Comparative PK Performance of Solution and Suspension Based Formulations For a BCS Class II Molecule in a Soft Gelatin Based Dosage Form

Haley Judd-Pulito, Saujanya Gosangari

haley.pulito@thermofisher.com | saujanya.gosangari@thermofisher.com

Thermo Fisher Scientific

aaps PharmSci 360

ADVANCING PHARMACEUTICAL SCIENCES, CAREERS, AND COMMUNITY

PURPOSE

The purpose of the present study was to determine the effect of solution and suspension based matrices on PK response for a novel, hydrophobic Biopharmaceutical Classification System (BCS) II compound.

OBJECTIVE

The objective of this study was to screen various excipients based on the active ingredients physicochemical properties to determine a suitable fill for a soft gelatin based formulation. The PK performance of the various formulations were evaluated. Formulations were developed to be delivered within a soft-gel based dosage form and pharmacokinetic studies were conducted on each formulation matrix in animal models.

METHOD(S)

Solubility Study:

Excipients were selected based on physicochemical properties of the active ingredient. Preliminary solubility studies for the model drug were conducted in a variety of pharmaceutical excipients spanning an HLB range of 1-16. The excipients selected for the solution based formulation include Medium chain triglycerides, Maisine CC, Capmul, and Labrasol. The suspension based matrix was prepared using super refined corn oil, super refined soybean oil, olive oil, and lecithin.

Formulation Design:

Formulas were developed with wide range of lipid based excipients to yield Type II, Type IIIA, and Type IIIB formulations. For the solution based formulations, the lipid excipients were dispensed into a suitable glass container and heated between 50-60°C and mixed to obtain homogenous solutions. The excipient mixture was then cooled to 40 °C and API was added to it. The admixture was mixed to achieve complete dissolution of the active. With the solution based approach, at least 10-11% API loading was achieved with different types of lipid based formulations. The API was suspended in the bulk vehicle (medium and long chain oils) with mixing and homogenization to achieve at least 30-40% drug loading.

METHOD(S)

Formulation Characterization:

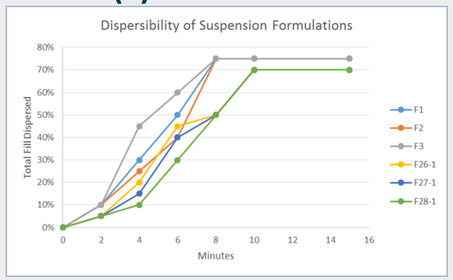
For solutions, formulation characterization was performed by conducting freeze thaw studies, dispersibility in simulated gastric fluid and emulsification studies. Three lead candidates were selected (Formula A, B and C) and further tuned to formulation D to investigate effect of increased lipophilic components on bioavailability. Formula A was a Type IIIB lipid formula with hydrophilic surfactants and water. Formulation B and C were Type II and Type IIIA lipid formulations, respectively. For suspensions, formulation characterization was performed by conducting sedimentation studies, flow-ability evaluations, dispersibility in water (Figure 1) and viscosity (Figure 2). The fills were encapsulated into two piece hard shell capsules as well as in soft-gel capsules and evaluated in animal models for pharmacokinetics studies. The solution based fills at 10-11% loading were dosed in rat and dogs along with a suspension in vegetable oils at < 5% loading.

RESULT(S)

Formulation B showed superior PK performance when compared with Formulation A and C. It is likely that due to the hydrophilic components used in Formulation A and C, potential precipitation of the active may have occurred upon dilution in the gastrointestinal fluids which resulted in lower Cmax and AUC values for these formulations. Although Formulation B performed better than Formulation A and C, it showed lower Cmax and AUC compared to the suspension dose at 3% loading. In addition, all formulations A, B and C showed significant inter subject variability.

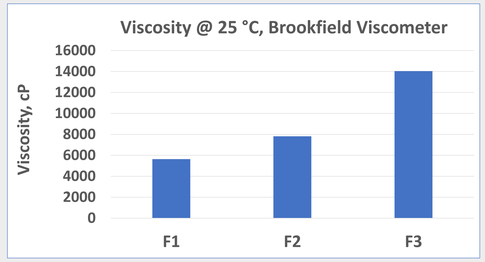
Formula C was tailored to increase the amount of medium chain triglycerides while Capmul was removed and replaced with low HLB lipid to increase lipophilic components. Formulations B and D (11% drug loading) were taken into another PK study along with the suspension in vegetable oil (< 5% loading). It was observed that the PK performance of Formula D was superior than formulation B and equivalent to the suspension. However, when API loading was increased in formulation D, it did not achieve linear PK response as that was observed with the suspension. It is likely that with the solubilized formulations, with additional doses no further benefit was realized due to saturation and precipitation during PK study. However, it should be noted that for the PK study, the drug loading (<5%) used in suspension formulation was lower when compared to solution formulations (10-11%). This could also lead to higher bioavailability with the suspensions as more amount of lipidic components might have enhanced drug absorption. Hence suspension formulations, F1, F2, F3, F26, F27 and F28 were prepared to target 16-40 % drug loading. Formulation F3 had high viscosity and could not be encapsulated. The PK performance is outlined in Figure 3.

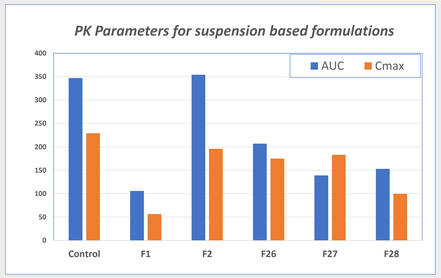
RESULT(S)



Dispersibility studies showed that all formulations achieved complete dispersion in the dissolution media and no aggregation was noted for any of the formulations. Dissolution Conditions: 100 rpm, Paddles, Simulated Gastric Fluid, 900 mL.

Viscosity is critical for encapsulation feasibility for a softgel based formulation. Viscosity of F3 formulation was ~ 14,000 cP, which caused significant pump and lead line clogging issues during encapsulating.





As seen from Figure 3, equivalent PK performance was achieved for the F2 formulation which was at 40 % drug loading compared to the control (<5% drug loading). For the control almost 4g of vehicle had to be dosed vs. 330mg of the F2 formulation.

CONCLUSION(S)

Conventionally, higher bioavailability and linear dose response are expected with solution based formulations for BCS Class II drugs. However, the study performed as part of this research did not yield such typical results. The study also highlights the importance of using lipidic components which upon digestion do not lose the solubilization capacity helping in vivo absorption as compared to using hydrophilic components in systems where solubilized drug precipitates to give poor performance in vivo.

patheon by Thermo Fisher Scientific