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Evaluation of fasted and fed simulated intestinal fluid in predicting poorly soluble drugs using 9-point approach

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SUMMARY

The extent of absorption of orally administered drugs depends on their solubility in human intestinal fluid (HIF). Simulated intestinal fluid is used as biorelevant media to determine drug solubility *in vitro*. In this study, 9-point bioequivalent simulated intestinal media was used to assess the solubility of three poorly soluble drugs (prednisolone, valsartan, and itraconazole) in the fasted and fed state using the shake flask method. The composition of simulated intestinal fluid was found to influence the equilibrium solubility results. This influence varies depending on the compound's ionisation nature (neutral, acid, base).

INTRODUCTION

Orally administered drugs are the most common form of medication mainly because of patient convenience. Drug substances should be in solution in the intestinal fluid to cross the luminal wall and provide the body with the intended therapeutic effect. This depends on drug solubility which is influenced by drug characteristics such as lipophilicity and ability to be ionised, in addition to the gastrointestinal fluid components such as bile salts, phospholipids, fatty acid and the pH of this fluid. The complexity of intestinal fluid is greater in the fed state as a result of lipolytic components from food digestion (Riethorst et al.,2016).

A recent study (Pyper et al.,2020) applied a multidimensional approach to analyse human intestinal fluid (HIF) characteristic data taken from 20 volunteers in both fasted and fed states based on work published by Riethorst et al., 2016. This approach provided nine simulated media recipes for each state that covered over ninety per cent of HIF variability.

In this study, the equilibrium solubility of three poorly soluble drugs (prednisolone, valsartan and itraconazole) was determined in each of the 9 simulated media in both fasted and fed states to better understand the potential variability in gastrointestinal solubility.

MATERIALS AND METHODS

Bile salts (Sodium taurocholate TC), cholesterol, free fatty acid (sodium oleate), sodium chloride, hydrochloric acid, potassium hydroxide, valsartan, and itraconazole were purchased from Merk Chemical Ltd. Prednisolone was purchased from Sigma. Phosphatidylcholine (Lecithin) was purchased from Lipoid company, Germany. Chloroform was from Rathburn Chemical company. Sodium phosphate monobasic monohydrate from Fisher Scientific. Acetonitrile was HPLC gradient, and the water was ultrapure Milli-Q.

The bioequivalent media was prepared stated in Table 1 for fasted state and Table 2 for the fed state.

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Taurocholate, lecithin, and sodium oleate were added together and then dissolved using chloroform. cholesterol was prepared separately as a stock chloroform solution with 100 times higher concentration then 100 µl from it was added to other components. The mixture was dehydrated with nitrogen gas and rehydrated with water. A tube with an excess drug in combination with 0.267 µl phosphate buffer and 0.267 µl NaCl solution for each media was prepared. The pH of the resulting material was adjusted using HCl and KOH to the values stated in Table 1 or Table 2. After 24 hours at 37 °C a sample was taken from each media for HPLC analysis for equilibrium solubility quantification. The samples were centrifuged at 10,000 rpm for 15 min prior to analysis.

***Table 1**: Compositions of each bioequivalence media in the fasted state (mM).*

Media	TC	LC	FFA	CL	pH
1	1.06	0.16	1.04	0.01	6.64
2	11.45	2.48	2.88	0.38	7.12
3	3.4	0.33	2.88	0.09	8.04
4	3.56	1.18	1.04	0.06	5.72
5	3.62	1.25	3.43	0.03	7.14
6	3.35	0.31	0.87	0.17	6.62
7	5.33	0.4	2.96	0.07	6.42
8	2.27	0.96	1.01	0.08	7.34
9	3.46	0.52	1.64	0.032	6.54

TC= Taurocholate, LC= Lecithin, FFA= Free Fatty Acid, CL=Cholesterol.

***Table 2**: Compositions of each bioequivalence media in the fed state (mM).*

Media	TC	LC	FFA	CL	pH
1	4.94	2.02	10.5	0.98	5.97
2	19.04	7.94	47.51	0.34	6.59
3	5.65	2.43	18.06	0.1	6.13
4	16.65	6.59	27.63	3.45	6.42
5	15.66	5.1	10.92	0.5	6.24
6	6	3.14	45.68	0.65	6.32
7	7.34	6.17	21.82	0.57	5.97
8	12.81	2.6	22.85	0.58	6.59
9	10.94	4.02	23.38	0.32	6.26

TC= Taurocholate, LC= Lecithin, FFA= Free Fatty Acid, CL=Cholesterol.

RESULTS AND DISCUSSION

The equilibrium solubility for valsartan, prednisolone and itraconazole was measured for each media for both fasted and fed states (figure 1).

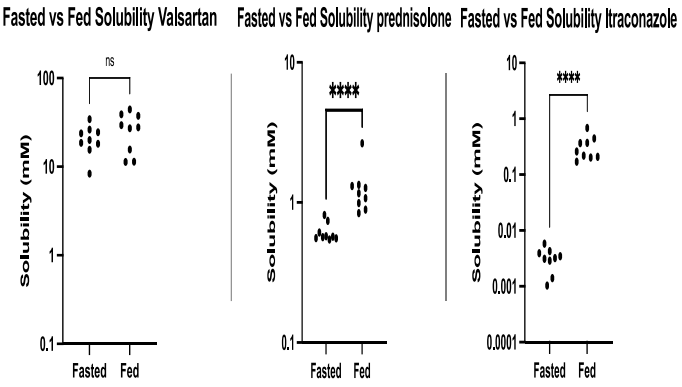

***Figure 1**: The equilibrium solubility for valsartan, prednisolone and itraconazole in fasted and fed 9 points bioequivalence media.*

From the results, the difference in valsartan solubility between the fasted and the fed states was not significant. Prednisolone solubility was higher in the fed state as a result of higher concentrations of solubility surfactant (TC, LC, FFA). The solubility of Itraconazole was very low in the fasted state, while its solubility was significantly increased in the fed state.

CONCLUSIONS

This study highlighted the influence of media components on drug solubility. Moreover, the ionisation state of the drug plays an important role in drug solubility. In addition, the fed state with higher concentrations of solubilising surfactant doesn't always increase drug solubility.

REFERENCES

Pyper, K., Brouwers, J., Augustijns, P., Khadra, I., Dunn, C., Wilson, C. G., & Halbert, G. W. (2020). Multidimensional analysis of human intestinal fluid composition. Eur J Pharm Biopharm, 153, 226-240.

Riethorst, D., Mols, R., Duchateau, G., Tack, J., Brouwers, J., & Augustijns, P. (2016). Characterization of Human Duodenal Fluids in Fasted and Fed State Conditions. J Pharm Sci, 105(2), 673-681.