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Study of in-vitro poorly soluble drug solubility into fasted state simulated intestinal fluid reflective of in vivo gastrointestinal variability

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SUMMARY

Solubility and dynamic light scattering (DLS) studies of three poorly soluble drugs (naproxen, indomethacin and phenytoin) in simulated intestinal fluid (SIF) were carried out in order to calculate the number of drug molecules per micelle based on the assumption of monodisperse spherical micelles. As the total amphiphile concentration increased in the SIF the solubility of the drug also increased. The size of the micelles formed decreased with increasing amphiphile concentration in combination with drug and the number of drug molecules per micelle decreased. Further work is planned to provide more information of the particle size and geometry of the drug loaded micelles.

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INTRODUCTION

Orally administered drug bioavailability is affected by many factors including gastrointestinal motility and gastric emptying as well as the composition of the intestinal fluid. Based on a clinical study that characterised fasted human adult intestinal fluid (HIF) aspirates, five simulated intestinal fluid (SIF) recipes were created which encompassed the full range of samples in this study (Riethorst et al., 2016). These were the minimum, Q1, median, Q3 and maximum [pH x total amphiphile concentration (TAC)] points.

The enhanced solubility observed in simulated intestinal fluid is known to be related to the colloidal structures within this media, yet predictions of the extent of solubility enhancement are not accurate. The aim of this work was to use experimental data to predict the number of drug molecules per mixed micelle. This aids in the study of variability between three different poorly soluble drugs (naproxen, indomethacin and phenytoin) and how the structures vary between drug and between the different composition of media. This will enable a better understanding of the complex formation and behaviour of drug loaded mixed micelles in our suite of SIF.

MATERIALS AND METHODS

Sodium taurocholate (bile salt, BS), sodium oleate (free fatty acid, FFA) cholesterol (CL), ammonium formate, sodium chloride, hydrochloric acid, potassium hydroxide, naproxen, indomethacin and phenytoin were purchased from Merck Chemicals Ltd. Soybean lecithin (PL) was purchased from Lipoid company. Chloroform was purchased from Rathburn Chemical Company. Formic acid, sodium phosphate monobasic monohydrate, 1 mL syringes and 0.45 µm syringe filters from Fisher Scientific. Acetonitrile was HPLC grade from VWR. Capillary cells were bought from Malvern Panalytical.

Solubility studies were conducted in triplicate. Table 1 shows the composition of each media point. An excess

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of drug was added to each media and pH was adjusted to target (± 0.02) using KOH and/or HCl. The tubes were placed in an orbital shaker for 1 hour after which the pH was measured and adjusted if required. They were then secured in a rotary shaker at 37 °C for 24 hours. Post-incubation the sample was filtered and the particle size measured by dynamic light scattering (DLS).

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

Media	BS	PL	FFA	CL	pH	[pH x TAC]
Minimum	1.60	0.17	0.07	0.04	2.41	4.54
Q1	2.34	0.16	1.18	0.06	7.23	27.04
Median	3.10	0.39	1.69	0.08	7.92	41.63
Q3	5.43	0.57	2.59	0.12	7.75	67.58
Maximum	36.18	5.78	15.03	0.20	8.01	458.05

RESULTS AND DISCUSSION

From the hydrodynamic diameter data measured by DLS and solubility data previously measured in another study (McKinnon et al., 2022), it is possible to estimate the mean number of drug molecules per colloid (mixed micelle) in SIF using the method described from Jamil *et al.* (Jamil and Polli, 2022). These values can be found in Table 2.

The assumptions made to perform this calculation include (i) each mixed micelle is made of bound drug and surfactant, (ii) all components contribute proportionally to each micelle and (iii) a spherical particle geometry and density of 1 g/mL.

Table 2. *Number of drug molecules per micelle ($x10^3$).*

Drug	Minimum	Q1	Median	Q3	Maximum
Naproxen	1,190	1,850	45.4	207	0.187
Indomethacin	471	5.40	8.68	0.148	0.014
Phenytoin	733	1.54	1.39	0.078	0.007

As the drug solubility generally tends to increase with increasing media point (from minimum to Q1 to median to Q3 to maximum), the DLS size of the drug loaded micelle diameter tends to decrease and with this, the number of drug molecules per micelle also decreases. Contrary to this, the size of the blank media tends to increase with increasing media point suggesting that the drug is solubilised in the media, creating drug loaded mixed micelles which are smaller in size than those without drug. Interactions between the sodium taurocholate and lecithin result in the mixed micelles formation with the addition of the sodium oleate increases the variability of size and charge. The formation of the mixed micelle structures occurs when the intramicellar concentration of the phospholipid reaches the critical micellar concentration (Xie et al., 2014). With increasing bile salt and phospholipid quantities used with increasing media point, there is increasing variability observed in the blank media measurements.

CONCLUSIONS

This study shows that poorly soluble drugs are sensitive to changes in the composition of simulated intestinal fluid. From the work carried out using DLS, it is known that it is incorrect to assume the spherical geometry and monomodal distribution of the particles. Further work using small/wide angle x-ray scattering and nanoparticle tracking analysis is planned to provide more information on particle size and shape of the drug loaded mixed micelles.

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