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Ultrasound-assisted modulation of concomitant polymorphism of curcumin during liquid antisolvent precipitation

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ABSTRACT

Curcumin polymorphs were found to precipitate concomitantly during liquid antisolvent precipitation. While, commercially available curcumin exists in a monoclinic form, the curcumin particles when precipitated in presence of additives and ultrasound were either found to be the mixtures of orthorhombic (Form 3) and monoclinic form (Form 1) or were found to be in orthorhombic form (Form 3) or monoclinic form (Form 1). The experimentally observed particle morphologies did not match clearly with the predicted BFDH morphologies of curcumin and the experimentally observed morphologies were more elongated as compared to the predicted BFDH morphologies. At lower ultrasonic irradiation times, the monoclinic form (Form 1) was found to dominate the mixture of particles. However, an increase in ultrasonic irradiation time was found to increase the percentage of orthorhombic form (Form 3) in the particles indicating that the increase in ultrasonic energy facilitates formation of orthorhombic form over the monoclinic form, irrespective of the additive used. These results therefore suggest that the ultrasonic energy can be effectively used to manipulate the polymorphic outcome of the precipitation.

1. Introduction

Formulation development of poorly water soluble active pharmaceutical ingredients (APIs) is one of the important topics of research as the lower aqueous solubility hinders the bioavailability of such drugs and decreases the drug efficacy [1]. Enhancement in aqueous solubility of APIs can be achieved through various formulation strategies, [2] especially by decreasing the particle size of these APIs to nano/micron level. Decrease in particle size increases the dissolution rates due to an increase in surface area available for dissolution [2]. Liquid antisolvent precipitation is one of the widely reported bottom-up techniques to produce nano/micro particles of poorly water soluble drugs [3]. However, as applicable to various formulation techniques, processing of APIs during liquid antisolvent precipitation may induce the polymorphic transformations [4,5], The processing parameters such as operating conditions, temperature, pH, supersaturation, nucleation rates, and presence of additives can greatly affect the overall polymorphic outcome [6–8]. The knowledge of any such polymorphic behavior of APIs is highly essential from the formulation development perspective as different polymorphs exhibit different physicochemical properties as well as different aqueous solubilities. At times, two or more polymorphs can crystallize together from the solution [8]. Such a behavior is called as concomitant polymorphism which poses increased difficulty to API formulation mainly because such polymorphs have ability to cocrystallize at the same operating conditions [8]. The polymorphs precipitate together mainly due to interplay of the governing kinetic factors such as supersaturation, nucleation rates and growth [8]. Understanding the effect of such kinetic factors on concomitant polymorphism can help in controlling precipitation of the desired polymorph [8]. The nucleation rate (J) of a particular polymorphic form can be expressed as [3]

$$J = A \exp\left\{\frac{-\Delta G_{cr}}{kT}\right\} \quad (1)$$

where, A is the pre-exponential factor and ΔG_{cr} is the critical free energy or energy barrier to be crossed to start nucleation events, k is the Boltzmann's constant and T is the absolute temperature.

Among the pair of polymorphs if a particular form, e.g. Form I appears during precipitation, then it indicates that the nucleation barrier for Form I is lower than that for Form II and J_I is higher as compared to J_{II}. Thus, if $\Delta G_{crI} < \Delta G_{crII}$, Form I would precipitate and if $\Delta G_{crII} < \Delta G_{crI}$ then Form II would precipitate. In case of concomitant polymorphism, as mentioned by Bernstein and coworkers [8], if at any point the rates of nucleation of two forms are

Abbreviations: APIs, active pharmaceutical ingredients; CMC, critical micelle concentration; DSC, differential scanning calorimetry; FE-SEM, field-emission scanning electron microscope; FTIR, Fourier Transform Infra Red spectroscopy; LAS, liquid antisolvent; PF68, Pluronic F68; Pol-JR, Polymer JR 400; PXRD, powder X-ray powder diffraction; Na-Alg, sodium alginate; SDS, sodium dodecyl sulfate.

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equal or the profiles of variation in ΔG_{cr} with ln S of the two forms cross each other at a particular condition, the outcome of the precipitation at such a condition will be the concomitant nucleation of both the polymorphs, Form I as well as Form II.

In this paper, we present the evidences of the concomitant polymorphism of curcumin during its precipitation in presence of ultrasound and additives by liquid antisolvent technique. Curcumin is a poorly water soluble ingredient found in a spice "turmeric" popular in India and has various medicinal properties [9]. Three different polymorphs of curcumin have been reported; two polymorphs exhibit orthorhombic structure (Form 2 and Form 3) and one polymorph exists in a monoclinic structure (Form 1) [10]. Commercial curcumin used in these studies was found to exist in a monoclinic form. However, precipitation of curcumin in presence of additives and ultrasound results in appearance of orthorhombic form (Form 3) in some cases. However, in other cases, mixtures of orthorhombic (Form 3) and monoclinic form (Form 1) were obtained. Both, the additives as well as the ultrasonic irradiation time were found to affect the composition of the mixture of polymorphs obtained.

2. Methods and materials

2.1. Materials

Curcumin, Sodium dodecyl sulfate, Tween 80, sodium alginate, polymer JR 400, Pluronic F68 were purchased from Sigma–Aldrich Inc. Ethanol (99.8% pure) was purchased from Chinachangshu Yangyuan Chemicals Pvt Ltd. All of these chemicals were used without further purification. Deionized Millipore water was used as an antisolvent.

2.2. Precipitation of curcumin particles

A jacketed glass vessel of 7 cm diameter and *L*/*D* ratio of 1.7 was used to carry out the precipitation of curcumin. The vessel volume was approximately 500 mL. Organic solution of Curcumin in ethanol (5 mg/ml) was introduced in water (100 ml) containing stabilizer (0.02 wt%) or without stabilizer, maintained at a constant temperature (1 °C) in the glass vessel, for all experiments. The measurement of temperature was carried by placing the resistance temperature detector (RTD) in the aqueous solution inside the glass vessel. During experiments concentration of SDS of 10 mM was used for experiments with SDS above CMC and also concentration of Tween 80 of 20 μM was used for experiments with Tween 80 below CMC. The ultrasound horn was immersed in antisolvent. The tip (1″ ID) of an ultrasound horn (Sonics, USA) is directed over a surface of solvent-antisolvent mixture solution such that the solution can be dispersed instantaneously by vibrations (at 100% amplitude (105 W power input) for 3 min, 10 min and 20 min).

2.3. Characterization of particles

Particle morphology of curcumin was examined using SEM mode on Field Emission-SEM (JSM 7600F, JEOL Japan). The curcumin suspensions were freeze-dried using Martin Christ (ALPHA 2–4 LD plus) freeze dryer at vacuum and temperature of 0.09 mbar and −43 °C respectively. The lyophilized curcumin powder was then used for powder-X-ray diffraction (PXRD) analysis using X-ray Diffraction System (XRD), (D8 Discover, Bruker AXS GmbH, Germany) at room temperature. Anton Paar high temperature assembly was used to record the XRD at higher temperatures. Differential scanning calorimetry (DSC) analysis was carried out using NETZSCH STA 449F3 Jupiter® –simultaneous TGA (Germany) in temperature range of 30–200 °C, with heating rate of 10°/min. FTIR spectra were recorded using Thermoscientific Nicolet iS10 spectrophotometer.

3. Results and discussion

3.1. Influence of additives on the polymorphism of curcumin

Powder X-ray diffraction (PXRD) patterns of unprocessed curcumin, curcumin particles precipitated in presence of additives and ultrasound (at ultrasonic irradiation time of 10 min), and XRD patterns of monoclinic (Form 1) [10] and orthorhombic form (Form 3) [10] are presented in Fig. 1. While raw curcumin was

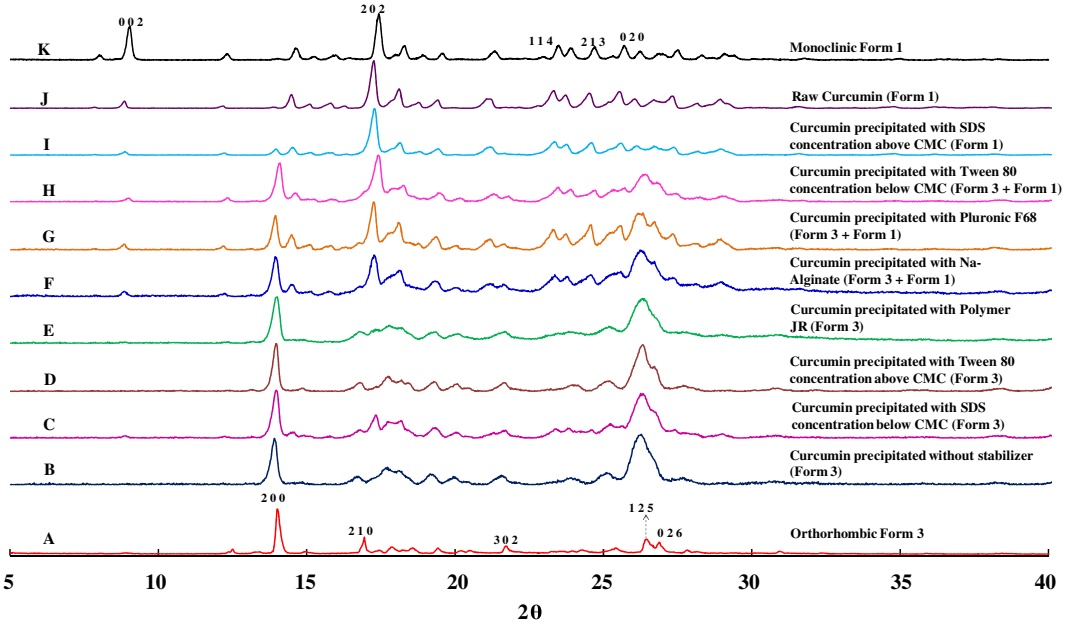

Fig. 1. Overlay of powder X-ray diffraction patterns of (A) Form 3 (orthorhombic form of curcumin), Curcumin precipitated in presence of ultrasound and (B) no additives, (C) SDS as additive with concentration below CMC (0.70 mM), (D) Tween 80 as additive with concentration above CMC (137 μM), (E) Polymer JR 400, (F) Sodium Alginate, (G) Pluronic F68, (H) Tween 80 as additive with concentration below CMC (20 μM), (I) SDS with concentration above CMC (10 mM), (J) Raw curcumin, (K) Form 1 (monoclinic form of curcumin).