P-109 **Hydrogel-based solid lipid nanoparticles (SLN) for oral delivery of drugs**

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INTRODUCTION

Nowadays, the need of developing alternative oral delivery systems are increasing, related with the discovery of new active molecules with specific features, which requires special care in formulation processes. Lipid-based drug delivery-systems gained attention during the last years, since they are known to promote oral absorption of drugs (Charman, 1992). In between these systems the most promising ones seem to be the so-called solid lipid nanoparticles (SLN) (Muchow, 2008). SLN can be incorporated into hydrogels, acquiring a semi-solid consistency that permits an increase of drug bioavailability and long-term stability of nanoparticles (Souto, 2004). Furthermore, these systems can be used as alternatives to facilitate oral/peroral administration of some drugs (Bernkop-Schnürch, 2000). The aim of this work was the preparation and characterization of a SLN dispersion proposed for oral drug delivery of poor water-soluble drugs. After SLN preparation, the systems were incorporated into perfluorocarbon (PFC) based hydrogel, in order to achieve an adequate consistency and to increase their long-term stability. The rheological behaviour of prepared hydrogels was evaluated, before and after the incorporation of the nanoparticles.

MATERIALS AND METHODS

Imwitor® 900K and Tagat® S were gifts from Sasol (Germany) and Goldschmidt (Germany), respectively. Sodium deoxycholate was purchased from Sigma-Aldrich (Portugal) and the model poor water-soluble drug was kindly provided from Janssen-Cilag (Belgium). For the hydrogels preparation, perfluorocarbon (PFC), Germal and triethanolamine were provided by Guinama (Spain). Propylenoglicol were obtained from Merck (Germany). The water used in all experiments was purified, obtained from a MilliQ Plus, Millipore.

Preparation of SLN

SLN were produced containing 10% (w/w) Imwitor® 900K, stabilized with 2.5% (w/w) Tagat S® and 0.5% (w/w) of Sodium deoxycholate, by ultrasound technique. Firstly, the solid lipid was heated 5-10ºC above its melting point, and then added to a mixture of surfactants and water, previously heated at the same temperature. A pre-emulsion was obtained under stirring with an Ultra-Turrax T25 (Janke & Kunkel GmbH, Germany), at 8000 rpm for 5 minutes. This emulsion was further putted under a sonication probe, by means of an Ultrasonic processor VCX130 (Sonics, Switzerland), applying an amplitude of 70% during 15 minutes. For drug-loaded SLN, the drug was added to the solid lipid before melting and sonication. The drug was used in a concentration of 1 % (w/w) with regard to the solid lipid matrix.

Particle size analysis and zeta potential measurements

SLN dispersions were previously diluted with purified water to suitable concentration, and the particle size analysis were performed by photon correlation spectroscopy (PCS), using a Zetasizer Nano ZS (Malvern Instruments, Malvern, UK) and by laser diffractometry (LD), using a Mastersizer 2000E (Malvern Instruments, Malvern, UK). For zeta potential (ZP), the dispersions were diluted with purified water with an adjusted conductivity and ZP was accessed by laser Doppler electrophoresis (LDE) with a Zetasizer Nano ZS.

Preparation of hydrogels

PFC was dispersed in purified water. Subsequently, propylenoglycol and Germal was added to the aqueous solution, which was immediately neutralized, until pH 6,5, with triethanolamine. Hydrogels were then left equilibrating for 24 hours. Fresh drug-loaded SLN dispersions were incorporated into PFC hydrogels, using a high speed stirrer (Cito Unguator Konietzko, Bamberg, Germany) at 1000 rpm for 1 min., in a concentration of 40% (w/w) of the dispersion in the gel.

Rheological measurements

Comparative evaluations of shear rate versus shear stress of the hydrogels based SLN-placebo, SLN-drug loaded and placebo PFC, were evaluated in order to determine its rheological properties.

Rheological tests were performed on a rheometer RheoStress RS 100 (Haake, Karlruh, Germany) at 25 ± 1ºC. The rheological properties of the developed hydrogel containing SLN were studied by continuous shear investigations, which were performed in order to evaluate the shear rate [1/s] as a function of shear stress [Pa]. This study started with a shear rate of 0.1 1/s up to a maximum of 500 1/s, and the resulting shear stress was measured.

RESULTS AND DISCUSSION

The mean particle sizes and the ZP of SLN formulations were measured before the entrapment in the gel network (Table 1).

Table 1: Particle sizes (Z-ave), polydispersity index (PI) and ZP values of drug-free (DF) and drug-loaded (DL_1) formulations, measured on the production day.

	Z – ave (nm)	PI	ZP
DF	107.4±0.04	0.288±0.01	-34.3±0.06
DL_1	114.6±0.04	0.305±0.01	-32.3±0.07

From the results, we can see that were obtained SLN dispersions with sizes in the nanometer range and low PI values. Additionally, by LD analysis (data not shown), we confirmed that 90% of SLN were in the nanometer scale. The ZP results obtained for DF and DL_1 predict good storage stability. After admixing with hydrogel, LD analysis of particle sizes of DF and DL_1 hydrogel-based show that 90% of nanoparticles remain lower than 602 nm and 476 nm, respectively (data not shown).

Three different PFC hydrogel formulations were developed for the present investigation: placebo, SLN-DF and SLN-DL_1. In order to clarify the effect of the addition of SLN dispersions on the physicochemical properties of the prepared semi-solid formulations, rheological analysis of hydrogels were performed on day 1 and after 30 days of storage at room temperature (25ºC). Figures 1 and 2 depict the plots of the shear stress [Pa] as a function of shear rate [s^{-1}] of the hydrogels after the incorporation of DF and DL_1 SLN.

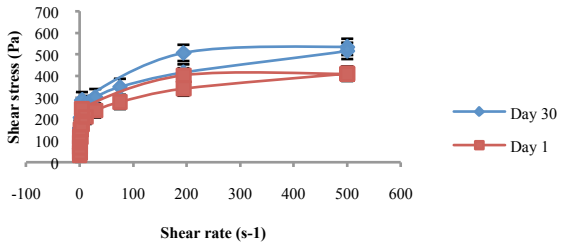

Figure 1: Shear stress as a function of the shear rate of PFC hydrogel with DF, measured on day 1 and after 30 days of storage at 25ºC.

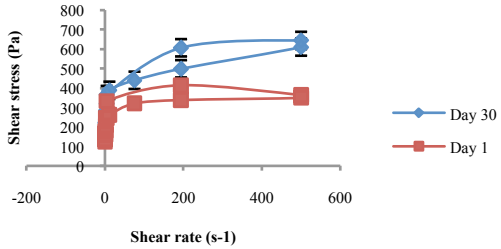

Figure 2: Shear stress as a function of the shear rate of PFC hydrogel with DL1, measured on day 1 and after 30 days of storage at 25ºC.

The flow curves of PFC hydrogel without nanoparticles showed a viscoelastic-like behaviour, i.e., when applying continuous shear tests from 0 to 500 [Pa] shear rate has been recorded revealing a characteristic shape of pseudoplastic flows (data not shown). After admixing DF and DL_1 dispersions to the hydrogel, a decrease in the shear stress values was observed, although the pseudoplastic characteristics remained (Figures 1 and 2). Thixotrophy was also observed after incorporation of the nanoparticles in the hydrogel, because the up and down curves did not overlap. Moreover, this phenomenon increases with storage time, which is probably due to the evaporation of water from the formulations. These results indicate that the developed hydrogel-based SLN formulations are promising systems for topical use on oral mucosa (Bernkop-Schnurch 2000; Silva 2009).

CONCLUSIONS

Lipid-based colloidal carriers have been successfully produced and a poorly soluble model drug has been incorporated within their matrix. A typical shear thinning behaviour has been observed in all developed semi-solid formulations, which is useful to predict their suitability for the development of oral formulations. These results indicate that the semi-solid formulations was shown to be a promising vehicle for improve the bioavailability of poor water-soluble drugs for oral mucosal delivery. Further in vitro studies should be performed, to assess the release profile of the drug from such formulations in simulated gastric conditions. Also the suitability of the hydrogels for oral mucosal drug delivery should be tested.

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