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In vivo predictive dissolution: relevant gastrointestinal factors and methodological approaches

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In-vivo predictive dissolution methods (iPD) should incorporate the physiologically relevant characteristics of the "gold standard dissolution beaker" i. e. the human gastrointestinal (GI) tract. To design iPD methodologies, it is necessary to observe directly in-vivo drug dissolution in the intestinal lumen. We have observed in vivo Ibuprofen levels on the GI tract after the administration of an oral immediate release ibuprofen product to human volunteers by using a specialized manometric catheter with 4 sampling ports that allowed the measurement intestinal drug concentrations, pH values as well as intestinal wall motility. Ibuprofen formulation was administered with a solution of Phenol Red (PR) as a non-absorbable marker. The relationship of GI variables (as luminal pH and GI motility) with Ibuprofen absorption rates has been explored. Results show that Ibuprofen luminal concentration is determined principally by the luminal pH and the GI Ibuprofen profiles follow closely the pH versus time fluctuations. In addition, the modelling of PR concentrations has allowed the characterization of the range of gastric emptying profiles and their variability. All the in vivo modelled parameters have been incorporated in the Gastrointestinal simulator (GIS), a physiological based multi-compartment dissolution device. Examples of application of GIS dissolution experiments to discriminate non bioequivalent formulations of etoricoxib, posaconazole, and desketoprofen trometamol, will be presented. These results demonstrate the relevance of the gastrointestinal variables, pH and motility in oral absorption. iPD methodologies incorporating these variables in combination with mass transport computational methods will be an invaluable tool for formulation optimization.

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