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Inhalable curcumin formulations by supercritical technology

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ABSTRACT

Inhalable dry formulations for pulmonary delivery of curcumin have been produced by supercritical antisolvent micronization. The antioxidant curcumin was co-processed with hydroxypropyl-beta-cyclodextrin (HP-β-CD) and polyvinylpyrrolidone (PVP) to form binary and ternary composites with enhanced flow-ability for pulmonary delivery. The micronization process adopted was the atomized rapid injection solvent extraction (ARISE) system, and was operated at 95 bar and at temperatures of 25 °C and 40 °C. The products were evaluated in terms of morphology, composition, crystallinity and aerodynamic particle size distributions. A synergistic effect of the excipients on the aerodynamic properties of micronized curcumin formulations has been found. The fine particle fraction (FPF) of curcumin in ARISE-processed powders was as high as 61% in ternary systems, whilst untreated curcumin had a FPF of 10% and micronized binary systems had FPF below 40%. The process produced yields of about 80%, demonstrating significant potential for further development of curcumin formulations for pulmonary administration.

1. Introduction

Curcumin is a natural polyphenolic compound mainly extracted from *Curcuma longa* [1]. Curcumin has demonstrated biological-pharmaceutical properties, and has potential application in the treatment of metabolic diseases such as hypoglycaemia, rheumatism, cancer and cardiovascular disorders [1–3]. However, curcumin development for therapeutic purposes has been impeded by its low oral bioavailability and hydrophobicity, reflected by an aqueous solubility as low as 0.4 μg/mL [2]. The poor water solubility of curcumin is directly related to the rapid clearance of the molecule from the human body which results in low absorption in the gastrointestinal tract, and low oral bioavailability [2,4]. A strategy to address this aspect is the development of alternative administration routes. Alternative routes to oral delivery are considered when the therapeutic compounds are poorly absorbed in the oral pathway.

Pulmonary administration can be suitable for local and systemic delivery of a range of pharmaceutical ingredients. Delivery of therapeutic compounds through the pulmonary pathway can offer a rapid onset of action since it bypasses the complex metabolic pathways in the gastrointestinal tract. Lungs offer a large absorption surface area to active ingredients, up to 100 m^2, which can improve bioavailability and thus reduce the dosage requirements compared to other administration routes [5]. Reducing the dosage may reduce the risk of unwanted side effects. Therapeutic inhalable formulations have been commonly produced as dry powders due to the high stability and patient compliance, as well as low manufacturing costs [6].

Most dry formulations for pulmonary delivery include carriers, which are frequently derived from sugar-based moieties such as lactose, trehalose and mannitol. In addition, biodegradable polymers such as polyvinylpyrrolidone (PVP) and polylactic-co-glycolic acid (PLGA) are commonly used [7]. Modified cyclodextrins have also been proposed as carriers in pulmonary drug formulations because of their low toxicity and ability to increase powder flow-ability and dissolution properties of hydrophobic compounds [8,9]. Among the modified cyclodextrins, hydroxypropylated derivative compounds show potential in pulmonary administrations. The use of hydroxypropyl-β-cyclodextrin (HPβCD) facilitated an increase of bioavailability in pulmonary applications of as high as 80% [10]. In addition, HPβCD promotes aerosolization and has low toxicity effect on lungs and kidneys [11]. In a study of acute lung injury treatment, the complexation of curcumin with hydroxypropyl-γ-cyclodextrin (HP-γ-CD) increased curcumin interaction with human airway epithelial cell monolayers and effectively reduced oxidant stress in the lungs [12].

Pulmonary applications of dry powders require certain particle characteristics such as aerodynamic diameter between 1 and 5 μm. Particle engineering techniques can be used to generate particles with the desired properties [13]. Supercritical technologies provide a versatile micronization platform for particle engineering. A supercritical fluid is any fluid exceeding its critical points with reduced temperature and pressure between 1 and 2 [14]. Fluids in these conditions exhibit unique properties that are intermediate to those of gases and liquids and can be varied simply by changing the operating pressure and temperature [15]. In chemical processing, CO_2 has often been the process fluid of choice

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due to its non-toxic, inert nature and relative inexpensiveness [16]. The applicability of supercritical based technology has been investigated to develop pulmonary products such as cyclosporine [17], budesonide [18] trehalose, insulin [19] lactose [20] and cyclodextrins [21].

A major limitation in the supercritical particle processing is the application of micrometric spray devices such as nozzles. The use of nozzles has been implemented in antisolvent processes to improve mass transfer between the solvent-rich phase and the supercritical antisolvent. Nozzles are used to atomize the solvent phase and enhance mixing patterns promoting mass–heat transfer, nucleation and particle growth. In supercritical applications, problems such as nozzle blockages and premature precipitation have frequently occurred which decrease reproducibility of the processing. The atomized rapid injection solvent extraction (ARISE) system is a batch antisolvent method that was invented to overcome the use of spraying devices. The ARISE system employs a pressure difference to perform atomization. Rapid contact between antisolvent and solution in the ARISE process leads to rapid precipitation in a substantially homogeneous environment thus favoring the formation of particles with controlled morphologies. Processing drawbacks such as nozzle blockages, which have been problems in other supercritical antisolvent methods, are circumvented due to the absence of a micrometric spray device [22].

In this study, ARISE was applied to the co-processing of curcumin with hydroxypropyl-β-cyclodextrin (HP-β-CD) and polyvinylpyrrolidone (PVP) in binary and ternary formulations. Supercritical CO_2 was the antisolvent in all experiments. The aim of the study was the production of micronized curcumin and curcumin containing micro-composites for pulmonary administration. The effects of the composition of the feed solution on product morphology, composition, crystallinity and aerodynamic performance were investigated. Composites were also produced by physical mixing for comparative purposes.

2. Materials and methods

2.1. Materials

Curcumin (>90% purity) was purchased from Cayman Chemicals. For calibration purposes, curcumin was purchased from Sigma Aldrich with analytical standard grade (>98.5% purity). Hydroxypropyl-β-cyclodextrin was kindly donated by Cavasol Wacker-Chemie. Polyvinylpyrrolidone (PVP, 40 KDa) was purchased from Sigma Aldrich. Acetone and ethanol (HPLC grade) were purchased from Mallinckrodt and Scharlau, respectively. Methanol, acetic acid and acetonitrile (HPLC grade) were purchased from Ajax Finechem. Propylene-glycol with 99.5% purity was purchased from Sigma Aldrich. High-purity argon and carbon dioxide (>99.99%) were purchased from Coregas Australia.

2.2. Experimental

2.2.1. Supercritical (ARISE) processing

Curcumin was precipitated from acetone, ethanol and methanol solutions at different initial concentrations. Curcumin was also reprocessed from acetone–ethanol (1–1 v/v) solutions.

Curcumin composites were prepared by dissolving curcumin and excipients (HPβCD, PVP, or both) in ethanol, methanol and acetone–ethanol (1–1 v/v). The overall content of solutes in the feed solutions was 10 mg/mL in all cases. In binary HPβCD mixtures, a 1:4 curcumin/cyclodextrin weight ratio was used corresponding to an equimolar feed ratio. Binary curcumin–polymer (1:1 wt) mixture was processed from acetone–ethanol solutions.

A schematic of the ARISE rig is presented in Fig. 1. The rig comprises a solution chamber (upper vessel) and a precipitation chamber (lower vessel), the two vessels are separated by a valve. The valve is initially closed so that a pressure differential can be established between the chambers. Once the selected operating conditions are reached, the valve is opened rapidly and the pressure differential between the two chambers drives the rapid atomization of the feed solution in the precipitation chamber.

In each experiment, a 10 mL aliquot of organic solution was pressurized by argon at 165 bar. The precipitation chamber was pressurized with CO_2 at 95 bar and thermally equilibrated. An equilibration time of 5 min was allowed prior to feed injection. The organic solutions were delivered to the precipitation chamber through a tube (SS-316 L, 1/8 in. OD, 0.028 in. wall-thickness, Swagelok, USA) with 13.2 cm length by a pressure differential. After the rapid injection of the solution in the precipitation vessel, precipitates were washed with 300 mL of fresh CO_2 delivered to the precipitation chamber at a flow rate between 5 and 7 mL/min. The volume and flow rate of CO_2 used in the washing stage were measured at 5 °C and at the operating pressures. The operating

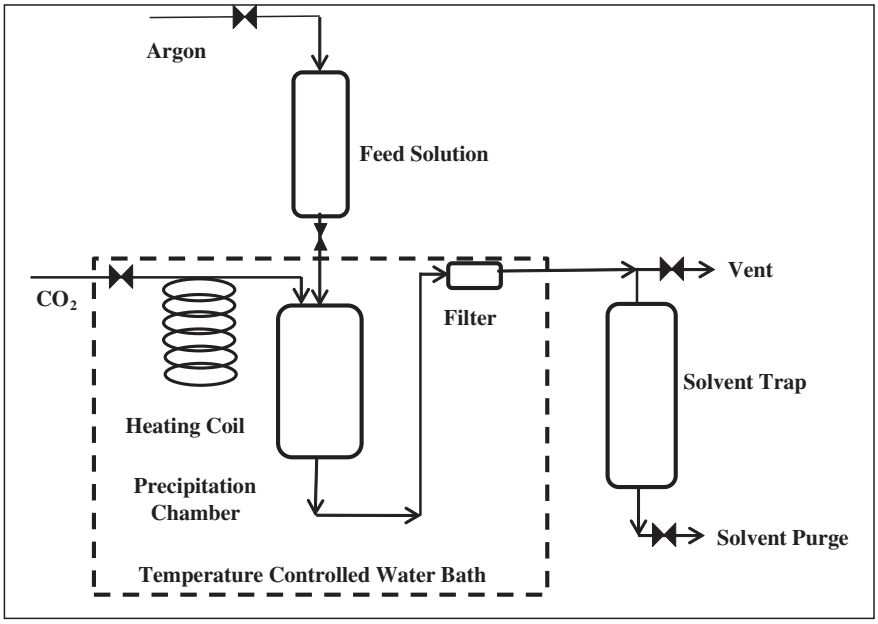

Fig. 1. The experimental rig for ARISE processing.