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Solid-state transformation of different gabapentin polymorphs upon milling and co-milling

Shan-Yang Lin[a,*], Cheng-Hung Hsu[b], Wen-Ting Ke[b]

[a] Lab. Pharm. Biopharm., Department of Biotechnology, Yuanpei University, No. 306, Yuanpei Street, Hsin Chu, Taiwan, ROC
[b] Depart. Res. and Develop., Orient Pharma Co., Ltd., Taoyuan, Taiwan, ROC

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ABSTRACT

The purpose of this study was to investigate the milling effect on the polymorphic transformation of four gabapentin (GBP) Forms I–IV in the absence of additive. Four polymorphs of GBP were previously prepared and identified, in which the GBP Form I was proven to be a monohydrate, but other GBP Forms II–IV belonged to anhydrate. The GBP Form II was the most stable polymorph available in the market. The co-milling process affecting the polymorphic stability of GBP Form II with different additives was also examined. During the 120-min-milling or co-milling course, the milled sample was withdrawn at prescribed intervals for Fourier transform infrared (FTIR) microspectroscopic determination. In the absence of additive, each polymorph of GBP exhibits a different polymorphic transformation behavior in the 120-min-milling course. The results indicate that GBP Form I was previously dehydrated and transited to Form II; GBP Form II was first transformed to Form III and then changed to Form IV; GBP Form III was previously transited to Form II, then changed to Form III and transformed to Form IV at last; whereas GBP Form IV was first changed to Form II, then transited to Form III and finally to Form IV. It was clearly evidenced that if GBP Form III or IV appeared in the milled mixture a little amount of GBP-lactam was certainly detected. In the presence of additives, there was almost lack of polymorphic transition for GBP Form II by co-milling GBP Form II with Emcompress, β-cyclodextrin, mannitol, corn starch or magnesium stearate. By co-milling GBP Form II with Avicel, dextrin, hydroxypropyl β-cyclodextrin, hydroxypropyl methylcellulose, Kollidon K-30 or gelatin, GBP Form II was transformed to Form IV alone. On the other hand, the GBP Form IV and a little amount of GBP-lactam were also found in the co-milled mixture after co-milling with GBP Form II with Aerosil or talc. This reveals that the solid-state transformation of GBP Form II after co-milling was markedly dependent on the types of additive used.

1. Introduction

Milling or grinding is one of the most common manufacturing processes used in pharmaceutical industry (Morris et al., 2001; Oguchi, 2004). The energetic input of solid-state milling can not only change the particle size, surface area and crystallinity of the drugs but also induce a solid-state polymorphic conversion of drugs, resulting in the modification of physico-chemical properties of drugs and the changes in their dissolution rates and bioavailability (Chaumeil, 1998; Rasenack and Müller, 2004; Datta and Grant, 2004; Chawla and Bansal, 2004; Yu et al., 2004). Many studies have reported the diversity of transformations of active pharmaceutical ingredients (APIs) upon milling (Vippagunta et al., 2001; Brittain, 2002; Oguchi, 2004; Kesisoglou et al., 2007). The thermodynamic and kinetic behaviors of polymorphic transformation of famotidine by grinding have been examined in our previous studies (Lin et al., 2006, 2007).

Although milling technique is widely performed in practical application, this process may easily cause several undesired phenomena of drugs such as aggregation of fine particles, formation of electrostatic force, mechanochemical transformation, formation of instability and solid-state reactivity (Bailey, 1984; Descamps et al., 2007a,b; Atkinson et al., 2008; Barzegar-Jalali et al., 2010), leading to limitation in the use of milling process itself. In order to overcome these problems and improve the milling efficiency, a favorable technique by co-milling drug with additives has been successfully applied (Descamps et al., 2007a,b; Bahl et al., 2008; Colombo et al., 2009). Furthermore, the co-milling process can not only prepare amorphous solids, nanoparticles, inclusion complexes, and solid dispersions (Watanabe et al., 2003; Wongmekiat et al., 2007; Balani et al., 2010; Ranpise et al., 2010) but also produce sustained release behavior for drug particles (Nokhodchi et al., 2009). More recently, co-milling process is also used to prepare the co-crystal of API with other molecular component and causes the co-crystal

* Corresponding author. Tel.: +886 03 5381183x8157; fax: +886 03 6102328.
E-mail address: sylin@mail.ypu.edu.tw (S.-Y. Lin).

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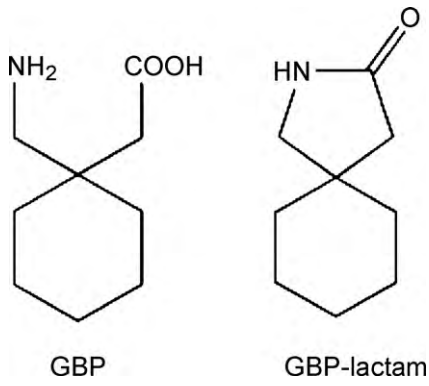


Fig. 1. The chemical structures of GBP and GBP-lactam.

with strikingly different and advantageous properties (Friscić and Jones, 2009; Ainouz et al., 2009).

Gabapentin (GBP) is a useful anticonvulsant for treatment of epilepsy and postherpetic neuralgia, and also for prevention of seizures (Goa and Sorkin, 1993; Dobecki et al., 2006). Since GBP structurally resembles the γ-aminobutyric acid (GABA), one of neurotransmitters, it may freely cross the blood–brain barrier to cause the higher level of GBP in the brain for treatment of seizures (Sills, 2006). Recently, GBP is also widely recommended to relieve pain, especially migraine headache and neuropathic pain (Moretti et al., 2000). In addition, GBP has been found to provide benefits in terms of alleviation of pain and overall quality of life in patients with chronic radiculopathy (Yildirim et al., 2009).

GBP has been reported as a zwitterion form existed in the solid state and also easily forms a GBP-lactam via intramolecular cyclization (Zour et al., 1992; Ciavarella et al., 2007). The chemical structures of GBP and GBP-lactam are indicated in Fig. 1. The thermal stability and thermodynamics of solid-state GBP had been examined to have the continuous processes of intramolecular lactamization of GBP and evaporation of GBP-lactam after melting of GBP (Hsu and Lin, 2009). Although four GBP polymorphs have been issued in many patent applications (Pesachovich et al., 2001; Satyanarayana et al., 2004), there is scant study for solid-state chemistry of GBP (Braga et al., 2008). In our previous study, GBP Form I was proven to be a monohydrate, but other GBP Forms II–IV belonged to anhydrate. The GBP Form II was the most stable polymorph available in the market (Braga et al., 2008; Reece and Levendis, 2008). Thermal-induced polymorphic transition of GBP has been evidenced as follows: GBP Form I was previously dehydrated beyond 55 °C and transformed to Form III after heating to 90 °C, and then converted to Form IV up to 125 °C heating, but Forms II over 126 °C and Form III after heating to 75 °C directly transformed to Form IV. The GBP Form IV was the last polymorph before intramolecular lactamization of GBP (Hsu et al., 2010). It is worthy of further investigation in the milling effect on the polymorphic transformation of different GBP polymorphs, as compared with that of the thermal-induced result. Moreover, the effect of co-milling process on the polymorphic stability of GBP Form II with different additives was also examined.

2. Materials and methods

2.1. Materials

A pharmaceutical grade of gabapentin (GBP, Sun Pharma. Ind. Ltd., Gujarat, India) was used without further purification. Several additives such as mannitol, corn starch, dextrin, β-cyclodextrin (β-CD) and gelatin (Wako Pure Chemical Industries Ltd., Osaka, Japan and Nacalai Tesque Inc., Kyoto, Japan), hydroxypropyl β-cyclodextrin (HP-β-CD, Roquette Freres, Lestrem, France), hydroxypropyl methylcellulose 4000 (HPMC 4000, Shin-Etsu Chemical Co. Ltd., Tokyo, Japan), polyvinyl pyrrolidone K-30 (Kollidon K-30, BASF, Ludwigshafen, Germany), microcrystalline cellulose (Avicel PH-101, Asahi Kasei Co. Ltd., Tokyo, Japan), dicalcium phosphate dihydrate (Emcompress, Edward Mandell Co., Inc., Carmel, NY, USA), colloidal silicon dioxide (Aerosil 200, Degussa, Rheinfelden, Germany), magnesium stearate (Mg-St) and talc, were chosen. An analytical reagent grade of KBr cubic crystal (5 mm × 5 mm × 5 mm, Jasco Co., Tokyo, Japan) was cut into thin plate for use.

2.2. Preparation of different GBP polymorphs and GBP-lactam

The commercial API of GBP used in this study was Form II, which was the most stable polymorph available in the market (Braga et al., 2008; Reece and Levendis, 2008). GBP Forms I, III, IV and GBP-lactam were prepared according to the procedure of our previous study (Hsu and Lin, 2009; Hsu et al., 2010).

Form I

A saturated solution of GBP dissolved in double distilled water at 40 °C was stored in a refrigerator at 4 °C for one day. The precipitated crystals were isolated by filtration.

Form II

The commercial API of GBP used without further purification was characterized to be form II (Satyanarayana et al., 2004; Dobecki et al., 2006). The peak temperature of GBP Form II in DSC curve was 169 °C (Hsu and Lin, 2009).

Form III

The GBP form III was prepared by rapidly heating the GBP form I to 85 °C in a DSC system (DSC-910, TA Instruments Inc., New Castle, DE, USA) and isothermally maintained at 85 °C for 3 h, and then cooled to 25 °C.

Form IV

The GBP form IV was prepared by rapidly heating the GBP form III to 120 °C in a DSC system and isothermally maintained at this temperature for 90 min, and then cooled to 25 °C.

GBP-lactam

The GBP-lactam was also prepared by directly heating the GBP sample to 176 °C in DSC system (DSC-910, TA Instruments Inc., New Castle, DE, USA), and then cooling to 25 °C (Hsu and Lin, 2009). The peak temperature of GBP-lactam was 91 °C in DSC curve (Ciavarella et al., 2007; Hsu and Lin, 2009). All the above GBP polymorphs and GBP-lactam were stored within 6 months at 25 °C and 70% relative humidity for study.

2.3. Preparation of various milled samples

Each type of GBP polymorph was respectively milled in an oscillatory ball mill (Mixer Mill MM301, Retsch GmbH & Co., Germany) at 20 Hz for different times up to 120 min at room temperature. A 0.2 g powder sample was placed in a 25 ml volume stainless steel milling jar containing two 15 mm diameter stainless steel balls. GBP Form II was also co-milled with each additive at a weight ratio of 1:1 for 120 min. During milling, the milled sample was withdrawn at prescribed intervals for further examination. All the milled or co-milled samples were stored in an air tight container over silica gel for further study.

2.4. Identification of each sample

Each GBP polymorph, GBP-lactam or milled sample was determined using FTIR microspectroscopy (IRT-5000-16/FTIR-6200, Jasco Co., Tokyo, Japan) equipped with a mercury cadmium telluride (MCT) detector via a transmission technique (Lin and Chien,

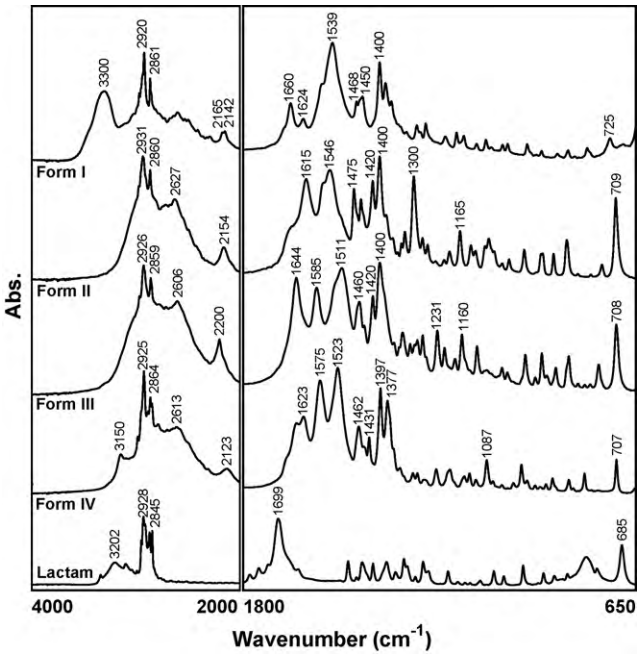


Fig. 2. FTIR spectra of intact GBP Forms I–IV and GBP-lactam.

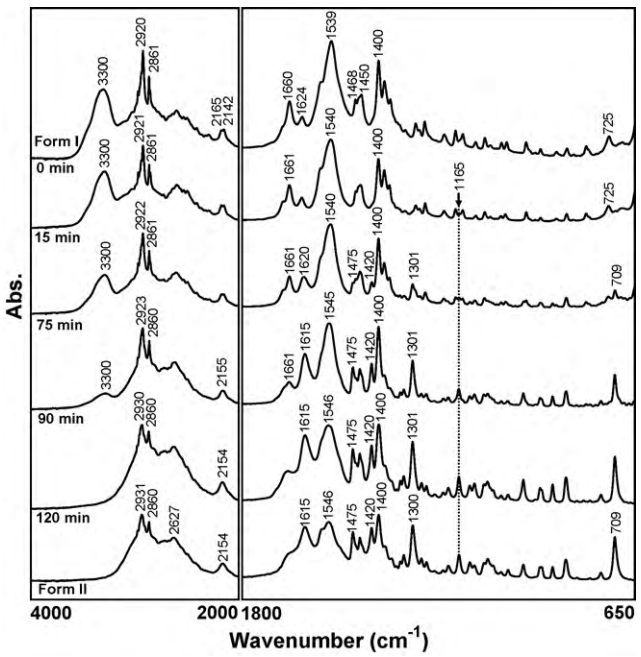


Fig. 3. The milling effect on the changes in FTIR spectra of GBP Form I.

2003; Wang et al., 2007; Hsu and Lin, 2009; Hsu et al., 2010), A trace amount of each sample was smeared on one piece of KBr plate and directly compressed by a hydraulic press under 200 kg/cm^2 for 15 s. There was no polymorphic transformation occurred for GBP under this compression procedure. The position and focus of the sample on KBr plate were adjusted microscopically by means of an aperture through optical system (ATOS) for analysis. All the spectra were obtained at a 4 cm^{-1} resolution and at 100 scans. The determinations were undertaken at 25 ± 2 °C and 65 ± 5% RH condition.

3. Results and discussion

3.1. Identification of different GBP polymorphs and GBP-lactam

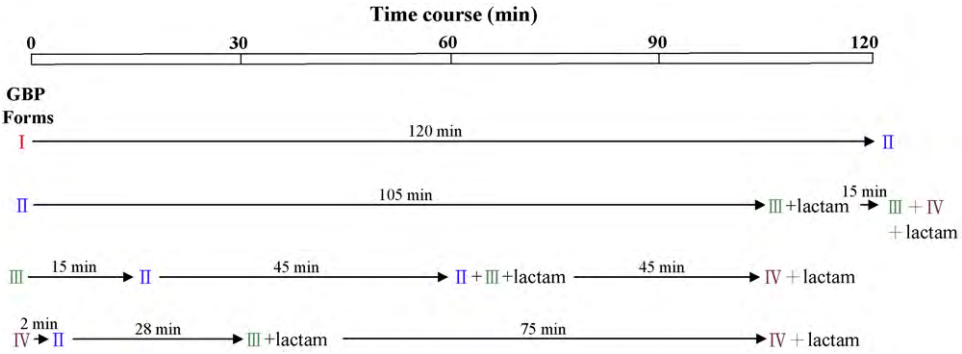
Fig. 2 shows the FTIR spectra of intact GBP Forms I–IV and GBP-lactam. Since GBP exhibits a zwitterion in the solid state, there was no IR peak absorption in the usual NH stretching regions (3500–3300 cm^{-1}). The IR band absorptions for all GBP polymorphs within 3200–2800 cm^{-1} region were due to the NH_3^+ stretching vibration (Chimatadara et al., 2007). The broad peak at 3300 cm^{-1} for GBP Form I might be attributed to the OH stretching vibrational mode of water molecule in the structure of GBP monohydrate. The peaks near 2123–2200 cm^{-1} were corresponded to the distinct side chain and/or CN stretching vibration of all GBP polymorphs. In the region of 1700–1500 cm^{-1}, the IR bands could be assigned as the ionized asymmetric carboxylate and NH_3^+ deformation vibration, respectively. The IR bands within 1500–1350 cm^{-1} region were also attributed to the asymmetric carboxylate band and/or CH_2 deformation band. Several characteristic peaks for each GBP polymorph in Fig. 2 might be clearly identified as follows: 3300, 2920, 1660, 1539, 1400 and 725 cm^{-1} for GBP Form I; 2931, 2154, 1615, 1546, 1475, 1400, 1300, 1165 and 709 cm^{-1} for GBP Form II; 2926, 2200, 1644, 1585, 1511, 1400, 1231 and 1160 cm^{-1} for GBP Form III; 3150, 2925, 2123, 1623, 1575, 1523, 1462, 1397, 1377 and 1087 cm^{-1} for GBP Form IV. On the other hand, the peaks at 3202, 2928 and 1699 cm^{-1} were the unique bands of GBP-lactam.

3.2. Milling effect on polymorphic transition of each GBP polymorph

It has been proposed that phase changes in the solid state require three steps: molecular loosening, solid solution formation and crystallization of new phase (Byrn et al., 1999). The stresses applied to crystals during mechanical milling can create new lattice defects in their crystal lattices and contribute to lattice disorder, leading to different packing arrangements and/or conformations within the crystal lattice. The nucleation and growth of new lattice defects may result in solid-state polymorphic interconversion upon milling (Brittain and Fiese, 1999; Vippagunta et al., 2001; Brittain, 2002).

The effect of milling time on the changes in FTIR spectra of GBP Form I is displayed in Fig. 3. It is clearly evident that the peak intensity at 3300 cm^{-1} due to the stretching OH vibrational mode of water molecule in the GBP monohydrate structure was gradually reduced with the increase of milling time and disappeared up to 105 min. The peak intensity at 1660 cm^{-1} (C=O) was also decreased, but the peak near 1624 cm^{-1} (carboxylate) was shifted to 1620 cm^{-1} at 75 min and then to 1615 cm^{-1} at 90 min with milling time. The changes in peak intensities at 1660, 1624, 1620 and 1615 cm^{-1} might be due to the decrease in hydrogen bonding between hydroxyl groups of H_2O and carboxyl groups of GBP after dehydration from anhydrate of GBP Form I. Moreover, the unique peak at 1301 and 709 cm^{-1} for GBP Form II appeared from 75 min and continuously increased its peak intensity. After milling for 105 min, the IR spectrum of the milled sample was consistent with that of the IR spectrum of GBP Form II. This suggests that GBP Form I was gradually dehydrated and also simultaneously transformed to GBP Form II under milling process. The detailed polymorphic transition of GBP Form I in the milling process is shown in Table 1 and Scheme 1.

There was almost lack of change for the specific peaks at 2931, 1615, 1546 and 1400 cm^{-1} in the IR spectrum of GBP Form II after milling for 60 min, as shown in Fig. 4, but two small peaks at 1699 and 1677 cm^{-1} attributed to GBP-lactam appeared. The persistence of GBP Form II after milling for 60 min was consistent with the result of Braga's study, in which GBP Form II kept its original form after 15 min manual milling (Braga et al., 2008). With the increase of



Scheme 1. Time-dependent polymorphic transformation of different GBP polymorphs in the 120-min-milling course.

Table 1
Effect of milling process on the polymorphic transformation of GBP Form I.

Form I	120-min-milled sample	Form II
3300	–	–
2920	2930	2931
2165	2154	2154
2142		
1660	–	–
1624	1615	1615
1539	1546	1546
–	1475	1475
1400	1400	1400
–	1301	1300
–	1165	1165
725	709	709

milling time, the peaks at 1644, 1584, 1510, 1462, 1400, 1231 and 1160 cm^{-1} assigned to the characteristic peaks of GBP Form III were observed in the IR spectrum after milling for 105 min. In this milling process, GBP Form II was transformed to GBP Form III with a trace amount of GBP-lactam. A small amount of GBP-lactam formation was attributed to the heating effect induced by milling. When the milling process was further continued to 120 min, several peaks at 3150, 1523, 1397, 1377 and 1087 cm^{-1} appeared. These IR peaks were corresponded to the characteristic peaks of GBP Form IV, suggesting that the polymorphic transformation was further occurred from GBP Form III to GBP Form IV. The effect of milling process on the polymorphic transition of GBP Form II is illustrated in Table 2 and Scheme 1.

Upon milling GBP Form III, the polymorphic transformation is seen to occur progressively in Fig. 5. It is interesting to note that GBP Form III was transited to GBP Form II after milling for 15 min, due to the appearance of several specific peaks at 2930, 2153, 1615, 1547, 1301 and 1165 cm^{-1}. This was also consistent with the result of Braga's study, in which GBP Form III was transformed to GBP Form II after manual milling for 15 min (Braga et al., 2008). When the milling process was continued to 45 min, the peaks at 1615 and 1301 cm^{-1} assigned to GBP Form II was still presented but its peak intensity was reduced. Three peaks at 1644, 1584 and 1512 cm^{-1}

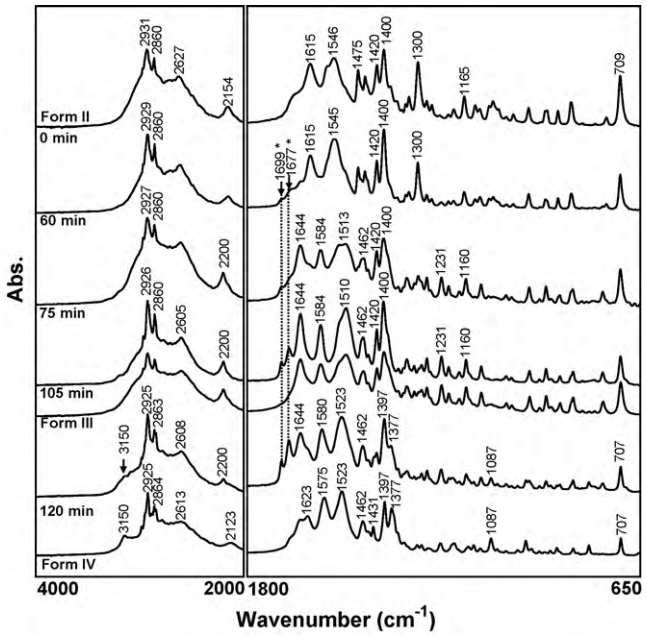


Fig. 4. The milling effect on the changes in FTIR spectra of GBP Form II.

Table 2
Effect of milling process on the polymorphic transformation of GBP Form II.

Form II	105-min-milled sample	Form III	120-min-milled sample	Form IV
–	–	–	3150	3150
2931	2926	2926	2925	2925
2154	2200	2200	2200 (III)	2123
–	1699 (lactam)	–	1699 (lactam)	–
–	1677 (lactam)	–	1677 (lactam)	–
1615	1644	1644	1644 (III)	1623
–	1584	1585	1580	1575
1546	1510	1511	1523	1523
1475	1462	1462	1462	1462
1400	1400	1400	1397	1397
–	–	–	1377	1377
1300	–	–	–	–
–	1231	1231	1231	1231
1165	1160	1160	–	–
–	–	–	1087	1087
709	709	708	707	707

Table 3
Effect of milling process on the polymorphic transformation of GBP Form III.

Form III	15-min-milled sample	Form II	60-min-milled sample	Form III	105-min-milled sample	Form IV
–	–	–	–	–	3150	3150
2926	2930	2931	2926	2926	2925	2925
2200	2153	2154	2200	2200	2121	2123
–	–	–	1699 (lactam)	–	1699 (lactam)	–
–	–	–	1677 (lactam)	–	1677 (lactam)	–
1644	–	–	1644	1644	1621	1623
–	1615	1615	1615 (II)	–	–	–
1585	1547	–	1584	1585	1574	1575
1511	–	1546	1512	1511	1524	1523
1462	1475	1475	1462	1462	1462	1462
1400	1400	1400	1400	1400	1397	1397
–	–	–	–	–	1377	1377
–	1301	1300	1301 (II)	–	–	–
1231	–	–	1231	1231	1231	1231
1160	1165	1165	1160	1160	–	–
–	–	–	–	–	1087	1087
708	708	709	709	708	707	707

Table 4
Effect of milling process on the polymorphic transformation of GBP Form IV.

Form IV	2-min-milled sample	Form II	30-min-milled sample	Form III	105-min-milled sample	Form IV
3150	–	–	–	–	3150	3150
2925	2930	2931	2927	2926	2925	2925
2123	2155	2154	2201	2200	2125	2123
–	–	–	1699 (lactam)	–	1699 (lactam)	–
–	–	–	1678 (lactam)	–	1678 (lactam)	–
1623	1615	1615	1644	1644	1622	1623
1575	–	–	1584	1585	1574	1575
1523	–	–	1511	1511	1523	1523
1462	1475	1475	1462	1462	1461	1462
1397	1400	1400	1400	1400	1397	1397
1377	–	–	–	–	1377	1377
–	1301	1300	–	–	–	–
1231	–	–	1231	1231	1231	1231
–	1165	1165	1160	1160	–	–
1087	–	–	–	–	1087	1087
707	709	709	708	708	707	707

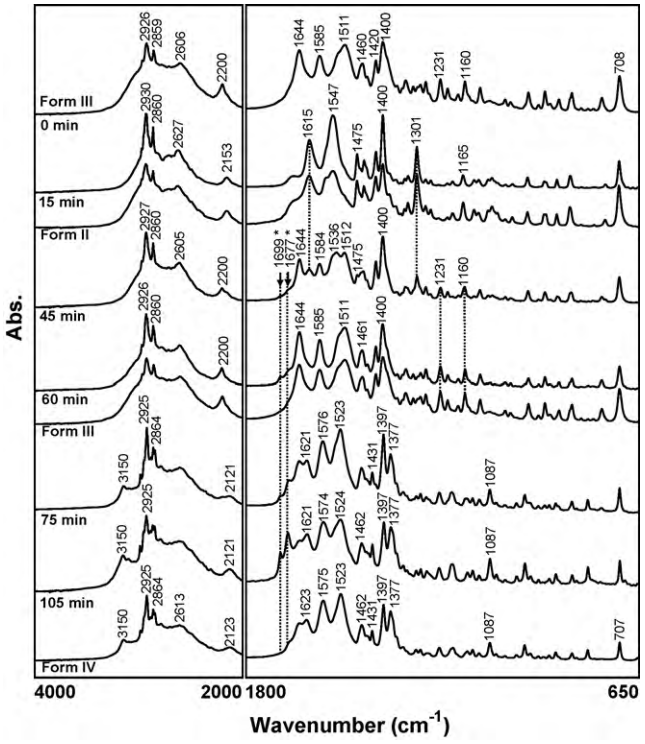


Fig. 5. The milling effect on the changes in FTIR spectra of GBP Form III.

due to GBP Form III appeared again, indicating the coexistence of GBP Forms II and III in the milled mixture. In the mean time, the peaks at 1699 and 1677 cm^{-1} assigned to GBP-lactam were also observed in the IR spectrum of the mixture. By continuous increasing the milling time up to 60 min, the milled mixture was almost transformed to GBP Form III (2926, 1644, 1585, 1511, 1231 and 1160 cm^{-1}) with a small amount of GBP-lactam. After milling for 75 min, several peaks at 3150, 2121, 1621, 1576, 1523, 1431, 1397, 1377 and 1087 cm^{-1} corresponded to GBP Form IV were found from the IR spectrum of milled mixture. Moreover, the peaks at 1699 and 1677 cm^{-1} assigned to GBP-lactam exhibited a more sharp intensity after milling for 105 min, illustrating an increased amount of GBP-lactam formation. The polymorphic transition of GBP Form III under milling process is also indicated in Table 3 and Scheme 1.

IR spectra of the milled samples of GBP Form IV are presented in Fig. 6. Obviously, the transformation was occurred from GBP Form IV to Form II after milling for 2 min, in which several unique peaks of GBP Form II were observed at 2930, 2155, 1615, 1546, 1475, 1301 and 1165 cm^{-1}. Once milling was up to 15 min, a number of peaks at 2927, 2200, 1644, 1584 and 1510 cm^{-1} due to GBP Form III appeared, indicating the coexistence of GBP Form II and Form III in the milled sample. Further continuous milling to 30 min, the IR spectral peaks corresponding to GBP Form II disappeared but the GBP Form III played a predominant component in the milled sample. While two peaks at 1699 and 1678 cm^{-1} due to GBP-lactam were also found in the IR spectrum of 30-min-milled sample, showing that 30-min-milled sample consisted of GBP Form III with a little amount of GBP-lactam. By continuous milling to 60 min, the GBP

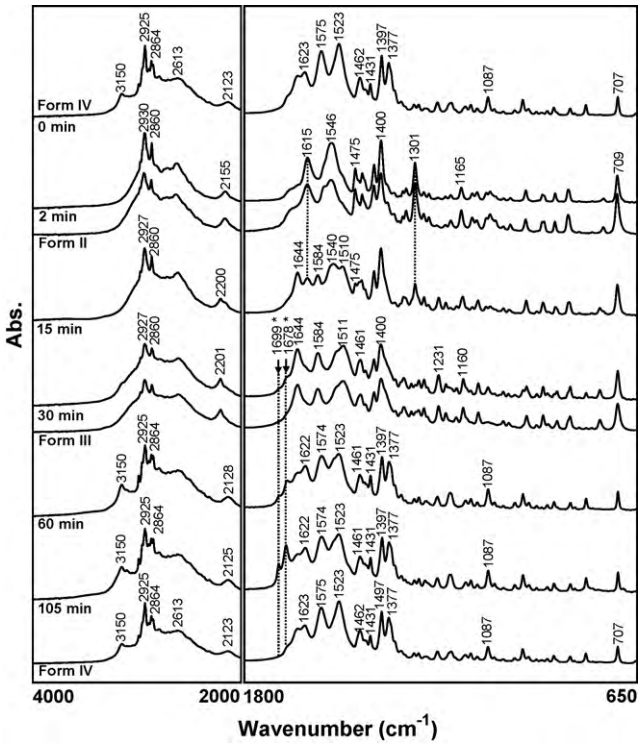


Fig. 6. The milling effect on the changes in FTIR spectra of GBP Form IV.

Form III was transited to GBP Form IV due to the characteristic peaks appeared at 3150, 1622, 1574, 1523, 1397, 1377 and 1087 cm^{-1}. By increasing the milling time to 105 min, except the presence of GBP Form IV, two peaks at 1699 and 1677 cm^{-1} with more intense peak intensity were shown, indicating that an increased amount of GBP-lactam was co-mixed with GBP Form IV in the 105-min-milled sample. Table 4 and Scheme 1 also reveal the polymorphic transition of GBP Form IV upon milling.

3.3. Co-milling effect on polymorphic stability of GBP Form II with different additives

Since the co-milling technique plays an important role in the pharmaceutical industry, the effect of co-milling process on the polymorphic transition of GBP Form II with different additives was investigated. After milling GBP Form II with 13 additives for 120 min, the polymorphic phase transformation behavior of GBP Form II can be divided into three types, as shown in Figs. 7–9.

By co-milling GBP Form II with dicalcium phosphate dihydrate, magnesium stearate, β-CD, mannitol or corn starch, there was lack of polymorphic change for GBP Form II, as shown in Fig. 7. The characteristic peaks at 1615, 1546, 1475, 1420, 1400 and 1300 cm^{-1} of GBP Form II were still presented in the FTIR spectra of the milled samples, implying that Emcompress, β-CD, mannitol, corn starch or magnesium stearate (Mg-St) failed to induce the polymorphic transformation of GBP Form II in the co-milling process and formation of GBP-lactam. On the other hand, the co-milled mixture of GBP Form II with Avicel, dextrin, HP-β-CD, HPMC, Kollidon K-30 or gelatin exhibited the specific peaks at 2123–2124, 1619–1621, 1571–1574, 1522–1524, 1461–1462, 1397–1398, 1377–1379 and 1087 cm^{-1}, which was similar to that of IR spectral peaks of GBP Form IV (Fig. 8). This illustrates that GBP Form II could be transformed into GBP Form IV in the presence of Avicel, dextrin, HP-β-CD, HPMC, Kollidon K-30 or gelatin after milling process. It was different from the result of Fig. 4, in which GBP Form II might be changed to large amount of GBP Form IV with a small amount of

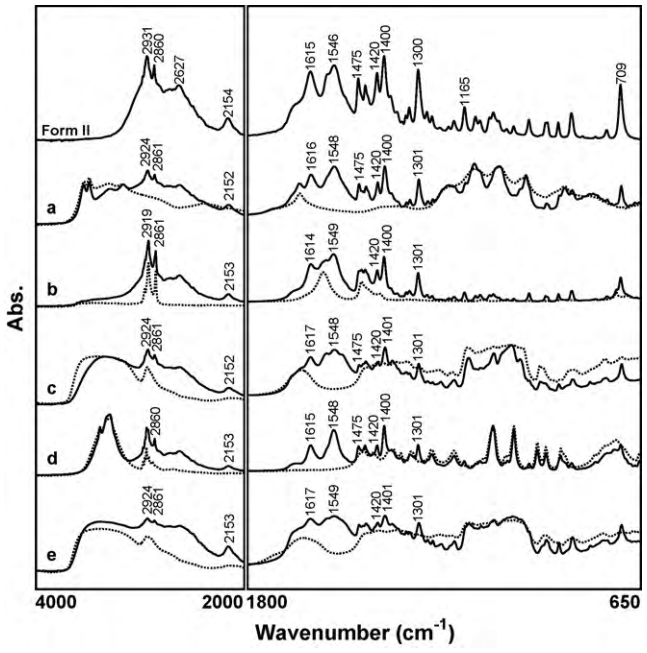


Fig. 7. The changes in FTIR spectra of GBP Form II after co-milling with dicalcium phosphate dihydrate (a), magnesium stearate (b), β-CD (c), mannitol (d) or corn starch (e). Solid line: co-milled mixture; dotted line: additive alone.

GBP Form III and GBP-lactam after milling GBP Form II alone. The detailed mechanism is unclear, but the coexistence of these additives for preventing the over-heat of GBP Form II during co-milling process might be responsible for this result. After co-milling GBP

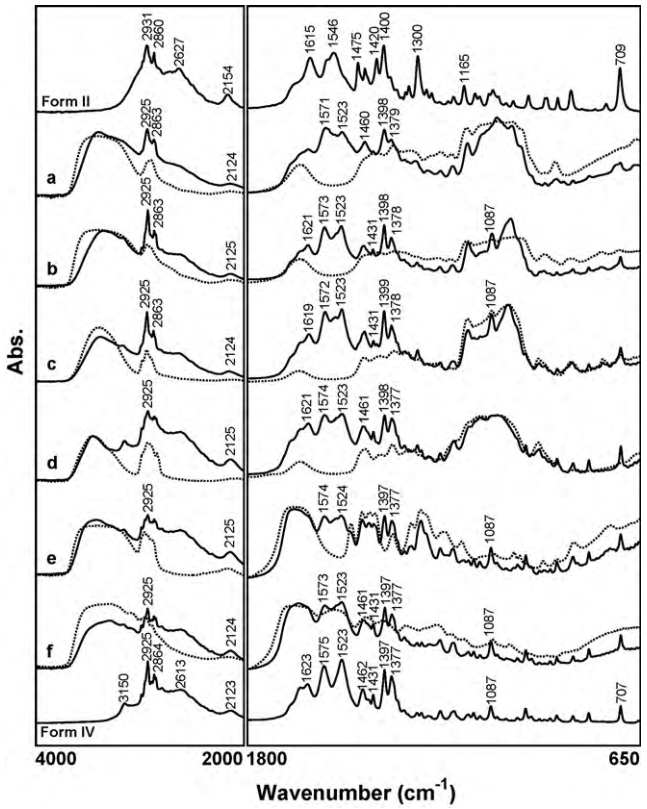


Fig. 8. The changes in FTIR spectra of GBP Form II after co-milling with Avicel (a), dextrin (b), HP-β-CD (c), HPMC (d), Kollidon K-30 (e) or gelatin (f). GBP Form IV was acted as a control. Solid line: co-milled mixture; dotted line: additive alone.

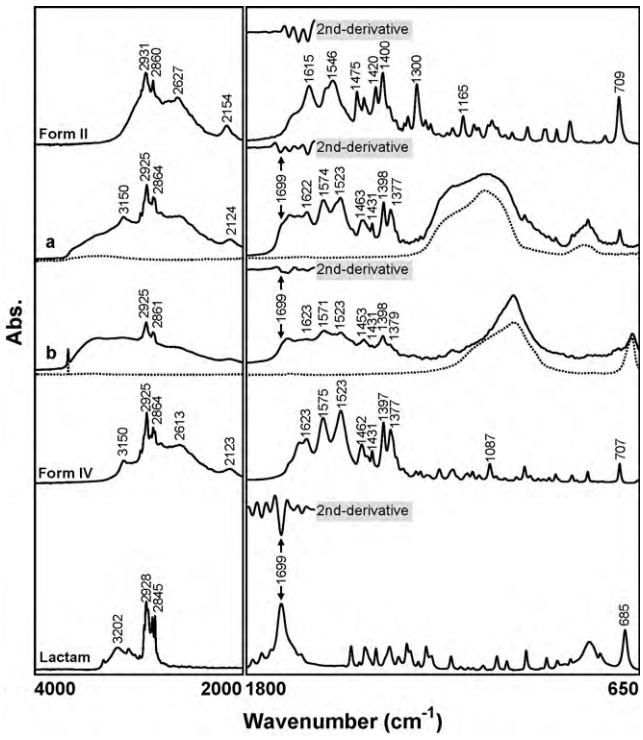
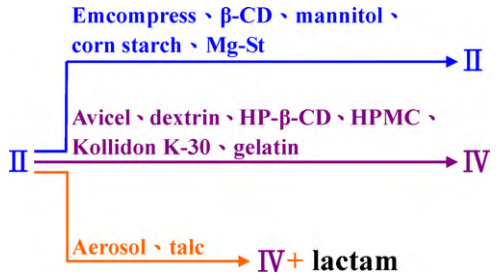


Fig. 9. The changes in FTIR spectra of GBP Form II after co-milling with Aerosil (a) or talc (b). GBP Form IV or GBP-lactam was acted as a control. Solid line: co-milled mixture; dotted line: additive alone



Scheme 2. Polymorphic transformation of GBP Form II after 120-min-co-milling with various additives.

Form II with Aerosil or talc, except the appearance of several unique peaks at 1622–1623, 1571–1574, 1522–1523, 1431, 1397–1398 and 1377–1379 cm^{-1} belonging to GBP Form IV, the predominant peak at 1699 cm^{-1} was also found in the second-derivative IR spectrum (Fig. 9). This clearly evidences that co-milling GBP Form II with Aerosil or talc could not only largely induce the polymorphic transformation from GBP Form II to GBP Form IV but also produce a small amount of GBP-lactam in the co-milled mixture. The transition of GBP Form II upon co-milling with additives was summarized in Scheme 2.

4. Conclusions

In the present 120-min-milling course study, the polymorphic transformation of each GBP polymorph was summarized as follows: (I) in the absence of additive: GBP Form I was previously dehydrated and transited to Form II; GBP Form II was first transformed to Form III and finally changed to Form IV; GBP Form III was previously transited to Form II, then changed to Form III and transformed to Form IV at last; whereas GBP Form IV was first changed to Form II, then transited to Form III and finally to Form IV. A little amount of GBP-lactam was also detected in the milled mixture when GBP Form III or IV was contained. (II) In the presence of additive: the co-milling effect on the polymorphic change of GBP Form II was dependent on the types of additive used. There was almost lack of polymorphic transition for GBP Form II by co-milling GBP Form II with Emcompress, β-CD, mannitol, corn starch or Mg-St. By co-milling GBP Form II with Avicel, dextrin, HP-β-CD, HPMC, Kollidon K-30 or gelatin, however, GBP Form II was transformed to Form IV alone. The GBP Form IV and a little amount of GBP-lactam were also formed in the co-milled mixture after co-milling with GBP Form II with Aerosil or talc.

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