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Mechanistic Modelling using Classical Nucleation Theory of Fluid Dynamics and Dissolution Media Effects on Supersaturation and Precipitation Behaviour based upon a USP 2 Style Transfer Apparatus: A Simulation Exercise

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PURPOSE

In vitro transfer experiments based upon USP 2 paddle-style dissolution apparatus (Fig. 1) have been developed to attempt to mimic *in vivo* drug dissolution, supersaturation and precipitation behaviour which, for example, can be of particular relevance to poorly soluble weak bases. Such experiments can be used as a qualitative assessment of risk for precipitation of API *in vivo*. Alternatively mechanistic modelling of *in vitro* supersaturation/precipitation processes can be undertaken with a view to assessing and/or parameterizing such models before applying them to *in vivo* predictions. The latter can be undertaken within the framework of population-based Physiologically-based Pharmacokinetic (PBPK) models wherein *in vivo* conditions and their inter-individual variability can be accounted for (*i.e.*, gastric emptying, pH, fluid volumes *etc.*). There are few reports of the application of mechanistic models to exploit *in vitro* transfer experiments in this way.

This exploratory simulation study was performed to investigate the impact of fluid volume dynamics, fluid viscosity, fluid velocity and fluid transit rate as well as dissolution medium (FaSSIF, FeSSIF) on drug supersaturation and precipitation behaviour based upon using a mechanistic model of a USP 2-style transfer system (Fig. 1).

METHODS

A mechanistic model of data obtained from transfer experiments (Fig. 1) was developed based on classical nucleation theory (CNT) (Sugano 2009; Lindfors 2008) and an enhanced fluid dynamics dissolution model (Liu *et al*., 2016); the latter has been incorporated into the SIVA - Simcyp In Vitro (data) Analysis – software*. Various experimental conditions were assessed based upon the model drug dipyridamole (Kostewicz *et al.*, 2004). The apparent viscosity ranged from 1 cP to 10,000 cP, 1st order transit rate (between compartments) from 0.0001 to 0.1 s^{-1} and rotation rate from 10 to 250 RPM; simulations were undertaken in both FaSSIF (pH 6.5) and FeSSIF (pH 5.0) media. Dipyridamole solubility is 8 mg/mL in SGF , 0.0115 mg/mL in FaSSIF and predicted solubility using SIVA is 1.08 mg/ml; a dose of 100 mg was used.

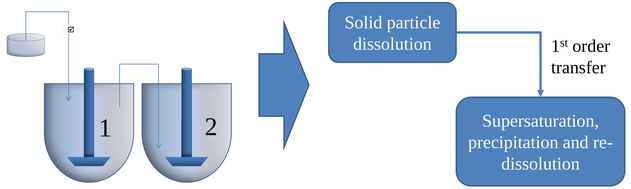

Figure 1: Schematic of a USP 2-style transfer model.

RESULTS & DISCUSSION

The simulations suggest that fluid transit rate, apparent viscosity and dissolution medium can have a significant effect on the supersaturation and precipitation (S&P) behaviour of dipyridamole (Fig. 2), while paddle rotation speed has nearly no effect (Fig. 2D); the latter has been verified experimentally by Kostewicz et al. which suggests that GI contractions are expected to have little effect on S&P behaviour *in vivo*. Another important issue *in vivo* is food effects upon S&P. The presence of food in the GI tract results in changes to gastric emptying rate, fluid volumes, bile salt micelle concentration, pH, viscosity and other factors. Simulations were performed in fasted and fed state simulated media (FaSSIF pH 6.5, FeSSIF pH 5.0). The increased solubility of dipyridamole in FeSSIF means that no supersaturation and therefore precipitation is predicted in the fed state. In order explore the potential impact of viscosity (raised significantly during the fed state) it was necessary for the chosen model drug dipyridamole to use FaSSIF medium; the simulations indicated a significant impact of viscosity on S&P behaviour – at higher viscosity nucleation rate is reduced (Fig. 2C). Precipitation inhibitors (*e.g.*, HPMC or PVP) also raise local viscosity, which is expected to reduce the nucleation rate and prolong the supersaturated state. Transit rate is also an important factor for explaining supersaturation and precipitation process. The lowest transit rate 0.0001 s^{-1} achieves the lowest maximum concentration and the lowest precipitation rate; if the transit rate is 0.1 s^{-1}, there is extremely rapid precipitation from a highly supersaturated solution.

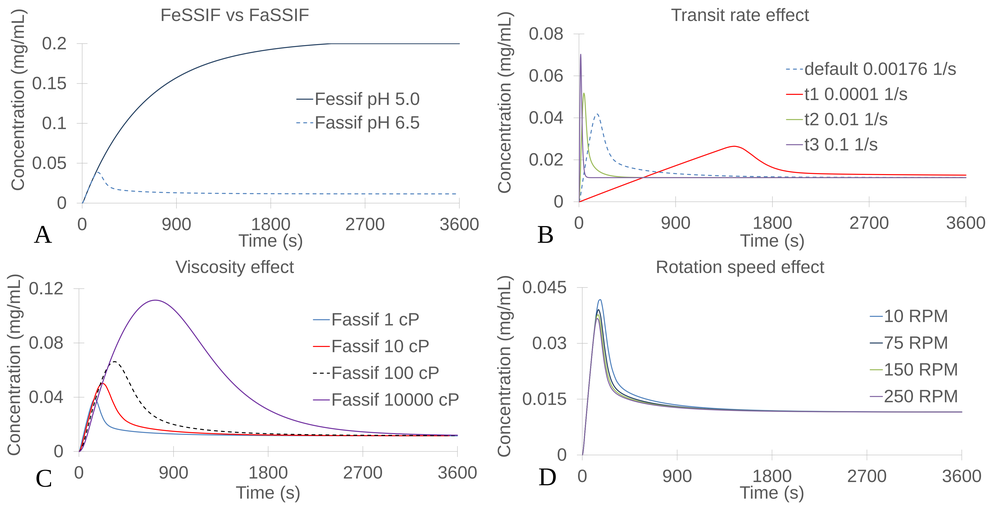

Figure 2: Simulated impact of dissolution media, viscosity, transit rate and rotation speed on the dipyridamole concentration in the transfer apparatus acceptor compartment (*i.e.*, mimicking the duodenal environment).

HOMOGENEOUS vs. HETEROGENEOUS NUCLEATION

The described USP 2 system transfers only solution and not API particles from vessel 1 to 2 and, assuming the container surfaces and solution impurities do not play a role, homogeneous nucleation is expected. However, *in general* heterogeneous nucleation *in vivo* is expected because of impurities and where both solution and solid can transfer from the stomach to the small intestine. The barrier energy for heterogeneous nucleation is reduced compared to homogenous nucleation; Fig. 3 illustrates he relationship of $\Delta G_{heterogeneous}/\Delta G_{homogeneous}$ to contact angle. The low barrier energy contributes a fast nucleation rate.

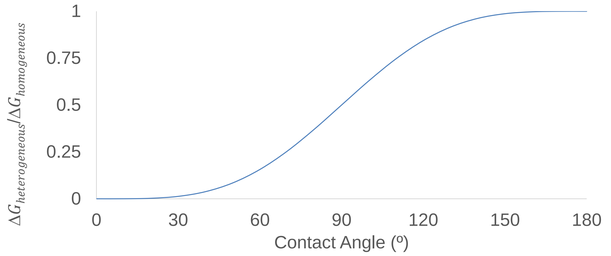

Figure 3: $\Delta G_{heterogeneous}/\Delta G_{homogeneous}$ vs. contact angle

CONCLUSIONS

Mechanistic modelling has been used to simulate the impact of various factors expected to be of importance to supersaturation and precipitation behaviour *in vivo*, including dissolution medium, transit time, viscosity and fluid dynamics, all of which exhibit inter-individual variability *in vivo*. Although transit rate, fluid viscosity (physiological and formulation effect) and dissolution media are in general different *in vitro* to *in vivo*, the model developed in this study can in principle be used to anticipate *in vivo* drug supersaturation and precipitation behaviour and its population variability based upon models assessed and/or parameterised against *in vitro* experiments and knowledge of the *in vivo* physiological parameters.

REFERENCES

Sugano 2009, IJP; Lindfors 2008, JCIS; Kostewicz et al., 2004, JPP; Liu et al., 2016 (ms. in preparation);
* SIVA and the Simcyp Population based simulator are available from Simcyp/Certara (www.certara.com).