Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 335 (2007) 12–19
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Effects of solid-state reaction between paracetamol and cloperastine hydrochloride on the pharmaceutical properties of their preparations

Yukoh Sakata [a,*], Eishi Tanabe [b], Toshiharu Sumikawa [a], Sumihiro Shiraishi [a], Yoshihiro Tokudome [c], Makoto Otsuka [c]

[a] *Healthcare Research Institute, Wakunaga Pharmaceutical Co., Ltd., 1624 Shimokotachi, Kodacho, Akitakatashi, Hiroshima 739-1195, Japan*
[b] *Western Hiroshima Prefecture Industrial Research Institute, 3-13-26 Kagamiyama, Higashi-Hiroshima 739-0046, Japan*
[c] *Department of Pharmaceutical Technology, Research Institute of Pharmaceutical Sciences, Faculty of Pharmacy, Musashino University, Shinmachi 1-1-20, Nishi-Tokyo 202-8585, Japan*

Received 7 July 2006; accepted 23 October 2006
Available online 29 October 2006

Abstract

Tablets containing both paracetamol (PM) and cloperastine hydrochloride (CLH) in a combination formulation prepared by standard vertical granulation technology were found to have altered pharmaceutical properties. The hardness and disintegration time of tablets containing both PM and CLH gradually increased during storage, and the cross-screw did not operate smoothly during preparation of the mixed powder. The objective of the present study was to investigate the mechanism of formation of eutectic mixtures consisting of PM and CLH. Binary mixtures of PM and CLH in various proportions were prepared as physical mixtures and analyzed by DSC to study their thermal behavior. Phase diagrams obtained from the endothermic peaks due to melting of physical mixtures of PM and CLH demonstrated the formation of eutectic mixtures with eutectic temperatures of 86.9–110.2 °C depending on the ratio of constituents. The formation of the eutectic mixture was studied for a 50:50 mol.% ratio of PM and CLH. PXRD analysis revealed that the eutectic mixture of PM and CLH is structurally different from native PM and CLH. The most probable interaction sites between PM and CLH were demonstrated by DSC analysis of a binary mixture of PM and CLH prepared by melt quenching.
© 2006 Elsevier B.V. All rights reserved.

Keywords: Paracetamol; Cloperastine hydrochloride; Vertical granulation; Eutectic mixture; Interaction

1. Introduction

In general, it is well-known that pharmaceutical preparations containing multiple components can undergo interactions between various components or additives that may lead to the degradation of certain constituents. Together, such changes can cause difficulties in the preparation process and lower the quality of the final preparation, for example by changing the color or delaying disintegration and dissolution. Most cough/cold preparations currently available on the global market contain combinations of antipyretics/analgesics together with therapeutic agents of other pharmacological groups, such as antihistamines, sympathomimetics and antitussives. However, use of antipyretic/analgesic combinations can cause formulation difficulties because of various physico-chemical interactions between the therapeutic agents. Formation of eutectic mixtures as a result of such interactions is a common phenomenon which is known to cause difficulties during manufacture of some combination formulations, particularly solid dosage forms (Patel, 1970), and affect their shelf life. PM is a well-known analgesic/antipyretic used both alone and in combination. Because of the presence of –NH and –OH in its structure, PM interacts with other compounds containing the same groups and/or carbonyl groups, such as phenazone (Dearden, 1972; Grant et al., 1980), through formation of dipolar or hydrogen-bonding complexes. Muller and Beer (1982) reported that PM forms eutectic mixtures with aspirin and propylphenazone. Similarly, Zalac et al. (1999) performed a DSC preformulation study of a combination

* Corresponding author. Tel.: +81 826 45 2331; fax: +81 826 45 4351.
E-mail address: sakata_y@wakunaga.co.jp (Y. Sakata).

0378-5173/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2006.10.038

of these two compounds with caffeine and codeine phosphate hemihydrate and reported that the interaction between PM and propylphenazone led to a eutectic mixture. CLH is a well-known antitussive agent that is also used in both combination and single formulations. However, there have been no reports that CLH interacts with other compounds. In general, mixing and granulation are key processes in the production of many pharmaceutical dosage forms. Mixing is performed to secure uniformity of the medicine, whereas granulation is believed to improve significantly the uniformity of the medicine in the tablet and the flowability of powders before tableting. Vertical granulators are widely used to obtain high-grade pharmaceutical dosage forms, and have many advantages from a handling point of view. For these reasons, tablets containing PM and CLH in a combination formulation were prepared by vertical granulation in this study. However, the cross-screw did not operate smoothly, although the blade functioned during mixing. When the cross-screw was stopped, scorching was observed in the mixed powder. Therefore, the mixing process before granulation was performed with the blade only. Moreover, tablet hardness and disintegration time were significantly increased during storage of the combination formulation containing PM and CLH powder. Thus, mixing of PM and CLH is associated with various problems. However, no studies on the interaction between PM and CLH have been reported. Therefore, the objective of the present study was to ascertain the sites of interaction of PM and CLH powders, which is the basic information required to predict the physico-chemical properties of tablets containing PM and CLH.

2. Materials and methods

2.1. Materials

Paracetamol (acetaminophen; PM) (MW = 151.17) was purchased from Yamomoto Co., Ltd. (Osaka, Japan). Two polymorphs of PM have been described: form I (Haisa et al., 1976; Al-Zoubi et al., 2002) is a monoclinic crystal and form II (Al-Zoubi et al., 2002; Haisa et al., 1974) is an orthorhombic crystal. The powder X-ray diffraction pattern (PXRD) and the main diffraction angles of PM agreed with the data for form I of PM from a previous study (Haisa et al., 1976; Al-Zoubi et al., 2002). Amorphous PM was prepared by melt quenching in a cell of a differential scanning calorimeter (DSC EXSTRA 6000 with measuring cell DSC 30E; Seiko) with a dry nitrogen gas purge at 50 mL/min. Cloperastine hydrochloride (CLH) (MW = 366.32) was purchased from Yoshitomi Fine Chemical Co., Ltd. (Osaka, Japan). The chemical structures of PM and CLH are shown in Fig. 1. Potassium guaiacolsulfonate and DL-methylephedrine hydrochloride were purchased from ALPS Pharmaceutical Ind. Co., Ltd. (Gifu, Japan). Clemastine fumarate, lysozyme hydrochloride and anhydrous caffeine were purchased from Daito Co. (Toyama, Japan), Kewpie Co. (Tokyo, Japan), and Shiratori Pharmaceutical Co., Ltd. (Chiba, Japan). Low-substituted hydroxypropylcellulose (Shin-Etsu Chemical Industries Co., Ltd., Tokyo, Japan) and microcrystalline cellulose (Avicel PH101; Asahi Chemical Industries Co., Tokyo, Japan) were used as excipients. Magnesium stearate (Mg-St; Taihei Chemical Industries Co., Ltd., Osaka, Japan) and anhydrous silicic acid (Maikon F; Tomita Pharmaceutical Co., Ltd., Tokushima, Japan) were used as a lubricant and a glidant, respectively.

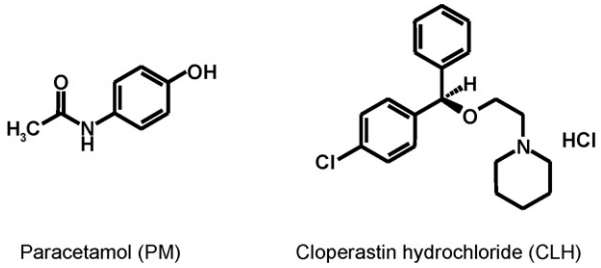

Fig. 1. Chemical structures of paracetamol and cloperastine hydrochloride.

2.2. Vertical granulation conditions

A combination formulation containing PM and CLH was prepared by the vertical granulation method. Granulation conditions were as follows: sample weight, 500 g; cross-screw speed, 3600 rpm; blade speed, 350 rpm; temperature and humidity, about 10–30% RH at 25 ± 3 °C.

2.3. Preparation of tablets

PM, CLH, potassium guaiacolsulfonate, DL-methylephedrine hydrochloride, clemastine fumarate, lysozyme hydrochloride and anhydrous caffeine were each blended with low-substituted hydroxypropylcellulose and microcrystalline cellulose and granulated by the vertical granulation technique using 80% (w/w) ethanol aqueous solution as a binder. The granules were dried in a fluid bed drier (MP-01), screened through a 16 mesh sieve, mixed with anhydrous silicic acid and magnesium stearate and compressed into tablets by using 8 mm diameter round and shallow concave punches on a rotary tablet press (Kikusui Engineering, Kyoto, Japan).

2.4. Storage conditions

The stability of tablets containing PM and CLH was tested at 25, 40 and 60 °C with glass bottles as containers.

2.5. Standard physical testing of tablets

Physical testing of tablets was performed after a relaxation period of at least 24 h. The tablet hardness of 10 tablets was determined by diametrical loading with a Shuleuninger-6E tester (Shuleuninger, Greifensee, Switzerland). Disintegration testing was performed at 37 °C in distilled water (1000 mL) with a Model NT-2HF (Toyama Sangyo Co., Ltd., Osaka, Japan) apparatus with discs. The disintegration times reported are averages of six determinations. Disintegration times were determined by observation.

2.6. Preparation of samples

Binary mixtures of paracetamol and cloperastine hydrochloride at mol ratios of 100:0, 98:2, 92:8, 71:29, 62:38, 55:45, 38:62, 21:79, 18:82, 14:86 and 0:100 were used to study the interaction between PM and CLH by DSC, SEM, PXRD and FT-IR. Samples were prepared as physical mixtures of the compounds.

2.7. Differential scanning calorimetry (DSC)

Thermal analysis of the samples was performed with a differential scanning calorimeter (DSC EXSTRA 6000 with measuring cell DSC 30E; Seiko). Approximately 10 mg of sample was weighed into the DSC pan. The sealed pan was placed in the sample side of the instrument. An identical reference pan was placed in the reference side. Scans between 25 and 300 °C were carried out at a rate of 10 °C min^{-1} with a nitrogen gas purge at 50 mL/min. The heated samples were then cooled at the same scanning rate and reheated again under the same conditions. The onset temperatures of the exotherms/endotherms were considered as the temperatures of the peaks, except for construction of phase diagrams. Peak height temperature (T_m) was used for construction of the phase diagrams because it was difficult to calculate onset temperatures for complex peaks representing multiple processes.

2.8. Scanning electron microscopy (SEM)

Samples were mounted onto aluminum stubs and gold coated in a sputter coater to a thickness of about 10 μm. The coated samples were then viewed at 400× magnification in the FE-SEM (JEOL, Tokyo, Japan). The beam accelerator voltage was set to 25 kV and the current was set to 12 μA.

2.9. PXRD analysis

PXRD analysis was carried out at room temperature with a type Rint2550VHF diffractometer (Rigaku, Tokyo, Japan). Measurement conditions were as follows: target, Cu; filter, Kα; voltage, 40 kV; current, 400 mA; time constant, 1 s; step slit, 1.0°; counting time, 0.5 s; measurement range, $2\theta = 5–60°$. In order to avoid particle orientation during sample preparation, the loosely packed sample was prepared by pouring the powder into the holder without compressing.

2.10. FT-IR spectroscopy

A dispersion (about 1%) of the sample in potassium bromide (KBr) was prepared by mixing the mass with KBr. FT-IR spectra of the prepared mixing with KBr was obtained on a Nicolet Magna-IR 760 spectrometer over the 4000–400 cm^{-1} region. The number of scans were 16 and the resolution was 4 cm^{-1}.

3. Results and discussion

3.1. Formation of eutectic mixture due to interaction between PM and CLH

Preparation of a combination formulation containing PM and CLH powders was performed by the vertical granulation technique. However, the cross-screw did not operate smoothly during the mixing process, although the blade functioned correctly. Moreover, extensive scorching was observed in the mixed powders after the cross-screw had stopped, and this was observed only with mixtures of PM and CLH. Therefore, the surface states of the powdered mixtures were changed significantly by mixing with a vertical machine. It is well-known that the cross-screw and the blade function in granulation and mixing, respectively. Therefore, the mixing operation was performed with the blade only, whereas granulation was performed with a combination of blade and cross-screw. Moreover, the hardness of tablets containing a combination formula with CLH increased significantly during storage at 25, 40 and 60 °C. Hardness increased by 20% compared with that immediately following preparation. Disintegration time also increased with increasing tablet hardness (data not shown). Discoloration of tablets was not dependent on the presence of CLH, and no significant change in the content of the active materials was observed in tablets stored under these conditions (data not shown). It is known that PM interacts with various compounds as a result of formation of eutectic mixtures (Dearden, 1972; Grant et al., 1980; Muller and Beer, 1982; Zalac et al., 1999). In contrast, there have been no reports that CLH interacts with other compounds. To optimize the manufacture of

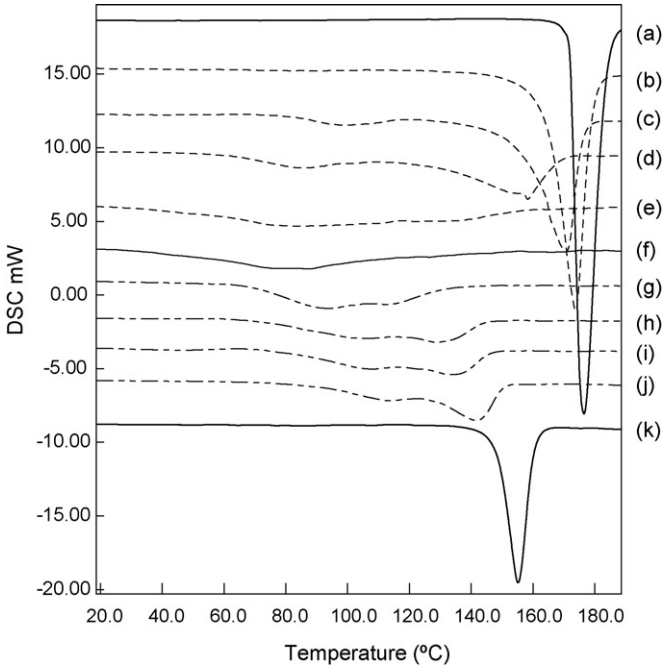

Fig. 2. DSC thermograms obtained during first heating of physical mixtures of paracetamol and cloperastine hydrochloride. Key: ratio of paracetamol to cloperastine hydrochloride (mol%) was (a) 100:0, (b) 98:2, (c) 92:8, (d) 71:29, (e) 62:38, (f) 50:50, (g) 38:62, (h) 21:79, (i) 18:82, (j) 14:86, (k) 0:100.

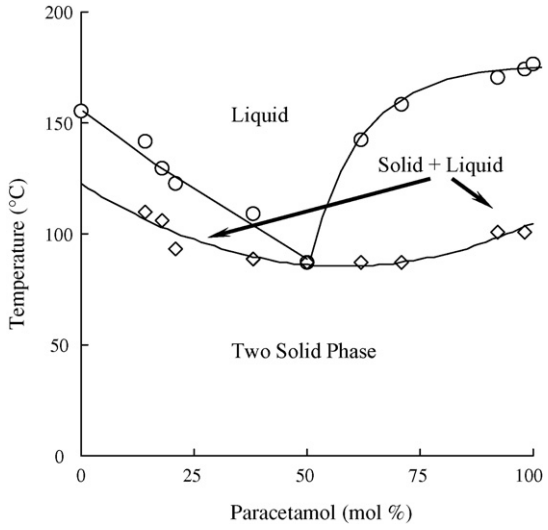

Fig. 3. Phase diagrams constructed from the onset temperatures obtained during first heating of physical mixtures of paracetamol and cloperastine hydrochloride.

a combination formula containing PM and CLH, we investigated the interaction between PM and CLH by thermo-analytical and PXRD methods.

Fig. 2 shows the DSC thermograms obtained during the first heating cycle of PM, CLH and their physical mixtures with various ratios of PM to CLH. During heating, the DSC curves of PM (100:0) and CLH (0:100) showed only single sharp endothermic melting peaks; these occurred at 169 °C (T_m 176.4 °C) with an enthalpy of 182 J/g (Fig. 2a), confirming the presence of form I, and 145.9 °C (T_m 155.3 °C) with an enthalpy of 51.8 J/g (Fig. 2k), respectively. All physical mixtures of PM and CLH containing 14–38 mol.% PM showed two endothermic peaks (Fig. 2g–j); the first occurred at a specific temperature and the second at a higher temperature which varied according to the PM/CLH ratio. The temperature and enthalpy of the second peak progressively decreased and then increased as the concentration of PM increased from 14 to 38 mol.% of PM. In these physical mixture samples, the second peak disappeared when the PM concentration reached 50 mol.%. At this concentration, only one endothermic peak appeared with a specific temperature of 86.8 °C. Above 50 mol.% PM (Fig. 2b–e), the combination samples also showed two peaks; the first one occurred at about the same temperature as in the samples containing 14–38 mol.% PM with the second peak at a higher temperature which progressively increased with PM concentration. Phase diagrams constructed from the T_m values obtained during the first heating cycle of the physical mixtures are presented in Fig. 3, and suggest formation of a eutectic mixture at about 50:50 PM–CLH (mol.%) ratio.

Since physical mixtures consisting of PM and CLH formed eutectic mixtures, we studied the interaction between PM and CLH by using SEM and PXRD. Fig. 4 shows SEMs of typical crystals of PM, CLH and their physical mixtures prepared with various ratios of PM to CLH. The crystalline particles of PM and CLH appeared as monoclinic and needle-like crystals, respectively (Fig. 4a and g). CLH significantly affected the particle states of PM, and the extent of aggregation between PM and CLH particles increased as the proportion of CLH increased (Fig. 4b–f). In particular, physical mixtures prepared with a 50:50 molar ratio of PM to CLH appeared oily, indicating the formation of a eutectic mixture (Fig. 4f).

Fig. 5 shows the PXRD profiles of PM, CLH and their physical mixtures prepared with various ratios of PM to CLH. The diffraction pattern and the main diffraction angles of PM agreed with the data for form I of PM from a previous study (Haisa et al., 1976; Al-Zoubi et al., 2002). In contrast, the diffraction pattern of PM was significantly changed by the addition of CLH, and the diffraction intensities of physical mixtures consisting of PM and CLH decreased with increasing proportion of CLH. These results suggest that the crystal structure of PM is strongly affected by mixture with CLH. Moreover, the surface states of both PM and CLH crystals were significantly different from those of their physical mixtures, and their physical mixtures demonstrated strong aggregation between particles, as shown by the SEM results. Aggregation between particles was also observed in physical mixtures of PM and CLH prepared with a vertical granulator. Thus, formation of a eutectic mixture led to aggregation between particles and the formation of crystal structures different from those of native PM and CLH; this implies formation of complexes between PM and CLH.

3.2. Sites of interaction between PM and CLH

FT-IR spectroscopy is a powerful tool used widely for the study of chemical and physical changes in the molecular structure of biological materials. Wang et al. (2002) confirmed the structure of PM as form I by FT-IR, which is consistent with the IR spectrum of PM determined by the Nujol method (Acetaminophen monograph in JP IX). They also reported that the physical stability of PM was unchanged by the compression involved in making a KBr disc. Consequently, we used the KBr disc method to study changes in the interaction between PM molecules (form I) on addition of CLH.

Fig. 6 shows the FT-IR spectra of PM, CLH and their physical mixtures at various molar ratios of PM and CLH. The assignment of the peaks of PM is as follows: 3325 cm^{-1}, N–H stretching vibration; 3161 cm^{-1}, hydrogen-bonded OH stretching vibration plus other combination bands; 1653 cm^{-1}, C=O stretching vibration; 1564 cm^{-1}, N–H in-plane bending; 1610 cm^{-1}, 1506 cm^{-1} and 1440 cm^{-1}, aromatic ring mode; 1327 cm^{-1}, O–H bending vibration (the disappearance of 1564 and 1327 cm^{-1} in D_2O solution can be used to explain these assignments); 1259–1227 cm^{-1}, C–O and/or C–N stretching vibrations (Wang et al., 2002; Moynihan and O'Hare, 2002). The representative IR bands of native PM (Fig. 6a) were shifted as the proportion of CLH powder increased, although the physical mixture consisting of PM and CLH at 98:2 mol.% was not significantly different from native PM (Fig. 6b). In the physical mixture consisting of PM and CLH at 92:8 mol.%, the peak at 3161 cm^{-1} assigned to hydrogen-bonded OH stretching vibration and that at 1440 cm^{-1} assigned to aromatic ring mode shifted to 3163 and to 1442 cm^{-1}, respectively. Moreover, the position of the peak at 1506 cm^{-1} corresponding

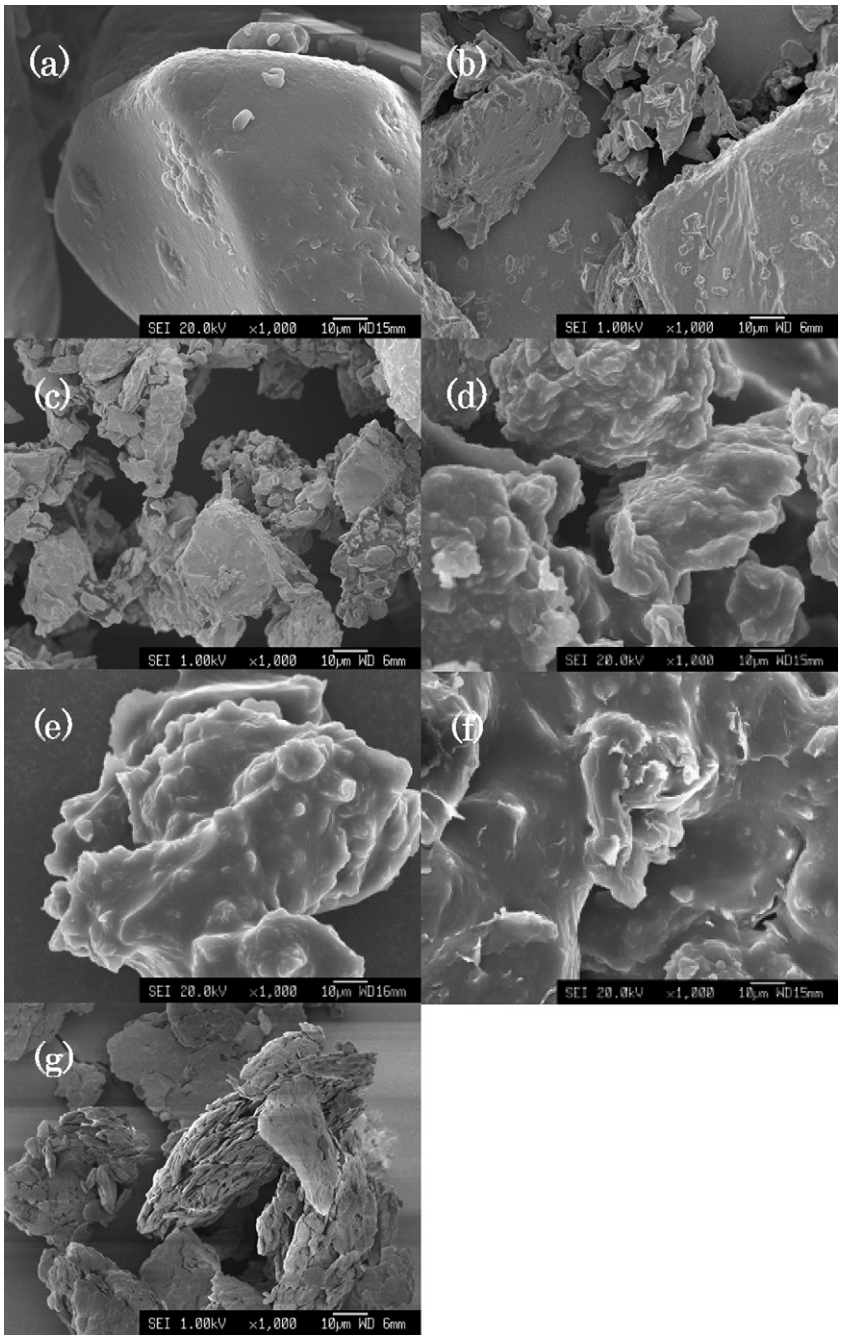

Fig. 4. SEMs of physical mixtures of paracetamol and cloperastine hydrochloride. Key: ratio of paracetamol to cloperastine hydrochloride (mol%) was (a) 100:0, (b) 98:2, (c) 92:8, (d) 71:29, (e) 62:38, (f) 50:50, (g) 0:100.

to the aromatic ring mode was dependent on the addition of CLH, and in a physical mixture consisting of PM and CLH at 71:29 mol.% was shifted to 1508 cm^{-1} from 1506 cm^{-1}. The peak at 3161 cm^{-1} assigned to hydrogen-bonded OH stretching vibration and those at 1506 and 1440 cm^{-1} corresponding to the aromatic ring mode shifted to 3163, 1510 and 1442 cm^{-1}, respectively, when a eutectic mixture was formed from PM and CLH powder. Moreover, the peak intensities corresponding to native PM were decreased slightly by addition of CLH powder, since the atoms or molecules occupied a fixed site with very little vibrational motion in the solid-state. Thus, CLH formed different polymorphisms with PM, which might strongly affect the intermolecular hydrogen-bonding of PM.

Dearden (1972) and Grant et al. (1980) reported that PM interacts with other compounds containing the same group(s) and/or the carbonyl group through formation of dipolar or hydrogen bonds. Takahashi et al. (2005) reported that the carbonyl group of PM interacts with the amide group of chitosan. Moreover, Miyazaki et al. (2004) reported that polyacrylic acid (PAA), which contains a carboxylic group, inhibits the crystallization of amorphous PM. In contrast, CLH does not contain a carboxylic

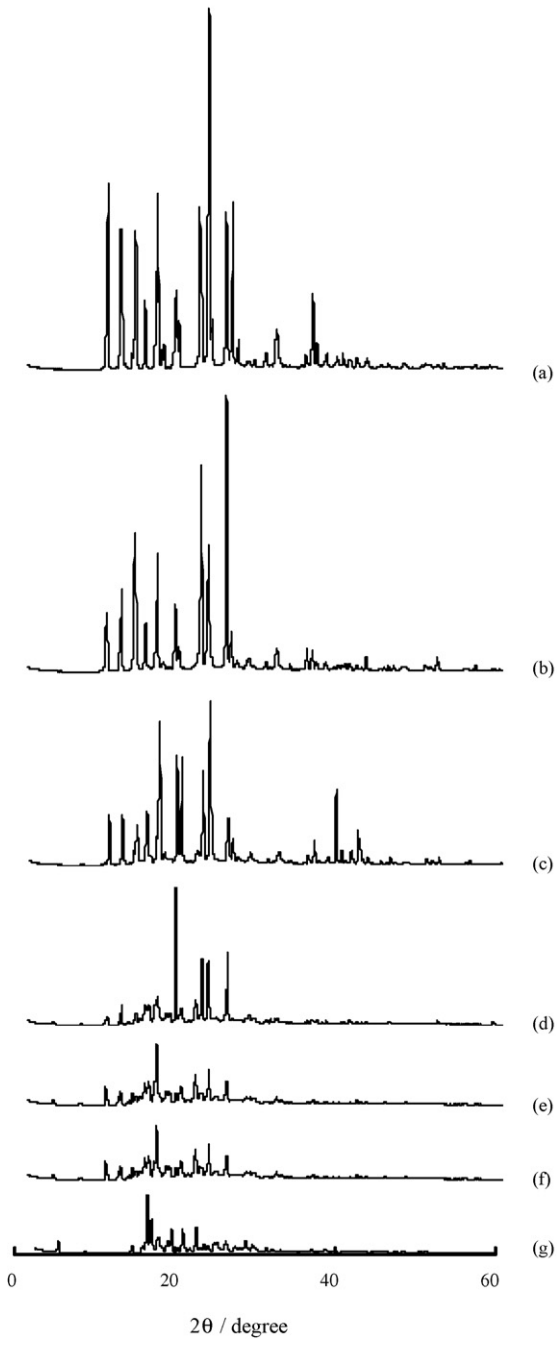

Fig. 5. Powder X-ray diffractograms of physical mixtures of paracetamol and cloperastine hydrochloride. Key: ratio of paracetamol to cloperastine hydrochloride (mol%) was (a) 100:0, (b) 98:2, (c) 92:8, (d) 71:29, (e) 62:38, (f) 50:50, (g) 0:100.

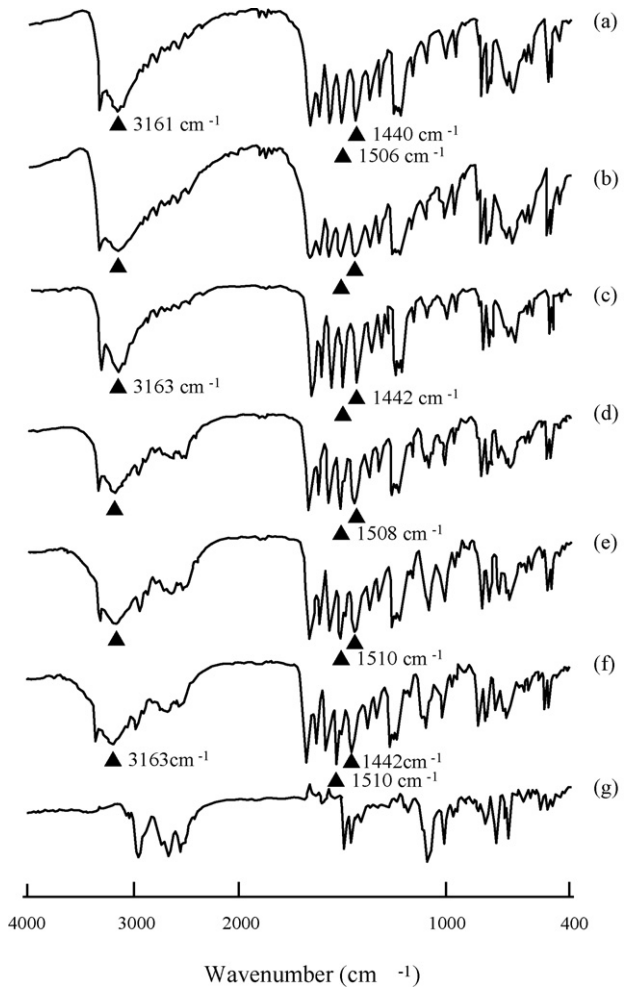

Fig. 6. FT-IR spectra of paracetamol, cloperastine hydrochloride and their physical mixtures. Key: ratio of paracetamol to cloperastine hydrochloride (mol%) was (a) 100:0, (b) 98:2, (c) 92:8, (d) 71:29, (e) 62:38, (f) 50:50, (g) 0:100.

group (Fig. 1) and the mechanism of formation of a eutectic mixture between PM and CLH remains unknown.

Since the FT-IR results indicated that CLH might affect the intermolecular hydrogen-bonding of PM (form I), we performed DSC analysis of mixed powders prepared by melt quenching of physical mixtures consisting of PM and CLH. Three polymorphic forms of PM (forms I, II and III) have been reported (Haisa et al., 1976; Al-Zoubi et al., 2002; Haisa et al., 1974; Martino et al., 1997; Szelagiewicz et al., 1999). Form I, with a melting temperature of 168–169 °C, is the most stable form; form II, with a melting temperature of 157–158 °C, is a metastable form; and form III, which is unstable, easily transforms into form II at approximately 125 °C (Martino et al., 1997, 1996, 2000; El-said, 1995; Joris et al., 1998). In contrast, Wang et al. (2002) reported that the DSC curve of amorphous PM indicated two exothermic peaks near 73 and 125 °C and one endothermic peak at 159 °C, and they suggested that the exothermic peak at 73 °C might result from the recrystallization of the glassy form of solidified PM melt. As shown in a previous study, the exothermic peak at 125 °C represents the polymorphic phase transformation from form III to form II. The endothermic peak at 159 °C was attributed to the melting of form II. In the present study, amorphous PM prepared by melt quenching showed a T_g at 23.9 °C (inflection point), two exothermic peaks and one endothermic peak (Fig. 7a). The exothermic peak at 76.2 °C with an enthalpy of 95 J/g might be due to the crystallization of form III. The exothermic peak at 126.3 °C with an enthalpy of 5.60 J/g might represent the polymorphic phase transformation from form III to form II. The endothermic peak at 159.1 °C was attributed to the melting of form II, which has been con-

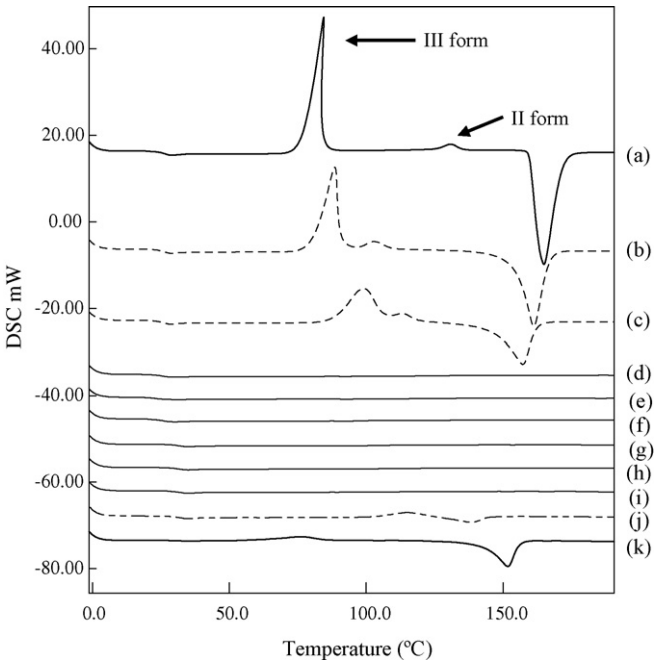

Fig. 7. DSC thermograms obtained during second heating of fused mixtures of paracetamol and cloperastine hydrochloride. Key: ratio of paracetamol to cloperastine hydrochloride (mol%) was (a) 100:0, (b) 98:2, (c) 92:8, (d) 71:29, (e) 62:38, (f) 50:50, (g) 38:62, (h) 21:79, (i) 18:82, (j) 14:86, (k) 0:100.

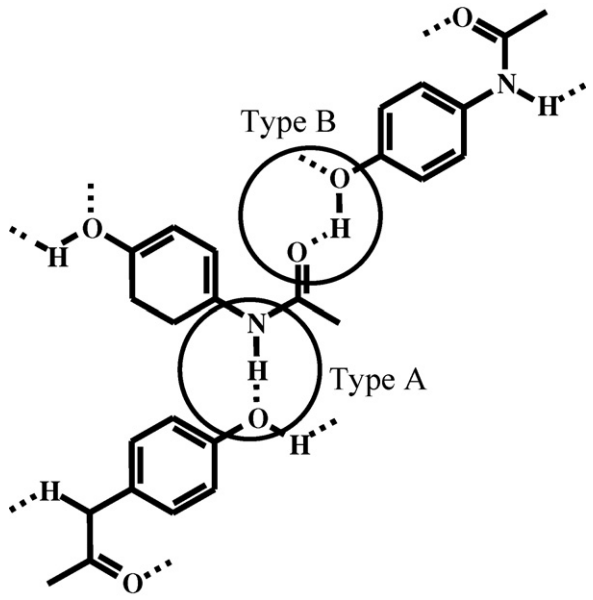

Fig. 8. The hydrogen-bonding structure of paracetamol.

firmed by other studies (Martino et al., 1997, 1996; de Wet et al., 1998). Moreover, amorphous CLH prepared by melt quenching showed a T_g at 28.1 °C (inflection point), one exothermic peak at 57.2 °C with an enthalpy of 10.4 J/g and a melting endothermic peak at 141.8 °C with an enthalpy of 36.9 J/g (Fig. 7k). A single T_g was observed in the amorphous solid dispersions prepared with CLH (Fig. 7b–j), indicating completely miscibility of PM and CLH within the sensitivity limit of the DSC method. The peak distance between the two exothermic crystallizations attributed to forms II and III decreased with increase in CLH, as shown in Fig. 7b and c. Moreover, the exothermic crystallization peak observed for the PM/CLH dispersion disappeared in the presence of 29–82 mol.% of CLH (Fig. 7d–i). From these results, we suggest that CLH inhibits the crystallization of PM. Miyazaki et al. (2004) reported that PAA inhibits the crystallization of amorphous PM in the dry state. It is likely that CLH will affect the intermolecular interaction of forms II and III. As shown in Fig. 8, PM has been reported to have two types (type A and type B) of intermolecular hydrogen-bonding (Wang et al., 2002). Type A and type B hydrogen-bonding contribute to the NH–O and OH–O intermolecular interactions of PM, respectively. Form II of PM has strong type A hydrogen-bonding, whereas form III has strong type B hydrogen-bonding (Haisa et al., 1976; Al-Zoubi et al., 2002; Joris et al., 1998; Nichols and Frampton, 1998). Wang et al. (2002) reported that the two types of hydrogen-bonding of PM form I are stronger than those of PM form II. They also reported that the distance between the atoms causing intermolecular interactions in PM crystals is dependent on the melting point. Moreover, since the melting point attributed to form II decreased with increasing CLH (Fig. 7a–c), it is reasonable to assume that the CLH will affect the distance of hydrogen-bonding, thus contributing to the intermolecular interactions of form II. Similarly, the melting point of form I decreased progressively with increasing CLH (Fig. 2). It is clear that CLH strongly affects the two types of intermolecular hydrogen-bonding of PM. These results suggest, therefore, that eutectic mixtures consisting of form I PM and CLH might be formed by a mechanism similar to that operating for other types of PM.

4. Conclusions

A physical mixture of PM and CLH at a molar ratio of 50:50 formed a eutectic mixture, which affected the pharmaceutical properties of the dosage form and the operating conditions during mixing. Studies with mixed powders of PM and CLH prepared by melt quenching indicate that CLH strongly affects the two sites of intermolecular hydrogen-bonding in PM. PM interacts with other compounds containing the same groups and/or the carbonyl group through dipolar or hydrogen-bonding, but the mechanism by which PM interacts with CLH is unknown. The formation of a eutectic mixture during the vertical granulation process led to the arrest of the cross-screw during mixing. However, formation of a eutectic mixture was not found in a fluid bed, indicating that this process is dependent on mechanical force. Since the formation of a eutectic mixture caused various problems in formulation, an appropriate preparation method must be used for this dosage form.

References

Acetaminophen monograph in JP IX, p. C-70.

Al-Zoubi, N., Koundourellis, J.E., Malamataris, S., 2002. FT-IR and Raman spectroscopic methods for identification and quantitation of orthorhombic and monoclinic paracetamol in powder mixes. J. Pharm. Biomed. Anal. 29, 459–467.

de Wet, F.N., Gerber, J.J., Lotter, A.P., van der Watt, J.G., Dekker, T.G., 1998. A study of the changes during heating of paracetamol. Drug Dev. Indus. Pharm. Technol. 224, 447–453.

Dearden, J.C., 1972. Nature of acetaminophen–antipyrine aomplex. J. Pharm. Sci. 61, 1661–1663.

El-said, Y., 1995. Effect of co-solvents on water content and physical properties of acetaminophen crystallized from aqueous solutions. STP Pharma. Sci. 5, 232–237.

Grant, D.J.W., Jacobson, H., Fairbrother, J.E., Patel, C.G., 1980. Phases in the paracetamol–phenazone system. Int. J. Pharm. 5, 109–116.

Haisa, M., Kashino, S., Kawai, R., Maeda, H., 1976. The monoclinic form of *p*-hydroxyacetanilide. Acta Crystallogr. B 32, 1283–1285.

Haisa, M., Kashino, S., Maeda, H., 1974. The orthorhombic form of *p*-hydroxyacetanilide. Acta Crystallogr. B 30, 2510–2512.

Joris, E., Martino, P.D., Berneron, C., Guyot-Hermann, A.M., Guyot, J.C., 1998. Pharm. Res. 15, 1122–1130.

Martino, P.D., Conflant, P., Drache, M., Huvenne, J.P., Guyot-Hermann, A.M., 1997. Preparation and physical characterization of forms II and III of paracetamol. J. Therm. Anal. 48, 447–458.

Martino, P.D., Guyot-Hermann, A.M., Conflant, P., Drache, M., Guyot, J.C., 1996. Molecular mobility of the paracetamol amorphous form. Int. J. Pharm. 128, 1–8.

Martino, P.D., Palmieri, G.F., Martelli, S., 2000. Molecular mobility of the paracetamol amorphous form. Chem. Pharm. Bull. 48, 1105–1108.

Miyazaki, T., Yoshioka, S., Aso, Y., Kojima, S., 2004. Ability of polyvinylpyrrolidone and polyacrylic acid to inhibit the crystallization of amorphous acetaminophen 93, 2710–2717.

Moynihan, H.A., O'Hare, I.P., 2002. Spectroscopic characterization of monoclinic and orthorhombic forms of paracetamol. Int. J. Pharm. 247, 179–185.

Muller, B.W., Beer, Y., 1982. Polymorphie und Trachtänderung von Propyphenazon. Acta Pharm. Techn. 28, 97–102.

Nichols, G., Frampton, C.S., 1998. Physicochemical characterization of orthorhombic polymorph of paracetamol crystallized from solution. J. Pharm. Sci. 87, 684–693.

Patel, N.K., 1970. Experimental in physical pharmacy. IV. Pharmaceutical eutectic mixtures. Am. J. Pharm. Educ. 34, 47–53.

Szelagiewicz, M., Marcolli, M., Cianferani, S., Hard, A.P., Vit, A., Burkhard, A., von Raumer, M., Hofmeier, U.Ch., Zilian, A., Francotte, E., Schenker, R., 1999. In situ characterization of polymorphic forms. The potential of Raman techniques. J. Therm. Anal. Cal. 57, 23–43.

Takahashi, H., Chen, R., Okamoto, H., Danjo, K., 2005. Acetaminophen particle design using chitosan and a spray-drying technique. Chem. Pharm. Bull. 53, 37–41.

Wang, S.L., Lin, S.Y., Wei, Y.S., 2002. Transformation of metastable forms of acetaminophen studied by thermal Fourier transform infrared (FT-IR) microspectroscopy. Chem. Pharm. Bull. 50, 153–156.

Zalac, S., Khan, M.Z.I., Gabelica, V., Tudja, M., Mestrovic, E., Romih, M., 1999. Paracetamol-propyphenazone interaction and formulation difficulties associated with eutectic formation in combination solid dosage forms. Chem. Pharm. Bull. 47, 302–307.