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Effects of Grinding on the Physical and Chemical Properties of Crystalline Medicinals with Microcrystalline Cellulose. IV. Comparison of the IR Spectra of Medicinals in the Solid State and in Solution

YOSHINOBU NAKAI,[1] SHIN-ICHIRO NAKAJIMA,[1a] KEIJI YAMAMOTO,
KATSUHIDE TERADA, and TSUTOMU KONNO[1]

Faculty of Pharmaceutical Sciences, Chiba University[1]

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The infrared (IR) spectra of aspirin, benzoic acid, and salicylic acid, which exhibit intermolecular hydrogen bonding in their crystals, were measured in dilute CCl_4 solution. Two carboxyl carbonyl stretching bands were observed in these spectra, due to monomeric and dimeric species. IR spectral changes of carbonyl stretching bands attributed to hydrogen bonding between monomeric medicinals and 1-butanol were also measured. This hydrogen-bonded band was always observed at higher frequency than the intermolecular hydrogen-bonded band (dimer), and at lower frequency than the band of the monomeric medicinal. The shifts of the carbonyl stretching bands measured in the ground mixtures were compared with those of the solution spectra.

In the ground mixtures, it was confirmed that the medicinal molecules were dispersed monomolecularly and were hydrogen-bonded with hydroxyl groups of cellulose or β-cyclodextrin molecules.

The new band observed at 1748 cm^{-1} in the β-cyclodextrin dispersed system of aspirin was considered to be due to overlapping of (i) the band of the acetoxyl group of aspirin hydrogen-bonded with hydroxyl groups of β-cyclodextrin, and (ii) the free carboxyl band of aspirin.

Keywords——hydrogen bonding; IR; grinding; cyclodextrin; drug dispersion; aspirin; microcrystalline cellulose; mechanochemistry

In the previous paper,[2] infrared (IR) spectral analysis was undertaken to examine the dispersed state of medicinals in ground mixtures of microcrystalline cellulose or β-cyclodextrin. These results led us to conclude that the medicinal molecules were present in monomolecular form in the ground mixtures, interacting with cellulose or β-cyclodextrin by hydrogen bonding.

The purpose of the present study was to examine the interaction of medicinals with cellulose in the ground mixtures in more detail. Simple carboxylic acids are well known to exist as an equilibrium mixture of monomer and dimer in dilute CCl_4 solution, and the IR spectra of aspirin, benzoic acid, and salicylic acid have been measured in CCl_4 solutions.[3] Changes in $\nu_{C=O}$ (carbonyl stretching) vibration were examined as a function of butanol concentration added to the CCl_4 solutions. The results were considered in terms of hydrogen bonding between the acids and butanol. These spectra were compared with the solid state IR spectra of ground mixtures reported previously.[2]

Experimental

(1) **Materials**——Aspirin, benzoic acid, and salicylic acid were of JP IX grade. Methyl *p*-hydroxybenzoate,[4] phenyl acetate,[4] and 1-butanol[4] were of special reagent grade. Spectral grade CCl_4[4] was used without further purification.

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1) Location: *1-33 Yayoicho, Chiba*; *a*) Present address: *Hospital Pharmacy, the University of Tsukuba, 2-1-1 Amakubo, Sakuramura, Niiharigun, Ibaraki.*

2) Y. Nakai, S. Nakajima, K. Yamamoto, K. Terada, and T. Konno, *Chem. Pharm. Bull.*, **26**, 3419 (1978).

3) M. Hoeke, *Rec. Trans. Chim.*, **82**, 17 (1963).

4) Wako Chemical Co., Ltd.

(2) **IR Absorption Spectroscopy**——The IR spectra were recorded on a Hitachi EPI-G3 infrared spectrophotometer. All measurements were carried out at 20 ± 1°. CaF_2 liquid cells, with a path length of 2 or 20 mm, were used for the solution IR measurements. The concentrations of the medicinals were 3.0×10^{-3} M for the 2 mm cell and 3.0×10^{-4} M for the 20 mm cell. Butanol was added to the sample solutions at various concentrations from 100 to 1000 times that of the medicinals. When butanol was added to the sample solution, a corresponding solution containing butanol was placed in the reference cell.

(3) **Separation of Overlapping IR Spectral Bands**——Computer separation of overlapping IR spectral bands was carried out on the basis of Stone's method[5] using a Mercom 9100 machine. This method is based on an iterative least-squares procedure. The line position, intensity, and half-width of each band in the spectra were determined.

Results and Discussion

(1) Comparison of the IR Spectra of Medicinals in CCl_4 Solution with and without Butanol

The IR spectra of aspirin in the $\nu_{C=O}$ region in CCl_4 solution are shown in Fig. 1. Curve (A) shows the IR spectrum of 3.0×10^{-4} M aspirin in CCl_4. Three sharp $\nu_{C=O}$ bands can be observed; the band at 1779 cm^{-1} is due to acetoxyl $\nu_{C=O}$, and the bands at 1749 and 1706 cm^{-1} are due to "free" and "hydrogen-bonded" carboxyl $\nu_{C=O}$, respectively.[6] Curve (B) shows the IR spectrum of aspirin in CCl_4 solution containing butanol at 100 times the concentration of aspirin. A new band appeared at 1728 cm^{-1} and the absorption intensity at 1749 cm^{-1} decreased, suggesting hydrogen bonding between the carboxyl C=O group of aspirin and butanol. Curve (C) shows the IR spectrum of aspirin in CCl_4 solution containing

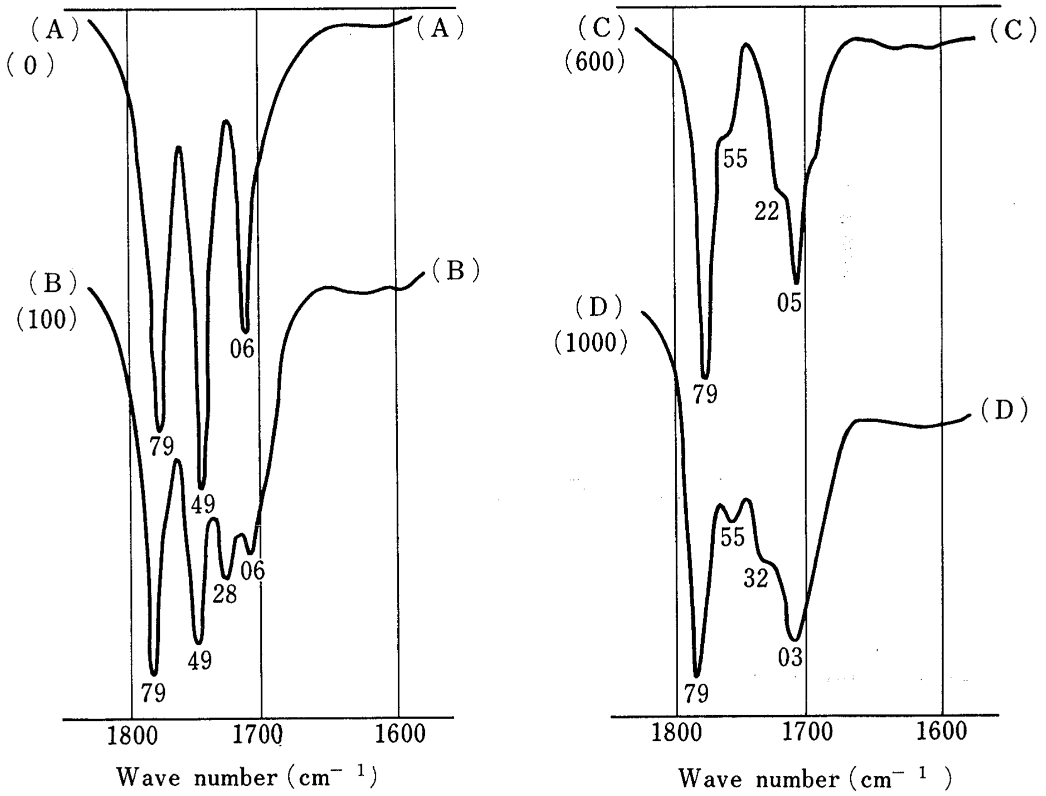

Fig. 1. IR Patterns of Aspirin in CCl_4 Solution Containing Various Amounts of Butanol

Each spectrum was measured using a 20 mm CaF_2 cell.
The concentration of aspirin was 3.0×10^{-4} M.
Numbers in parentheses indicate the concentration ratio of butanol to aspirin.

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[5] H. Stone, *J. Opt. Soc. Am.*, **52**, 998 (1962).

[6] R.M. Silverstein and C.C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed., John Wiley and Sons, Inc., New York, 1967.

butanol at 600 times the concentration of aspirin. The "free" carboxyl $\nu_{C=O}$ band at 1749 cm^{-1} has disappeared. With butanol at 1000 times the concentration of aspirin, a new band was observed at 1755 cm^{-1}, as shown in curve (D), and this was thought to arise from hydrogen bond formation between the acetoxyl C=O group and the hydroxyl group of butanol.

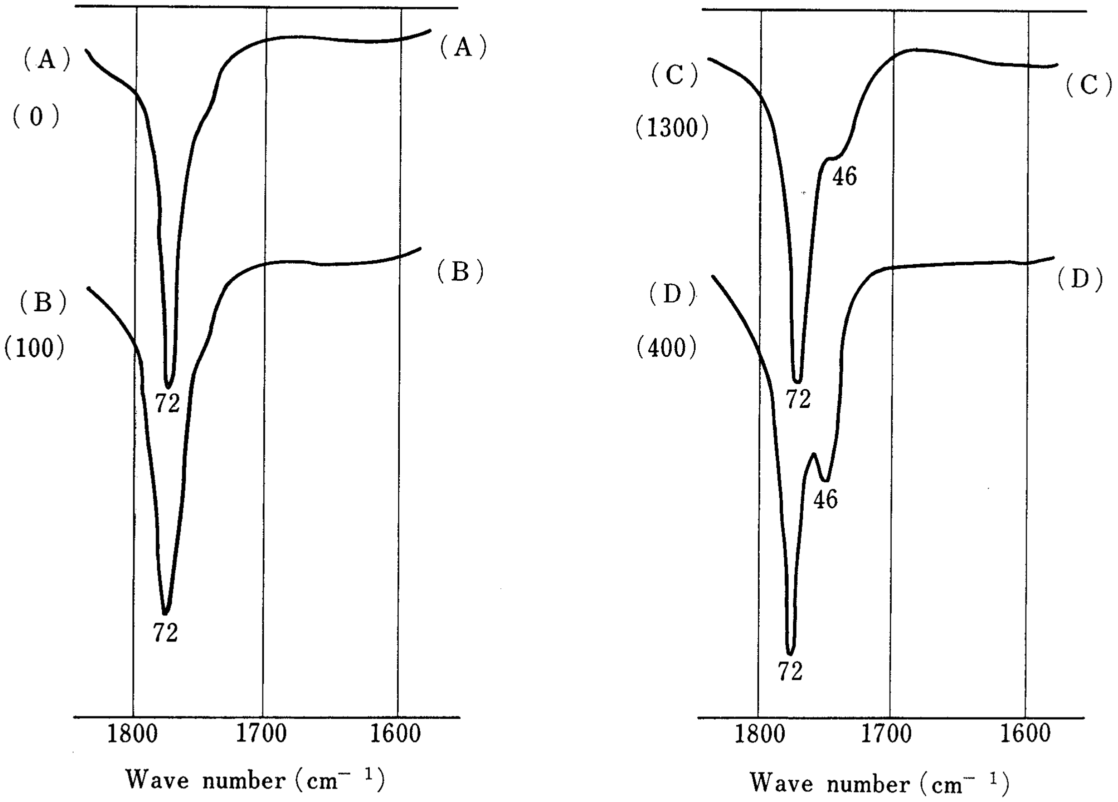

Fig. 2. IR Patterns of Phenyl Acetate in CCl_4 Solution containing Various Amounts of Butanol

Spectra (A), (B), (C) were measured using a 20 mm CaF_2 cell, while (D) was measured using a 2 mm cell. The concentrations of phenyl acetate were (A), (B), (C) 3.0×10^{-4} M and (D) 3.0×10^{-3} M. Numbers in parentheses indicate the concentration ratio of butanol to phenyl acetate.

To investigate the hydrogen bonding between the acetoxyl group and butanol, phenyl acetate instead of aspirin was subjected to IR measurements. Figure 2(A) shows the IR spectrum of 3.0×10^{-4} M phenyl acetate using a 20 mm CaF_2 liquid cell. The acetoxyl $\nu_{C=O}$ band was observed at 1772 cm^{-1}. Curves (B) and (C) show the IR spectra of phenyl acetate in CCl_4 solutions containing butanol at 100 and 1300 times the concentration of phenyl acetate, respectively. A new slight shoulder appeared at a frequency below 1772 cm^{-1}. Curve (D) shows the IR spectrum of phenyl acetate CCl_4 solution at concentrations of 3.0×10^{-3} M with 1.2 M butanol (400 times the concentration of phenyl acetate) using a 2 mm CaF_2 liquid cell. The shoulder at 1746 cm^{-1} developed into a peak and was consequently assigned to the hydrogen bonding between the acetoxyl C=O group and butanol. To examine the IR spectral changes of the carboxyl C=O bands of aspirin due to the hydrogen bonding between the carboxyl C=O group of aspirin and butanol, benzoic acid was used as a representative carboxylic acid. Figure 3(A) shows the IR spectrum of benzoic acid in CCl_4 solution using a 20 mm CaF_2 cell. The bands at 1746 and 1698 cm^{-1} are due to "free" and "hydrogen-bonded" $\nu_{C=O}$ respectively.[7] Curve (B) shows the IR spectrum of benzoic acid in CCl_4 solution

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[7] G. Allen, G. Watkinson, and K.H. Webb, *Spectrochim. Acta*, **22**, 807 (1966).

containing butanol at 100 times the concentration of benzoic acid. A new band was clearly observed at 1725 cm^{-1}, and this was assigned to hydrogen-bonding between the C=O group of benzoic acid and butanol. Upon the addition of more butanol, the band at 1746 cm^{-1} due to "free" $\nu_{C=O}$ disappeared and a shoulder around 1725 cm^{-1} was observed.

Based on the butanol concentration dependence of the $\nu_{C=O}$ band shifts, it appears that butanol forms hydrogen bonds more easily with the carboxyl group than with the acetoxyl group. IR spectral changes of an equimolar mixture of benzoic acid and phenyl acetate upon addition of butanol were measured in CCl_4 solution. The C=O band shifts of the equimolar solution due to hydrogen bonding with butanol showed the same tendency as that observed in the case of aspirin.

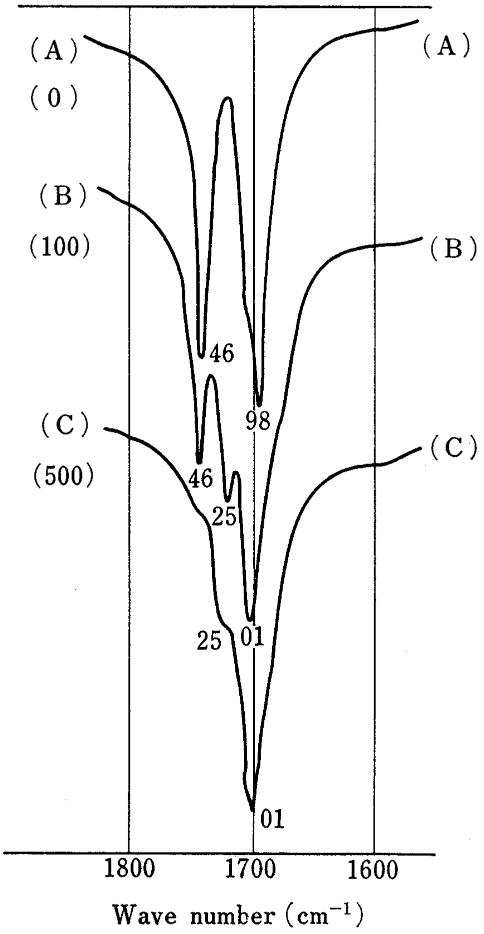

Fig. 3. IR Patterns of Benzoic Acid in CCl_4 Solution containing Various Amounts of Butanol

Each spectrum was measured using a 20 mm CaF_2 cell. The concentration of benzoic acid was 3.0×10^{-4} M. Numbers in parentheses indicate the concentration ratio of butanol to benzoic acid.

(2) Comparison of the IR Spectra of Aspirin in the Solid State and in Solution

To investigate the dispersed state of the medicinal molecules in ground mixtures of microcrystalline cellulose or β-cyclodextrin, the solid state IR spectra reported previously[2] were compared with the solution IR spectra obtained above[8]. Figure 4 shows the wave numbers of $\nu_{C=O}$ bands of aspirin obtained from various measurements. A wide line in the figure corresponds to a broad IR band and an upper line only represents a shoulder.

In the case of the carboxyl $\nu_{C=O}$ in CCl_4 solution, the hydrogen-bonded band with butanol (1732 cm^{-1}) was observed at 29 cm^{-1} higher frequency than the hydrogen-bonded cyclic dimer band (1703 cm^{-1}) (see Fig. 4F). The carboxyl C=O bands (1715—1724 cm^{-1}) in the ground mixtures (4-B and C) and the inclusion compound (4D) were observed at 20—30 cm^{-1} higher frequency as compared with the dimer species in the crystal (4A), as reported previously.[2] These solid state IR spectral shifts are comparable with the shifts observed in the CCl_4 solution spectra. Thus, it can be concluded that stable dimer species of aspirin molecules are not present in the ground mixtures and in the inclusion compound, and that the carboxyl C=O groups of aspirin form hydrogen bonds with hydroxyl groups of cellulose or β-cyclodextrin.[9]

On the other hand, as regards the acetoxyl $\nu_{C=O}$ vibration, the results for phenyl acetate show that the acetoxyl C=O band shifted to a lower frequency in CCl_4 solution when hydrogen bond formation occured. In the ground mixture of microcrystalline cellulose (4B), a band shift to lower frequency was observed which suggests hydrogen bonding between the acetoxyl group of aspirin and hydroxyl groups of cellulose.

As reported in the previous paper,[2] in β-cyclodextrin dispersion systems (ground mix-

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8) G.R. Parker and J.D. Korp, *J. Pharm. Sci.*, **67**, 239 (1978).
9) B.L. Chang, N.O. Nuessle, and W.G. Haney, Jr., *J. Pharm. Sci.*, **64**, 1787 (1975).

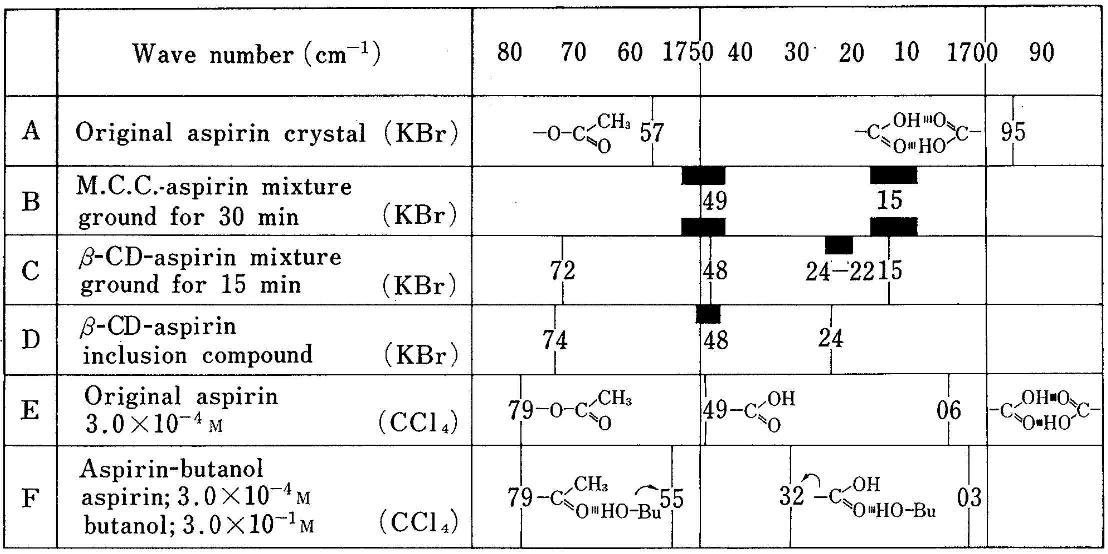

Fig. 4. Comparison of the Carbonyl Stretching Vibration of Aspirin in Various States

M.C.C. and β-CD indicate microcrystalline cellulose and β-cyclodextrin, respectively.

tures and inclusion compounds), the acetoxyl C=O band shifted significantly to higher frequency (4-C and D). This suggests most of the acetoxyl groups to be in the "free" state.

It can also be concluded from Fig. 4 that the band observed at 1748 cm^{-1} in β-cyclodextrin dispersion systems (4-C and D) is assignable to the overlapping of (i) the free carboxyl $\nu_{C=O}$ band and (ii) the hydrogen-bonded band of the acetoxyl C=O group with the hydroxyl group of β-cyclodextrin.

In the case of the other medicinals used, *i. e.* methyl *p*-hydroxybenzoate and salicylic acid, their hydrogen-bonded $\nu_{C=O}$ bands with butanol were shifted to higher frequency than those of the associated species in CCl_4 solution, as was observed in the case of aspirin.

These data confirm that in the ground mixtures and inclusion compounds the medicinal molecules formed hydrogen bonds with the hydroxyl groups of microcrystalline cellulose or β-cyclodextrin, and that the medicinal molecules were dispersed monomolecularly in the system.