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Short communication

In silico assessment of intestinal precipitation: Case study of a poorly soluble, weakly basic compound

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Introduction

Precipitation of a drug substance in the small intestine is a phenomenon relevant to weak bases due to their pH-dependent solubility. Because of the low solubility at higher pH, upon entry in the small intestine, a weak base may get into a supersaturated state, which is thermodynamically unstable and tends to precipitate (Makitalo, 2019). Consequently, precipitation in the gastrointestinal (GI) tract may significantly limit oral bioavailability (BA) of poorly soluble, weak bases.

Several *in vitro* and *in silico* tools are available for assessing the precipitation kinetics of weakly basic compounds (Kou et al., 2018). The dynamic nature of physiologically based *in silico* models and their ability to treat drug dissolution and precipitation as variables affecting concomitant drug bioperformance make *in silico* models a powerful tool to assess the impact of these variables on drug absorption.

The aim of this work was to *in silico* evaluate the influence of possible variations in the values of GI physiological parameters on the potential precipitation and absorption of a weakly basic, poorly soluble and highly permeable compound.

Materials and methods

Simulations were performed using GastroPlus™ software version 9.8.3 (Simulations Plus., Inc. Lancester, CA). The Advanced Compartmental Absorption Transit (ACAT) human fasted model was used to simulate drug bioperformance in the GI tract. The drug-specific model was constructed using the data on drug biopharmaceutical properties retrieved from the literature or estimated by ADMET Predictor™ 8.5 (Simulations Plus., Inc.). The selected physiological parameters values were varied in the predetermined range (Table 1) to reflect possible interindividual variation, as well as to simulate the drug performance under certain pathological conditions. In addition, particle size of the precipitate was varied in the range of 1-1000 μm, to simulate different rates of the precipitate redissolution (Patel et al., 2019).

Table 1. Values of GI physiological parameters used in the simulations

Parameter	Default value	Adjusted value
Stomach pH	1.2	3.0; 5.0; 7.0
Stomach volume	50	10; 200; 250
Small intestine volume (% of total fluid volume)	40	10; 5
Small intestine and colon volume (% of total fluid volume)	40; 10	10; 0.5

Results and discussion

The obtained results showed that under normal physiological conditions, precipitation of the model drug may occur only after oral administration of doses greater

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than 100 mg, but no precipitation is expected for therapeutic oral drug doses (up to 30 mg). The obtained results coincide with the results from the literature (Jakubiak et al., 2016). As seen in Figure 1, dose increment leads to the increase in the precipitated drug fraction. Also, the amount of precipitated drug fraction increases with the increase in the precipitate particle size.

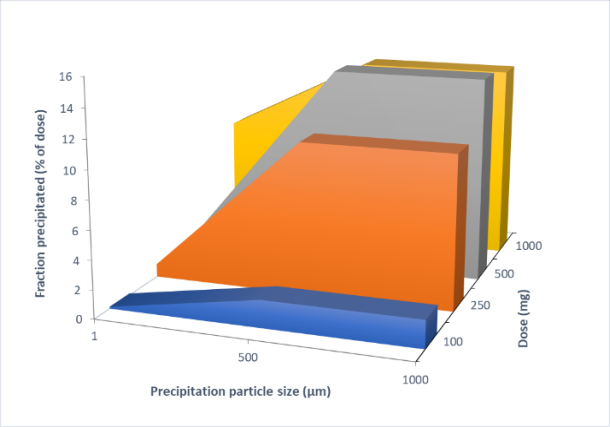

Figure 1. Predicted fraction of precipitated drug in relation to dose and precipitate particle size

Moreover, the results indicated that the drug mostly tends to precipitate in distal parts of the intestine (caecum and colon) and to a lesser extent in the proximal jejunum. This observation can be explained by relatively long drug retention time in distal intestine (cc. 18 h) and proximal jejunum (cc. 1 h) in comparison to the other GI segments. Such an outcome also implies that regional pH value is not the sole factor affecting drug precipitation.

To assess the influence of changes in the stomach pH on the model drug precipitation, stomach pH was varied in the range reflecting interindividual variability or alterations induced by concomitant drugs (Table 1). Interestingly, it was observed that under fasting conditions, and when taken in therapeutic doses, increase in the stomach pH up to 7 would not lead to the model drug precipitation.

Another physiological parameter varied was the volume of GI fluids. The simulations revealed that variation in the stomach volume in the range of 10-250 mL would not lead to drug precipitation. On the other hand, variations in the small intestine and/or colon volumes may result in drug precipitation, but only after administration of doses higher than 30 mg. Figure 2 illustrates the dependence of precipitated drug fraction to the volume of GI fluids and precipitate particle size, and clearly indicates that, under certain conditions, the precipitated drug fraction may reach nearly 10% of the administered dose. Such an outcome may significantly decrease the extent of drug absorption

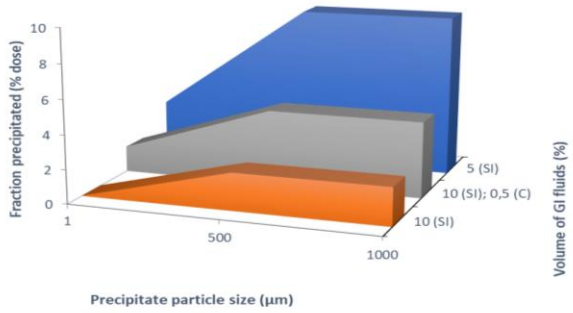

Figure 2. Predicted fraction of precipitated drug in relation to % of total GI fluids volume and precipitate particle size, for 30 mg dose

Conclusion

This work illustrates the potential of physiologically based *in silico* modeling tools to identify, evaluate and mechanistically explain the influence of possible changes in physiological parameters on GI precipitation of poorly soluble, weakly basic compound. The obtained results indicated that no GI precipitation is expected for therapeutic doses of the model drug. As reported in the literature (Patel et al., 2019), some other poorly soluble, basic drugs also show a lack of *in vivo* precipitation

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