Selection and Parameters Affecting Dissolution Media

Priyal Jangla[1] and Roopam Raut[1*]
[1]Department of Pharmaceutics, Principal K. M. Kundnani College of Pharmacy, Mumbai, India.

e-mail: roopam4pharma@gmail.com

ABSTRACT

Dissolution of oral solid dosage forms refers to the process by which active pharmaceutical ingredient(s) are released from the dosage form into a liquid vehicle, called the dissolution medium. Dissolution is an essential test for the development and quality control of almost all dosage forms. The availability of the drug to release from the dosage form into the dissolution medium can be often linked to the availability of the drug for absorption and eventually for therapeutic action. Therefore, it is crucial to investigate the choice of dissolution media, especially in the case of poorly soluble drugs (BCS class 2 and 4). This article reviews the various parameters of dissolution media that influence drug release for research and development of pharmaceutical formulations, including temperature, pH, ionic strength, surfactant, enzymes, dissolved gas, hydrodynamics, viscosity, and the type of dissolution apparatus. Understanding the impact of these parameters will help in making a straightforward, realistic, and objective decision regarding the most effective dissolution medium.

KEYWORDS: biorelevant media, solubility, dissolution, Biopharmaceutical Classification System (BCS)

INTRODUCTION

Dissolution is the transformation process of a drug substance from a solid to a solution (i.e., mass transfer from the solid surface to the liquid phase) (*1*). The dissolution process demonstrates that the drug is being released from the product and is readily accessible in solution form for gastrointestinal (GI) absorption. The dissolution rate is determined by the amount of drug substance that goes into solution per unit of time under standard temperature, pH, and solvent composition conditions (*2*). The dissolution test is a pharmacopeial test to determine the extent and rate of drug release from solid oral dosage forms, such as immediate and sustained-release tablets and capsules (*3, 4*).

In the early 19th century, dissolution studies were carried out to study the physicochemical properties of a substance. These studies set the basic laws for dissolution, which were later extended to different dosage forms. After it came into use for the development of dosage forms, several developments led to an understanding of various factors that affect bioavailability. Nowadays, much research is being done on dissolution because the drug release profile has great importance in the development of pharmaceutical products. Dissolution studies assist with selection of the drug, excipients, manufacturing process, and final dosage form to design a suitable formulation for in vivo studies. For example, a small change in the formulation may change the drug release profile of the developed formulation and thus, bioavailability. The drug release data obtained by use of different dissolution parameters may correlate with in vivo availability of the drug. In general, the parameters with the best correlation are used for developing the final drug release specifications. Dissolution tests are used to establish the in vitro-in vivo correlation (IVIVC) and develop clinically successful products in a short time with less cost. The results obtained from dissolution studies are analyzed with the help of certain mathematical formulas.

For immediate-release solid dosage forms, dissolution begins with disintegration of tablets or capsules into granules, which are further disintegrated into fine particles. This process continues in the dissolution medium, cumulatively leading to the drug in solution form (it may be in vitro or in vivo). In vivo, the drug in solution undergoes absorption and enters the blood, fluids, and tissues. Therefore, dissolution studies are important with respect to regulatory approval and commercial success of the dosage form. Dissolution studies are used to determine if the active ingredient is released as expected in the treatment location, if the drug meets established acceptance criteria, and if the formulation is stable over time.

This review focuses on the impact of the parameters and selection of dissolution media for research and development of pharmaceutical formulations.

PARAMETERS OF DISSOLUTION MEDIA THAT AFFECT DRUG RELEASE

The selection criteria for dissolution media considers both physiological and physicochemical characteristics of the drug substance and formulation. The first stage in creating a discriminating dissolution method is pH solubility and stability profiling. To create a robust and repeatable dissolution procedure, the analyte must be stable in the dissolution medium to allow adequate time to complete the test. The choice of pH and buffered media is crucial in creating a sink environment for weakly soluble ionizable drugs that exhibit pH-dependent solubility. A surfactant may need to be added if the sink condition cannot be satisfied with the buffered medium alone (5). Hence, before the selection of dissolution media, one must be familiar with the parameters affecting it.

A sink condition is achieved when the concentration of drug in the dissolution medium is significantly lower than its solubility limit. When a sink condition is maintained, the concentration gradient between the undissolved drug in the tablet and the dissolved drug in the medium remains constant. Sink conditions in the dissolution medium more closely resemble the conditions in the gastrointestinal (GI) tract, where the drug is rapidly and effectively dissolved in a large volume of fluid, ensuring optimal bioavailability and absorption. Maintaining sink conditions is essential to ensure batch-to-batch consistency and predict how the drug will behave in the body for proper dosing and therapeutic efficacy. Sink conditions are affected by temperature, pH, ionic strength, surfactant, dissolved gases, hydrodynamics, viscosity, and dissolution apparatus. When choosing the composition of the dissolution media, the influence of these characteristics on the drug's solubility and stability must be considered (6).

Temperature

As the solubility of many drugs is temperature dependent, the drug release rate profile is significantly influenced by the temperature of the dissolution media. For oral dosage forms, 37 ± 0.5 °C is the permissible temperature for the dissolution media. Studies can be carried out by altering the media's temperature to evaluate the effect on drug release. Heng et al. examined the effects of environmental variables on the dissolution rate of amorphous and crystalline lurasidone hydrochloride

(LH) (7). They observed that when the temperature of the dissolution medium increased, an increase in dissolution was observed for both the forms. This was attributed to the endothermic nature of LH dissolution. At corresponding temperatures, amorphous LH showed lower drug release than crystalline LH. The investigation revealed that amorphous LH converted to crystalline LH, resulting in a decrease in dissolution rate (7). Changes in temperature also affect the solubility and swelling index of many excipients like diluents, binders, and disintegrants, which influence the release of drug from the dosage form.

pH

The pH of the dissolution medium chosen is usually one that supports sink conditions. Knowledge of the acid dissociation constant (pKa), its impact on solubility, and ruggedness of the dissolution technique must all be considered (8). Kincl et al. estimated the impact of different factors on diclofenac sodium drug release, including the type of dissolution apparatus, rotation speed, pH, and ionic strength (9). The authors concluded that pH had a major impact on drug release, i.e., the release of active ingredients mostly depends on pH of the dissolution medium (9). If the dissolution medium is a buffered solution, adjust the solution so that its pH is within 0.05 units of the specified pH given in the individual monograph.

Ionic Strength

Ionic strength of the media is usually varied over a range of 0–0.4 M to simulate fed and fasted states and various physiological pH conditions in the GI tract. NaCl and KCl are some salts that are used in dissolution media to mimic biological fluids under fed and fasted conditions. Nashed et al. conducted experiments with various KCl concentrations and found that solubility was improved by alkaline ions like potassium, which led to an increase in the release rate (10). Also, increasing the ionic strength beyond a certain point eventually resulted in decreased dissolution efficiency by indicating the salting out of the polymer by the organic ions in the media, prolonging the drug release (10). Along with temperature, Heng et al. studied the dissolution profiles of crystalline and amorphous LH in 0.025, 0.05, and 0.1 M NaH_2PO_4 solutions (7). They found that increasing ionic strength slowed crystalline LH dissolution, as water molecules are attracted by salt ions, reducing interaction. Similar trends were seen with amorphous LH, but there was slower dissolution in buffer solutions with each concentration. Decreased dissolution in buffer solutions was attributed to the precipitation and gelation of amorphous LH (7).

Addition of Surfactants

The number of new drug candidates with poor solubility has been increasing. Surfactants can either be anionic, cationic, zwitterionic, or neutral, which can help enhance the solubility of the drug. It is preferable to use chemically well-defined surfactants, such as sodium dodecyl sulphate. Other utilized surfactants include polyoxyethylene 23 lauryl ether (Brij 35), polysorbates (Tween 20 or 80), and cetyltrimethylammonium bromide. The most commonly utilized chemicals are sodium dodecyl sulfate (SDS) and polysorbate 80 (Tween 80) (11, 12). The reported concentration of SDS ranges from 0.01–3% (13).

The pH of the medium has less effect on dissolution for poorly water-soluble drugs (BCS class 2 and 4). For achieving higher solubility in the dissolution medium, a solubility enhancer (surfactant) can be added (14). The incorporation of different types of surfactants and levels can be of key importance for poorly soluble drugs (15). According to Dressman et al., poorly soluble drugs do not exhibit an IVIVC because they have limited solubility and need more surfactant to dissolve (16). To maintain the discriminatory power of the dissolution method, the concentration of the surfactant should be the lowest required to produce sink conditions and be supported by solubility data at 37 °C. Efentakis et al. studied the effect of surfactants (sodium lauryl sulfate, sodium taurocholate, cetylpyridinium chloride, cocamidopropyl betaine [CDB], and cetrimide) on drug release rates (17). They concluded that the drug release was rapid when the surfactant was more soluble due to the formation of pores or disruptions in the matrix (17).

Enzymes

Biorelevant media are fluids that are physiologically relevant and remarkably realistic approximations of the fluid found in the gut. These media are used to study the behavior of drugs and dosage forms in a laboratory to mimic the in vivo environment of the GI tract. Biorelevant media include fasted state simulated gastric fluid (FaSSGF), fed state simulated gastric fluid (FeSSGF), fasted state simulated intestinal fluid (FaSSIF), fed state simulated intestinal fluid (FeSSIF), fasted state simulated colonic fluid (FaSSCoF), and fed state simulated colonic fluid (FeSSCoF). (18). Surfactants, enzymes, and other substances found in the physiological environment are common components in biorelevant media. The most common enzymes in these media are pepsin, pancreatin, or papain. The concentration of enzymes, enzyme activity, and a pre-treatment procedure should be determined when the dissolution medium contains surfactant, or any other components suspected to inactivate the enzyme being used (19). Pennings et al. investigated the role of enzymes and found that dosage forms tested in media containing pancreatin or pepsin had improved dissolution performance of stressed hard gelatin capsules compared with deionized water or 0.1 N HCl (20).

Dissolved Gas

The dissolution profile can be affected by dissolved gases present in the medium. The dissolved gases can provide an abrasive force on the dosage form in the dissolution media. For example, air bubbles can cause the intact or disintegrated dosage form to float, spin, agglomerate, which can impact the drug release behavior (21). The air bubbles can act as a barrier to dissolution when present on the dosage unit or basket mesh. Heating the medium to 41 °C followed by filtration through a filter with porosity of 0.45 µm or less, room temperature filtration, sonication, and helium sparging are deaeration methods described in the *United States Pharmacopeia* (*USP*) (22). Transfer of deaerated dissolution medium to a jar and the rate of stirring with the paddle/ basket apparatus are the prime contributors of reaeration during dissolution. The importance of deaeration should be investigated by comparing the dissolution data with non-deaerated and deaerated mediums. However, because surfactant-containing dissolution media equilibrate quickly compared to aqueous media, the impact of dissolved gases is less of a problem. The reproducibility and quality of dissolution results increase after the dissolved gases reach equilibrium (22). A total dissolved gas pressure meter can be used for measuring dissolved gases.

Hydrodynamics

A good understanding of hydrodynamics is beneficial in the development of dissolution methods and formulations, as well as in complying with the pharmaceutical industry's quality requirements, such as batch-to-batch control. If the mass transfer mechanism is controlled by convection and/or diffusion, as is typically the case with poorly soluble compounds, hydrodynamics dominates the overall dissolution rate. The fundamentals of hydrodynamic laminar and turbulent flow are relevant to dissolution. Hydrodynamics is generally considered a variable for alteration in the creation of dissolution methods. Although a hydrodynamic environment can affect the rate of dissolution, hydrodynamic features of the dissolution conditions are normally not studied as part of dissolution testing, other than choosing an agitation rate and seeking to reduce fluctuation. Because dosage form placement and behavior (i.e., motion and disintegration) during a dissolution test might differ between apparatus, it

is challenging to evaluate the influence of hydrodynamics on dissolution between apparatus (*23*). Bai et al. used a computational-based model and experimental approach to investigate the effect of tablet position on dissolution rate and overall dissolution process (*24*). The enhanced hydrodynamics experienced by off-center tablets led to faster dissolution and disintegration of the tablet, resulting in a greater dissolved concentration of the drug during the early phase of the dissolution process (*24*).

Viscosity
The rate of transport of the reactants to and from the interface, which is determined by the transport process, is substantially slower than the interaction between the solid and the dissolution medium. Therefore, diffusion-controlled interactions are anticipated to decrease as viscosity increases. Elworthy and Lipscomb confirmed these findings by noting that at high surfactant concentrations, the viscosity of the dissolution medium increased significantly, thus slowing the dissolution rate of griseofulvin (*25*). When researching the effects of viscosity and solubilization on dissolution rate, Braun et al. discovered that the dissolution rate was inversely proportional to the viscosity (*26*). The viscosity of micellar solutions is raised by high polysorbate 80 concentrations to the extent that the dissolution rate is retarded even when overall solubility is markedly increased.

Dissolution Apparatus
The USP has seven different apparatus for dissolution testing; however, most tablets and capsules employ apparatus 1 or 2, popularly known as the basket and paddle, respectively. Wu et al. demonstrated the type of dissolution apparatus used to test tablet dissolution has an effect on the dissolution rate (*27*). The paddle method resulted in higher dissolution for class 1 drugs like theophylline, which has high dissolution and absorption, as well as class 2 drugs like naproxen, which has poor dissolution and high absorption. The paddle method provided faster dissolution rates than the basket method, and as rotational velocity increased, so did the drug release.

SELECTION OF DISSOLUTION MEDIA
Careful selection of a suitable dissolution medium is necessary in dissolution testing (*28*). The choice of dissolution medium is crucial for batch-to-batch quality testing, ensuring acceptable sink conditions are met. The task of finalizing the evaluation parameters comes after the dosage strength and intended release pattern for an oral solid dosage form are established. Thus, after understanding the parameters affecting the dissolution

media, it is feasible to select the media. Most of the time, the active pharmaceutical ingredient (API) should dissolve in the fluid of the GI tract. Therefore, the location at which the drug is to be released for the drug product, chemical composition of the media in the GI tract, solubility in those media, as well as the overall time for a drug to be released from the product, should all be taken into consideration when choosing biorelevant dissolution media and conditions (*29*, *30*). The development of media over the years for determining solubility as well as dissolution and its applications in drug development was summed up by Bou-Chacra et al (*31*).

To evaluate the dissolution properties of oral formulations, media with a physiological pH range of 1.2–6.8 should be used (*32*). According to the percentage of drug release, the chosen dissolution media can be deemed satisfactory. Dissolution medium selection can be made according to the pharmacopeias, Biopharmaceutical Classification System (BCS), or U.S. Food and Drug Administration (FDA) database.

Pharmacopoeia
The dissolution media can be chosen using a number of pharmacopoeias, including the *Indian Pharmacopoeia*, *United States Pharmacopeia*, *British Pharmacopoeia*, and *European Pharmacopoeia*. These publications offer information on the unique monograph of each drug, depending on the dosage. They provide different dissolution media based on the drug's release profile. The choice of dissolution media for new drugs can be made using the pharmacopoeia's list of dissolution media for drugs in the same chemical class and dosage.

BCS Classification
A scientific framework for categorizing drug substances according to their aqueous solubility and intestinal permeability is known as the BCS. The BCS was created in 1995, and it has become the standard for regulating the bioequivalence of oral drug products. The BCS divides APIs into four classes based on solubility and permeability (*33*, *34*).

For drugs in classes 1 and 3, simple aqueous media such as simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) (with or without enzymes) are recommended. However, dissolution tests for classes 2 and 4 should be conducted in a biorelevant medium.

Most registered drugs are class 2 (high permeability, low solubility) or 4 (low permeability, low solubility) by the BCS (*34*, *35*). The oral absorption of BCS class 2 drugs is primarily limited by their solubility and/or dissolution

in the GI tract (*36, 37*). In such a scenario, it would be advantageous to have an in vitro dissolution test that could be utilized to predict in vivo behavior at different stages of formulation development. The rate-limiting step for the in vivo absorption of class 2 drugs is dissolution (*38*). Class 1 and 3 drugs display rapid or very rapid dissolution, and BCS provides for the waiver of in vivo bioavailability and bioequivalence testing for immediate-release solid dosage forms (*39*).

Fagerberg et al. tested 10 substances, including three bases and three acids with no net charge in the study pH range, for apparent solubility and dissolution rates of BCS class 2 drugs. In comparison to the corresponding blank buffers, most of the compounds demonstrated higher solubility and dissolution rates in FaSSIF and FeSSIF. Compounds with a neutral or positive charge were more soluble in FeSSIF compared to FaSSIF. Even though there were more solubilizing agents in FeSSIF than in FaSSIF, the acidic compounds still displayed a pH dependence (*40*).

Table 1 gives some examples of the development of dissolution profiles containing different media for dissolution of BCS class 2 drugs (*41–47*). The selection of dissolution media was primarily done based on solubility (*44*). The drug release profiles were then examined and the dissolution media were selected for the particular drug (*45–47*).

FDA Database
The selection of dissolution media can also be done by using data provided by the U.S. FDA. Information on a variety of media, including water or basic buffer solutions with varying pH levels and solutions with additional surfactants, organic solvents, and enzymes, is available in the FDA Dissolution Database. This database offers information that complies with suggestions made by the Division of Biopharmaceutics, Office of Pharmaceutical Quality for drug products without a dissolution test method in the *USP* (*48*). Along with the dissolution medium, the FDA database also provides the dosage form, USP apparatus, speed in rpm, and volume of the media for drugs (*13*). The database provides information specific to the drug and its dosage form, and it is independent of the variables such as excipients used, size, shape, etc. of the product.

CONCLUSIONS
The administration of medicine is necessary for the treatment of disease, and the dissolution of solid dosage forms is essential for evaluating the distribution of APIs. Thus, in dissolution testing, selection of an appropriate and effective dissolution medium is critical. The review is focused on the selection of a dissolution medium for correlating the in vitro and in vivo performance of the drug. Different dissolution media have different effects on the solubility of the dosage form. Temperature, pH, ionic strength, surfactant, enzymes, dissolved gas, hydrodynamics, viscosity, and the type of dissolution apparatus can affect the drug release profile. Pharmacopeias, BCS classification, and the FDA dissolution method database provide helpful information on drug dissolution specifications to aid in selecting a medium based on the drug's dosage form.

Table 1: Compilation of Case Studies on Dissolution for BCS Class 2 Drugs

No.	Summary of Case Studies
1	The dissolution profile of celecoxib tablets was studied by Babu et al. in seven different dissolution media: a) water, b) 0.1 N HCl (pH 1.2), c) phosphate buffer (pH 7.4), d) phosphate buffer (pH 8.0), e) methanol in water (5%, 10% v/v), f) Tween 80 in water (0.25%, 0.5%, 1% v/v), and g) SLS in water (0.25%, 0.5%, 1%, 1.5%, 2% w/v). The results suggested that 2% w/v SLS in water had the best correlation with in vivo studies (*41*).
2	Dissolution profile of aceclofenac was studied by Soni et al. using dissolution media: a) double distilled (DD) water, b) SLS in DD water (0.6%, 0.8%, 1%, 1.5%, 2% w/v), c) Tween 80 in DD water (0.2%, 0.5%, 1%, 2% v/v), d) 0.1 N HCl (pH 1.2), e) acetate buffer pH 4.5, f) phosphate buffer pH 6.8. The results suggested pH 6.8 phosphate buffer was satisfactory (*42*).
3	The dissolution profile of glipizide was studied by Mandal et al. using dissolution media: a) water, b) 0.1 N HCl (pH 1.2), c) acetate buffer (pH 4.5), d) methanol in water (5%, 10% v/v), e) phosphate buffer (pH 6.8, 7.2), f) SLS in water (0.5%, 0.75%, 1%, 2%, 3%, 4% w/v SLS in water, g) SLS in phosphate buffer (pH 6.8) (0.5%, 0.75%, 1%, 2%, 3%, 4% w/v), h) Tween 80 in water (0.5%, 0.75%, 1%, 2%, 3%, 4% v/v), i) Tween 80 in phosphate buffer (pH 6.8) 0.75% v/v. Satisfactory results were found with 0.75% w/v SLS in phosphate buffer pH 6.8 (*43*).
4	The dissolution profile of gliclazide was studied by Priya et al. using dissolution media: a) 0.1 N HCl pH 1.2, b) acetate buffer pH 4.5, c) distilled water pH 7.0, and d) phosphate buffer pH 7.4. The results suggested pH 7.4 phosphate buffer was satisfactory. Also, more discrimination in the dissolution profile was observed in 0.1 N HCl (*45*).
5	The dissolution profile of satranidazole was studied by Pawar et al. using different dissolution media: a) 0.1 N HCl (pH 1.2), b) 0.01 N HCl (pH 2.1), c) acetate buffer (pH 4.5), d) phosphate buffer (pH 6.8), e) phosphate buffer (pH 7.4), f) distilled water. The results suggested 0.1N HCl was satisfactory (*46*).
6	The dissolution profile of valdecoxib was studied by Subramanian et al with different dissolution profiles: a) water, b) 0.1N HCl, c) SLS (0.6%, 0.8%, 1.0%, 1.5%, 2.0% w/v), d) pH 7.4, e) Tween 80 in water (0.5%, 1% v/v), f) methanol in water (5%, 10% v/v). The results suggested 0.6% w/v SLS in water was satisfactory (*47*).

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