CHAPTER 9

DISSOLUTION TESTING

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Abstract

Dissolution testing measures the rate and extent of drug release from pharmaceutical dosage forms. USP apparatus types 1-7 simulate *in-vivo* conditions with specific designs for various dosage forms, each requiring proper calibration and qualification. Method development considers media composition including pH, buffer capacity, and surfactants alongside hydrodynamic conditions, sampling strategies, and analytical finish methods. Immediate release, modified release, and poorly soluble drug formulations require tailored dissolution approaches. Data analysis applies model-dependent approaches using zero-order, first-order, and Higuchi equations alongside model-independent methods like dissolution efficiency and similarity factors. Mathematical modeling enables profile comparison and discrimination with statistical significance testing. Regulatory agencies establish method validation requirements, acceptance criteria, and specification setting practices globally. *In vitro-in vivo* correlation links dissolution behavior to pharmacokinetic parameters through levels A-C correlations, supporting biowaivers, formulation optimization, and specification setting.

Keywords: *Dissolution Profile, Biorelevant Dissolution Media, Modified Release Testing, In-Vitro In-Vivo Correlation*

Learning Objectives

After completion of the chapter, the learners should be able to:

- Describe different USP dissolution apparatus types
- Explain correlation between dissolution and bioavailability
- Select appropriate dissolution testing conditions
- Analyze dissolution profiles using various approaches
- Evaluate method discriminatory power
- Develop biorelevant dissolution methods

INTRODUCTION

Dissolution testing is a pivotal analytical procedure that measures the rate and extent at which an active pharmaceutical ingredient (API) is released from a solid dosage form under controlled conditions. This testing methodology serves multiple crucial functions in pharmaceutical development and quality control. It provides essential information about drug release kinetics, helps predict *in vivo* performance, and serves as a surrogate marker for bioavailability in many instances.

The fundamental principle of dissolution testing involves placing a dosage form in a defined volume of dissolution medium maintained at a specific temperature and subjecting it to controlled agitation. The rate at which the API dissolves is measured by sampling the medium at predetermined time intervals and quantifying the amount of drug released using appropriate analytical techniques.

Dissolution testing has evolved significantly since its introduction in the 1950s. What began as a simple quality control test has transformed into a sophisticated biopharmaceutical tool with applications spanning the entire drug development lifecycle. The test now plays a critical role in formulation development, process optimization, batch-to-batch quality assessment, establishing *in vitro-in vivo* correlations, and supporting biowaivers.

Regulatory authorities worldwide recognize dissolution testing as a mandatory requirement for solid oral dosage forms. Pharmacopeial standards, including those from the United States Pharmacopeia (USP), European Pharmacopoeia (Ph. Eur.), and Japanese Pharmacopoeia (JP), provide detailed guidelines on apparatus specifications, calibration procedures, and acceptance criteria. These standards ensure consistency and reliability in dissolution testing across the pharmaceutical industry

DISSOLUTION APPARATUS

USP Apparatus Types

Apparatus 1 (Basket)

The basket apparatus consists of a cylindrical stainless steel wire mesh basket (apertures 0.38-0.40 mm, wire diameter 0.22-0.24 mm) attached to a metal shaft. The basket dimensions (40 mm height, 22.2 mm internal diameter) are standardized for reproducibility.

The operating principle involves rotating the basket containing the dosage form in dissolution medium. Standard rotation speeds range from 50-100 rpm, with 100 rpm common for immediate-release formulations and 50 rpm for extended-release products.

Apparatus 1 is suitable for formulations that float or disintegrate into particles that might otherwise float on the medium surface.

Table 9.1: USP Dissolution Apparatus Specifications and Applications

Apparatus Type	Description	Parameters	Rotation/Flow Rates
USP 1 (Basket)	Rotating wire mesh basket containing sample	Basket mesh size, height, rotation speed	50-100 rpm
USP 2 (Paddle)	Rotating paddle with sample at vessel bottom	Paddle position, rotation speed, sampling position	50-75 rpm
USP 3 (Reciprocating Cylinder)	Sample in reciprocating cylinder with mesh ends	Dip rate, mesh size	5-35 dpm
USP 4 (Flow-Through Cell)	Sample in cell with continuous media flow	Flow rate, cell type, filter porosity	4-50 mL/min
USP 5 (Paddle Over Disk)	Paddle with sample trapped on disk	Disk dimensions, rotation speed	50-100 rpm
USP 6 (Cylinder)	Rotating cylinder with sample attached	Cylinder dimensions, rotation speed	25-50 rpm
USP 7 (Reciprocating Holder)	Sample in reciprocating holder	Stroke height, frequency	5-35 dpm

Limitations include potential mesh clogging, complex hydrodynamics creating "dead zones," and material accumulation at the basket bottom resulting in inconsistent medium exposure.

Calibration requires verification of dimensions, rotation speed, temperature control (37 ± 0.5°C), basket integrity, and shaft verticality.

Apparatus 2 (Paddle)

The paddle apparatus consists of a shaft with a blade (74-76 mm long, 19-20 mm wide) positioned 25 ± 2 mm from the vessel bottom. Vessels are identical to Apparatus 1, typically 1000 mL with hemispherical bottoms. Hydrodynamics are characterized by complex flow patterns, creating a vortex with high velocity at outer edges and low velocity in the center bottom region. This can result in a "cone" of undissolved particles beneath the paddle in a relatively low agitation "dead zone."

The paddle method is widely used for tablets that sink in dissolution medium. Typical rotation speeds range from 50-75 rpm, with 50 rpm standard for most applications. Critical factors affecting performance include paddle height, vessel centering, vibration, and dosage form position. Maintenance includes regular inspection of paddle dimensions and surface finish, verification of shaft verticality, and checking for vessel irregularities.

Apparatus 3 (Reciprocating Cylinder)

The reciprocating cylinder consists of glass cylinders with mesh screens at each end. The dosage form is placed within the cylinder, which moves vertically in the dissolution medium. Standard specifications include 9.9-10.1 cm stroke length and 5-30 dips per minute. The operation involves programmed immersion in a series of vessels containing different media, allowing for media changes during testing to simulate transit through different physiological environments.

Apparatus 3 excels in testing extended-release formulations, particularly those designed for release under varying pH conditions. Specialized applications include gradient dissolution testing, simulating different segments of the gastrointestinal tract. Calibration protocols include verification of dip rate, stroke length, cylinder dimensions, mesh integrity, and temperature control.

Apparatus 4 (Flow-Through Cell)

The flow-through cell system consists of a reservoir, pump forcing medium upward through a vertically positioned cell containing the dosage form, and temperature control devices. The transparent cell (typically 12 or 22.6 mm internal diameter) contains a filter system preventing undissolved particles from escaping. Flow dynamics are characterized by laminar flow patterns providing continuous exposure to fresh medium, creating conditions closer to sink conditions than static methods. Flow rates are typically 4-16 mL/min, with 8 mL/min standard.

Apparatus 4 is valuable for poorly soluble drugs where maintaining sink conditions is challenging. It accommodates specialized dosage forms including implants, stents, suppositories, powders, and semisolids. The system can operate in open loop (single pass) or closed loop (recirculating) configurations. Critical parameters include flow rate stability, medium degassing, filter selection, cell assembly, and temperature uniformity.

Equipment Qualification

Installation Qualification (IQ)

Equipment specifications must be thoroughly verified, including confirmation of manufacturer, model, and serial number. All components must be inspected for damage before installation proceeds.

Installation requirements encompass physical placement on stable, level surfaces free from vibration, with sufficient space for operation and maintenance. Environmental factors including temperature, humidity, and air quality must fall within specified ranges.

Documentation includes comprehensive records of specifications, installation conditions, verification results, and deviations. Certificates of conformity, calibration certificates, and verification of materials of construction must be archived.

Safety features including emergency stop mechanisms, overheating protection, and mechanical safeguards must be verified. Utility requirements including electrical specifications, water quality, compressed air systems, and waste handling provisions must be verified against equipment specifications.

Operational Qualification (OQ)

Mechanical calibration covers vessel dimensions, shaft verticality (within ±2° tolerance), and vessel centering (maximum 2 mm deviation from center axis for Apparatus 1 and 2).

Temperature control systems must maintain 37 ± 0.5°C throughout the vessel during operation. Temperature mapping studies document uniformity across all vessel positions and throughout testing duration.

Rotation and speed verification measures actual rotation rates against set values under both unloaded and loaded conditions. Speed accuracy must typically fall within ±2% of set value.

System suitability testing examines the complete system under actual operating conditions, often using USP calibrator tablets. Additional performance parameters requiring verification include vibration levels, drive system stability, vessel-to-vessel variation, and system response to environmental influences.

Performance Qualification (PQ)

USP calibrator tablets serve as reference standards for verifying system performance. Prednisone tablets (sensitive to hydrodynamic conditions) and salicylic acid tablets (sensitive to temperature variations) are commonly used. Results must fall within established acceptance ranges.

System performance verification must demonstrate consistent production of accurate and precise results, examining not only mean dissolution values but also variability between vessels and across multiple test runs.

Method verification focuses on demonstrating that established methods perform as expected on qualified equipment, including verification of specificity, precision, accuracy, linearity, and robustness.

Ongoing qualification involves periodic requalification activities at established intervals, including mechanical calibration, performance verification testing, and preventive maintenance. Maintenance schedules typically include daily checks, weekly cleaning, monthly calibration verification, and semiannual comprehensive maintenance.

METHOD DEVELOPMENT

Pre-development Considerations

Drug Properties

Solubility profile characterization across physiologically relevant pH range (1-7.5) is a prerequisite for method development. Dose/solubility ratio calculations help predict dissolution limitations and guide medium selection. For poorly soluble compounds,

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