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Antisolvent precipitation technique: A very promising approach to crystallize curcumin in presence of polyvinyl pyrrolidon for solubility and dissolution enhancement

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ABSTRACT

Curcumin with a vast number of pharmacological activities is a poorly water soluble drug which its oral bioavailability is profoundly limited by its dissolution or solubility in GI tract. Curcumin could be a good anticancer drug if its solubility could be increased. Therefore, the aim of the present study was to increase the dissolution rate of curcumin by employing antisolvent crystallization technique and to investigate the effect of polyvinyl pyrrolidone K30 (PVP) as colloidal particles in crystallization medium on resultant particles. Curcumin was crystalized in the presence of different amounts of PVP by antisolvent crystallization method and their physical mixtures were prepared for comparison purposes. The samples were characterized by scanning electron microscopy (SEM), differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD) and Fourier transform infrared spectroscopy (FT-IR). The solubility and dissolution of the treated and untreated curcumin were also determined. Antisolvent crystallization of curcumin led to the formation of particles with no definite geometric shape. It was interesting to note that the DSC and XRPD studies indicated the formation of a new polymorph and less crystallinity for particles crystallized in the absence of PVP. However, the crystallized curcumin in the presence of PVP was completely amorphous. All crystalized curcumin samples showed much higher dissolution rate compared to untreated curcumin. The amount of curcumin dissolved within 10 for treated curcumin in the presence of PVP (1:1 curcumin:PVP) was 7 times higher than untreated curcumin and this enhancement in the dissolution for curcumin samples crystallized in the absence of PVP was around 5 times. Overall' the results of this study showed that antisolvent crystallization method in the absence or presence of small amounts of PVP is very efficient in increasing the dissolution rate of curcumin to achieve better efficiency for curcumin.

1. Introduction

There are lots of techniques that have been used to enhance the dissolution rate or solubility of poorly water-soluble drugs [1]. Crystal engineering or crystal manipulation has been the focus of many research activities to achieve this goal during the past few years. Crystal manipulation has been performed by either top-down or bottom-up techniques [2,3,4].

Top-down procedures involve the breaking of drug particles by milling and/or homogenization while bottom-up methods involve the building up particles from drug molecules via precipitation

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techniques. The top-down methods suffer from some disadvantages such as the need for high-energy input, long processing time, possibility of metal contamination and wide particle size distribution [5,6]. This has led to the popularity of bottom-up methods for the purpose of crystal manipulation. In most of these techniques the main aim is to achieve small particle size in order to increase the effective surface area of particles and consequently the dissolution rate, while other objectives such as increasing solubility and wettability were also sought. Among different bottom-up methods, spray freezing into liquid and supercritical antisolvent precipitation have not found widespread use due to the complexity of the operation procedure (need very low temperature and high pressure) and also their expenses [7–9]. However antisolvent precipitation which could be implemented at ambient temperatures and atmospheric pressure with no need for expensive equipment has widely been used in order to improve the dissolution rate of poorly soluble drugs. In this method supersaturation is achieved by the addition of an antisolvent to the organic solution of drug with low solubility leading to nucleation of drug and consequently precipitation of particles [10–13]. In this process the addition of some stabilizers during the precipitation procedure could be beneficial as they could retard or prevent particle growth by covering the surface of precipitated particles in short-term. However, an immediate drying is required to prevent further growth of particles [14,15].

Curcumin, a hydrophobic polyphenol extracted from herbal spice turmeric, is a poorly water-soluble drug. It has antioxidant, anti-inflammatory, antitumor, anti-HIV, and antimicrobial properties [16–19]. Different approaches have been implemented in literature in order to address the issue of its poor dissolution rate or low solubility. The use of polymeric nanoparticles [20–23], solid lipid nanoparticles [24–26], the use of micelles [27,28,29] and preparation of amorphous solid dispersion systems are some examples. However there are few studies regarding the use of a crystallization procedure like antisolvent precipitation in order to achieve this goal. Thorat and Dalvi described the mechanism of particle formation pathways and polymorphism of curcumin induced by ultrasound and additives during liquid antisolvent precipitation [30,31]. They obtained loose aggregates with amorphous nature and proposed that the use of polymeric stabilizer such as PVP could prevent crystal fusion, however no attempts have been made to investigate their dissolution rates. Kakran et al. have prepared curcumin nanoparticles via antisolvent precipitation in absence of any stabilizer for oral administration [32]. The authors have compared two preparation methods: antisolvent precipitation with a syringe pump and evaporative precipitation of nanosuspension. Yadav and Kumar investigated the antisolvent precipitation process to prepare curcumin nanoparticles in presence of gelatin as stabilizer for parenteral administration [33]. The effect of different process variables on particle size and size distribution of curcumin during particle formation was investigated. In the present study the antisolvent precipitation procedure has been used for manipulation of curcumin particles for oral use in the presence of different concentrations of PVP as stabilizer.

2. Materials and methods

2.1. Materials

Curcumin was purchased from Hindustan Herbal Limited Company (Haryana, India), polyvinyl pyrrolidone K30 was obtained from Fluka (Switzerland) and sodium dodecyl sulfate was obtained from Merck (Germany). All other solvents and chemicals were of analytical grade.

2.2. Methods

2.2.1. Precipitation of curcumin by antisolvent crystallization

Accurate weighed amount of curcumin (1 g) was dissolved in 10 mL acetone. Different quantities of PVP (0, 0.5, 1 and 2 g) was separately dissolved in beakers containing 100 mL distilled water. The solution of curcumin in acetone was added dropwise (at rate of 5 mL/min) using a syringe equipped with needle gauge No. 22, into the aqueous solution of PVP while stirred at 800 rpm at 25 °C. The final ratios of curcumin: PVP in the solutions after adding the curcumin solution to PVP solution were 1:0, 1:1, 1:2 or 2:1. The obtained suspension was immediately freezed at −80 °C for 24 h and then freeze dried using Heto freeze dryer (Denmark) for 48 h. Each crystallization experiment was repeated three times.

2.2.2. Preparation of physical mixtures of curcumin and PVP K30

The physical mixtures of curcumin and PVP with the similar ratios as above were also prepared for comparison purposes. The sieved fractions (passed through 60 mesh sieve) of the curcumin and PVP were mixed in tumbling mixer rotating at 50 rpm for 15 min. The obtained mixtures were kept in glass vials until further studies.

2.2.3. Morphological analysis of samples

A scanning electron microscope (LEO 1450 VP, Germany) was used to investigate the morphologies of untreated curcumin and precipitated samples. Untreated curcumin and all freeze-dried samples were coated with a thin gold-palladium layer by sputter coater (SC 7620, England) prior to observation.

2.2.4. Solubility measurement

The solubility of untreated curcumin, physical mixture and crystallized samples was determined by adding an excess amount of samples (about 5 mg) to screw-capped glass vials containing 20 mL distilled water. The vials were shaken for 48 h at 25 °C. The suspensions were then filtered through a 0.45 μm filter and the concentration of curcumin was determined spectrophotometrically at 426 nm (Cecile 900, USA). The test was repeated three times and the mean was reported.

2.2.5. Differential scanning calorimetry (DSC)

DSC analysis was conducted using DSC 822e (Mettler Toledo, Switzerland) equipped with a refrigerated cooling system to study the thermal behaviors of the samples. The instrument was calibrated using indium standard. 2–3 mg samples of untreated curcumin and precipitated curcumin in the presence or absence of PVP were placed in aluminum pans sealed with a lid and were scanned from 20 to 200 °C at a scanning rate of 10 °C/min under nitrogen gas at a flow rate of 80 mL/min.

2.2.6. X-ray powder diffraction studies (XRPD)

X-ray powder diffraction patterns of the selected samples were obtained by a X-ray diffractometer (Philips, Germany). Each sample was scanned in the range of 5–60° (2θ) with a step size of 0.02° at a scan rate of 0.04/s.

2.2.7. Fourier transform infrared spectroscopy (FT-IR)

FT-IR was used to investigate any changes in the precipitated curcumin formulations at the molecular level. The spectrum was obtained using a spectrum II FT-IR spectrometer (PerkinElmer, Waltham, USA). The specimens were prepared by mixing of each sample with KBr at a ratio of 1:5 and then compressing it at a pressure of 7 tons for 2 min using a hydraulic press. The obtained discs (sample-KBr) were scanned against pure KBr disc at wavenumbers ranging from 450 to 4000 cm^{-1} with a resolution of 1.0 cm^{-1}.