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In Vitro Comparative Dissolution and Permeation Testing Using the In-vitro Dissolution Absorption System (IDAS) for Expanding Biowaivers to Non Q1/Q2 BCS Class III Products

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PURPOSE

Although the ICH M9 guideline allows biowaivers of pharmacokinetic bioequivalence studies for Biopharmaceutics Classification System (BCS) Class III drugs (high solubility, low permeability), the BCS biowaiver pathway for this class of drugs may be underutilized due to the current criteria for excipient similarity for BCS Class III drug products. A novel in-vitro technology was used to evaluate the effects of common excipients on the dissolution and permeation of BCS Class III drug products. The in-vitro dissolution absorption system (IDAS) enables simultaneous measurement of dissolution and permeation of finished drug products (tablets and capsules). The objective of this study was to compare the dissolution and permeation of Class III drug substances in four pairs of commercial reference listed drug (RLD) and generic drug products that were previously demonstrated to be bioequivalent in clinical studies.

METHODS

IDAS consists of a 500 mL dissolution vessel with a polarized monolayer of Caco-2 cells mounted in the interface with each of two permeation chambers (see diagram). A single capsule or tablet was added to the dissolution chamber, and the medium was mixed with a basket at 100 rpm (for acyclovir capsules) or a paddle at 50 rpm (for tablets of all other model drugs). 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 in culture). Snapwell inserts with Caco-2 cell monolayers were mounted vertically in IDAS permeation chambers for the permeation experiments. The dissolution medium 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 D-glucose, HEPES buffer, pH 7.4, and 4.5% BSA. Each IDAS dissolution chamber contained FaSSIF with a drug tablet or capsule containing acyclovir, atenolol, hydroxychloroquine, or rasagiline; an RLD and approved generic product for each drug were tested side-by-side. Two permeation chambers were lowered into each dissolution chamber at T=20 min to start the permeation experiment. Multiple donor (dissolution) samples were collected from 5 to 60 min and immediately filtered through a 0.45 µm pore size syringe filter to remove undissolved drug substance. Multiple receiver (permeation) samples were collected from 20 to 120 min. All samples were analyzed by LC-MS/MS. For drug permeation, % permeation and area under the permeation vs. time curve up to 120 min (AUC) were calculated. Dissolution profiles were evaluated based on a similarity factor, f2 (f2 > 50 indicates that two dissolution profiles are similar).

RESULTS

The dissolution profiles of all 4 pairs of RLD and generic drug products except acyclovir were similar based on f2 analyses (Table 1). The only difference in drug release for acyclovir generic vs. RLD (200 mg dose, at which acyclovir is BCS Class III) was observed at the first time point, 5 minutes (Figure 1), which did not translate into a difference in permeation (Figure 2). In fact, as shown in Figure 3, the calculated AUC of permeation from 20 to 120 minutes was comparable for all four pairs of drug products. The similar dissolution and permeation data obtained from IDAS testing for three of the four pairs of RLD and generic drug products showed a clinical correlation for these generic products that had been previously demonstrated to be bioequivalent to the respective RLD in clinical studies.

Table 1. Dissolution Summary: RLD vs. Generic

Model Drug	f2	Similar?[#]
Acyclovir in FaSSIF	40.9	No
Atenolol in FaSSIF	64.8	Yes
Hydroxychloroquine in FaSSIF	63.6	Yes
Rasagiline in FaSSIF	53.9	Yes

[#] Statistical similarity is concluded when f2 is between 50 and100

Schematic Diagram of IDAS

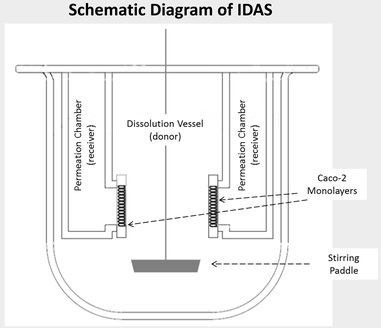
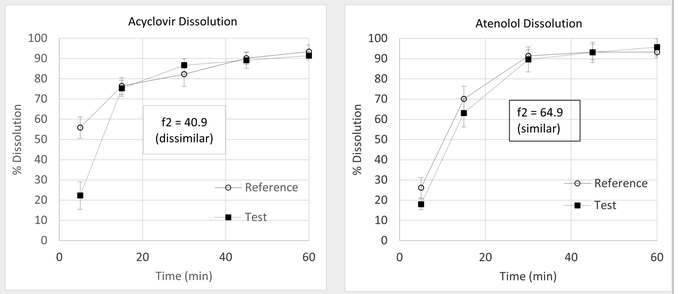
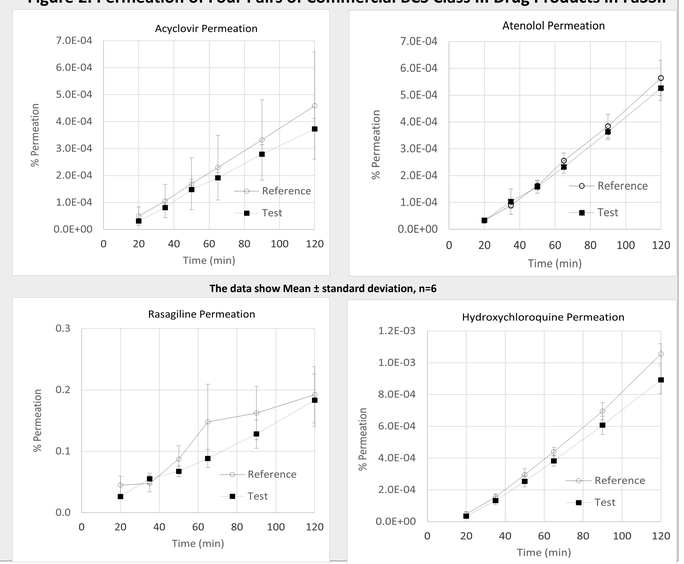


Figure 1. Dissolution of Four Pairs of Commercial BCS Class III Drug Products in FaSSIF



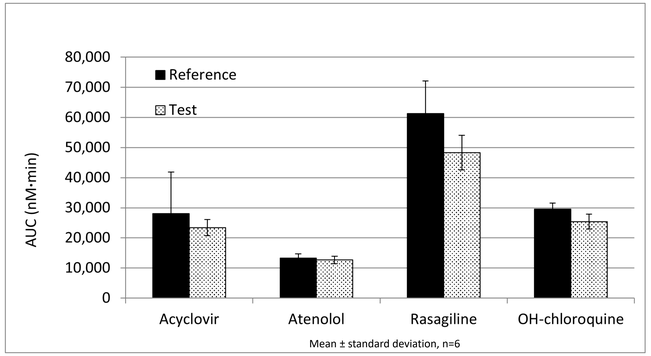
The data show Mean ± standard deviation, n=6

Figure 2. Permeation of Four Pairs of Commercial BCS Class III Drug Products in FaSSIF



The data show Mean ± standard deviation, n=6

Figure 3. Permeation Summary of Commercial Drug Products in FaSSIF: RLD vs. Generic



Mean ± standard deviation, n=6

CONCLUSIONS

IDAS is a useful platform for comparing the performance of finished drug products by making it possible to measure drug dissolution and permeation at the same time, which mimics what happens in vivo, as opposed to the traditional paradigm of measuring the two phenomena separately.

It is likely that if IDAS demonstrates no difference in dissolution and subsequent permeation of a BCS Class III drug even under worst-case conditions with a long exposure time (up to 2 hours) to Caco-2 cell monolayers, the results would be consistent with the in vivo findings.

In this study, we have demonstrated clinical relevance of permeation for four pairs of BCS Class III RLD and approved generic products using IDAS, despite the differences observed in the initial release of acyclovir between generic and RLD.

Additional investigations using non-bioequivalent products are warranted for further demonstrating the clinical relevance and sensitivity to detect potential in-vivo performance difference of this combined dissolution and permeation platform.

ACKNOWLEDGEMENT

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