

# Drug Dissolution Testing: Selecting a Dissolution Medium for Solid Oral Products

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## Abstract

Choice of a dissolution medium is an important and critical variant for drug dissolution testing. The reported choices range from a simple solvent (water) to complex solutions, often drug and/or product dependent. However, making a choice is not so simple or straightforward, but confusing and often scientifically or logically not convincing or valid. This article provides a discussion in this regard leading to suggestions for selecting an appropriate dissolution medium.

## Introduction

Dissolution tests are employed to establish drug (Active Pharmaceutical Ingredient, API) release characteristics of solid oral products, such as tablets and capsules. The rationale for conducting these tests is that for a product to be therapeutically effective, the drug must be released from the product and should generally be dissolved in the fluid of the gastrointestinal (GI) tract. The API in solution form facilitates the absorption of the drug from the GI tract into the systemic (blood) circulation to reach its desired target (site of action) to exert its effect. Therefore, a dissolution test may be considered as a critical step for the development and assessment of the quality of products linking to their safety and efficacy attributes.

An important consideration, therefore, in conducting a dissolution test is that the test be conducted using experimental conditions representing the GI tract environment as closely as possible. One such experimental condition is the choice of a dissolution medium, with the appropriate pH, to represent fluid present in the GI tract. At present, a large number of different media are employed, from water or simple buffer solutions having different pH values as described in the USP monographs [1], to complex solutions reported in the literature [2-3].

There appears, however, to be a lack of a systematic approach in selecting a dissolution medium. The selections appear speculative in nature, based on the expected or desired dissolution characteristics of a product. Such an approach may be the cause of the difficulties in selecting an appropriate dissolution medium.

This article provides a discussion based on some practical scenarios for conducting dissolution tests, leading to an appropriate choice for a dissolution medium.

It is to be noted that in this article, the terminology of drug release and drug dissolution mean one and the same thing and are used interchangeably.

## Required Common Characteristics of a Dissolution Medium

Since the objective of drug dissolution testing is to assess the expected drug dissolution in the GI tract, the medium should be representative of the liquid-phase present in the tract, which is aqueous. Therefore, to be physiologically or bio-relevant, the dissolution medium has to be water or water-based. However, one may not use media such as potassium or sodium hydroxide solutions which, although water-based, their use is restricted by their high pH values not found in the GI tract.

A general restriction imposed upon the choice of a dissolution medium by the physiological aspect is, therefore, that the medium be aqueous and have a pH in the range of 1 to 7. Furthermore, considering the physiological aspect with regard to dissolution testing, it is generally recognised that the most of time, if not always, absorption of drugs occurs in the intestinal part of the GI tract where the pH ranges from 5-7, and not in the gastric (stomach) section where the pH is usually 1 or sometimes 2-3 [4].

Thus, since drug absorption depends on dissolution, and most absorption occurs in the intestine, physiological aspects dictate that a medium should be aqueous having pH in the range of 5-7.

Based on the preceding discussion, a logical first choice for a dissolution medium would be water itself. Incidentally, the pH of purified water falls in the range of 5-7 [5], thus it would fulfil the physiological relevancy of the pH aspect well.

The following discussion will be built on this choice, with modifications as needed, for developing an appropriate dissolution medium to test a variety of products containing different types of APIs, having different release characteristics.

Before proceeding to selecting a dissolution medium, it is important to note that one needs to make sure that the apparatus being used for testing must be able to provide gentle but thorough interaction of the test product, and its disintegrates, with the dissolution medium. Numerous examples of poor product/medium interaction and its potential negative impact on dissolution results have been described in the literature [6-7], and should be taken into consideration when selecting an appropriate apparatus for testing.

## Dissolution medium for immediate-release (IR) products with water-soluble drugs:

Let us consider a scenario in which one is aware of a product of a drug (API-1, say propranolol.HCl) having composition of excipients (X, Y, Z) and its manufacturing process. The product shows a dissolution rate of 100% dissolved in 30 minutes, in water at a certain stirring rate, which is considered acceptable for this product.

Next the analyst is given an assignment to develop a product of another freely soluble drug (API-2, say diltiazem.HCl) having exactly the same drug release characteristics as that of the API-1 as previously described. The most logical approach would be to prepare the product using the same formulation (excipients X, Y, Z) and the same manufacturing process. As the API is freely soluble in water, formulation and manufacturing are exactly the same as in the previous case; the product will behave exactly the same as the product with API-1 because the dissolution is dependent on the characteristics of excipients and manufacturing which are the same in both cases. Therefore, changing an API would not require a change of dissolution medium.

If the dissolution results obtained are different than expected then it would demonstrate that there is potential interaction of API-2 with formulation/manufacturing. In such cases, dissolution testing served its purpose well and the formulator has to determine the cause of the problem and address it by changing the formulation or manufacturing attributes so that the required dissolution rate may be achieved. It is important to note that one should not change the dissolution medium to obtain the required dissolution rate since the medium has a link to the physiology which has not changed. Therefore, for IR products having highly soluble drugs, water appears to be an appropriate dissolution medium.

## Dissolution medium for immediate-release (IR) products with low water solubility drugs:

Consider a scenario that a formulator is given an assignment to develop a product of an API-3 with low aqueous solubility (say carbamazepine) but having exactly the same dissolution characteristics as described before for the highly soluble API-1. As previously described, one cannot change the dissolution medium as dissolution is linked to physiology and physiology remains the same even if the API happens to be of low water solubility. Therefore, the analyst has to use water as a dissolution medium. Furthermore, from the previous discussion, if the analyst aims to obtain the same dissolution rate as before, then the first logical step is to use the same formulation and process to manufacture the product. After fabricating the product having exactly the same formulation and manufacturing process, but with the API-3, a dissolution test was conducted to evaluate release characteristics of the product. Although, the product would disintegrate and API would release, the analyst would not be able to see the dissolved drug. The reason is not that there is a problem with the product or releasing of the drug but because of the low solubility, the drug would not dissolve in water (dissolution medium) to be able to be quantified. Therefore, in reality, it is not a dissolution or product issue but a detection/quantitation issue. What should one do? In this particular case, one would be required to add a solubiliser in the dissolution medium so that API could be dissolved and quantitated appropriately. For the choice of a solubiliser, the compound should also be physiologically "relevant"; otherwise the medium would not maintain its physiological relevancy. It is generally accepted that the GI tract contains bile salts which help in achieving the solubility of

such drugs. One may use bile salts or substitutes to address this issue. In this regard, the most commonly used compound is sodium lauryl sulphate (SLS). Therefore, for low solubility APIs rather than using water alone one would use water with some quantity of SLS. As the formulation and manufacturing was the same as described before, the rate has to be the same for this low solubility drug and now the detection issue has been resolved as well. Thus, for IR products with low water solubility APIs, the dissolution medium should also be water but with some solubilising agent (e.g. SLS).

This leads to an important conclusion that before conducting a dissolution test, one is required to establish the solubility of the API in the dissolution medium. The API must be freely soluble in the medium by itself or with the addition of a solubilising agent. It should be noted that APIs may have different aqueous solubilities, high or low, but for dissolution testing purposes API must be freely (highly) soluble in the dissolution medium. It is an important concept, often overlooked in practice that for dissolution testing the API always has to be freely soluble in dissolution medium, whether the API is a low or high solubility drug. This aspect needs to be established first, experimentally, whether it is water alone or if a solubiliser is required for a particular API to be freely soluble at 37 °C.

## Dissolution medium for extended-release (ER) products with water soluble drugs:

Since the GI tract physiology remains the same as assumed for IR products where the medium is linked to the GI tract environment, the choice of medium will therefore remain the same. The difference here would be that the ER products are different from IR products in formulation and/or manufacturing attributes to retard or slow the dissolution/release of the API. Therefore, to evaluate the impact of change in formulation and/or manufacturing attributes or differences in IR vs ER, all other experimental conditions, including dissolution medium, must remain constant. To observe differences/discrimination in release rates between IR and ER products or within the ER category, one has to alter the formulation/manufacturing not the medium. The changing of dissolution medium would imply that somehow human physiology will change with an ER product, which is not a correct assumption. Thus, the choice of a dissolution medium in case of ER products of highly soluble drugs remains the same as for IR products, i.e., water.

## Dissolution medium for extended-release (ER) products with low solubility drugs:

As describe before, if the drug has low aqueous solubility one would require a solubilising agent in the medium. Since physiological environment is the same and comparison has to be made against the IR product, the appropriate medium choice would exactly be the same as for low solubility drugs in IR type products.

It is important to note that the choice of a dissolution medium is independent of product type i.e. IR vs ER, hence water for soluble drugs and water with solubilizer for others [9].

## Dissolution medium for enteric-coated products:

An enteric-coat is usually a layer of a polymer on a product to avoid its disintegration, and thus release of drug in the stomach. These coatings are usually insoluble at low pH of 1-3. Thus the product remains intact in stomach where pH is low, but are dissolved releasing the drug at higher pHs which are observed in the intestinal tract.

The commonly suggested dissolution testing approach for such products is based on two media; one to test if the product resists the stomach acidic environment by testing in dilute HCl (pH ~1) and the second in a dissolution medium of higher pH (6.8) representing intestinal phase.

The testing of the first part, in HCl, is in fact similar in analogy to a friability test, where tablets are tested to establish the integrity of the product, i.e. they would not get chipped or peeled of while in transit to patients. Similarly, to establish that the enteric-coated products remain intact while passing through the stomach, testing is conducted using HCl to ascertain that no drug be released in stomach.

Once the product passes through the stomach into the intestine, it would face the same physiological or dissolution environment as that of any product. Therefore, testing of such products should not require any different dissolution medium than would be used for any other IR or ER product. This reasoning suggests that in fact enteric-coated products should also be tested using water or a water-based medium as previously described.

Using a buffer at pH 6.8, as commonly used, appears to indicate that the intestinal pH is 6.8 which is not accurate for most common situations. If experimental studies, however, demonstrate otherwise that the pH 6.8 is indeed reflective of appropriate intestinal pH for dissolution testing, then obviously all dissolution tests are to be conducted at pH 6.8, not for enteric-coated products only. However, there is a lack of such experimental evidence, resulting in extensive use of water as dissolution medium for pharmacopeial testing purposes. Thus, water appears to remain the choice for a dissolution medium.

For convenience, a summary of choices of dissolution media for different combinations of drugs and products is provided in the Table.

Drug (API) aqueous solubility	Product Type		
	IR	ER	Delayed-release (enteric-coated)*
High	Water	Water	Water
Low	Water + Solubilising compound (e.g. SLS)	Water + Solubilising compound (e.g. SLS)	Water + Solubilising compound (e.g. SLS)

\*Following testing in HCl as described in the USP.

Table: Choice of a dissolution medium based on a drug and product combination.

## Water as a dissolution medium – potential concern:

One concern often expressed with the use of water, is its low buffering capacity, i.e., pH of water may be affected during testing because of the nature of the API and/or the excipients. It is to be noted that this concern is not related to the change in pH but potential change in solubility of the API with the change in pH of the medium. However, as noted before, such concern would be relevant only if dissolution testing be done at saturation level of APIs, which is not the case as dissolution testing is always conducted at levels where the drug is freely soluble in the medium. The important requirement for dissolution testing is that the drug must be freely soluble in the dissolution medium during testing. This solubility aspect has to be established before one starts the dissolution testing. For cases where indeed there is an issue of limited buffering capacity, supported by experimental data, the use of buffers with appropriate buffering capacity of pH equivalent to of water at 37 °C should be employed. Such a scenario should be considered as an exception not a general rule.

## Dissolution medium for Quality Control vs. Bio-relevant Testing:

In the preceding discussion, choice of a dissolution medium is described based on its link to a physiological environment. It is, therefore, safe to assume that the choice of water with or without solubilising agent lends itself as an appropriate bio-relevant dissolution medium. The purpose of a quality control test is to perform the testing that will determine if the product (drug dissolution) would behave in humans as expected. Therefore, QC testing dictates that test should be as bio-relevant as possible. The use of water is bio-relevant. Therefore its use for QC purpose should be extended without any modifications i.e. there should not be any differences in dissolution medium for QC and bio-relevant purposes.

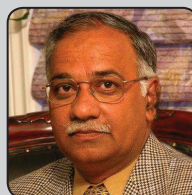
## Summary

The choice of a medium, like any other experimental condition for dissolution testing, should be linked to appropriate physiological characteristics. In this case, the relevant physiological part is the GI tract in particular the large intestinal part, which dictates that dissolution medium should be water or water-based having a pH in the range of 5-7 at 37 °C. Water alone or with added appropriate amount of a solubilizing agent (e.g. SLS) appears to fulfill this requirement well. The use of water as the medium has been extensively described in the USP, providing further support for its use.

Since the choice of medium reflects a link to the physiological environment, which remains constant, independent of product characteristics (IR vs. ER), this dictates that the choice of the medium should remain constant as well and independent of product attributes. The use of water, alone or with a solubilizing agent, fulfills this requirement. Therefore, both IR and ER type products should be analysed using the same medium. The discussion provided should help in making a choice for an appropriate dissolution medium simple, practical and unbiased.

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