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International Journal of Pharmaceutics 325 (2006) 140–146
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Pharmaceutical Nanotechnology

Solid lipid nanoparticles incorporated in dextran hydrogels: A new drug delivery system for oral formulations

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Received 23 February 2006; received in revised form 5 June 2006; accepted 6 June 2006
Available online 10 June 2006

Abstract

Solid lipid nanoparticles (SLN) containing or not (*S*)-(+)-2-(4-isobutylphenyl)propionic acid (ibuprofen) were prepared with Preciol ATO 5 as lipid phase by the hot homogenization technique and characterized through particle size analyses and zeta potential measurements. DSC experiments carried out on the freeze-dried samples of loaded SLN showed a shift of the melting endotherm of the lipid phase, with the maximum at a temperature value higher then that of the"empty" SLN. ^{1}H NMR of the nanosuspension allowed to calculate the encapsulation efficiency of the particles that was $52 \pm 3\%$. By adding dextran methacrylate (DEX-MA) to the aqueous phase and submitting the mixture to UV irradiation, systems of SLN (drug-loaded and unloaded) incorporated into a dextran hydrogel were prepared. Finally, dissolution studies of ibuprofen from the freeze-dried samples were performed. The comparison among the release profiles of ibuprofen from SLN, DEX-MA hydrogel and SLN/DEX-MA-hydrogel allows to affirm that this last system, retaining about 60% of the drug after 2 h in acid medium and releasing it slowly in neutral solution, is suitable for modified delivery oral formulations.

Keywords: Solid lipid nanoparticles; Dextran methacrylate; Photochemical cross-linking reaction; Ibuprofen; Controlled release

1. Introduction

Hydrogels are polymeric networks which are able to adsorb and retain large amounts of water, maintaining intact their structure (Peppas et al., 2000). The principal methods to obtain the cross-links among the chains that avoid the dissolution of the hydrophilic polymers, have been recently revised (Henning and van Nostrum, 2002). Hydrogels deriving from biocompatible polymers find wide application in the biomedical field (Hoffman, 2002; Drury and Mooney, 2003) and in the pharmaceutical one as drug delivery systems (Gupta et al., 2002). The drug, physically entrapped into the network, is usually released with a rate strictly related to the characteristics of the hydrogel, in particular to its swelling degree. Previous studies carried out by our group (Pitarresi et al., 2003; Giannuzzo et al., 2006) have demonstrated that the functionalization of dextran with glycidyl methacrylate produces a derivative (DEX-MA) that can be easily crosslinked when submitted to UV irradiation of opportune wavelength. The hydrogels prepared in this way do not need purification processes, because DEX-MA is reactive enough to undergo photochemical reactions without any initiator or catalyst. These hydrogels have been employed as modified delivery systems for hydrophilic drugs, dissolving the drug into the polymer solution to be irradiated. In the case of drugs that are too lipophilic and cannot be added to the solution to be irradiated even adding a co-solvent, the soaking procedure is used. In this procedure the necessity to have, at the same time, a good swelling degree of the crosslinked polymer and a concentrated solution of the drug, restricts the available solvents to methanol and ethanol. Moreover, after the loading process, the solvents have to be completely removed by evaporation at reduced pressure and, in the case of methanol, GC analyses are necessary in order to verify the absence of such a toxic compound. The difficulty of loading lipophilic molecules into the hydrophilic networks represents a limitation to the use of these matrices.

On the contrary solid lipid nanoparticles (SLN) represent a colloidal carrier system for the controlled delivery of lipophilic drugs (Müller et al., 2000; Mehenert and Mäder, 2001). They

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doi:10.1016/j.ijpharm.2006.06.012

are composed of physiological lipids and for the low toxicity can find application not only in cosmetic and dermatological preparations (Müller et al., 2002) but even in parenteral and oral drug formulations (Almeida et al., 1997; Yang et al., 1999; Cavalli et al., 2000; Fundaro et al., 2000; Hu et al., 2004).

We have now planned to develop a new system which includes the advantages of these two approaches. At first we have prepared by the hot homogenization technique, SLN loaded or not with ibuprofen chosen as the model lipophilic drug. These systems were characterized through particle size analyses and zeta potential measurements. The influence of the process of sonication on the particle size distribution was also investigated. After freeze-drying, SLN were submitted to thermal analysis by differential scanning calorimetry in order to verify the incorporation of the drug into the lipid phase. The analysis of ^{1}H NMR spectra carried out on all the components of the preparation and on the nanosuspension allowed the determination, after addition of an internal standard, of the encapsulation efficiency achieved with the lipid particles. Then dextran methacrylate (DEX-MA) was added to the aqueous phase in order to allow the formation of hydrogels through UV irradiation. Finally the release profiles of the drug from the freeze-dried samples of SLN, DEX-MA hydrogel and of the new system, DEX-MA hydrogels containing SLN, were studied and discussed.

2. Materials and methods

2.1. Materials

All the used reagents were of analytical grade. Dextran (DEX) from *Leuconostoc* spp. (Mr 40,000), dimethylsulfoxide (DMSO), 4-dimethylaminopyridine (DMAP), cholic acid sodium salt, 2-hydroxyethyl methacrylate (HEMA), Sepharose 4B and ibuprofen, were purchased from Fluka (Switzerland). Glycidyl methacrylate (GMA) was from Sigma (USA), D_2O from Aldrich Chemical (USA), Pluronic F68 from BASF (Germany). Precirol ATO 5 (glyceryl palmito-stearate) was kindly provided as a gift by Gattefossè (France). Dialysis membrane (cut-off 12,000–14,000) was from Medicell International (UK).

2.2. Synthesis of dextran methacrylate (DEX-MA)

Dextran methacrylate was synthesized as already reported (Pitarresi et al., 2003). To a solution of dextran (5.0 g) in DMSO (40 mL), DMAP (1.0 g) and GMA (0.73 g, 1 mol/6 mol of repetitive units) were added. The solution was maintained 24 h under stirring at room temperature, and then added drop wise to EtOH (200 mL). The precipitate was filtered and dissolved in water (15 mL). The solution, having pH about 10, was adjusted to pH 8 with 0.1 M HCl, introduced into the dialysis membrane and submitted to exhaustive dialysis against distilled water. The process was stopped when the conductivity of the dialysis medium had the same value of the starting distilled water. The solution was freeze-dried employing a LIO 5P freeze-dryer (5 Pascal, Italy) equipped with a vacuum pump RV12 (Edwards, England). After freeze-drying, the polymer was characterized by FT-IR and ^{1}H NMR. FT-IR spectra were recorded with a Perkin-Elmer Paragon 1000 spectrophotometer (USA) in the range 4000–400 cm^{-1} using KBr pellets (resolution of 1 cm^{-1}). ^{1}H NMR spectra were obtained with a Bruker AC-400 instrument (Germany). The degree of derivatization (number of methacrylic groups every 100 repetitive units, DD), calculated on the basis of the ^{1}H NMR spectrum as reported in the literature (Van Dijk-Wolthuis et al., 1997), was 24 ± 1.

2.3. Preparation of solid lipid nanoparticles (SLN)

Solid lipid nanoparticles were prepared with the hot homogenization technique (Ahlin et al., 1998). To the lipid phase (Precirol ATO 5, 10.0 g) heated at 70 °C the aqueous solution (90 ml) of the surfactants (sodium cholate, 1.0 g and Pluronic F68, 2.5 g), heated at the same temperature, was added (Radtke and Müller, 2000). The mixture was stirred with a T45 Ultra-Turrax (IKA-WERK, Germany) for 10 min at 10,000 rpm. The emulsion was separated into two aliquots, one of which was submitted to probe sonication (V.C.X. 400 Sonics, 400 W, 20 Hz, USA) for 20 min at 70 °C. These samples were indicated as SLN (sonicated or not).

By adding ibuprofen (400 mg) to the lipidic phase and following the previously described procedure, SLN_I samples (sonicated or not) were obtained. The addition of DEX-MA (2.5 g) to the aqueous phase following the same procedure yielded samples SLN_D (sonicated or not).

Finally by adding ibuprofen (400 mg) to the lipid phase and DEX-MA (2.5 g) to the aqueous one samples SLN_{ID} (sonicated or not) were prepared.

2.4. Particle size analysis and zeta potential measurements

The particle size analysis of all SLN samples was performed by photon correlation spectroscopy (PCS), within 1 week from the preparation. The PCS analysis yielded the mean diameter of the particles (*Z*-average) and the polydispersity index (PDI) as a measure of the width of the particle size distribution. The samples were diluted with twice distilled water to reach a suitable concentration and analyzed with a Malvern Zetasizer nano ZS90 (Malvern Instruments, UK). The surface charge of all the samples was determined by measurements of the zeta potential carried out with the same instrument.

2.5. Differential scanning calorimetry (DSC) measurements

DSC measurements were carried out with SETARAM DSC 131 (France), equipped with SETSOFT 2000. The samples were quickly frozen in liquid nitrogen and freeze-dried at room temperature and pressure of 0.4–0.5 Hgmm. All freeze-dried samples were left under vacuum on P_2O_5 for 3 days before the DSC investigation was carried out, in order to ensure the complete elimination of the moisture. Ten milligrams of each sample were sealed in a DSC aluminium pan (30 μl) and submitted to calorimetric analysis at scan rate of 10 °C/min in the temperature range 15–90 °C.

2.6. Preparation of DEX-MA hydrogels

The hydrogels were prepared for UV irradiation performed with a Helios Italquartz Photochemical Multirays Reactor (Italy) equipped with ten 14 W medium pressure mercury lamps ($\lambda_{maximum}$: 310 nm). The photo-crosslinking reaction was carried out under nitrogen, on each sample of SLN containing DEX-MA, in quartz tubes of 1 cm diameter, with an irradiation time of 4 h. In order to obtain DEX-MA hydrogels without SLN inside, 3% w/v DEX-MA in water was submitted to UV irradiation for 4 h. In order to obtain a sample of the hydrogel loaded with ibuprofen, a solution of 3% DEX-MA and ibuprofen (80 mg) in H_2O/EtOH (5:5 v/v, 17 ml) was submitted to irradiation for 4 h. All the hydrogels were freeze-dried without purification.

In order to evaluate the stability of ibuprofen in the conditions employed in the hydrogels preparation, samples of the drug (16 mg) in H_2O/EtOH (5:5 v/v, 3.4 ml) were submitted to UV irradiation for 4 h. HPLC analyses of the solutions and FT-IR of the solid, recovered after freeze-drying, showed the stability of the drug under photocrosslinking conditions.

2.7. Scanning electron microscopy (SEM)

A freeze-dried sample of dextran methacrylate hydrogel containing SLN was mounted onto an aluminium stud and sputter-coated with gold employing an Emitech-K Sputter Coater in order to make it conducting. The sample was submitted to SEM analysis using the scanning electron microscope Philips XL 30 (The Netherlands). An acceleration voltage of 15.0 kV was employed.

2.8. Determination of the amount of loaded drug

In order to verify the total amount of drug present in the system, 200 mg of each freeze-dried SNL_{ID} sample were extensively extracted with EtOH (5×10 ml) at 70 °C. The liquids of extraction were collected and evaporated at reduced pressure. The obtained residue was dissolved in a precise volume of EtOH; the amount of ibuprofen was detected by HPLC analysis, monitoring the drug at 215 nm. HPLC apparatus consisted of a Perkin-Elmer Series 200 LC pump, equipped with a 235 Diode Array (USA). The analyses were carried out using a Merck Hibar LiChrocart (250–4, 5 μm) RP-18 column, CH_3CN/H_3PO_4 10^{-2} M mixture (7:3) as eluant (flow 1 ml/min). In all cases the total amount of the extracted drug was equal to that measured at the end of the dissolution tests.

The amount of unloaded drug was determined by ^{1}H NMR analysis. The spectrum was recorded on samples of the suspension (100 mg) diluted with 3.1 mM HEMA in D_2O (0.7 ml) just before the experiment. The addition of the internal standard allowed the determination of the un-encapsulated drug as ratio of the integral of the aromatic signals of ibuprofen (7.3–7.1 ppm) and that of one of the vinyl protons of HEMA (6.1 ppm). At the pH of the suspension (7.2) the solubility of ibuprofen is > 10 mg/ml (Brittain, 2001), value that is much higher than the total amount of drug contained in the sample (0.5 mg/ml after dilution).

In order to confirm the results of entrapment efficiency obtained by ^{1}H NMR, an exactly weighted sample of SLN_I was quickly passed through a column of Sepharose 4B employing distilled water as eluant. The elute, that contained the loaded SLN, was freeze-dried and the residue was extracted with ethanol and analyzed as described before. The experiment, carried out in triplicate, gave an entrapment efficiency of $42 \pm 5\%$.

2.9. Release studies of ibuprofen from SLN, DEX-MA hydrogel and hydrogel of DEX- MA containing SLN

Aliquots (200 mg) of the freeze-dried powder were employed for the release studies carried out in 0.1 M HCl solution for 2 h (simulated gastric transit) and in phosphate buffer solution (Na_2HPO_4, KH_2PO_4, pH 7.4, simulated intestinal fluid, SIF) for further 6 h. Dissolution experiments were carried out with the rotating basket technique at 37.0 ± 0.1 °C and 100 rpm according to U.S.P. XXIV. The apparatus was a SOTAX AT7 Smart (Switzerland). Drug release was followed by means of HPLC analysis, according to the previously described procedure. The experiments were carried out in triplicate and the results agreed with each other within 5% of standard error.

2.10. Swelling studies

Swelling ability of DEX-MA hydrogels containing or not SLN was determined at 37 ± 0.5 °C in 0.1N HCl solution and in phosphate buffer (pH 7.4). Precisely weighed aliquots were placed in tarred 5 ml sintered glass filters (Ø 10 mm; porosity, G3) and left to swell at 37 ± 0.1 °C by immersing the filters in the swelling media. After 24 h, the liquid in excess was removed by percolation at atmospheric pressure. The filter was placed in a properly sized centrifuge test tube, centrifuged at 3000 rpm for 5 min and weighed. The filter tare was determined after centrifugation with the same swelling medium alone. The swelling ratio (q) was calculated as:

$$q = \frac{W_s}{W_d}$$

where W_s and W_d are the weights of the swollen and dry hydrogels, respectively.

Each experiment was carried out in triplicate and the results were reported as mean ± S.D.

3. Results and discussion

We have planned to prepare DEX-MA hydrogels loaded with solid lipid nanoparticles, containing or not the drug, according to the procedure schematized in Fig. 1.

The model lipophilic drug (ibuprofen) is dissolved into the melted lipid phase. After addition of DEX-MA to the aqueous phase, the homogenization of the system gives rise to a nanoemulsion that, submitted or not to the sonication process, is left to cool down to room temperature. UV irradiation of the sus-

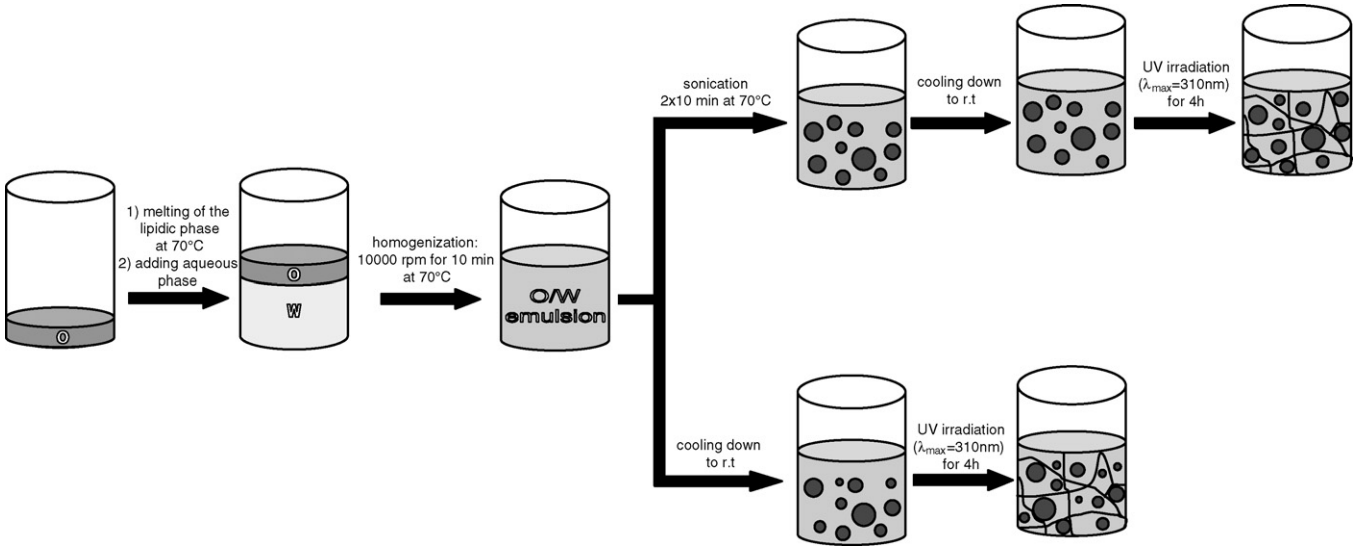

Fig. 1. Schematization of the preparation process of loaded SLN entrapped into DEX-MA hydrogel.

pension should yield the dextran hydrogel having loaded SLN into its meshes.

3.1. Preparation of SLN

The starting point of our research was the preparation and characterization of SLN according to a standard procedure reported in the literature (Ahlin et al., 1998). We used Precirol AT0 5 as lipid phase and a mixture of Pluronic and sodium chlorate as surfactants (Radtke and Müller, 2000). It is known that the employ of two surfactants, respectively of hydrophilic and lipophilic nature, yields a better stabilization of the disperse system. The homogenization was carried out at 70 °C, a temperature that assured the complete melting of the lipid phase. After homogenization, the emulsion was divided into two aliquots and one of them was submitted to sonication; these samples were indicated as SLN (sonicated or not). The addition of ibuprofen, chosen as model lipophilic drug, to the lipid phase allowed us to obtain SLN_I samples (sonicated or not) with the above described procedure. The addition of DEX-MA to the aqueous phase before the homogenization yielded SLN_D samples (sonicated or not). When ibuprofen and DEX-MA were added to the lipidic and aqueous phase respectively, samples of SLN_{ID} (sonicated or not) were obtained.

3.2. Characterization of SLN

All the prepared samples were analyzed in order to determine their particle size distributions and zeta potential values. The results obtained after particle size analysis are shown in Fig. 2.

It is evident that sonication does not produce particle populations having smaller mean diameters. For an easier comparison, the values of the mean diameter and of the polydispersity index (PDI) for all the samples are reported in Table 1.

The effect on the PDI is not univocal whereas the particle mean diameter values increase in the sonicated samples with respect to the non-sonicated ones. It is likely that the sonication produces the coalescence of the particles, that are in liquid phase at the working temperature, and the formation of a new population of particles. For these reasons the sonication process does not seem to play a positive role in the preparation of SLN. In order to exclude the presence of particles having mean diameter bigger than that measurable with this technique, a precisely weighed amount of SLN was passed through a filter of porosity 0.8 μm. This latter, after complete evaporation of the water was weighed showing that less than 5% of the SLN remained on the filter. In this way it was possible to exclude the presence of a

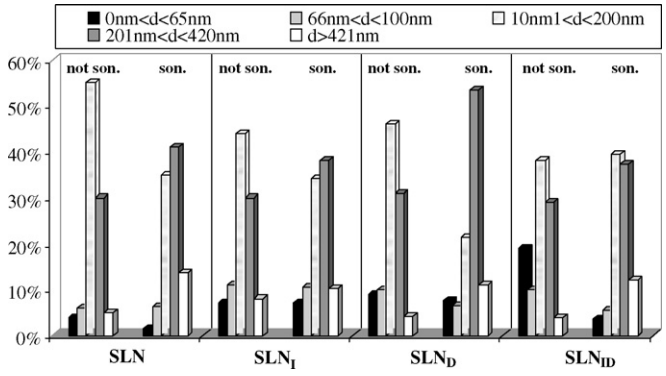

Fig. 2. Particle size distribution of the four samples of SLN submitted or not to the sonication process (*d* is the particles diameter in nanometers).

Table 1
Mean diameter (*Z*-average) and polydispersion index (PDI) of SLN samples submitted or not to sonication process

	Z-average (nm)		PDI	
Sample	Sonicated	Non-sonicated	Sonicated	Non-sonicated
SLN	184 ± 4	141 ± 3	0.286 ± 0.030	0.261 ± 0.013
SLN_I	131 ± 2	118 ± 1	0.267 ± 0.005	0.282 ± 0.024
SLN_D	192 ± 7	138 ± 7	0.253 ± 0.019	0.262 ± 0.009
SLN_{ID}	173 ± 4	117 ± 5	0.270 ± 0.022	0.283 ± 0.032

Values are means ± S.D., $n = 3$.

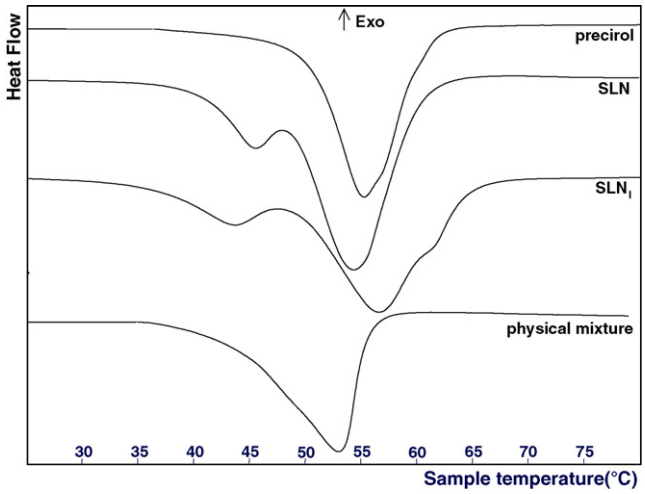

Fig. 3. DSC thermograms of precirol, SLN, SLN_I and of the physical mixture precirol–ibuprofen.

high percentage of particles in the dimensional range out of the instrument limits.

The results of the zeta potential measurements are reported in Table 2.

The surface charge of the different samples of SLN is always negative and the values are high enough to assure a good stability of the nanosuspension.

DSC experiments suggested that interactions between drug and lipid particles occurred. The thermograms of precirol, SLN and SLN_I samples and that of the physical mixture precirol–ibuprofen are reported in Fig. 3. For a better observation they have been displaced along the ordinate.

The melting point of pure precirol is 55.2 °C. When it is employed for the preparation of SLN, this value decreases to 54.0 °C, probably for the presence of the surfactants. As reported in the literature (Hamdani et al., 2003) the peak at 46.1 °C is due to a polymorphic form of the lipid phase, that can be detected on freshly solidified samples. In the sample of SLN containing ibuprofen (SLN_I), the melting point rises till 58.1 °C showing that an interaction between lipid phase and drug (melting point 75.6 °C) has taken place and that this latter is at least in part loaded into the particles. This behaviour is already described in the literature for similar systems (Zimmermann et al., 2005). In confirmation of this hypothesis, the physical mixture precirol–ibuprofen shows an endothermic peak at 52.9 °C. DSC experiments on SLN_{ID} and SLN_D samples were also carried out. In the thermograms a large and broad peak is present that covers all the other ones, probably due to the water bonded to the polymeric material. In fact this peak is absent in the second scan performed on SLN_D after cooling it from 180 °C to room temperature that is equal to the SLN one. Moreover it was impossible to carry out a second scan on the samples containing ibuprofen because the drug decomposes, probably for loss of carbon dioxide, and the profile of the thermogram changes completely.

Table 2
Zeta potential values

Sample	Zeta potential (mV)
Ibuprofen	−61.1 ± 0.4
SLN	−27.9 ± 1.0
SLN_D	−26.0 ± 0.8
SLN_I	−21.1 ± 0.5
SLN_{ID}	−21.9 ± 0.7

Values are means ± S.D.; $n = 3$.

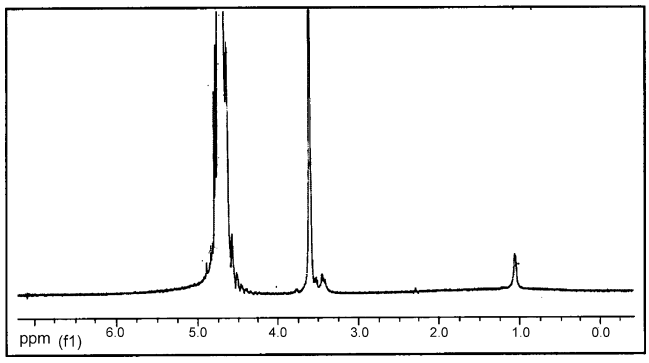

Fig. 4. ^{1}H NMR spectrum of a sample of SLN in D_2O.

3.3. Determination of the amount of unloaded drug

The analyses of ^{1}H NMR spectra allow to obtain further information regarding the system. In Fig. 4 the spectrum of a sample of unloaded SLN is reported.

The signals above 4 ppm are masked by the huge water signal with a maximum around 4.7 ppm. The other signals are due to the protons of Pluronic, the hydrophilic surfactant employed to stabilize the preparation. In particular the signals in the range 3.6–3.4 ppm are due to CH_2O and CHO protons whereas that at 1.05 ppm is relative to the methyl groups of the polaxamer. The signals of both sodium cholate and lipid phase are totally absent. These data agree with the hypothesis that the surfactant has the lipophilic portion inside the colloidal particles and that they are almost completely in the solid state (Zimmermann et al., 2005; Jenning et al., 2000). The spectrum of a sample of SLN_D diluted in D_2O containing HEMA as internal standard is reported in Fig. 5.

The signals of ibuprofen and HEMA are well visible, together with the SLN ones described before. In particular the signals at 0.9 (6H, $2CH_3$), 1.5 (3H, CH_3), 1.8 (1H, CH), 2.4 (2H, CH_2) and 7.3–7.1 ppm (4H, aromatic) are due to the drug, whereas those at 1.9 (3H, CH_3), 3.8 (2H, CH_2). 4.2 (2H, CH_2), 5.7 and

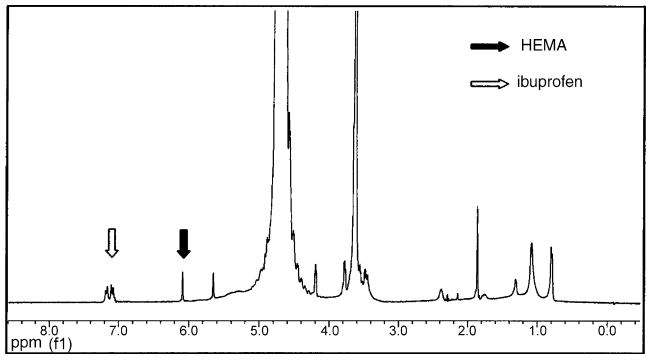

Fig. 5. ^{1}H NMR spectrum of the mixture SLN_I and HEMA in D_2O.

6.1 ppm (2H, CH_2=) are related to HEMA. The ratio between the integral of the signals at 7.3–7.1 ppm (indicated with the white arrow) and that at 6.1 ppm (bold arrow), known the weight of the added standard, allowed to determine the amount of ibuprofen in the aqueous phase. The encapsulation efficiency (EE) was calculated as:

$$EE = \frac{W_I - W_{NMR}}{W_I} \times 100$$

where W_I is the amount of ibuprofen in the sample and W_{NMR} s that calculated by ^{1}H NMR. This procedure gave for SLN_I samples an EE = 52 ± 3%. The solubility of ibuprofen at the pH value of the nanosuspension (7.2) is >10 mg/ml, moreover the total amount of ibuprofen containing in the SLN dispersion after dilution with D_2O is 0.5 mg/ml. These data support the hypothesis that the drug unloaded into the SLN is dissolved in water. The validity of the procedure was confirmed by comparison with a chromatographic method. (Section 2.8). The value obtained with both methods is probably a little bit smaller than the exact one, because the dilution of the samples alters the pre-existent equilibrium of the drug partition between lipidic and aqueous phase. The low value of EE suggests that the crystallization of the lipid phase produces a partial expulsion of the drug on the particle surface. The same analyses carried out on samples of SLN_I submitted to sonication, gave a value of EE of 40 ± 3%. It is probably that the sonication promotes the migration of the drug on the surface of the particles. It is also for this reason that all further studies were performed on the non-sonicated samples.

3.4. Synthesis of the hydrogel having SLN inside the network

Samples of SLN_{ID} were submitted to UV irradiation according to the procedure described in Section 2.6. Fig. 6 reports SEM micrograph of the freeze-dried hydrogel where a porous surface is evident.

Similar photographs of DEX-MA hydrogels are already reported in the literature (Kim and Chu, 2000). The formation of the hydrogel was confirmed by FT-IR experiments carried out on the freeze-dried samples after removal of lipid phase and ibuprofen by extraction with chloroform. The spectra were equal to those of DEX-MA hydrogels already described (Pitarresi et al., 2003).

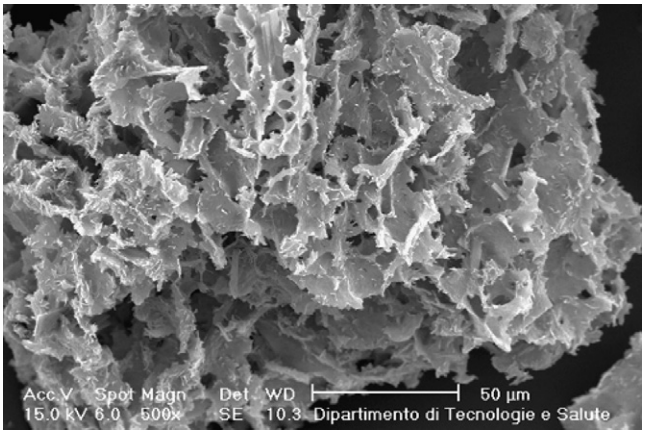

Fig. 6. SEM photograph of the outside surface of DEX-MA hydrogel having SLN into the network.

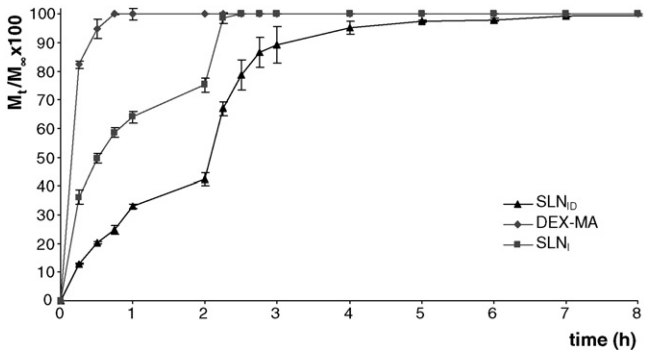

Fig. 7. Release profiles [$(M_t/M_\infty) \times 100$] of ibuprofen from DEX-MA hydrogels, SLN and SLN entrapped into DEX-MA hydrogel, maintained at 37.0 ± 0.1 °C in HCl solution (pH 1.0) for 2 h and in phosphate buffer solution (pH 7.4) for further 6 h.

3.5. Drug release studies

The release profiles of ibuprofen from freeze-dried samples of DEX-MA hydrogel, SLN and SLN-hydrogel are reported in Fig. 7.

The release of ibuprofen from DEX-MA hydrogel is complete in 1 h of permanence in HCl solution, showing that the network is very loose and thus unable to retain the drug into its meshes. The release from the sample of SLN is slower: about 25% of the drug is still entrapped into the lipid phase after 2 h in acid medium (simulating the transit through the stomach). An initial burst effect is evident and it can be probably ascribed to the presence of the unloaded drug. In the system SLN-hydrogel, almost 60% of ibuprofen is retained after 2 h of permanence in HCl solution and the release of the drug is quantitative only after further 6 h in neutral solution. The system represents a significant improvement with respect to the previous ones, also because the burst effect is much less evident in this case.

As in principle the release of a drug from polymeric matrices is related to their swelling degree, swelling experiments were performed on freeze-dried samples of DEX-MA hydrogel having or not SLN inside the network. The results are reported in Table 3.

The swelling degree in different media of DEX-MA hydrogels follows the trend $q_{water} > q_{pH\ 7.4} > q_{NaCl} > q_{HCl}$ already reported for hydrogels deriving from neutral polymers (Pitarresi et al., 2003), but there are differences between the systems containing or not SLN. Conditions being equal, the hydrogel containing SLN shows q values smaller than those of the "empty" hydrogel. This behaviour can be related to the lipophilic nature of the particles that prevents the entrance of the aqueous medium. The slow release of the drug can be due to the poor swelling of the matrix that does not allow the drug diffusion. Therefore the obtained results represent a remarkable improvement with respect to the two separately employed approaches (DEX-MA hydrogel and SLN). It is possible to underline other advantages of this new system. The presence of the hydrogel

Table 3
Swelling degree (q, expressed as W_s/W_d) after 24 h of permanence in different media of the freeze-dried hydrogels obtained after 4 h of irradiation of 3% (w/v) DEX-MA solution and of SLN_{ID}

Sample	q (pH 1.0)	q (water)	q (pH 7.4)	q (0.1 M NaCl)
DEX-MA hydrogel	12.3 ± 0.5	20.1 ± 0.5	16.5 ± 0.5	15.1 ± 0.3
DEX-MA hydrogel with SLN	7.1 ± 0.4	8.6 ± 0.4	7.9 ± 0.1	8.1 ± 0.1

Values are means ± S.D.; $n = 3$.

increases the stability of the preparation that does not present the problems characteristic of nanosuspensions. The freeze-drying process can be carried out without particular devices, such as cry protectors or other. Finally the residue obtained after the freeze-drying, is an easy to manipulate powder, identical to DEX-MA hydrogels, that can be employed for the preparation of oral formulations, such as tablets and capsules. In the literature the use of hydrogels to stabilize SLN is restricted to topical formulations (Souto et al., 2004; Uner et al., 2005), whereas our system is much more versatile. SLN entrapped into DEX-MA hydrogels seem to be particularly useful for loading lipophilic drugs, that can be released in a sustained way, and are suitable for topical as well as for oral formulations.

4. Conclusions

We have prepared and characterized SLN with and without a model lipophilic drug (ibuprofen) loaded inside. The amount of unloaded drug was determined by ^{1}H NMR analyses. The addition of dextran functionalized with methacrylic groups (DEX-MA) to the aqueous phase, yielded after UV irradiation a hydrogel having SLN loaded with the lipophilic drug into the network. The analysis of the dissolution profiles of ibuprofen carried out on the freeze-dried samples in conditions simulating the gastrointestinal tract, allows to affirm that the system SLN-hydrogel is suitable for the preparation of oral formulations for the modified release of lipophilic drugs.

Acknowledgements

This work was carried out with the financial support of MIUR. The authors wish to thank Dr. Luigi Paoletti of Istituto Superiore di Sanità of Rome for SEM photographs.

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