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The Utility of the Biopharmaceutics Classification System in Obtaining Waivers for Bioequivalence Studies

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Introduction

The concept of a biopharmaceutical classification system was first proposed by Amidon et. al in 1995 (1). In 2000, the US Food and Drug Administration (FDA) issued a Guidance For Industry describing criteria that would allow the use of a biopharmaceutics classification system to obtain waivers for bioequivalence studies (2).

The biopharmaceutics classification system categorizes drugs into four classes:

Class 1: High Solubility - High Permeability

Class 2: Low Solubility - High Permeability

Class 3: High Solubility - Low Permeability

Class 4: Low Solubility - Low Permeability

The guidance indicates that biowaivers can be justified for high solubility/high permeability drugs in solid oral formulations which exhibit rapid dissolution.

High solubility drugs are defined as those where the highest dose strength is soluble in 250 mL of aqueous media over the pH range of 1-7.5. High permeability drugs must have 90% or more of the administered dose absorbed. Rapidly dissolving dosage forms are those where 85% of the labeled amount of drug dissolves within 30 minutes using USP Apparatus 1 at 100 rpm (or Apparatus 2 at 50 rpm) in a volume of 900 mL or less in each of the following media: (1) 0.1N HCl or Simulated Gastric Fluid USP without enzymes (2) pH 4.5 buffer and (3) pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

Drug permeability can be determined in human studies using mass balance, absolute bioavailability or intestinal perfusion approaches. Alternately, non-human studies can be conducted using in vivo or in situ intestinal perfusion in a suitable animal model and/or in vitro permeability methods using excised intestinal tissues or monolayers of suitable epithelial cells.

To demonstrate the suitability of a permeability method, a rank-order relationship between test permeability values and the extent of drug absorption data in human studies should be established using a sufficient number of model drugs. Metoprolol is listed in the guidance as one of the compounds that can be used as an internal standard in the permeability study. Drugs that are less permeable than metoprolol are considered to have low permeability.

In order to evaluate the utility of the biopharmaceutical classification system for achieving biowaivers, solubility, permeability and dissolution rates were assessed for four developmental drugs where absolute bioavailabilities were known. The permeability was assessed using three different systems: rabbit ileum tissue; rabbit distal colon tissue and Caco-2 cell monolayers.

Materials and Methods

Solubility

Solubilities were determined at pH 1.2, 4.5, 6.5 and 7.5 at 37°C. Buffers were prepared as described in the USP.

Dissolution

Dissolution rates were determined using USP Apparatus 2 at 50 or 75 rpm rotation speed. Buffers used included 0.1N HCl, pH 4.5, pH 6.5, pH 6.8 and pH 7.5. In addition, for two drugs, the surfactants sodium taurocholate and sodium lauryl sulfate (SLS) were added to the media.

Permeability

Rabbit ileal and colon segments and Caco-2 monolayers were prepared as described by Ellens et al (3). The permeation was measured using pH 6.0 and 7.4 on the mucosal side of the membrane and pH 7.4 on the serosal side.

Results and Discussion

A description of the four drugs studied is shown in Table 1. The permeabilities of the drugs are shown in Table 2. The solubilities of the drugs are shown in Table 3 and their dissolution in Tables 4-7.

Table 1 **Drug Characteristics**

Drug	Chemical Class	pKa	Maximum Dose (mg)	Absolute Bioavailability	Pharmaco-Kinetics
A	Weak acid/base	6.1, 6.8	8	99%	Dose linear
B	Weak base	9.7	5	94%	Dose linear
C	Weak acid	4.6	15	95%	Dose linear
D	Weak acid	5.5	50	80%	Dose linear

Table 2 **Permeability**

Drug	pH(mucosal/serosal)	Permeability (cm/sec x10^{-6}) Ileum	Colon	Caco-2
A	7.4/7.4	22	71	120
	6.0/7.4	26	60	180
B	7.4/7.4	1.8	6.5	48
	6.0/7.4	0.6	1.6	13
C	7.4/7.4	13	34	NA
	6.0/7.4	17	49	91
D	7.4/7.4	0.8	27	68
	6.0/7.4	<0.03	49	214
Metoprolol	7.4/7.4	33	50	78

Table 3 **Solubility**

Drug	Dose (mg)	Solubility (mg/250 mL)				Solubility Classification
		pH 1.2	pH 4.5	pH 6.5	pH 7.5	
A	8	2240	4	1	1.5	Low
B	5	$1.1x10^5$	$1.2x10^5$	$1.1x10^5$	$2.4x10^4$	High
C	15	1.5	4.7	335	1090	Low
D	50	0.005	0.04	42	88	Low

Table 4 **Dissolution for Drug A**

Media	Percent Dissolved		
	15 minutes	30 minutes *	45 minutes
0.1N HCl	100	104	105
pH 4.5	98	100	100
pH 6.5	54	73	83
pH 6.5 + sodium taurocholate	73	96	105
pH 7.5	73	93	101

* Dissolution classification is slow dissolution

Table 5 **Dissolution for Drug B**

Media	**Percent Dissolved**		
	15 minutes	30 minutes*	45 minutes
0.1N HCl	75	101	101
pH 4.5	63	101	100
pH 6.5	67	103	102
pH 7.5	57	99	101

* Dissolution classification is rapid dissolution

Table 6 **Dissolution for Drug C**

Media	**Percent Dissolved**		
	15 minutes	**30 minutes ***	**45 minutes**
0.1N HCl	<1	<1	<1
pH 4.5	<10	<10	<10
pH 6.5	93	94	94

* Dissolution classification is slow dissolution

Table 7 **Dissolution for Drug D**

Media	**Percent Dissolved**		
	15 minutes	**30 minutes***	**45 minutes**
0.1N HCl	ND	ND	ND
pH 4.5	ND	ND	ND
pH 6.5	41	49	52
pH 6.8 + 0.05% SLS	94	94	94

* Dissolution classification is slow dissolution

The classifications of the four drugs based on the FDA Guidance are summarized in Table 8.

Table 8 **Biopharmaceutics Classification**

Drug	Permeability	Solubility	Dissolution
A	Low/High	Low	Slow
B	Low	High	Rapid
C	Low	Low	Slow
D	Low	Low	Slow

The results indicate that none of the four drugs would fall into the high solubility/high permeability class even though they are all well absorbed. The permeability assessment using metoprolol as an internal standard seems to understate the fraction of drug that can be absorbed.

The three drugs that have pKa values in the range 1-7.5 are all classed as "low solubility" even though their solubilities exceed the threshold at some pH values. It is likely that most drugs with a pKa in this range would be classified as "low solubility".

The dissolution results generally reflect the solubility data and indicate slow dissolution in pH regions of low solubility. The inclusion of a surfactant in the media for drugs A and D changed the dissolution class from slow to rapid suggesting that the use of physiologically relevant media, as recommended by Dressman et al (4), may lead to a better prediction of biological performance.

Conclusions

The biopharmaceutics classification system has potential for eliminating the need for unnecessary bioequivalence studies. However, the existing criteria for permeability and solubility appear too stringent to be of much practical value. Either the permeability criterion of 90% is too high or the choice of metoprolol as an internal standard is inappropriate. The in vitro models used appear to be too variable for an accurate prediction of permeability. Extension of biowaivers to high solubility compounds with both

high and low permeability would make the guidance more useful. The solubility and dissolution criteria would be more meaningful if they were based on physiologically relevant media. The data from this study suggest that the biowaiver criteria could be extended to drugs that are soluble in part but not all of the pH range 1-7.5.

References

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