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The role of ultrasound in controlling the liquid-liquid phase separation and nucleation of vanillin polymorphs I and II

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ABSTRACT

The influence of ultrasound on liquid–liquid phase separation (LLPS) and polymorphism of vanillin in aqueous solution has been investigated for the first time by varying the ultrasonic parameters such as power, pulse rate and insonation time at ambient condition. Results reveal that the application of ultrasound controls the impact of LLPS and accelerates the nucleation of vanillin within a short period at lower levels of ultrasonic process parameters, and also enhances the quality of the nucleated crystals. Moreover, the application of ultrasound induces the nucleation of rare and metastable polymorph of vanillin Form II in aqueous solution. But, at higher levels of power, pulse rate and insonation time, the rate of LLPS is found increased and the quality of the crystals becomes deteriorated. Morphology of the nucleated polymorphs were identified through optical microscopy and confirmed by optical goniometry. The internal structure and thermal stability of the grown stable Form I and metastable Form II of vanillin were confirmed through powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC) analyses. Further, results suggest that the ultrasound has profound effect in controlling the LLPS and nucleation of vanillin polymorphs in aqueous solution.

1. Introduction

In recent times, the application of ultrasound on the crystallization of various materials carried out by different researchers proved it as a significant tool in providing high quality crystallization and better yield [1–3]. But the mechanism behind the accomplishment of the ultrasound on the crystallization process remains unclear in many cases. It is well known that the physical and chemical effects of ultrasound is mainly contributed by the acoustic cavitation i.e. the formation, growth, and implosive collapse of bubbles in a liquid, and it does not come from any direct interaction with molecular species [4–7]. Vanillin is the naturally occurring compound; it is a primary component of the extract of vanilla bean. However, it can also be synthetically produced, which is commonly used as a flavouring agent in the food, fragrance, beverage and pharmaceutical industries [8]. Crystallization of vanillin is a significant process in aforementioned industries that demands the crystal quality.

Crystallization of vanillin had faced a number of struggles during its early development (at the nucleation level), which includes the tendency of a compound to separate into two liquid phases of widely different solute concentrations known as oiling out. Oiling out, also termed as demixing or liquid−liquid phase separation (LLPS), refers to the appearance of a secondary liquid phase during the crystallization of a compound from solution. The occurrence of LLPS during crystallization of vanillin delays the nucleation and growth processes which ultimately results in impure final products [9,10]. The control of LLPS becomes an important key factor in designing food and pharmaceutical products with desired properties. Also, the isolation of specific crystalline form with preferred properties is a challenging task. To overcome this handicap, it is mandatory to control the occurrence of LLPS and separation of specific polymorph at the laboratory scale which will be useful for industrial scale applications. In the previous reports, the polymorphic behaviour of vanillin was not well resolved. In 1950, W. C. McCrone has reported that vanillin has four different polymorphic forms such as (i) Form I – stable crystalline form, (ii) Form II – metastable form, (iii) Form III and (iv) Form IV. The rapid cooling of small volume of the solution resulted in mixtures of Form I and Form II, Form III was only observed in the course of melt fusion conditions and the occurrence of Form IV polymorph is very rare [11]. Most of the literature reports disclose only the crystallization of stable polymorph of vanillin Form I which can be easily crystallized at normal growth conditions and has many industrial applications [12–16].

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Only very few reports exist on the crystallization of metastable polymorph of vanillin Form II and stated that the nucleation of Form II occurs only in specific conditions [17,18]. In this scenario, it is great emphasis to isolate the rare and metastable polymorph of vanillin Form II using elegant methods. In 2015, Y. Mori et al., reported the selective crystallization of metastable polymorph of acetaminophen using ultrasonic irradiation of different frequencies from the highly supersaturated solution [19]. In 2017, the same group reported the crystallization of the metastable phase of acetaminophen with increased probability and reduced induction time by using the plastic balls during the ultrasonic irradiation process of the aqueous acetaminophen solution [20]. They also reported the metastable growth of acetaminophen using solution-mediated phase transformation (SMPT). They achieved Form II polymorph of acetaminophen with high stability from the low supersaturated solution of trihydrate by using the seed of Form II obtained from the ultrasonic irradiation, to the SMPT process in order to triggering the SMPT process [21]. Till now, no literature report is available on the crystallization of vanillin under the application of external field such as ultrasound. In this regard, an attempt was made to control the LLPS and to study the nucleation behaviour of vanillin in aqueous solution at ambient condition by implementing the sonocrystallization for the first time. Here, we have tuned and optimized the sonication parameters to achieve high quality vanillin polymorphs, because, each polymorph has different molecular arrangements with different crystal structures which may be useful for various industrial applications. Further, the nucleated polymorphs were confirmed by PXRD. Similarly, the possible polymorphic phase transformation and melting point of the polymorphs were identified by DSC analysis. Our intriguing result confirms that the sonication parameters play crucial role for tailoring the polymorphs of vanillin.

2. Experimental

2.1. Materials and methods

Vanillin was purchased from Alfa Aesar (Ward Hill, MA) with 99% purity. The laboratory double distilled water (DD) was used as a solvent. Saturated solution was prepared by dissolving 2.94 g of vanillin in 200 ml of DD water at 32.5 °C. The solution was kept in a round bottom flask attached with ground sleeve and Polytetrafluoroethylene stirrer shaft with blades. The solution was stirred at a rate of 150 rpm for 30 min and kept in constant temperature bath. The solution was filtered using Whatmann No. 41 filter sheets and the filtrate was poured into two clean beakers of 250 ml capacity such that each having 100 ml of solution. One beaker was covered with perforated polyethylene sheets and the solution was allowed for slow evaporation at 32.5 °C. Subsequently, another solution was transferred to sonication chamber as shown in Fig. 1. The sonicator consists of a generator, transducer, temperature probe, probe or horn and a pump which circulate air into the chamber to compensate the increase in solution temperature.

The solution was insonated by varying the power, pulse rate and insonation time. The frequency of ultrasound used in this experiment was 20 kHz. During ultrasonic irradiation, the temperature of the solution was measured using a temperature probe attached to the instrument. After insonation, 25 μL of sonicated solution was withdrawn using micropipette and placed inside a nucleation cell for *in-situ* optical observation. The solution exposed to ultrasound was continuously monitored for nucleation and the nucleated crystals were analysed using Olympus stereo zoom microscope provided with an image analysis system. The same experimental procedure was followed for all 75 experiments by varying the ultrasonic parameters such as, power (from 10 to 30% of 750 W in steps of 5%), pulse rate (10, 30 and 50%) and insonation time (1–5 min). The ultrasonic variables chosen for investigation are shown in Table 1.The crystals grown from the solution exposed to the ultrasound were compared with the crystals grown from the solution without the exposure of ultrasound.

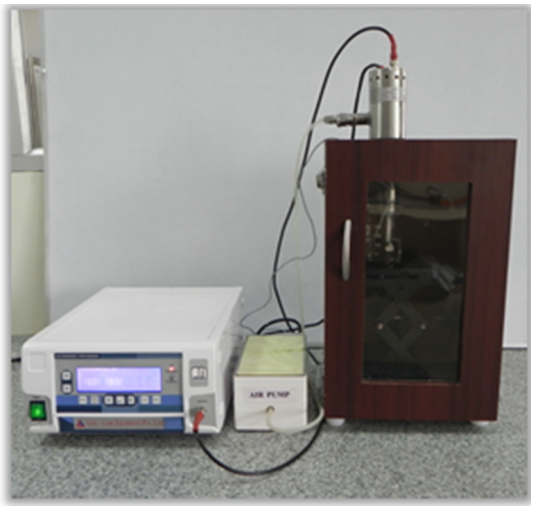

Fig. 1. Experimental setup for the preparation of vanillin polymorphs by sonication.

2.2. Characterization

X-ray powder diffraction of nucleated crystals from the solution with and without the exposure of ultrasound were obtained using Bruker AXS D8 Advance Diffractometer with Cu Kα radiation of 1.5406 Å with scan range of 10–60° in 2θ and step size of 0.05° in 0.5 s respectively. In order to observe the possible polymorphic phase transformation of the harvested polymorphic sample, the DSC thermogram was recorded. Thermograms of the nucleated polymorphs from the solutions with and without the exposure of ultrasound were recorded on a TA Instruments DSC-Q20 V24. The thermal behaviour of samples, placed in sealed aluminum pans, was studied under a nitrogen purge with a heating rate of 10 °C/min covering a temperature from 40 to 90 °C.

3. Results and discussion

3.1. Nucleation of vanillin without ultrasonic irradiation

LLPS of vanillin is a major hitch during the solution crystallization of vanillin polymorphs which impedes the crystallization process. Generally, LLPS occurs in saturated vanillin solution when the concentration and temperature exceeds their critical values. The inclusion of secondary liquid phase within the growing crystal strongly influences the quality of final product and its transparency. The intrusion of LLPS in the solution delays the nucleation and growth of the vanillin crystals [22]. Fig. 2 describes the microscopic images of crystallization of vanillin from the solution without the exposure of ultrasound. It can be seen that the presence of LLPS has strongly affected the crystallization and transparency of the crystal.

3.2. Nucleation of vanillin with ultrasonic irradiation

To control the augmentation of LLPS in aqueous solution, the solution was irradiated with ultrasound under various power, insonation time and pulse rate.