Supersaturation of Zafirlukast in Fasted and Fed Intestinal Media Measured In Situ by UV/Vis Fiber-Optic Probes: Effectiveness of Precipitation Inhibitors

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Purpose
The aim of this study was to examine the effectiveness of precipitation inhibitors (PI) on the supersaturation of Zafirlukast in vitro and compare these results with in vivo behavior.

Zafirlukast (ZA) is a leukotriene antagonist marketed for treatment of asthma (Accolate®). Oral administration of ZA with food can reduce the bioavailability by 40%. ZA is poorly water soluble, and formulated in its amorphous form (aZA). aZA has a solubility and dissolution advantage compared to the crystalline hydrate form. It has been shown that aZA will supersaturate upon dissolution with respect to its crystalline form, and thus in theory the bioavailability of ZA increases upon amorphisation. However, due to the unstable nature of a supersaturated system, ZA precipitates as the hydrate form and the concentration decreases accordingly. The precipitation can be inhibited, and the supersaturation period prolonged by addition of polymers such as hydroxypropylmethylcellulose (HPMC) and polyvinylpyrrolidone (PVP). HPMC and PVP are excipients in Accolate®.

Methods
The level and duration of supersaturation was examined by powder-dissolution with in situ measurements of absorbance with an UV/Vis probe in simulated intestinal media in vitro. Preliminary studies suggested the method to be beneficial as a screening tool, but not as a precise prediction tool for in vivo behavior.

Results
A prolonged duration of supersaturation of aZA was demonstrated in presence of HPMC and PVP (w/w, aZA:PI, 1:1) in vitro. PVP also raised the level of supersaturation (fig. 1). The duration of supersaturation was shorter in fed than in fasted state simulated intestinal media (fig. 2). The effectiveness of the precipitation inhibitor PVP was lowered in fed state intestinal medium in vitro (fig. 3). These results are in accordance with the observed in vivo behavior of ZA.

Conclusion
This study indicates that dissolution experiments in vitro can be used to examine supersaturation, effectiveness of PI and potential food effects on these.

Figure 1

Figure 2

Figure 3