New lipid formulation of amphotericin B

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Amphotericin B (AmB) is a polyenic aromatic antibiotic used to treat fungal diseases and Leishmaniasis. This drug has low solubility in water and high toxicity. Its main adverse effects are hemolytic toxicity and decreased renal function, which may cause nephrotoxicity. Because of this, there have been conducted different studies to develop alternative formulations of AmB. The use of lipid formulations as a means of transporting lipophilic drugs has been increasing in the literature. Self-emulsifying drug delivery systems (SEEDS) are composed of a mixture of oil, surfactant and co-solvent with the drug. They facilitate the solubility of drugs, their absorption in the gastrointestinal tract, the protection of the drug from variations in pH and enzymes present in the gastrointestinal tract. Thus, this type of formulation would be a good strategy to minimize the problems related to the low solubility and bioavailability of amphotericin B.

This work aims to develop a SEED capable of transporting amphotericin B. First, the solubility of AmB was determined against 20 lipid excipients. It solubility was evaluated by the first derivative method by UV spectroscopy. Then, it was made a fractional factorial experimental design (DOE) using the lipid excipients as an independent variable (7) and 4 dependent variable: incorporation of AmB, particle size, transmittance and polydispersity index (PDI). The DOE was evaluated at the Design-Expert® software.

Based on the ability to solubilize AmB, of the 20 lipid compounds 8 were selected: Capmul MCM, Peceol, Dhaytan L20, Span 80, Labrasol, Tween 20, Transcutol HP and Phosal 50PG. These compounds were used as independent variables of the DOE fractional factorial analysis and the Capmul® MCM EP were used in fixed amount in all the experiments. The experimental design allowed to maximize the amount of information acquired and to minimize the number of experiments to be performed. The best fitting mathematical model was selected based on analysis of variance (ANOVA) with 0.5% and the comparisons of several statistical parameters including the multiple correlation coefficient (R2) and adjusted multiple correlation coefficient (adjusted R2). Based on the analysis, the DOE were optimized to obtain the maximal incorporation of AmB and transmittance value, the smaller particles size and PDI value. The combination of excipients which met all of the above restrictions was Capmul® MCM, EP and Tween® 20. The addition of a small amount of Labrasol® and/or Trancutol® HP leads to a slight decrease at the particle size and an increase in AmB solubility.

In conclusion, it was possible to select 8 lipid excipient out of the 20 tested in the test of AmB solubility. With the DOE by factorial analysis, it was possible to maximize the amount of information in a reduced number of experiments, selecting only 4 lipid excipients for future study of the formulation of the SEED.