Statistical investigation of the composition of simulated Intestinal Fluid on the equilibrium solubility of oral drugs and in silico prediction using gCOAS

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INTRODUCTION

Purpose

A statistical design of experiment (DoE) was employed to investigate the influence of simulated intestinal fluids (SIF) composition on the equilibrium solubility of BCS class II compounds. The aim is to enhance understanding of how orally-administered drugs are taken up from the intestinal tract and combine this knowledge with in silico models to predict in the early stages of development the absorption and therefore the performance of these compounds.

Method

Using Minitab® 17.2.1 a DoE was constructed in the fasted and in the fed state with 7 and 8 factors respectively and 2 levels (upper and lower limits of factors). Thirteen BCS class II and IV compounds were tested (acids, bases and neutrals). The PSE software gCOAS 1.3.0 (solubility analysis module) was then used to predict the solubility of nine compounds (two acids, four bases and two neutrals) and compared to the experimental data previously generated.

RESULTS

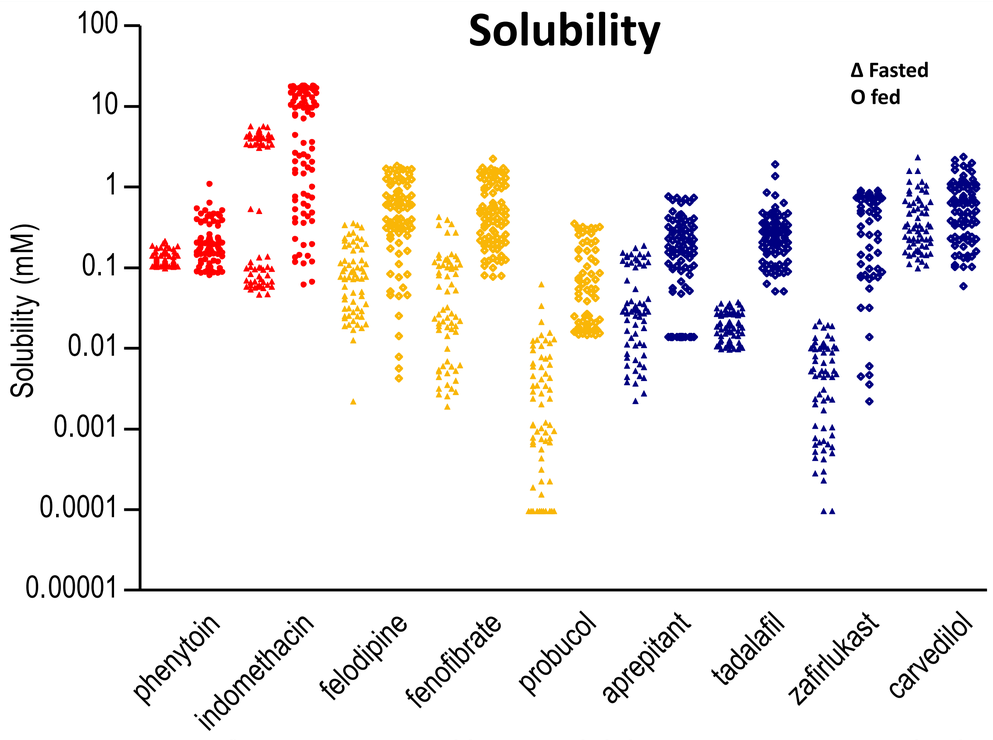


Figure 1 : Design of experiment equilibrium solubility measurements Red coloured data points for acidic drugs, yellow for neutral drugs and blue basic drugs

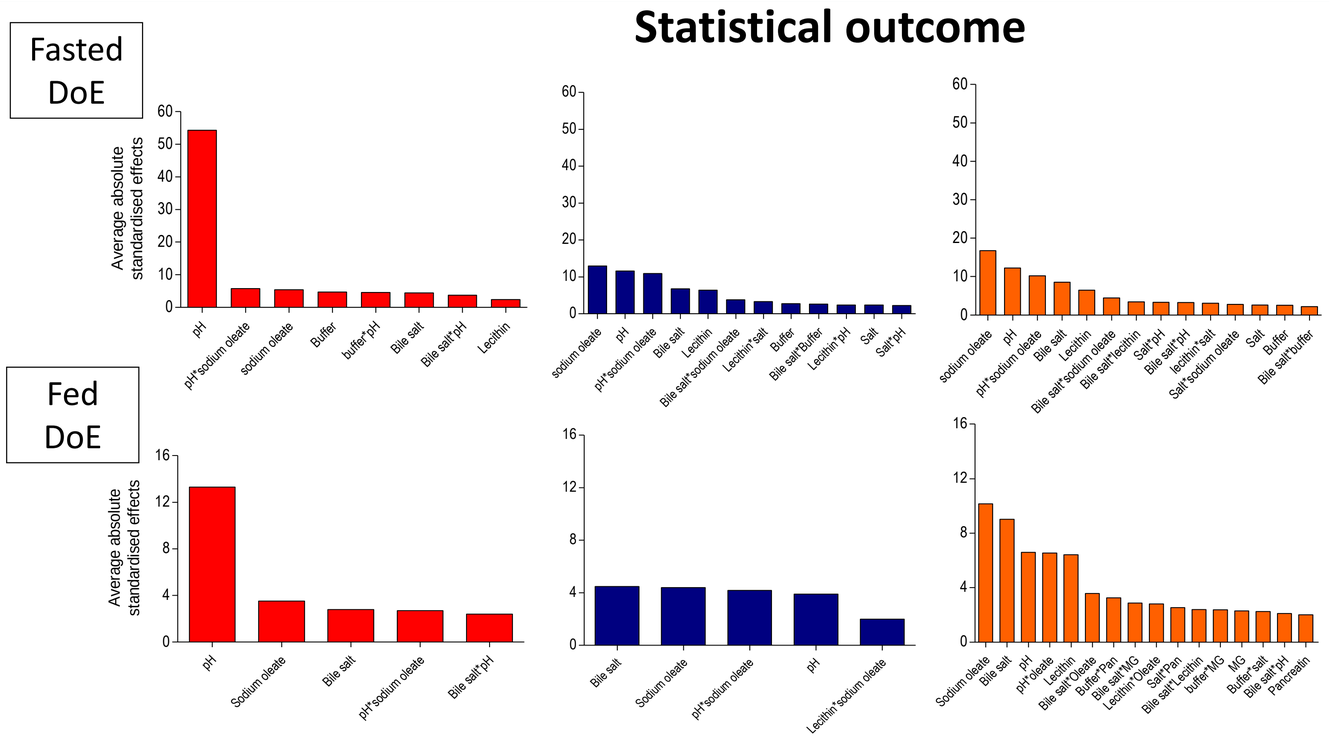
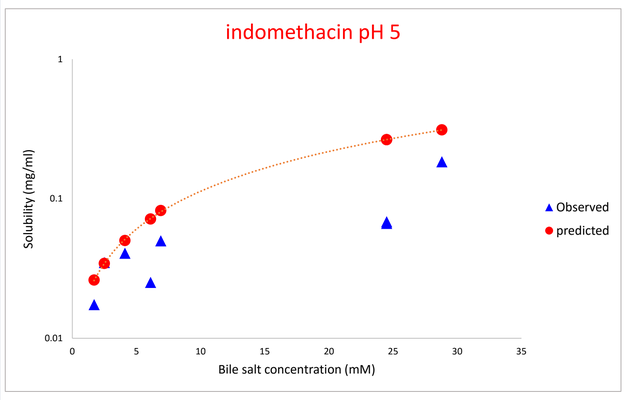
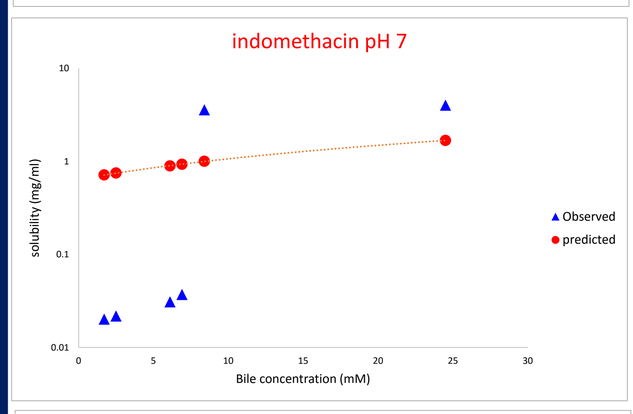


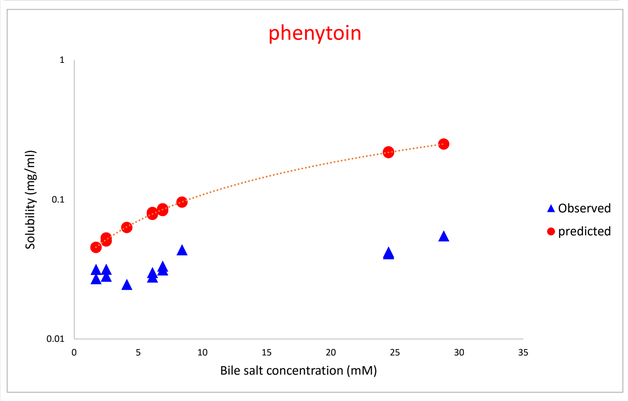
Figure 2 : Average significant absolute standardised effects Single terms and interactions Red coloured for acidic drugs, yellow for neutral drugs and blue basic drugs

SIMULATIONS

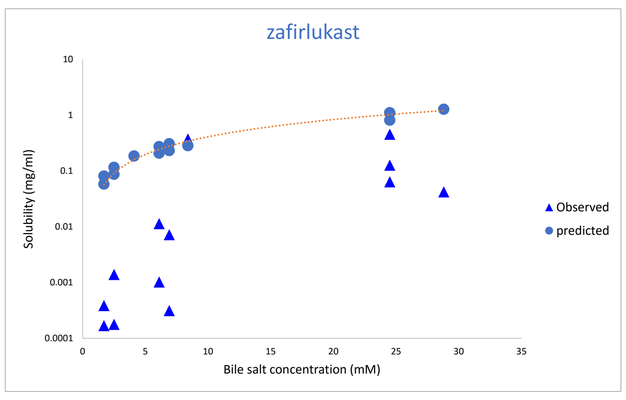
Acids

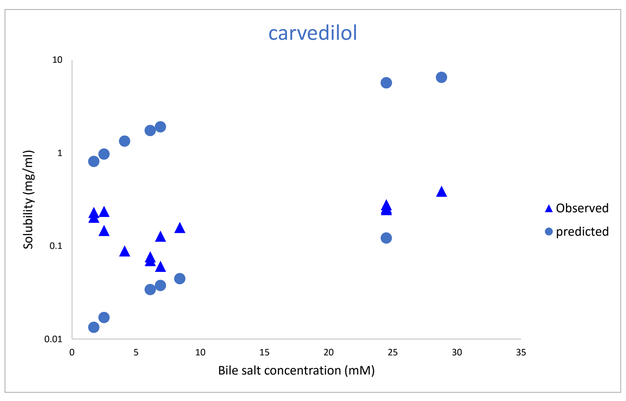


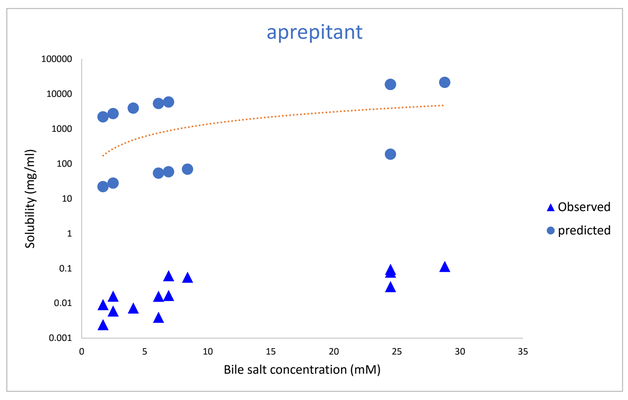


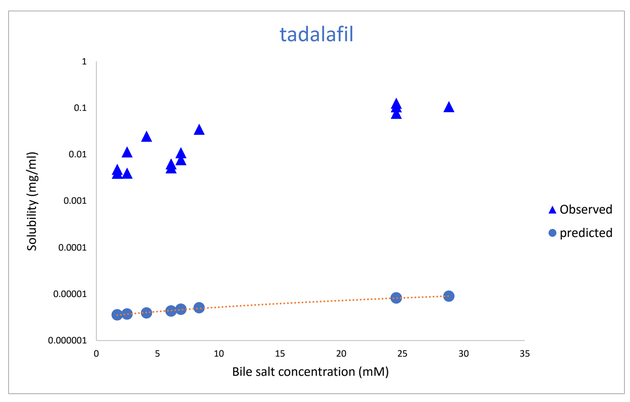


Bases

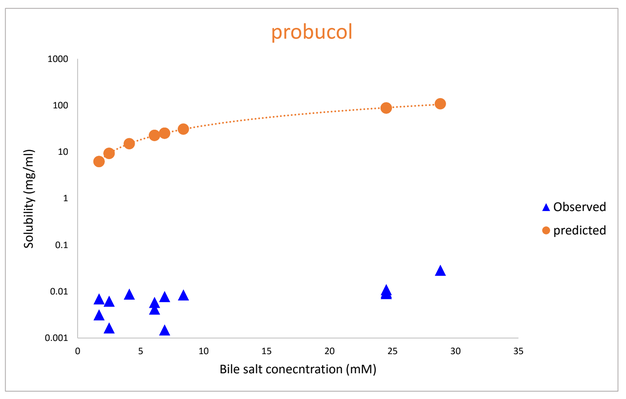


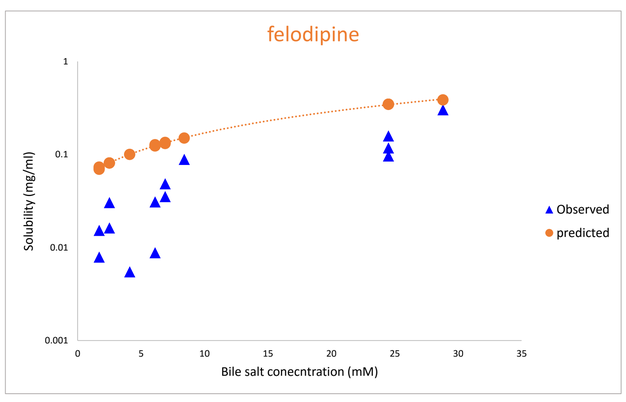


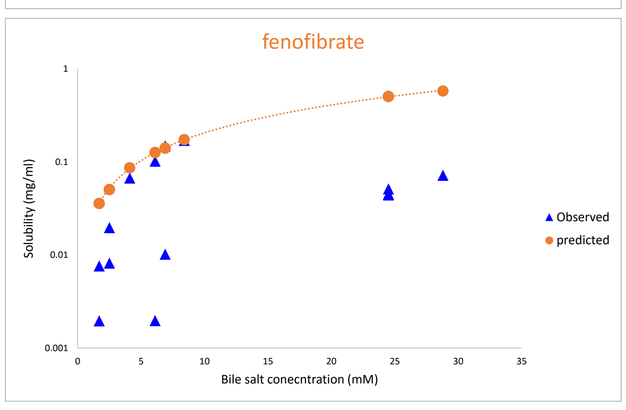




Neutrals







Input parameters	
Drug properties	Conditions for solubility
- Solid type (acid, base, neutral) - Molecular weight - pKa, Log P - Intrinsic solubility	- Bile concentrations custom defined - Default Bile salt partitioning (Sugano et al. 2009) - Observed data for comparison

CONCLUSION

References

[1] Khadra, I., Zhou, Z., Dunn, C., Wilson, C. G., & Halbert, G. (2015). Statistical investigation of simulated intestinal fluid composition on the equilibrium solubility of biopharmaceutics classification system class II drugs. *European Journal of Pharmaceutical Sciences : Official Journal of the European Federation for Pharmaceutical Sciences*, *67*, 65–75.

[2] Zhou, Z., Dunn, C., Khadra, I., Wilson, C. G., & Halbert, G. (2017). Statistical investigation of simulated fed intestinal media composition on the equilibrium solubility of oral drugs. *European Journal of Pharmaceutical Sciences : Official Journal of the European Federation for Pharmaceutical Sciences, 99: 95-104.*

Conclusion

The fasted state experiment proved the feasibility of this systematic approach, simulated the inherent solubility variabilities and determined the key factors controlling solubility. The fed state experiment confirmed the suitability of this approach expanded to the food effect with logically higher solubility values. Similar results were observed for acidic and basic drugs while neutral drugs behaved differently. The simulations were challenging for the correlation of observed vs predicted solubility values. The results showed a compound specificity however a refinement of the simulations would certainly improve the correlations.

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