This is a peer-reviewed, author's accepted manuscript of the following conference abstract:
Halbert, G., Inês Silva, M., Abuhassan, Q., Khadra, I., Pyper, K., Augustijns, P., & Brouwer, J. (2023).
Acidic drugs - intestinal solubility correlation fasted and fed in vitro vs ex vivo.
Abstract from 4th European Conference on Pharmaceutics, Marseille, France.

Acidic Drugs - Intestinal Solubility Correlation Fasted and Fed in vitro vs ex vivo

Gavin Halbert[1], Maria Inês Silva[1], Qamar Abuhassan[1], Ibrahim Khadra[1], Kate Pyper[2], Patrick Augustijns[3], Joachim Brouwer[3]

[1] **Strathclyde Institute of Pharmacy and Biomedical Sciences,** University of Strathclyde, 161 Cathedral Street, Glasgow, G4 0NR, UK, g.w.halbert@strath.ac.uk**;**
[2] **Department of Mathematics and Statistics,** University of Strathclyde, Livingstone Tower, 26 Richmond Street, Glasgow G1 1XH, United Kingdom
[3] **Drug Delivery and Disposition,** KU Leuven, ON2, Herestraat 49 Box 921, 3000 Leuven, Belgium.

INTRODUCTION

A solid oral dosage form is the commonest method for self-administration, but solid drug must dissolve before absorption. Gastrointestinal solubility is a key parameter controlling oral absorption and fundamental to the Biopharmaceutics and Developability Classification Systems [1]. A reliable in vitro measurement of intestinal solubility is therefore critical to assess potential in vivo behaviour during development [2].

This group applied a five dimensional analysis (pH, bile salt, phospholipid, free fatty acid and cholesterol) to fasted and fed human intestinal fluid (HIF) composition to calculate nine simulated intestinal (SIF) fasted (FaSIM) and nine simulated fed (FeSIM) fluid recipes [3]. In each state the media recipes covered 95% of the HIF compositional variability. FaSIM and FeSIM could therefore be considered bioequivalent with the potential to measure HIF solubility in vitro covering 95% of the range. In this abstract we have compared FaSIM and FeSIM equilibrium solubility data for acidic drugs against published HIF values.

MATERIALS AND METHODS

Materials:

Media components were from Merck Chemicals Ltd., UK, except soya bean phosphatidylcholine from Lipoid. Chloroform was from Rathburn Chemical Company, $NaH_2PO_4 \cdot H_2O$ was purchased from Fisher Scientific, acetonitrile (ACN) and methanol (MeOH) were HPLC quality from VWR. Water is ultrapure Milli-Q water. Furosemide, indomethacin, naproxen, and piroxicam were from Merck Chemicals Ltd., ibuprofen was obtained from BSAF and mefenamic acid from Sigma Aldrich.

Method:

Equilibrium Solubility Measurement

The equilibrium solubility measurement method has been published for FeSIM [4], FaSIM [5] and DoE studies [6]. In brief, individual media recipes were prepared [4, 5], an excess of solid drug was weighed into a centrifuge tube, the media adjusted to final volume (4 mL) and pH adjusted using KOH or HCl. The tubes were shaken for 1 hour and the pH readjusted. Tubes were then shaken for 24 hours at 37 ºC and 240 rpm. The presence of solid drug was visually confirmed and 1 mL of each solution centrifuged (10,000 rpm for 15 minutes) and the supernatant was analysed by HPLC for drug content. Three replicate measurements of each media system were performed.

HPLC Analysis

HPLC analysis was performed using a Shimadzu High Performance Liquid Chromatography Prominence-I LC-2030C system [4, 5]. For each drug, calibration curves were constructed, and the line´s equation used to interpolate drug concentration.

Data Analysis

Data analysis and comparison was conducted using Graphpad Prism 9 for MacOSX.

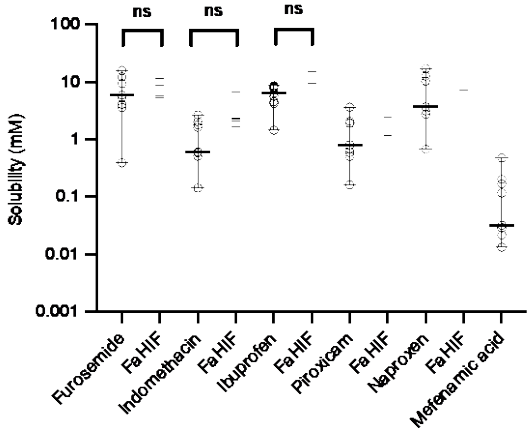

Figure 1. Fasted Equilibrium Solubility FaSIM and FaHIF.

RESULTS

Equilibrium Solubility Comparison:

The FaSIM and FeSIM equilibrium solubility results for the six drugs and literature HIF values [7] are presented in Figures 1 and 2. For situations with three or more HIF values (3 fasted, 2 fed) a Mann-Whitney comparison with the nine simulated media was performed and did not detect a statistically significant difference ($P < 0.05$). The four additional available HIF data points (3 fasted, 1 fed) also lie within the FaSIM and FeSIM solubility range for the drugs concerned. For mefenamic acid no literature HIF values were located. The overall low number of HIF points available 23 (15 fasted, 8 fed) compared to 108 for the simulated media, highlights the difficulty of obtaining HIF and the consequent low measurement coverage available. Irrespective of this limitation all of the HIF values are statistically equivalent to or lie within the FaSIM or FeSIM solubility envelope.

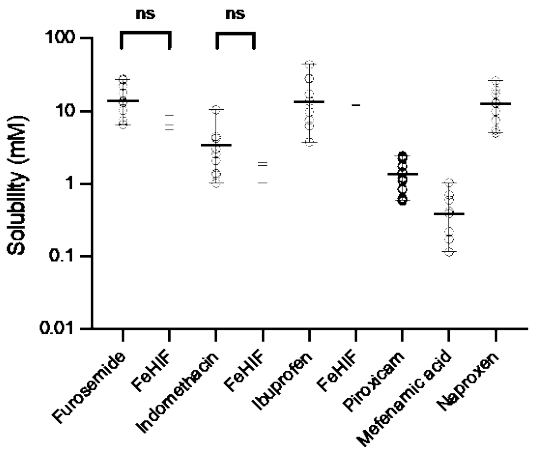

Figure 2. Fed Equilibrium Solubility – FeSIM and FeHIF

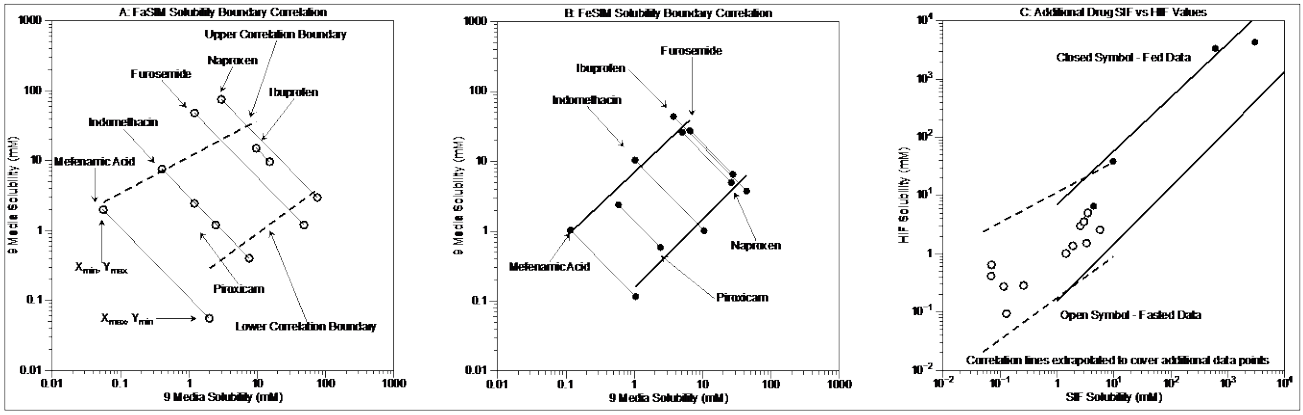

Figure 3: Solubility Boundary Correlation FaSIM, FeSIM and additional literature values

Equilibrium Solubility Correlation:

The minimum and maximum FaSIM and FeSIM solubilities can be used to determine an upper and lower correlation boundary for both states (Figure 3A & B). Using these boundaries SIF and HIF solubility values for 10 additional acidic drugs [7] can be compared. For the 16 additional values only 1 is outside, indicating a 94% correlation between FaSIM, FeSIM and published SIF and HIF values. A close agreement with the original mathematical analysis of HIF composition.

CONCLUSION

Correlation is difficult due to restricted HIF data sets and also limited to the acidic drugs in this study. The available HIF data correlates to FaSIM and FeSIM when analysed as a direct comparison or using a correlation approach to cover additional drugs. This indicates that correlation is possible and further study is warranted, since a SIF = HIF correlation would allow QbD, modelling and prediction of multiple oral biopharmaceutical behaviours from simple in vitro measurements.

REFERENCES

[1] J.M. Butler, J.B. Dressman, J.Pharm.Sci., 99 (2010) 4940-4954.

[2] L. Di, et al., Drug Discov Today, 17 (2012) 486-495.

[3] K. Pyper, et al., Eur.J.Pharm.Biopharm, 153 (2020) 226-240.

[4] M. Ines Silva, et al., Eur.J.Pharm.Biopharm, 177 (2022) 126-134.

[5] Q. Abuhassan, et al., Eur J Pharm Biopharm, 168 (2021) 90-96.

[6] I. Khadra, et al., Eur.J.Pharm.Sci., 67 (2015) 65-75.

[7] P. Augustijns, et al, Eur.J.Pharm.Sci, 57 (2014) 322-332.