Scale-up strategy for lipidic mesophases production

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Ulcerative colitis (UC) is a chronic inflammatory disorder involving the colon and rectum which has no cure. The severe dose-dependent side effects caused by oral therapies combined with the favourable localization of the disease encouraged the development of local therapies using enemas and foams as dosage forms. However, the efficacy of these formulations is limited due to insufficient retention time in the rectum. In this scenario, our research group developed an in situ forming gel, named TIF-Gel, for the treatment of UC aiming for high local retention and low systemic drug exposure [1]. TIF-Gel is a lipidic mesophase (LMP)-based formulation characterized by a low viscosity lamellar phase at room temperature, which provides an easy application by the patient, and a high viscosity cubic phase at the rectal temperature, providing high drug retention. The TIF-Gel process flow chart is shown in Figure 1, which is the method commonly used for the preparation of LMP-based drug delivery systems. In such a method, however, critical process parameters (CPP) that could affect the quality of the final formulation were identified. Quality deviation due to CPP becomes a bigger issue when larger batches, for example, for preclinical studies, need to be produced.

We aimed thus to develop a more reproducible and robust production method for LMP. With our optimized approach, we could avoid lyophilization and the use of organic solvents, making the large-scale production of LMP more sustainable. In this study we used a Quality by Design approach based on a Design of Experiments to select the best conditions to produce the TIF-Gel. We selected the mixing and equilibration times of the formulation as independent variables, and the LMP phase geometry, the drug homogeneity within the syringe, and the drug release rate as dependent variables. We evaluated the versatility of our optimized approach by incorporating five drugs with diverse physicochemical properties into the TIF-Gel. Overall, using the new production method, we obtained LMP with lamellar phase geometry at 25 ^{0}C and cubic phase at 38 ^{0}C, high drug homogeneity within the syringe and drug release rates comparable to the formulation produced by the standard methodology.

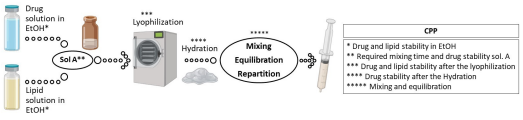

Figure 1. Process flow chart and the critical process parameters that could affect the quality of the final product using (A) a standardized method and (B) the dual syringe method.

[1] Marianna Carone, Marianne R. Spalinger, Robert A. Gaultney, Raffaele Mezzenga, Aart Mookhoe k, Philippe Krebs, Gerhard Rogler, Paola Luciani, Simone Aleandri, *Nature Communications*, **2023**, In press. Pre-print available at bioRxiv doi.org/10.1101/2022.09.28.509483.