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Silica lipid composite microparticles as controlled release system

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There is still a need for new sustained release drug delivery systems with new functionalities. To overcome the lack of new raw materials for administration, strategy to combine existing and already approved ones is an interesting challenge. Among drug delivery systems, solid lipid microparticles (SLM) are made of solid fat core stabilized by surfactant that present the advantages to be stable, biodegradable, low toxic and to incorporate high charge of low water soluble drugs. Nevertheless, burst releases due to the presence of surfactant at their surface limit their use.

The present study aims to prepare new composite solid lipid microparticles (CSLM) by hot melt homogenization of a solid lipid, cetyl alcohol, at room temperature, in the presence of hydrophobic silica nanoparticles, Aerosil® R974, to replace the surfactant. Silica nanoparticles are dispersed in water in the same way as the preparation of pickering emulsions, instead of their addition in the melt lipid¹. We prepared unloaded CSLM or loaded with ibuprofen, a model drug to establish the role of hydrophobic silica nanoparticles on physical characteristics of microparticles, lipid and drug and on release after their incubation in PBS medium.

Materials & Methods

Materials: Cetyl alcohol, SIPOL C16 was from Henkel (Germany), hydrophobic colloidal silica, Aerosil® R974 from Degussa (Germany), ibuprofen from Global bulk drugs and fine chemicals limited (India).

Preparation of CSLM: Cetyl alcohol, heated to 65°C, above its melting temperature with or without ibuprofen (5-15% w/w of particle) was dispersed in an aqueous phase in a ratio 30: 1

(w/w) containing silica nanoparticles (0.1-0.5% w/v) at pH 9 and high ionic strength (NaCl 0.1M), using a turbine Ika Eurostar (IKA® Werke GmbH & Co. KG, Germany), with a 3-blade Teflon® propeller at 750 rpm. Microparticles were obtained by cooling the hot emulsion at 20°C after 1 hour mixing. They were separated by filtration, washed with distilled water before being freeze-dried.

Analysis of size and morphology of CSLM: Particle-size measurements were determined in aqueous dispersion using the laser Mastersizer 2000 (Malvern instruments Ltd, UK).

Scanning electron micrographs (SEM) of the microparticles were obtained using an S-4500 I (Hitachi, Japan) (voltage=10kV) after platinum metallization. Si composition was recorded on cross section of dried particles by using an EDX microprobe on a Cambridge Stereoscan 260 apparatus.

Differential scanning Calorimetry (DSC): The system used was a DSC Perkin-Elmer 7 apparatus (Perkin-Elmer, USA). Heating scan was 25 to 90°C at 5°C/min.

X-ray diffraction (XRD): A D8 Advance Bruker Theta Theta (Bruker, USA) was used; power-used at wide angles=40 kV and 40 mA.

Determination of silica loading: Thermo-gravimetric analysis was conducted on a Perkin Elmer STA 6000 apparatus (USA) under air flow (40 ml/min) and heating scan from 25 to 900°C at 5°C/min. % of silica was determined by the residual mass at 500°C.

Determination of ibuprofen loading:

Ibuprofen-loading was determined by UV spectroscopy (Spectrometer UV/Visible Lambda 35, Perkin Elmer, USA) at $\lambda = 222$ nm.

In vitro release studies: drug release from the particles was studied in phosphate buffer pH 7.4 at 37°C (USP XXVII) using USP/EP flow-through method (dissolutest CE1) at a constant ibuprofen concentration of 25 mg/l. The flow rate of dissolution medium through the cell was set at 8mL/min. Samples were analyzed

¹ Beatrice Albertini et al., "Effect of Aerosil® on the properties of lipid controlled release microparticles," *Journal of Controlled Release* 100, 2 (November 24, 2004): 233-246.

UV Spectro-photometrically (Spectrometer UV / Visible Lambda 35, Perkin Elmer, USA), at 222nm.

Results and discussion

Different formulations of composite solid lipid microparticles (CSLM), loaded or unloaded with ibuprofen were carried out by one pot emulsification without any surfactant. The freeze-dried CSLM are free flowing and relatively hard particles as compared with agglomerated and soft SLM. Their surface observed by SEM showed an irregular surface in the presence or absence of ibuprofen (figure 1a and b) as compared with SLM (not shown). EDX analysis specified that silica is dispersed on all the cross section of the particles (figure 1c and d). Focus on Si elements spots reveals agglomeration of silica nanoparticles inside the matrix of CSLM. This local agglomeration should be promoted by the presence of both basic pH and high ionic strength in aqueous phase.²

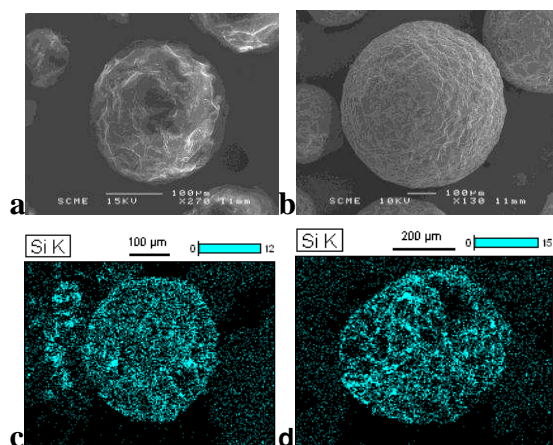


Figure 1: SEM micrographs of a) unloaded CSLM, 2.7% silica, b) ibuprofen-loaded CSLM 2.7% silica 4.5% ibuprofen. Si element mapping with EDX microprobe analysis coupled with SEM technique of microparticles cross section of c) unloaded CSLM, 2.7% silica and d) ibuprofen-loaded CSLM 2.7% silica, 4.5% ibuprofen (% correspond to experimental silica or ibuprofen loadings).

The mean diameters of unloaded CSLM vary from 154 to 767 μ m as a function of silica loading. On the contrary ibuprofen loaded CSLM are larger particles (for the same silica

loading) but less dependent on the ibuprofen charge (mean diameter around 450 μ m).

DSC thermograms principally reveal that amounts of ibuprofen in CSLM have a more important role in the amorphization of the lipid than silica has. Ibuprofen melting peak at 75°C disappears whatever ibuprofen loaded CSLM formulation while typical signals of ibuprofen were detected on X-ray diffraction patterns even at low drug charge. It suggests that a small fraction of ibuprofen is still in crystalline form inside microparticles (increasing with the charge of ibuprofen).

In our study the ibuprofen crystals were completely dissolved in 3 hours in the PBS (data not shown). Incorporation of ibuprofen in cetyl alcohol SLM decreased the dissolution rate of ibuprofen. In the same way the addition of silica reduces the kinetics of release of the drug as compared with silica free microparticles (figure 2) proportionately to the charge of silica. Hydrophobic silica should be implied in the disappearance of burst release and in the reduction of the diffusion of the drug inside lipid matrix.

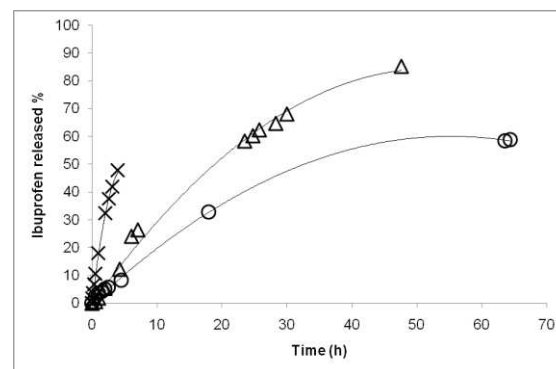


Figure 2: Kinetics of ibuprofen release from SLM and CSLM containing 12.8% Ibuprofen: X SLM, Δ CSLM 4% silica and ○ CSLM 8% silica

Conclusion

These data show that it was possible to prepare for the first time SLM without surfactant. Control the release of low water soluble drug encapsulated in these SLM has been obtained by the presence of few amounts of agglomerated hydrophobic silica nanoparticles present in the lipid matrix. Silica (amounts and its way of introduction in the primary emulsion) can be considered as a key parameter dominating release rate of drug in CSLM.

² Clive A. Prestidge et Spomenka Simovic, "Nanoparticle encapsulation of emulsion droplets," *International Journal of Pharmaceutics* 324, 1 (October 31, 2006): 92-100.