Solubility Measurement of Poorly Soluble Drugs in Fasted State Simulated Intestinal Fluid Reflective of In-Vivo Gastrointestinal Variability

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Abstract

Adequate drug solubility in the gastrointestinal tract is essential for systemic therapy of orally administered medications. To carry out research on the solubility of poorly soluble drugs *in vitro*, simulated intestinal fluid (SIF) is used in place of human intestinal fluid (HIF). However, typical SIF reflects average compositions of HIF rather than the full range of compositions previously reported. This study examines a new suite of SIF media, based on variability observed in HIF, to explore the range of solubility of four poorly soluble drugs (naproxen, indomethacin, phenytoin and tadalafil) in the fasted state.

Introduction

Based on a recent study by the Augustijns Group that characterised fasted human intestinal fluid (HIF) aspirates, five simulated intestinal fluid (SIF) recipes were designed which encompassed the full range of HIF samples[1]. This work was based on previous multidimensional analysis of these fluids[2]. These were the minimum, Q1, median, Q3 and maximum [pH x Total Amphiphile Concentration (TAC)] points.

Aim

The equilibrium solubility of four poorly soluble drugs (naproxen, indomethacin, phenytoin and tadalafil) was determined in each of the five SIF media to better understand the potential variability in gastrointestinal solubility.

Methods

To create each of the five media, a concentrated stock solution was made and an aliquot was transferred to a centrifuge tube with the other components of the sample. Figure 1 shows an overview of this process and the composition of each media point can be found in Table 1.

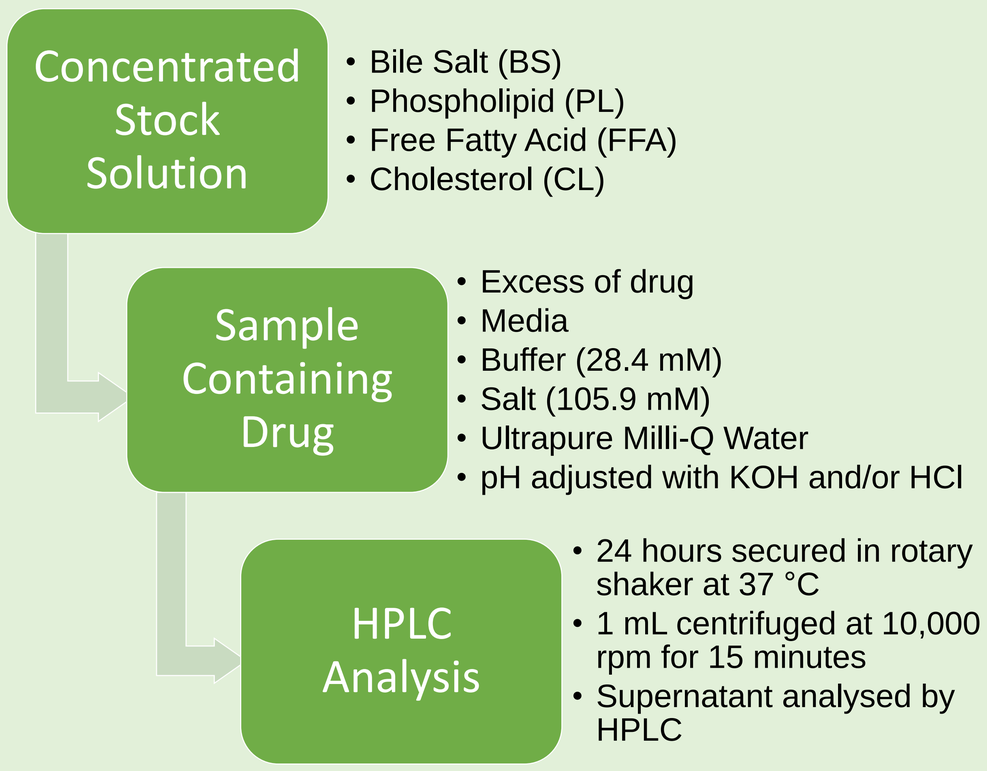

Figure 1: *Overview of the experimental process*.

Table 1: *Composition of each media point (mM).*

Media	BS	PL	FFA	CL	[pH x TAC]
Minimum	1.60	0.17	0.07	0.04	5.54
Q1	2.34	0.16	1.18	0.06	27.04
Median	3.10	0.39	1.69	0.08	41.63
Q3	5.43	0.57	2.59	0.12	67.58
Maximum	36.18	5.78	15.03	0.20	458.05

BS = Bile Salt, PL= Phospholipid, FFA=Free Fatty Acid, CL= Cholesterol, TAC= Total Amphiphile Concentration, Q1 = Lower Quartile, Q3= Upper Quartile

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Results and Discussion

The individual equilibrium solubility measurements for each of the four drugs under fasted conditions in each of the five representative fluids was measured and the average solubility values obtained can be found in Table 2 and displayed graphically in Figure 2.

Table 2: *Average drug solubility values (mM) obtained for each media point.*

Drug	Minimum	Q1	Median	Q3	Maximum
Naproxen	0.129	5.663	6.328	5.935	6.605
Indomethacin	0.040	1.069	1.241	1.250	1.306
Phenytoin	0.121	0.135	0.204	0.187	0.382
Tadalafil	0.002	0.004	0.021	0.036	0.214

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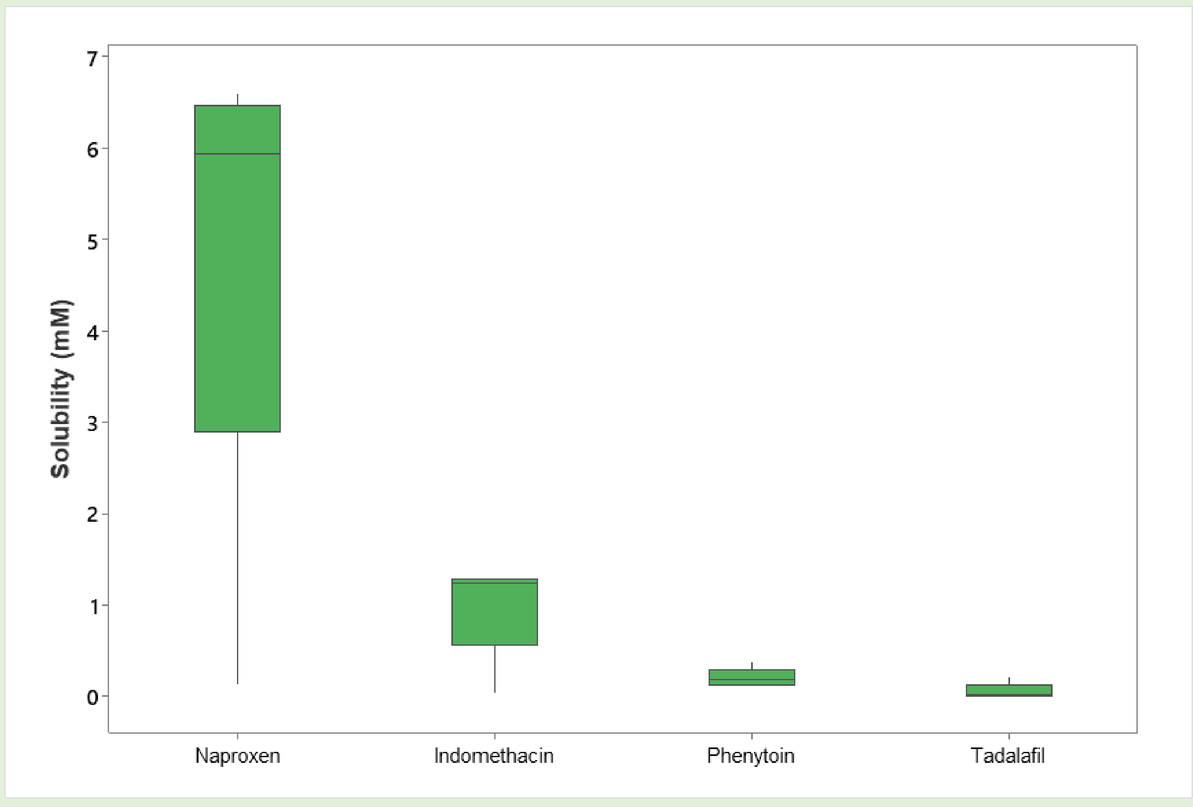

Figure 2: *Plot of average drug solubility data of the four drugs analysed.*

Conclusions

This study used a range of simulated intestinal fluid media that represents the diversity of a real population to show that poorly soluble drugs are sensitive to changes in the composition of simulated intestinal fluid. The predicted intestinal solubility of a drug is a key parameter used in the prediction of drug exposure and the formulation strategy for that drug. The use of a range of simulated intestinal fluids is likely to better reflect both paediatric and adult solubility values which can de-risk the development of oral medications.

References

1. Riethorst, D.; Mols, R.; Duchateau, G.; Tack, J.; Brouwers, J.; Augustijns, P., Characterization of Human Duodenal Fluids in Fasted and Fed State Conditions. *Journal of Pharmaceutical Sciences* **2016,** *105* (2), 673-681.
2. Pyper, K.; Brouwers, J.; Augustijns, P.; Khadra, I.; Dunn, C.; Wilson, C. G.; Halbert, G. W., Multidimensional analysis of human intestinal fluid composition. *European Journal of Pharmaceutics and Biopharmaceutics* **2020,** *153*, 226-240.