Enhanced Solubilization of an Analgesic/Antipyretic Drug With The Use of Polymeric Excipients

Haley Pulito, Harry Wang, Saujanya Gosangari

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

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PURPOSE

The purpose of the present study was to increase the solubility of an analgesic/antipyretic drug to achieve a concentrated formula and consequently a smaller capsule compared to the marketed formulations.

OBJECTIVE(S)

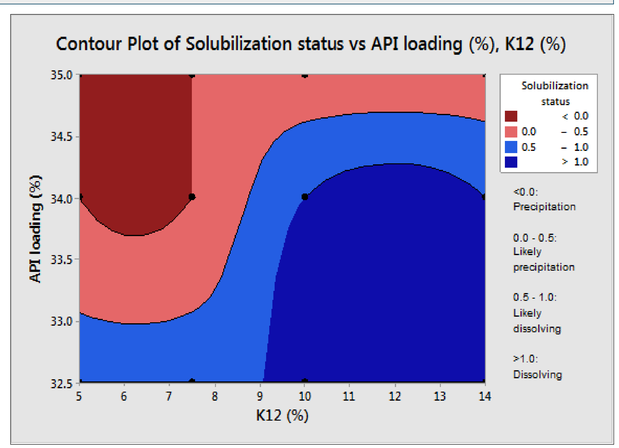
The objective was to design a **clear** fill formulation at high drug loading to achieve a significant size reduction in the overall capsule size. Analgesic drug products are widely marketed in the softgel based dosage form as better absorption and faster onset of action is achieved with the softgel format. The objective to reduce the capsule size was based on the intent of improving marketability and patient compliance.

METHOD(S)

Formulation was designed to have hydrophilic excipients as bulk vehicles in addition to Capmul MCM and Oleic acid as cosolubilizers. Several grades of Povidone marketed by BASF were explored as part of the study. A DOE design was set up around drug loading and Povidone concentrations. Povidone solubilization was achieved in the base formula by heating at 55 ± 5 °C. API loading was varied from 30-40%. Freeze thaw studies were conducted on the formulations for a minimum of three cycles to evaluate precipitation behavior in the anhydrous state. 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. Die tooling design was based on the fill weight and the overall density of the new fill formulation.

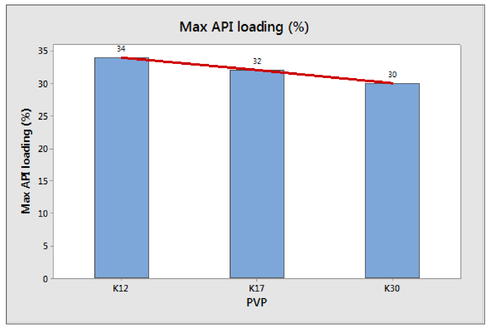
RESULT(S)

Povidone helped enhance the solubility of the active and also acted as a precipitation inhibitor. Povidone concentrations from 1-14% were explored. Solubilization capacity of formulation was impacted by two factors: Povidone grade & concentration and the pH modifier concentration. Significant viscosity was noted for the K90 based formulations which could have potentially resulted on encapsulation issues. Hence the K90 grade was not further pursued. Higher drug loading was achieved with lower grades of Povidone. Upon relative assessment, the rank order in which the Povidone enhanced solubilization was PVP-K30 < PVPK17 < PVP-K12. The viscosity profile for the K12 based formulations as a function of temperature was generated. For encapsulation, a temperature range of 37-40 °C was targeted to enable improved flowability for the formulations. Original formulations at 32% drug loading were encapsulated in a 22 Oblong die. With the 34% drug loading, the capsule size was reduced to 20 Oblong achieving almost a 20% reduction in size of the overall capsule. From a critical quality attributes perspective, relatively improved physical characteristics in terms of capsule integrity were noted for the acid bone gel based capsules versus the lime bone gel on accelerated stability.

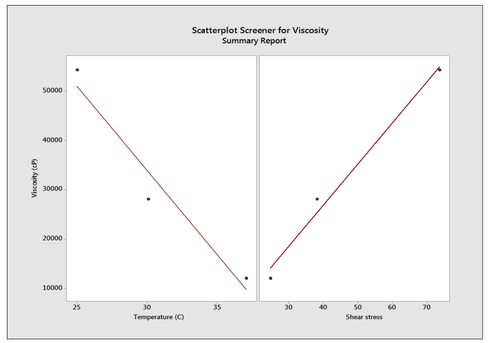


Higher drug loading was able to be achieved once the K12 level was ≥ to 9% in the formulation.

However, above 10% K12, significant viscosity increase was noted for fills which resulted in flowability and encapsulation issues.



Typically, 30-32% loading is the upper limit of solubilization for this API within the fill matrix. With the use of lower grade Povidone, almost 34% drug loading was able to be achieved. Solubilization capacity of the formulation improved with lower grades of Povidone.



Viscosity of formulation with 10% Povidone K12 was ~54,000 cP at 25° C, which posed a significant challenge during encapsulation as fill flowability issues were noted. Viscosity at 37° C was ~12,000 cP. At this temperature, fill flowability was improved and encapsulation could be successfully executed.

CONCLUSION(S)

Povidones are typically used to stabilize micro-molecular structures in liquid fill formulations. They form hydrogen bonds with active molecules with complementary structures for improved dissolution. Kollidon® 12 PF serves as a solubilizing agent and crystallization inhibitor particularly for injectables. The results of this research indicate that the lower grade of Povidone K12 (Plasdone) was very effective in solubilizing a significant amount of the active which reduced the overall size of the capsule. A smaller softgel can help with improvement in patient compliance while enhancing overall bioavailability of the molecule.

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