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Nanocapsule@xerogel microparticles containing sodium diclofenac: A new strategy to control the release of drugs

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ABSTRACT

The aim of this work was to evaluate the potentiality to control the drug release of a new architecture of microparticles organized at the nanoscopic scale by assembling polymeric nanocapsules at the surface of drug-loaded xerogels. Xerogel was prepared by sol–gel method using sodium diclofenac, as hydrophilic drug model, and coated by spray-drying. After coating, the surface areas decreased from 82 to 28 m^2/g, the encapsulation efficiency was 71% and SEM analysis showed irregular microparticles coated by the nanocapsules. Formulation showed satisfactory gastro-resistance presenting drug release lower than 3% (60 min) in acid medium. In water, the pure drug dissolved 92% after 5 min, uncoated drug-loaded xerogel released 60% and nanocapsule coated drug-loaded xerogel 36%. After 60 min, uncoated drug-loaded xerogel released 82% and nanocapsule coated drug-loaded xerogel 62%. In conclusion, the new system was able to control the release of the hydrophilic drug model.

Microparticles have been extensively studied in the past 30 years. Their advantages, among others, are: ready distribution, higher bioavailability and accuracy in reproducibility dose by dose, more constant drug plasma levels, minor risk of toxicity due to the dose dumping, gastrointestinal tract protection and labile drug protection in the gastrointestinal tract (Benita, 1996). To prepare microparticles, the spray-drying technique exhibits advantages such as rapid and one step process, low cost and ease of industrial transposition (Wan et al., 1992).

Nanoparticles have also been widely studied as drug carriers (Couvreur et al., 2002). Their main advantages are drug sustained release, increase of drug selectivity and effectiveness, improvement of drug bioavailability and decrease of drug toxicity. Polymeric nanoparticles are named nanocapsules, when they contain a polymeric wall and an oil core (Jäger et al., 2007), or nanospheres, when they are formed by polymeric matrix stabilized by surfactants (Pohlmann et al., 2007). The spray-drying technique has been employed to dry nanoparticles improving their physico-chemical stability (Guterres et al., 2000). Powders have been obtained using Aerosil 200®, as drying adjuvant (Guterres et al., 2001) (Fig. 1a).

The spray-drying technique has also been used to prepare organic–inorganic systems, in which the drug was dispersed in agglomerates of Aerosil 200®, the inorganic phase, and the polymeric nanoparticles were used as coating material (Beck et al., 2004) (Fig. 1b). The Aerosil 200® is an agglomerate of non-porous primary silica particles about 40 nm. So, the drug is entrapped in the silica macropores.

Drug-loaded porous silica microparticles have been synthesized by sol–gel method (Unger et al., 1983), which is based on the catalyzed hydrolysis and condensation of alkoxysilanes giving a cross-linked network (Novak, 1993). The sol–gel method forms an inorganic matrix (xerogel silica) under soft conditions and low temperature allowing the incorporation of labile molecules in the gel (Santos et al., 1999). Two methods for drug incorporation in the xerogel have been used: drug incubation (Ahola et al., 1999) and the drug *in situ* incorporation (Kortesuo et al., 2000).

The use of xerogels instead of Aerosil 200® to encapsulate drugs could have the advantage of delaying the drug release because the drug is also encapsulated in the mesoporous besides its encapsulation in the xerogel macropores. To diminish the burst release of drugs from xerogel mesopores, different strategies have been proposed (Slowing et al., 2007). Our strategy to avoid a high burst release is based on the use of polymeric nanocapsules as coating material for the agglomerates of drug-loaded xerogel. This complex architecture (Fig. 1c) considers that the polymeric nanocapsules are hydrophobic and, as a consequence, they could retard the contact of the microparticles with water (continuous phase), avoiding a burst and delaying the drug release.

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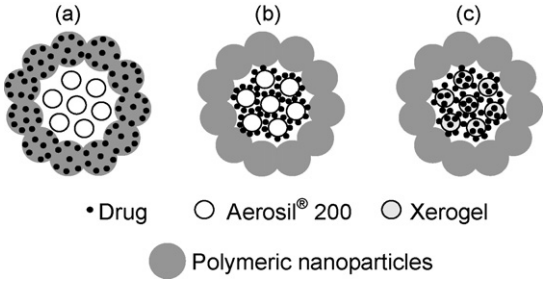

Fig. 1. Illustrative representation of the architecture of different microparticles obtained by sequential assembly of silica and polymeric nanoparticles: (a) the drug is encapsulated in the polymeric nanoparticles; (b) the drug is adsorbed on the Aerosil® 200 macropores; (c) the drug is adsorbed on mesopores and macropores of the xerogel.

In this way, the aim of this study was to evaluate the nanocapsule-coated xerogel microparticles, a new drug delivery system. Despite this new system can be designed to deliver lipophilic or hydrophilic drugs, sodium diclofenac (a water soluble salt) was used as hydrophilic drug model.

The drug-loaded xerogel was prepared using pre-optimized reactional conditions (Arenas et al., 2006). NaF (40 mg) aqueous solution (1.6 mL) was added into a solution of tetraethylorthosilicate (TEOS) (5 mL), sodium diclofenac (50 mg) in ethanol (10 mL). The mixture was stored for gelation and solvent evaporation within 10 days at room temperature. Then, the sample (Xerogel core-DicONa) was separately milled using a mortar and pestle for 10 min. Placebo sample was prepared omitting the drug (Xerogel core-Placebo).

Polymeric nanocapsules (NC) were prepared by dissolving Eudragit S100® (EUD) (1.0 g), capric/caprylic triglyceride (3.0 mL), Span 60® (0.385 g) in acetone (250 mL). This solution was poured into an aqueous phase (530 mL) containing Tween 80® (0.385 g). The acetone was eliminated and the suspension concentrated to a final volume of 100 mL. Nanocapsule suspensions ($n = 3$) had pH of 4.0 ± 0.3 (Micronal, B-474, Brazil), mean diameter (angle 90°) of 260 ± 2 nm and polydispersity lower than 0.3 (Goniometer BI-200M/2.0 version, Brookheaven Instruments, Holtsville, USA; BI9863 detection system; Laser He–Ne source 35 mW, 127 model, $\lambda = 632.8$ nm, Spectra Physics View, USA).

For coating, the drug-loaded xerogel (3.0 g) was dispersed in the nanocapsule suspension (100 mL) using triacetin (NC@xerogel) and fed into a mini-spray-dryer MSD 1.0 (Lab Maq, Brazil) (feeding rate of 0.2 L h^{-1}, air flow rate of 500 N L h^{-1}, atomizing air pressure of 200 kPa, inlet and outlet temperatures of 150 ± 1 and 95 ± 2 °C and nozzle diameter of 1.0 mm). To compare the release behavior of architectures 1b and 1c (Fig. 1), a sample containing Aerosil 200® was also prepared (NC@Aerosil). Drug unloaded formulations were prepared using xerogel or Aerosil 200® to be references for the quantitative analyses by UV spectroscopy (NC@xerogel-Placebo and NC@Aerosil-Placebo).

The mean diameter over the volume distribution ($d_{4,3}$) and particle size distribution (span) (Eq. (1)) were determined by laser diffractometry (Mastersizer 2000, Malvern Instruments, UK).

$$\text{SPAN} = \frac{d_{0.9} - d_{0.1}}{d_{0.5}} \quad (1)$$

where $d_{0.9}$, $d_{0.1}$ and $d_{0.5}$ are the particle diameters determined at the 90th, 10th and 50th percentile of the undersized particle distribution curve. The particle sizes ranged from 26 to 48 μm presenting span values between 2.8 and 4.6 (Table 1).

The specific surface areas were determined by the classical Brunauer–Emmett–Teller multipoint technique on a volumetric apparatus using nitrogen as probe. The samples were previously degassed for 1 h under vacuum (Edwards *1.5 EXC 120, UK) at 40 °C. Measurements were made using a capillary Hg barometer and an active Pirani gauge. Alumina was used as standard. After coating, the surface areas decreased from 134 to 35 m^2/g (Placebo) and from 82 to 28 m^2/g (Drug-loaded) (Table 1).

Microscopy analyses were carried out (Olympus BX41TF, Japan) to observe the samples (30×) using normal and polarized light. For SEM analysis, samples have been gold and carbon sputtered (JEOL Jee 4B SVG-IN, Japan). NC@xerogel observed by optical microscopy did not show any crystal under polarized light (air, oil or water). SEM analysis (JEOL, JSM-5800, Japan) (Centro de Microscopia Eletrônica—UFRGS) (1000×) showed irregular microparticles with rugged surfaces. The surface of the NC@xerogel-Placebo and NC@xerogel (30,000×) are coated with nanocapsules, which mean diameter is 365 ± 124 nm (Fig. 2).

To determine the drug content and encapsulation efficiency, an exact amount of powder was added in phosphate buffer pH 7.4. Samples were withdrawn at 1, 3 and 24 h, filtered (0.45 μm, Millipore®) and quantified by UV spectroscopy (UV-1601 PC, Shimadzu, Japan) at 280 nm. Linear calibration curves for sodium diclofenac were obtained in the range of 5.00–50.00 μg mL^{-1} ($R^2 > 0.9998$). Inter- and intraday variability (5.00, 30.00 and 50.00 μg mL^{-1}) did not exceed 3.6% and accuracy was $103.4 \pm 1.0\%$ (10 μg mL^{-1}), $97.5 \pm 1.0\%$ (30 μg mL^{-1}) and $101.6 \pm 1.0\%$ (50 μg mL^{-1}). The calculated limit of quantification was 0.2807 μg mL^{-1}. The drug concentration after 1, 3 and 24 h were not significantly different ($p < 0.05$) indicating that the equilibrium of extraction was reached. So, the drug content for NC@xerogel was 9.0 ± 0.4 mg/g. Before and after coating, the powders showed encapsulation efficiencies of $75 \pm 3\%$ and $71 \pm 3\%$, respectively. Previous works have demonstrated that xerogels synthesized under similar conditions in the presence of organic substances showed occlusive pores (Pavan et al., 2002) in which 27 to 41% of the substance was retained. Our results suggest that sodium diclofenac was retained in part in the xerogel occlusive pores.

The drug release from formulations was determined by dispersing an exact amount of the samples (equivalent to 3 mg of drug) in simulated gastric fluid (pH 1.2) or deionized water (pH

Table 1
Microparticles sizes, span and surface area for the samples: Xerogel core-Placebo and Xerogel core-DicONa (before coating) and NC@xerogel-Placebo and NC@xerogel (after coating)

Diameter (μm)						
Samples	D_{10}	D_{50}	D_{90}	$D_{[4,3]}$	Span	Surface area (m^2/g)
Xerogel core-Placebo	7	26	125	48	4.6	134 (0.99)[a]
NC@xerogel-Placebo	6	19	63	29	2.9	35 (0.99)
Xerogel core-DicONa	6	16	52	26	2.8	82 (0.96)
NC@xerogel	7	17	63	29	3.2	28 (0.98)

[a] Values in parentheses correspond to the respective correlation coefficients of the curves calculated using BET method.

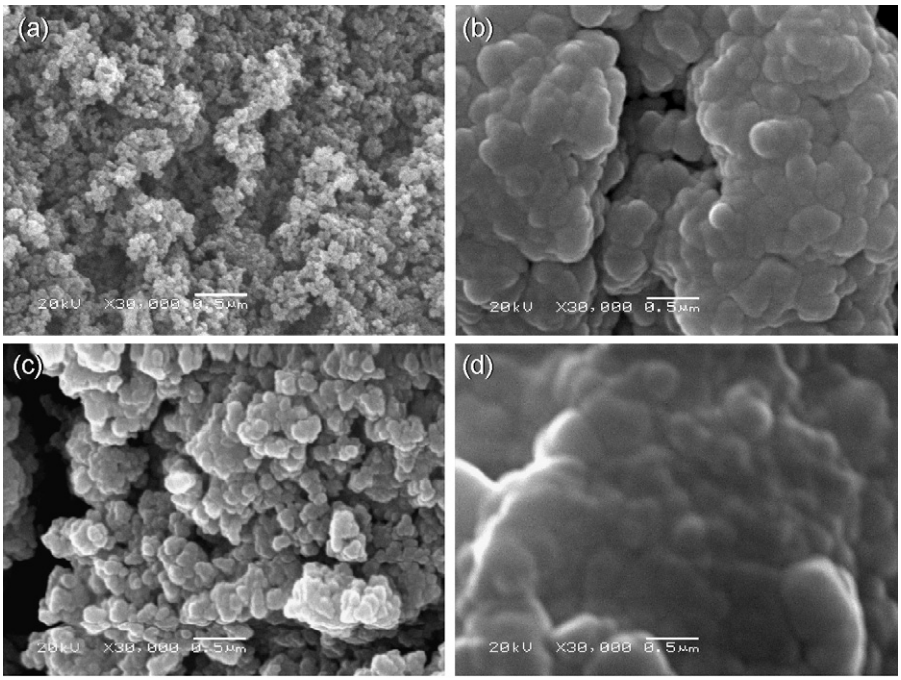

Fig. 2. SEM micrographs (30,000×; bar = 500 nm) before coating: Xerogel core-Placebo (a), Xerogel core-DicONa (c) and after coating: NC@xerogel-Placebo (b), NC@xerogel (d).

5–6) (100 mL), at 37.0 ± 0.5 °C. Aliquots (3 mL) were withdrawn, filtered (0.45 μm, Millipore®) and quantified (280 nm). NC@xerogel and NC@Aerosil released 1 ± 1% and 3 ± 1% within 60 min at pH 1.2, showing a good gastro-resistance. In water, after 5 min, the pure drug and Aerosil core-DicONa dissolved 92 ± 3 and 98 ± 1%, while Xerogel core-DicONa, NC@Aerosil and NC@xerogel released 60 ± 1, 58 ± 1 and 36 ± 1%, respectively (Fig. 3). The coating was effective in reducing the burst release. Within 10 and 60 min, the drug was gradually released from NC@Aerosil, Xerogel core-DicONa and NC@xerogel reaching 81 ± 1%, 83 ± 2% and 62 ± 2%, respectively. NC@xerogel showed a drug sustained release.

The dissolution efficiencies (DE) were calculated (Eq. (2)) in order to compare the release profiles. ANOVA (Statgraphics Plus for Windows version 5.1) showed significant differences ($p < 0.05$) for the DE values comparing, respectively, the uncoated and coated xerogel microparticles (69 ± 1 and 52 ± 1%).

$$\mathrm{DE} = \frac{\int y \times \mathrm{d}t}{y_{100} \times t} \times 100 \quad (2)$$

where $\int y \times \mathrm{d}t$ is the area under the dissolution curve up to a time t and $y_{100} \times t$ is the area of the rectangle described by 100% of drug dissolution at the same time.

In conclusion, the nanocapsule-coated drug-loaded xerogel microparticles were successfully developed. The drug release experiments demonstrated the gastro-resistance and the efficacy of the new system in reducing the burst release and in sustaining the sodium diclofenac dissolution profile. The nanocapsule-coated drug-loaded xerogel microparticles showed potential use for controlling the release of hydrophilic drugs.

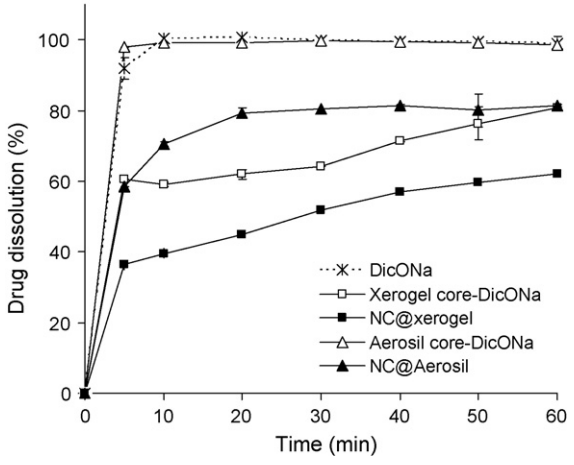

Fig. 3. Sodium diclofenac dissolution profiles in deionized water from microparticles without coating: Xerogel core-DicONa and Aerosil core-DicONa, and coated with polymeric gastro-resistant nanocapsules: NC@Aerosil and NC@xerogel.

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