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Insights on Prospects of Prediction of Drug Bioavailability from in Vitro Models

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Abstract

The various pharmacopoeias contain descriptions of different dissolution media but these are however not predictive of bioavailability. To solve this problem, biorelevant media and different models have been developed as alternatives. The aim of this report was to highlight some of the biorelevant media and appraise their relevance to predict in vivo drug performance. It was apparent that the biorelevant media reflect contents of the gastrointestinal fluids better than the pharmacopoeial media. Also, bio-relevant dissolution methods, combined with permeability measurements and other models along with computational simulations have been used to predict the oral absorption of drug. Prediction of bioavailability from in vitro data involves the establishment of an in vitro-in vivo correlation (IVIVC) between an in vitro measurement such as dissolution rate data and the in vivo performance of the drug formulation such as the bioavailability parameters.

Keywords: Biorelevant Media; *In vitro-in Vivo* Correlation; Bioavailability

Abbreviations: API: Active Pharmaceutical Ingredient; GIT: Gastrointestinal Tract; BCS: Biopharmaceutical Classification System; FeSSIF: Fed State Simulated Intestinal Fluid; FaSSIF: Fasted State Simulated Intestinal Fluid; QC: Quality Control; IVIVC: In Vitro-In Vivo Correlation.

Introduction

Following the oral administration of a solid dosage form, such as an immediate release tablet, the dosage form goes through the process of disintegration followed by dissolution/solubilization of the active pharmaceutical ingredient (API). The drug in solution within the gastrointestinal tract (GIT) is then absorbed into the systemic circulation. The rate and extent at which the drug molecules appear into the systemic circulation in an intact form is termed bioavailability. It is noteworthy that the bioavailability of drugs that fall into the Biopharmaceutical Classification System (BCS) Class II or IV are poorly water-soluble, can be limited by their dissolution rate and/or solubility in the GIT. Thus, studies from our laboratories and by several other authors have shown that the improvement of the solubility of poorly water-soluble drugs can be achieved through various approaches including crystal form modification, micronization, use of surfactants, salt formation, cyclodextrin complexation and complexation

with other agents, solid dispersion, nanoparticles formulations and others [1-3]. Although dissolution testing devices and processes as described in the various pharmacopeia have been in use worldwide for decades to assess the performance of solid oral dosage forms, these devices do not reflect the variable GIT conditions and the dynamic processes associated with the drug passage through the GIT. Rather than going through the long process of determining the bioavailability of a new solid oral dosage formulation in humans, different biorelevant media or predictive dissolution models aimed at being able to predict the in vivo performance of the drug have been developed [4-6]. With availability of a variety of biorelevant dissolution media, an investigator must be able to select the most appropriate media that can predict the performance of the drug in human body. Replacing bioavailability studies carried out in healthy human volunteers with suitable in-vitro substitutes has the potential of saving enormous costs and time involved in the biostudies.

Biorelevant Media and its Selection

Over the years, different biorelevant dissolution media have been developed which differ in compositions, properties, buffer species and capacities, while some contain bile salts, lipids, surfactants and additional compounds which enhance drug solubility. Table 1 thus, fluid composition and hydrodynamics in the GIT are important considerations in the development of biorelevant dissolution media.

Biorelevant FaSSIF (pH = 6.5)	Biorelevant FeSSIF (pH = 5.0)	Biorelevant FaSSGF (pH = 1.6)	Biorelevant FeSSGF (pH = 5.0)
Sodium taurocholate (3 mM)	Sodium taurocholate (15 mM)	Sodium taurocholate(80 µM)	NaCl (237.02 mM)
Lecithin (0.75 mM)	Lecithin (3.75 mM)	Lecithin(20 µM)	Acetic acid (17.12 mM)
NaH2PO4(3.438 g)	CH3COOH (8.65 g)	Pepsin(0.1 mg/ml)	Sodium acetate (29.75mM)
NaCl (6.186 g	NaCl(11.874 g)	NaCl	Milk: buffer (1:1)
NaOH qs ad pH 6.5	NaOH pellets 4.04 g	HCl conc. qs ad pH 1.6	NaOH/HCl qs pH 5
Deionized water	Deionized water qs ad 1 L	Deionized water ad 1 L	
qs ad 1 L			
Osmolality (mOsmol/kg) ~270	Osmolality (mOsmol/kg)670	Osmolality (mOsmol/kg) 120.7 ± 2.5	Osmolality (mOsmol/Kg) 400
Buffer capacity (mEq/pH/L) ~12	Buffer capacity (mEq/pH/L) 72	Surface tension (mN/m) 42.6	Buffer capacity (mml/pH) 25
Surface tension (mN/m) 54	Surface tension (mN/m) 48		

NB:FaSSIF = Fasted State Simulated Intestinal Fluid
FeSSIF = Fed State Simulated Intestinal Fluid
FaSSGF = Fasted State Simulated Gastric Fluid
FeSSGF = Fed State Simulated Gastric Fluid

Table 1: Sample Compositions of Some Biorelevant Dissolution Media [4,5].

Appropriate selection of a biorelevant dissolution media requires

- Knowledge of the physiochemical properties of the API so that the media should contain constituents that promote solubility and dissolution rate of the drug. Generally BCS class II (Low solubility and high permeability) and BCS Class IV (Low solubility and low permeability) drugs require special biorelevant media for improvement of their solubility while the dissolution of BCS class 1 drugs (High solubility and high permeability) do not require special biorelevant media. To aid in the selection of appropriate biorelevant dissolution media and parameters, these BCS II and IV drug classes have been further sub-classified into acidic, basic, and neutral compounds.
- An important consideration of the need to create sink conditions in various dissolution media so as to prevent drug precipitation. Various techniques including altering pH, use of surfactants and co-solvents like alcohols, are

widely used to enhance drug solubility thereby ensuring sink condition.

- That all these media are made to simulate the gastric or intestinal fluid in the fed and fasted states [6]. These are Fasted State Simulated Intestinal Fluid (FaSSIF), Fed State Simulated Intestinal Fluid (FeSSIF), Fasted State Simulated Gastric Fluid (FaSSGF) and Fed State Simulated Gastric Fluid (FeSSGF). The intraluminal compositions in the postprandial stomach and upper small intestine can also be made differentially to simulate "early", "middle," and "late" phases of digestion.

These media can be streamlined by grouping them into categories:

Aqueous Buffers

These media can be phosphate, bicarbonate or other buffers that mainly reflect the gastric and intestinal pH conditions. Their limitations include the fact that they do not simulate other important aspects of the compositions of the GIT contents such as ionic strength, viscosity, osmolality and surface tension which are known to be capable of influencing drug release or dissolution. Also, aqueous buffers cannot be used to simulate GIT contents in the fed state. They are compendial and not biorelevant media.

Media Containing Lipids and Bile Salts

These media are meant to reflect contents of the GI fluid in the fed state. Normal adult diet contains some amount of lipids and phospholipids, while the presence of food in the GIT induces simulation of pancreatic secretion of bile salts and lipase. These media can increase the dissolution rate or solubility of poorly water soluble drugs similar to what is observed in enhanced bioavailability in the fed state. But, the extent of in vivo enhancement may be higher because the presence of food has an additional effect of decrease in intestinal motility with resultant prolongation of gastric emptying time with consequent increase in the time available for drug solubilization.

Media Containing Surfactants and Compounds that Enhance Drug Solubility

Aqueous solutions containing surfactants are used as dissolution media for poorly water-soluble drugs. Although they may simulate the physiological environment better than some other drug solubility-enhancing media, studies have shown that they may not always predict in vivo drug performance [5].

Prediction of Bioavailability

In recent years, several biorelevant models have been developed aimed at predicting the bioavailability of oral drug products. Unlike the standardized dissolution methods used in quality control (QC), these biorelevant tools have often been produced by research groups and commercial companies and they are deployed for few specific formulations. The biggest challenge in predicting the in vivo performance of a drug from in vitro dissolution tests is the simulation of a dynamic in-vivo environment in an in-vitro test. Although these biorelevant media can reflect the biochemical aspect of the GIT conditions, the media alone can hardly simulate the mechanical aspects. Thus, bio-relevant dissolution methods have been combined with different devices to design several predictive models to replicate the physiological environment which more accurately predict in vivo drug availability [7,8].

Prediction of bioavailability from dissolution data involves the establishment of an in vitro-in vivo correlation (IVIVC) between an in vitro measurement such as dissolution rate data and the in vivo performance of the drug formulation such as the bioavailability parameters (eg maximum concentration (C_{max}), time for maximum concentration (T_{max}) and the area under the plasma drug concentration-time curve (AUC)). For example, from the in vitro data, parameters such as time to have 10, 50 or 90 % of drug dissolved, dissolution rate, or dissolution efficiency can be related to the in vivo data such as Cmax, Tmax, AUC, and time to have 10, 50, 90 % of drug absorbed [5].The FDA guidance provides that to develop and validate an IVIVC model, upto three different formulations should be studied both in vitro and in vivo [6]. The drug products should contain the same amount of API but the drug release-rates from the product may vary due to differences in the nature and amount of the excipients. If a good correlation is established between the in vitro data and in vivo measurements, the drug formulation can be exempted from a bioequivalence study [6].

Where the use of biorelevant dissolution media alone cannot produce an adequate in vitro-in vivo correlation, the use of an in vivo predictive dissolution model becomes necessary. These models Table 2 include dissolution-permeation simulating systems, biphasic dissolution system, dynamic gastric model and artificial stomach-duodenum models [8,9]. In the recent years, the prediction of in vivo performance has also been achieved using physiologically based absorption modeling developed with dissolution data input from biorelevant media [8,9]. Thus, mathematical and computational tools have been hugely exploited to correlate dissolution testing with in vivo data.

Model	Brief Description
Dissolution/ Permeability model	Designed to investigate the dissolution and absorption of drugs simultaneously. It consists of two side-by-side chambers separated by a membrane which is either synthetic of a living cell (eg Caco-2 cell monolayer) and this reflects the permeability or absorption across the intestinal wall.
Biphasic dissolution system	Consists of two immiscible liquid phases: an aqueous phase and organic phase. The operational principle is the transfer of dissolved drug from aqueous layer to organic layer so as to mimic the drug absorption from GIT fluid and also maintain the sink condition.
Dynamic gastric model	This is a complex in vitro model designed to replicate the physicochemical and mechanical features of the GIT environment. This is a computer controlled system with ports for addition of gastric acid and enzyme at a controlled rate to simulate GIT fluid and secretion. It also has a region which mimics peristalsis and mixing of stomach contents with gastric fluid.
Artificial Stomach–Duodenum Model	This is a computer-controlled dynamic dissolution apparatus which consists of two compartments each representing the stomach and duodenum, respectively. The system was designed to simulate various physiological processes from the stomach to the duodenum.

Table 2: Some in vivo Predictive Dissolution Models [8,9].

Conclusion

Most of the dissolution media described in international pharmacopoeia are meant for drug quality control purposes and are not adequate for predicting in vivo performance. To achieve this prediction, various Biorelevant dissolution media have been developed which simulate physiological processes of in vivo drug availability. With advancement in technology and application of computational tools, significant progress has been made in developing different in vivo predictive models that improve the possibility of prediction of drug bioavailability from in vitro data with resultant lowering of overall cost of drug product development.

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