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Using the In-vitro Dissolution Absorption System (IDAS) to Evaluate the Effects of Excipients on the Permeation of Putative Biopharmaceutics Classification System Class III Drugs

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PURPOSE

Currently, the ICH M9 guideline allows biowaivers of in vivo bioequivalence (BE) studies with pharmacokinetic endpoints for Biopharmaceutics Classification System (BCS) Class I drugs (highly soluble and highly permeable) and BCS Class III drugs (high solubility, low permeability). However, the current criteria for excipient similarity for Class III drug products are quite stringent (i.e., Q1 the same and Q2 very similar), which may have led to underutilization of the BCS biowaiver pathway for this class of drugs. In addition, there is a need for a robust, predictive in-vitro testing system for evaluating the effects of excipients on drug permeation. A novel in-vitro technology, the in-vitro dissolution absorption system (IDAS), was used to evaluate the effects of common excipients on the permeation of a cassette of five model drugs across Caco-2 cell monolayers. Four of the model drugs (acyclovir, atenolol, cimetidine, and ranitidine) are BCS Class III, and one (minoxidil) is BCS Class I.

METHODS

IDAS is comprised of a dissolution vessel and two permeation chambers, with polarized monolayers of Caco-2 cells mounted in the interface between the dissolution and permeation chambers (see diagram). Caco-2 cells were seeded on collagen-coated, 6-well, polycarbonate membranes in Costar Snapwell® plates (0.4 µm pore size) and maintained in culture until confluent, polarized cell monolayers were established (21-28 days). Snapwell inserts with Caco-2 cell monolayers were mounted vertically in IDAS permeation chambers. The donor medium (for the dissolution chamber) was fasted-state simulated intestinal fluid (FaSSIF), pH 6.5; the receiver buffer (in the permeation chamber) was Hanks' balanced salt solution (HBSS) with added glucose, HEPES buffer, pH 7.4, and 4.5% BSA. Each IDAS dissolution chamber was filled with dosing solution, consisting of a cassette of five pre-dissolved model drugs with or without excipients. Fifteen excipients, representing all major functional classes, were evaluated across a range of pharmaceutically relevant concentrations (Table 1). A negative control (no excipients) and a positive control (sodium lauryl sulfate (SLS) at 0.6%, a higher concentration than the range used for SLS as an excipient) were run in parallel with each set of excipient treatments, which were run with n=3 dissolution chambers/6 permeation chambers in a total of 18 separate experiments. Two permeation chambers were lowered into each dissolution chamber to start the permeation experiment. Multiple receiver samples were collected over the course of the 120-minute permeation experiment. The extended exposure time in vitro is necessary to allow measurable amounts of drug to permeate to the receiver side of the cell monolayers and differs from the transient exposure of a given intestinal enterocyte in vivo. Samples were analyzed by LC-MS/MS and apparent permeability (P_{app}) values were calculated[1].

RESULTS

Only a few of the tested excipients produced obvious, dose-dependent effects on the permeation of any of the five model drugs, including the four BCS Class III drugs. As shown in Fig. 1, sodium lauryl sulfate (SLS), a known absorption enhancer in vitro, was the only excipient that caused dose-dependent increases in the permeation of all model drugs (BCS Class I and III). Seven of the excipients (hydroxypropyl methylcellulose (HPMC) at two viscosities, microcrystalline cellulose, croscarmellose sodium, talc, mannitol, and silicon dioxide) had no effect on the permeation of any of the Class III model drugs (Table 2). A representative graph, showing the lack of effect of croscarmellose sodium, is shown in Fig. 2. Another six excipients (povidone K30, magnesium stearate, lactose, calcium phosphate, pregelatinized starch, and PEG-400) had minor effects, generally not dose-dependent, on only one or two of the model drugs (Table 2). A representative graph, showing the effects of PEG-400, is shown in Fig. 3, although the affected model drugs were not always the same for different excipients. The majority of the tested excipients, within the investigated concentration ranges, did not significantly impact the permeation of the BCS Class III model drugs.

Table 1: Excipients and Concentration Ranges

Excipient	Conc. (mg/mL)	Excipient	Conc. (mg/mL)
Povidone K30	0.05-0.8	Croscarmellose sodium	0.045-0.72
HPMC	0.0125-0.21	Sorbitol	1.25-20
SLS	0.0375-0.3	Dibasic calcium phosphate dihydrate	0.16-2.54
PEG-400	0.26-4.23	Silicon dioxide	0.04-0.64
Lactose monohydrate	0.5-8	Pregelatinized starch	0.113-1.81
Microcrystalline cellulose	0.39-6.21	Talc	0.04-4
Magnesium stearate	0.1-1.6	Mannitol	0.17-2.73

Schematic Diagram of IDAS

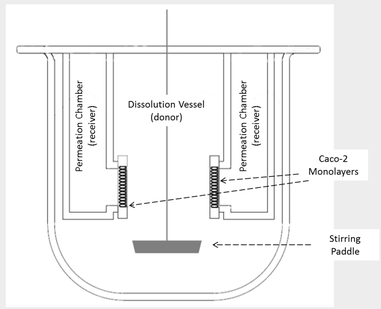
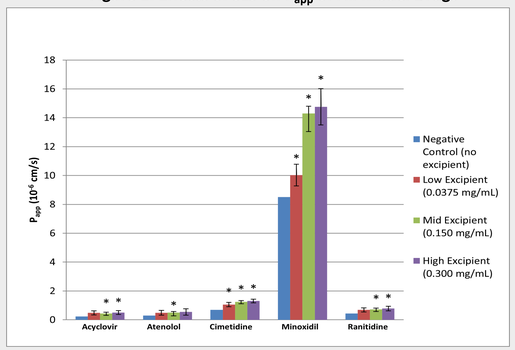


Figure 1: Effects of SLS on P_{app} of All Model Drugs



* Both the mean of the treatment and the mean of the negative control were more than 2 SD from the other
All figures show Mean ± standard deviation (n=6)

Figure 2: Lack of Effect of Croscarmellose Sodium on P_{app} of Model Drugs

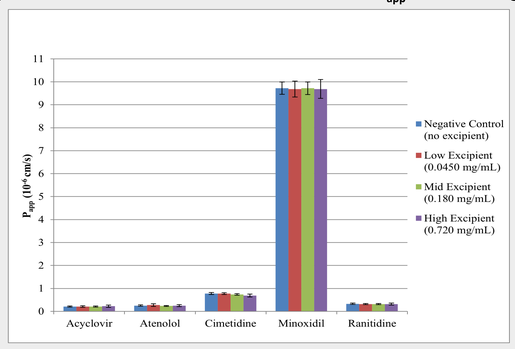
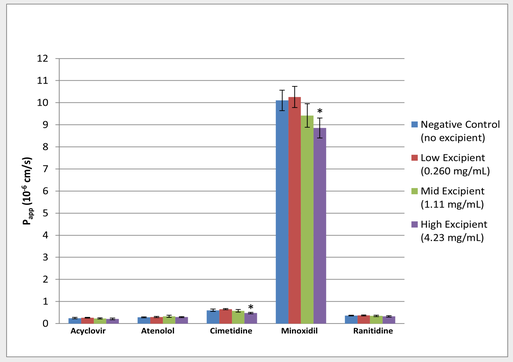


Figure 3: Effect of PEG-400 on P_{app} of Two of the Five Model Drugs



* Both the mean of the treatment and the mean of the negative control were more than 2 SD from the other

Table 2: Summary of Effects of Excipients on Drug Permeation in IDAS

Effects	Excipients	Change in Permeation
None	HPMC, microcrystalline cellulose, croscarmellose sodium, talc, mannitol, silicon dioxide	No effects on permeation of any model drugs
Not consistent effect on all BCS Class III drugs	Povidone K30, magnesium stearate, lactose, calcium phosphate, pregelatinized starch, PEG-400	Effects on only one or two of the model drugs
Multifactorial	Sorbitol	Major impact is on GI motility, which requires a different test system for evaluation
Consistent	SLS	Dose-dependent increase in permeation of all model drugs

CONCLUSIONS

IDAS appears to be a useful platform for evaluating excipient effects. As the in-vitro study design tests the worst-case scenario of a long exposure to a constant concentration of drug substance and excipient, if IDAS demonstrates no effect of a given excipient on the permeation of a BCS Class III drug, the excipient may have no impact on in-vivo permeation either. The results raise the possibility of extending the biowaiver pathway to BCS Class III generic drug products that are Q1 not the same as, and/or Q2 dissimilar to, the reference listed drug.

Next steps:

1. Extend these in-vitro findings to marketed oral drug products and research formulations with clinical data
2. In-vitro data to be used to predict in-vivo performance in combination with a PBPK model.

ACKNOWLEDGEMENT

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DISCLAIMER:

This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.

REFERENCE

1. See poster number W1230-02-08, to be presented on Wednesday at 12:30, for real-world application of the assay platform and methods validated in this poster.