Dynamic Change in pH by Low Buffer Capacity of Gastrointestinal Fluids Along The Human Gastrointestinal Tract: Implications For In Vivo Dissolution and Absorption of Ionizable Compounds

B. Hens¹, Y. Tsume¹, M. Bermejo², P. Paixão³, M. J. Koenigsknecht¹, J. R. Baker¹, W. L. Hasler¹, R. Lionberger⁴, J. Fan⁴, J. Dickens¹, K. Shedden¹, B. Wen¹, J. Wysocki¹, R. Loebenberg⁵, A. Lee¹, A. Frances¹, G. Amidon¹, A. Yu¹, G. Benninghoff¹, N. Salehi¹, A. Talattof¹, D. Sun¹, G. L. Amidon¹

¹University of Michigan, ²Universidad Miguel Hernandez, ³Universidade de Lisboa, ⁴U.S. Food and Drug Administration, ⁵University of Alberta

Purpose
The purpose of our study was to assess the crucial underlying gastrointestinal (GI) variables that are responsible for inter- and intrasubject variability in systemic drug exposure (in terms of plasma Cₘₐₓ and Tₘₐₓ) for ibuprofen, a BCS class 2a compound.

Methods
A clinical study was conducted where intraluminal concentrations of ibuprofen were monitored by aspiration of GI fluids along the human GI tract in 37 healthy subjects (20 fasted state subjects and 17 fed state subjects). After oral intake of 800 mg of ibuprofen (immediate release tablet; reference listed drug), GI fluids were aspirated as a function of time up to 7 hours and blood samples were collected simultaneously for 24 hours. The GI fluids were analyzed for solution and total concentrations of ibuprofen and the pH and buffer capacity of the aspirated fluids were measured ex vivo. Additionally, GI motility patterns were monitored by making use of manometry.

Results
Because of its weakly acidic properties (pKa ≈ 4.85), solution concentrations of ibuprofen were determined by the present pH along the GI tract. Our results clearly demonstrated the dynamic change in pH as a function of time and, most significantly, the extremely low buffer capacity along the GI tract. The buffer capacity on average was 2.26 μmol/mL/ΔpH in fasted state (range: 0.26 and 6.32 μmol/mL/ΔpH) and 2.66 μmol/mL/pH in fed state (range: 0.78 and 5.98 μmol/mL/ΔpH) throughout the entire upper GI tract (stomach, duodenum, proximal and mid/distal jejunum). The low buffer capacity along the GI tract is responsible for the slow dissolution of ibuprofen along the intestine. As a result of that, ibuprofen concentrations were still measured after 7 h of along the GI tract.

Conclusion
Our results clearly demonstrated the dynamic change in pH as a function of time and, most significantly, the extremely low buffer capacity along the GI tract. The implication of this very low buffer capacity of the human GI tract is profound for the oral delivery of both acidic and basic active pharmaceutical ingredients (APIs). The extremely low buffer capacity of the upper GI human fluids is one of the likely reasons why the usual quality control (QC) dissolution methods, containing high buffer capacity dissolution media (e.g. FaSSIF, USP SIF), are usually not predictive of in vivo dissolution and systemic plasma levels for immediate release oral dosage forms. An in vivo predictive dissolution method would not only require a bicarbonate buffer, but more significantly, a low buffer capacity of dissolution media to reflect in vivo dissolution conditions.