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

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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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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

which is less when compared to that of pure acetic acid. Due to the gelation, supersaturation is generated throughout the gel column. There is always a possibility of higher supersaturation to be generated at the top of the gel column due to the evaporation of the solvent molecules when compared to the rest of the portions. High concentration generated at the top of the gel column slowly diffuses into it in due course results in setting up a concentration gradient.

This led to a situation where higher concentration always persisted at the top of the test tube when compared to the bottom portion. The nucleation of different polymorphs of paracetamol took place at different sections of the gel column wherever they could avail their corresponding favorable supersaturation condition. Hence, the metastable orthorhombic polymorph which always requires higher supersaturation for nucleation comparatively, nucleated at the top of the gel column and the monoclinic polymorph which nucleates relatively at lower supersaturation was observed at the bottom of the test tube. This outcome was observed in the experiment for the volume of SMS added in the order of about 7–7.5 mL to set the pH values in the range 4.25–4.5.

In this pH range, both monoclinic form I (prismatic) and orthorhombic form II (needle-like) were found to be grown in the gel column. Needle like metastable orthorhombic crystals were observed inside the gel originating from the top interface and growing downwards towards the gel column. This is due to higher supersaturation created as a result of faster evaporation of solvent molecules at the top portion of the gel. There is an accumulation of higher concentration of solute molecules at the top interface of the gel leading to the nucleation of needle like orthorhombic crystals. At the same time, the concentration is comparatively low at the bottom of the gel column where there is no possibility of evaporation and it favors only the nucleation of monoclinic form I crystals. It was found that the grown orthorhombic single crystals were about 10 mm in size along their long axis and its population density increased with time. The size of the obtained monoclinic crystals was found to be around 8 mm along their long axis. It was also found that the transparency of the growing crystals reduced and became yellowish orange in color. This can be due to the longer exposure to light. This effect was also observed in our conventional solution growth experiments and was also reported by other researchers [11]. Photographs of the grown mono and ortho polymorphs of paracetamol single crystals at pH 4.45 and their corresponding morphologies are shown in Fig. 1.

The above procedure was followed by further increasing the volume of SMS solution in the range 7.6–15.5 mL to set the pH value in the range 4.55–6.5. The addition of SMS solution A into solution B further increased the water content and the height of the gel column, thereby decreasing the initial supersaturation levels of paracetamol to an undersaturated state. In the pH range from 4.55–4.75, microcrystalline mass of monoclinic form I of comparatively poor quality was observed as the first precipitate at the gel interface followed by the typical distribution of monoclinic form I paracetamol single crystals in the middle of the gel column. The resulting supersaturation achieved in this second set of experiments does not favor the nucleation of the metastable orthorhombic polymorph and favors only the stable monoclinic form. The supersaturation created initially at the interface of the gel in this second set of experiments was less when compared to that of the first set of experiments and hence favored only the nucleation of the monoclinic polymorph. This was based on the local concentration of chemical species distributed by diffusion according to the available supersaturation in the gel medium. The monoclinic crystals thus obtained have prismatic morphology with size of about 5 mm.

With increase in pH in the range 4.8–4.95, prismatic monoclinic crystals with size of about 4 mm along their long axis were formed. As the pH increases in the range 5–5.25, monoclinic crystals with diamond shaped platelet like morphology with size of about 3 mm along their long axis were observed. Further increase in pH in the range 5.3–6.5 results in small crystals with size ≪3 mm along their long axis. Photographs of the paracetamol single crystals grown at pH 4.65, 4.9, 5.2 and 6.5 and their corresponding morphologies are shown in Fig. 2a–d respectively.

It was observed that at pH 6.5, a change in color was observed in the gel column as well as in the crystals due to prolonged exposure to light for about 25 days during the growth process. The variations in the gelation and nucleation times with respect to pH are shown in Figs. 3 and 4 respectively. It was observed that as the pH increases above 6.5, the crystals obtained were not well defined. This can be due to the reduction in diffusion rate, which affects the supply of nutrients readily to the already nucleated growing crystals and their growth rate significantly; which at the same time enhances the number of fresh nucleation locally. Hence the number of crystals growing per unit area reduces and the crystals were scattered in regions throughout the gel column. The repeatability of the results obtained reveals that the nucleation of mono and ortho polymorphs of paracetamol very much depends on the pH of the mother solution in the gel column.

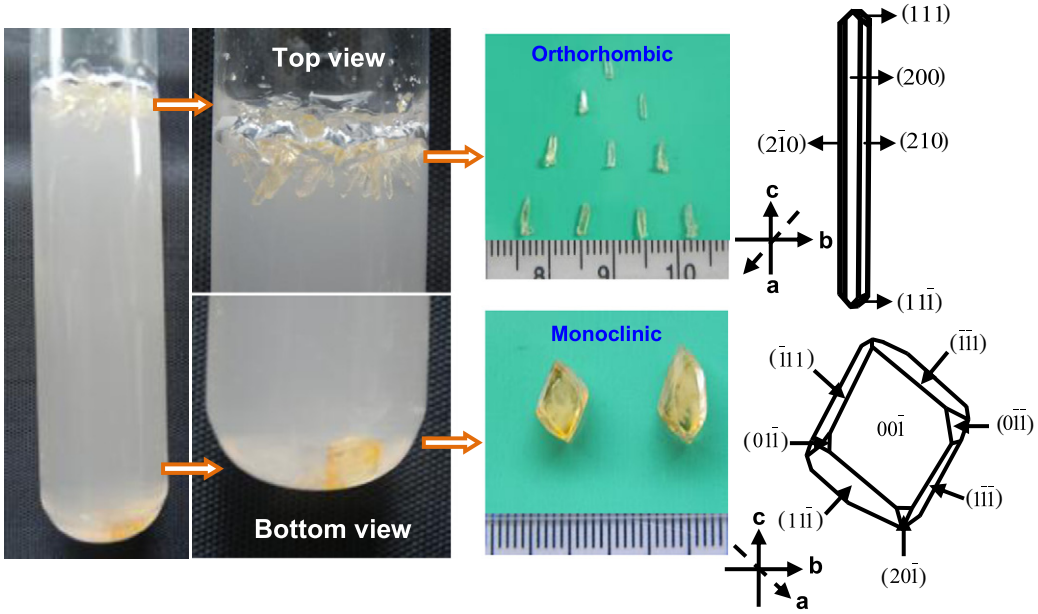

Fig. 1. Photograph of the grown monoclinic and orthorhombic single crystals of paracetamol observed at pH 4.45.

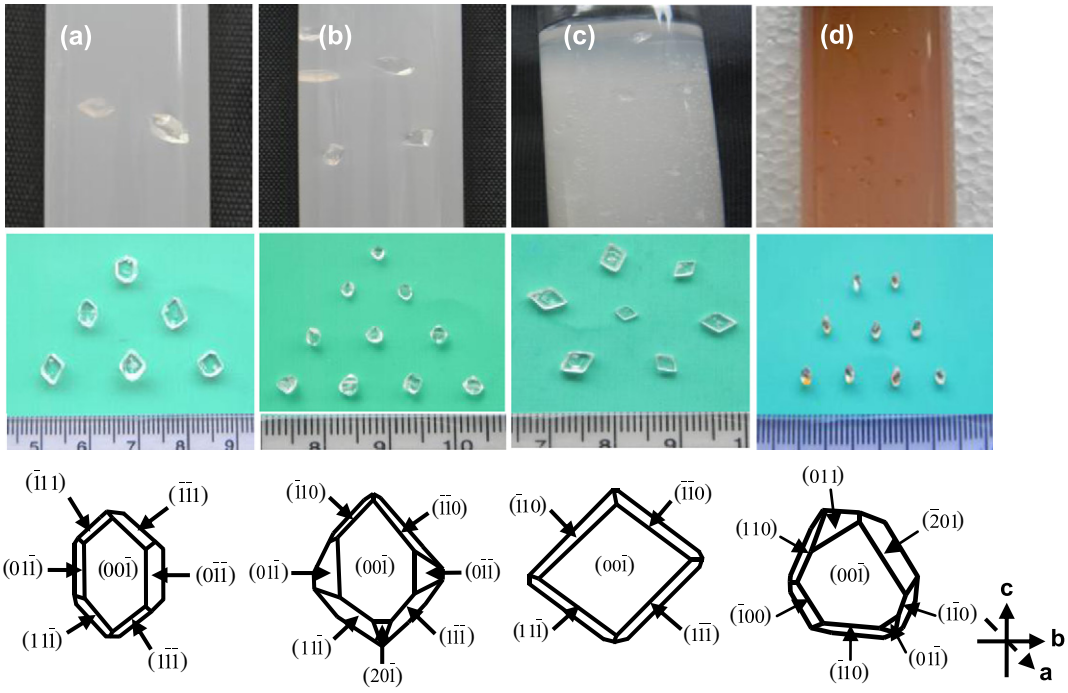

Fig. 2. Photograph of the grown monoclinic paracetamol single crystals observed at (a) pH 4.6, (b) pH 4.9, (c) pH 5.2 and (d) pH 6.5 and their corresponding morphologies.

From our experimental results, we observed that the size of nucleated paracetamol crystals at lower pH 4.25 shows relatively larger than that of the crystals nucleated at higher pH 6.5. This variation in crystal size is very much dependent on the nature of gel density formed at different pH levels. In general at lower pH, the form of long-chain polymerization builds up well developed three dimensional network having pore size larger and hence the gel densification is found to be tender. Whereas at higher pH, the gel densification increases resulting the pore size to be narrower [22,23].

3.2. Variation in nucleation and growth periods of the crystals at different levels of the gel column

It was evidently observed that the nucleation period as well as the growth period of paracetamol single crystals grown at different sections of the gel column in all the experiments in the present work greatly depend on the supersaturation level in the solution. The time taken for the nucleation was monitored continuously and is found to vary from 7 min to 61 h. The total period of growth observed for all the grown crystals varied between 2–10 days. It was also found that the growth rate of the crystals varied at different levels of the gel column. The growth rate was fast around the top interface section which can be due to the availability of higher concentration near the interface and comparatively slow near the bottom of the gel column due to the availability of comparatively lower concentration of the growth species.

3.3. Growth morphology

Morphology of the grown paracetamol crystals was analyzed by an optical goniometer. There were three different morphologies of the grown crystals obtained from all the experiments carried out in the present study: prismatic, diamond shaped platelet like and needle like. It was observed that the growth processes and the crystal morphology for the growth of the paracetamol crystals were strongly supersaturation dependent. The prismatic and diamond shaped platelet monoclinic crystals show the $(00\bar{1})$ as the prominent face in their morphology which represents the slow propagation of this face. The side facets such as $(01\bar{1})$, $(0\bar{1}\bar{1})$, $(\bar{1}11)$, $(\bar{1}\bar{1}1)$, $(11\bar{1})$, $(1\bar{1}\bar{1})$, $(\bar{1}10)$, $(\bar{1}\bar{1}0)$, $(\bar{1}00)$ and $(20\bar{1})$ are the fast growing faces. The needle shaped orthorhombic crystal shows (200), (210) and $(2\bar{1}0)$ faces as the dominant, whereas the faces (111) and $(11\bar{1})$ are the fastest growing faces. This observed growth rate anisotropy of these crystals was due to the occurrence of change in growth mechanism of the respective growth faces with respect to the available supersaturation levels of the system locally.

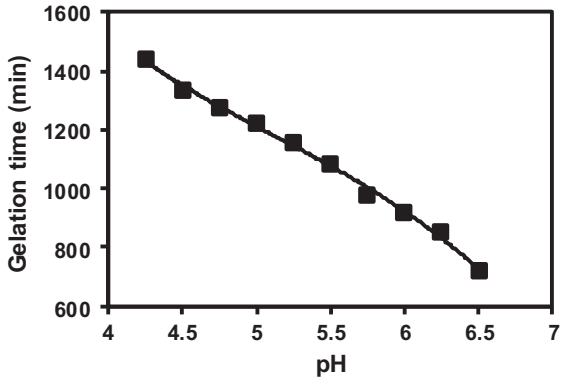

Fig. 3. Variation in gelation time with pH.

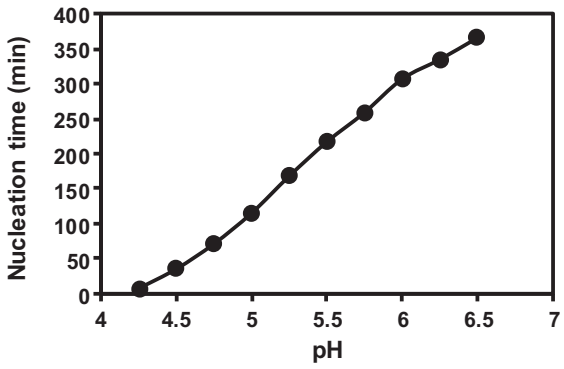

Fig. 4. Variation in nucleation time with pH.

3.4. Crystal yield

The total crystallization yield was calculated using the relation

$$\text{Percentage Yield}(Y\%) = \frac{\text{Mass of the collected crystals}}{\text{Mass of the solute dissolved in 10 mL of solvent}} \times 100$$

where 'Y' denotes the total % of the crystallization yield. From the experimental observation it was significantly noted that the total crystallization yield ranged from 72 to 35% covering the pH range from 4.25–6.5. An appreciable yield of ortho crystals was observed in the pH range 4.25–4.5 (i.e. $Y_o = 43$–20% where, 'Y_o' is the % of ortho crystals calculated from the value of Y) below which nucleation of ortho was absent. Whereas the yield of mono crystals was found to ascend from the pH range 4.25–4.5 (i.e. $Y_m = 57$–80% where, 'Y_m' is the % of mono crystals calculated from the value of Y) after which a 100% of nucleation of mono crystals was observed in the pH range 4.5–6.5 as shown in Table 2. Hence, it was clear that the optimal pH to obtain the highest proportion of the orthorhombic form is at 4.25.

3.5. Powder X-ray diffraction analysis

Fig. 5 shows the PXRD patterns of the grown paracetamol single crystals at room temperature. In Fig. 7(a), the characteristic peaks observed at 15.52°, 18.16°, 24.36° and 26.5° 2θ correspond to (101), (146), (240) and (116) reflections respectively of the monoclinic form I and in Fig. 7(b), the diffraction peaks observed at 14.95°, 19.20°, 24.02° and 26.2° 2θ correspond to (020), (022), (200) and (202) reflections respectively of the orthorhombic form II. The lattice parameters determined from the XRD data collected for the monoclinic form I such as a = 7.12 Å, b = 9.81 Å, c = 11.74 Å and β = 97.63° further confirm the crystal system. Similarly, the lattice parameters determined from the observed XRD data for the orthorhombic form II such as a = 17.12 Å, b = 11.81 Å and c = 7.24 Å confirm the form of crystallization. Moreover the calculated lattice parameter values are in line with the literature values [4].

3.6. Fourier transform infrared spectroscopy

Fig. 6 shows the FTIR spectra of the grown paracetamol mono and ortho single crystals. The vibrational frequencies attributed to various functional groups corresponding to the paracetamol molecules were identified by FTIR analysis. Noticeable differences were observed in the assignment of functional groups such as N–H stretching (3327 cm^{-1} for mono and 3329 cm^{-1} for ortho), O–H stretching (3162 cm^{-1} for mono and 3180 cm^{-1} for ortho), C═O stretching (1649 cm^{-1} for mono and 1654 cm^{-1} for ortho), C–H symmetric stretching mode vibration (1502 cm^{-1} for mono and 1512 cm^{-1} for ortho) and C–N stretching mode vibration (1226 cm^{-1} and 1217 cm^{-1}) for both form I and form II. The absorption peaks observed at 837, 684, 605 cm^{-1} for mono and 836, 682, 603 cm^{-1} for ortho are due to out of plane C–H bending (aryl-1, 4 disubstituted) [24,25].

Table 2
Percentage of variation in crystallization yield.

pH	Total crystalline yield (Y %)	Crystal yield (%)	
		Mono (Y_m)	Ortho (Y_o)
4.25	72	57	43
4.3	67	62	38
4.35	63	68	32
4.4	59	72	25
4.45	56	79	21
4.5	53	80	20
4.55–6.5	49–35	100	–

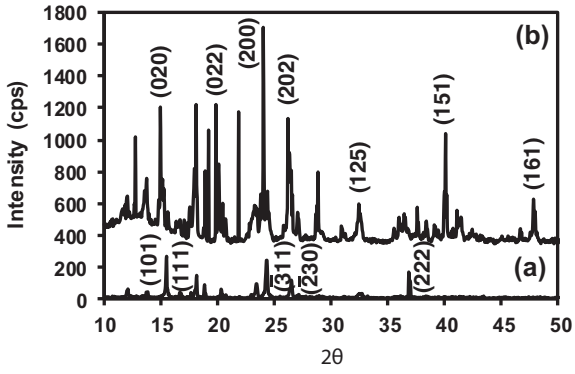

Fig. 5. Powder X-ray diffraction pattern of the grown paracetamol crystals (a) form I and (b) form II.

3.7. Differential scanning calorimetry

Fig. 7 shows the DSC thermograms of the grown paracetamol mono and ortho single crystals. In Fig. 7a, the sharp endothermic peak appearing at 168.87 °C indicates the melting point of the monoclinic form I. In Fig. 7b the DSC curve of orthorhombic form shows an endothermic peak before its melting transition which starts at 89.18 °C and peaked at 89.47 °C followed by a sharp endothermic peak at 168.48 °C. This shows that the crystal undergoes a solid-state transformation of forms II to I at 89.47 °C [26], followed by the melting of form I at 168.48 °C [4,27].

It is important to note from the above characterizations that the crystallized paracetamol polymorphs in the present work exist with 100% purity and no reaction took place between the components dissolved in the gel constituents during their growth. It can be clearly seen that the dissolved components such as water–ethanol mixture act only as the solvent and the acetic acid acts only as the gelating agent during the nucleation and growth processes of the crystals and there was no chemical reaction between the above solution mixtures and the paracetamol solute during the experiments in gel column.

4. Conclusion

Stable mono and metastable ortho polymorphs of paracetamol single crystals were isolated and crystals of good quality were grown successfully for the first time in gel media. From our present experimental investigations, we concluded that the optimized pH range of 4.25–6.5 is the best suitable for growing paracetamol single crystals in the gel matrix. The concurrent evaporation and diffusion processes occurring in the gel medium offered the necessary driving force for the isolation of paracetamol polymorphs and for the formation of crystals with different morphologies. Morphological variation in the grown paracetamol

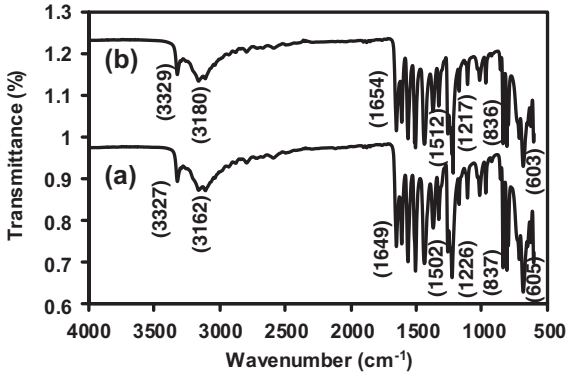

Fig. 6. FTIR spectra of the grown paracetamol crystals (a) form I and (b) form II.

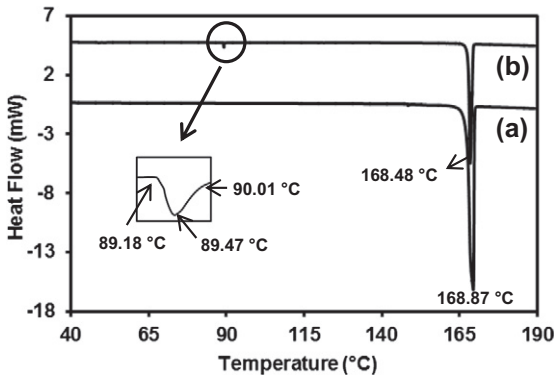

Fig. 7. DSC thermogram of the grown paracetamol crystals (a) form I and (b) form II.

crystals is related to the changes in supersaturation existed in the system. The metastable orthorhombic paracetamol single crystals grown by gel technique remained stable at room temperature for quite long period of time without undergoing any phase transformation. The type of nucleated ortho and mono polymorphs and their form of crystallization was confirmed using powder X-ray diffraction method. The functional groups were identified by FTIR and the phase transformation of forms II to I was confirmed by DSC analyses. In conclusion, an elegant and simple method to achieve the nucleation and crystallization of the most wanted orthorhombic form of paracetamol with high state of purity is presented.

Acknowledgments

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