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Supporting food effect prediction using biorelevant small scale *in vitro* solubility approaches

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SUMMARY

This study applies biorelevant fasted and fed simulated intestinal media (SIM) to compare the solubility of griseofulvin, ibuprofen, and dipyridamole to investigate the prediction of food effects. These media cover over 90% of the human intestinal fluid variation in each state providing a comprehensive solubility range in vitro. The results highlight that ibuprofen is unaffected by food but dipyridamole and griseofulvin show an increased solubility in the fed state, suggesting positive food effects in line with in vivo literature data. Drugs with solubility limited absorbable dose (SLAD) lower or close to the oral dose are more likely to present a food effect, thus SLAD analysis could aid the prediction of food effects. This approach may be applied in early drug development as a preliminary prediction tool.

INTRODUCTION

Food can significantly influence the absorption of oral drugs. Gastrointestinal conditions in the fed state, along with food-drug interactions, can lead to changes in bioavailability, potentially affecting the therapeutic effect of drugs (Silva, Khadra et al. 2023). In early drug development, studying food effects is challenging due to limited amounts of compounds. These studies usually involve human volunteers and demand significant resources and time. While prediction models based on permeability and solubility may not fully support regulatory decisions, they offer valuable insights to the drug development process. Comparing solubility measurements in fasted and fed states can help identify variations that may indicate potential food effects. In this study, nine simulated intestinal media recipes representative of the fasted and fed state were used to measure the equilibrium solubility of griseofulvin, ibuprofen and dipyridamole. These media recipes resulted from a multi-dimensional analysis of human intestinal fluid (Pyper, Brouwers et al. 2020) and cover over 90% of the variation of human samples in each state and thus may be considered biorelevant. This approach results in a solubility range that provides more information on solubility behaviour than single measurement approaches. The data collected for fasted and fed state were compared and studied for possible food effect prediction.

MATERIALS AND METHODS

Stock solutions for each media were prepared with sodium taurocholate, lecithin, sodium oleate, cholesterol, salt and buffer as described in (Silva, Khadra et al. 2023). An excess of drug was added to each media sample and the pH was adjusted accordingly. The samples were left in the agitator for 1 hour followed by pH re-adjustment and 24 hours incubation at 37°C. The equilibrium solubility of each drug was determined using HPLC. Full protocol for media sample preparation available at (Silva, Khadra et al. 2023).

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RESULTS AND DISCUSSION

The solubility ranges for ibuprofen, dipyridamole and griseofulvin for both fasted and fed state are displayed in Fig.1. Ibuprofen´s solubility shows no significant differences between the fasted and fed states. Food does not influence its solubility profile which is in line with the literature data where no food effect was found (Moore, Derry et al. 2015). Dipyridamole and griseofulvin display a significant increase in solubility in the fed state. When solubility changes significantly between fasted and fed states, it may be an indication of the occurrence of food effects. It is extensively reported that griseofulvin exhibits in vivo a positive food effect (Kawai, Fujii et al. 2011), which is in line with the *in vitro* result.

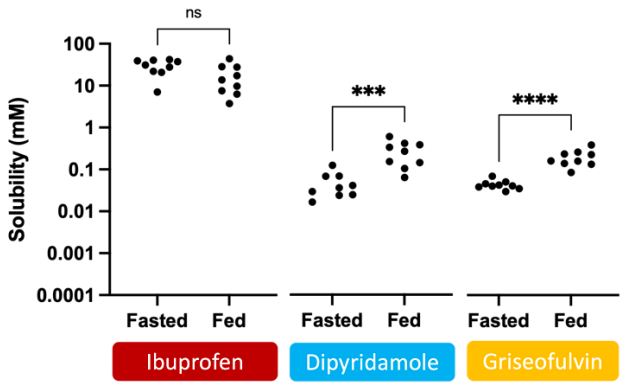

Fig. 1. *Drugs solubility ranges in the fasted and fed state.*

In Fig. 2, solubility limited absorbable dose values (SLAD) for all bioequivalent solubility points were linked to the intestinal media population cumulative percentage incidence (Silva, Khadra et al. 2023). Ibuprofen´s SLAD distribution is comparable in the fasted and fed states with all SLAD values above the drug´s oral dose. No solubility limitations were found, and no food effects are expected. Griseofulvin and Dipyridamole display solubility limitations in the fasted state with SLAD distributions lower than their oral dose. Fed conditions improved their solubility profile with griseofulvin´s solubility limitations resolved in 40% of fed HIF compositions and dipyridamole´s limitations resolved in 60% of fed HIF compositions. Both drugs are known to present positive food effects which could be an indication that when the SLAD values for fasted and fed state are lower than the oral dosage and when SLAD values cross the oral dosage line, oral drug absorption may be impacted by food.

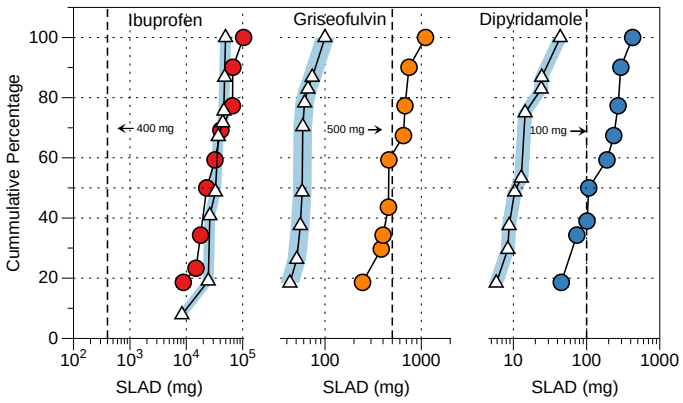

Fig. 2. *Cumulative Percentage of SLAD. ○ fed; Δ fasted; blue: 80%-125% food effect limits; Vertical lines: oral dose.*

CONCLUSIONS

Variations in drug solubility in the fasted and fed state might be indicative of a food effect. Drugs with SLAD values higher than their oral dose do not seem to be affected by food. Drugs with SLAD values lower or close to the oral dose are more likely to present a food effect. Solubility and SLAD analysis could aid the prediction of food effects in drug development without the need for human studies. A larger data set of drugs could be studied to confirm this trend.

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REFERENCES

Kawai, Y., Y. Fujii, F. Tabata, J. Ito, Y. Metsugi, A. Kameda, K. Akimoto and M. Takahashi (2011). "Profiling and trend analysis of food effects on oral drug absorption considering micelle interaction and solubilization by bile micelles." Drug Metab Pharmacokinet 26(2): 180-191.

Moore, R. A., S. Derry, P. J. Wiffen and S. Straube (2015). "Effects of food on pharmacokinetics of immediate release oral formulations of aspirin, dipyrone, paracetamol and NSAIDs - a systematic review." Br J Clin Pharmacol 80(3): 381-388.

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

Silva, M. I., I. Khadra, K. Pyper and G. W. Halbert (2023). "Fed intestinal solubility limits and distributions applied to the Developability classification system." European Journal of Pharmaceutics and Biopharmaceutics 186: 74-84.