Evaluation of Viscosity Effects on Drug Dissolution and Permeation across Caco-2 Monolayers Using In Vitro Dissolution and Absorption Systems

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Absorption Systems

Purpose
1) To determine the effect of medium viscosity on drug diffusion and permeation of oral drugs using a novel in vitro dissolution permeation system (IDAS1), and 2) To delineate the role of drug product dissolution and drug (API) diffusion on permeation across a Caco-2 monolayer using a proprietary in vitro dissolution absorption system (IDAS2).

Methods
Illustrated in Figures 1 and 2, IDAS1 and IDAS2 are comprised of dissolution chamber/vessel and permeation chamber, separated by human Caco-2 cell monolayers. Both systems enable simultaneous measurements of drug dissolution and permeation in vitro, while IDAS2 permits evaluation of intact solid dosage forms (tablets or capsules). Dissolution media were formulated to possess low viscosity (LV) or high viscosity (HV). Test drugs were selected from four BCS classes, i.e. propranolol (Class I), carbamazepine (II), atenolol (III) and acetazolamide (IV). Intact drug tablets in LV or HV media were evaluated using IDAS2, dissolution and permeation were simultaneously measured by LC-MS/MS methods. Viscosity effects on permeation of API drugs were evaluated using IDAS1.

Results
There was no apparent effects of medium viscosity on the permeation of all 4 compounds (propranolol, carbamazepine, atenolol and acetazolamide) tested in IDAS1. However, in IDAS2, high viscosity caused an apparent reduction in the dissolution and permeability of propranolol, carbamazepine and acetazolamide, with lesser effect on atenolol dissolution. Dissolution of propranolol tablet reached nominal concentration (1082 μM) as early as 5 minutes in LV medium, while it took 60 minutes to reach the same concentration in HV medium. The high viscosity also decreased propranolol permeation across Caco-2 cell monolayers (e.g.: the receiver concentration was 24.6 ± 2.4 μM in HV and 31.4 ± 3.2 μM in LV at the end of 2 hour assay). More profound effects were found with the Class IV drug acetazolamide and Class II drug carbamazepine. Dissolution of acetazolamide in HV medium at the end of the 2 hour assay was only around 50% of that in LV medium; a similar effect was found with acetazolamide permeation (the receiver concentration was 0.759 ± 0.13 μM with HV versus 1.44 ± 0.21 μM with LV at the end of assay). Carbamazepine dissolution in HV medium was also only half of that in LV buffer, while the effects of HV on carbamazepine permeation were even greater (the receiver concentration was 40.7 ± 9.8 μM with HV versus 132 ± 16 μM with LV).

Conclusion
Viscous media drastically decreased the dissolution and permeation of intact dosage forms of various BCS drug classes (especially on Class II and IV) in IDAS2, while permeation across Caco-2 cells of APIs s were not affected in IDAS1. Results indicated that medium viscosity has predominant effects on the dissolution of poorly water-soluble drugs, presumably by delaying dosage form disintegration/dissolution. Combination of IDAS1 and IDAS2 enable distinguishing between the roles of intrinsic drug properties and product-related factors that may affect drug dissolution and/or permeation, a critically important distinction for drug formulation development.