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Physicochemical properties of amorphous salt of cimetidine and diflunisal system

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Abstract

The purpose of this study was to prepare amorphous precipitates of the binary system of cimetidine (CIM) and diflunisal (DIF) and to investigate the physicochemical properties of the precipitates. To achieve this, the interaction between CIM and DIF molecules was studied by means of nuclear magnetic resonance (NMR) and Fourier-transform infrared (FTIR) measurements. The binary system of CIM and DIF was found to become amorphous upon precipitation from ethanol solution, without heating or melting. In the thermal analysis by TG–DTA equipped with a mass spectrometer, decarboxylation of DIF was found to occur below its melting temperature. In NMR studies, the chemical shifts of a proton in the imidazole ring of CIM and the carbon to which the DIF carboxyl group is bound were found to change depending on the composition of the binary system. The change in NMR chemical shifts suggested that a salt was formed between CIM and DIF. The precipitates had higher solubility than intact drugs due to this salt formation. The results suggest that CIM may be useful as an amorphous carrier, without requiring heating or melting, due to the formation of a salt with acidic drugs. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Amorphous; Salt formation; Intermolecular interaction; Cimetidine; Diflunisal

1. Introduction

Diflunisal (DIF) is a salicylic acid derivative with analgesic and anti-inflammatory properties and it is one of the non-steroidal anti-inflammatory drugs (NSAIDs) used in the management of moderate pain, osteoarthritis, and anti-rheumatoid arthritis. It is known that NSAIDs sometimes have side effects such as gastrointestinal disturbances, headache, and rash (Masubuchi et al., 1998). Cimetidine (CIM) is an H_2-receptor antagonist widely used in the treatment of patients with gastrointestinal dysfunction, including dyspepsia, and may be used to counteract the gastric erosion and major upper gastrointestinal bleeding that occurs as side effects resulting from NSAID therapy (Emami and Gespach, 1986).

The rate of dissolution and bioavailability of poorly water-soluble drugs are known to depend on the solubility of the solid pharmaceuticals (Miyazaki et al., 1975; Ampolsuk et al., 1974). There have been reports indicating that the ad-

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ministration of drugs in the form of an amorphous solid is an effective means of improving the bioavailability of the drugs (Yamamoto et al., 1976; Fukuoka et al., 1986). These amorphous systems are sometimes prepared as binary systems consisting of drugs with polymers (Sekikawa et al., 1979; Lu and Zografi, 1998; Van den Mooter et al., 1998; Tantishaiyakul et al., 1996) or with low molecular-weight compounds by cooling the melts (Summers and Enever, 1976; Timko and Lordi, 1979).

We have previously reported that binary systems of CIM and some NSAIDs (naproxen, NAP; or indomethacin, INDO) form amorphous precipitates upon precipitation from ethanol solution, without heating or melting (Yamamura et al., 1996, 2000). The amorphous CIM–NSAIDs precipitates were considered to have two advantages: (1) the dissolution rate of NSAIDs is increased due to both salt formation and a loss of crystallinity; and (2) the side effects of NSAIDs, such as gastrointestinal disorders, can be prevented by the pharmacological effect of CIM. In our previous studies, the hydrogen bonding between the hydrogen of the imidazole ring of CIM and the carboxyl group of NAP or INDO was investigated by nuclear magnetic resonance (NMR) spectroscopy (Yamamura et al., 1996, 2000).

In the present study, we prepared precipitates of the CIM–DIF binary system from ethanol solution without heating or melting, and we investigated the physicochemical properties of the CIM–DIF precipitates by X-ray diffraction and thermal analysis. Furthermore, an interaction between CIM and DIF was studied by Fourier-transform infrared (FTIR) and NMR spectroscopy. From the results, we revised the mechanism of formation for amorphous precipitates of the CIM–NSAIDs system, taking into account the results of CIM–NAP and CIM–INDO systems reported previously.

2. Materials and methods

2.1. Materials

CIM (Tokyo Kasei, Tokyo, Japan) and DIF (Sigma, St. Louis, MO) were used. All other reagents were of reagent grade. The composition of each binary system examined in this study is expressed as the molar ratio of the components.

2.2. Preparation of binary systems

Mixtures consisting of CIM and DIF in various molar ratios were prepared by dissolving 1 g into 100 ml of ethanol in each instance, and then evaporating the solvent under reduced pressure at 40 °C. The residual solvent in the precipitates was completely removed by placing the precipitates under vacuum for at least 2 days in a desiccator containing P_2O_5. The precipitates were stored in a desiccator with silica gel as the desiccant until use in the experiments.

2.3. Powder X-ray diffraction

A RINT 2500 X-ray diffractometer (Rigaku, Tokyo, Japan) was used. The X-ray source was Cu–Kα radiation, the voltage was set at 50 kV and the current was set at 100 mA. The diffracted X-ray beam was monochromated by means of a bent-type graphite monochromator, and a scintillation counter was used as the detector. Symmetric-reflection geometry was employed for the measurements. Diffraction intensities were measured by a fixed-time step-scanning method in the range of 5–40° at 0.02° intervals. Sample powders were lightly ground and passed through a 75 μm sieve before measurement.

2.4. FTIR spectroscopy

FTIR spectra were obtained on an FTIR spectrophotometer (FTIR-500, Nihon Bunko, Tokyo, Japan) equipped with a diffuse reflectance attachment (DR-81, Nihon Bunko, Tokyo, Japan). The measurements were carried out based on a total of 1000 scans and a resolution of 4 cm^{-1} over a wave number range of 600–4000 cm^{-1}.

2.5. Thermal analysis

Thermogravimetric analysis–differential thermal analysis (TG–DTA) was performed using a TG-DTA2000 (MAC Science, Tokyo, Japan) under N_2 gas flow (100 ml min^{-1}). The sample powders were packed in an aluminum sample pan (open type) and heated at a rate of 1 °C min^{-1} using an empty pan as a reference. A TG–DTA system equipped with a quadropole mass spectrometer was also used (TG–DTA/MS, model VG, MAC Science, Tokyo, Japan) to investigate the cause of weight loss during heating. The TG–DTA/MS measurements were carried out under He gas flow and the fragment peaks were detected by a secondary electron multiplier in the range between $m/e = 15$ and 100. The sample powder was packed in an aluminum sample pan (open type) and heated at a rate of 10 °C min^{-1}. The weight of the sample powder was about 20 mg for TG–DTA measurement.

2.6. NMR spectroscopy

^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL, α-500 spectrometer (Nihon Denshi, Tokyo Japan) at 37 °C. About 40 mg of CIM and the drug powder were dissolved in 0.8 ml of DMSO-d_6. Chemical shifts were expressed in δ (ppm) downfield from the internal standard (tetramethylsilane).

2.7. High-performance liquid chromatography (HPLC)

HPLC chromatograms were recorded using a PU-980 + UV-980 system (Nihon Bunko, Tokyo, Japan) to check the extent of degradation during preparation of the binary systems. An octadecyl silica (ODS) column was used and the mobile phase consisted of methanol–acetonitrile–water (75:10:5). The flow rate was 0.5 ml min^{-1} and ultraviolet absorption was monitored at 215 nm.

2.8. Solubility

The solubility DIF in the presence of CIM in ethanol was determined at 37 ± 2 °C. An excess amount of DIF was added to 5 ml of ethanol containing various amounts of CIM in test tubes sealed with stoppers. The test tubes were kept in a constant-temperature bath maintained at 37 °C for at least 66 h. The solution was then appropriately diluted with ethanol and the concentration of the drug was determined by an ultraviolet (UV) absorption method using a spectrophotometer (U-3300 Hitachi, Tokyo, Japan). Equilibrium solubility was determined by repetitive sampling.

3. Results and discussion

3.1. Characterization of CIM–DIF precipitates

Fig. 1 shows the molecular structure of CIM and DIF with the NMR chemical shifts determined in a single-component system. We have reported that the CIM–NAP and CIM–INDO

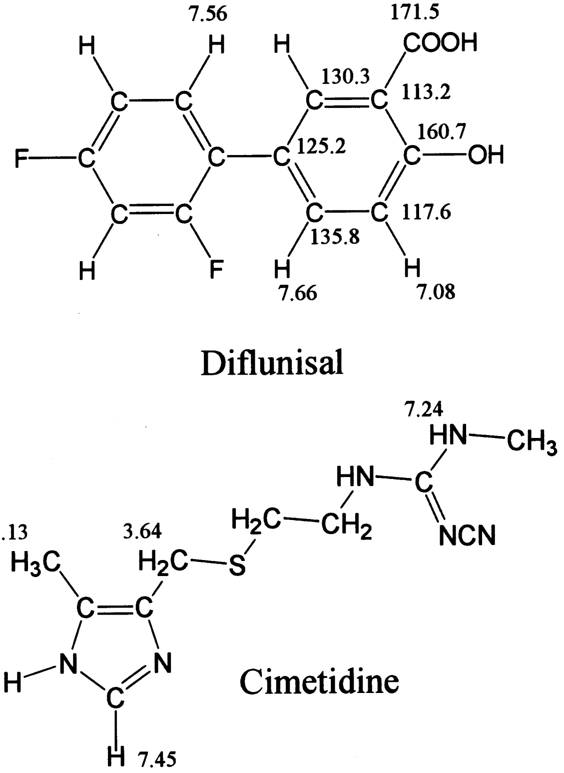

Fig. 1. Molecular structures of CIM and DIF. The details of the peak assignments will be discussed elsewhere.

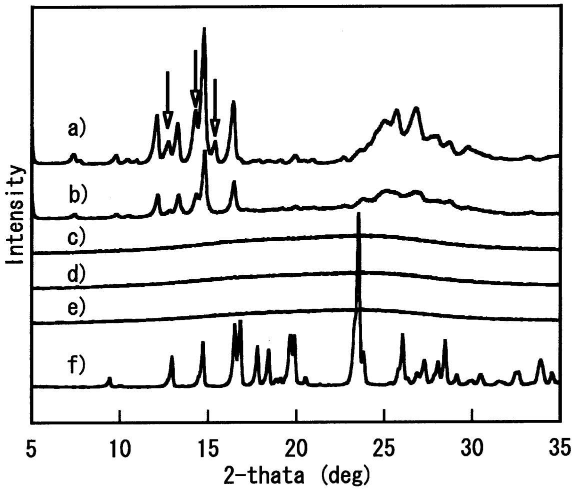

Fig. 2. X-ray diffraction patterns of CIM, DIF and CIM–DIF precipitates: (a) DIF; (b) CIM–DIF (20:80); (c) CIM–DIF (40:60); (d) CIM–DIF (60:40); (e) CIM–DIF (80:20); (f) CIM.

binary systems become amorphous upon precipitation without heating (Yamamura et al., 1996, 2000). From the molecular structure, it is evident that the carboxyl group of DIF is bound to an aromatic carbon whereas that of NAP or INDO is bound to an aliphatic carbon.

Fig. 2 shows the X-ray diffraction patterns of the precipitates prepared with various ratios of CIM and DIF. The precipitates containing more than 40% CIM showed no distinct diffraction peaks, indicating that the CIM–DIF binary precipitates became amorphous upon precipitation from ethanol solution without heating. No additional peaks were detected in the HPLC chromatograms of any of the precipitates, indicating that no degradation occurred upon precipitation.

The X-ray diffraction pattern of the precipitate of DIF (Fig. 2a) without CIM showed additional diffraction peaks indicated by arrows at 12.7, 14.2 and 15.4° (2θ) absent in the pattern of intact DIF crystals, suggesting that some polymorphic modification occurred upon precipitation. Some polymorphic forms of DIF crystals have been reported (Martinez-Oharriz et al., 1994). According to the classification, the intact DIF crystals used in this study were Form II and the DIF crystals obtained upon precipitation consisted of a mixture of Forms II and III.

The X-ray diffraction pattern of the precipitate of CIM–DIF (20:80) (Fig. 2b) showed broad diffraction peaks of DIF and no distinct peaks for CIM crystals. This result indicates that the precipitates of CIM–DIF (20:80) consisted of amorphous CIM and poorly crystallized DIF.

Fig. 3 shows the TG–DTA curves of precipitates of the CIM–DIF systems. No clear endothermic peaks were observed in the case of precipitates characterized as amorphous by X-ray measurements. In the DTA curve of the CIM–DIF precipitates (Fig. 3b–e), some fluctuation

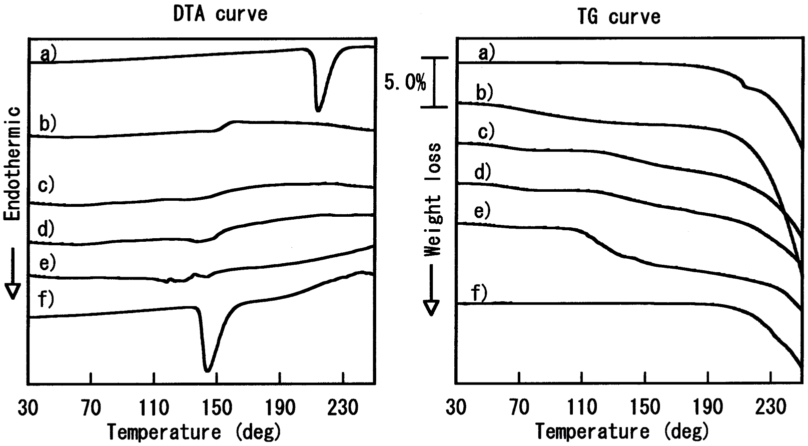

Fig. 3. TG–DTA curves of CIM, DIF and CIM–DIF precipitates; (a) DIF; (b) CIM–DIF (20:80); (c) CIM–DIF (40:60); (d) CIM–DIF (60:40); (e) CIM–DIF (80:20); (f) CIM.

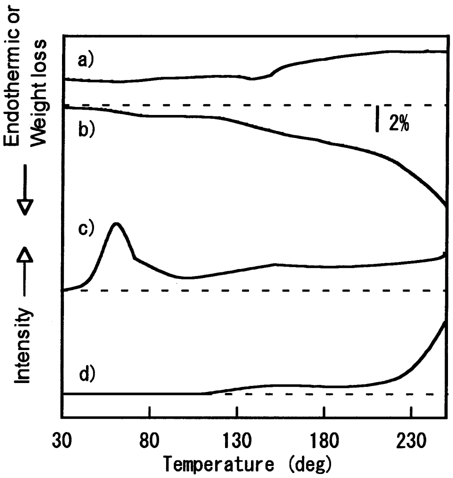

Fig. 4. TG–DTA/MS curves of CIM–DIF precipitate (50:50): (a) TG curve; (b) DTA curve; (c) MS $m/e = 18$; (d) MS $m/e = 44$.

was observed in the baseline, between round 110 and 145 °C. This is considered to be due to melting of DIF crystals with poor crystallinity, or release of adsorbed water from the precipitates, as will be described later.

The results of X-ray diffraction and thermal analysis indicate that at a particular molar ratio the CIM–DIF binary system becomes amorphous upon precipitation from ethanol solution as observed in the case of the CIM–NAP and CIM–INDO systems. Considering that DIF, NAP, and INDO all have a carboxyl group in their molecular structure, the CIM molecule may be useful as an amorphous carrier for particular drugs having a carboxyl group.

Although neither CIM nor the DIF crystals showed weight loss, the binary precipitates of the CIM–DIF system showed some weight loss in the temperature range between 110 and 150 °C during heating. In order to determine the cause of the weight loss during heating, TG–DTA/MS measurements were performed. Fig. 4 shows the TG–DTA/MS curves of the precipitate of the CIM–DIF (50:50) binary system. The intensities of the signals of the fragments at $m/e = 18$ and 44 were found to increase during heating. The intensities of the signals of other fragments were negligible, with intensities less than 1/100th that of the fragments at $m/e = 18$ and 44. The fragments at $m/e = 18$ and 44 were attributed to molecules of water and carbon dioxide, respectively. The intensity of the signal of the fragment at $m/e = 18$ increased concurrently with the weight loss observed starting at around 50 °C in the TG curve, indicating the release of adsorbed water from the precipitates. Because the signal of the fragment at $m/e = 18$ was observed at all temperatures up to the melting temperature, water molecules were considered to be incorporated in the precipitates through adsorption of varied strength. Thus, the water molecules were released from the precipitates depending on the strength of adsorption or sorption during heating. The signal intensity of the fragment at $m/e = 44$ was observed from about 120 °C and the intensity of the signal gradually increased with increasing temperature, suggesting that decomposition (decarboxylation) of DIF occurred below the melting temperature of the DIF crystal.

These results indicate that the binary amorphous precipitate of the CIM–DIF system has a strong affinity for water and that the physicochemical stability of the binary system becomes poor upon precipitation.

3.2. FTIR spectra of the CIM–DIF system

Fig. 5 shows the FTIR spectra of the CIM–DIF binary precipitates. The FTIR spectra of

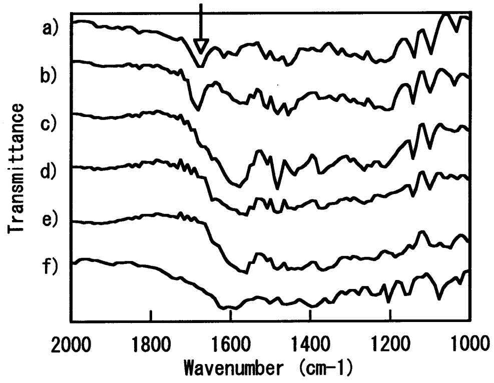

Fig. 5. FTIR spectra of CIM, DIF and CIM–DIF precipitates: (a) DIF; (b) CIM–DIF (20:80); (c) CIM–DIF (40:60); (d) CIM–DIF (60:40); (e) CIM–DIF (80:20); (f) CIM.

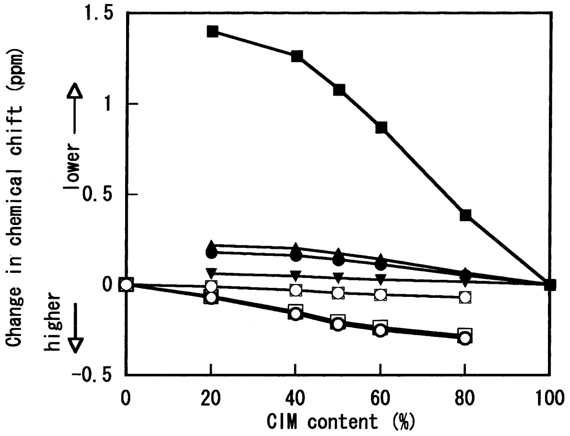

Fig. 6. Changes in the ^{1}H-NMR chemical shift of some protons of CIM and DIF in CIM–DIF binary systems. Key: ●, CH_3– bound to the imidazole ring of CIM (2.13 ppm); ■, H bound to C in the imidazole ring of CIM (7.45 ppm); ▲, CH_2 in CH_2S of CIM (3.64 ppm); ▼, H in –$NHCH_3$ of CIM (7.24 ppm); □, H bound in DIF (7.08 ppm); ○, H bound in DIF (7.66 ppm); □, H bound to the benzene ring of DIF (7.56 ppm).

precipitates containing crystalline DIF (Fig. 5a and b) showed an absorption peak at 1650 cm^{-1} attributable to $\nu_{C=O}$. In the amorphous precipitates, the peak at 1650 cm^{-1} disappeared and the peak for an asymmetric stretching vibration of a carboxylate ion was observed at approximately 1580 cm^{-1} (Fig. 5c–e). This result suggests that CIM and DIF molecules form an organic salt during amorphous precipitation.

3.3. NMR spectra of the CIM–DIF system

Fig. 6 shows the changes in the ^{1}H-NMR chemical shift of some protons of CIM and DIF molecules with varying CIM content. A partial assignment of the NMR peaks is shown in Fig. 1 together with the molecular structure; the details of the peak assignments in the CIM–DIF system will be discussed elsewhere. No significant changes (less than 0.03 ppm) in the ^{1}H-NMR chemical shift were observed for other protons in CIM or DIF molecules, except for those shown in Fig. 6. The chemical shift of the proton bound to the carbon in the imidazole ring of CIM (■) was found to shift 1.39 ppm from 7.45 ppm (CIM–DIF = 100:0) to 8.84 ppm (CIM–DIF = 20:80). If a salt was formed between CIM and DIF, a proton of NH in the imidazole ring is likely to play an important role in the interaction between them. The signal of the NH proton, however, is always observed as a very broad peak, therefore a change in the chemical shift of the NH proton would not be detectable. The change in the chemical shift observed in the proton bound to the carbon in the imidazole ring of CIM was considered to be due to the influence of salt formation causing an interaction between the NH proton in the imidazole ring of the CIM and DIF molecules.

The pK_a values of the acidic DIF, INDO, and NAP were reported to be 3.00, 4.5, and 4.2, respectively, and that of the basic CIM was reported to be 6.80 (Drayton, 1990). From the pK_a data, the magnitude of the interaction between DIF and CIM in salt formation is considered to be larger than in the case of the INDO–CIM and the NAP–CIM systems. Therefore, the magnitude of the change in chemical shift in the CIM–DIF system (about 1.39 ppm) was much larger than that in the case of the CIM–NAP (about 0.05 ppm) or CIM–INDO (about 0.06 ppm) systems (Yamamura et al., 1996, 2000).

Fig. 7 shows the change in the ^{13}C-NMR chemical shift of some carbons of the DIF molecule, with varying CIM content. A partial assignment of the NMR peaks is shown in Fig. 1 together with the molecular structure. The change in the ^{13}C-NMR chemical shift of carbons in CIM and other carbons in DIF was negligible. The aromatic carbon to which the carboxyl group is bound (●) was found to shift about 6.3 ppm from 113.2 ppm (CIM–DIF = 0:100) to 119.5 ppm (DIM–DIF = 80:20). In the CIM–INDO system, the largest change in ^{13}C-NMR chemical shift was found in the carboxyl carbon in the INDO molecules, about 0.08 ppm (Yamamura et al., 2000). The shift to a lower magnetic field observed in the carboxyl carbon of DIF (▲) was about 0.3 ppm from 171.5 ppm (CIM–DIF = 0:100) to 171.8 ppm (CIM–DIF = 80:20), which is larger than that of INDO but much smaller than that of the aromatic carbon to which the carboxyl group is bound.

The reason that a larger change in chemical shift was found in the aromatic carbon, but not the carboxyl carbon, in the CIM–DIF system was considered to be that since the carboxyl group in DIF is bound to an aromatic carbon, the C=O in the carboxyl group and the aromatic ring would form a conjugated double-bond structure. Because the π electrons in the conjugated system move easily, when the electron charge around C=O changes by the formation of the salt, the change in charge would be compensated by the conjugated system. Therefore, the change in the chemical shift of carboxyl carbon would become smaller, and that of the carbon to which the carboxyl group is bound would became larger. On the other hand, because the C=O in the carboxyl group in INDO molecule does not form a conjugated double-bond structure, the change in electron density as a result of the interaction is suggested to be localized at the carboxyl group in the molecule.

Furthermore, the NMR peaks of the carbon in the benzene ring observed at 125.2 (□), and 135.8 ppm (○), and of the carbon to which the hydroxyl group is bound observed at 160.7 ppm (■) were found to shift to a higher and to a lower magnetic field, respectively. These changes in chemical shift would be due to a strong and complicated interaction between the CIM and DIF molecules, since not only the carboxyl group but also the conjugated system of the DIF molecules contributes to the interaction.

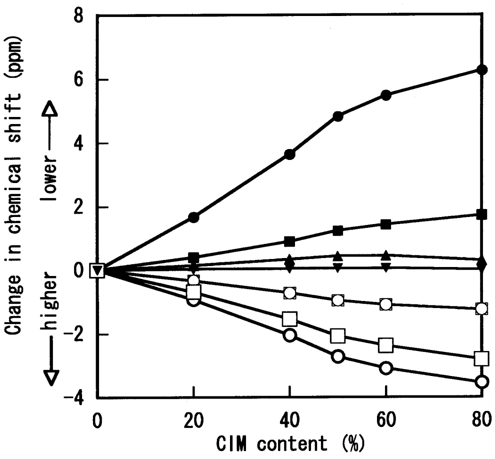

Fig. 7. Changes in the ^{13}C-NMR chemical shift of some carbons of CIM and DIF in CIM–DIF binary systems. Key: ▲, –COOH of DIF (171.5 ppm); ●, C to which the –COOH of DIF is bound (113.2 ppm); ■, C to which the –OH of DIF is bound (160.7 ppm); ▼, C in benzene ring of DIF (130.3 ppm); □, C in benzene ring of DIF (117.6 ppm); ○, C in benzene ring of DIF (135.8 ppm); □, C in benzene ring of DIF (125.2 ppm).

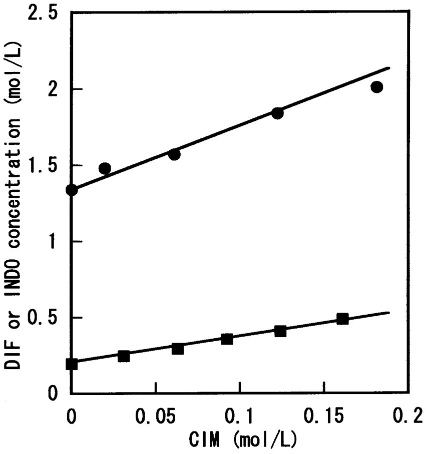

Fig. 8. Phase solubility diagram of DIF with CIM: ●, DIF; ■, INDO. The results for the CIM–INDO system were published in the preceding paper[4] (Yamamura et al., 2000).

The result showing that there was a larger change in ^{13}C-NMR chemical shift in the CIM–DIF system than in the CIM–INDO and CIM–NAP systems was considered to be due to the formation of a salt between CIM and DIF with a low pK_a; the same as the result described above.

The precipitates of the salt between the CIM and NSAIDs molecules would lose crystallinity and consequently become amorphous. Although the interaction occurring with salt formation between the CIM and DIF molecules was considered to be stronger than that between the CIM and INDO molecules, an amorphous precipitate was not obtained when the DIF content was high. This may be due to substantial mutual interaction between the DIF molecules. As a result, there were some DIF crystals remaining in the CIM–DIF precipitates (CIM–DIF = 20:80).

3.4. Solubility of DIF in CIM solution

Fig. 8 shows the solubility of DIF in the presence of various concentrations of CIM in ethanol. The solubility of DIF was found to increase in a linear manner with the CIM concentration. The slope of increase of DIF solubility was three times larger than the value for INDO (Yamamura et al., 2000). The increase of solubility of NSAIDs was considered to be due to the formation of a soluble salt with CIM. Since the interaction between the CIM and DIF molecules with salt formation was stronger than that between the CIM and INDO molecules, as described above, the increase in DIF solubility was greater than that for INDO. The increase in the solubility of DIF in ethanol solution would result in an increase in the dissolution rate in gastrointestinal truct, so the CIM–DIF binary system would have better absorption characteristics while preventing the gastrointestinal side effects caused by DIF.

4. Conclusion

We have shown that the CIM–DIF binary system becomes amorphous upon precipitation from ethanol solution. An interaction between CIM and DIF was demonstrated by means of FTIR and NMR. The results indicate that our previously reported results should be revised as amorphous precipitates of the CIM–NSAIDs system were obtained due to salt formation between CIM and NSAIDs molecules upon precipitation, and not as a result of non-bonding intermolecular interactions as previously thought. The interaction between a hydrogen in the imidazole ring of CIM and the carboxyl group of DIF plays an important role in salt formation. A conjugated double-bond structure in DIF was also considered to participate in the interaction between the CIM and DIF molecules. The poor crystallinity of the salt obtained was due to rapid evaporation, resulting in the precipitate becoming amorphous. The physicochemical stability of the CIM–DIF precipitates decreased upon precipitation. The solubility of DIF increased in the presence of CIM due to soluble salt formation. The salt of CIM and acidic drugs with a carboxyl group can be applied to the preparation of amorphous systems formed upon precipitation without the need for heating. Using the CIM molecules to prepare an amorphous system with acidic NSAIDs, amorphous precipitates formed would show a higher dissolution rate and may prevent NSAID's side-effects through the pharmacological effect of CIM.

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