Opinion Article

Current updates on in vitro dissolution testing for immediate release oral dosage forms

Abstract:

Immediate-release oral dosage forms, also known as IR dosage forms, have become a popular choice for administering medication due to their ability to dissolve at an accelerated rate. This means that the medication is quickly released into the bloodstream, providing fast relief to patients. In the formulation development process, dissolution is a crucial aspect to consider as it can provide valuable information for quality control. In vitro dissolution testing, a laboratory method that simulates the dissolution of medication in the body, can offer insight into various stages of drug development.

From a regulatory perspective, the review of preclinical and clinical data is greatly facilitated by the validation of dissolution for the product. In some cases, it may even be appropriate to use dissolution test results to evaluate the biopharmaceutical implications of a product change. This type of testing helps to ensure that the medication is not only effective, but also safe and reliable for patients.

In vitro dissolution testing can be used to evaluate a variety of factors including the rate of dissolution, the amount of medication released, and the effect of different formulations on dissolution. This can help researchers and manufacturers to optimize the formulation of the medication and ensure that it meets the necessary standards for efficacy and safety.

In conclusion, in vitro dissolution testing is an essential tool for evaluating the quality and performance of immediate-release oral dosage forms. It provides valuable information for the development and regulatory approval of medication, and can help to ensure that patients receive safe and effective treatment.

Key Words: BCS class, in vitro dissolution, FDA, EMA, immediate release dosage forms

Introduction:

Therapeutic impact of a drug largely depends on its absorption, distribution, metabolism, and excretion- which are summed up to be called as pharmacokinetics (PK) [1, 2]. While oral drug administration is the most widely used route of drug-intake, there are so many variables that impact oral drug absorption. The gastrointestinal variables including intestine structure, blood flow to the different parts of intestine, surface area, pH, etc. are some of them [3, 4]. Orally administered drugs experience a lot of harsh conditions before being available in the systemic circulation. Where immediate effect is desired with the most convenient route of administration, which is oral, immediate release drug product is the first choice.

"Immediate drug release dosage forms disintegrate rapidly after administration with an increased rate of dissolution" [5]. In the formulation of the tablet, super disintegrants such as croscarmellose, sodium starch glycolate, crospovidone, etc., play a fundamental role [6, 7]. These super disintegrants allow immediate disintegration of the tablet after administration in the stomach [6]. In this dosage form, 70-85% of the indicated dose dissolves within 30 minutes [8]. This class is beneficial when an immediate onset of action is needed for therapeutic effect [9]. Usually, immediate-release dosage forms dissolve or disperse in a single action according to a first-order kinetics profile [10]. "This demonstrates that the drug is initially released very rapidly and then travels through the mucosal membrane into the body, reaching its maximum plasma concentration (termed C_{max}) in a relatively short amount of time (termed t_{max})" [3, 11].

"The drug product release rates depend on the high solubility of the drug substance" [12]. "For immediate-release dosage form, drug products containing highly soluble drug substances may release at least 70% (preferably 80%) of the active ingredient within 30 minutes" [13]. "Immediate-release dosage forms formulated with poorly soluble active pharmaceutical ingredients (APIs) frequently require the use of surfactants to ensure complete release within 60 minutes" [14].

Immediate-release dosage forms 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) [16].

“Dissolution is the method by which a solid drug enters the solvent phase to form a solution” [17]. “In vitro dissolution testing is performed throughout drug product development to facilitate formulation process development and to control product quality” [14, 18-22]. “The purpose of dissolution testing can provide information regarding the rate and extent of drug absorption in the body, and it can also examine the impact of drug substance biological properties and formulation principles on the release qualities of a drug product” [23]. “For the development and approval of generic dosage forms, in vitro dissolution testing is a key necessity” [24]. Bioavailability and therapeutic effectiveness depend on how well a drug dissolves [25]. The purpose of in vitro dissolution testing is to determine the variables that influence the rate and extent of drug substance release from the finished dosage form [18-22, 24]. Dissolution testing is rigorously used for stability and quality control purposes for different dosage forms [26]. It is employed to assist formulations and thereby select excipients for the formulations with the aim of selecting the most suitable and reproducible release profile [27]. If the dissolution test is not conducted under the required conditions, it may be difficult to predict the in vivo performance of the drug product [28].

The Food and Drug Administration (FDA) issued four guidance documents about in vitro dissolution and the regulatory implications of its application [29]. The first guidance outlines FDA requirements for immediate release dosage form dissolution and statistical methods for comparing dissolution characteristics [30]. FDA issued two guidelines on scale-up and postapproval modifications for immediate-release dosage forms [31]. These guidelines explain the types of information required for manufacturing modification approval [29]. “The publication of these guidelines highlighted the FDA's substantial reliance on in vitro dissolution to rule out bioequivalence and confirmed the use of in vitro dissolution as a replacement for in vivo bioequivalence” [32].

The European Medicines Agency (EMA) has published specific guidelines for immediate-release (IR) dosage forms [33]. This guideline is known as "the IR guideline" since it focuses on active chemical components in oral immediate-release (IR) formulations with systemic action [33, 34]. The European Medicines Agency (EMA) also issued a guideline for in vitro dissolution testing where the suitability of the dissolution method and the specifications for in vitro dissolution of orally administered generic drug products with immediate release characteristics are discussed

[35]. The most recent approach by both the FDA and the EMA is to provide product-specific recommendations on the design of bioequivalence studies [36].

Test conditions:

Dissolution apparatus and agitation rate:

"Generally, there are seven types of USP apparatuses that can be used within a regulatory environment to analyze the release of drug substances from a finished dosage form" [23, 37]. "USP Apparatus 1, the basket, and USP Apparatus 2, the paddle, are more commonly used for the evaluation of in vitro dissolution of immediate-release solid oral dosage forms" [38, 39]. Table 1 describes the comparison between these two USP apparatuses [40, 41].

Table 1. Comparison of USP Dissolution Apparatuses.

USP Apparatus	**Apparatus Name**	**Agitation Rate**	**Dosage Form**
I	Basket Method	50-100 rpm	Solid oral dosages forms like capsules or tablets
II	Paddle Method	50-75 rpm 25-50 rpm	Solid oral dosages forms like capsules or tablets, Suspensions

Table 1 shows the agitation speeds recommended by FDA. During the method development, the appropriateness of the agitation speed should be examined for each drug product formulation. An excessive agitation rate might result in foaming, which can lead to a failure to differentiate between formulations that are not equivalent [42].

"But in some cases, USP apparatus three may also be used for the dissolution testing of IR products for highly soluble drugs, for example, metoprolol and ranitidine, as well as for some IR products of poorly soluble drugs, such as acyclovir. It is demonstrated that, with the proper agitation rate, USP apparatus three can generate dissolution profiles comparable to USP apparatus 2" [43].

Dissolution media:

The selection of dissolution medium in the development of dissolution methods can be arbitrary at times [44]. The selection of dissolution media depends on the solubility and stability of the drug substance, formulation, and component interactions [44]. “In the case of dissolution studies, the media consist of acidic or basic solutions, buffers, surfactants, and surfactants with acid or buffers [45]. Media containing bile salts and other relevant physiologically based components, commonly referred to as relevant media, can be applied in regulatory tests but are mainly used as research tools or in vitro–in vivo correlation studies” [46].

“During the development of dissolution testing methods, the BCS (Biopharmaceutical Classification System) classification system can assist in determining the process/formulation variations” [47]. “Immediate-release solid oral dosage forms consisting of highly soluble compounds such as BCS class I (high solubility, high permeability) or BCS class III (High solubility and low permeability), which achieve ≥85% dissolved in 500 mL of 0.01 N HCl and agitation rate is either 30 min (BCS class I) or 15 min (BCS class III)” [14]. BCS class II (low solubility, high permeability) and BCS class IV (low solubility, low permeability) drugs are mainly induced by pH and the type or nature of surfactant [44]. The use of various excipients may affect the solubility and permeability of these drugs [48]. The use of suitable surfactants, such as sodium lauryl sulfate (SLS), is believed to increase the solubility of the drug substance [48]. Classification of drug substances based on the Biopharmaceutics Classification System is shown in Table 02 [49], and The requirements of a dissolution media are shown in Table 03.

Table 2. Classification of drug substances based on the Biopharmaceutics Classification System

	High Solubility	**Low Solubility**
High Permeability	BCS Class 1	BCS Class 2
Low Permeability	BCS Class 3	BCS Class 4

Table 03: The requirements of a dissolution media

Requirements	Description
Buffer selection	The selected buffer should have the ability to maintain a constant PH throughout the dissolution test duration. In the case of weak acids or weak bases drug substance, the pH of the media can change as the drug

	substance dissolves. it is necessary to select the types of buffer and the amount of buffer to ensure the necessary buffer capacity [50].
pH	pH influences drug solubility and dissolution rate. The selection of pH depends on the drug substance. If the drug is weak acids, then the dissolution rate increases with an increase in pH, and if the drug is weak bases, the dissolution rate increases with a decrease in pH [51].
Media Volume	Typical media volumes are 500 ml, 900 ml, or 1000 ml for USP apparatus 1 and 2 [52].
Sink conditions	It is the ability of the dissolution media to dissolve at least three times the amount of drug that is present in the dosage form. Using sink conditions in the in-vitro dissolution test makes the test more robust and biologically relevant [53].
Surfactant	Surfactants are used to enhance the solubility or wettability of a drug. Surfactants minimize solution and surface interfacial tension by replacing water molecules on the surface [54]. For acidic drugs, media with cationic surfactants are better able to separate dissolution rates than media with other types of surfactants [55]. In addition, it is crucial to carefully consider the interactions among the ions and the type of surfactant used when dissolution media are selected. For example, potassium ions can react with SLS, making an insoluble product [56].
Common ion effect	The presence of a common ion can decrease the solubility of the drug substance. So the absence of a common ion should be ensured in dissolution media [57].
Deaeration	Gases dissolved in the dissolution media impact dissolution results. Degassing the media before use is required in this case. However, there are many methods and techniques available for removing air bubbles from the media [58, 59].

Dissolution temperature:

Generally, dissolution tests are conducted at 37°C to replicate normal human body temperature [60]. For immediate-release dosage forms, dissolution tests should be carried out at 37±0.5°C [61].

Sampling time points/ volume/ replenishment:

For immediate release, the sampling time points will typically be 15, 30, 45, and 60 minutes. When disintegration is rapid, the sampling time points are considered as 5 minutes and 10 minutes [62].

How to validate in vitro dissolution testing for a certain product?

Validation is performed to ensure that a method or procedure achieves its intended purpose.[63]. For immediate release, dosage form method validation was performed according to the USP and the International Conference on Harmonization (ICH) requirements [64-66]. Validation of the dissolution method includes the dissolution steps and the analytical endpoint. Dissolution steps are the release of a drug substance from the formulation of the product into the dissolution medium like performance evaluation parameters such as precision, linearity, repeatability, reproducibility, the limit of quantitation, etc., and the analytical endpoint includes the sample handling and the analytical methods that are used to determine the amount of drug substance dissolved during the dissolution step such as spectroscopic or chromatographic (HPLC and/or GC) [67-69]. Furthermore, the dissolution method should be capable of distinguishing between acceptable and unacceptable batches [70].

How to set an in vitro specification for in vitro dissolution testing for a certain product?

"The in vitro dissolution test is thought to be a surrogate for the in vivo dissolution test. It will affect pharmacokinetic behavior, which is a substitute for clinical effectiveness" [49]. "The dissolution specification is specified in terms of the quantity (Q) of active substance dissolved in a specified time, represented as a percentage of the content stated on the product label" [71]. "When the test conditions for dissolution have been determined, a suitable dissolution specification should be established. The specification should be written in such a way that compliance with batches may be expected during routine production and testing" [72]. "Establishing appropriate dissolution specifications will ensure that the dosage form is

manufactured consistently and successfully throughout the product's life cycle and that each dosage unit within a batch has the same pharmaceutical qualities that relate to those that have been shown to have an adequate safety and efficacy profile" [29].

The function of the release specification

"The dissolution specification for product release or shelf-life stability of a pharmaceutical product includes both the validated test method and the acceptance criteria for the test" [73]. "The expected acceptability criteria vary depending on the dosage form and must be justified in relation to in vivo performance, processing factors, and the outcomes of long-term stability tests" [52, 67]. "The objective is to assure consistent performance from lot to lot over the life of the product, and it may be beneficial for showing product equivalence during scale-up or justifying specific postapproval adjustments" [52]. "The acceptance criteria are established based on a comprehensive examination of the dissolution data collected during development, including data from stability tests, with a focus on the testing of products used in clinical investigations" [74].

Method Validation:

The validation of a dissolution test technique requires assessing the test's operational parameters as well as the acceptability of the analytical finish. The purpose is to demonstrate the method's capability to detect variations in the test product, which is significant enough to impact in vivo performance. The level of validation may vary depending on the stage of development. When the product is planned for commercialization, new elements or stricter criteria may be implemented. [74, 75].

Acceptance Criteria:

For immediate-release drugs, the acceptance criterion is usually a minimum amount of drug released (Q) at a single time point (usually less than or equal to 60 minutes). Typical release times for fast-acting dosage forms are 15 or 30 minutes. Products that release more slowly may need a second-time point, like an initial time point of 15 minutes and a second-time point at a later time, to make sure they release everything they are required to. The acceptance criteria chosen must be able to distinguish between batches that are non-bioequivalent and batches that expose the limits of acceptable process parameters [76-78].

Considerations for generic products:

For generic products, the dissolution specifications depend on some parameters, for example, dissolution profiles and data of the batches of the dosage form that shows similar acceptance criteria during in vivo bioequivalence studies. Once a dissolution specification has been established for the generic product based on the batch employed in the in vivo bioequivalence study, the generic product must adhere to that specification throughout its shelf life [24, 79, 80].

Scale-Up and Postapproval Changes

When a new drug product is developed, the batch sizes that are used in early human studies are generally small. With time the batch sizes are increased, which is called scale-up. The scale-up process and the changes that are made after approval of the manufacturing process, formulation of the drug, batch size, manufacturing equipment, or change of site have known as Scale-Up and Postapproval Changes or SUPAC [81, 82]. The first SUPAC guidelines for immediate-release oral solid dosage formulations were issued in 1995. (SUPAC-IR) [83]. Primarily, SUPAC-IR was intended to reduce the regulatory burden of the industry when making postapproval changes while still maintaining formulation quality and therapeutic product performance. Among the postapproval modifications authorized by SUPAC-IR were changes in the formulation's ingredients and composition, manufacturing site, batch size, manufacturing equipment, and manufacturing method [84]. The guidance set levels of changes based on susceptible risk are to happen and how postapproval changes could affect the safety and effectiveness of a drug product [85-87].

Biowaiver Considerations

A biowaiver explains that in vivo bioavailability and/or bioequivalence studies may be waived [88]. Instead of doing expensive and time-consuming "in vivo" studies, a "dissolution test" could be used to decide if the two pharmaceutical products are the same. Even if a complete clinical investigation is conducted, the likelihood of therapeutic inequivalence between two immediate-release drugs cannot be minimized. The objective of biowaiver guidance is to decrease bioequivalence risk to a tolerable level [12, 89]. In August 2000, the FDA provided industry guidelines on waivers of in vivo bioavailability and bioequivalence studies for IR solid oral dosage forms based on the BCS [36]. BCS guidance suggests that sponsors may obtain biowaivers for highly soluble and highly permeable drug compounds (Class I) in IR solid oral dosage forms with rapid in vitro dissolution if the following conditions are met: 1) The medicine

must be gastrointestinally stable, 2) excipients used in the IR solid oral dosage forms have no major effect on the rate and extent of oral drug absorption; 3) the medication must not have a narrow therapeutic index; and 4) the product is not developed for oral absorption [90-92].

Conclusion:

In vitro dissolution is gaining importance in a variety of regulatory aspects. Recently, regulatory agencies in the European Union (EU) and the United States (US) have been at the forefront of dissolution guidelines. However, recent trends indicate a rise in dissolution similarity criteria from regulatory authorities around the world. This results in different dissolution profile standards and a substantial amount of unnecessary and duplicated work that does not contribute to the safety or efficacy of the product.

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