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Review

Supercritical Assisted Atomization for the production of curcumin-biopolymer microspheres

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ABSTRACT

Supercritical Assisted Atomization (SAA) has been applied to the formation of microspheres curcumin (CUR)-polyvinylpyrrolidone (PVP) to be used for biomedical applications. CUR has antioxidant, anti-inflammatory and antitumoral properties and is poorly water soluble; whereas, PVP is highly water soluble. The aim was to entrap CUR in form of nanoparticles in a polymeric hydrosoluble carrier, to protect the active principle and to enhance its bioavailability. Four CUR/PVP weight ratios were selected: 1/2, 1/4, 1/6 and 1/8 and processed by SAA at 80 °C and 99 bar in the saturator and 80 °C and 1.50 bar in the precipitator. Spherical particles of CUR/PVP were obtained in all cases, characterized by a mean size, calculated on particle number %, smaller than 400 nm and a D_{90} lower than 1 μm. X-ray, DSC, FTIR analyses showed that the microspheres were amorphous and that the drug was intimately mixed with the polymer. UV–vis spectrometric analyses confirmed an high loading efficiency of the active principles microspheres, ranging between 94 and 100%. Dissolution tests in aqueous environment at different pH values were performed to measure the improvement of the dissolution rate. It resulted up to 4.5 times faster with respect to the physical mixture for the most favorable 1/8 ratio, with a complete CUR dissolution time of 5.5 h at pH 6.5.

Contents

1. Introduction

Curcumin (CUR) is contained in large quantities in the roots of *Curcuma longa*; it possesses well known antioxidant, antimicrobial, anti-inflammatory and anticancer properties [1,2,3]. But, it is characterized by very low solubility in water based systems and consequently shows a poor bioavailability, that represents a great limitation to its use as a powerful pharmaceutical agent. Indeed, the low solubility in aqueous media induces low absorption, fast metabolism and quick systemic elimination [4]. Moreover, CUR is relatively unstable in aqueous solution and undergoes rapid hydrolytic degradation, that severely reduces its bioavailability [5,6].

To increase bioavailability, micronization techniques can be applied, to produce small particles with increased dissolution rate. Another possible way to improve the bioavailability of highly hydrophobic drugs is to coprecipitate them in form of nanoparticles together with an hydrophilic polymer.

Martins et al. [7] used spray-drying to prepare microparticles of *Curcuma longa* extract plus PVP and colloidal silicon dioxide. CUR-PVP microparticles were generally larger than 5 μm with a maximum yield

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of 53%. Comparison of the dissolution profiles of these microparticles with starting materials and residual solvent analysis were not reported. Paradkar et al. [6] used the same technique to produce microspheres of CUR in PVP, obtaining irregular and spherical particles of 3–10 μm. Solid dispersions of CUR at different PVP ratios were also prepared. Dissolution studies on CUR and its physical mixtures in 0.1 N HCl (pH 1.2) showed negligible release of CUR (0.25%) after 90 min. During the same time microspheres release up to 1.5% CUR for the 1/10 ratio. Farazuddin et al. [8] proposed the encapsulation of CUR in PLGA microparticles to increase its bioavailability and facilitate slow release kinetics. Microparticles were prepared using an oil-in-water emulsion plus solvent evaporation technique. PLGA microparticles showed 17% release of CUR in 48 h, which increased slowly with time. Wasique et al. [9] prepared CUR alone nanoparticles via solvent-nonsolvent nanoprecipitation using a spinning disc reactor. CUR particle diameter size was in the range 180–220 nm in presence of PVP used as stabilizer. They showed a decrease of crystallinity and displayed larger water dissolution rates than pure CUR: complete dissolution in about 50 min in water; whereas, the starting material in the same time dissolved at no more than 5%. In Krausz et al. [10] CUR and chitosan were dissolved in methanol together with PEG400 and tetramethyl orthosilicate (TMOS)-HCl inducing polymerization. The resulting gel was dried and processed by ball milling cycles to produce uniform particles. They obtained particles with a mean diameter around 220 nm containing CUR at 1% embedded in a porous lattice. An incomplete release (around 80%) of CUR was obtained in 24 h. CUR loaded in dextran sulphate and chitosan nanoparticles was prepared by simple coarcevation method by Anitha et al. [11]. These particles had a spherical morphology with an average size around 200 nm. Drug entrapment efficiency was found to be 74%. In vitro drug release studies showed a burst release in the first 3 h, followed by a release of CUR over a period of one week; about 70% of drug was released in this time.

However, these traditional processes have some drawbacks: for example, spray drying often requires high temperatures, that can be problematic for thermolable compounds; it is generally difficult to obtain the control of particle size and a drying step can be required to reduce residual solvents to acceptable levels. Also coprecipitation suffers of the same limitations and suitable polymers are required.

To overcome the limits of the traditional techniques, supercritical fluids (SCFs) based techniques can be used. They have been successfully applied in several fields such as the micronization of several kind of materials [12,13,14,15,16,17,18], membranes formation [19] and scaffolds production [20].

For example, Xie et al. [21] used Supercritical Antisolvent processing (SAS) with a coaxial injector and hexafluoroisopropanol as the solvent, to form a silk fibroin plus 0.5–1% CUR solution. These authors produced nanoparticles generally smaller than 100 nm. They obtained low drug loading and encapsulation efficiencies of 12% ± 0.62 and 36% ± 1.9, respectively. In vitro studies in phosphate buffer saline solution showed that 75% of curcumin was released from silk-fibroin in about 200 h. Nanoparticles produced by SAS are formed by nucleation and growth; therefore, the composite nanoparticles can be produced by homogeneous nucleation and/or chemical interactions between the compounds to be coprecipitated. This mechanism can explain the low encapsulation efficiencies they obtained [22]. Zabihi et al. [23] produced CUR nanoparticles coated by poly(lactic-*co*-glycolic acid) (PLGA) using a fluidization assisted supercritical anti-solvent process. PLGA solution was sprayed into supercritical CO_2 medium, in which CUR nanoparticles were

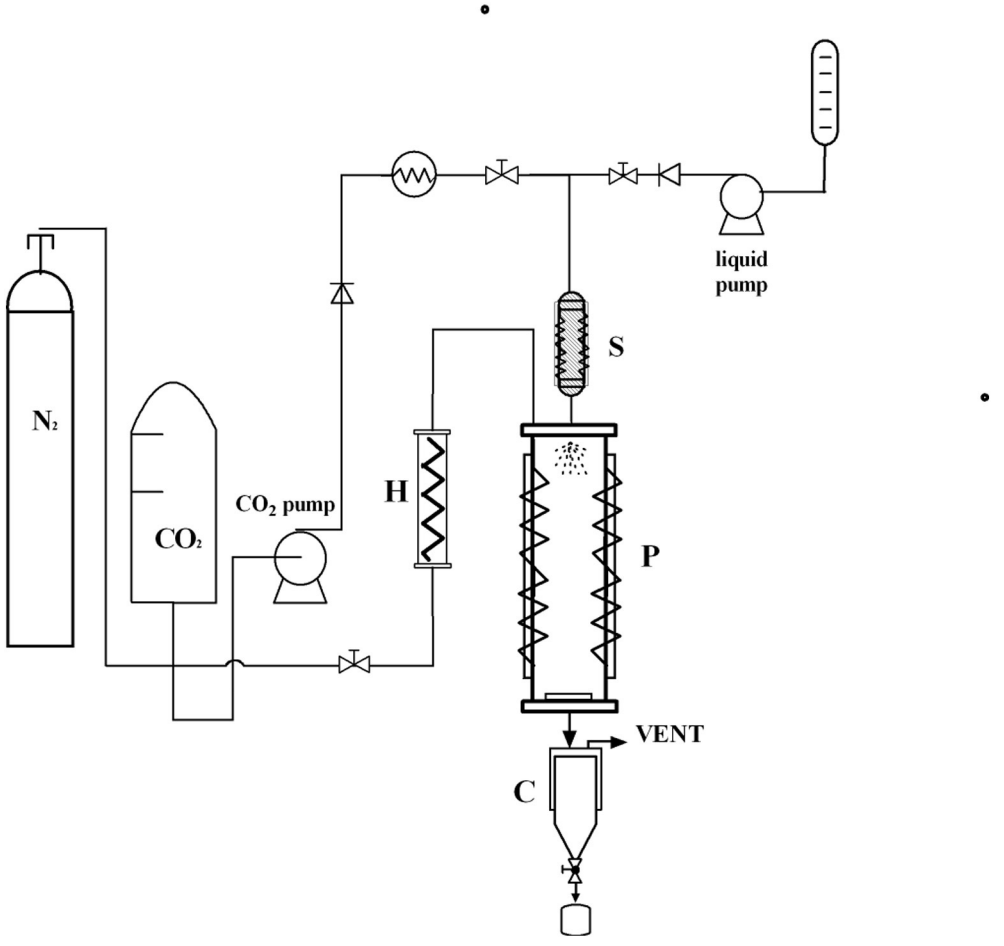

Fig. 1. A schematic representation of SAA plant: S, saturator; P, precipitator; H, heat exchanger; C, liquid condenser.