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Molecular behavior, dissolution characteristics and chemical stability of aspirin in the ground mixture and in the inclusion complex with di-O-methyl-β-cyclodextrin

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Summary

Effects of grinding with di-O-methyl-β-cyclodextrin (DMβCD) on the physicochemical properties of aspirin have been studied. Ground mixture of aspirin with DMβCD was prepared by grinding them in a vibrational mill. Inclusion complex of aspirin and DMβCD in 1 : 1 molar ratio was also prepared in solid powder form using the slow evaporation method. An amorphous state of drug and DMβCD was revealed in the ground mixture by powder X-ray diffraction analysis and differential scanning calorimetry. The results of infrared analysis indicate that aspirin molecules were included in the cavity of DMβCD by the grinding. The dissolution rate of aspirin from the ground mixture was shown to be higher than that of aspirin alone, while the dissolution rate of the inclusion complex was extremely low. The decomposition rates of aspirin were measured in four samples, aspirin crystal, physical mixture, ground mixture and inclusion complex. Aspirin in the ground mixture and in the inclusion compound is markedly unstable at 40°C as compared with the crystal and the physical mixture. At 79% relative humidity, the decomposition rate of the ground mixture decreased relatively due to the crystallization of the complex.

Introduction

In preparing pharmaceutical dosage forms as powder form, grinding is generally used for reducing the particle size of a solid, since the dissolution rate is strongly affected by the particle size. It has been reported that a vigorous grinding force causes not only the increase of surface area but also the degradation of the drug and changes in polymorphic form (Lantz, 1981). A number of papers have been published recently about the effect of grinding on the physical and chemical properties of organic compounds (Terada et al., 1984; Otsuka and Kaneniwa, 1984; Ikekawa and Hayakawa, 1984; Krycer and Hesey, 1981; El-Shall and Somasundaran, 1984). When organic compounds were ground with microcrystalline cellulose or cyclodextrins, both components became amorphous and the ground mixtures showed some peculiar properties, that is, loss of the heat of fusion, the repression of sublimation, faster dissolution and improved bioavailability (Nakai et al., 1978; Yamamoto et al., 1976).

Cyclodextrins have been extensively applied to improve the solubility, stability and bioavailability

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of various drugs (Saenger, 1980; Uekama, 1981; Nakai et al., 1984). Recently many derivatives of cyclodextrins were synthesized to improve the functions and properties (Croft and Bartsch, 1983). Di-O-methyl-β-cyclodextrin(DMβCD) has a higher water solubility (57 w/v % at 25°C) than β-cyclodextrin, and an excellent inclusion capacity (Imai et al., 1984). The primary purpose of this work was to evaluate the dispersed state of aspirin in the ground mixture with DMβCD. The objective was also to examine the physicochemical properties, such as dissolution characteristics and the decomposition rate of aspirin in the ground mixture and the inclusion complex.

Experimental

Materials

Di-O-methyl-β-cyclodextrin (heptakis(2,6-di-O-methyl)-β-cyclodextrin: DMβCD) was purchased from Toshin Chemicals Co. and was used after heating at 120°C for 3 h. Aspirin and other materials and solvents were of analytical reagent grade.

Preparation of ground mixtures

Ground mixtures were prepared by using vibrational mill of Heiko Seisakusho Model TI-200, which was made of tungsten carbide. Volume of the mill was 140 cm^3, and height of the rod is 55 mm. Total weight of each sample was about 2.16 g. The molar ratio of aspirin to DMβCD was 1 : 1. The decomposition of aspirin was not observed by the grinding.

Solubility studies

Solubility measurements were carried out according to the method of Higuchi and Conners (1965). Excess amount of aspirin (5×10^{-2} mol) was added to 10 ml of 0.1 N HCl aqueous solutions containing various concentration of DMβCD and the mixtures were shaken at 20°C. After equilibration had been attained, an aliquot was pipetted through a cotton filter. A portion of the sample (0.5 ml) was then diluted with 0.1 N HCl aqueous solution and analyzed spectrophotometrically at the UV maximum (275 nm) of aspirin, as the effect of DMβCD on the absorbance of aspirin was negligible. An apparent stability constant, K, was calculated from the initial straight line portion of the phase solubility diagram.

Preparation of aspirin and DMβCD inclusion complex

Aspirin and DMβCD inclusion complex was prepared according to the slow evaporation method (Czugler et al., 1981). The DMβCD (2.857×10^{-3} mol) was dissolved in 40 ml water, then 2.857×10^{-3} mol of aspirin was added to the solution. The mixture was agitated until a clear solution was obtained. The crystal of the 1 : 1 inclusion complex of aspirin and DMβCD was obtained by slow evaporation of that aqueous solution for 24 h at room temperature. The product was placed in desiccator over phosphorous pentoxide for another 24 h to obtain a completely dried product.

X-ray diffractometry (powder method)

Powder X-ray patterns were measured using Rigakudenki 2204 Diffractometer. Conditions: target Cu, filter Ni, voltage 30 kV, current 5 mA, receiving slit 0.15 mm, count range 2000 cps, time constant 0.5 s, scanning speed 2 degrees/min.

Differential scanning calorimetry (DSC)

The DSC patterns were carried out with Perkin-Elmer Model DSC-1B. The measurements were done using the sample pan for the liquid sample, at a scanning speed 8 K/min under N_2 stream from 320 to 480 K. Sample weight was about 4.5 mg.

Infrared (IR) absorption spectroscopy

This was carried out with Hitachi 295 infrared spectrophotometer using KBr disc method.

Dissolution rate measurement

A disc 9.5 mm in diameter containing 50 mg of aspirin (net weight) was made by compressing the powder under 200 kg/cm^2 pressure for 30 s using hydraulic press Rikin Seiki model P-1B. The disc was fixed on flat surface glass using white hard paraffin and was put into 250 ml of 0.1 N HCl in a 500 ml beaker kept at 37°C by means of a

thermostated water bath. The dissolution medium was stirred with a glass two-bladed propeller at a rate of 100 rpm. Five ml of sample solution was pipetted through a cotton plug and equivalent volume (5 ml) of fresh preheated at 37°C dissolution medium was added, the absorbance of the sample was measured at 275 nm after dilution with 0.1 N HCl.

Measurement of decomposition rate

To determine the percentage of remaining aspirin in the stored samples, aspirin and salicylic acid were analyzed spectrophotometrically in a 0.1 N HCl aqueous solution at 275 nm and 303 nm, respectively (Tinker and McBay, 1954).

We investigated the effect of DMβCD on the decomposition of aspirin as follows. The samples used were crystalline aspirin, the physical mixture with DMβCD, the ground mixture with DMβCD, and the inclusion complex with DMβCD. A series of vials, each containing about 35 mg of aspirin (net weight), were kept in desiccators in which the relative humidities (RHs) were maintained at 31%, 48% and 79%. Saturated salt solution systems were used to achieve constant humidities. The desiccators were kept in an oven thermostat at 40°C. At intervals, samples were removed for analysis.

Results and Discussion

Physicochemical properties of aspirin DMβCD system

In order to characterize the ground mixtures and the inclusion complex of aspirin and DMβCD, preliminary examinations by DSC, X-ray diffractometry, IR, and phase solubility diagram were conducted. Fig. 1 shows the Bs type phase solubility diagram obtained for the aspirin DMβCD system. A microcrystalline complex was precipitated at higher DMβCD concentrations. The stoichiometric ratio of the complex in the solid phase was analyzed on the basis of data in the plateau region of the solubility diagram, and was estimated to be 1 : 1. This is consistent with the result obtained by analysis of the solid complex. Thus, the 1 : 1 stability constant ($K_{1:1}$) at 20°C was calculated from the initial linear portion of

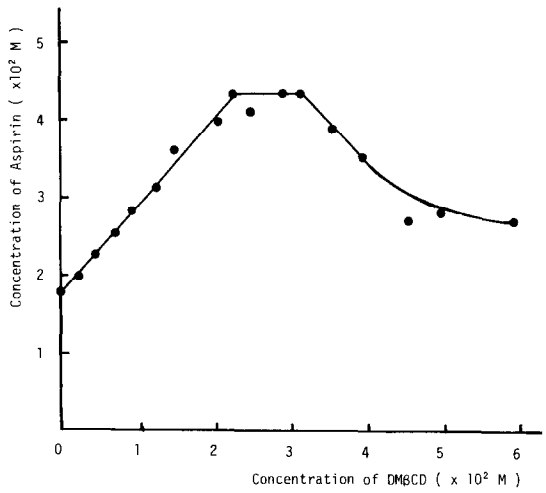

Fig. 1. Phase solubility diagram of aspirin and DMβCD in 0.1 N HCl aqueous solution at 20°C.

the solubility diagram, and it was found to be 55 M^{-1}. This value is significantly lower than the $K_{1:1}$ value, 2070 M^{-1}, which was obtained for β-cyclodextrin aspirin system (Nakai et al., unpublished data).

Fig. 2 shows DSC curves of DMβCD, aspirin and the 12% aspirin and 88% DMβCD system. Two endothermic peaks were observed in the physical mixture (curve C). One of them was

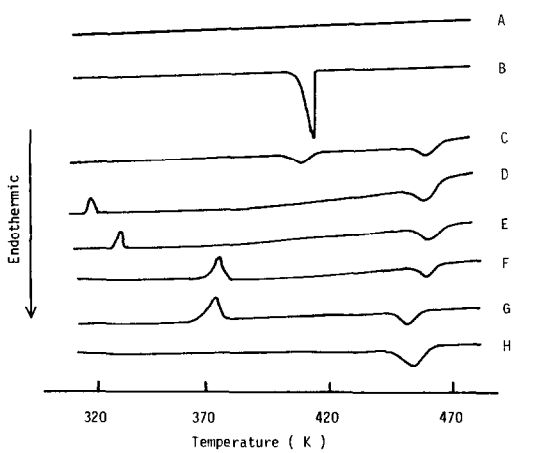

Fig. 2. DSC curves of the mixture and inclusion compound of aspirin with DMβCD (molar ratio 1 : 1). A = DMβCD crystal; B = aspirin crystals; C = physical mixture; D = ground mixture (ground for 0.5 min); E = ground mixture (ground for 1.0 min); F = ground mixture (ground for 2.0 min); G = ground mixture (ground for 10.0 min); H = inclusion compound.

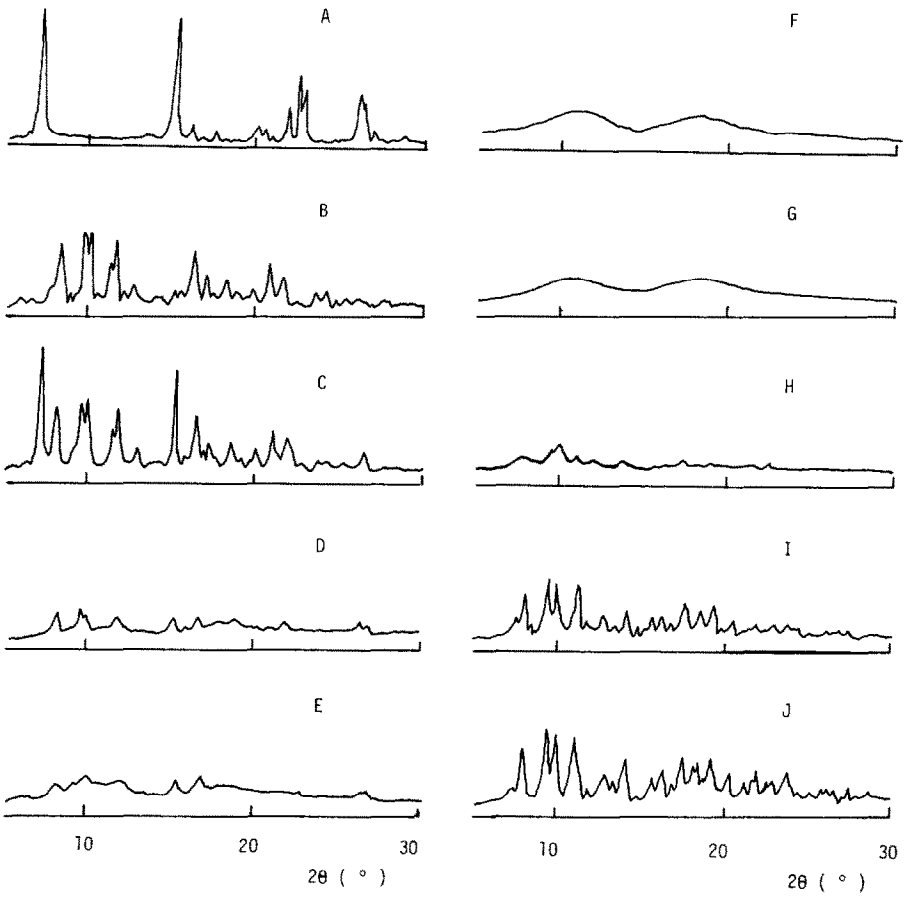

Fig. 3. X-Ray diffraction patterns of the mixture and inclusion compound of aspirin with DMβCD (molar ratio 1 : 1). A = aspirin crystals; B = DMβCD; C = physical mixture; D = ground mixture (ground for 0.5 min); E = ground mixture (ground for 1.0 min); F = ground mixture (ground for 2.0 min); G = ground mixture (ground for 10.0 min); H = ground mixture (ground for 10.0 min) was heated at 150°C for 1 h; I = inclusion compound; J = ground mixture (ground for 10.0 min) was stored at 40°C, 79% RH for 7 days.

around 413 K due to the fusion of aspirin crystal, and the other was around 460 K due to the fusion of inclusion complex which was produced during heating process. The 2nd run of the physical mixture showed only one endothermic peak at 460 K like curve H (inclusion compound). In the ground mixtures, a new exothermic peak and the endothermic peak around 460 K were observed, the peak around 413 K disappeared. From the X-ray analysis (as will be described in Fig. 3H), the exothermic peaks in the ground mixtures were interpreted to be due to the crystallization of aspirin–DMβCD complex, although the temperatures of the peak varied with samples. These results indicate the possibility of inclusion complex formation by the grinding of the physical mixture.

The X-ray diffraction patterns in Fig. 3 indicate that aspirin, which was originally in crystalline form (curves A and C), is clearly transformed into an amorphous state by the grinding with DMβCD. A halo pattern was obtained after 2 min grinding. It is remarkable that the grinding effects extended not only to the destruction of crystal lattice of both aspirin and DMβCD, but also to the inclusion formation between aspirin and DMβCD molecules which was predicted from the results of DSC and IR. From the comparison of curves H and I, it was suggested that the heating of amorphous ground mixture caused recrystallization of inclusion complex which confirms DSC findings.

Fig. 4 shows the IR spectra of aspirin–DMβCD

system. There is no absorption band for DMβCD in the region of carbonyl stretching vibration (1780–1650 cm^{-1}). Therefore, the discussion will be focused on the region of carbonyl stretching bands near 1700 cm^{-1}. The spectrum of aspirin (curve A) showed two absorption bands, one of them at 1756 cm^{-1} is due to acetoxyl carbonyl stretching and the other at 1685 cm^{-1} is due to hydrogen-bonded carboxyl carbonyl stretching. These two bands were not affected by the grinding of aspirin alone.

Curve B shows the spectrum of physical mixture. In this case, there is no change in the above two absorption bands.

Curves C–F show the time course of IR spectra of the ground mixtures of aspirin–DMβCD system. From these spectra, it can be seen that the carbonyl stretching absorption frequencies are changed with increasing grinding time. Curve C shows IR spectrum of the 0.5 min ground mixture, there are two new bands of aspirin. As the two new bands (1774 cm^{-1} and 1730 cm^{-1}) increased with increasing the time of grinding, the two original bands which observed at 1756 cm^{-1} and 1685 cm^{-1} diminished. The IR spectra of 1 min ground mixture shows that the 1756 cm^{-1} and 1685 cm^{-1} bands completely disappeared with the keeping of the two new bands only.

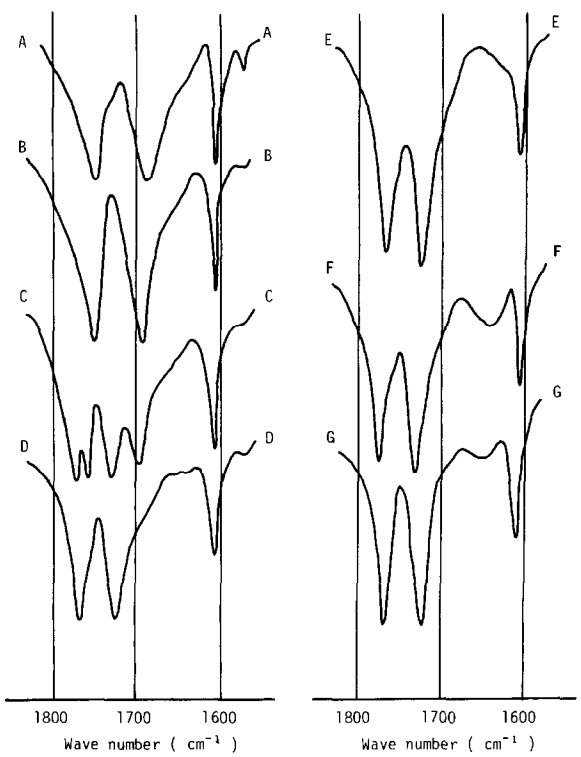

Fig. 4. IR spectra of the mixture and inclusion compound of aspirin with DMβCD (molar ratio 1:1). A = aspirin crystals; B = physical mixture; C = ground mixture (ground for 0.5 min); D = ground mixture (ground for 1.0 min); E = ground mixture (ground for 2.0 min); F = ground mixture (ground for 10.0 min); G = inclusion compound.

Curve G in Fig. 4 shows the IR spectrum of the inclusion complex. The acetoxyl carbonyl and the carboxyl carbonyl bands were shifted to higher frequencies at 1773 cm^{-1} and at 1723 cm^{-1}, respectively. The absorption bands at 1773 cm^{-1} and 1723 cm^{-1} could be assigned to the free acetoxyl carbonyl stretching and the non-dimerized carboxyl carbonyl stretching of aspirin dispersed in DMβCD respectively (Nakai et al., 1980). The good agreement of IR spectra between the ground mixture and the inclusion complex indicate that in both dispersion systems aspirin molecules exist in a monomolecular dispersed state, and that in the ground mixture aspirin molecules were included in the DMβCD cavity.

A similar IR shift was observed in the experiments in which benzoic acid was used as a drug. For benzoic acid crystal, the carboxyl carbonyl band appeared at 1691 cm^{-1}, the band was shifted to a higher frequency after the grinding with DMβCD and was observed at 1730 cm^{-1}.

Dissolution characteristics of aspirin DMβCD systems

Fig. 5 shows dissolution profiles of aspirin from a disc with constant surface area in 0.1 N HCl at 37°C. It is evident that the DMβCD ground mixtures dissolved faster than the aspirin and the physical mixture, but in the case of inclusion complex, the dissolution rate was extremely low. The dissolution rate is known to depend upon crystallinity, crystal form and other physicochemical parameters (Higuchi and Pitman, 1973). The difference between the ground mixture and the inclusion complex was observed in the degree of crystallinity, that is, the ground mixture was in amorphous state while the inclusion complex is in crystalline state.

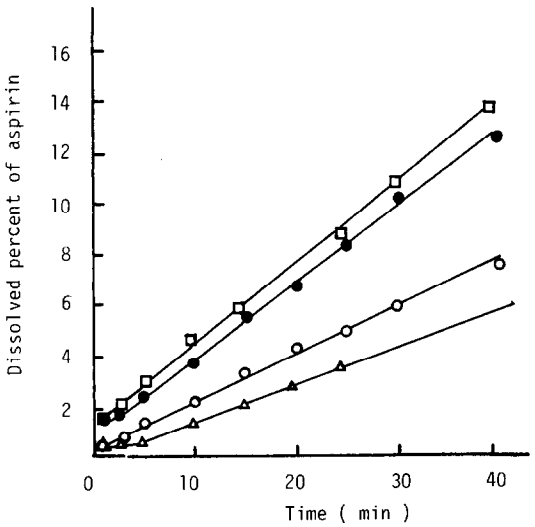

Fig. 5. Dissolution patterns of aspirin from aspirin–DMβCD system (molar ratio 1 : 1). △ = inclusion compound; ○ = aspirin crystals; ● = physical mixture; □ = ground mixture (10.0 min).

The enhanced dissolution rate may be due to the decrease in crystallinity and the increase in solubility of the drug on the ground mixtures.

Effect of DMβCD on the stability of aspirin

Fig. 6A, B, C and D illustrate the time course of remaining aspirin percentage at 40°C and at different relative humidities (RHs) 31%, 48% and

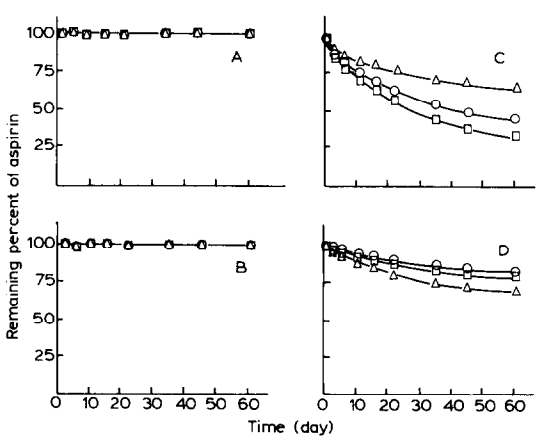

Fig. 6. The effect of DMβCD on the stability of aspirin at 40°C; A: aspirin crystals. B: physical mixture. C: ground mixture (ground for 10.0 min). D: inclusion compound. ○ = 31% RH; □ = 48% RH; △ = 79% RH.

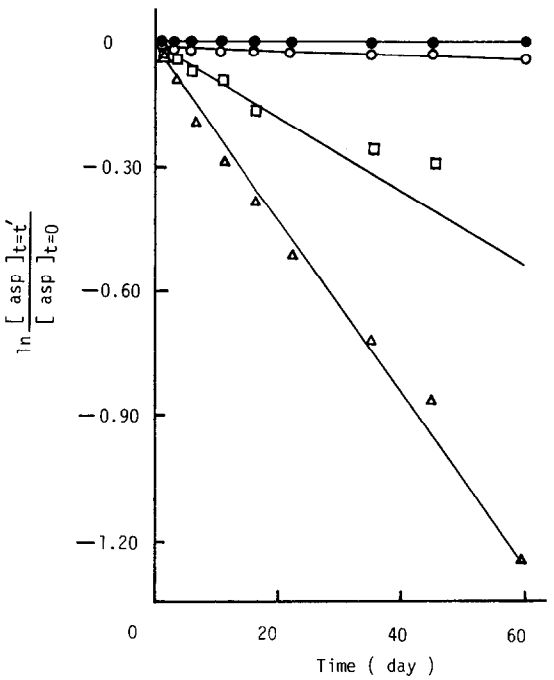

Fig. 7. First-order plots of aspirin decomposition in aspirin–DMβCD system at 40°C and relative humidity 48%. ● = aspirin crystals; ○ = physical mixture; □ = inclusion compound; △ = ground mixture.

79%. In the ground mixtures, aspirin decomposition occurred to a great extent. Also, in inclusion complex, aspirin decomposition occurred to a significant extent. However, storage of crystalline aspirin alone as well as physical mixture resulted in negligible decomposition. When the natural logarithms of remaining percentage of aspirin were plotted versus time, linear relationships were found as shown in Fig. 7. As similar relationships were also obtained in other experiments, the apparent

TABLE 1

SOLID STATE DECOMPOSITION RATE CONSTANTS (K) OF ASPIRIN IN ASPIRIN–DMβCD AT 40°C

Compound	$K \times 10^4$ day^{-1}		
	31% RH *	48% RH *	79% RH *
physical mixture	6.8	5.7	5.0
ground mixture	169.0	210.0	113.0
inclusion compound	75.0	88.2	94.0

* Relative humidity.

first-order rate constants were calculated. The results are summarized in Table 1. At all three RHs, the decomposition rates observed in the ground mixture and in the inclusion complex were greater than other two samples. As the RHs increased, the stability of aspirin in the ground mixture and inclusion complex was markedly reduced as compared with that in the physical mixture and the intact crystals. At 79% RH, however, the decomposition rate of aspirin in the ground mixture was slightly decreased in relation to the decomposition rates at 31.3% and at 48%. This decreasing in the decomposition rates could be attributed to the phase transformation, since amorphous form changed to crystalline form, as indicated in Fig. 3J.

In the ground mixture and in the inclusion complex, the aspirin molecules are dispersed monomolecularly, which results in an increase in the number of reaction sites, and leads to enhanced decomposition of aspirin.

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