The Biopharmaceutics of Successful Glipizide Controlled-Release Product: Segmental-Dependent Permeability Throughout the Entire Intestinal Tract
M. Zur, O. Wolk, A. Dahan
Ben Gurion University of the Negev

Purpose
The purpose of this work was to investigate the biopharmaceutics of oral administration of the sulfonylurea antidiabetic drug glipizide, with emphasis on controlled release drug products.

Methods
The BCS solubility class of glipizide was determined, and its physicochemical properties and intestinal permeability were thoroughly investigated, both in-vitro and in-vivo in rats, throughout the entire small and large intestine. Metoprolol was used as the low/high permeability class boundary marker.

Results
Glipizide was found to be a low-solubility compound. Log D of glipizide at the three pH values 6.5, 7.0, and 7.5 (representing the conditions throughout the small intestine), PAMPA studies at these pH conditions, and in-vivo small intestinal permeability data, revealed similar trend; as the intestinal region becomes progressively distal, and the pH gradually increases, the permeability of glipizide decreases. The opposite trend was shown for metoprolol. At the large intestine, similar and high permeability was evident for glipizide and metoprolol. Throughout the entire intestinal tract, at any given intestinal segment/pH, the permeability of glipizide matched/exceeded metoprolol's jejunal permeability, which is the low/high permeability class boundary marker. Theoretical physicochemical analysis based on ionization, pKa and partitioning of these drugs predicted the same trend and confirmed the in-vivo results.

Conclusion
We have been advocating to allow high-permeability classification to drugs with permeability that matches/exceeds the low/high class benchmark anywhere throughout the intestinal tract and not restricted necessarily to the jejunum. In light of this proposal, the fact that at any intestinal segment the permeability of glipizide matched/exceeded metoprolol's jejunal permeability, clarifies the mechanism of its success as controlled-release product; wherever the release of glipizide may occur along the intestinal tract, the drug will have high permeability. Slow release of glipizide may also be advantageous from the solubility point of view, as only small portion of the drug is released at any time point, which may allow its solubilization, as opposed to immediate release of the whole dose. However, this is hard to predict since the aqueous volume available for solubilization is unknown.