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Solubility measurement of poorly soluble drugs in fasted state simulated intestinal fluid reflective of in-vivo gastrointestinal variability

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SUMMARY

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

The most common and preferred route of treatment is oral administration of solid drugs due to the straightforward and non-invasive nature of administration which aids in patient compliance. The drug material must pass through the gastrointestinal tract which is an intricate system where many factors control oral bioavailability including the solubility and dissolution of the drug material in the gastrointestinal environment. Gastrointestinal fluid is a complex media with many components that is variable dependant on location in the tract and prandial state (Pyper et al., 2020).

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 (Riethorst, Mols, Duchateau, Tack, Brouwers & Augustijns, 2016). This work was based on previous multidimensional analysis of these fluids (Pyper et al., 2020). These were the minimum, Q1, median, Q3 and maximum [pH x Total Amphiphile Concentration (TAC)] points. 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.

MATERIALS AND METHODS

Sodium taurocholate, sodium oleate, cholesterol, ammonium formate, sodium chloride, hydrochloric acid, potassium hydroxide, naproxen, tadalafil, indomethacin and phenytoin were purchased from Merck Chemicals Ltd. Phosphatidylcholine from soybean lecithin was purchased from Lipoid company. Chloroform was purchased from Rathburn Chemical Company. Formic acid and sodium phosphate monobasic monohydrate from Fisher Scientific. Acetonitrile was HPLC grade from VWR.

Solubility studies were performed in triplicate. To create each of the five media, a concentrated stock solution 15 times the mass was prepared of bile salt (BS, sodium taurocholate), phospholipid (PL, soybean

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lecithin) and fatty acid (FFA, sodium oleate) in chloroform. For each of the media recipes, a solution 1500 times greater the mass of cholesterol (CL) in chloroform was prepared and an aliquot was transferred to the stock solution. The chloroform was then evaporated off with a nitrogen gas to produce a dry film which was resuspended in 3 mL of water and stirred to create a homogenous mixture. This was transferred to a 5 mL volumetric flask and made to volume with water. Aqueous buffer (sodium phosphate monobasic monohydrate, 28.4 mM) and salt (sodium chloride, 105.9 mM) were also prepared. Table 1 shows the composition of each media point.

An excess of drug and aliquots of media, buffer, salt, and water were added to a centrifuge tube then the pH was adjusted to target using KOH and/or HCl. The tubes were placed on an orbital shaker for 1 hour after which the pH was adjusted accordingly. Tubes were secured in a rotary shaker at 37 °C for 24 hours. Post-incubation, 1 mL from each tube was centrifuged for 15 minutes then the supernatant was analysed by HPLC.

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

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 1.

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

Drug	Mini-mum	Q1	Median	Q3	Maxi-mum
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

BS = Bile salt, PL= Phospholipid, FFA=Free fatty acid
CL= Cholesterol, TAC= Total amphiphile concentration,
Q1 = Lower quartile, Q3= Upper quartile

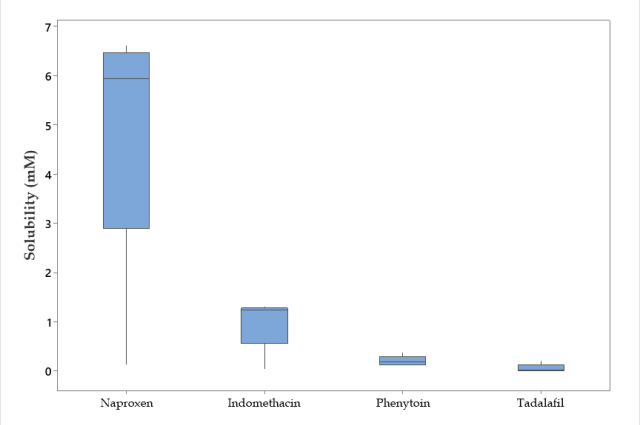

Figure 1. *Plot of average drug solubility data of the four drugs analysed.*

CONCLUSIONS

This study shows 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.

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