Materials Science and Engineering C 47 (2015) 150–155

Contents lists available at ScienceDirect

Materials Science and Engineering C

journal homepage: www.elsevier.com/locate/msec

A novel method for the separation of mono and ortho polymorphs of paracetamol in gel matrix

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ARTICLE INFO

Article history:
Received 9 July 2014
Received in revised form 21 September 2014
Accepted 13 November 2014
Available online 15 November 2014

Keywords:
Acetic acid
Diffusion
Ethanol
Mixing
Nucleation
Crystal morphology

ABSTRACT

The nucleation control and separation of mono and ortho polymorphs of the important pharmaceutical solid paracetamol were carried out through a crystallization process in gel media for the first time. Crystallization of mono and ortho polymorphic forms of paracetamol was achieved by optimizing the experimental parameters such as the specific gravity, pH, height of the gel column and solute concentration at ambient temperature. The optimized experimental conditions favor the generation of necessary supersaturation responsible for the nucleation of preferred polymorph at different levels in the gel column and also endure the stability of the grown orthorhombic polymorphs at ambient conditions. Accordingly the needle like metastable orthorhombic polymorph nucleates at the top portion of the gel column whereas the prismatic stable monoclinic polymorph nucleates mostly at the bottom level. Morphology of the nucleated polymorphs was analyzed and their crystalline structures were confirmed by PXRD. FTIR analysis revealed the shifting of absorption peaks of few functional groups corresponding to both the polymorphs due to the difference in their structural nature. DSC analysis revealed that the grown ortho polymorph form II transforms to mono form I at 89.47 °C while the grown mono form I retains its phase until melting.

1. Introduction

The process of separation of polymorphs of a specific pharmaceutical material at nucleation level has gained enormous momentum in various industrial processes. Necessary experimental conditions optimized for obtaining specific polymorphs at the laboratory scale will be useful for most of industrial processes. Paracetamol, a widely used analgesic and antipyretic drug, crystallizes in three polymorphic forms: monoclinic (form I), orthorhombic (form II) and unstable form (III) [1–4]. Commercially available monoclinic form I lacks slip planes in its crystal structure and has poor compression for compactability. Orthorhombic form has well developed slippage planes and it undergoes plastic deformation under compaction. Consequently, form II becomes potentially more attractive in the industrial stand point for direct compression of tablets [4]. It is often easy to obtain the thermodynamically stable monoclinic form from solutions with different solvents by slow evaporation of solvent method at room temperature [4,5]. However, the crystallization of metastable orthorhombic form is very difficult under normal growth conditions. There have been various reports in the literature on the crystallization of orthorhombic form by different experimental methods, but most of them involve vast sophisticated instrumentation like FBRM, multicomponent crystallization principle, polymer heteronuclei or the presence of selective additives [6–12]. Among various crystallization techniques, gel growth has gained attraction as a fascinating technique, offering several practical benefits due to its simplicity and cost effectiveness [13–16]. The use of gels as growth media has been reported previously in the literature for a wide range of compounds, including both inorganic and organic compounds and also proteins [17–20].

Though there are several reports available on the growth of paracetamol polymorphs by solution method [4,6,7], no reports are so far available on the growth of paracetamol polymorphs by gel method. For the first time we report the nucleation and crystallization of paracetamol polymorphs through gel media. The nucleation of metastable and stable polymorphs was successfully separated at different sections of the gel column by optimizing different experimental parameters such as specific gravity, pH, height of the gel column and solute concentration. Morphology of the polymorphs was analyzed and their internal crystallographic structure was confirmed by powder X-ray diffraction. Functional groups present in the grown polymorphs were analyzed by FTIR. Thermal stability of the polymorphs in the temperature range from ambient to its melting point was studied by DSC.

2. Experimental procedure

2.1. Materials and methods

Acetaminophen (Sigma Aldrich,), sodium metasilicate (Central Drug House), ethanol (Hayman) and acetic acid (Merck) were received with

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http://dx.doi.org/10.1016/j.msec.2014.11.053
0928-4931/

Batch No. 030M0071V, 09122, 00/240A3 and AC8A580119, respectively. Silica gel prepared from sodium metasilicate aqueous solution was used as the crystallizing growth medium and test tubes were used as crystallizing vessels. Sodium metasilicate stock solution (SMS) of specific gravity 1.06 g/cm^3 (A) was prepared at ambient temperature by dissolving sodium metasilicate in laboratory double distilled water, filtered and stored in an amber bottle in order to avoid the oxidation of sodium metasilicate from outer atmosphere. The water–ethanol solvent mixture with mixing ratio 1:1 was used as the solvent to prepare saturated paracetamol solution at ambient temperature. The experimental solution (B) was prepared by mixing equal volumes of the following two stock solutions (i) water–acetic acid (0.072 mole fraction) solution and (ii) water–ethanol (1:1) and paracetamol (0.03 mole fraction) solution. These chemical combinations were optimized by conducting several trial experiments. The prepared experimental solution was prefiltered by vacuum method followed by online pressure filtration with microfilter of 15–40 μm pore size using peristaltic pump. Different volumes of SMS stock solution (A) were mixed with the experimental solution (B) to attain the desired pH of the resultant experimental solution (C) which in turn leads to the variation in the height of the gel column as shown in Table 1. The pH value of the final experimental solution (C) was measured using EUTECH pH TUTOR instrument.

Table 1
Variation in pH and height of the gel column with respect to the volume of SMS solution (A).

Volume of SMS solution A (mL)	Net pH	Height of the gel column (mm)
7	4.25	270
7.1	4.3	271
7.2	4.35	272
7.3	4.4	273
7.4	4.45	274
7.5	4.5	275
7.7	4.55	277
7.9	4.6	279
8.1	4.65	281
8.3	4.7	283
8.5	4.75	285
8.7	4.8	287
9	4.85	290
9.1	4.9	291
9.25	4.95	292.5
9.45	5	294.5
9.6	5.05	296
9.75	5.1	297.5
9.95	5.15	299.5
10.1	5.2	301
10.35	5.25	303.5
10.6	5.3	306
10.75	5.35	307.5
10.9	5.4	309
11.15	5.45	311.5
11.3	5.5	313
11.45	5.55	314.5
11.7	5.6	317
11.95	5.65	319.5
12.2	5.7	322
12.45	5.75	324.5
12.65	5.8	326.5
12.8	5.85	328
12.95	5.9	329.5
13.15	5.95	331.5
13.4	6	334
13.55	6.05	335.5
13.75	6.1	337.5
14	6.15	340
14.2	6.2	342
14.5	6.25	345
14.75	6.3	347.5
14.9	6.35	349
15.05	6.4	350.5
15.25	6.45	352.5
15.5	6.5	355

In order to achieve the maximum possible uniformity of the final experimental solution (C) throughout the gel column, it was mixed effectively with magnetic stirrer before being transferred into the experimental test tube. Then the test tubes were sealed with perforated rubber corks for controlled evaporation of the solvent molecules from the top of the gel column during the growth process. Five test tubes with similar combination of solutions were prepared for each pH in order to minimize the errors during the experimental runs. The entire experimental setup was kept undisturbed in the controlled evaporation chamber to prevent atmospheric contamination of the exposed surface of the gel column. The gelation time varies from 12–24 h at room temperature and this variation of the gelation time with respect to pH of the solution was noted down. The gel column was continuously monitored for nucleation and the nucleation time of the polymorphs was measured precisely. Similar systematic procedures were followed and the pH of the gel solution was varied in the range from 4.25–6.5 in steps of 0.05 by altering the volume of the stock solution (A) in the mixture (B) and best condition for the growth was optimized. After the completion of the growth, crystals were harvested carefully by separating them from the gel using double distilled water. The harvested crystals were air dried and photographed. The grown paracetamol single crystals were characterized by powder X-ray diffraction using a Bruker D8 Advanced diffractometer with CuKα radiation of wavelength 1.5406 Å with operating voltage of 40 kV and current of 30 mA and FTIR was recorded in the wavenumber range 4000–400 cm^{-1} using a Bruker Tensor 27 spectrometer by KBr pellet technique. The thermal stability of the grown crystals was studied using DSC TA Q20 model by heating the sample in the temperature range 40–200 °C at a heating rate of 1 °C/min in nitrogen atmosphere.

3. Results and discussion

3.1. Effect of supersaturation on the growth of paracetamol single crystals

Generally the solubility of paracetamol in water is very low in the order of about 1.8 g/100 mL whereas, in ethanol the solubility is comparatively high and is about 18 g/100 mL; in pure acetic acid it is about 10.9 g/100 mL. The determined solubility value of paracetamol was compared with the previous literature value [21]. In our experimental study the solubility of paracetamol in the 1:1 water–ethanol solvent mixture was about 19.2 g/100 mL which is higher than the solubility in pure ethanol. The solubility of paracetamol in water, ethanol and acetic acid mixture was about 19.7 g/100 mL. The solubility of paracetamol was determined by gravimetric method by dissolving solute in the solvent maintained at a constant temperature with continuous stirring. On reaching the saturation, the equilibrium concentration of the solute was determined. A sample of clear supernatant liquid was withdrawn by means of a warmed pipette and a weighed quantity of the sample was analyzed. The solubility of paracetamol was determined in (i) pure ethanol, (ii) 1:1 water–ethanol mixture and (iii) water, ethanol and acetic acid mixture by repeating the following procedure.

Saturated solution of paracetamol prepared with water–ethanol solvent mixture became under saturated on addition to the water–acetic acid solution. Thus the experimental solution B contains water, ethanol, acetic acid and paracetamol but in an under saturated state. When the SMS stock solution A was added to B, the saturation of paracetamol reduces further due to the presence of additional water content in solution A. When this final experimental solution C was transferred to the test tube and left undisturbed, gelation occurs. There was liberation of water molecules in the solution which led to the dilution of the acetic acid concentration and results in the variation in gel density when the gelation took place. The dilution of acetic acid leads to the solubility reduction because the solubility of paracetamol in diluted acetic acid {water–acetic acid (0.072 mole fraction)} was found to be 3.6 g/100 mL