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Nucleation control and separation of paracetamol polymorphs through swift cooling crystallization process

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ABSTRACT

Polymorphic nucleation behavior of pharmaceutical solid paracetamol has been investigated by performing swift cooling crystallization process. Saturated aqueous solution prepared at 318 K was swiftly cooled to 274 K in steps of every 1 K in the temperature range from 274 K to 313 K with uniform stirring of 100 rpm. The resultant supersaturation generated in the mother solution favours the nucleation of three different polymorphs of paracetamol. Lower supersaturation region $\sigma = 0.10–0.83$ favours stable mono form I; the intermediate supersaturation region $\sigma = 0.92–1.28$ favours metastable ortho form II and the higher supersaturation region $\sigma = 1.33–1.58$ favours unstable form III polymorphic nucleation. Depending upon the level of supersaturation generated during swift cooling process and the corresponding solubility limit and metastable zone width (MSZW) of each polymorph, the nucleation of a particular polymorph occurs in the system. The type of polymorphs was identified by in-situ optical microscopy and the internal structure was confirmed by Powder X-ray diffraction (PXRD) study. By this novel approach, the preferred nucleation regions of all the three polymorphs of paracetamol are optimized in terms of different cooling ranges employed during the swift cooling process. Also solution mediated polymorphic transformations from unstable to mono and ortho to mono polymorphs have been studied by in-situ.

1. Introduction

Polymorphism occurs when a molecule can pack in more than one stable orientation, giving two or more different crystal structures and thus polymorphs can have divergent physical properties. Most important characteristics are the differing solubility and dissolution rates, as they significantly alter pharmacokinetic factors, such as rate of absorption and drug availability [1]. Therefore systematic screening for polymorphs has become an essential step in drug development to select as far as possible optimal properties for the drug materials [2]. Paracetamol ($C_8H_9NO_2$) an excellent analgesic and antipyretic drug crystallizes in three different polymorphs monoclinic form I, orthorhombic form II and unstable form III [3–5]. The chemical formula of the two known polymorphs form I and form II are the same but they vary only in their crystallographic structure through hydrogen bonding. Form III polymorph has been shown to be highly unstable and has only been crystallized in confined environments [6,7]. Several different operating parameters such as slow cooling, seeding strategy, additives, multicomponent crystallization and polymer heteronuclei [8–12] have been tried to control the polymorphic behavior of paracetamol during crystallization process. All these methods employed experienced mysterious of assessing polymorphic behavior of this compound and were able to crystallize only the two polymorphs form I and form II under different experimental conditions and until now it remains a formidable challenge. Recently, by the novel swift cooling crystallization process, a method which has recently been employed for the nucleation control and separation of L-glutamic acid polymorphs [13,14], we have isolated the nucleation regions of all the three different polymorphs of paracetamol in terms of supersaturation ranges from pure aqueous solution by varying the initial concentration of the mother solution at fixed temperature 278 K [15].

In the present study, we have employed the same swift cooling crystallization process in which the experimental solutions are saturated initially at 318 K and swiftly cooled down to various temperatures in the range 274 K–313 K in steps of every 1 K. As a consequence different supersaturation levels were achieved through different cooling ranges employed and preferred nucleation regions of different polymorphs were identified. Also solution mediated polymorphic transformation from (i) unstable to stable mono and (ii) metastable ortho to stable mono has been studied under in-situ optical microscopy. Hence the nucleation control and separation of the polymorphs is achieved through different cooling ranges employed by this novel method.

2. Experimental procedure

2.1. Swift cooling crystallization process

Saturated pure aqueous solution of paracetamol was prepared at 318 K in 100 mL of laboratory double distilled water according to the solubility (2.9 g/100 mL), filtered and taken in an airtight

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round-bottom flask with ground sleeve stirrer gland attachment for effective stirring. This setup was kept inside the digitally controlled full visibility constant temperature bath (CTB) with in-built cryostat facility having temperature accuracy of ± 0.01 °C. The temperature of the CTB was maintained at 353 K and the solution was stirred continuously for 3 h at a speed of 100 rpm constantly through a digitally controlled stepper motor drive. After that, the solution was filtered twice with Whatmann no. 1 filter sheet; the filtered solution was collected into another similar round bottom flask with similar stirring assembly and maintained for about 1 h at 353 K for seasoning. Then the solution was swiftly transferred to another similar CTB which was kept nearby and maintained at a temperature 274 K. The solution was carefully monitored through the full visibility window of CTB under bright light illumination and the events were recorded with time. After 10 min i.e., after the attainment of the experimental temperature, the solution turns milky white indicating the beginning of nucleation and within another 4min, accumulation of small crystalline particles appears at the bottom of the flask. The induction period of nucleation, time taken by the solution to nucleate after attaining the experimental temperature was noted down. A small portion of the solution containing these nucleated crystalline particles were carefully taken in a nucleation cell maintained at the same temperature and examined under Olympus Stereozoom microscope SZX16 attached with Jenoptic ProgRes CT3 digital camera. The morphology of the nucleated crystalline particles of paracetamol polymorphs were identified and photographed. The experiment was repeated in steps of every 1 K in the temperature range 274 K–313 K and the nucleated crystals in each case were photographed. The internal structure of the nucleated polymorphs was confirmed by PXRD.

3. Results and discussion

3.1. Effect of supersaturation on the nucleation of paracetamol polymorphs

Supersaturation as the driving force of crystallization is the key thermodynamic variable that affects the kinetics of crystal nucleation and growth for the occurrence of different polymorphs. In swift cooling crystallization process, the superheated experimental solution was swiftly cooled to various low temperatures which would be liable for the creation of different initial supersaturation levels in the solution. Upto the maximum of $\sigma = 1.58$, the relative supersaturation levels generated corresponding to different cooling rates employed in the present work is shown in Fig. 1. The concentration–temperature plot shown in Fig. 2 was constructed with respect to solubility and corresponding metastable zone width (MSZW) of all the three polymorphs in the experimental temperature range 274 K–353 K. The point (c, t) in the phase diagram represents the concentration of

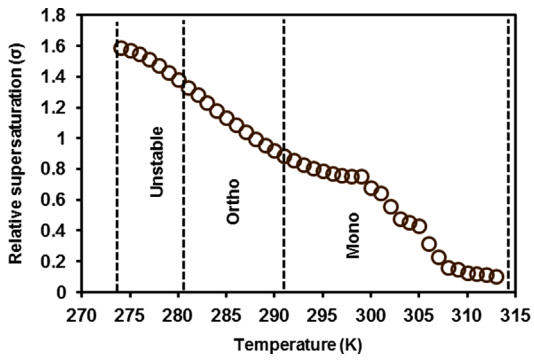

Fig. 1. Variation in supersaturation with respect to temperature.

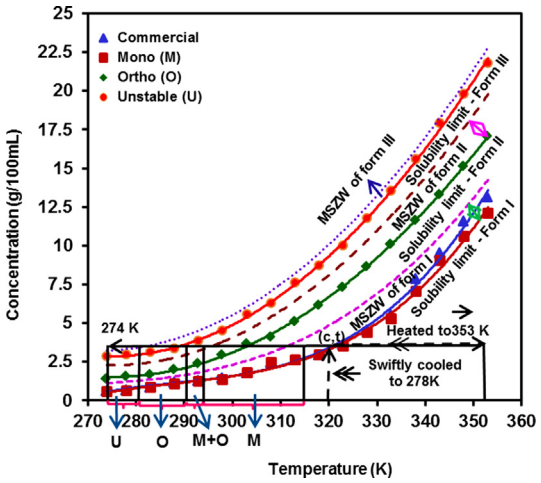

Fig. 2. Phase diagram of swift cooling crystallization process of paracetamol polymorphs.

the solute 'c' and the corresponding temperature 't' considered. When the prepared experimental paracetamol solution with this initial concentration is swift cooled from 353 K to 274 K, the concentration position line corresponding to the temperature 274 K in the concentration temperature field (point c, t) crosses the MSZW and enters into the labile region of form III. Hence the resultant supersaturation $\sigma = 1.58$ corresponding to the temperature 274 K favours the nucleation of unstable form III polymorph. With further increase in temperature in steps of 1 K, in the supersaturation range $\sigma = 1.58$–1.33 corresponding to the temperature range 274 K–281 K, the point (c, t) lies well above the MSZW of form III yielding 100% form III polymorph.

In the case of supersaturation $\sigma = 1.28$ corresponding to the temperature 282 K, the point (c, t) ends up well below the MSZW of form III and well above the solubility line of form III. Even though the concentration of the solution is above the solubility line of form III, nucleation is not yet observed as the point (c, t) ends within the MSZW. Hence this region is more favorable for form II nucleation. Thus in the supersaturation range $\sigma = 1.28$–0.85 corresponding to the temperature range 282 K–290 K, the point (c, t) is well above the MSZW of form II yielding only 100% form II nucleation. Moreover in the supersaturation level $\sigma = 0.88$ and $\sigma = 0.85$ corresponding to the temperature 291 K and 292 K, mixture of both form II and form I was observed as the point (c, t) lies below the MSZW of form II and moves towards the labile region of form I. In the supersaturation level $\sigma = 0.83$ corresponding to the temperature 293 K, the concentration of the solution decreases and makes the point (c, t) ends up well below the MSZW of form II. Hence no nucleation of form II was observed and only the nucleation of form I was observed. Thus the resultant supersaturation in the solution in the range $\sigma = 0.83$–0.10 corresponding to the temperature range 293 K–313 K is low. As the temperature increases, the concentration of the solution decreases further and moves the point (c, t) towards the labile region of form I yielding 100% form I nucleation.

3.2. Variation in induction period with respect to supersaturation

The induction period of nucleation of all the three polymorphs decreases with respect to increase in the level of supersaturation in the solution. Among the three polymorphs, the induction period for the nucleation of unstable polymorph is very short it is of the order of 5 min initially when $\sigma = 1.58$ and it increases to 16 min when the supersaturation $\sigma = 1.33$. The induction period for the nucleation of orthorhombic polymorph is about 18 min when the supersaturation $\sigma = 1.28$ and it increases to 43 min when the