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Investigations on the lyophilisation of MPEG-hexPLA micelle based pharmaceutical formulations.

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Abstract

Lyophilisation is a common procedure to increase the long-term stability of pharmaceutical formulations. Its applicability to polymeric micelles is usually an issue because of the aggregation of materials during freeze-drying steps. The feasibility of this process was studied on polymeric micelles based on methoxy poly(ethylene glycol)-poly(hexyl-lactide) (MPEG-hexPLA) with and without Cyclosporin A, in order to increase the stability of these pharmaceutical formulations. Freeze-thawing tests were carried out to determine the protective effect of various excipients on the freezing step. Mannitol, trehalose, glucose and sucrose showed the best effectiveness in micelle protection. The lyophilisation process was optimised by thermal analysis (DSC) on excipients to determine the glass transition temperature of the cryoconcentrate solutions (T(g)') and their glass transition temperature (T(g)). The freeze-dried powders were characterized in terms of morphology (SEM) and of moisture content (Karl Fisher titration). The reconstituted micelle formulations were analysed for size by DLS with and without goniometer, for morphology by TEM, for drug loading by HPLC. The formulation presenting the best characteristics before and after reconstitution contained 10% (w/v) sucrose in phosphate buffer. This lyophilised formulation was constituted of a brittle and white cake, with a residual water content of around 2% and it was easily reconstituted in a transparent and clear solution giving back a colloidal system with spherical micelles in the submicron range (<250 nm). The drug loading was not affected by the freeze-drying procedure. This study showed that the MPEG-hexPLA micelles can be efficiently lyophilised and this process can be usefully applied to increase the pharmaceutical stability of these pharmaceutical micelle formulations.