Studies on the Number of Contacts between Ibuprofen and Ethenzamide Using Thermal Analysis

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We studied a method of estimating the number of contacts in a solid dosage form using thermal analysis. Ibuprofen (IB) and Ethenzamide (ET) were used as model actives. IB and ET were granulated and sieved with each other. We prepared mixtures of IB and ET using different diameter granules. The number of contacts between the samples was calculated by the expression method of Ouchiyama and Tanaka. By thermal analysis, we measured the quantity of endotherm up to 60—63 °C from 56 °C. The quantity of endotherm up to 61 °C from 56 °C was in good proportion to the number of contacts calculated by the expression.

Key words ibuprofen; ethenzamide; number of contact; thermal analysis

Recently, combination drugs incorporating ibuprofen (IB) have been developed. It is very important when developing those drugs to study the physical and chemical compatibility between IB and the combined drug. It has been reported that IB is incompatible with ethenzamide (ET).[1)] For this reason, we studied a formulation to decrease the number of contacts between IB and ET for the development of combination drugs using the two. Specifically, the formulation method consisted of the ET being added after the granulation containing IB. As a second method, ET and IB were granulated with each other. However, there have been few reports concerning such separate-granulation formulations.

A theoretical estimation of the number of contacts was reported by Ouchiyama and Tanaka,[2)] which was confirmed by several experimental data (Shirai and Tanaka[3)]). These results have not been used in the pharmaceutical field, but in the inorganic chemical field.

Alternatively, thermal analysis has been frequently used to investigate compatibility in the pharmaceutical field.[4)] We estimated the composition ratio of the eutectic IB and ET[1)] using thermal analysis. In this paper, we investigated a method for estimating the number of contacts using thermal analysis.

Experimental

Material and Preparation IB (d50; 17.4 μm) was purchased from Knoll Co., Ltd., and was granulated alone by the melting method. The granules were sieved using 16, 30, and 100 mesh. ET (d50; 27.1 μm) was purchased from Iwaki Co., Ltd., and was granulated with ethanol. The resulting wet granules were dried at 60 °C. After drying, the ET granules were sieved using the same size mesh as for the IB granules. We weighed IB (2 g) and ET (0.8 g), and mixed them using a small vinyl bag. Several samples (A—G) were prepared which combined the different particle sizes of IB and ET.

Table 1. Sample of d50 of IBP and d50 of ET

Sample No	d50 of IB (μm)	d50 of ET (μm)	ε (−)
A	740	290	0.536
B	290	290	0.503
C	113	290	0.513
D	17.4	290	0.478
E	740	27.1	0.381
F	290	27.1	0.387
G	113	27.1	0.505

The mean particle size of IB and ET of samples A to G, and the porosity of those, are shown in Table 1. Figure 1 illustrates schematic diagrams of sample A and sample G. The illustrations show that in sample A, which was prepared with large particle sizes of IB and ET, the number of contacts of IB with ET is smaller than that of sample G, which was prepared with small particle sizes IB and ET.

Thermal Analysis Differential Scanning Calorimetry (DSC) DSC7 (Perkin-Elmer Co., Ltd.) was used for the thermal analysis. Thermograms were obtained by heating at a constant rate of 5 °C per minute, and were calculated for a quantity of endotherm which was measured by the Perkin-Elmer 7 series/UNIX DSC 7 procedure.

Results and Discussion

The eutectic of IB and ET is not influenced by the preparation (not shown), and its melting point is about 56 °C.[1)] Figure 2 shows thermograms of IB, ET, and samples. In contrast, the DSC patterns of samples A, C, and G, when compared, were shown to be remarkably different. Particularly, the endothermic peak of sample A was shifted from about 56 °C to 69 °C. The contact point of IB and ET generally melted at about 56 °C in samples. However, since the number of contacts of sample A is much smaller than that of sample G (see Fig. 1), this resulted in the amount of endotherm being very small at around 56 °C of sample A. No endothermic peak over 76 °C was observed in samples A to G. This means IB and ET were melted completely at this temperature. Between 56 and 76 °C, the samples were in a mixed condition of both solid and liquid. It was difficult to separate the quantity of endotherm at the contact points from the other components. We assumed that there is a correlation be-

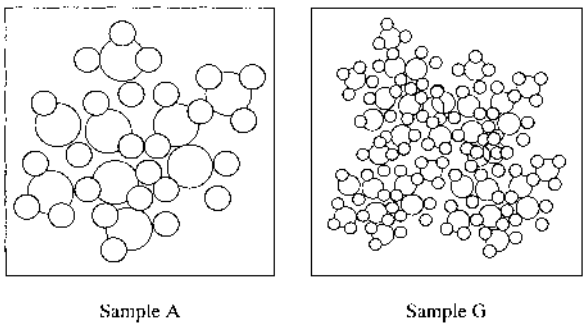

Fig. 1. Schematic Diagram of Sample A and Sample G
○: IB, ●: ET.

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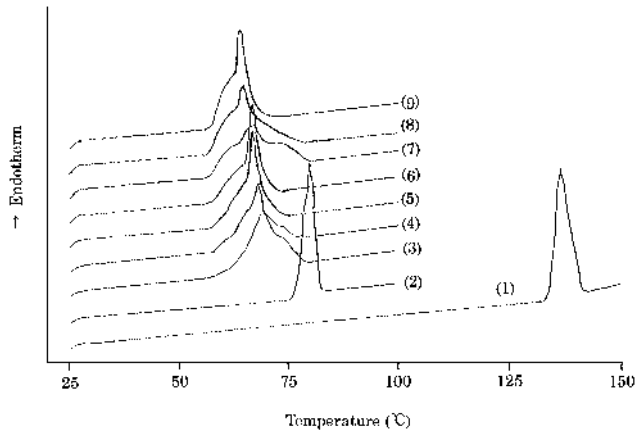

Fig. 2. DSC Thermogram of ET (1), IB (2), Sample A (3), B (4), C (5), D (6), E (7), F (8), and G (9)

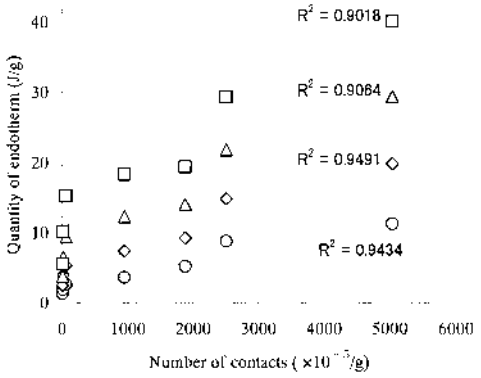

Fig. 3. Relationship between the Quantity of Endotherm and the Calculation of the Number of Contacts

The quantity of endotherm up to 60 °C from 56 °C (○), up to 61 °C from 56 °C (◇), up to 62 °C from 56 °C (△), and up to 63 °C from 56 °C (□).

tween the quantity of endotherm, which appeared under the endothermic peak (60—63 °C, see Fig. 2), and the number of contacts between IB and ET.

A theoretical expression to estimate the number of contacts has been presented by Ouchiyama and Tanaka.[2] The expression is as follows:

$$Nab=\frac{32}{13}(7-8\varepsilon)\times\frac{\left(\frac{ra+\bar{r}}{2\bar{r}}\right)^2\times\left(\frac{rb+\bar{r}}{2\bar{r}}\right)^2}{\frac{3+(\bar{r}^2/(\bar{r})^2)}{4}}\times Xnb \quad (1)$$

$$Xnb=\frac{Nb}{Na+Nb} \quad (2)$$

$$\bar{r}=ra\times Xna+rb\times Xnb \quad (3)$$

$$\bar{r}^2=ra^2\times Xna+rb^2\times Xnb \quad (4)$$

Na: numbers of a spheres [−]

Nb: numbers of b spheres [−]

ra: mean diameter of a spheres [cm]

rb: mean diameter of b spheres [cm]

ε: porosity [−]

Figure 3 shows the relationship between the quantity of endotherm up to 60—63 °C from 56 °C and the number of contacts using expression (1). It was thought that the quantity of endotherm should be measured accurately and in close correlation with the melting point of the eutectic compound. In this study, a suitable quantity of endotherm is suggested to occur at 56—61 °C. A markedly good correlation was found. This finding illustrated that it is possible to estimate the number of contacts using thermal analysis, and it will be useful in estimating the stability of medicine made using separate-granulation formulations.

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