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Encapsulation efficiency of solid lipid hybrid particles prepared using the PGSS® technique and loaded with different polarity active agents

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ABSTRACT

The manufacture of particulate hybrid carriers containing a glyceryl monostearate (Lumulse® GMS-K), a waxy triglyceride (Cutina® HR), silanized TiO_2 and different active agents (caffeine, glutathione or ketoprofen) was investigated with the aim of producing controlled drug delivery systems based on solid lipid particles. Particles were obtained using the supercritical PGSS® (particles from gas saturated solutions) technique. Experiments were performed at 13 MPa and 345 K, according to previous measurements of lipid melting points. Solid lipid particles were loaded with silanized TiO_2 and caffeine, glutathione or ketoprofen in percentages of 6–7 wt% for the mineral filler and 4.2, 5.6 and 16.1 wt% for the respective drugs. The particles obtained were analyzed in the solid state by thermogravimetric and X-ray diffraction analysis and scanning electron microscopy. Drug contents in the precipitated lipid samples and their elution profiles were studied by HPLC. Hydrophobic drugs, such as ketoprofen, were more efficiently encapsulated in the lipophilic lipidic matrix than hydrophilic drugs, such as caffeine and glutathione.

1. Introduction

Pharmaceutical and cosmetic industries are working on the development of new strategies for the formulation and processing of matrixes containing active compounds for controlled release. Particulate and colloidal carrier systems have attracted growing interest concerning drug delivery. Based on the carrier material, the conventional vehicles can generally be divided into polymeric and lipidic systems. To avoid potential toxicological problems associated with the degradation of synthetic and semi-synthetic polymeric systems, a great deal of interest is currently being focused on lipid-based carrier systems, inter-alia liposomes and lipid oil-in-water emulsions [1,2]. These vehicles are composed of physiological lipids, such as phospholipids, cholesterol or triglycerides, and, thus, their toxicological risk is null. However, the storage stability of liposomes is limited and the large scale production and sterilization of these carriers is complicated. Many drawbacks associated with conventional liquid-like lipid drug carriers can be overcome using solid lipid particles (SLPs) that combine the superior biodegradability and biocompatibility as well as ease of manufacture of lipids with the advantages of the solid-like state. In SLPs, the solid matrix provides enhanced physical and chemical stability, facilitates surface modification for targeting, and drug release is controlled by degradation of matrix constituents rather than by diffusion [3–8].

Conventional methods for the production of SLPs, such as solvent-emulsification-evaporation, double emulsion, ultrasonication and spray chilling or drying, are either multi-step processes or operate with organic solvents [1,9]. Conversely, technology based on the use of supercritical carbon dioxide ($scCO_2$) has been described as a one-pot strategy capable of encapsulating drugs into organic solvent-free lipid particles [10–21]. In this work, hybrid SLPs composed of a lipid matrix entrapping mineral filler nanoparticles and loaded with an active compound were obtained using the particles from gas saturated solutions (PGSS®) supercritical method [22]. The technique consists of dissolving $scCO_2$ in the bulk of a melted lipid mixture with dispersed titanium dioxide (TiO_2) nanoparticles and dissolved/dispersed drugs, and the subsequent quick expansion through a nozzle, causing the atomization of the melt, the complete evaporation of the gas and the precipitation of the SLPs.

A mixture of two C_{18} triglycerides (Lumulse® GMS-K and Cutina® HR) was used as a matrix. Both lipids have applications in cosmetic and pharmaceutical industries [23,24]. The mixture

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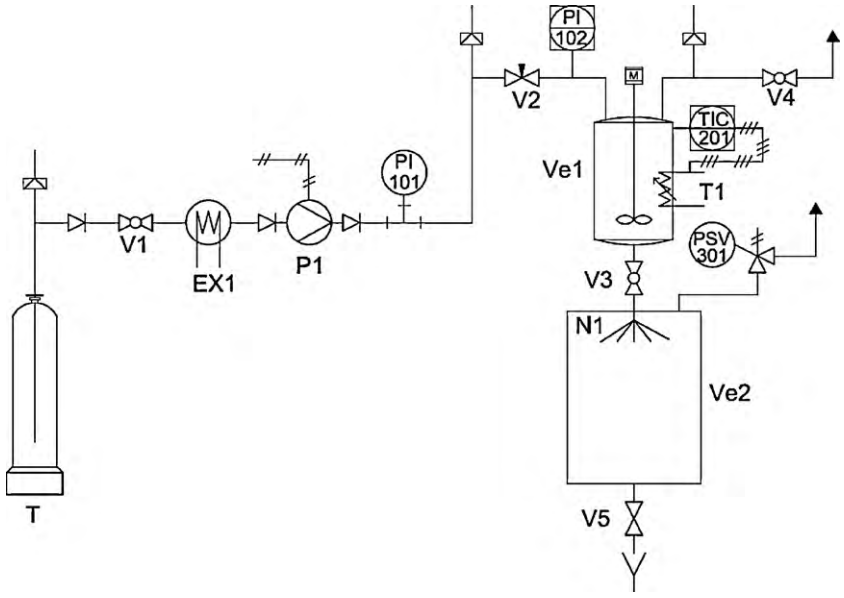

Fig. 1. Process flow diagram of the equipment used for PGSS® SLPs formation. T: CO_2 reservoir, EX1: CO_2 cooling unit, P1: pump, V1–V5: valves, Ve1: high pressure mixing chamber, Ve2: collector vessel, T1: heater, N1: nozzle.

of two lipids was preferred as a matrix to individual compounds, since together they form crystals with many imperfections offering space to accommodate the additives [13,17,25]. Supercritically silanized nanoparticulate titanium dioxide (TiO_2) [26–29] was incorporated to the mixture as an anticaking additive. This material is also an effective UV-blocker [13,30,31]. The hybrid SLPs were loaded with three different active agents: caffeine, glutathione and ketoprofen. Caffeine and glutathione are hydrophilic active compounds with photoaging prevention capacity [32,33]. Ketoprofen is a lipophilic non-steroidal antirheumatic drug available in the form of coated tablets for oral administration and gel for topical application. To counteract the short elimination half-life of ketoprofen, encapsulation of the drug in lipidic formulations is the method usually chosen for sustained delivery [34–36]. These three active agents were chosen as model compounds for encapsulation in the lipidic matrix because of their different lipophilic behaviours. Solid state characterization of the prepared samples together with preliminary drug dissolution tests in water were used to analyze the encapsulation ability of the chosen lipidic mixture.

2. Experimental

2.1. Materials

Lumulse® GMS-K (GMS, glyceryl monostearate) and Cutina® HR (HCO, hydrogenated castor oil) were kindly provided by Lambent Technologies and José M. Vaz Pereira S.A., respectively. TiO_2 nanometric particles (~20 nm in diameter) were supplied by Degussa (TiO_2 P25) and silanized with octyltriethoxysilane following a $scCO_2$ procedure published elsewhere [37]. Ketoprofen (Kt), caffeine (Cf) and glutathione (Gl) were purchased from Sigma–Aldrich. Carbon dioxide (CO_2, 99.998 mol% purity) was supplied by Air Liquide. Chemicals utilized for high pressure liquid chromatography (HPLC) characterization were sodium hydroxide, phosphoric acid (85%), ammoniumformate and formic acid, all of them from Sigma–Aldrich (analytical reagents). Ultrapure water (Millipore, Milford), methanol and ethanol (both from Merck, HPLC grade) were used for the preparation of mobile phases and standard solutions.

2.2. Equipment and procedure

The process flow diagram of the PGSS® equipment used to produce the SLPs is shown in Fig. 1. CO_2 was fed by a high-pressure piston pump (P1, Haskel model MCPV-71) to a 0.5 L high-pressure stirred vessel (Ve1, Parr Instruments) until the desired working pressure was reached. The autoclave contained a mixture constituted by GMS:HCO in a ratio 50:50 wt%, 5 wt% of TiO_2 nanoparticles and different amounts (from 9 to 17 wt%) of active compound. In some of the performed experiments, a certain amount of water was also added to the vessel. The autoclave was heated using a thin band heater (T1, Watlow STB3J2J1). After 1 h of stirring, necessary for mixture equilibration, the system was depressurized by opening valve V3 (Parker 4M4Z-B2LJ) and atomized through a 600 μm cone nozzle (N1, Spraying Systems Co.) into a 10 L atmospheric collector (Ve2) where particles were recovered.

2.3. Analytical methods

2.3.1. Solid state characterization

The thermal stability of the obtained samples was determined using thermogravimetric analysis (TGA, Perkin Elmer 7) under Ar atmosphere and raising the temperature at a rate of 5 K min^{-1}. Photographs of the samples were taken using a JEOL JSM 6300 scanning electron microscope (SEM). Samples were also analyzed by X-ray diffraction (XRD) from a 2θ-value of 5–30° with a Rigaku Rotaflex RU200 B instrument, using a step of 0.02° and the $CuK\alpha_1$ radiation.

2.3.2. HPLC characterization

The chromatographic system consisted of an Agilent 1100 Series Instrument (Agilent Technologies, Waldbronn, Germany) equipped with a G1311A quaternary pump, a G1379A degasser, a G1315B diode-array detector furnished with a 13-μL flow cell, a G1329B automatic injector and a chemstation for data acquisition and analysis. A CyberScan model 2500 potentiometer (precision of ±0.1 mV) with a combined pH electrode ORION 9103SC was used for pH measurements. The analytical column was a Synergi Hydro-RP C_{18} column (150 mm × 4.6 mm i.d., particle size 4 μm, 80 Å) equipped with a guard column (4 mm × 3 mm i.d.), both from Phenomenex (Torrance, CA, USA). An isocratic elution at the constant flow rate of 1 mL min^{-1} was utilized. For caffeine analysis, the chro-