W1230-05-32

In Vitro and *In Vivo* Assessment of the Potential of Supersaturation to Enhance the Absorption of Poorly Soluble Basic Drugs

Yuri Bukhtiyarov, Jibin Li, Nicole Spivey, Svitlana Silchenko, Christopher Force, Carlos Hidalgo, Yuehua Huang, Albert J. Owen, Ismael J. Hidalgo.

Absorption Systems LLC

436 Creamery Way, Suite 600, Exton, PA 19341–2556, Phone: 1.610.280.7300, Website: www.absorption.com

aaps PharmSci 360

Advancing Pharmaceutical Sciences, Careers, and Community

PURPOSE

Inducing supersaturation is an attractive approach for increasing the systemic absorption of poorly soluble drugs. Delayed precipitation of weakly basic drugs in supersaturated state following their transition from the acidic gastric environment to the near-neutral proximal small intestinal fluid is emerging as a promising tactic for achieving higher transitional solubility and improved bioavailability of such drugs. The purpose of this study was to assess the effect of pH-shift induced supersaturation on drug dissolution and permeation in vitro, and to evaluate the approach of extending supersaturation to enhance drug oral absorption in vivo.

METHODS

The dissolution and permeation of drugs in tablet form were measured using the in vitro dissolution absorption system 2 (IDAS2). Supersaturation of weakly basic drugs was induced in vitro using a 2-stage procedure mimicking the shift from gastric pH 1.6 to intestinal pH 6.5. As control drugs were also tested under non-inducing conditions (1-stage procedure at constant pH 6.5). Delaying precipitation of drugs in supersaturated state was accomplished with a polymeric precipitation inhibitor, hydroxypropyl methycellulose acetate succinate (HPMC-AS). The weakly basic drug ketoconazole was selected for further in vivo evaluation. Excess amount of ketoconazole was formulated in acidic aqueous medium to produce a high concentration, which was administered orally, in the presence or absence of HPMC-AS, to rats. Plasma samples were collected up to 24 hrs and analyzed by LC-MS/MS.

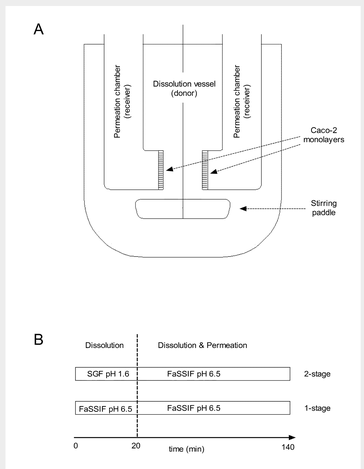

Fig 1. Schematic representation of **A** IDAS2 device and **B** flowchart of 1-stage and 2-stage IDAS2 assays.

RESULTS

Following *in vitro* dissolution under 2-stage conditions, the BCS 2 weakly basic drugs dipyridamole, ketoconazole and itraconazole exhibited supersaturation and enhanced permeation. More specifically, compared to 1-stage conditions, dissolution of dipyridamole, ketoconazole and itraconazole increased by 393%, 161% and 71%, respectively; which led to 543%, 264% and 46% increase in *in vitro* permeation. In contrast, the BCS 2 acidic drug warfarin exhibited 9% decrease in dissolution and a 21% decrease in permeation. The BCS 1 drugs (minoxidil and metoprolol) exhibited no change in dissolution or permeation. In the rat study, HPMC-AS increased ketoconazole systemic exposure (plasma $AUC_{0\text{-}24h}$) by 54%, presumably by enhancing dissolution or prolonging supersaturation.

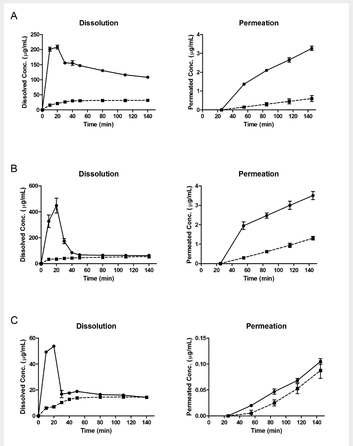

Fig 2. Dissolution and permeation time profiles of **A** dipyridamole, **B** ketoconazole, and **C** itraconazole in the 2-stage (circle) and 1-stage (square) IDAS2 assays.

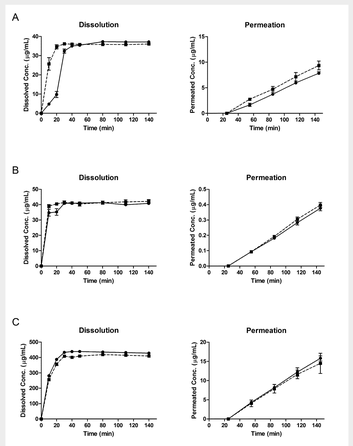

Fig 3. Dissolution and permeation time profiles of **A** warfarin, **B** minoxidil, and **C** metoprolol in the 2-stage (circle) and 1-stage (square) IDAS2 assays.

Table 1. Area under the concentration-time curve of dissolved and permeated drugs in 1-stage and 2-stage assay conditions

Drug	$AUC_{dissolved}$ (μg·min/mL)		%Change	$AUC_{permeated}$ (μg·min/mL)		%Change
	1-stage	2-stage		1-stage	2-stage	
Dipyridamole	3889 ± 56	19164 ± 352***	393	36.2 ± 10.7	232 ± 9***	543
Ketoconazole	6292 ± 148	16443 ± 1376***	161	75.5 ± 7.3	275 ± 19***	264
Itraconazole	1724 ± 34	2941 ± 77***	71	3.9 ± 0.9	5.7 ± 0.3**	46
Warfarin	4726 ± 39	4316 ± 72**	-9	578 ± 51	458 ± 20***	-21
Minoxidil	5550 ± 139	5388 ± 9	-3	23.7 ± 0.6	22.4 ± 0.9	-5
Metoprolol	53541 ± 643	56625 ± 459	6	924 ± 115	979 ± 46	6

** $p < 0.01$, *** $p < 0.001$

RESULTS (Cont.)

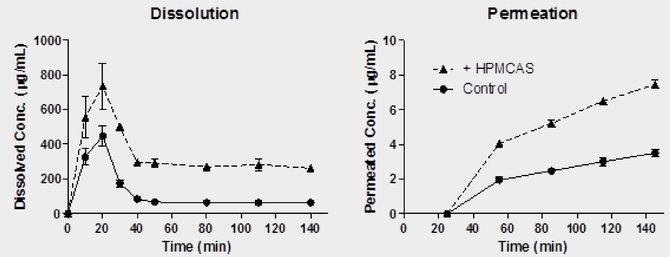

Fig 4. *In vitro* prolongation of ketoconazole supersaturation and permeation in the presence of the polymeric precipitation inhibitor HPMCAS.

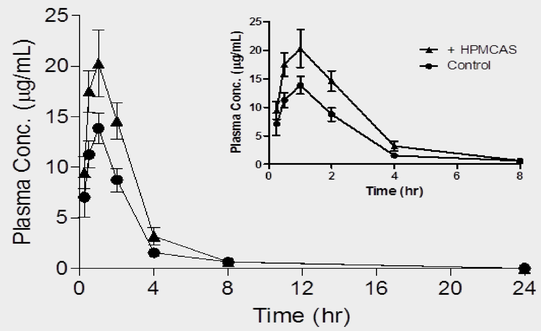

Fig 5. *In vivo* enhancement of oral absorption of ketoconazole in rats in the presence of the polymeric precipitation inhibitor HPMC-AS.

CONCLUSION

This study demonstrates that the in-vitro dissolution – absorption system (IDAS2) can be useful tool to evaluate the potential utility of supersaturation as a means to improve the oral absorption of weakly basic drugs with poor aqueous solubility.

ABSORPTION SYSTEMS®