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MOLECULAR BEHAVIOR OF MEDICINALS IN GROUND MIXTURES WITH MICROCRYSTALLINE CELLULOSE AND CYCLODEXTRINS

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INTRODUCTION

A drug is prepared in a suitable dosage form through many unit operations. Studies on the properties of pharmaceutical preparations, the preparation plans and the unit operations are necessary to obtain the good products which have high qualities and excellent bioavailabilities. Solid drugs contained in a preparation can vary in their pharmaceutical properties during the unit operations. The properties could be divided into two groups, namely, primary characteristics and

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secondary characteristics as shown in Fig. 1. The primary characteristics are of molecular level, including crystallinity, lattice disorder parameter, polymorphism, molecular interaction between drugs and additives, water nature of crystal water and adsorbed water and so on. The secondary characteristics are of dosage form level and include particle size, specific surface area, tablet disintegration, and content uniformity. An unit operation has the physical and the chemical effects over a wide range on both the primary and the secondary characteristics. The changes in the primary characteristics can provide much effects on the secondary one.

Hitherto, the researches on powdered preparations have mainly been focussed on the secondary characterritics. The studies from the view point of molecular level, however, seem to be necessary to make a great advance in pharmaceutical preparations.

It has been recently reported that grinding or milling not only reduces the particle size but also causes the changes in the molecular behavior such as phase transition of polymorphs, crystallinity, and chemical reaction rate in solid phase.

The researches in this field is named as mechanochemistry, being mainly applied to the inorganic substances. Recently, mechanochemical studies have been

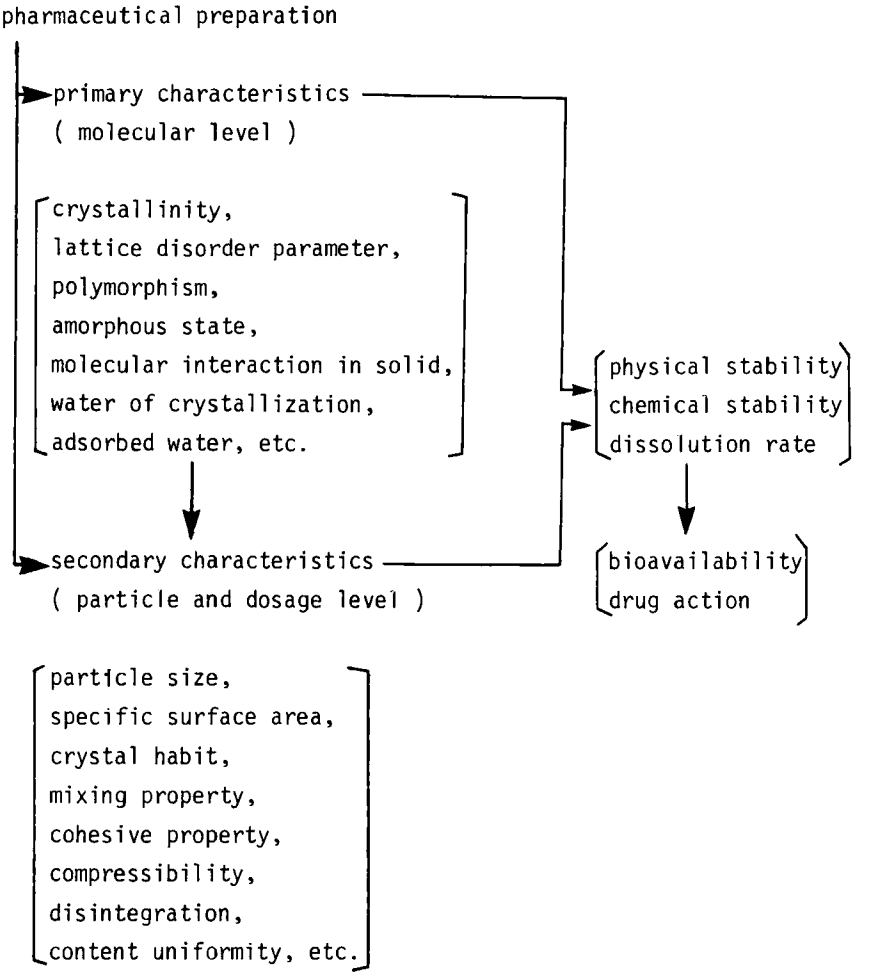

FIGURE 1

Characterization of Pharmaceutical Preparation

made for organic compounds of pharmaceuticals and the changes in the properties during the grinding or compression have been reported.

In this review, the effects of grinding and grinding with additives on the properties of the drugs are

investigated and the molecular behaviors of the ground drugs are interpreted.

I Grinding effects on crystalline properties

Grinding is an important industrial operation that is used for the size reduction of materials in order to enhance the dissolution rates. Grinding also have an striking effect on the properties of the crystals in addition to the size reduction.

Many works have been done for the effect on crystallinities[1,2,3,4,5,6], dissolution rates[9,10], stabilities[7,8,11], wettabilities of solid[12], and polymorphic changes[13,14]. Grinding efficiency is improved by the addition of additives[15], and the molecular interactions between drugs and polymer additives can occurr in the ground mixtures. When crystalline drugs were ground with microcrystalline cellulose[16,17,23], β-cyclodextrin[19], chitin (or chitosan)[20,21], gelatin, polyvinylpyrrolidone, and methyl cellulose[22], the drugs became amorphous and their dissolution rates and bioavailabilities were markedly improved. On the other hand, the chemical stabilities were decreased by the grinding.

II Molecular behavior of drugs in the ground mixtures with microcrystalline cellulose

Microcrystalline cellulose (Avicel) has widely been used as a vehicle for tabletting and encapsulation.

When microcrystalline cellulose was ground by a vibratory mill, the X-ray diffraction patterns changed in their intensities with grinding times as shown in Fig. 2[24].

The crystallinities of the respective ground samples were determined by the X-ray diffraction patterns using Hermans' method[25], IR method[24] and density method[26]. Table 1 shows that the crystallinity of microcrystalline cellulose decreased with increasing the grinding time from 63 % of intact sample to 0 % amorphous of 32 hr grinding time[24]. The ground samples had nearly constant surface areas of about 1 m^2g^{-1} for N_2 gas adsorption method while the values of water adsorption method were very large and increased with grinding time from 146 m^2g^{-1} of intact to 361 m^2g^{-1} of 64 hr grinding.[27,28]

The results showed that the dense structure was constructed in amorphous region for nitrogen gas adsorption while the structure was open to water vapor. The dense structure was made by hydrogen bonding between cellulose molecules in amorphous region[27].

Figure 3 shows the X-ray diffraction patterns of the mixture of 10 % benzoic acid and 90 % microcrystalline cellulose with varied grinding times[29]. Indices of the reflections of benzoic acid crystal are indicated in the figure (A). The peak intensities of benzoic acid and microcrystalline cellulose decreased with

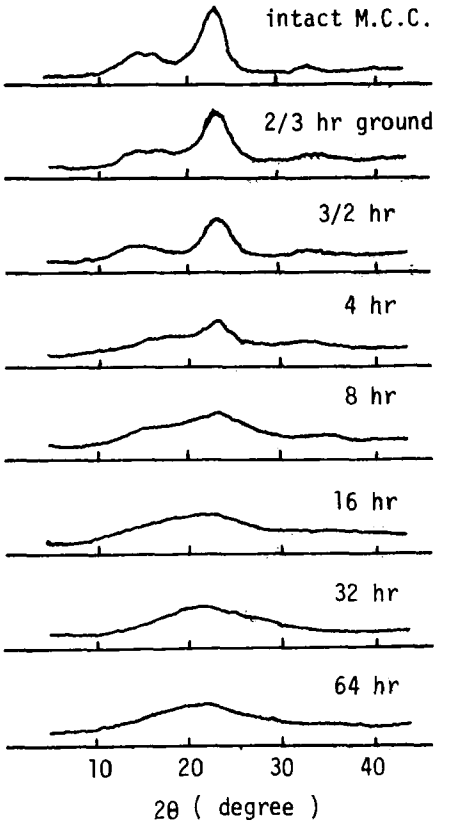

FIGURE 2

X-ray Diffraction Patterns of Intact and Ground Microcrystalline Cellulose (M.C.C.)

increasing grinding time and after 2 hr grinding, there was no reflection peak on the diffractogram. The heat of fusion of benzoic acid was not observed on DSC curve of the ground mixture.

These results were obtained in all tested drugs such as aspirin, salicylic acid, chloramphenicol palmitate[18], diazepam, mefenamic acid, sulfisomezol,

TABLE 1

Crystallinity, Specific Surface Area of Microcrystalline Cellulose as a Function of Grinding Time

Grinding Time (hr)	Crystallinity (%)	Specific Surface Area (m^2/g) N_2 Adsorption	H_2O Adsorption
0	63	1.0	149
2/3	49	1.2	161
3/2	34	—	—
4	20	—	—
8	14	—	278
16	6	—	306
32	0	1.0	350
64	0	1.0	361

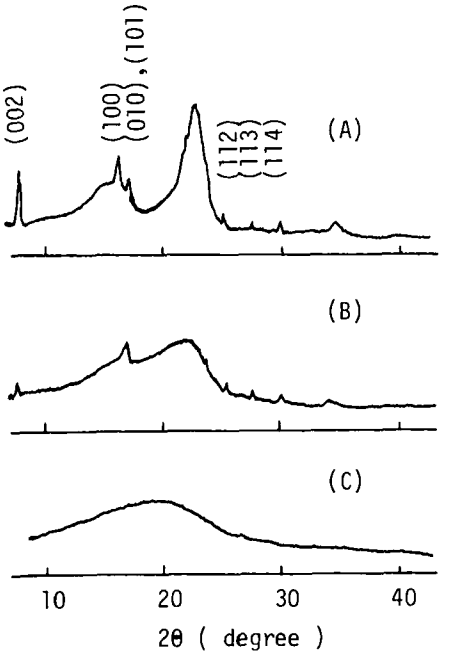

FIGURE 3

X-ray Diffraction Patterns of the Mixture of 10 % Benzoic Acid and 90 % M.C.C.
A: physical mixture, B: ground for 1/2 hr,
C: ground for 2 hr.

phenytoin[16], and griseofulvin[17]. The same results have been reported for the ground mixtures of various combinations of drugs and polymer additives;, that is, predonisolone and phenytoin - chitin or chitosan[20,21]; butanamide derivatives - gelatin, polyvinyl pyrrolidone, methyl cellulose and microcrystalline cellulose[22]; phenytoin, indomethacine and sulfaisomezole - gelatin, lyspozyme chloride and defatted milk powder[23].

III Interesting properties of the ground mixtures

The ground mixtures have the interesting properties; retaining of volatile drugs and high dissolution rate of drugs. Figure 4 shows the remaining amount of d-camphor and naphthalene in the ground mixture and physical mixture (simple blended mixture) after heating at 80 °C in vacuo[30]. Nearly all amount of the drugs remained in the ground mixtures. Figure 5 shows the dissolution profiles of d-camphor and naphthalene from the ground mixtures in water at 20 °C[30]. The drugs were released rapidly from the ground mixtures than from the physical mixtures especially at initial stages. The dissolution amount reached at the maximum value, followed a gradual decrease, which means the recrystallization of the dissolved drugs in the solutions.

Generally, the releasing rates of drugs from the ground mixtures are very high and the enhanced dissolu-

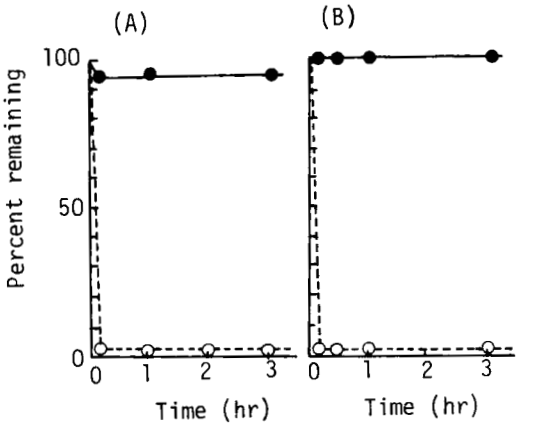

FIGURE 4

Remaining Amount of d-Camphor and Naphthalene in Ground(—●—) and Physical(--○--) Mixtures as a Function of Heating Time at 80 °C in vacuo
(A): mixture of 5% d-camphor and 95% M.C.C.,
(B): mixture of 3% naphthalene and 97% M.C.C..

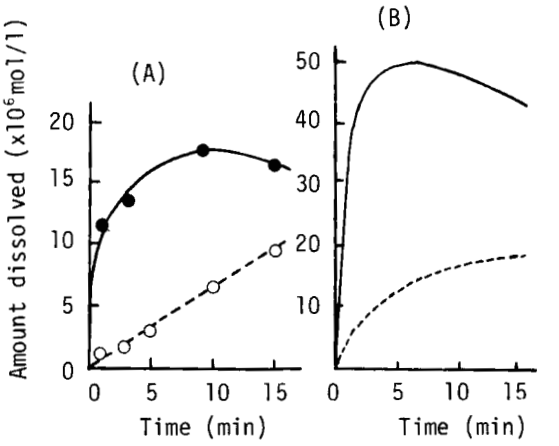

FIGURE 5

Releasing Patterns of d-Camphor and Naphthalene from 3 hr Ground (———) and Physical (----) Mixtures
(A): mixture of 5% d-camphor and 95% M.C.C.,
(B): mixture of 3% naphthalene and 97% M.C.C..

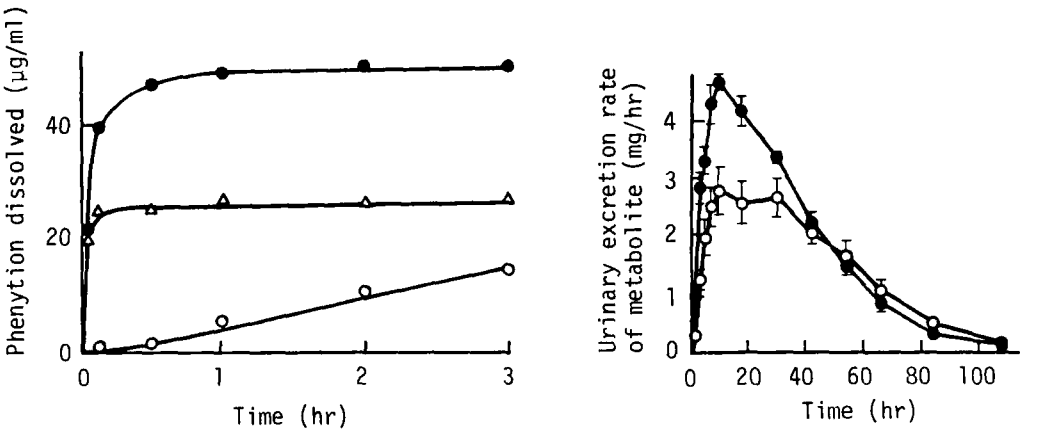

FIGURE 6

Dissolution Profiles and Urinary Excretion Patterns of Phenytoin from a Fine Powder and the Ground Mixture with Microcrystalline Cellulose
(left hand): dissolution profiles of phenytion from three preparations in 1 liter of JP X disintegration medium No 1 (pH 1.2) at 37 °C. each data point represents the mean of three determinations. key: ●, 1000 mg of the ground mixture(1:9); △, 109 mg of a sodium salt powder; and ○, 100 mg of a fine powder. (right hand): urinary excretion patterns of total 5-(p-hydroxyphenyl)-5-phenylhydantoin after oral administration of 250 mg of the fine powder(○) and 2500 mg of the ground mixture(●) to five volunteers (mean ± SEM).

tion causes the rapid absorption of the drugs[16,17]. Figure 6 shows the dissolution rates of phenytoin from the ground mixture, the sodium salt, and the fine powder in pH 1.2 solution and also shows the the urinary excretion patterns in five human subjects following oral administration of 250 mg of phenytoin samples[16]. The ground mixture had higher dissolution rate than a fine powder, which reflected in the urinary

excretion of the metabolite. Excretion rates during the first 20 hr differed significantly between the two preparations.

Figure 7 shows the IR spectra of microcrystalline cellulose, aspirin crystals and the ground mixtures around 1700 cm^{-1} [19]. Curve B shows the IR pattern of aspirin crystals where two absorption bands at 1757 cm^{-1} and 1695 cm^{-1} are assigned to acetoxyl and carboxyl carbonyl stretching vibrations respectively. Curves C and D illustrate the IR patterns of the ground mixtures showing the band broadening and the peak shifts. These results show that the drugs changed in their molecular behavior during the grinding with microcrystalline cellulose.

IV Ground mixtures with cyclodextrins

It is well known that cyclodextrins include drug molecules and that the inclusion compounds have interesting properties such as high solubility and high chemical stability.

Many studies have been made on the pharmaceutical application of α-, β-, γ-cyclodextrins and β-cyclodextrin derivatives, namely dimethyl-β- cyclodextrin, trimethyl-β-cyclodextrin, and poly-β-cyclodextrin. When cyclodextrin crystals were ground by a vibratory mill, the crystallinities of cyclodextrins decreased

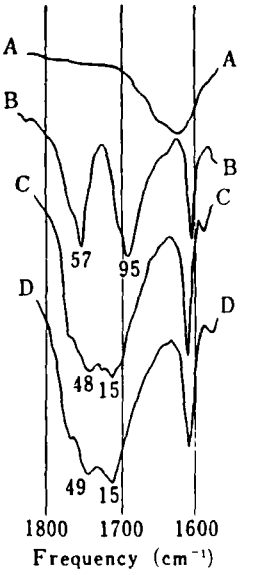

FIGURE 7

IR Spectra of the Ground Mixtures of Aspirin with M.C.C. A: M.C.C., B: aspirin crystals, C: ground mixture (10% aspirin, ground for 30 min), D: ground mixture (20% aspirin, ground for 240 min).

with increasing grinding time and became amorphous in a short grinding time [5]. When aspirin was ground with β-cyclodextrin, the halo pattern was observed on the X-ray diffractogram and the endothermic peak due to the fusion of aspirin diminished on DSC thermogram as in the case of ground mixture with microcrystalline cellulose [19]. These results indicate that aspirin became amorphous in the ground mixture with β-cyclodextrin.

Figure 8 shows the time course of IR spectra of the equimolar ground mixture of aspirin and β-cyclodextrin.[19]

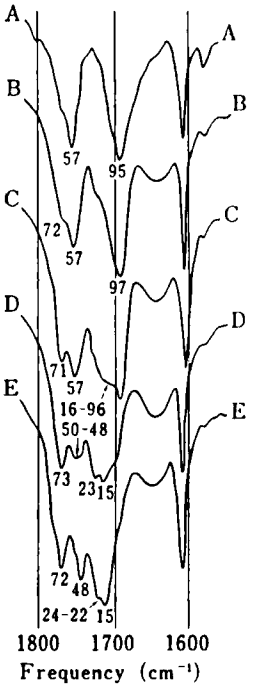

FIGURE 8

IR Spectral Change of Ground Mixture of Aspirin with β-Cyclodextrin (Molar Ratio=1:1)
A: aspirin crystals, B: ground for 2 min, C: ground for 3 min, D: ground for 4 min, E: ground for 15 min.

The carbonyl stretching vibration band positions varied with grinding time and three peaks clearly appeared after 15 min grinding. Two peaks at 1715 - 24, and 1772 cm^{-1} were assigned to the carbonyl stretching vibrations of carboxyl and acetoxyl functions respectively. The peak shifts to the higher frequencies indicate the difference in molecular behavior between the crystal and the ground mixture. From IR experi-

ments in CCl_4 solution[31,32], the new absorption band at 1748 cm^{-1} was assigned to the acetoxyl carbonyl which was hydrogen bonded with the hydroxyl of cyclodextrin. The IR spectrum of the ground mixture was the same as that of aspirin - β-cyclodextrin inclusion compound which was crystallized from aqueous solution.

On the other hand, IR spectrum of the ground mixture of aspirin and α-cyclodextrin was very different from that of aspirin and β-cyclodextrin and was coincident with that of microcrystalline cellulose shown in Fig. 7[33,34]. The results are considered to be due to that α-cyclodextrin does not include aspirin molecules because of the small cavity size.

Through IR measurements, the ground mixtures fell into two main groups which had their characteristic IR patterns of aspirin depending on whether the systems have their inclusion compounds. One group (group A) has the spectrum of aspirin of Fig. 8 and the ground mixtures of β- and γ-cyclodextrin which include aspirin come under this group. The other group (group B) have the spectrum of Fig. 7 and the ground mixture of microcrystalline cellulose and α-cyclodextrin which do not include aspirin come under group B.

These results of IR spectral experiments, in addition to the thermal and X-ray diffractive experiments, show that aspirin are monomolecularly dispersed

in the ground mixtures in two ways along with the molecular behavior; one way is observed in the group A where the aspirin molecules are included in the cavity of the cyclodextrin molecules during the grinding. The other is in the group B where aspirin molecules are dispersed in the networks of cellulose or cyclodextrin molecules which are intermolecularly hydrogen bonded.[19]

V Chemical stability of aspirin in the ground mixtures with α-, β-, γ-cyclodextrin

The grinding with the additives has a great effects on the stability of aspirin. The molecular behaviors closely relate to the stabilities.

Figure 9 shows the time course of the decomposition of aspirin in the physical mixtures (simple blend) and the ground mixtures with α-, β-, and γ-cyclodextrin at 40 °C and RH 32.3 %[33]. Figure 9 (I) shows the decomposition of aspirin in the α-cyclodextrin/aspirin system and the intact crystals. The decomposition of aspirin in the ground mixture was significantly fast.

Figure 9 (II) illustrates the decomposition of the β-cyclodextrin/aspirin system. Aspirin rapidly decomposed as in the case of the ground mixture with α-cyclodextrin. On the other hand, aspirin was relatively stable in the inclusion crystals although the rate was a little greater than that of the physical

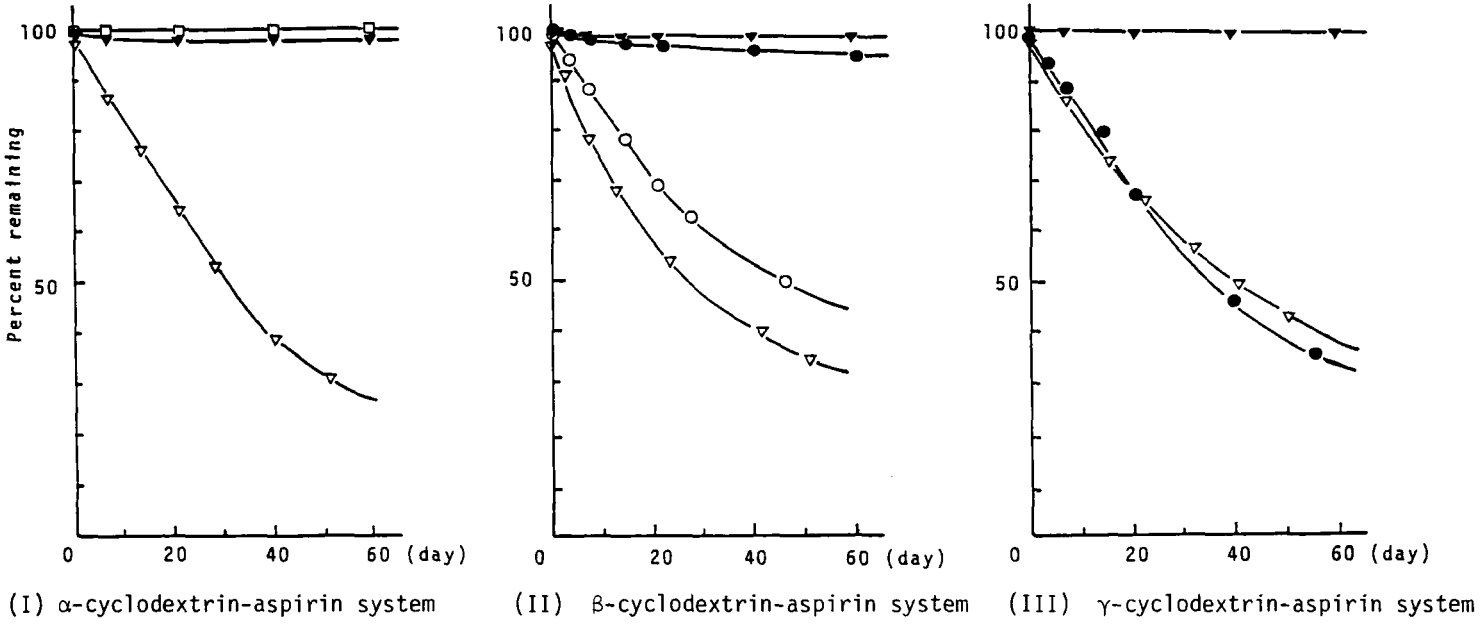

FIGURE 9

Solid State Aspirin Decomposition in Aspirin and Cyclodextrin Systems at 40 °C, RH 32.3 %
—□—: intact crystal, —▼—: physical mixture,
—●—: inclusion compound, —○—: ground sample of inclusion compound, —▽—: ground mixture (15 min ground).

mixture. When the inclusion crystals were ground, the stability of aspirin lowered remarkably and the degradation pattern was similar to the ground mixture.

Figure 9 (III) shows the decomposition patterns of γ-cyclodextrin/ aspirin system. Both the inclusion compound and the ground mixture showed a rapid decomposition of aspirin almost equal to each other. It should be noted that β-, and γ-cyclodextrin had a different influence on the stability of aspirin in their inclusion compounds, that is, the decomposition rate of γ-cyclodextrin inclusion compound was 40 times greater that of β-cyclodextrin inclusion compound.

The apparent first order rate constants were calculated from the linear relationship between time and the logarithms of the remaining percent of aspirin as shown in Table 2 [33]. The aspirin decomposition in the inclusion compound of γ-cyclodextrin, in the ground mixture of α-, β-, and γ-cyclodextrin, and in the ground sample of the β- and γ-cyclodextrin inclusion compound showed great values of about 100 times of respective physical mixtures.

The decomposition rate constants were correlated with the state of the acetoxyl groups of aspirin in the samples assumed from IR spectra.

The absorption intensity at 1748 cm^{-1} represents the strength of hydrogen bonding between aspirin

TABLE 2

Solid State Decomposition Rate Constants of Aspirin in Aspirin and Cyclodextrin Systems at 40 °C, RH 32.3 %

	($\times 10^4$ day^{-1})		
	α-Cyclodextrin	β-Cyclodextrin	γ-Cyclodextrin
Physical mixture	1.71	1.38	1.26
Inclusion compound	———	5.15	208
Ground mixture	203	228	156
Ground sample of inclusion compound	———	148	———
Aspirin crystal		0.16	

acetoxyl and cyclodextrin hydroxyl functions, that is, a great intensity shows a high degree of the interaction[31,32]. Figure 10 shows the comparison of the IR patterns of aspirin among the crystalline inclusion compound of β-cyclodextrin (Fig. 10 A), the ground inclusion compound(grinding the sample A) (Fig. 10 B), and the ground mixture (Fig. 10 C)[33].

The absorption intensity at 1748 cm^{-1} of the ground inclusion compound was greater than the crystalline inclusion compound and same as the ground mixture. This result shows that the aspirin molecules hydrogen bonded strongly with cyclodextrins in the ground inclu-

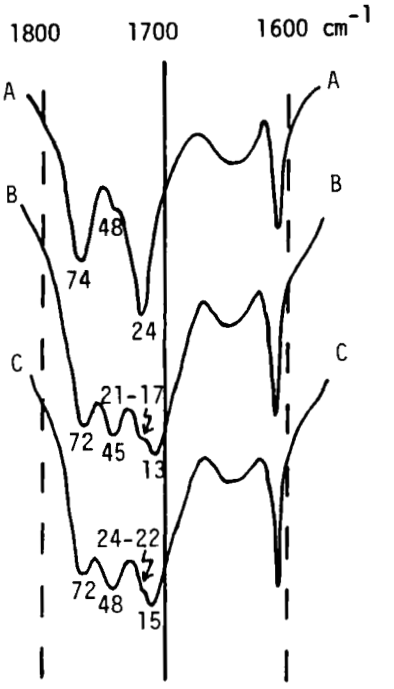

FIGURE 10

IR Spectra of β-Cyclodextrin and Aspirin System
A: inclusion compound, B: ground sample of inclusion compound (15 min ground), C: ground mixture (15 min ground).

sion compound and the ground mixture, having a stable position in the cavities.

The hydrogen bonding causes the proton transfer from the hydroxyl group of cyclodextrin to acetoxyl group of aspirin, resulting the high rate of the hydrolysis of aspirin in the ground inclusion compound and in the ground mixture[34].

For γ-cyclodextrin systems the crystalline inclusion compound and the ground mixture had the same IR

spectra of aspirin as the ground mixtur with β-cyclodextrin, that is, they had a strong absorption at 1748 cm^{-1}. The IR spectral results show the presence of strong hydrogen bonding between aspirin and γ-cyclodextrin. Aspirin molecule could be allowed to move in the cavity because of the large diameter of γ-cyclodextrin and to rest on a stable position mainly determined by the hydrogen bonding, which causes the enhancement of aspirin hydrolysis.

The ground mixtures of α-cyclodextrin had the same IR spectrum of aspirin as that of microcrystalline cellulose ground mixture shown in Fig. 7 where the strong absorption at 1749 cm^{-1} was observed and the aspirin decomposition rate was high[33,34].

These close correlation between the IR spectral patterns and the decomposition rates show that the molecular behavior of aspirin determined the stability in the preparations with cyclodextrins[33].

VI The mechanism behind the rapid drug release from the ground mixtures with microcrystalline cellulose

Drugs rapidly released from the ground mixture regardless of the solubilities and the dissolution mechamism was discussed on the basis of the molecular behavior of the drugs[34,35].

When particles of a ground mixture are put in water, water can rapidly penetrate into the particles

and loose the network structure in which the drug molecules are enclosed by the hydrogen bonding between cellulose molecules. All molecules of the drug can release simultaneously from the ground mixture. When an amount of the drug was greater than the solubility, the excess drugs immediately crystallized in the solution. The dissolution mechanism of the ground mixtures is, therefore, different from that of crystals where drug molecules dissolve from the crystal surface according to concentration gradient.

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