Dissolution Testing: An overview

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Figure 1: Different types of dosage forms.

Introduction

Dissolution is a test used throughout the life cycle of a pharmaceutical product to evaluate the rate of release of a drug substance from the dosage form. Dissolution testing is routinely used for quality control purposes to test batch-to-batch consistency, stability and detect manufacturing deviations of pharmaceutical products. Dissolution is not only for orally ingested products such as tablets and capsules, it also applies to suspensions, beads, granules, topical formulations i.e. ointments, creams, gels, transdermal patches, implants, powders for inhalation, suppositories etc.

However oral dosage forms remain one of the most flexible and effective treatments available to patients. Dissolution testing is a requirement for all solid oral dosage forms and is used throughout the development life cycle for product release and stability testing. It is a pivotal analytical test used for detecting physical changes in an active pharmaceutical ingredient and formulated product. At the early stages of the drug development process, in-vitro dissolution testing underpins the optimisation of drug-release from a given formulation.

The exact dissolution technique employed is determined by the dosage form characteristics and the intended route of administration. For solid dosage forms, the industry standard dissolution testing methodologies are the United States Pharmacopoeia (USP) Apparatus I (Basket) and USP Apparatus 2 (Paddle). Immediate, modified and extended release are usually tested in standard dissolution baths with USP 2 paddles. Apart from the above-mentioned apparatus types, there are also other techniques available such as USP 3 (Reciprocating Cylinder), USP 4 (Flow-through-Cell), USP 5 (Paddle-over-Disc), USP 6 (Rotating Cylinder) and USP 7 (Reciprocating Holder or Disc).

This paper focuses on solid dosage forms, different modes of drug release, critical parameters for development of dissolution method to evaluate the release of drug form these dosage forms and how excipients impact the rate of dissolution.

Critical parameters to control whilst selecting excipients:

Excipients are an essential component of pharmaceutical formulations, and their physical properties can have a significant impact on the performance and stability of the final drug product. Excipients can be incorporated in the formulation to assist in the dissolution process of the drug, or specialized dosage forms can be formulated that improve dissolution rate through various mechanisms. Some key physical properties of excipients that are important to consider during formulation development include:

Particle size and distribution – The particle size and distribution of excipients can impact the flow properties, mixing characteristics, and dissolution rate of the final drug product. Smaller particle sizes can improve dissolution and bioavailability, while larger particle sizes can improve flow properties and ease of handling.

Bulk density – The bulk density of excipients can impact the flow properties and compressibility of the final drug product. Higher bulk density can improve flow properties, while lower bulk density can improve compressibility.

Porosity – The porosity of excipients can impact their ability to absorb or release moisture, which can impact the stability and performance of the final drug product. Higher porosity can improve the flow properties and compressibility of excipients but can also increase their moisture sensitivity.

Hygroscopicity – Hygroscopicity refers to the ability of excipients to absorb and hold moisture from the environment. Excipients that are highly hygroscopic can be more difficult to handle and can impact the stability of the final drug product.

Compressibility – The compressibility of excipients can impact the tablet hardness and disintegration of the final drug product. Excipients with higher compressibility can improve the compressibility and tablet hardness of the final product.

Flowability – The flowability of excipients can impact the ease of handling and processing during formulation development. Excipients with good flowability can improve the efficiency of the manufacturing process and reduce the risk of segregation or blending errors.

Chemical stability – The chemical stability of excipients can impact the stability and efficacy of the final drug product. Excipients should be chemically stable under the intended storage conditions to ensure the stability of the final product.

Compatibility with active pharmaceutical ingredient (API) – Excipients should be compatible with the API and not interact with it chemically or physically, as this can impact the stability, efficacy, and safety of the final drug product.

Critical parameters to consider when developing a dissolution method:

Dissolution testing is a critical step in drug development and quality control. Dissolution assesses the performance of drug products. To be effective, the test should be:

- Predictive
- Comparative
- Discriminatory
- Reproducible

When developing a dissolution method, it is important to take a logical, systematic approach to the process, and ensure that both the scientific and regulatory principles are borne in mind. A robust dissolution method should be free of significant interferences (e.g. matrix effects due to excipients), give low variability (precision) and produce a good profile shape. The method should also be challenged to discriminate between batches of material with different quality attributes., but still maintain acceptable precision and robustness.

Important considerations to bear in mind when developing a dissolution method:

Active Pharmaceutical Ingredient (API) – This is the primary component of a drug that provides the therapeutic effect. For a dosage form to be efficacious, the API must be both extracted (dissolved in solution) and then absorbed into the systemic circulation to facilitate its transport to the active site. This process influences the overall bioavailability of the API. A simple diagrammatic representation is given on the left (Figure 2).

Dosage form – The fundamental characteristics of the dosage form type (capsule, tablet etc.), strength, excipients, release type (immediate, sustained, delayed), stability data and surface coatings, should all be considered during the method development phase. A well-developed dissolution method should allow discrimination of the various product attributes.

Excipients – Excipients are the inactive ingredients used in the formulation of a drug product. API are not administered to patients on their own as single compounds but are formulated into carefully designed dosage forms using different types of excipients which play different roles in the formulation. The functions of excipients in dosage forms are related to all the different aspects of the final product including its manufacturability, the stability of the API, dose uniformity, effective delivery of the API to the systemic circulation after administration.

Sink conditions – Sink conditions are defined as 'the solution concentration corresponding to typically 5-10 times the nominal working concentration of the API in the dissolution medium'. Confirmation of achievement of sink is critical in establishing a suitable dissolution method. If these are not able to be achieved (and hence the media reaches saturation point), the dissolution rate cannot be consistently measured. It is important that when conducting dissolution testing, the only influences on the result should be the agitation rate and solubility of the product.

Dissolution Media – This is the medium used in dissolution testing to simulate the physiological conditions in the body. Different media can be used to mimic different parts of the gastrointestinal tract or other biological environments.

The initial focus when screening potential media is to start with those which are aqueous based, within the pH range of 1.2-6.8 at the recommended ionic strength (as per USP/EP). When assessing APIs that display low solubilities in aqueous media throughout the pH range, incorporation of a surfactant is advisable, although the levels used should be as low as possible.

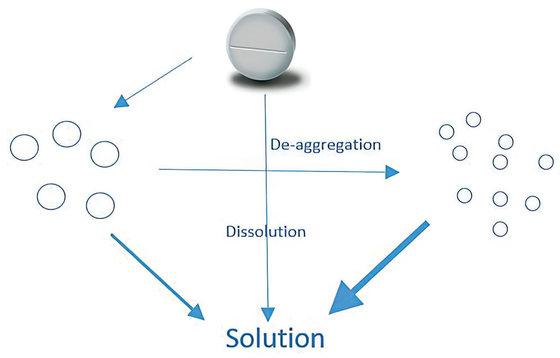

Figure 2: Dissolution of a solid oral dosage form.

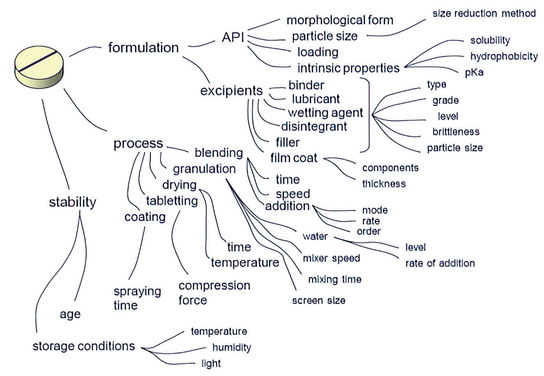

Figure 3: Factors which may affect the in-vitro Dissolution. (Adapted from Predictive in vitro dissolution tools: application during formulation development: Emmanuel Scheubel)

Apparatus – The apparatus used for dissolution testing can also influence the dissolution profile. Different types of apparatus are available, such as the USP apparatus 1, 2, 3, 4, 5, 6 and 7 and the choice of apparatus depends on the specific drug product and the purpose of the test.

Analytical Method – The analytical finish for the dissolution needs to be established. Where possible, in order to maintain simplicity and efficiency (and assuming the presence of a suitable chromophore), a simple UV finish could be employed.

Acceptance criteria – These are the criteria established for the dissolution test results to determine if the drug product meets the required quality standards. Acceptance criteria should be based on regulatory requirements, pharmacopeial standards, and the specific characteristics of the drug product.

Types of dosage forms and considerations to take into account whilst developing a robust dissolution method:

There are two main types of solid dosage forms in terms of mode of release of API from the formulation.

1. Immediate/Conventional release dosage forms
2. Modified release dosage form

Further, Modified release dosage form can be extended release or delayed release, with each having further subclasses. Some examples of these are site specific release, timed release, pulsatile release (release of drug in sudden bursts at specific time intervals), and biphasic release (first phase being sudden release then 2nd phase with slow extended release to maintain therapeutic effect) etc.

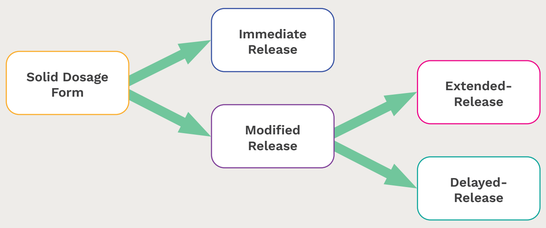

Figure 4: Types of Solid Dosage Forms.

Immediate Release Dosage Form:

Immediate release dosage forms are intended to release the active pharmaceutical ingredient (API) immediately upon administration to achieve a rapid onset of action. To allow immediate release of API, disintegrant like sodium starch glycolate Polyvinylpyrrolidone (PVP) etc. are widely used in these type of dosage forms which provides in instantaneous disintegration of tablet after administration.

Extended-Release Dosage Form:

Extended-release dosage forms are designed to release the active pharmaceutical ingredient (API) over an extended period of time, typically over several hours or even days. The extended-release mechanism is achieved through the use of the hydrophobic polymer matrix, which acts as a diffusion barrier to control the release of the drug over time. As water enters the matrix, it slowly penetrates and dissolves the drug, which then diffuses out of the matrix and is released into the surrounding medium.

The specific shape of the dissolution profile can vary depending on the specific formulation and release mechanism, but generally an extended-release dissolution profile should show a controlled release of the drug over an extended period of time, with minimal fluctuations in drug release rate. This ensures consistent and effective drug delivery over the intended dosing interval.

Delayed-Release Dosage Form:

Delayed release dosage forms are designed to release the active pharmaceutical ingredient (API) after a certain amount of time or after passing through a specific region of the gastrointestinal tract. The subsequent release is similar to that of an immediate release dosage form or extended release. The delayed release mechanism can be achieved through the use of enteric coatings which is designed to remain intact in the acidic environment of the stomach, but to dissolve rapidly in the more alkaline environment of the small intestine. This delayed release allows for targeted drug delivery to specific regions of the gastrointestinal tract and can improve drug efficacy and reduce side effects.

Examples of delayed-release systems include repeat action tablets and capsules, and enteric-coated tablets where timed release is achieved by a barrier coating.

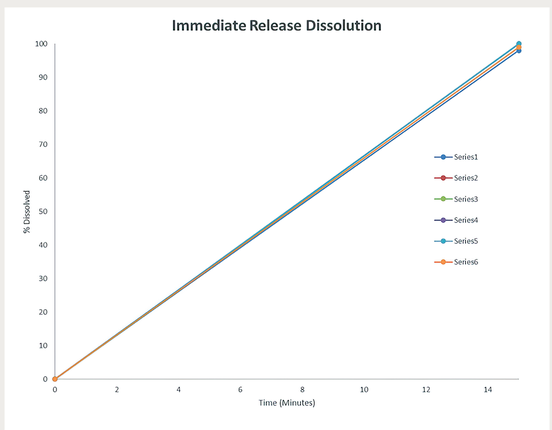

Figure 5: Immediate release dissolution profile showing instantaneous release of acetaminophen within 15 minutes using 0.1M HCl as a dissolution medium and USP 2.

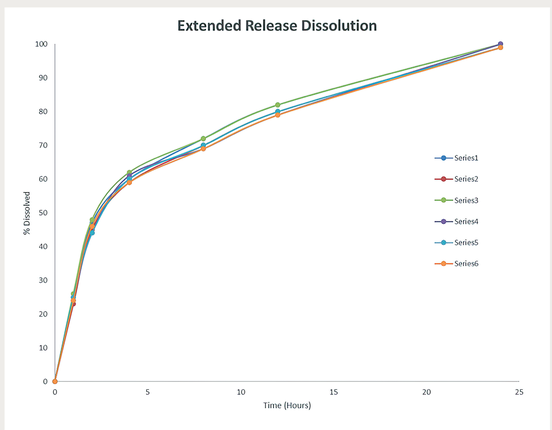

Figure 6: Extended-release dissolution profile of a drug product showing slow and steady release of API for 24 hours using phosphate buffer as a dissolution medium and USP 2.

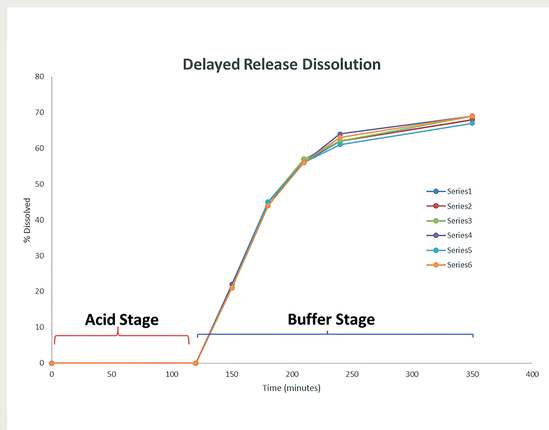

Figure 7: Delayed-release dissolution profile of a delayed release capsule containing enteric-coated beads. At the beginning, there is a lag time during which no drug is released, followed by a gradual increase in drug release over time.

Key requirements for above mentioned dosage forms:

- **Dissolution rate** – Immediate release formulations should have a rapid dissolution rate to ensure that the API is released quickly upon administration. The dissolution rate should be determined using appropriate methods, such as USP apparatus 1 or 2. Extended-release formulations should have a controlled and predictable release profile to ensure that the API is released at a constant rate over the desired time period. The delayed release formulation should have a mechanism to delay the release of the API until the desired time or location. This can be achieved through the use of enteric coatings or pH-sensitive polymers.
- **Consistent and reproducible release profile** – The release profile of the API from the formulation should be consistent and reproducible to ensure the efficacy and safety of the drug product. Variations in the release profile could result in inconsistent therapeutic effects or adverse events.
- **Uniformity of dosage units** – The dosage units, such as tablets or capsules, should be uniform in weight, size, and composition to ensure consistent dosing and release of the API.
- **Compatibility with excipients** – The excipients used in the formulation should be compatible with the API and each other to ensure the stability and efficacy of the drug product. Any incompatibilities could lead to degradation of the API or reduced efficacy.
- **Appropriate choice of excipients** – Excipients used in immediate release formulations should be carefully chosen to ensure the rapid dissolution and release of the API. For example, disintegrants, such as croscarmellose sodium or sodium starch glycolate, can be added to the formulation to aid in rapid disintegration and release of the API. Excipients used in extended-release formulations should be carefully chosen to ensure the controlled and sustained release of the API. For example, hydrophilic polymers, such as hydroxypropyl methylcellulose, can be used to form a matrix that controls the release of the API over time. Excipients used in delayed release formulations should be carefully chosen to ensure the delayed release of the API. For example, enteric coatings made of polymers like methacrylic acid copolymers can be used to delay the release of the API until it reaches the desired location in the gastrointestinal tract.
- **Appropriate choice of manufacturing process** – The manufacturing process used to produce the formulation should be appropriate for the specific drug product and should ensure consistent and reproducible quality.
- **Stability** – The formulations should be stable under appropriate storage conditions to ensure that the API remains active and effective throughout the shelf life of the drug product.
- **Quality control** – Quality control procedures should be established to ensure that the formulation meets the required quality standards. These procedures should include testing for purity, potency, and stability.
- **In vitro-in vivo correlation** – In vitro-in vivo correlation (IVIVC) studies may be required to establish the relationship between the in vitro release profile and the in vivo performance of the drug product. This can help ensure that the formulation is effective and safe for its intended use.

Conclusion:

Dissolution is a critical test required to demonstrate the in-vitro release of drug from the drug product and as mentioned above there are several critical parameters to watch when developing a dissolution method.

At RSSL, we can support you with all the analytical needs required for your product. RSSL expertise is not limited to only this, we have an expert team to support you with product development from start to end of the drug product life cycle.

References: Internet based contents and various research papers

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