Enhanced Dissolution Performance of  BCS Class II Compound
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**Purpose**
The purpose of the present study was to design supersaturatable SMEDDS formulations of a BCS Class II anticancer compound (Compound A) for increased absorption and enhanced bioavailability. The SMEDDS formulated using Capryol 90, Labrasol, PEG 400 showed good emulsification properties and rapid drug release. Several polymeric precipitation inhibitors such as polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC) were evaluated as additives to the base SMEDDS composition to achieve sustained supersaturation of the drug. Incorporation of HPMC in the SMEDDS formulation resulted in high drug concentrations upon dispersion, which were sustained for several hours as compared to the SMEDDS formulation without the polymer. Upon relative assessment, the rank order in which the polymers inhibited precipitation was PVP-K30 < PVP-K90 < HPMC.

**Methods**
Preliminary solubility studies for Compound A were set up in various compositions consisting of different oils, surfactants and cosolvent mixtures. Formulations were based on Capryol 90 as the oil phase, with Labrasol and PEG 400 as the surfactant and cosolvent respectively. API loading was kept at 5% w/w level. Oil and surfactant/cosolvent were mixed in different volume ratios (5:95, 10:90, 20:80, 30:70, 40:60, 50:50, 60:40, 70:30, 80:20, 90:10 and 95:5) and evaluated for clarity, particle size, phase separation and precipitation. Three different types of self-emulsifying vehicles (type IIIA, type IIIB and Type IV) were chosen for in vitro evaluations. Polymeric precipitation inhibitors such as PVP-K30, PVP-K90 and HPMC were suspended in the SMEDDS with high speed mixing. For bench scale experiments (~ 10 g) the formulations were filled in Size “0” 2-piece hard gelatin capsules and evaluated for dissolution performance in simulated gastric fluid (SGF). Once the final formulation was selected based on vial studies, the formulation was encapsulated in two gelatin shell formulas (acid bone and lime bone) and prototype capsules were put on ICH stability at 30 °C/65% RH and 40 °C/75% RH conditions.

**Results**
The base SMEDDS formulations resulted in immediate release of drug in SGF media. The type IIIA formulation resulted in a drug concentration of ~0.017 mg/ml at 0.5 hours. For the Type IV formulation composed of cosolvent and surfactant only, drug levels of 0.18 mg/ml at 0.5 hr were observed. For the Type IIIB formulation, high drug concentrations of ~ 0.288 mg/ml were observed at 0.5 hrs. The levels of drug reduced two-fold over the next 30 minutes and 4–fold over the next 2 hours. Since the Type IV formulation contains highly hydrophilic components it results in the formation of a highly supersaturated solution of drug, but this formulation is very prone to precipitation as evidenced by the rapid 3-fold decline in drug concentration at 1 hr and almost a 100-fold decrease in drug levels at 2 hrs and 3 hrs. The presence of 5% Capryol 90 in the Type IIIB formulation had a significant impact on the release of the drug and sustaining better drug concentrations as compared to the Type IV and Type IIIA formulations. Type IIIB formulation was further evaluated for supersaturatability using PVP-K30, PVP-K90 and HPMC as precipitation inhibitors. The use of PVP-K30 in the Type IIIB SMEDDS formulation results in much lower concentrations of drug at 0.5 hours, and the concentration declines to < 0.01 mg/ml at the end of 3 hours. The PVP-K90 results in a drug concentration of 0.05 mg/ml at 0.5 hours followed by a 2-fold decline within the next 30 minutes. The HPMC-SMEDDS formulation results in 0.45 mg/ml drug and sustains the high levels as opposed to the Base-SMEDDS formulation. Since HPMC is a relatively more hydrophobic polymer than PVP-K30 and PVP-K90, it performs better in inhibition of the drug precipitation. HPMC was further evaluated at several concentrations in the SMEDDS formulation to evaluate the lowest amount that would still be effective for supersaturation. HPMC was loaded at 1, 2.5, 5 and 10% in the SMEDDS formulation. At 5% and 10% HPMC loading, the drug concentrations over 3 hours are not significantly different.

**Conclusion**
The results of this research indicate that the therapeutic potential of Compound A can be significantly increased by the use of conventional SMEDDS formulations coupled with precipitation inhibitors. The supersaturatable SMEDDS would serve to increase the drug solubility and sustain the increased levels in GI fluids which would in turn allow for increased oral absorption and bioavailability. These formulations can be delivered using conventional soft gelatin based dosage forms allowing for convenient administration and better compliance in patients and could serve to highly increase the efficacy of Compound A in existing therapeutic modalities relating to cancer and other inflammatory diseases.