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Development and validation of dissolution procedures

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ABSTRACT

Dissolution test is required to study the drug release from the dosage form and its in vivo performance. Dissolution test is used to asses 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.

Key words: Dissolution procedure development, Dissolution apparatus, Dissolution medium, Validation parameters, Quality control.

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INTRODUCTION

The dissolution test is required for various dosage forms for product release testing. It is also commonly used as a predictor of the in vivo performance of a drug product. To satisfy dissolution requirements, the USP provides information in the way of a general chapter on dissolution, as well as related chapters on disintegration and drug release (USP 32-NF 27, 2009). The USP and FDA also provide guidelines on development and validation of dissolution procedures (USP 32-NF 27, 2009; ICH guideline, 2005; Guidance for Industry 1997, 2000) and while this white paper will draw from this information and will discuss the available guidance in some detail, the reader is encouraged to consult the reference for additional details. In vitro dissolution data, together with bioavaibility and chemistry, manufacturing and control data, is a critical component of any new drug application (NDA) submitted to the FDA. A dissolution test is really a simple concept; a tablet or capsule is placed into a known volume of media and as it dissolves the resulting solution is sampled over time, and assayed (often by HPLC or by spectrophotometry) for the level of active pharmaceutical ingredient (API) present. However, the design, development, and the validation of the procedure can be quite involved, especially when one considers that not only the dissolution procedure must be developed and validated, but also any analytical technique used for the assay.

QUALIFICATION AND CALIBRATION

Prior to undertaking the task of dissolution procedure development and validation, it is necessary to invest some time and energy up-front to ensure that the dissolution system itself is

validated or qualified. Qualification is a subset of the overall validation process that verifies proper module and system performance prior to the instrument being placed on-line in a regulated environment (Cardot et al, 2001; Abdou Hamed et al, 2001). Analysts for years have used salicylic acid tablets to qualify and "chemically" calibrate dissolution instruments. While UV spectrophotometric methods are commonly used for dissolution sample analysis. Figure 1 illustrates example HPLC methods commonly used for this purpose.

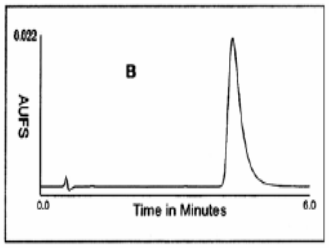

Fig.1 HPLC separation of a 20 µL injection of a 0.1 mg/mL (in water) salicylic acid USP standard. Column: 3.9 by 50 mm C18. A Mobile phase of 1.6% acetic acid/methanol 85/15, at a flow rate of 1.0 mL/min was used. Detection was by UV @ 270nm.

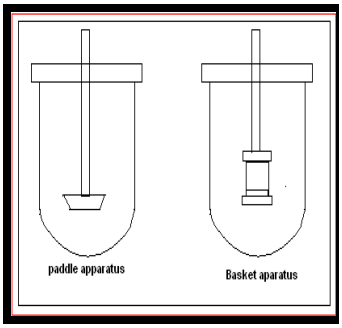

Fig. 2: USP Dissolution apparatus I and II

DISSOLUTION PROCEDURE DEVELOPMENT

The dissolution procedure has several distinct components**.** These components include a dissolution medium, an apparatus, the study design (including acceptance criteria) and the mode of assay. All of these components must be properly chosen and developed to provide a method that is reproducible for within laboratory day-to-day operation and robust enough to enable transfer to another laboratory.

The Dissolution Medium

When selecting the dissolution medium, physical and chemical data for the drug substance and drug product need to be considered, e.g. the solubility and solution state stabitily of the drug as a function of pH value. Other critical drug product properties include the release mechanism (immediate, delayed or modified) and disintegration rate as affected by formulation hardness, friability, presence of solubility enhancers and other excipients. When selecting the composition of the medium (Refer Table No.1), the influence of buffers, molarity, pH, and surfactants on the solubility and stability of the drug also need to be evaluated.

Table 1: Dosage forms with specific recommended dissolution medium (Cardot Et Al, 2001).

Sr.No.	Dosage form	Modulation in dissolution medium
1.	Semi-solid Topical Dosage forms (Creams, ointments, Gels)	Depending upon the solubility of the drug substance, the receptor medium may need to contain alcohol and /or surfactant. De-aeration is critical to avoid bubble formation at the interface with the membrane. As with transdermal products the test temperature is typically set at 32°C to reflect the usual skin temperature.
2.	Suppositories	Lipophilic suppositories release the drug after melting in rectal cavity and are significantly affected by rectal temperature (36.0-37.5°C). The test temperature should take into consideration physiological conditions but may also be at or slightly above the melting point, e.g. at 37.0 – 38.5 °C (e. g. Suppositories, used for patients with fever).
3.	Oral Suspensions	Rotating paddle method utilizing an aqueous dissolution medium. Sample introduction and agitation rate should be established on the basis of the viscosity and composition of suspension matrix.
4.	Buffered or Effervescent Tablets	Consider the physicochemical characteristics of the active ingredient (solubility, pKa or pKb, etc), buffered medium. Verify buffering capacity and ionic strength of the media.
5.	Lipid filled Capsules	An enzyme (lipases) in addition to surfactants to simulate digestion if this is a rate-limiting step for dissolution. Lipases more closely reflect physiological conditions, but it is costly.
6.	Chewing Gums	Test media with a pH 6.0 are commonly used, since this pH corresponds to saliva pH values of 6.4 (adults) or 7.3 (children).
7.	Powders, Granules, Solid Solutions and Solid Dispersions	The dissolution behavior of these dosage forms may be greatly influenced by their wettability, surface area and particle size distribution. For powders, when exhibiting poor wettability, it may be necessary to add a surfactant to the dissolution medium to obtain reproducible dissolution results. Care should be taken to use a level of surfactant that does not increase the solubility of the drug to the extent where the test is no longer discriminatory. Since solid solutions and dispersions usually lead to super saturation of the medium, it is often of interest to run the in vitro release test somewhat longer so that the potential for precipitation can be evaluated.
8.	Parenterals: Implants and Microparticles	The flow rate of the medium has to be set very slow. As tests are often run over a very long time period (e.g. Several weeks) measures have to be taken to compensate against evaporation and to prevent microbial growth in the medium. The composition of the medium should be taken into account for osmolarity, pH and buffer capacity of the fluids at the site of application, which are usually assumed to resemble to that of plasma.
9.	Transdermal Patches	The patch should be properly positioned so that the drug-loaded surface is exposed to the medium. The pH of the medium ideally should be adjusted to 5.0-6.0, reflecting physiological skin conditions. For the same reason, test temperature is typically set at 32.0°C.
10.	Dosage form with more than one active ingredient	Depending on the differences of the solubilities of the active ingredients, it may be necessary to have separate sets of dissolution conditions, one for each API.

The most common dissolution medium is dilute hydrochloric acid, however other media commonly used includes buffers in the physiologic pH of 1.2 to 7.5, simulated gastric or intestinal fluid (with or without enzymes), water and surfactants

(with or without acids or buffers) such as polysorbate 80, sodium lauryl sulfate and bile salts. The use of aqueous-organic solvent mixtures, while generally discouraged, can also be used if justified. Enzymes are also sometimes used in the media when testing gelatin capsule products. Media volumes are typically in the range of 500-1000 ml, with 900 ml the most common volume. Volumes as high as 2-4 L have been used and as low as 100 ml for high potency (low dosage strength) drug formulations. Media deaeration is usually required, and can be accomplished by heating the medium or (more commonly) filtering the medium or placing it under vacuum for short period of time. USP chapter 711 contains additional information on deaeration (USP 32-NF 27). During method development, results from dissolution samples run in nondeaerated medium versus a deaerated medium should be compared to determine whether deaeration is necessary. When developing dissolution procedure, one general goal is to have "sink" conditions. Sink conditions are defined as the volume of medium that is at least three times that required in order to form a saturated solution of drug substance. Dissolution results will more accurately reflect the properties of the dosage form when sink conditions are present.

The Dissolution Apparatus

The choice of apparatus is based on the dosage form performance in the in vitro test system. (Refer Table No 2 and 3). Figure 2 illustrates USP dissolution apparatus I and II. (Abdou Hamed, 2001; Bramankar et al, 2006; Shargel Leon et al,) Somewhat recently, an AAPS committee published recommendations for the type of apparatus recommended for novel or special dosage forms (Shargel Leon et al,).

These recommendations are summarized in Table 3. While changes to the approved apparatuses are allowed, justification must be provided. For some dosage forms, particularly capsules that might float on the media surface, "sinkers" may be required.

Table 2: USP Dissolution Apparatus

Type of Apparatus	Name of appartus As per usp
Type I	basket apparatus
Type II	paddle apparatus
Type III	Reciprocating cylinder
Type IV	flow through cell apparatus
Type V	Paddle over disk
Type VI	Cylinder
Type VII	reciprocating holder

USP chapter 711 (USP 32-NF 27, 2009) and USP chapter 1092 (USP 32-NF 27, 2009) provides additional detail for construction and usage of sinkers4. If sinkers are required, steps must be taken in method development to evaluate different types and construction, as sinkers can significantly affect dissolution. Agitation is also an important part of dissolution procedure. Coning or mounding problems can be solved by increasing the paddle speed. If justified, 100 rpm may be used, especially for extended release products (Refer Table No.4). Decreasing or increasing the apparatus rotation speed may also be justified (Abdou Hamed, 2001; Bramankar et al, 2006; Shargel Leon et al,). Selection of site for placing apparatus is also important; vibrations from doors closing or pumps (e.g. mass spectrometry instrument vacuum pumps) can cause significant variability.

Table 3: USP Dissolution Apparatus Selection For Various Dosage Forms

Dosage form	Apparatus (USP)
Solid dosage form (Immediate release, Modified release Products), chewable tablets	Type I -Basket apparatus Type II -Paddle apparatus
Bead type Modified release dosage form	Type III -Reciprocating cylinder apparatus
Modified release dosage form that contain active ingredients with limited solubility.	Type IV -Flow through cell apparatus.
Soft gelatin capsules, suppositories, poorly soluble drugs, implants	Type III & IV (Reciprocating cylinder and Flow through cell apparatus)
Transdermal dosage form	Type V -Paddle over disk Type VI –Cylinder apparatus
Nondisintegrating oral modified dosage form as will as traditional dosage form	Type VII -Reciprocating holder apparatus

Dissolution study design

Dissolution is evaluated by measuring rate release profile or the amount dissolved over time. Single or multiple points in time can be measured, depending upon the dosage type or data desired.

Table 4: USP Apparatus And Agitation Criteria

USP APPARATUS	DESCRIPTION	ROTATION SPEED	DOSAGE FORM
I	Basket	50-120 rpm	IR, DR, ER
II	Paddle	25-50 rpm	IR, DR, ER
III	Reciprocating cylinder	6-35 rpm	IR, ER
IV	Flow through cell	N/A	ER, POORLY SOLUBLE API
V	Paddle over disk	25-50 rpm	TRANSDERMAL
VI	Cylinder	N/A	TRANSDERMAL
VII	Reciprocating holder	30 rpm	ER

Where, IR= Immediate Release, DR= Delayed Release, ER= Extended Release

For immediate release dosage forms, the procedure duration is usually 30 to 60 minutes and in most cases, a single time point specification is adequate. However for formulation development comparison purposes, profile comparison is required and it is common to collect data from numerous time points (Refer Table No. 5).

Table 5: Various methods used to compare dissolution profile data

APPROACHES	METHODS	PARAMETERS/EQUATIONS
ANOVA-based (analysis of variance)	➢ Multivariate ANOVA	Statistical method (Uses formulation and time as class variable)
MODEL INDEPENDENT	➢ Ratio test procedure	o ratio of % dissolved o ratio of area under the dissolution curves o ratio of mean dissolution time
	➢ Pair wise procedures	o difference factor (f_1) o similarity factor (f_2) o index of Rescigno (ξ_1 ξ_2)
MODEL DEPENDENT	➢ Zero order	% dissolved = k * t
	➢ First order	% dissolved = 100(1- e^{-kt})
	➢ Hixson – Crowell $M_o^{-1/3} - M^{-1/3} = K \times t$	% dissolved = 100 [1 – (1 – $\underline{k \times t}$ / $4.616mg^{1/3}$)^3]
	Where M_o = 100 mg.	
	➢ Higuchi model	% dissolved = k × $t^{0.5}$
	➢ Quadratic model	% dissolved= 100 × ($k_1t^2 + k_2t$)
	➢ Gompertz model	% dissolved=A × $e^{-k-k(t-\gamma)}$
	➢ Logistic model	% dissolved = A/[1+$e^{-k(t-\gamma)}$]
	➢ Weibull model	% dissolved = 100[1-$e^{-(t/\tau)\beta}$]
	➢ Korsemeyar and peppas model	Mt/Ma = Kt^n

For extended release dosage forms, at least three test time points are typically chosen to characterize the in vitro drug release profile (Polli et al, 1997; Banker et al, 2001; Gibaldi et al, 1967; Higuchi et al, 1961). Sampling probe can affect the hydrodynamic of the system and so that change in dissolution rate. For position of sampling, USP / NF states that sample should be removed at approximately half the distance from the basket or paddle to the dissolution medium and not closer than 1 cm to the side of the flask. Filter material must be saturated with the drug by repeated passage to avoid losses that might go undetected during the test sampling. Accumulation of the particulate matter on the surface may cause significant error in the dissolution testing. Acceptance criteria must also be considered during test development. The acceptance criteria should be representative of multiple batches from the same nominal composition and manufacturing process, include key batches used in pivotal studies and batches that are representative of the drug product performance in stability studied. Acceptance criteria are derived in the form of "Q-factors" a minimum amount dissolved at a given time as a percentage of the labeled content. Dissolution tests can have a single Q-factor, or may have multiple Q-factors. A Q value in excess of 80% is not generally used, because allowance needs to be made for assay and content uniformity ranges. Finally, the dissolution test procedure should be discriminating enough to be capable of distinguishing significant changes in a composition or manufacturing process that might be expected to affect in vivo performance. In general, a properly designed dissolution test should result in reproducible data. Too much result variability can make it difficult to identify trends, true batch differences or effects of formulation changes. If too much variability is observed, the usual remedies include changing the apparatus type, speed of agitation, or deaeration; consideration and/ or examination of sinker type; and changing the composition of the medium. During routine testing of the product, variability outside the expected range should be investigated from analytical formulation and processing perspectives.

Assaying the results

There are two common ways of analyzing dissolution test samples, spectrophotometric (UV) determinations and HPLC. Typically the drug substance UV spectrum is observed to choose the optimum wavelength for analysis. Cells with path lengths ranging from 0.02 to 1 cm are used. HPLC methods, however, have distinct advantages, particularly when there is significant interference from excipients or between multiple active ingredients in the formulation. It also requires less sample volume.

DISSOLUTION PROCEDURE VALIDATION

Validation

According to FDA, Validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes. According to EU-guidelines, Validation means the action of proving, in accordance with GMP-principles that any procedure, process, equipment, material, activity or system actually leads to the expected results.

Validation is required for GMP-legislation, good economics and good science practices. Various guidance documents are ICH Q2A, ICH Q2B, FDA and Pharmacopoeias (USP and European Pharmacopoeia). Methods commonly validated are Identification, quantitative tests for content of impurities, limit tests for control of impurities, quantitative tests for active moiety in drug substances and drug products, dissolution testing and particle size determination (drug substance). Methods validated at different stages of product development are:

Phase 1: No validation data required.

Phase 2: For both drug substance and drug product supporting validation data on analytical methods should be available on request.

Phase 3 (Pivotal studies): Appropriate validation information should be provided. Assay validation should cover accuracy, precision, specificity (including stress testing), quantitation & detection limits, linearity and range (where appropriate).

Degradation should be identified, qualified and quantified and then NDA submission. Full validation reports of relevant methods must be included.

Table 6: recommended validation characteristics of various types of tests.

Type of tests/ characteristics	Identific-ation	Testing for impurities		Assay/ dissolution	Specifi c tests
		Quantitative	Limits		
Accuracy	-	+	-	+	+
Precision-repeatability	-	+	-	+	+
Precision-Intermediate precision	-	+	-	+	+
Specificity	+	-	+	+	+
Detection limit	-	+	+	-	-
Quantitation limit	-	+	-	-	-
Linearity	-	+	-	+	-
Range	-	+	-	+	-
Robustness	-	+	-	+	+

Validation is carried out to make sure that method or procedure accomplishes its intended purpose (USP 32-NF 27, 2009; ICH guideline, 2005). Dissolution testing fits into USP category III, which are analytical procedures for the determination of performance characteristics. Since dissolution is a quantitative test, all of the analytical performance characteristics apply, with the exception of the limit of detection. For HPLC based assay in a dissolution test, in addition to the procedure used to perform dissolution and assay the test results, some individual "sub-procedures" (e.g. filtration, solution stability) must also be validated.

Specificity/Placebo Interference

The ability to assess unequivocally the analyte in the presence of components which may be expected to be present (Impurities, degradants, matrix) is known as specificity. The aspects for specificity are identification; purity tests and assay (Content/potency).To evaluate specificity in dissolution procedure, it is necessary to demonstrate that the results are not affected by placebo constituents, other active drugs, or degradants in the drug product. A proper placebo should consist of everything in the formulation, except the active ingredients. Placebo interference may be evaluated by weighing samples of placebo blend and dissolving or dispersing it into the dissolution medium at concentrations that would normally be encountered during testing. The interference should not exceed 2%. For extended-release products may be appropriate to evaluate potential interference at multiple sampling points in the release profile. If the placebo interference exceeds 2%, then method modification, such as: (1) choosing another wavelength, (2) baseline subtraction using a longer wavelength, (3) using HPLC, may be necessary in order to avoid the interference. Absence of interfering peaks in the placebo chromatogram or lack of absorbance by the placebo at the analytical wavelength demonstrates specificity.

Linearity and Range

Linearity is the ability (within a specified range) to obtain test results which are directly proportional to the concentration of analyte in the sample. The aspects for linearity are testing across the range (at least 5 concentrations), to evaluate linearity by visual inspection of the plot and by statistical techniques; to calculate correlation coefficient, y-intercept and slope. Range is defined as an interval between upper and lower concentration of the analyte in the sample for which it has been demonstrated that the procedure has a suitable level of precision, accuracy and linearity. Range can be defined from linearity study and it depends on the application of the method of assay, dissolution test and content uniformity. Linearity and range are established by preparing solutions of the drug, ranging in concentration from below the lowest expected concentration to above the highest concentration during not to exceed the linearity limits of the instrument. Linearity is typically calculated and reported by least squares linear regression analysis of the curve generated from a minimum of five points. Typically, a square of the correlation coefficient demonstrates linearity. ICH recommends that for dissolution testing, linearity should be demonstrated as ± 20% over the range of the dissolution test.

Accuracy and Recovery

Accuracy expresses the closeness of agreement between the values which are accepted either as a conventional true value or an accepted reference value and the value found practically. Accuracy is measured by (1) Use of reference standard with known purity and (2) Comparison with independent, well-characterized procedure. Accuracy and recovery can be established by preparing samples containing the drug and any other constituents present in the dosage form ranging in concentration from below the lowest

expected concentration to above the highest concentration during release. ICH recommends a minimum of nine determinations over a minimum of three concentrations, e.g. three concentrations, three replicates each. The measured recovery is typically 95% to 105% of the amount added.

Precision

It is defined as a closeness of agreement ('scatter') between a series of measurements obtained from multiple sampling of the same homogeneous sample. The aspects for precision are (1) Repeatability, (2) Intermediate precision and (3) Reproducibility (Frank et al,2004).

Precision – Repeatability

Repeatability expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision. Repeatability is sometimes also termed within-run or within-day precision.

Precision - Intermediate precision

Intermediate precision expresses within-laboratories variations: different days, different analysts, different equipment etc. The ISO definition used the term "M-factor different intermediate precision", where the M-factor expresses the number of factors (operator, equipment or time) that differ between successive determinations. Intermediate precision is sometimes also called between-run, between-day or inter-assay precision.

Precision – Reproducibility

Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology). Reproducibility only has to be studied, if a method is supposed to be used in different laboratories. Unfortunately, some authors also used the term reproducibility for within-laboratory studies at the level of intermediate precision. This should, however, be avoided in order to prevent confusion.

For dissolution method validation purpose, precision is measured over two levels, repeatability and intermediate precision. Repeatability refers to the application of the procedure within one laboratory over a short period of time by one analyst using one instrument. Repeatability is determined by replicate measurements of standard and/or sample solution. It can be measured by calculating the RSD of the multiple HPLC injections or spectrophotometer readings for each standard solution. Repeatability can also be measured from the same samples used in the accuracy, recovery and linearity experiments. Intermediate precision is 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.

Limit of Detection

It is defined as a lowest amount of an analyte in a sample which can be detected but not necessarily quantitated. Detection methods like visual evaluation, signal-to-noise ratio (3:1) and standard deviation (SD) of response and slope (DL=3.3xSD/S).

Limit of Quantitation

It is defined as a lowest amount of an analyte in a sample which can be quantitatively determined with a suitable precision and accuracy. Quantitation methods like visual evaluation, signal-to-noise ratio (10:1) and standard deviation (SD) of response and slope (DL=10xSD/S).

Robustness

The robustness of an analytical procedure is the measure of its capacity to remain unaffected by small deliberate variations in parameters internal to the procedure (USP 32-NF 27, 2009; ICH guideline, 2005). For dissolution testing, parameter to be varied includes medium composition, pH, volume, agitation rate and temperature. These parameters would be investigated in addition to those typically evaluated during validation of assay method, either spectrophotometric or HPLC.

System Suitability Test

The test requires a set of parameters and criteria thereof to ensure the system is working properly. It depends on type of test. For chromatographic methods: tailing factor, relative retention times, resolution factor, relative standard deviation and number of theoretical plates should be calculated. The number of theoretical plates to be checked before start of run and to be verified afterwards. The suitable test is also described in Pharmacopoeias.

REMAINING VALIDATION TESTS

In addition to the common analytical performance characteristics normally evaluated for procedure validation, standard and sample solution stability and filter validation must also be validated.

CONCLUSION

Dissolution testing plays a very important role as an in-vitro test for evaluating drug products. 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. However, like any task, a systematic and methodical approach taking into account all the components that make up the dissolution test procedure, including the dissolution medium, the choice of apparatus, the test design (including the acceptance criteria), and determining the assay mode will pay great dividends in the end. There are only a few principle differences concerning validation of dissolution methods in the fields of pharmacokinetic studies and in quality control. Therefore, it seems reasonable to base the discussion on validation in the field of pharmaceutical technology on the experiences and consensus already existing in the closely related field of pharmacokinetic

studies for registration of pharmaceuticals and focus the discussion on those parameters, which are of special importance in quality control, i.e. selectivity, accuracy, precision and linearity. Need for pre-determined operational and performance user requirements (**URS**) of process or system to provide evidence on **consistency** of meeting these requirements.

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