Assessment of In Vitro Dissolution and Permeation of Nano- and Micro-sized Oral Indomethacin Formulations
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**PURPOSE**

The objective of study was to determine the effects of particle size of oral indomethacin formulation on drug dissolution and permeation using an in-vitro dissolution absorption system 1 (IDAS1).

**METHOD**

Illustrated in Figure 1, IDAS1 is comprised of a dissolution chamber and a permeation chamber, separated by human Caco-2 cell monolayers at interface; the unique feature of IDAS1 permits simultaneous measurement of drug dissolution and permeation across Caco-2 cells (1). The dissolution chamber contains Hank’s balanced salts solution supplemented with 15 mM glucose (HBSSg) at pH 5.75, while permeation chamber contains HBSSg with 4.5% BSA at pH 7.4. Nano- and micro-sized indomethacin formulations were dose at equal API level into the dissolution chamber, indomethacin dissolution and permeation were measured by LC-MS/MS methods. Dissolution constant ($k_d$) and permeation constant ($k_p$) were determined by modeling concentration – time profiles using a Nelder-Mead simplex algorithm.

**RESULTS**

Dissolution and permeation concentration-time profiles are shown in Figure 2. Compared to the micro-sized, the nano-sized indomethacin formulation increased the dissolution rate constant more than 300% (0.330 vs. 1.371 min$^{-1}$), the permeation rate constant by 30% (2.282x10$^{-3}$ vs. 2.967x10$^{-3}$ min$^{-1}$·cm$^{-2}$), and the maximum dissolution by 17% (55 vs. 65 μg/mL). These data are consistent with in vivo results showing that, in humans, orally-administered nano-sized indomethacin increased maximum plasma concentration ($C_{max}$) by 25% without changing total exposure (AUC).

Figure 2. In vitro measurements of indomethacin dissolution and permeation from micro-sized and nano-sized formulations using IDAS.

**CONCLUSION**

IDAS permits to assess the impact of particle size on dissolution and permeation, information that could be used to optimize formulation development and accelerate selection of suitable formulations for improving pharmacokinetics in humans.

**REFERENCE**