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DISSOLUTION METHOD DEVELOPMENT AND VALIDATION : A REVIEW

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ABSTRACT

The dissolution process started to develop about 100 years ago as a field of pharmacy and since then important progress has been made. Interest in drug related dissolution has grown only since the realisation that dissolution is an important factor of drug bioavailability in the 1950s. Dissolution test is required to study the drug release from the dosage form and its in vivo performance. Dissolution test is used to assess the lot to lot quality of drug product. The development and validation of dissolution procedures is of paramount importance during development of new formulation and in quality control. The dissolution procedure must be properly developed and validated. The objective of this paper is to review the development and validation of dissolution procedure(s) and to provide practical approaches for determining specificity, linearity, range, accuracy, precision, limit of detection, limit of quantitation and robustness of methods. Developing and validating dissolution test procedures can be a challenging process, on multiple fronts. Methods must be developed and validated not just for the dissolution test procedure itself, but also for any assay used to evaluate the test results.

KEYWORDS : *Dissolution apparatus, Dissolution Method development, Bioavailability Validation parameters, automation.*

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INTRODUCTION

Dissolution is a technique in which a solid substance solubilises in a given solvent i.e. Mass transfer from the solid surface to the liquid phase (Brahmankar et al., 1995). It is an analytical technique employed to measure the release profile from dosage forms such as tablets and capsules.

Dissolution examination is a process which is used to measure the release profile of the drugs from formulations which are commonly solid oral dosage forms like tablets and capsules. Dissolution mainly takes place in two steps,

1) Liberation of the drug from the formulation,
2) Dissolution of drug in the liquid medium

(Gowthamarajan.K, et al., 2010)

Dissolution testing of formulations was brought out in 1960s and it was recognized through health regulatory authorities in 1970s, and then the importance of dissolution has grown rapidly. Modern researches lead to the development of in-vitro dissolution tests as an alternate of animal bioequivalent studies (Rolf Rolli et al., 2003). The dissolution process needs an apparatus, a dissolution medium, and test conditions that provide a method i.e. Selective yet sufficiently rugged and reproducible for every day operation and capable of being transferred between research laboratory. The basic destination of dissolution testing is to allow the measurement of bioavailability of a dose in addition to bioequivalence of batch to batch. Hence properly organized dissolution test is necessary for biopharmaceutical formulations. The principle for carrying these tests is that, for a product to be therapeutically efficient, the drug must be discharged from the product and should broadly be dissolved in the fluids of the gastrointestinal tract. The API in solution form helps the absorption of the drug from the gastrointestinal tract into the systemic circulation to achieve its desired target area to exert its effect. The data received as a result of dissolution examination guides the development of novel formulation and product development and also dissolution is necessary for regulatory approval for product marketing. (Saeed A. Qureshi, et al) In these times all solid oral dosage forms need dissolution testing as a quality control test before brought in into market. For the development of advantageous dissolution tests respective regulatory, Pharmacopeial, and industrial organizations have published the guidelines that allow information about the development and validation of dissolution test methodology and specifications.

Dissolution is expressed in terms of a rate process. If the rate increases, the dissolution process also increases. Dissolution rate possibly defined as the amount of drug substance that enters solution per unit time below standardized experimental condition. Noyes-Whitney's equation is valuable in estimation of rate of dissolution. (Subrahmanyam C.V.S, et al., 2008)

The rate of dissolution is described as:

$dC / dt = KS (C_S - C)$

Where K = dissolution rate constant,

S = surface area of the particles,

C_S = equilibrium solubility of drugs,

C = concentration of drug in the bulk of drug (Subrahmanyam C.V.S, et al., 2008)

The theories which explain drug dissolution are:

1. Diffusion layer model/film theory
2. Danckwert's model/ surface renewal theory
3. Interfacial barrier model. (Brahmankar et al., 1995).

Validation is defined as attested evidence that allows assurance that particular instrument performs according to producer's specifications and user necessities. For dissolution setup, validation is obtained through installation qualification and operational qualification (Sharon M, et al., 2004)

PHYSICAL AND CHEMICAL PROPERTIES:

The initiative in the development of a fresh dissolution is the evaluation of physical and chemical information of drug content. Knowledge of these information will help the selection of dissolution medium and its volume. Some of the physicochemical properties of API that determine the dissolution characteristics are:

- Ionization constants (p*K*a),
- Solubility as a function of pH,
- Solution stability as a function of pH,
- Particle size,
- Crystal form, and
- Common ion, ionic strength, and buffer effects,
- Temperature
- Agitation
- Dissolution medium pH.

Knowledge of the pKa is valuable since it specifies the charge of the particle in solution at any given pH. The drug content solubility in dissolution medium shouldn't be the rate-limiting step. The

solution state solubility of API is also be studied on the designing of dissolution test, because the molecule stability in respective dissolution media might limit the pH scale range over which the drug product dissolution can be measured. (Cynthia k. Brown et al., 2005). During the first stages of drug development, dissolution test helps the formulation development. During this phage of drug development normally bioavailability data is not available. In the absence of bioavailability data, the dissolution medium choice should be based on physicochemical properties, the developed design, and the intended dose. The pH solubility of the drug and intended dose are necessary parameters to be considered in dissolution technique development. The suitable dissolution medium selection and dissolution apparatus can be decided based upon the physico-chemical properties of drug substance and dosage form. Deciding the type of release of dosage form and expected site of in-vivo absorption helps in selection of dissolution media, testing apparatus, and test duration. (Subrahmanyam C.V.S, et al., 2008)

DISSOLUTION APPARATUS SELECTION:

The selection of apparatus is based on formulation design and practical aspects of dosage form performance in the in vitro test arrangement. Dissolution testing is carried on equipment which has suitableness such as described in United States Pharmacopeia (USP) under the charters of Dissolution and Drug discharge. Various authorized types of dissolution apparatus are (Cynthia k. Brown et al., 2005).

- Basket type (USP apparatus 1)
- Paddle type (USP apparatus 2)
- Reciprocating cylinder type (USP apparatus 3)
- Flow -through cell type (USP apparatus 4)
- Paddle over disc type (USP apparatus 5)
- Cylinder type (USP apparatus 6)
- Reciprocating holder type (USP apparatus 7)

The basket method (USP) is habitually applied for solid oral dosage forms such as capsules and tablet (especially for immediate release products) formulations at an agitation of 50-100rpm. The paddle method (USP) for solid dosage forms such as tablets and capsules formulation at 50 or 75rpm. The paddle technique is also used for oral suspensions. The reciprocating cylinder (USP) is especially used for bead type modified-release dosage forms. Flow-through cell (USP) is for modified dosage forms particularly which contains active pharmaceutical ingredient with lower solubility. The reciprocating cylinder and flow-through cell also employed for soft gelatin capsules, bead products, suppositories, or poorly soluble drugs. The paddle over disk (USP) and cylinder (USP) are valuable for evaluation of Transdermal dosage forms. The reciprocating holder (USP) demonstrates the application to non-disintegrating oral modified release dosage forms in addition to Transdermal dosage forms. (Cynthia k. Brown et al., 2005),(Bhavesh Vaghela, et al., 2011).

Table 1.USP Apparatus and Agitation Criteria based on dosage form type

USP apparatus	Apparatus name	Rotation speed rpm	Dosage form
I	Basket method	50-100	Solid oral dosage forms like tablets and capsules
II	Paddle method	50-75	Solid oral dosage forms, oral suspensions and oral disintegrating tablets
III	Reciprocating cylinder	6-35	Bead type modified release dosage forms
IV	Flow through cell	-	Modified release dosage forms, that contain API with limited solubility

V	Paddle over disk	25-50	Transdermal patches
VI	Cylinder	-	Transdermal
VII	Reciprocating holder	30	Non-disintegrating oral modified-release dosage forms

DISSOLUTION MEDIUM SELECTION:

For natural selection of dissolution medium, physical and chemical properties of drug substance are to be considered which includes solubility, solution state solubility and pH. Additional drug product properties include release mechanism, disintegration rate which is affected by formulation hardness, friability, and excipients. When adjusting the composition of the medium to generate sink conditions, the influence of surface-active agents, pH value, and buffers on the solubility and stability of the drug should be measured. (Cynthia k. Brown et al., 2005). Key properties of the dosage unit that might affect the dissolution, enteric-coating, modified-release mechanism, and disintegration rate are hardness, friability, presence of solubility enhancers, and the presence of other excipients. Selection of dissolution medium is based on solubility data and dose of drug product in order to ensure that sink conditions are met. The term sink condition defined as the volume of medium at least greater than three times that need to form a saturated solution of drug matter. The selection of medium will depends upon the purpose of the dissolution test. The oral formulations should foremost valuated utilizing test media within the physiological pH range of 1.2 to 6.8. (Bhavesh Vaghela, et al., 2011)

Purified water is much used as the dissolution medium but isn't ideal for numerous reasons: the quality of water can alter depending upon the source of water; the pH value is inherently difficult to measure because the pH value can alter from day-after-day and may also modify during the run depending upon the active substance and excipients; and at last, the surface tension may also be variable and dependent on the excipients in the formulation. Apart from the limitations it is cheap, readily available, disposed of easily, ecologically satisfactory,

Generally used dissolution medium's are;

- Purified water
- Diluted hydrochloric acid (0.001N-0.1N)
- Buffered aqueous solutions (pH-4.8)
- Simulated gastric fluids (with or without enzymes)
- Simulated intestinal fluids (with or without enzymes)
- Surfactants (with or without acids and surfactants) (PatimaManeesatid, et al., 2005)

The basic dissolution medium is hydrochloric acid and other media includes artificial gastric fluids, water, surfactants such as Polysorbate 20, Polysorbate 40, Polysorbate 60 Polysorbate 80, sodium lauryl sulfate, and bile salts. The dissolution medium with a physiological pH of 1.2-6.8 is employed for oral formulations. For very poor soluble compounds aqueous solutions containing surfactants may be used. The medium volumes are within a range of 500 ml to 1000 ml where 900 mi is the common volume. Volumes as high as 2-4 L are used and as low as 100 ml for high strength drug formulations. Whenever the dissolution occurs in the intestinal tract, a broader pH range (pH of 6.8) will be more appropriate. Simulated intestinal fluid of pH 6.8 is used for those drugs. (Bhavesh Vaghela, et al., 2011).

KEY OPERATING PARAMETERS:

The key operating parameters includes Media volume, Temperature, Deaeration.

- **Media volume**: - The suggested volume of dissolution is 500 ml to 1000 ml, where as 900 ml is the more common volume used when using the basket and paddle apparatus. The volume is raised to 2 to 4L depending on the concentration and sink conditions of the drug.
- **Temperature**: - The acceptable temperature for the dissolution medium is 370C for oral dosage forms, increased

temperatures such as 380C for suppositories and low temperatures of 320C for topical dosage forms such as Transdermal patches and topical ointments. (Cynthia k. Brown et al., 2005).

- **Deaeration**: - The significance of deaeration should be determined bit-by-bit, air bubbles can intervene with the test results, acting as a barrier to dissolution whenever present on the dosage unit or basket mesh. Air bubbles can also cause particles cling to apparatus walls and this may step-up the dissolution rate or drop-off the dissolution rate. (Cynthia k. Brown et al., 2005).

The fallowing methods are described in USP for deaeration:

a. Heating of medium fallowed by filtration,
b. Room temperature filtration,
c. Sonication,
d. Helium sparging.

VALIDATION:

The method should be validated for linearity, accuracy, precision, specificity, and ruggedness. The extent of validation depends upon the form of the product development. For products containing more than a single active ingredient, the dissolution method demands to be validated for each active ingredient.

Linearity:

Linearity should be checked over the entire range of concentrations expected during the procedure. The ICH recommendation for range of dissolution methods is 20% of the specification limits. Ex: whenever the specification of an immediate-release tablet is ''no tablet less than 80% in 45 min" then the range to be checked would be from 60% to 100% of the tablet's lay claim. The concentration range is separated into five equally spaced concentrations. Linearity testing of the dosage form should cover the entire range of the product. Linearity is measured by appropriate statistical procedure such as calculation of regression. The linearity results should include the coefficient of correlation, y-intercept, and slope of the regression curve. . (Cynthia k. Brown et al., 2005).

Accuracy:

Accuracy samples are developed by dissolving bulk drug and excipients in the specified volume dissolution fluid. If the dosage form is a capsule, the equivalent size and coloring material of capsule shell should be added to the mixture. The solution should be examined according to the parameters fixed in method includes temperature, rotation speed, filters, sampling mode, and detection mode. (Cynthia k. Brown et al., 2005).In cases of poor drug solubility, it possibly appropriate to develop a stock solution by dissolving the drug substance in a little amount of organic solvent (typically not exceeding 5%) and diluting to the final concentration with dissolution medium. An amount of stock solution equivalent to the targeted label claim may be added to the vessel instead of the drug powder. (Bhavesh Vaghela, et al., 2011)

Precision:

Precision should be checked by examining at least six times a homogeneous sample of each dosage strength. The precision should be evaluated at each specification interval for the dosage form. It can be determined by calculating the relative standard deviation of each solution. The dissolution profiles on the same sample may be run by at least two different analysts, each analyst preparing the standard solutions and the medium. . (Cynthia k. Brown et al., 2005). Intermediate precision may be evaluated to determine the effects of random events on the precision of the analytical procedure. This evaluation is typically done later in the development of the drug product. (Bhavesh Vaghela, et al., 2011)

Specificity:

The dissolution method must be particular for the bulk drug substance in the presence of placebo. A mixture of dissolution fluid and the excipients should be tested for specificity. The placebo consists of all the excipients and coatings without the active ingredient. (Bhavesh Vaghela, et al., 2011).Placebo interference may be decided by weighing samples of the placebo blend and dissolving or dispersing them in dissolution

medium at concentrations that would be encountered during testing. Specificity testing should be confirmed by analyzing accuracy samples with a selective analysis mode such as HPLC.(Cynthia k. Brown et al., 2005)

Ruggedness:

Ruggedness testing should find out the critical parameters for a particular dissolution medium. Ruggedness testing should assess the effect of pH, media volume, rate of flow, rotation speed; apparatus sample position, media deaeration, temperature and filters. Ruggedness of the technique should be evaluated by carrying the method with multiple analysts on multiple systems. .(Cynthia k. Brown et al., 2005).

Validation of analytical methods employed in quantitative analysis of dissolution samples includes temperature distribution study, rotation speed study.

AUTOMATED SYSTEMS:

Laboratories automatize the dissolution tests to increase capability, improve accuracy, and to reduce the cost per test. SOTAX has developed the automation concept. To automate dissolution tests, the fallowing criteria's are to be considered;

- Quantity of tests
- Type of test
- Duration of test
- pH changes during the test
- media replacement
- time and number of sampling points
- standard monitoring

The medium preparation device is the initiative in automation. Dissolution methods are time consuming and require a significant amount of labour. The true cost of expanded regulatory requirements and documentation can be better managed by automation. (Rolf Rolli et al., 2003).

Automating the Manual Method:

Minor changes to the manual approach must be made in order to make the automatized process authentic and effective.

Ex: An example relating to dissolution is sampling. In manual method sampling would be done with syringe with cannula. In automation cannula is replaced by a filter and the medium carried through the filter. Attaining the method more automation requires verifying the suitableness of certain steps. The challenge of designing an automated system is to provide an automation-friendly approach that can improve the efficiency of manual process. (Dale VonBehren et al., 2005).

Advantages of automation:

- Easy validation of hardware and software
- Efficient sampling and cleaning system
- Easy media change procedures
- High accuracy and reproducibility
- Accurate sampling system
- Efficient cleaning system
- Easy validation. (Rolf Rolli et al., 2003).

There are two types of automated systems, they are Semi automated systems and Fully automated systems.

Semi automated systems:

The systems that execute sampling, filtration, and UV reading or collection are termed as semi automated systems. These are simple to arrange and can operate with lower cost. Procedures such as media preparation, dispensing, and cleanout are not executed by semi automated systems. (Dale VonBehren et al., 2005)

Fully automated systems:

Fully automated systems are automatize the whole process include some aspects of media preparation, media dispensing, tablet drop, sample removal, filtration, and also analysis. Media may be fully prepared by the system. (Dale VonBehren et al., 2005)

Table.2 An example of paddle method Fully automated system: (Rolf Rolli et al., 2003).

Testing step	Semi-automatic system	Automatic system
Medium preparation	Manually	Automatic
Sampling	Automatic	Automatic
Medium replacement	Not possible	Possible

calculation	Automatic	automatic
Emptying of vessels	Manually	Automatic
cleaning	Manually	Automatic
Start of the method	Automatic	Automatic

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