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A REVIEW ON CURRENT UPDATES ON DRUG DISSOLUTION EPLERENONE TESTING FOR IMMEDIATE RELEASE ORAL DOSAGE FORMS

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Abstract

Immediate-release oral dosage forms, also known as IR dosage forms, are widely favoured for medication delivery due to their rapid dissolution rate. This characteristic enables the medication to quickly enter the bloodstream, offering swift relief to patients. In formulation development, dissolution is a critical factor, providing essential insights for quality control. In vitro dissolution tests—a laboratory method simulating the medication's dissolution in the body—plays a key role across various stages of drug development. From a regulatory standpoint, validating dissolution enhances the review process for preclinical and clinical data. In certain situations, dissolution test results may also be utilized to assess the biopharmaceutical impact of product modifications. Such testing ensures that medications are not only effective but also safe and dependable for patients.

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Introduction

This information is provided to guide manufacturers in submitting new drug applications (NDAs) or investigational new drug applications (INDs), as applicable, for orally administered immediate-release (IR) drug products containing highly soluble substances. "Immediate-release dosage forms break down quickly after administration, leading to an accelerated rate of dissolution." These super disintegrates allow immediate disintegration of the tablet after administration in the stomach. In this dosage form, 70-85% of the indicated dose dissolves within 30 minutes. "Dissolution is the process by which a solid drug enters the solvent phase to form a solution. This document provides finalized guidance for the industry on Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms containing Biopharmaceutics Classification System (BCS) Class 1 and Class 3 drugs. "Innovative dosage forms have been designed to act quickly after administration, meeting the need for a rapid onset of

action in therapeutic situations where traditional treatments may be insufficient." "To address these limitations, immediate-release pharmaceutical dosage forms have been developed as a reliable alternative for oral drug delivery." The key strategy in developing these tablets involves incorporating superdisintegrants, which enable the tablet to disintegrate instantly upon administration. The developments of immediate release tablets which may release the drugs at an enhanced rate are very promising for the delivery of poorly soluble drugs high molecular weight protein and peptide. Eplerenone, an aldosterone receptor blocker akin to spironolactone, raises plasma renin and serum aldosterone levels by blocking aldosterone's negative feedback on renin secretion. Nevertheless, the therapeutic effects of eplerenone dominate despite these increases. Additionally, eplerenone selectively binds to human mineralocorticoid receptors with minimal interaction with glucocorticoid, progesterone, and androgen receptors. Undesirable adverse effects such as, gastrointestinal irritation, antiandrogenic and progestational activity are also minimized with the pharmaceutical compositions of the present Formulation.

In addition to being an in vitro dosage form, the drug product must meet all of the following conditions for the dissolution standards in this guidance to apply. The FDA's Biopharmaceutics Classification System (BCS) guidance should be followed to confirm that the drug product contains a highly

soluble drug substance. Immediate release dosage form are designed to disintegrate quickly into smaller granules and then disaggregate into fine particles .the dissolution media is exposed to a larger surface area, resulting in a faster dissolution rate [15]. For poorly soluble immediate-release drug substances, excipients are used to facilitate disintegration (disintegrants) and disaggregation (surfactants).

The following Biopharmaceutics Classification System (BCS), based on drug solubility and permeability, is recommended in the literature (Amidon, 1995):

Case 1 : High solubility- High permeability drugs

Case 2 : Low solubility - High permeability drugs

Case 3; High solubility- Low permeability drugs

Case 4 : Low solubility -Low permeability drugs3

This classification can serve as a foundation for establishing in vitro dissolution specifications and can also help predict the likelihood of achieving a successful in vivo-in vitro correlation (IVIVC). A drug substance is considered highly soluble when the dose/solubility volume of the solution is less than or equal to 250 mL. High-permeability drugs are typically those with an absorption extent greater than 90% in the absence of documented instability in the gastrointestinal tract or those whose permeability has been experimentally determined. The BCS suggests that for high solubility, high permeability (Case 1) drugs, and in some cases for Drugs with high solubility and high permeability (case 1), and in some cases high solubility with low permeability (case 3), can achieve 85% dissolution in 0.1N HCl within 15 minutes, ensuring that bioavailability is not restricted by dissolution. In these instances, gastric emptying becomes the rate-limiting factor for drug absorption. For low solubility and high permeability drugs (case 2), dissolution may limit absorption, and an in vitro-in vivo correlation (IVIVC) may be observed. A dissolution profile in various media is recommended for drugs in this category. For high solubility but low permeability drugs (case 3), permeability governs the rate of absorption, and a limited IVIVC may be possible, depending on the balance between dissolution and intestinal transit rates. Drugs in case 4 (low solubility/low permeability) face significant challenges in oral drug delivery.

IMPORTANCE OF DISSOLUTION

- Solubilization is the rate limiting step and controls the rate of absorptions.
- Bioavailability {INVIVO} can be correlated with the in vitro dissolution results.
- To evaluate batch to batch variation
- To determine key manufacturing variables
- Binding action
- Blending effect
- Granulation procedure
- Coating specifications
- Role of excipients in formulation6,7
- Comparative profile studies

HISTORY OF DISSOLUTION

1897 –Noyes and Whitney published a paper on the rate of solution of solid substances in their own solution, proposing that the dissolution rate is governed by a layer of saturated solution that rapidly forms around a solid particle.

1904 – Nernst and Brunner modified the Noyes-Whitney equation by incorporating Fick's law of diffusion, establishing a

relationship between the dissolution rate and the diffusion coefficient. 1930- Experiments typically progress from in vivo-in vitro studies.

- 1950- The first dissolution test was developed in by using simple apparatus such as beakers and stirrers.
- 1955- The united states pharmacopeia (USP) introduced the first official dissolution test, which used a 100ml beaker and a stirrer.
- 1960-Levy and Hayes correlated dissolution and absorption rates.

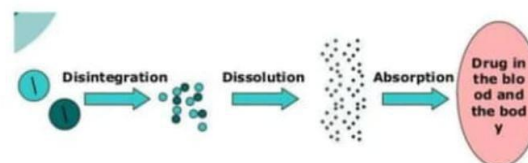
1960- The USP recognized the need for a standardized dissolution test and began experimenting with various basket and stirring devices.

1970- USP 18 introduced the first official dissolution test for solid dosage forms, with twelve monographs in USP–NF featuring the official dissolution test using a rotating basket. 1980- Regulatory agencies began requiring dissolution testing for certain dosage forms, such as tablets and capsules.10

- 1990- Advances in Dissolution Technology (1990s-2000s)
- **1. Flow-through Cell Apparatus (1990s):** The flow-through cell apparatus (Apparatus 4) was introduced in the 1990s, providing enhanced control over dissolution conditions for more accurate testing.
- **2. Biorelevant dissolution media (2000s):** The development of bio relevant dissolution media, such as simulated gastric and intestinal fluids, improved the accuracy of dissolution testing.



DISSOLUTION : Dissolution is the process in which a solid substance dissolves in a solvent, involving mass transfer from the solid surface to the liquid phase. Dissolution testing evaluates the extent at and rate which a dosage form, such as a tablet, capsule, or ointment, forms a solution. The dissolution of a drug is crucial for its bioavailability and therapeutic effectiveness¹¹



DISSOLUTION RATE

The dissolution rate is defined as the quantity of a solid substance that dissolves into solution per unit time, under standard conditions of temperature, pH, solvent composition, and a constant surface area.

IN VITRO DISSOLUTION TEST METHODS.

I .BASIC METHODS

1. Beaker methods (closed compartment system)
2. Flow- through (open compartment system)

3. Dialysis method.

Beaker methods (closed compartment system): The Beaker Method, also known as the "Beaker Dissolution Test," is a simple, manual dissolution testing method used to evaluate the release of active pharmaceutical ingredients (APIs) from solid dosage forms like tablets, capsules or powders. Equipment Beaker: A 100-400 ML glass beaker. Stirrer: A magnetic stirrer or mechanical stirrer. Thermometer: To monitor temperature. pH meter: To monitor pH (optional). Filter: To separate dissolved API from undissolved particles. Spectrophotometer: To measure API concentration. Procedure Preparation: Prepare the dissolution medium (e.g., water, buffer solution, or simulated gastric/intestinal fluid). Temperature control: Maintain the medium at a controlled temperature (e.g., 37°C). Add API: Add the API (tablet, capsule, or powder) to the beaker. Stirring: Stir the mixture at a constant rate (e.g., 50-100 rpm). Sampling: Withdraw samples at predetermined time intervals (e.g., 15, 30, 60 minutes). Filtration: Filter the samples to separate dissolved API from undissolved particles. Analysis: Measure the API concentration using a spectrophotometer or other analytical technique. Calculation: Calculate the percentage of API released at each time point.

Types of Beaker Methods **Static method:** The API is added to the beaker, and the mixture is stirred without changing the medium. **Dynamic method:** The medium is continuously replaced or refreshed during the test. **Recirculating method:** The medium is recirculated through the beaker to maintain a constant concentration.

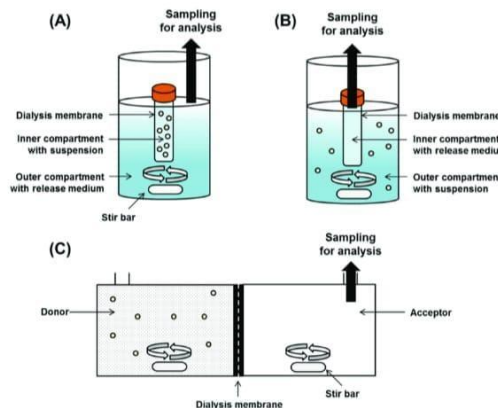


2. Flow-Through Open Compartment System: The Flow-Through Open Compartment Method is a dissolution testing technique designed to assess the release of active pharmaceutical ingredients (APIs) from solid oral dosage forms, such as tablets and capsules.

Principle The method involves placing a dosage form in a flow-through cell, where a dissolution medium is pumped through the cell at a controlled rate. The dissolved API is then collected and analyzed using a suitable detection method, such as UV spectroscopy or HPLC.

Apparatus The apparatus consists of: **Flow-through cell:** A cylindrical cell with a porous bottom and a dosage form holder. **Pump:** A pump that controls the rate at which the dissolution medium flows. **Dissolution medium reservoir:** A container that holds the dissolution medium. **Collection vessel:** A container that collects the dissolved API. **Detection system:** A system that analyzes the collected API, such as UV spectroscopy or HPLC.

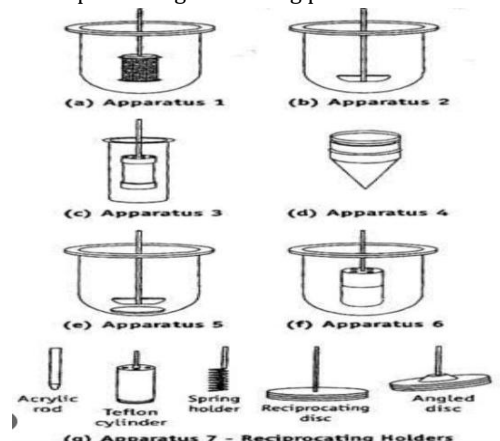
Procedure Preparation: Prepare the dosage form and the flow-through cell. **Dissolution testing:** Place the dosage form in the flow-through cell and start the pump. **Sampling:** Collect the dissolved API at predetermined time points. **Analysis:** Analyze the collected API using a suitable detection method. **Data analysis:** Calculate the dissolution rate and other relevant parameters.



PREVIOUS DAYS IN VITRO DRUG DISSOLUTION STUDY

In vitro drug dissolution refers to the process by which a drug dissolves in a solvent, typically in a laboratory setting. This process is crucial in determining the bioavailability and therapeutic effectiveness of a drug. A study investigated the in vitro dissolution of LAMOTRIGINE, an Antiepileptic drug, using a biphasic dissolution test. The study aimed to establish an in vitro correlation (IVIC) for LTG formulation.

The Biphasic dissolution test was performed using a USB apparatus II with a dual paddle modification, and the results showed a good correlation between the in vitro data and in vivo absorption of LTG. The study also highlighted the importance of using a biphasic dissolution system, which consists of an aqueous phase and organic phase to mimic the in vivo conditions of the gastrointestinal tract. The use of Octanol as the organic phase was found to be suitable for the biphasic dissolution test, as it provided a good correlation with the in vivo data. Overall, the study demonstrated the potential of biphasic dissolution testing in forecasting the in vivo performance of drug formulations, which can be useful in the development of generic drug products.



NOWA DAYS IN VITRO DRUG DISSOLUTION STUDY.

In vitro drug dissolution study are a crucial part of pharmaceutical development, and they are more relevant now than ever. These studies help determine the rate extent of drug release from a formulation, which is essential for ensuring the efficacy and safety of drugs.

There are several types of apparatus used for in vitro drug dissolution studies, including:

Apparatus 1: Rotating Basket - used for tablets, capsules, and delayed-release formulations.

Apparatus 2: Rotating Paddle - used for tablets, capsules, and suspensions.

Apparatus 3: Reciprocating Cylinder - used for tablets, beads, and controlled-release formulations.

Apparatus 4: Flow-Through Cell - used for low-solubility drugs, micro-particulates, and controlled-release formulations.

Apparatus 5: Paddle-Over-Disk - used for transdermal patches and ointments.

Apparatus 6: Cylinder - used for transdermal patches and solid dosage forms.

Apparatus 7: Reciprocating Disk - used for transdermal patches.

Recent studies:

A study published in the International Research Journal of Gastroenterology and Hepatology discussed the recent advancement in in vitro dissolution testing for immediate release oral dosage forms. Another study published in the Journal of Pharmaceutical Sciences focused on the development and validation of dissolution methods for eplerenone¹.



CONCLUSION

In vitro drug dissolution testing is crucial for ensuring the quality and performance of immediate release oral dosage forms. Novel in vitro dissolution methods such as custom made apparatus offer improved accuracy and reproducibility. Further research is needed to optimize dissolution testing methods and ensure efficacy and safety of eplerenone and other medications. This results in different dissolution profile standards and a substance amount of unnecessary and duplicated work that doesn't contribute to the safety and efficacy of the product.

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