

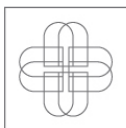
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Licaps® Drug Delivery System for Proof-of-Concept Clinical Study for an Innovative Gastro-Intestinal Disease Treatment W5057

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PURPOSE

The purpose of the study was to characterize and encapsulate within 8 weeks a lipid based formulation in a Licaps® Drug Delivery System (Licaps® DDS) intended for a clinical trial to obtain Proof-of-Concept for an innovative treatment of gastro-intestinal diseases developed by Synergy Pharmaceuticals.

The Licaps® DDS is a system based on a hard capsule format particularly suitable for encapsulation of liquid or semi-solid lipid-based formulations.

Compatibility testing was performed to evaluate compatibility of the formulation with Licaps® capsules.

Characterization of the formulation was also performed in view of the process recommendations for production on small scale filling and sealing equipment (CFS). A small scale clinical batch was targeted to be produced on CFS.



METHODS

Compatibility testing with Licaps® capsules

Hygroscopicity testing which shows any interaction between the environmental conditions, the capsule shell and the fill.

Mechanical robustness testing which demonstrates any alteration of the mechanical properties of the capsule shell due to an interaction between the fill and the shell.

Dissolution testing using an immediate release reference (i.e. acetaminophen) which indicates any delay in capsule dissolution due to gelatin cross-linking which can be caused by an interaction between the fill and the shell. Dissolution tests are performed using a USP apparatus type II at 50 rpm and 37°C.

Characterization of the formulation

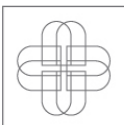
Density measurement was performed on a densimeter (DE40, Mettler Toledo). Thermorheological evaluation of the formulation was performed on an oscillating type rheometer (Mars II, ThermoFisher).

Clinical batch production on CFS

The clinical batch was manufactured using the lab-scale equipment CFS.

Synergy Formulation

Synergy Pharmaceuticals developed a formulation consisting of one active ingredient and one inactive ingredient (total fill weight: 795 mg). The formulation was prepared using the ratio defined by Synergy Pharmaceuticals' instructions. The formulation process was optimized prior to manufacturing.



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RESULTS

Compatibility testing

Hygroscopicity testing shows that the formulation was not within Capsugel recommendation at storage conditions below 10% RH and above 55% RH. However, the water uptake was stabilized after 2 weeks storage and no leakage or deformations were observed.

Mechanical robustness testing demonstrated brittleness of the capsules outside 35-65%RH.

Dissolution testing in water was within Capsugel recommendations after 3 weeks storage at 40°C/75% RH (i.e. 91.8%). After 3 and 6 months storage at 40°C/75% RH, a pepsin medium was needed to obtain results within Capsugel recommendations (i.e. 94.2% and 92.3% respectively). The dissolution was affected by a cross-linking reaction but in-vivo performance should not be impacted as the results in the pepsin medium were within specifications.

Formaldehyde analysis

It is important to consider the presence of certain chemical entities which may contribute to the occurrence of gelatin cross-linking, leading to changes in the *in-vitro* dissolution profiles of drugs. The presence of aldehydes, among other reactants, can lead to this reaction. Especially formaldehyde is considered as a main cross-linking agent related to the loss of solubility of gelatin capsules¹.

Therefore, formaldehyde level was measured in the formulations at the initial time point and after 6 months storage at 40°C/75%RH: a significant increase was observed after 6 months. Cross-linking reaction might occur

when the formaldehyde level is estimated to be higher than 5 ppm which was confirmed by the dissolution results obtained.

Based on these results, the Synergy formulation was considered as compatible with the Licaps® gelatin capsules if stored in the following conditions: 15-25°C and 35%-55% RH.

Characterization of the formulation

Density of the formulation

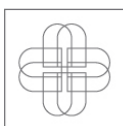
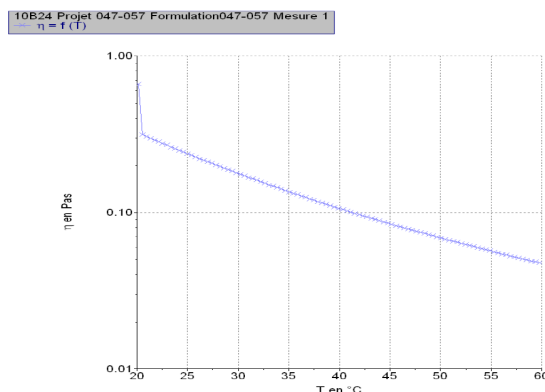
The density of the formulation is 1.02 g/cm³ at 35°C. Therefore 795 mg of the formulation can be filled in size 00 capsules (recommended max. fill volume of 0.79 ml).

Thermorheogram

The viscosity values as a function of temperature for the Synergy formulation are presented in Graph1.

Based on the results (Graph1), the filling temperature was set at 35°C to meet the requirements for liquid filling using lab-scale equipment².

Flow curves were determined for Synergy formulation (Graph2).



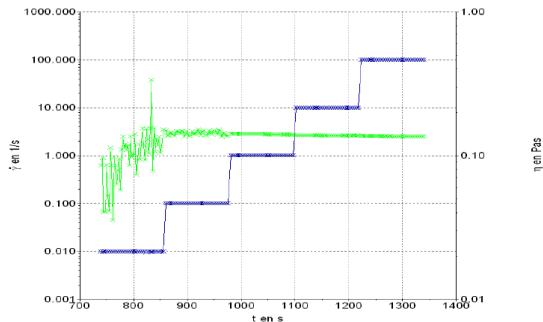
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Graph1: Viscosity as a function of temperature



Graph2: Flow curve for synergy formulation at 35°C

The viscosity (η , green points/crosses) of Synergy formulation was expressed as a function of the shear rate (γ , blue points/crosses), at the selected temperature of 35°C. Synergy formulation can be considered as a Newtonian formulation at 35°C as the viscosity value is stable while changing the shear rate step wise at this temperature of 35°C. Therefore, no issue was expected to be encountered during filling of the formulation using CFS small scale equipment.

Small scale-up production

Based on the characterizations performed on the formulation, a feasibility batch was realized. No issue was encountered during the preparation and encapsulation of the formulation in Licaps® capsules size 00.

Therefore, the clinical batch of 5000 capsules was produced using Licaps® capsules. The batch was successfully released and sent to Synergy for initiation of the clinical trial.

CONCLUSION

Following a rational formulation evaluation and a process development for the formulation developed by Synergy, a small scale clinical batch of Licaps® DDS was successfully produced. This clinical batch will allow Synergy to quickly obtain the Proof-of-Concept for their innovative gastro-intestinal disease treatment.

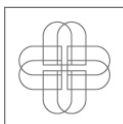
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