



Mini Review

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Challenges Encountered in Dissolution Testing the Development of Various Dosage Forms

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Abstract

In vitro dissolution testing is the process that helps to determine the performance of the drug product by drug dissolving in the fluids prior to absorption into the systemic circulation. Dissolution testing of solid and semisolid dosage forms for evaluating drug release is an official method used by the pharmacopeia. Dissolution test is a tool to ensure consistent product quality, performance qualification, and to predict in vivo drug bioavailability, it includes biopharmaceutical characterization of drug product. Nevertheless, despite wide use of dissolution testing by the regulatory and pharmaceutical industry, the biggest challenge is to explore and validate the relationship between invitro dissolution and in vivo bioavailability. The aim of the review is to represent factors that may lead to the error results while developing various dosage forms in dissolution test, and to highlight issues and challenges encountered in dissolution methods in different formulations.

Keywords: Invitro; Dissolution; Challenges

Introduction

Dissolution is the process in which it measures the portion (%) that has been released from a tablet or capsule matrix that has been dissolved in the dissolution medium. Dissolution testing is used for characterizing the biopharmaceutical quality of a product. Dissolution testing is used to test various dosage forms such as tablets, chewable tablets, suspensions, suppositories, soft gelatin capsule, creams, ointments, gels, transdermal patches, spansule, chewing gums, granules, dispersions, microparticles, stents, niosomes, liposomes, implants, nanoparticles, released erythrocytes, floating tablets, buccal and sublingual tablets etc... dissolution is an invitro laboratory test in which it is very important in assessing changes in production site, manufacturing process or formulation bioavailability studies. The principal function of the dissolution test to assure product quality and drug release is uniform batch to batch consistency, assessment of uniform production quality and to show that release is equivalent to those

batches proven to be clinically effective and bioavailable. Dissolution data are useful in early stages of development to optimize drug and dosage form characteristics, and it can also be used to investigate a number of critical processing and formulation parameters to produce a more robust and better-quality drug product [1,2,3].

Different USP Apparatus Used in Dissolution Testing

There are 7 different USP apparatus that can be used for dissolution testing. Almost tablets and capsule use apparatus 1 and 2 i.e., basket and paddle. The basket and paddle are the two apparatus developed through the 1960s and adopted by the USA in the 1970s.

APPARATUS 1 – Basket apparatus – used for tablets, capsules, floating dosage forms

APPARATUS 2 – paddle apparatus – used for tablets, capsules, enteric forms

APPARATUS 3 – reciprocating cylinder – used for extended-release drug product

APPARATUS 4 – flow through cylinder – used for implants, suspensions, powders

APPARATUS 5 – paddle over disk – used for TDDS, ointments

APPARATUS 6 – rotating cylinder – used for TDDS

APPARATUS 7 – reciprocating holder – used for extended-release drug product [4,5].

Concept of Dissolution / Drug Release Testing

In the pharmaceutical industry, dissolution testing is important in drug development and quality control. It is used throughout the drug development cycle for product release and stability testing. Initially, dissolution testing was developed for immediate release oral dosage form and then for modified release solid oral dosage form, and later it was expanded to a variety of novel and special dosage forms. For orally administered immediate release drug products the test is referred to as “dissolution” test and for non-oral dosage forms such as transdermal drug delivery system and suppositories the test is referred to as “drug release”. Invitro dissolution testing is an important tool for characterizing the biopharmaceutical quality of the product, for assessment of availability of active pharmaceutical ingredients and for the evaluation of possible risk such as food effects, dose dumping, interaction with other drugs [6].

Dosage Forms with Recommended Modulation in Dissolution Medium

Dissolution tests for various dosage forms should consider variables such as rotation speed, surfactant type, concentration, medium pH and apparatus.

Semi solid topical dosage form – Receptor medium should contain alcohol and surfactants which depends on the solubility of drug substance. Deaeration is critical to avoid bubble formation. Hence, transdermal products should test at temperature 32 °C to reflect the usual skin temperature.

Oral suspensions – rotating paddle method is used with an aqueous dissolution medium. Sample introduction and agitation rate should be established.

Chewing gums – In test media pH 6.0 should be used. Since pH corresponds to human saliva pH values of 6.4 or 7.3.

Liquid filled capsule – the medium selected must provide sink condition, and it must not interfere with activity of enzymes. The addition of enzyme to surfactant to simulate digestion if it is rate limiting step.

Suppositories – paddle method, basket method, membrane diffusion method / dialysis method, continuous flow method/

bead method are used in the in vitro dissolution test. Lipophilic Suppositories release the drug after melting in the rectal activity (36-37.5 °C). The temperature should be taken into consideration that slightly increased temperature such as 38±0.5 °C.

Buffered or effervescent tablet- USP apparatus 2 is used for dissolution testing. Consider the physicochemical characteristics of buffered medium and active ingredients. later verify buffering capacity and ionic strength of the media.

Parentals (microparticulate and implants) – USP 4 apparatus flow through cell is used. Flow rate of medium has to be set very low. The test should be done for very long period of time and to prevent microbial growth in the medium.

Transdermal patches – the patch should be properly positioned. The drugs loaded surface should be exposed to the medium. The pH of the medium should be adjusted to the skin condition [7].

Limitations / Challenges to the Dissolution Test

Dissolution testing is important in the pharmaceutical drug development. However, despite its importance it has serious concerns, problems and some limitations. Some problems often relate to:

- Failing of performance evaluation (calibration).
- Need to have a certain volume of dissolution medium.
- Lack of establishing an in vivo invitro correlation (IVIVC).
- Insufficient analytical sensitivity for low dose drugs.
- Lack of objectivity in selecting experimental conditions for products.
- Development of low drug solubility takes time and resources.

Some highlighted flaws such as the dissolution 2 apparatus (paddle) is poorly designed from hydrodynamic perspective, and it exhibits high levels of variability. The pharmacopeia has controlled some physical and mechanical parameters but still there are some non-controlled parameters such as rotational speed, shaft height, shaft center, vessel or shaft tilt, vessel variability, wobble, wear of basket and paddles, basket mesh sizes, coning of product, non-homogeneity of product and analytical variability. They have reported that small changes in the position leads to large differences in dissolution rate and variability in results.

Several attempts have been made to overcome this intrinsic flaw design (For example, peak vessels, mega paddles, crescent shaped spindles, metal strips, titled vessels, off center paddle, permanent line probes acting as baffles). None of these have gained support across industry, academia. Finally, a single dissolution method can ever be robust and sensitive [8,9,10,11].

Dissolution Specifications

Based on guidance of industry: extended-release oral dosage forms; development, evaluation, and application of invitro/in vivo correlations, at least three points on the dissolution profile should be used to have specifications.

Single point specifications – it is used to determine quality control test for highly soluble and rapidly dissolving drug products.

Two-point specifications – it is used for characterizing the quality of drug products such as slow dissolving or poorly water-soluble drug products.

Multiple time point specifications – it is used to obtain dissolution characteristics of extended release and immediate release drug products [12].

Immediate/ Conventional Release Formulation

The immediate release drugs are intended to be swallowed, and a limit is specified to ensure the active ingredients are released in a specific period of time. Different procedures are recommended for a deduction of limits depending on the individual characteristics. The following characterization concerns only the specification verification process, and it does not qualify or disqualify the drug formulation with dissolution properties, characterized by specified time >15 minutes. When measuring the dissolution rate the single time point specification is used for a very fast drug release with the samples taken between 20 - 30 minutes. When evaluating the slow dissolving drugs two-point specifications can be used with the samples taken between 30-45minutes. Immediate / conventional release formulations require an invitro in vivo a comparison study with a specified dissolution time of more than 30 minutes with several points obtained to specify the single point limits.

Semisolid Dosage Form

The evaluation and performance tests had been done for semisolid dosage forms such as ointments, gels, cream and lotions during the product development for post approval changes. After the test they have reported the theory behind the in vitro performance test, instruction of using available USP apparatus 4 and evaluating the results after post approval changes. In an investigation they have reported high variability associated with drug release, equipment troubleshooting, method validation and to improve the instruction to run equipment etc.

Dietary Supplements

In an investigation they have reported that USP General chapter <2040> of dietary supplement which contains recommendations on apparatus and procedure to evaluate release of active ingredients which contain dietary supplements. Later general chapter <2040> was included with specifications such as beakers

used in disintegration test, dissolution testing of delayed released soft gelatin capsules, vitamin A tablets and lipid filled soft gelatin capsules. Many factors which affect solubility of phytochemicals in botanical dietary supplements such as water solubility, stability in GIT tract etc... After the development of new delivery mechanism dietary supplements are made more bioavailable and manifested anticipated effect [13,14].

Modified Release Drug Products

In modified release drug development, there are enormous challenges to establish proper dissolution condition. Compendial equipment may lack ability to simulate aspects of in vivo dissolution. Hence, non-compendial methods were most discriminative to drug formulation differences. Invitro biphasic test method was used to examine release profile of poorly soluble model drug. The use of absorptive phase in biphasic dissolution test assisted in controlling the pH due to the drug removal from the aqueous medium. Low buffer capacity can be used to assess invitro drug product performance. To overcome the limitations of modified release formulation of dissolution testing at constant pH, a modified USP 2 apparatus was developed by combining biphasic dissolution with a pH – gradient in the aqueous medium.

Modified release formulation dissolution requirements are specified with multiple time points for characterization of the invitro dissolution rate. Delayed release requires two time point and for extended release it requires at least three time points. For modified /extended/delayed release dosage forms should show the dissolution testing over specified time intervals with the release of active ingredients. The first limit is to prevent dose dumping with 20-30% of labelled substance, second limit should define dissolution pattern with 50% of labelled substance. The final limit is to ensure quantitative drug release with ≥80% of drug release. The upper and lower limits are specified at any time point and the difference between them should not exceed more than 20% of labelled content of drug substance. The limits have been shown to provide reproducible and acceptable in vivo performance [15,16].

Gastro Resistant Drug Products

It should be treated like immediate release products to specify the limits of the second dissolution test period with initial acidic test phase. Compendial dissolution test apparatus which are used for investigation of drug release from common oral dosage form. Compendial methods are not suitable to study the drug release of Gastro retentive dosage forms. Hence, the paddle and rotating basket apparatus are made simple modifications and applied for testing of Gastro retentive dosage forms. Dissolution testing in compendial methods can be problematic for low density and floating Gastro retentive dosage forms as the relatively large surface area of the system is not in contact with dissolution medium. Later, the most widely accepted procedure is to use helical wire sinkers, the use of

a sinker may impede the swelling behavior of the dosage form. The alternative used to keep a floating system underneath a ring mesh, and they introduced one and to stainless steel ring meshes into a paddle apparatus.

The pH differences along the gastrointestinal tract are major issues that should be addressed in dissolution testing of Gastro retentive dosage forms which contain weak basic drugs. Later, based on the Rosett-Rice apparatus, they developed a multi compartment transfer model which consists of gastric, intestinal and an absorption compartment. In this device drugs can be easily transferred, and pH media can be adjusted via reservoirs containing in the stomach.

Mucoadhesive Systems

Mucoadhesive systems are designed to stick to the gastric mucosa. Compendial dissolution test methods seem to be less complicated for drug release testing of mucoadhesive systems. So, used a modified version of USP 2 paddle apparatus. In this model, the dissolution vessel of paddle 2 apparatus which is filled with polystyrol beads in order to mimic physiological stress occurs in stomach.

Later they applied this device to novel Gastro retentive dosage forms and demonstrated that one of the formulations did not provide controlled drug release due to the lack of mechanistic robustness. They developed a dissolution stress test device, and it used an inflatable balloon to exert realistic pressures on dosage forms. In an investigation they have reported that significant pressure sensitivity is one of the major issues to be considered during the development of novel Gastro retentive dosage forms. Besides the dissolution stress test device, there have been recent developments and most prominent in vitro models to simulate gastric physiology such as TNO's TIM-1 system, dynamic gastric model, simulate gastric model, human gastric simulator [17].

Liquid Filling Capsule

In liquid filling capsules basket may not be suitable. Because when the capsule breaks down the gelatin the shell may clog the baskets mesh and the oil phase released from the capsule may not disperse into fine enough droplets in the basket. In some instances, capsule shell may stick to the basket or the bottom of the vessel. To overcome this problem the reciprocating cylinder (USP apparatus 3) is used because of its different mechanism of agitation. USP apparatus 3 may have a tendency to form foam when the surfactants added to the media. Hence, that overcomes by an alternative rotating bottle apparatus.

The dissolution testing of a liquid filling capsule requires some conditions which are mentioned in the new USP General chapter <1904> liquid filling capsule. In an investigation they have reported the packing and manufacturing issues which affect dissolution testing, and they have demonstrated the biggest challenge is how

to use enzymes in presence of surfactant in dissolution medium. Liquid filled capsules may float in the dissolution media; it can be overcome by wire coil wound around the capsule or by the capsule being held loosely in a sinker.

Gelatin Capsules

The dissolution of encapsulated liquid formation depends on its design and gelatin capsule must rupture to release its content. The chemical and physical properties of liquid filled capsules poses unique challenges during development of dissolution methods. One of the most common problems is micelle formation and cross-linking of the gel. To overcome this issue formulators, use proteolytic preparations that contain pepsin or pancreatin enzymes to dissolution media when cross-linking occurs in the gelatin shell. In an investigation USP General chapter <711> have reported that use of enzymes in gelatin coated tablets and gelatin capsule failed in the dissolution test i.e., addition of pepsin and pancreatin to the dissolution medium doesn't show the optimal activity in pH ranges. After that a new activity assay method was proposed for pepsin and an influenced pepsin activity assay in the presence of surfactant is being evaluated [18].

Transdermal System

The USP apparatus 5, 6, 7 were developed to dissolution tests of transdermal system. It is always a challenge to set dissolution test conditions to reflect in vivo/in vitro skin permeation. The dissolution solution needs to have a larger dissolution solution to meet saturation limit requirements. The requirement of a larger volume of buffer for testing, reduce the optimality for the detection of low amounts of drug. The apparatus 5 (i.e., paddle) transdermal Delivery System, use paddle and vessel from Apparatus 2 with a stainless-steel disk assembly to hold the transdermal on the bottom of vessel, apparatus 6 (i.e., cylinder) Transdermal Delivery System, use Apparatus 1 except replace the basket shaft with a stainless-steel cylinder element, apparatus 7 (i.e., reciprocating cylinder). Selection of USP apparatus and the method to carry out the dissolution test depends on its size, shape and strength of the drug.

New delivery technologies have developed high potent water-soluble small molecules that are formulated as transdermal system that could prove problematic because detection of low amounts of drug requires a large large volume of buffer. Manufacturers need low volume apparatus to test patches hence apparatus 5, 6, 7 were incorporated with smaller vessels and less usage of buffer. There is a need to overcome the current challenges in dissolution study of transdermal drug delivery systems to yield more correlative results in vivo [19,20].

Conclusion

In a conclusion, it may be argued most of the deficiencies/problems and challenges of current practices of a dissolution. Dissolution test has attempted to maintain a level of in vivo

relevance and various dissolution media were designed to mimic the pH of a gastrointestinal tract. The intrinsically poor design of the dissolution apparatus may be related to hydrodynamic within the paddle and a basket apparatus. The poor hydrodynamic mixing may lead to an incomplete disintegration and dissolution. The appropriate selection of an apparatus and an experimental condition will reduce the significant workload by eliminating repeated IVIVC developments and the other non-relevant testing.

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Conflict of Interest

No conflict of interest.

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