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Investigation of supersaturation and permeation of a poorly water soluble drug Ezetimibe

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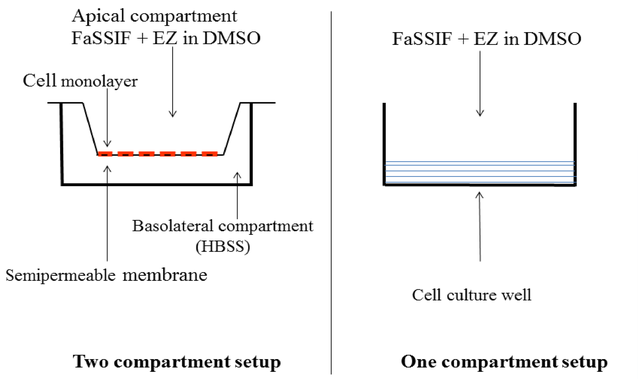
Introduction

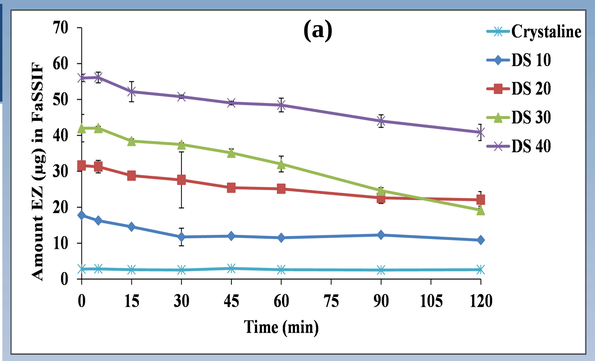
Newly developed formulations of the poorly soluble drugs are designed to create supersaturation in vivo. The transport across the intestinal membrane can influence precipitation kinetics of a supersaturated phase. Thus, it is important to understand the interplay among supersaturation-precipitation-permeability.

Aims

- The effect of permeation across Caco-2 cell monolayers on supersaturation of Ezetimibe, a poorly water soluble drug was investigated and compared to the supersaturation in a cell free one compartment setup.
- Polymer effect was also investigated using PVP K-30

Methods





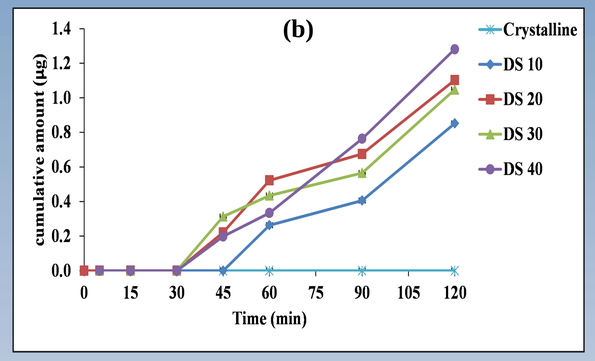
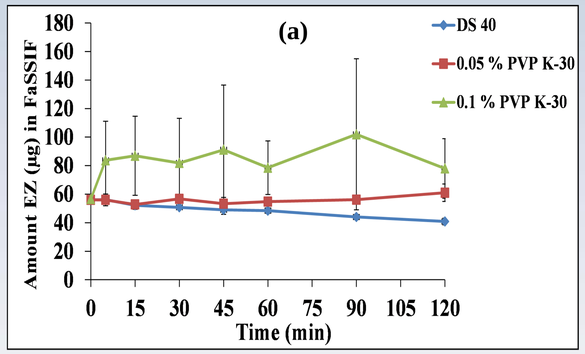


Figure 1. a) Amount of Ezetimibe (EZ) in FaSSIF on the apical side of Caco-2 cell monolayers as a function of time, after induction of supersaturation. b) Cumulative amount recovered from the basolateral acceptor medium (i.e. HBSS). (Mean ± SD; *n* = 3)



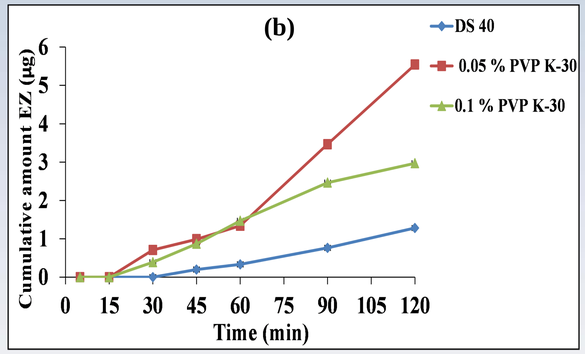
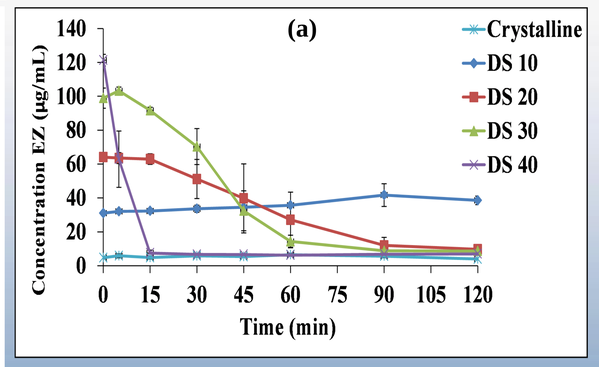


Figure 2. a) Amount of (EZ+PVP K-30) in FaSSIF on the apical side as a function of time. b) Cumulative amount recovered from the BL (i.e. HBSS), after transport across Caco-2 monolayers in the presence of polymer in the apical compartment. (Mean ± SD; *n* = 3)



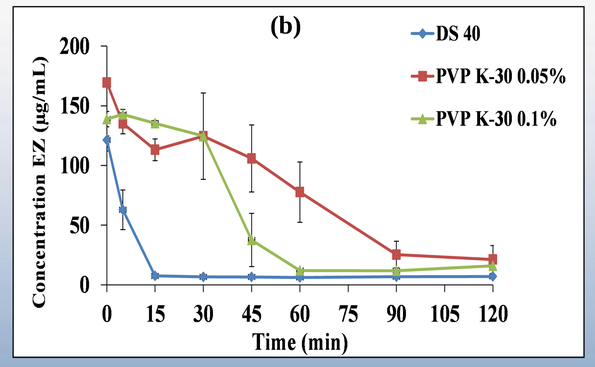


Figure 3. Concentrations of (EZ) in FaSSIF without (a) and with (b) PVP K-30 as a function of time, in the one compartment setup. (Mean ± SD; *n* = 3)

Results

- The transport of EZ to the BL side was low for all sample solutions under study.
- Higher degrees of supersaturation were associated with high transport levels reaching the highest amounts with DS 40.
- In one compartment setup high degrees of supersaturation was associated with rapid precipitation.
- The polymer PVP K-30 had maintained EZ in the supersaturated state when added to the apical side in two concentrations 0.05% (w/v) and 0.1% (w/v) but only 0.05 % (w/v) showed an improvement in the transport.

Conclusions

- Caco-2 cell monolayers affect supersaturation and precipitation of EZ.
- One compartment setup provides underestimation of supersaturation, precipitation and permeation
- PVP K-30 improved supersaturation and permeation

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