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Mechanistic Dissolution, Supersaturation and Precipitation Models to Simulate Simultaneous Dissolution of Two Solid State Mixtures of Ritonavir

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PURPOSE

The purpose of this study is to simulate simultaneous dissolution of two solid states (crystalline and amorphous) of an API using mechanistic models. Due to its instability the amorphous form may spontaneously crystallise during the formulation preparation, storage and transfer processes [1]. This may contribute to a significant difference in exposure in the clinic. Therefore it is of great interest to be able to anticipate via modelling the impact of solid state change on drug dissolution and ultimately to extrapolate to in vivo behaviour.

MODEL STRUCTURE

The model includes the parallel processes of dissolution, nucleation and crystal growth for two solid states (Fig 1). As the whole process is taking place in the same vessel, the supersaturation and precipitation process is affected by the total bulk dissolved concentration (solid states 1 and 2), which is the driving force for the dissolution (C_{bulk}<solubility) and nucleation/particle growth (C_{bulk} > solubility) processes.

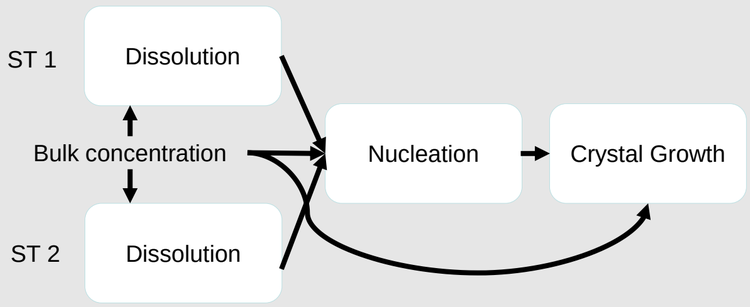
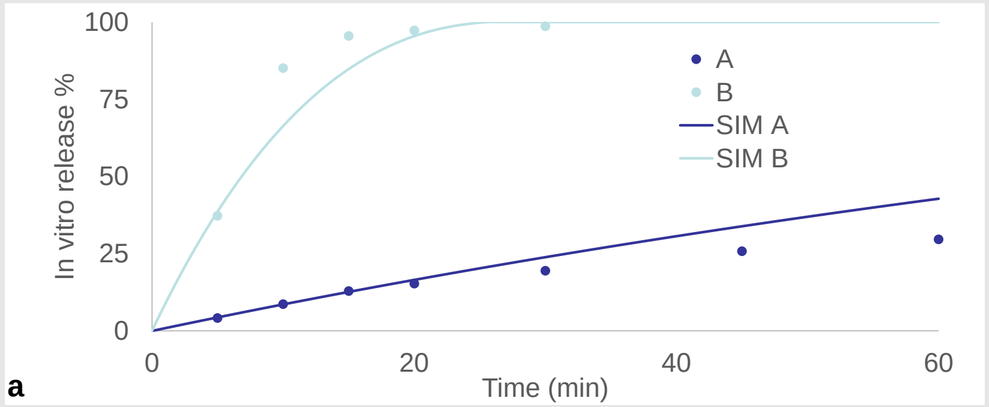


Figure 1 Model structure for two solid state (ST1 & ST2) dissolution, supersaturation and precipitation.

METHOD

A Classical Nucleation Theory (CNT) model [2] is applied to simulate the dissolution, supersaturation and precipitation behaviour of ritonavir in the USP 2 paddle apparatus. The mechanistic model is validated against *in vitro* experimental data for pure crystalline and pure amorphous states in 0.1 N HCl [3]. The model is then used to predict USP2 *in vitro* dissolution profiles of amorphous and crystalline mixtures of various proportions in 0.1 N HCl and pH 6.8 buffer media. The average particle size is 284 µm. The solubility of crystalline ritonavir is 0.4 mg/mL in 0.1 N HCl, 0.01 mg/mL in pH 6.8 buffer and that of the amorphous form is 4 mg/mL in both media. The dose is 100 mg.



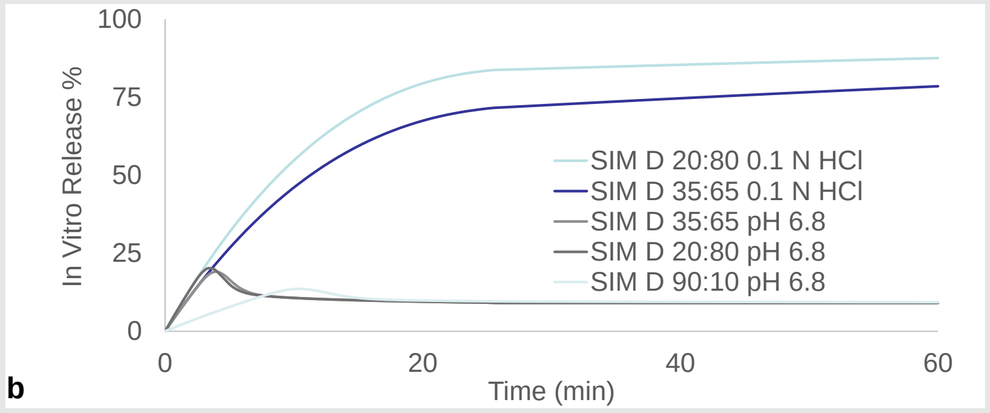


Figure 2(a) The predicted dissolution profile of A. crystalline, B. amorphous ritonavir in 0.1 N HCl; **(b)** The simulated behaviour of mixtures of crystalline and amorphous drug at different ratios (crystalline: amorphous) in 0.1 N HCl and pH 6.8 buffer.

RESULTS

The predicted dissolution profiles of the pure crystalline and amorphous states (Figure 2a) match the observed data well. The predicted dissolution profiles for mixtures of several different proportions of the crystalline and amorphous forms in 0.1 N HCl and pH 6.8 buffer are shown in Figure 2b. The crystalline equilibrium solubility directly affects the precipitation rate and maximum supersaturation ratio. The equilibrium solubility for crystalline ritonavir is 0.4 mg/mL in 0.1 N HCl, which is higher than that in pH 6.8 buffer. Therefore, supersaturation and subsequent precipitation is predicted to occur in pH 6.8 buffer.

CONCLUSION

The mechanistic model is in principle an appropriate approach to simulate *in vitro* supersaturation and precipitation for the various two solid state mixtures. Validation of the models for the two solid state mixtures with appropriate *in vitro* experiments is needed. The work is ultimately to be extended to simulations of *in vivo* outcomes within the Simcyp population-based PBPK simulator.

References

[1] Newman A. and Wenslow R. 2016, AAPS Open 2:2

[2] Liu B. et al, 2016, AAPS Arden Meeting

[3] Law D., et al, 2001, Journal of Pharmaceutical Sciences 90 (8)

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