drug dissolves depends on the Kw/o, it is also called as the intrinsic dissolution rate constant. It is a characteristic of drugs.

V - Volume of dissolution medium.

h - Thickness of the stagnant layer.

(Cs-Cb) - Concentration gradient for diffusion of drug.

Equation 2 represents first order dissolution rate process, the driving force for which is the concentration gradient (Cs-Cb).Under such a situation, dissolution is said to be under non sink

conditions. This is true in case of *in vitro* dissolution in a limited dissolution medium. Dissolution in such a situation slows down after sometime due to built-up in the concentration of drug in the bulk of the solution. The *in vivo* dissolution is always rapid than *in vitro* dissolution because the moment the drug dissolves, it is absorbed into the systematic circulation. As a result, Cb = 0, and dissolution is at its maximum. Thus, under *in vivo* conditions, there is no concentration built-up in the bulk of the solution and hence no retarding effect on the dissolution rate of the drug i.e., Cs>>Cb and sink conditions are maintained. Under sink conditions, if the volume and surface area of solid are kept constant, then equation 2 reduces to

$$\frac{dC}{dt} = K$$

Where, K incorporates all constants.

To obtain good in vitro-in vivo dissolution rate correlation, the in vitro dissolution should be carried underneath sink conditions. this could be achieved by

• Bathing the dissolving solid in recent solvent from time to time

• Increasing the amount of dissolution fluid

• Removing the dissolution drug by partition it from the liquid section of the dissolution fluid into an organic section placed either higher than or below the dissolution fluid-for example, solvent or chloroform.

• By adding chosen adsorbents to get rid of the dissolved drug.

• Adding a water miscible solvent like alcohol to the dissolution fluid.

• By adding chosen adsorbents to get rid of the dissolved drug

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The in vitro sink conditions area unit thus maintained that Cb is always but 100 pc of Cs. The Noyes-Whitney's equation assumes that the area of the dissolving solid remains constant throughout dissolution, that is much unacceptable for dissolving particles. Hence, dissolution ways that involve use of constant {surface area unita|area|expanse|extent} discs are utilized to determine the rate of dissolution. To account for the particle size decrease and alter in area

related to dissolution, Hixson and Crowell's cubic root law of dissolution is employed

$$W_0^{1/3} - W^{1/3} = Kt$$

Where, W_0 - Original mass of the drug

W - Mass of the drug remaining to dissolve at time t.

K - Dissolution rate constant.

Penetration or surface renewal theory (Danckwerts model): This theory didn't approve of the existence of a stagnant layer and instructed that turbulence in the dissolution medium exists at the solid/liquid interface. As a result, the agitated fluid consisting of macroscopical mass of eddies or packets reach the solid/liquid interface in a very random fashion due to eddy currents, absorb the substance by diffusion and carry it to the bulk of the answer. Such solute containing packets are unendingly replaced with new packets of contemporary solvent due to that the drug concentration at the solid/liquid interface never reaches cs and has a lower limiting price of Ci. Since the solvent packets are exposed to new solid surface each time, the theory is called as Surface renewal theory. Danckwerts model is expressed by equation

$$V\frac{dc}{dt} = \frac{dm}{dt} = A(Cs - Cb)\sqrt{\gamma D}$$

Where, m - Mass of solid dissolved.

Interfacial barrier model: In some cases, the interfacial barrier between the solid surface and the solvent is important and, an intermediate concentration less than saturation exist at the interface. This role of the solvation mechanism has been deduced from studies of dissolution as a function of solubility rather than diffusion. In earlier studies, Higuchi4 discussed the interfacial barrier and recommended that the true microscopic surface area not geometric should be considered. Since the different faces of a crystal should have different interfacial barriers

$$G = Ki\,(Cs - C) \rightarrow 1$$

Where G is the dissolution rate per unit area; Ki is the effective interfacial transport constant. If the interfacial concept is combined with the diffusion layer model.

$$G = \frac{D}{h} \times Cs - C/\left[1 + \frac{D}{hKi}\right] \rightarrow 2$$

And if Ki>>D/h it reduces back to the basic film theory equation. However if Ki <D/h it reduces to the interfacial barrier, for Danckwerts model, if the interfacial barrier concept is applied.

$$G = \sqrt{\gamma D(Cs - C)}/1 + \sqrt{\gamma D} \rightarrow 3$$

Which again reduces to the basic Danckwerts equation, if Ki >D or eq. if Ki<< D. Wurster and tailor reported that the double barrier mechanism better described the dissolution data on prednisolone. Also other studies on the dissolution of a single crystal showed that this substance dissolves by some interfacially controlled process in aqueous medium.(Leon S ,2005)

Factors: Factors to be considered for designing dissolution test are factors related to the dissolution apparatus; factors related to the dissolution fluid or medium; factors related to the test medium.

Factors related to the dissolution apparatus: Capacity of the vessel (in ml to litres); Design of the container (cylindrical, flat bottomed round bottomed or hemispherical; Method of agitation (rotating, stirring) and speed of agitation.

The design of the dissolution equipment should be in compliance with the compendia specifications. The equipment ought to allow convenient technique of introducing the capsule into the dissolution medium. It should enable the check operator to look at the capsule

throughout the check. The equipment ought to be made in such how that no part of it ought to contribute any type of agitations, motion or vibrations throughout the check except those caused by the swimmingly rotating stirring component. The speed of agitation ought to be controlled, high speed of agitation leads to quick dissolution of the drug and should hamper the discrimination between the formulations or batches. On the opposite hand, low speed of agitation results variations in mixture.

Factors related to the dissolution fluid or medium

Selection of the dissolution medium: Though the water is considered to be the most preferred medium but it is not a universal medium for all types of drugs because of solubility constrains and pH changes as the drug dissolves. Solubility of acidic drugs is tested in acidic medium and for basic drugs basic medium is selected. For this purpose, the pH of the medium is adjusted with buffers, so that the dissolution medium reflects the simulated acidic and basic environment of the gastric and intestinal fluids. Non-aqueous dissolution media are not preferred because they do not resemble the aqueous environment of gastrointestinal fluids.

Volume of the medium: The volume of the dissolution medium should be as per the specifications under each monograph. It should be sufficient enough to maintain sink conditions. Therefore, the volume of the medium should be about 3-5 times the saturated volume. The general practice is to take 900ml of the medium in a 1000ml vessel.

Temperature of the medium: The temperature of the dissolution medium is maintained at 37±5^{0}C to simulate with the body temperature.

Factors related to the test medium

Sampling technique: Two types of sampling techniques are i. Continuous sampling technique ii. Intermittent sampling technique In continuos sampling, a small volume of the dissolution medium is withdrawn from the dissolution vessel at specified intervals and analyzed to calculate the amount of dissolved drug. Volume corrections are not necessary because the dissolution medium for analysis is returned to the vessel after it is analysed. In intermittent sampling, the

medium withdrawn for analysis is not returned to the vessel. Hence volume corrections to necessary to account for the volume of drug content in the withdrawn medium or the dilution resulting from addition of fresh medium to maintain the constant volume.
(Abdou HM, 1989)

Apparatus-1

Rotating basket dissolution apparatus: The rotating basket apparatus (apparatus-1) consist of a cylindrical basket held by a motor shaft. The basket holds the sample and rotates in a round flask containing the dissolution medium. The entire flask is immersed in a constant temperature bath set at 370C. The rotating speed and the position of basket must meet specific requirements set forth in the current USP. The most common rotating speed for the basket method is 100 rpm. The dissolution calibration calculation standard is available to make sure that these mechanical and operating requirements are met. Figure 1 is generally preferred for capsules and for dosage forms that tend to float or disintegrate slowly.

Vessel: Cylindrical, 160-210 mm high, inside diameter 98-106 mm, nominal capacity is 1000 ml, sides are flanged at the top; Shaft: Positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble; Materials of Construction: Shaft and basket components are stainless steel, type 316 or equivalent; Basket position: the distance between the inside bottom of the vessel and the basket is maintained at 25± 2 mm during the test.

Apparatus-2

Rotating paddle dissolution apparatus: It consists of a special, coated paddle that minimizes turbulence due to stirring. The paddle is attached to vertically to a variable speed motor that rotates in a controlled speed. The tablet or capsule is placed into the round bottom dissolution flask, which minimizes turbulence of the dissolution medium. The apparatus is housed in a constant temperature water bath maintained at 37^0C, similar the rotating basket method. The

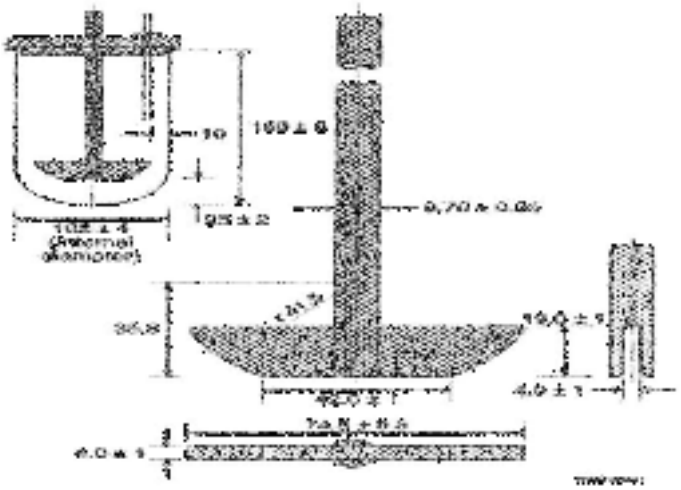
position and alignment of the paddle are specified in USP. The paddle method is very sensitive to tilting improper alignment may drastically effect the dissolution results with some drug products. The same set of dissolution calibration standard is used to check the equipment before tests are run .The most common operating speeds for apparatus 2 are 50 rpm for oral solid dosage form and 25 rpm for suspension. Figure 2 is generally preferred for tablets. A sinker, such as a few turns of platinum wire, may be used to prevent a capsule or tablet from floating. A sinker may also be used for flim-coated tablet that stickled to the vessels walls or to help position the tablet or capsule under the paddle. The sinker should not alter the dissolution characteristic of the dosage form.

Vessel: cylindrical, 160-210 mm high, inside diameter 98-106 mm, nominal capacity is 1000 ml, sides are flanged at the top; Shaft: positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble;

Materials of Construction: Shaft and blade are a single entity that may be coated with a suitable inert coating; Blade position: the distance between the inside bottom of the vessel and the blade is maintained at 25±2 mm during the test. The blade passes through the diameter of the shaft so that the bottom of the blade is flush with the bottom of the shaft.

Apparatus: The most commonly employed dissolution test methods are (1) the basket method (Apparatus1) and (2) the paddle method (Apparatus 2) (Shah 1989). The basket and the paddle methods are simple, robust, well standardized, and used worldwide. These methods are flexible enough to allow dissolution testing for a variety of drug products. For this reason, the official in vitro dissolution methods described in U.S. Pharmacopeia (USP), Apparatus 1 and Apparatus 2 should be used unless shown to be unsatisfactory. The *in vitro* dissolution procedures, such as the reciprocating cylinder (Apparatus 3) and a flow-through cell system (Apparatus 4) described in the USP may be considered if needed. These methodologies or other alternatives/modifications should be considered on the basis of their proven superiority for a particular product. Because of the diversity of biological and formulation variables and the evolving nature of understanding in this area, different experimental modifications may need to

be carried out to obtain a suitable *in vivo* correlation with *in vitro* release data. Dissolution methodologies and apparatus described in the USP can generally be used either with manual sampling or with automated procedures.(USP-NF-34,2011)



Schematic diagram Rotating paddle dissolution apparatus

Dissolution medium

Dissolution testing should be carried out under physiological conditions, if possible. This allows interpretation of dissolution data with regard to *in vivo* performance of the product. However, strict adherence to the gastrointestinal environment need not be used in routine dissolution testing. The testing conditions should be based on physicochemical characteristics of the drug substance and the environmental conditions the dosage form might be exposed to after oral administration. The volume of the dissolution medium is generally 500, 900, or 1000 ml. Sink conditions are desirable but not mandatory. An aqueous medium with pH range 1.2 to 6.8 (ionic strength of buffers the same as in USP) should be used. To simulate intestinal fluid (SIF), a dissolution medium of pH 6.8 should be employed. A higher pH should be justified on a case-by-case basis and, in general, should not exceed pH 8.0. To simulate gastric fluid (SGF), a dissolution medium of pH 1.2 should be employed without enzymes. The need for enzymes in SGF and SIF should be evaluated on a case-by-case basis and should be justified. Use of water as a dissolution medium also is discouraged because test conditions such as pH and surface tension can vary depending on the source of water and may change during the dissolution test itself, due

to the influence of the active and inactive ingredients. For water insoluble or sparingly water soluble drug products, use of a surfactant such as sodium lauryl sulphate is recommended. The need for and the amount of the surfactant should be justified. Use of a hydro alcoholic medium is discouraged. All dissolution tests for IR dosage forms should be conducted at 37±0.5°C. The basket and paddle method can be used for performing dissolution tests under multimedia conditions (e.g., the initial dissolution test can be carried out at pH 1.2, and, after a suitable time interval, a small amount of buffer can be added to raise pH to 6.8). Alternatively, if addition of an enzyme is desired, it can be added after initial studies (without enzymes). Certain drug products and formulations are sensitive to dissolved air in the dissolution medium and will need de aeration. In general, capsule dosage forms tend to float during dissolution testing with the paddle method. In such cases, it is recommended that a few turns of a wire helix (USP) around the capsule be used. The apparatus suitability tests should be carried out with a performance standard (i.e., calibrators) at least twice a year and after any significant equipment change or movement. However, a change from basket to paddle or vice versa may need recalibration. The equipment and dissolution methodology should include the product related operating instructions such as de aeration of the dissolution medium and use of a wire helix for capsules. Validation of automated procedures compared to the manual procedures should be well documented. Validation of determinative steps in the dissolution testing process should comply with the set standards for analytical methodology.

Agitation: In general, mild agitation conditions should be maintained during dissolution testing to allow maximum discriminating power and to detect products with poor *in vivo* performance. Using the basket method the common agitation (or stirring speed) is 50-100 rpm and with paddle method it is 50-75 rpm.

Temperature: Regarding media temperature, 37 ± 0.5°C should generally be used for oral dosage forms. Slightly increased test temperatures (38 ± 0.5°C) are under consideration for special applications e.g. for rectal dosage forms, lower temperatures (32 ± 0.5°C) for transdermal systems.

Validation: Validation of the dissolution apparatus/methodology should include, system suitability test; deaeration, if necessary; validation between manual and automated procedures and validation of a determinative step (i.e., analytical methods employed in quantitative analysis of dissolution samples). This should include all appropriate steps and procedures of analytical methods validation.

Dissolution test parameters

Temperature: Temperature control during the dissolution process is very important and should be maintained within 0.5^0C range as drug solubility is temperature dependent. Generally, a temperature of 37^0C is maintained during dissolution determined. The effect of temperature variations of the dissolution medium depends mainly on the temperature/solubility curves of the drug of excipients in the formulation.

Dissolution medium: The selection of proper fluid for dissolution testing depends largely on the solubility of the drug.

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 thereby improve the penetration process of the matrix. Conventional tablet formulae and capsules showed significant enhancement in the dissolution rate of poorly soluble drugs when surfactants were added to the dissolution medium, even at a level below the critical micelle concentration, probably by reducing the interfacial tension. Low levels of surfactants were recommended to be included in the dissolution medium as this seemed to give a better correlation between the *in vitro* data and *in vivo* condition.

pH of the dissolution medium: Great emphasis and efforts was first placed on simulating *in vivo* conditions, especially pH, surface tension, sink condition. Most of the early studies were conducted in 0.1N HCl or buffered solutions with a pH close to that of gastric juice (pH 1.2) the acidic solution tends to disintegrate the tablets slightly faster than water there by enhancing

dissolution rate by increase in the effective surface area. However, because of the corroding action of the acid fumes in the dissolution equipment became general practice to use distilled water unless investigative studies show a specific need for the acidic solutions in order to generate meaningful dissolution data. To avoid deleterious effects of hydrochloric acid, it can be replaced with acidic buffers, such as sodium acid phosphate, to maintain the required pH.

Adsorption and Sorption: Large number of pharmaceutical dosage forms, along with active ingredient contains excipients which may adsorb active ingredient. The contents of gastrointestinal tract as well as stomach and intestinal walls can be considered as potential adsorption sites for the drug molecules. Therefore, it is necessary to see effect of adsorption on dissolution. Physical properties of compressed tablets may change due to sorption of water which may influence disintegration and dissolution.

Applications:

• Dissolution testing is widely used in the pharmaceutical industry for optimization of formulation, quality control and in the pharmaceutical and biotechnology industry to formulate drug dosage forms, to develop quality control specifications for its manufacturing process.
• To identify the critical manufacturing variable, like the binding agent effect, mixing effects, granulation procedure, coating parameters and comparative profile studies. To select candidate formulation, simulate food effect on bio availability, support waiver for bio equivalence requirements and study of bio waivers.
• As a surrogate for *in vivo* studies and *in vitro in vivo* correlations. Even though less experience is available with novel/special dosage forms than is available with conventional dosage forms, *in vitro/in vivo* correlations have been established. In such cases it is legitimate to use *in vitro* dissolution as a surrogate for the *in vivo* performance of a drug product, as long as the rate-limiting step is the release of the drug from the formulation; regulations should also support this. Because of the typically higher variability of *in vivo* and *in vitro* data in the case of many novel/special dosage forms, expectations about the quality and level of *in vitro/in vivo* correlations might have to be adjusted in comparison to those for conventional dosage forms.

• It is worth noting that in general, an *in vitro* dissolution/release test is expected for each novel/special dosage form regardless of whether the intended effect is systemic or nonsystemic (eg, topical semisolid dosage forms), for formulation development, for investigations to support post approval changes, and for batch-tobatch quality control. It has to be noted, however, that because of the specific formulation design, because of potential (physicochemical) interactions between the dosage form and the physiological environment at the site of administration, and because of the necessary design of *in vitro* dissolution equipment for novel/special dosage forms, dissolution/release data *in vitro* might be more strongly influenced by test or equipment parameters or less predictable for *in vivo* release than is usually experienced for conventional dosage forms. Therefore, a scientifically sound assessment of the relevance and validity of an *in vitro* dissolution test should affect the final decision about the application of the test and the specifications set for batch-to-batch quality control. (Abdou HM, 1989).

Conclusion:

Dissolution research started to develop in 1897 by Noyes and Whitney .They derived their equation by dissolution studies using benzoic acid and lead chloride. The goal of dissolution testing is to assure the pharmaceutical quality of the product (manufacturing of product, release property & biopharmaceutical characteristics e.g. rate and extent of absorption). Dissolution testing is a routine work for pharmaceutical quality control for oral solid dosage forms like tablets, capsules and transdermal drug delivery systems. The science of dissolution testing is developing every day.

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