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RESEARCH PAPER

Compatibility of Ibuprofen and Ethenzamide

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ABSTRACT

The compatibility of ibuprofen and various drugs was investigated by thermal analysis. The results showed a lower melting point with many drugs. The compound of ibuprofen and ethenzamide was selected for detailed compatibility investigation. First, a ratio composition of a eutectic of ibuprofen and ethenzamide was estimated. A ratio composition of a eutectic of ibuprofen and ethenzamide of weight ratio 3:2 was suggested, and its melting point was approximately 56°C. Further, we investigated crystallization by powder x-ray diffraction. The resulting powder x-ray diffraction pattern of the compound that was heat treated was almost the same as that of the physical mixture, indicating that the crystallinity of ibuprofen and ethenzamide were not affected by the heat treatment. Next, we investigated the chemical stability of ibuprofen, ethenzamide, and a small amount of various excipients in capsule form, stored under conditions of 65°, 50°, and 40°C. It was established that ibuprofen and ethenzamide are stable. However, it was found that there is a remarkable delay of dissolution speed under conditions above 50°C.

INTRODUCTION

Ibuprofen, a nonsteroidal anti-inflammatory drug, has been considered effective and safe. Recently, however, combination drugs incorporating ibuprofen have been developed. For this reason, physical and chemical compatibility studies between ibuprofen and such drugs are considered very important.

Najib (1-3) and Mura (4) reported that the solid dispersion of ibuprofen in polyvinylpyrrolidone or urea results in an increase in the in vitro release of the ibuprofen. Imai (5) and Acarturk (6) reported the for-

mulation of ibuprofen using gelatin. Gordon (7) reported on the interaction between ibuprofen and stearates which were simple eutectics. While some studies have investigated the dissolution and absorption increase, papers reporting compatibility studies have been relatively few.

There have been many compatibility studies based on thermal analysis [Botha (9–12), Cotton (13), Signoretti (14), Hartauer (15), Gunawan (16)]. However, papers reporting the relation between thermal analysis and chemical stability are few.

Considering this, we investigated the compatibility of ibuprofen and various other drugs by differential scanning calorimetry (DSC). We chose a compound of ibuprofen and ethenzamide because the mixture melts at a very low temperature. We clarified the eutectic composition and investigated the eutectic mixture in regard to the crystallization, the dissolution, and the long-term stability.

EXPERIMENTAL

Materials

The following substances were used: ibuprofen (IBP), acetaminophen, ethenzamide (ETH), carbinoxamine maleate, anhydrous caffeine, thiamine nitrate, chlorpheniramine maleate, ascorbic acid, dextromethorphan hydrobromide, potassium guaiacolsulfonate, noscapine, bisibuthiamine, riboflavin, and bromovalerylurea. All of the substances were of pharmaceutical grade.

For measurement of powder x-ray diffraction, IBP and ETH at a weight ratio of 3:2, were used. After being melted in the compound, they shattered upon cooling.

We prepared capsules for stability tests. The formulations are shown in Table 1.

Table 1

Formulation Used in the Stability Studies

Materials	Amount (w/w%)
Ibuprofen	22.9
Ethenzamide	14.6
Anhydrous caffeine	8.0
Bromovaleryiurea	31.8
Microcrystalline cellulose	12.5
Light anhydrous silicic acid	1.6
Magnesium stearate	1.3
Talc	7.3

Thermal Analysis

A 1090B Thermal Analyzer (Dupon Co.) and a thermal analysis system, TAS100 (Rigaku), were used for the thermal analysis. Thermograms were obtained by heating at a constant rate of 5°C per minute. And in case of the compound of IBP and ETH, we calculated a quantity of heat up to 60°C.

Powder X-ray Diffractometry

The powder X-ray diffraction patterns were obtained on a Rigaku Denki Geiger RAD-C, using CuK α radiation, over a range of $2\theta = 3°–40°$ (speed 4°/min) at room temperature.

Stability Studies

The quantities of IBP and ETH were measured by the high-performance liquid chromatography (HPLC) method. The samples were stored at 65°, 50°, and 40°C.

RESULTS AND DISCUSSION

DSC of the Compound of IBP and Other Drugs

In this research, because of the very low melting point of the compound, stabilization problems and problems associated with the manufacturing process were considered likely to occur. The various melting points of compounds are shown in Table 2.

Various drugs were classified on the basis of compatibility with IBP into three types, as mentioned above. Drugs of group 1 were made eutectic with IBP, and the mixture melting point was about 56°–58°C. These mixtures have been considered to present problems in the manufacturing process and the stabilization. The melting point of mixture of IBP and drugs of group 2 were 60°–70°C, and these are probably suitable. Drugs of group 3 were compatible with IBP.

Then, we selected ETH from these drugs and conducted a further detailed examination of a ratio composition of a eutectic compound of IBP and ETH. A thermal analysis result is shown in Fig. 1. The samples consisted of a mixture of IBP and ETH in a weight ratio of 1:9–9:1. Gorden (7) suggested that stearic acid, stearyl alcohol, calcium stearate, and magnesium stearate made a simple eutectic with IBP, and estimated a ratio composition of the eutectic compound from an

Table 2

Melting Point of Mixture of IBP with Other Drugs

	m.p. (°)	Mixture m.p. (°)	Group
Ibuprofen	76	—	—
Acetaminophen	169	75.9	3
Ethenzamide	129	55.9	1
Carbinoxamine maleate	119	58.3	1
Chlorpheniramine maleate	134	62.7	2
Dextromethorphan hydrobromide	114	65.8	2
Noscapine hydrochloride	175	65.9	2
Potassium guaiacolsulfonate	252	75.6	3
Anhydrous caffeine	236	70.9	3
Thiamine nitrate	209[a]	75.1	3
Bisibuthiamine	151[a]	57.0	1
Riboflavin	297[a]	75.4	3
Ascorbic acid	193[a]	75.1	3
Bromovalerylurea	151	66.1	2

[a]Temperature of decomposition.

endothermic phase transition of the compound that further changes the ratio mix of stearates and IBP. We also estimated the ratio composition of the eutectic of IBP and ETH according to this method. It is shown in Fig. 2. The ratio composition of a eutectic was suggested to be 1:4, based on Fig. 2.

However, the results of the thermogram of No. 3 in Fig. 1 show a ratio composition different from the ratio composition of the eutectic. Because of this, there was thought to be a problem with the precision of estimation. We assume that the ratio composition of the eutectic forms a thermal analysis result of the sample of the ratio composition which is quite different from the ratio composition of the eutectic in the method used by Gorden (7).

Due to this problem, we tried to estimate the ratio composition of the eutectic using a method which measures an endothermic quantity of the eutectic's origin. This is, the endothermic peak from each thermogram of IBP and ETH up to 60°C is not admitted. Consequently, we think that a quantity of endotherm of a compound up to 60°C is the eutectic's origin. Accordingly, it is thought that the ratio composition of the eutectic have the highest endotherm up to 60°C.

The relationship between the quantity of endotherm up to 60°C and the composition ratio for each compound is shown in Fig. 3. It was suggested that the composition ratio of the eutectic was 3:2 in terms of weight ratio from a quantity of heat up to 60°C, and that the highest weight ratio was IBP:ETH at 60:40.

Crystallization of IBP, ETH, and Their Compound

The results of powder x-ray diffraction are shown in Fig. 4. The samples were IBP, ETH, and their compound weight ratio of IBP:ETH = 3:2) and a heat-treated sample of the compound. Imai (5) and Acarturk (6) reported that the crystallization of IBP produced little change, in the case of changing the method of mixing for making a compound with low molecular gelatin. The diffraction peaks in the compound coincided, which added the diffraction peak of IBP to that of ETH. And the diffraction pattern of the heat-treated sample was almost the same as that of the compound. In the case of IBP and ETH, the crystallization of IBP and ETH showed no change.

Stabilization of IBP and ETH

We investigated the stabilization of IBP and ETH using the sample described in Table 1: (i) stored at 50°C for 2 months; (ii) at 65°C for 1 month; (iii) and at 40°C for 3 months.

A storage temperature of 65°C is higher than the melting point of the eutectic of IBP and ETH. Conse-

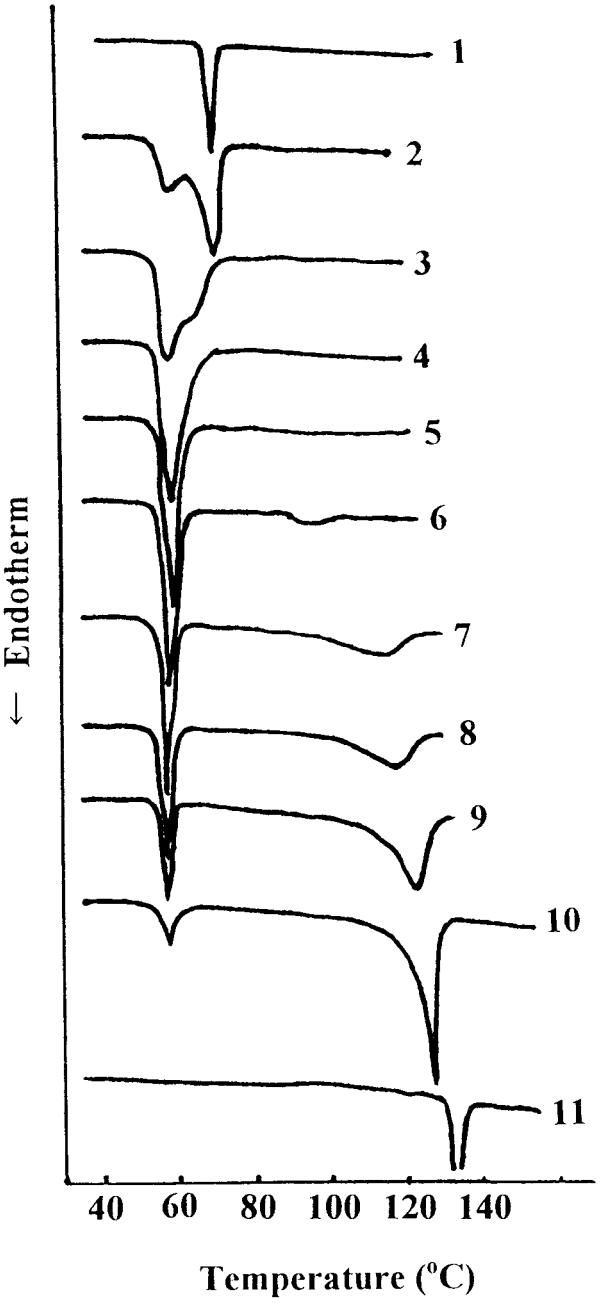

Figure 1. Thermograms of IBP–ETH system: IBP (1), 90% IBP + 10% ETH (2), 80% IBP + 20% ETH (3), 70% IBP + 30% ETH (4), 60% IBP + 40% ETH (5), 50% IBP + 50% ETH (6), 40% IBP + 60% ETH (7), 30% IBP + 70% ETH (8), 20% IBP + 80% ETH (9), 10% IBP + 90% ETH (10), ETH (11).

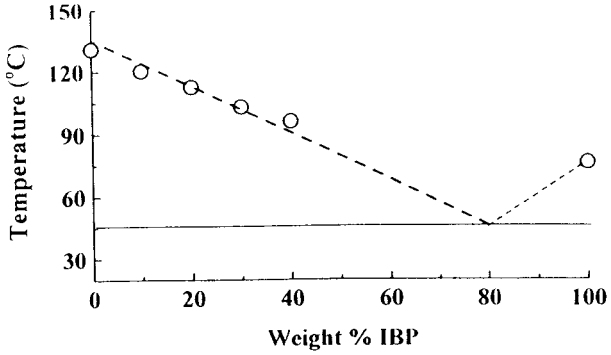

Figure 2. Phase diagram of IBP–ETH.

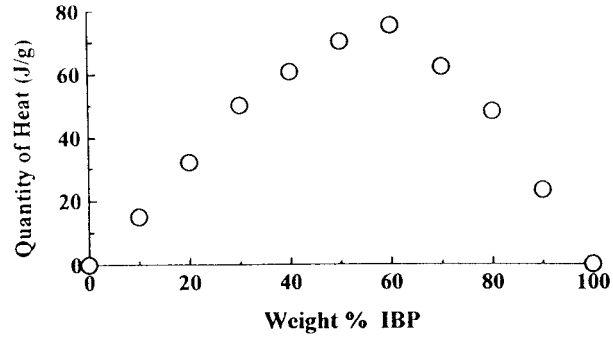

Figure 3. Quantity of heat up to 60°C of IBP and ETH mixture.

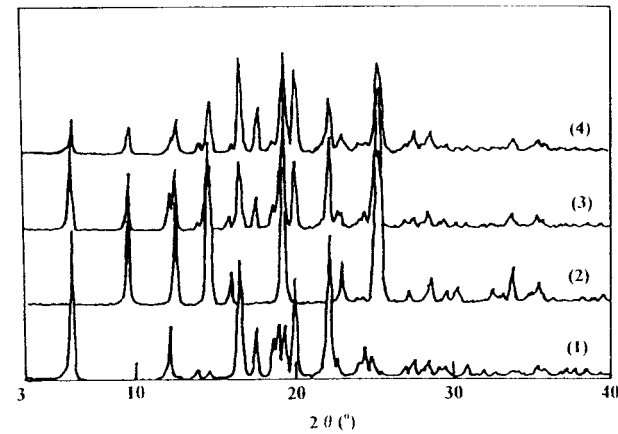

Figure 4. Powder x-ray diffraction of IBP (1), ETH (2), physical mixture IBP:ETH = 3:2 (3), and melted granulation of IBP:ETH = 3:2 (4).

Table 3

Stability of IBP and ETH

	65°C, 30 Days	50°C, 60 Days	40°C and 75% RH, 180 Days
IBP (%)	93.0	99.3	100.0
ETH (%)	99.0	102.7	99.2

quently, it was thought that samples were in the same state as that of excipients when dispersion of a melted object of the eutectic occurs.

A storage temperature of 50°C is less than the melting point of the eutectic compound. However, the sample displayed a semimelted state (an ointment-like state) because the temperature was very close to the melting point.

A sample with an inflected outside appearance was not admitted at 40°C.

As a result, we measured a quantity of the sample of IBP and ETH (Table 3), including stability on the condition that we stored it wholly. Even though IBP and ETH demonstrated a eutectic form, the chemical stabilization of their complex showed no change.

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