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Prospectus Review of Biorelevant Dissolution Medium

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A B S T R A C T

Dissolution testing is a valuable tool that provides key information about bioavailability or bioequivalency as well as batch to batch consistency of drug. Since the number of poorly soluble drug is increasing, the selection of adequate dissolution test for these becomes more and more important. Biorelevant is a term, used to describe a medium that has same relevance to the in vivo dissolution condition for the compound. The development of biorelevant dissolution medium includes simulation of gastrointestinal condition, hydrodynamic characteristics, and physicochemical parameters of drug, prediction of plasma profile and lastly the development of IVIVC. Simulation of gastrointestinal conditions is essential to adequately predict the in vivo behavior of drug formulations. To reduce the size and number of human studies required to identify a drug product with appropriate performance in both the fed and fasted states, it is advantageous to be able to pre-screen formulations in vitro. The choice of appropriate media for such in vitro tests is crucial to their ability to correctly forecast the food effect in pharmacokinetic studies.

Keywords: Biorelevant media, fasted state, fed state, simulated gastrointestinal condition, hydrodynamic, IVIVC.

A R T I C L E I N F O

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1. Introduction

Dissolution testing was first established more than half a century ago and for many years was mainly performed to address questions of quality control. However, in recent years, there has been a strong push to identify bioavailability (BA) problems of a drug formulation based on the results of appropriately designed dissolution experiments. Thus, the scope of dissolution testing has expanded considerably to include screening formulations and predicting the in vivo performance of drug formulations. To answer questions in terms of the BA of oral drug formulations, it is crucial to run dissolution tests under conditions that closely resemble the key parameters of human gastrointestinal physiology. In addition to the choice of adequate equipment and appropriate instrument parameters, the use of physiologically relevant dissolution media is of great importance. Many of the dissolution media described in international pharmacopoeia are not adequate for this purpose. During the last decade, biorelevant media have been developed to simulate conditions in the stomach and small intestine before and after meals. In the present paper, the composition of these media and examples of their application to predicting food effects from in vitro studies will be described. Particular attention will be given to poorly soluble compounds as it often can be observed that their BA is highly dependent on the dosing conditions.

- Approaches usually used in the design of a dissolution media for poorly water soluble drugs include:
- Bringing about drug solubility by increasing the volume of the aqueous sink or removing the dissolved drug.
- Solubilization of drug by cosolvents up to 40% by addition of anionic or non-anionic surfactants to dissolution medium in post micellar concentration.
- Alteration of pH to enhance the solubility of insoluble drug molecule.

Surfactant solutions are often proposed as dissolution media for drugs characterized by low water solubility. Generally, aqueous solutions of such surfactants may simulate the physiological environment more accurately rather than using adsorbents or hydroalcoholic and aliphatic media. However, Tang and coworkers showed that for a low solubility drug, increase in solubility by addition of surfactants to meet sink conditions (based on bulk drug solubility data) may not always produce biorelevant results.

Aqueous buffers can be used to reflect typical pH conditions in the stomach or small intestine, but do not represent other key aspects of the composition of the GI contents (e.g., Osmolality, ionic strength, viscosity, surface tension) that can be relevant to drug release from the dosage form to be tested. In particular, they cannot be used to simulate the influence of food ingestion on drug release.

Normal adult diet contains about 150gm of lipids, 95% of which are long-chain triglycerides and 4-8gm of phospholipids mainly composed of lecithin. In fed state bioavailability of drug can be increased when there will be change in GIT environment such as

- Prolonged gastric emptying and decrease in intestinal motility increasing the time available for Solubilization.
- Increased dissolution rate and Solubilization of drug substances in mixed micells due to simulation of pancreatic secretion of bile salts and lipase.
- Protection from gastric/luminal degradation, due to protection in lipids.
- Increased lymphatic transport, thus avoiding first pass metabolism.

Specifically in the case of poorly soluble compounds, it is often observed that the in vivo fraction absorbed increases when the drug is given with a meal. Thus, in order to simulate the effects of food on dissolution in the GI tract, it is equally important to develop representative dissolution tests for both the fasted and fed states11. This article mainly focuses on composition of Biorelevant dissolution medium for poorly water soluble drug with the necessary steps that need to be considered for development of Biorelevant Dissolution Medium.

2. Bio-relevant Dissolution Media

Compendial dissolution media often fail to yield IVIVC's for class 2 drugs because relevant physiological parameters are not taken into account. A suitable in vitro model should include a medium that mimics as much as possible the GIT contents after food intake. Biorelevant in vitro dissolution testing is useful for qualitative forecasting of formulation and food effects on the dissolution and availability of orally administered drugs. These biorelevant media can be used to assess the performance of different formulations for poorly water soluble compounds. Biorelevant media have been successfully applied over the past decade to obtain IVIVCs

Bio-relevant dissolution methods, combined with permeability measurements and computational simulations, were used to predict the oral absorption of drug. Due to their complex composition, these media are expensive and need to be prepared on the day of the experiment.

Before the development of biorelevant dissolution medium the following steps should be considered

1) Fluid composition in the GIT
2) Hydrodynamics in the GIT
3) API/formulation properties
4) Prediction of plasma profile
5) Development of IVIVCs

1) Fluid composition of GIT

The features of GI fluid are altered in fasted and fed condition and they affect the dissolution. Several physiochemical and physiological properties of GI fluids such as pH, buffer capacity, bile component concentration and state of aggregation and enzyme activity can greatly influence the drug dissolution process. For simulation of GI fluid the composition of GI fluid plays important role because upon simulating biological environment after a convenient alternative could facilitate routine and experimental in vitro dissolution work. Several physiologically based models for GI transit and absorption have been developed recently.

Stomach:

Motility in the stomach and small bowel is organized into two basic motor patterns fasting and fed. Fasting motor pattern is characterized by cyclic repetition of periods of quiescence altering with periods of contractile activity. Fed motor pattern is characterized by irregular but persistant phasic contractile activity. It develops almost immediately after ingestion of food and replaces the fasting pattern at whatever point in the interdigestive cycle the meal is eaten26. Under fasting condition pH of healthy human stomach is acidic, ranging between 1 and 3. Fluid volume in the stomach would initially be around 300ml in fasted state and 500ml or more in the fed state. The problem while carrying out the dissolution test in FeSSGF is that the medium contains milk, which cannot be filtered using filters with a pore size in the range of 20-500 nm.

Intestine:

Motility of intestine comprises of intraluminal flow, motion of the wall that induce the flow and systems that regulate the wall motions. Fluid volume in small intestine is of 200ml in fasted state and 1L in the fed state. It has been found that the bioavailability of poorly soluble drug can be markedly enhanced by meal intake and its related changes in GI tract physiology such as secretions, digestion processes and motility. The human intestinal fluid contains bile salts, phospholipids, monoglycerides, free fatty acids and cholesterol. The increased solubility in FeSSIF-V2 can be explained by the formation of solubilizing micelles from bile salts, lecithin, GMO and sodium oleate. Vertzoni et al have proposed that the surface tension could be lowered appropriately with combination of pepsin and very low concentration of bile salt. Bile salts and lecithin can increase the wetting process for the lipophilic drugs and solubilize the drug into the micelles formed by bile salts and lecithin.

Colon:

Unlike the motility of the stomach and small intestine which is characterized by the cyclic appearance of the migrating motor complex under fasted conditions, colonic motility is rather limited and in progress due to its inaccessibility and regional differences in structure and function. The composition of biorelevant media which are proposed by dissolution scientist in fasted and fed state.

2) Hydrodynamics:

The dissolution fluid flow characteristics should consist of a predictable pattern that is free of irregularities or variable turbulence. Hydrodynamics is predominant for the overall dissolution rate if the mass transfer process is mainly controlled by convection/diffusion as is usually the case for poorly soluble substances. A thorough knowledge of hydrodynamics is useful in the course of dissolution method development and formulation development for pharmaceutical industries quality needs. Muscular contraction in the wall of the small intestine achieve two objectives one is stirring of the contents to increase exposure to enzymes and to bring the luminaly digested products close to the wall and second propulsion of indigestible material towards the distal gut. Abrahamsson demonstrated that human intestinal hydrodynamics were reflected in vitro using the paddle method at stirring rates of about 140rpm. However, human studies to establish such correlation are expensive and time consuming. He had used, Labradors as the anatomy and physiology of GI tract of Labradors resembles those of the human GI tract. This canine breed can serve as a model to simulate human intestinal hydrodynamics. The pharmacokinetic of felodipine matrix tablet (poorly soluble, neutral and lipophilic) in Labrador was studied. On the other hand micronized and coarse felodipine dissolution was carried out in biorelevant medium at various speeds (slower, medium, fast). In vitro AUC ratio of this particular experimental set up showed best agreement with the pharmacokinetic parameters.

3) API/Formulation characteristics

Knowledge of the physiochemical nature of a compound in biorelevant media is useful for formulation development, which follows API phase selection. Based on this information the pKa profile of compound could be improved by modifying the surfactants or excipients in the formulation. Many new chemical entities possess physiochemical characteristics unfavorable for oral absorption.

BCS:

A biopharmaceutical classification system is a scientific framework for classifying the drug substance based on their aqueous solubility and intestinal permeability. The BCS was first devised in 1995, by Amidon et al and since then it has become a benchmark in the regulation of bioequivalence of oral drug products. According to BCS classification drugs can be categorized as follows

Class 1: High solubility and high permeability
Class 2: Low solubility and high permeability
Class 3: High solubility and low permeability
Class 4: Low solubility and low permeability

For drugs belonging to class 1 and 3, simple aqueous media such as SGF and SIF (with or without enzymes)are suggested. In contrast for class 2 and 4 use of biorelevant media is recommended for dissolution testing. There are various methods of determination of solubility and permeability. Galia et al 1998 showed use of biorelevant media to assess immediate release tablets. The study concludes that biorelevant media are preferable for BCS class 2 drugs, but do not improve the dissolution of BCS class 1 drugs.

Solubility:

Solubility is a crucial parameter for successful drug development as poor solubility compromises the Pharmacokinetic and Pharmacodynamic properties of drug .Solubility can be measured either thermodynamically or kinetically. Thermodynamic solubility can be defined as the concentration in solution of a compound in equilibrium with an excess of solid material at the end of the dissolution process and often considered as true solubility. Kinetic solubility considers the precipitation after dilution in a suitable solution of a compound predissolved in a co-solvent or in aqueous media by pH adjustment for ionizable compound. Solubility of drug in biorelevant dissolution media increased compared to the solubility in aqueous buffer because of enhanced wetting and micellar Solubilization

Particle Size: The dissolution rate is directly proportional to the surface area of the drug. Reducing particle size leads to an increase in the surface area exposed to the dissolution medium, resulting in a greater dissolution rate. Thus, the dissolution rate of poorly soluble drugs can often be enhanced markedly by undergoing size reduction (e.g., through micronization). However, particle size reduction does not always improve the dissolution rate. This is in part attributed to adsorption of air on the surface of hydrophobic drugs, which inhibits the wetting and hence reduces the effective surface area. In addition, fine particles tend to agglomerate in order to minimize the surface energy, which also leads to a decrease in the effective surface area for dissolution.

Drug pKa and gastrointestinal pH:

The amount of drug that exists in unionized form is a function of dissociation constant (pKa) of the drug and pH of the fluid at absorption sites.

4) Prediction of plasma profile

In vitro drug dissolution/release tests are conducted to estimate or predict in vivo drug release characteristics of a product. Direct estimation of in vivo drug dissolution is usually not possible and therefore blood drug concentration-time profiles are used for this purpose. The prediction of plasma profile can be done by using model dependent or model independent approaches. Wagner-Nelson, Loo-Riegelman and numerical deconvolution are such methods. Wagner-Nelson and Loo-Riegelman are both model dependent methods in which former is used for a one-compartment model and the latter for multi-compartment system. The prediction method using convolution analysis consists of following processes.

- The drug amount–time profile in each segment is calculated by the convolution method.
- The absorption rate–time profile in each segment is calculated by using the drug amount–time profile in each segment, calculated in step 1.
- The absorption rate–time profile in the whole GI tract is calculated as the sum of the absorption rate–time profiles of four segments obtained in step 2.
- Prediction of the plasma concentration–time curve of orally administered drug is performed by means of the convolution method.

The total absorption rate time data obtained in step 3 and pharmacokinetic parameters after intravenous administration correspond to the input function and the weight function, respectively. The inverse Laplace transformation of the obtained equation by the convolution program gives the predicted plasma concentration profile after oral administration without the first-pass metabolism in intestinal epithelium and/or liver.

5) Development of IVIVCs: The term correlation is frequently employed within the pharmaceutical and related sciences to describe the relationship that exists between variables. Mathematically, the term correlation means interdependence between quantitative or qualitative data or relationship between measurable variables and ranks. From biopharmaceutical standpoint, correlation could be referred to as the relationship between appropriate in vitro release characteristics and in vivo bioavailability parameters. Two definitions of IVIVC have been proposed by the USP and by the FDA.

United State Pharmacopoeia (USP) definition

The establishment of a rational relationship between a biological property and a parameter derived from a biological property produced by a dosage form, and a physicochemical property or characteristic of the same dosage form.

Food and Drug Administration (FDA) definition

IVIVC is a predictive mathematical model that shows relationship between an in vitro property of a dosage form and a relevant in vivo response. Generally, the in vitro property is the rate or extent of drug dissolution or release while the in vivo response is the plasma drug concentration or amount of drug absorbed.

3. Objectives of IVIVC

IVIVC plays an important role in product development which serves as a surrogate of in vivo and assists in supporting biowaivers, supports and / or validates the use of dissolution methods and specifications and assists in quality control during manufacturing and selecting appropriate formulations.

To develop and validate an IVIVC model, two or three different formulations should be studied in vitro and in vivo (FDA guidance, 1997). Typically, the qualitative composition of drug products is the same, but the release-controlling variable(s), e.g., the amount of excipients, or a property of the drug substance such as particle size, is varied. To develop a discriminative in vitro dissolution method, several method variables together with formulation variables are studied, e.g., different pH values, dissolution apparatuses and agitation speeds.

Mainly two approaches are used for development of correlation

Two step

Step 1: Estimate the in vivo absorption or dissolution time course using an appropriate technique for each formulation and subject

Step 2: establish link model between in vivo and in vitro variables and predict plasma concentration from in vitro using the link model.

One step

Predict plasma concentration from in vitro using a link model whose parameters are fitted in one step, so here it doesn't involve deconvolution.

The deconvolution technique requires the comparison of in vivo dissolution profile obtained from the blood profiles with in vitro dissolution profiles. It is the most commonly cited and used method in the literature. Perhaps that is the reason for the lack of success of developing IVIVC, since this approach is conceptually weak and difficult to use to derive the necessary parameters for their proper evaluation. For example: (1) Extracting in vivo dissolution data from a blood profile often requires elaborate mathematical and computing expertise. (2) It often requires multiple products having potentially different in vivo release characteristics (slow, medium, fast). These products are then used to define experimental conditions (medium, apparatus etc.) for

an appropriate dissolution test to reflect their in vivo behaviour. (3) This technique requires blood data (human study) for the test products to relate it to in vitro results

An IVIVC should be evaluated to demonstrate that predictability of in vivo performance of a drug product from its in vitro dissolution characteristics is maintained over a range of in vitro dissolution release rates and manufacturing changes. Since the objective of developing an IVIVC is to establish a predictive mathematical model describing the relationship between an in vitro property and a relevant in vivo response, the proposed evaluation approaches focus on the estimation of predictive performance or, conversely, prediction error. Methodology for the evaluation of IVIVC predictability is an active area of investigation and a variety of methods are possible and potentially acceptable. A correlation should predict in vivo performance accurately and consistently.

Objectives for Improving the Biorelevance of Dissolution Methods: To save time and costs associated with the need for pharmacokinetic and clinical studies, dissolution test systems capable of predicting BA by means of an in vitro–in vivo correlation would represent a valuable tool. Ideally, the methodology should be as simple as possible, reliable and reproducible, and make it possible to discriminate appropriately between different degrees of product performance (7). However, to achieve adequate predictability of the in vivo release behavior of a dosage form by use of in vitro dissolution data, physicochemical properties of the drug and its formulation as well as the relevant physiological conditions have to be considered in equal measure. Official methods and regulations (8–10) predominantly prescribe the use of USP apparatus 1 (basket) and 2 (paddle) combined with aqueous buffer media. Several advantages are associated with using these apparatus. They are robust, easy to operate, and almost universally available. Moreover, there has been a wealth of experience with these methodologies and they are well accepted both by the user and the regulatory agencies. The paddle apparatus is commonly used for developing biorelevant dissolution test methods for immediate-release (IR) dosage forms. However, the simple aqueous buffers typically used in quality control laboratories are often not suitable for this purpose. Aqueous buffers can be used to reflect typical pH conditions in the stomach or small intestine, but do not represent other key aspects of the composition of the GI contents (e.g., osmolality, ionic strength, viscosity, surface tension) that can be relevant to drug release from the dosage form to be tested. In particular, they cannot be used to simulate the influence of food ingestion on drug release. In the case of poorly soluble compounds, it is often observed that the in vivo fraction absorbed increases when the drug is given with a meal. Thus, in order to simulate the effects of food on dissolution in the GI tract, it is equally important to develop representative dissolution tests for both the fasted and fed states.

4. The Use of Biorelevant Dissolution Media

Passage is most efficient when drug release from the dosage form occurs at proximal SI sites, the more relevant pH values are those in the duodenum and the proximal jejunum. The use of an in vitro medium with an unsuitably high pH in contrast would most probably lead to false positive results, especially for poorly soluble, weakly acidic drugs and entericcoated dosage forms. Thus, with USP 24/NF19, the pH of the compendial SIF was revised to pH 6.8 , which can typically be measured in the mid-jejunum .

Compendial Media Simulating the Fed State Currently, none of the guidance or international pharmacopoeias describes media to simulate food effects. Thus, water SGF and SIF are still the most commonly used dissolution media. However, as mentioned before, they do not take into account additional key parameters of the changing gastrointestinal environment after food intake and are therefore not useful to predict any food effects.

5. Conclusion

The in vivo performance of oral drug formulations based on well-designed dissolution tests. For poorly soluble drugs, prediction of in vivo performance would not have been possible without biorelevant dissolution media. For this reason, the first generation of biorelevant test media is now among the standard tools of many prefomulation laboratories. Recently, the second generation of biorelevant dissolution media has been reported in literature. The development of Biorelevant dissolution medium mainly used as in vitro surrogate for in vivo performance. The compendial dissolution medium is unable to simulate the dissolution as that of in vivo so that the development of Biorelevant dissolution medium is necessary.

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