SOLUBILIZATION AND INTERACTION OF BCS II DRUGS WITH AN ENDOGENOUS GASTRIC ENZYME, PEPSIN

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Background:

Hydrophobic drugs suffer from poor and variable oral bioavailability due to their poor solubility in the gastrointestinal fluids. They pose a significant roadblock in drug development discovery. However, digestive proteins in gastrointestinal fluids may play a role in the solubilization of hydrophobic active pharmaceutical ingredients through binding to hydrophobic sites on the protein surfaces. To date, the solution concentration of two hydrophobic molecules, clofazimine citrate[1] and an unnamed drug[2], have been shown to increase in simulated gastric fluids in the presence of pepsin, an endogenous gastric enzyme. In the current investigation, pepsin has been explored for its potential to solubilize two additional BCS class II drugs, ketoprofen and carbamazepine.

[1] S. Pinnamaneni et al, "Effect of pepsin on maintaining the supersaturation of the HCl salt of a weakly basic drug: a case study.," Pharm. Dev. Technol., 2016, 21, 311–20.

[2]P. Bannigan et al, "Delivery of a hydrophobic drug into the lower gastrointestinal system via an endogenous enzyme-mediated carrier mechanism: An in vitro study," Eur. J. Pharm. Biopharm., 2018, 133, 12-19.

Methods:

Equilibrium solubility and dynamic dissolution of hydrophobic drugs individually and with varying concentrations of pepsin were assessed in simulated body fluids. To understand any change in the polymorphic nature of drugs during dissolution, powder X-ray diffraction was performed to understand the polymorphic nature of the drugs during dissolution. Binding energy and inhibitory constants between the ligands (drugs) and receptor (pepsin) were determined by molecular docking in the Autodoc program.

Results:

Carbamazepine and ketoprofen both exhibited improved solubility and dissolution profiles in the presence of pepsin by forming a drug-pepsin complex. The nature of the interactions in the drug-pepsin complex was further explored by molecular docking studies which indicated that carbamazepine bound to pepsin near the active site while ketoprofen, with lower binding energies, was found to bind at other locations on the pepsin structure. Powder X-ray diffraction showed conversion of a polymorphic form of carbamazepine during solubility studies while the added polymorph of ketoprofen remained unchanged.

Conclusions: *In-vitro* studies demonstrated the enhancement of solution concentration of two BCS II drugs in the presence of the endogenous enzyme. It was further shown by molecular interaction simulation in Autodoc. This endogenous enzyme could be further explored as a formulation strategy for improving the solution behavior of other poorly water-soluble drugs for oral administration.