[Chem. Pharm. Bull. 34(1) 315—319 (1986)]

Effects of the Degree of Polymerization of Oligosaccharides on the Properties of Ground Mixtures[1)]

YOSHINOBU NAKAI,* KEIJI YAMAMOTO, KATSUHIDE TERADA, and YASUHIKO UENO[2)]

Faculty of Pharmaceutical Sciences, Chiba University, 1–33, Yayoicho, Chiba 260, Japan

(Received May 23, 1985)

X-Ray analysis, differential thermal analysis (DTA) and infrared (IR) spectroscopy have been used to investigate the influence of the degree of polymerization of oligosaccharides on the dispersion state and the interaction of drugs (aspirin and methylparaben) during grinding with oligosaccharides. When a drug was ground with maltoheptaose or maltopentaose, the crystalline peaks of the drug in the powder X-ray diffraction pattern and the heat of fusion of the drug on DTA disappeared, and some IR spectral changes were observed. In the case of the ground mixture with maltotriose, an amorphous state of the drug was observed from the powder X-ray diffraction and DTA results, but there was no change in the IR spectrum. In the case of the ground mixture with maltose, the crystallinity of the drug was scarcely altered by the grinding.

These results indicate that in the ground mixtures with maltopentaose and maltoheptaose, drug molecules were dispersed monomolecularly in the hydrogen-bonded networks of oligosaccharides. On the other hand, in the maltotriose system, although the drug was in an amorphous state, the drug was not in a molecular dispersion due to the low degree of polymerization of maltotriose.

Keywords——amorphous; grinding; oligosaccharide; infrared spectrum; hydrogen bonding; molecular interaction

Previous studies showed that ground mixtures of drug with microcrystalline cellulose have some peculiar properties, such as solubilization of an insoluble drug[3)] and retention of a volatile drug.[4)] It was found by means of infrared (IR) spectral analysis that these peculiar properties were due to the molecular dispersion of the drugs in the hydrogen-bonded networks of microcrystalline cellulose.[5)] Drugs were also ground with cyclodextrins. The dispersed state of a drug in the ground mixture with cyclodextrin was very similar to that of the inclusion compound.[6)]

In the present paper, drugs were ground with linear oligosaccharides of different molecular weight. The dispersed state of the drugs was compared with those in the cases of microcrystalline cellulose and cyclodextrins, by using several techniques (powder X-ray diffraction, differential thermal analysis (DTA) and IR).

Experimental

Materials——Aspirin was of JPX. Methylparaben was of special reagent grade. Maltoheptaose (Seishin Pharm. Co., Ltd.), maltopentaose (Nakarai Pharm. Co., Ltd.), maltotriose (Tokyo Kasei Pharm. Co., Ltd.), maltose (Wako Pure Pharm. Co., Ltd.), β-cyclodextrin (Ando Kasei Pharm. Co., Ltd.), and microcrystalline cellulose (Asahi Chemical Industry Co., Ltd.) were dried *in vacuo* at 110 °C for 3 h and stored in a vacuum desiccator.

Preparation of Ground Mixtures——A vibrational mill (Heiko Seisakusho model TI-200) was used. The total specimen weight was 2.0 g. The mixing ratio was 10% drug and 90% oligosaccharide.

Powder X-Ray Diffraction——A Rigaku Denki 2027 diffractometer was used. The measurement conditions were as follows: target Cu, filter Ni, voltage 30 kV, current 5 mA, scintillation counter.

Thermal Measurement——A Shimadzu DT-20B was used. The measurement conditions were as follows: heating rate 5 K/min, range 25 μV, reference sample α-Al_2O_3.

IR Spectra——A Hitachi 295 infrared spectrophotometer was used. The measurements were carried out according to the KBr disk method. Wave numbers were corrected based on the standard absorptions of polystyrene film.

Results and Discussion

Grinding of Drug with Oligosaccharides

i) Grinding of Drug with Maltoheptaose——Maltoheptaose is a linear oligosaccharide consisting of seven α-1,4-linked glucose units. Figure 1 shows the powder X-ray diffraction patterns of a mixture of 10% aspirin and 90% maltoheptaose. The physical mixture shows only the crystalline peaks of aspirin as shown in Fig. 1(A), because the maltoheptaose is in an amorphous state. Figures 1(B) and (C) show the patterns for mixtures ground for 30 min and 60 min, respectively. The intensity of the crystalline peaks of aspirin decreased with grinding time and only a halo pattern was observed after 60 min. The thermal characteristics of the ground mixtures were measured by DTA. The endothermic peak due to the fusion of aspirin was not observed in the mixture ground for 60 min. These data clearly indicate that aspirin molecules exist in the amorphous state in this ground mixture. Figure 2 shows the IR spectra of the ground mixtures of aspirin–maltoheptaose and methylparaben–maltoheptaose. In the aspirin–maltoheptaose system, the aspirin crystals showed two carbonyl bands at 1759 and 1698 cm^{-1} (Fig. 2(A)). These two bands are assigned to the acetoxyl carbonyl stretching and the cyclic dimer carboxyl carbonyl stretching, respectively.[7] In the mixture ground for 60 min, the acetoxyl and the carboxyl carbonyl bands were shifted to 1749 and 1717 cm^{-1}, respectively.

In the methylparaben–maltoheptaose system, methylparaben crystals showed the carbonyl stretching band at 1685 cm^{-1}. When methylparaben was ground with maltoheptaose, an amorphous state was demonstrated by means of powder X-ray diffraction and DTA measurements after 30 min of grinding. In the amorphous sample, the carbonyl band was shifted about 20 cm^{-1} to higher frequency and appeared at 1704 cm^{-1}. Methylparaben

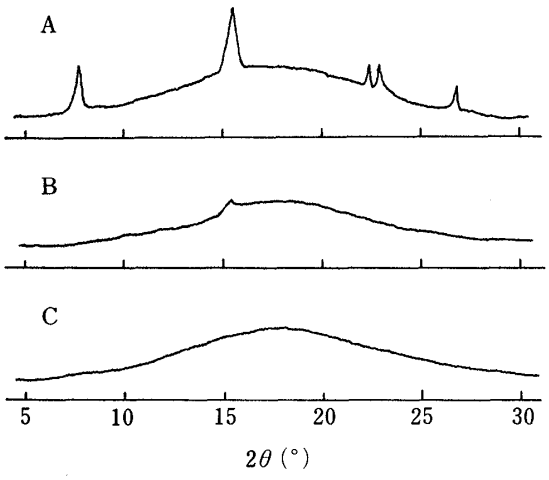

Fig. 1. Powder X-Ray Diffraction Patterns of Mixtures of 10% Aspirin and 90% Maltoheptaose

A, physical mixture; B, mixture ground for 30 min; C, mixture ground for 60 min.

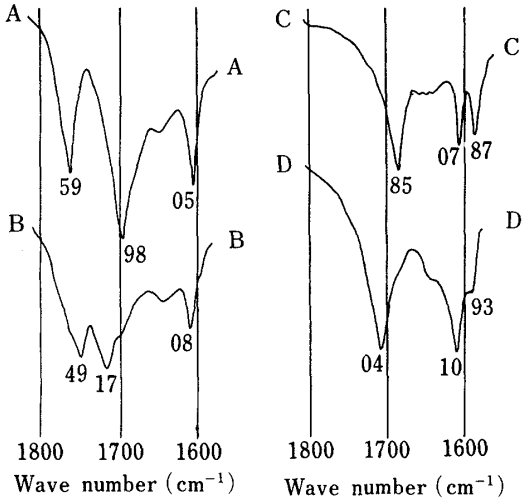

Fig. 2. IR Spectra of Mixtures of Aspirin and Methylparaben with Maltoheptaose (Containing 10% Drug)

A—B, aspirin–maltoheptaose system; C—D, methylparaben–maltoheptaose system; A, physical mixture; B, mixture ground for 60 min; C, physical mixture; D, mixture ground for 30 min.

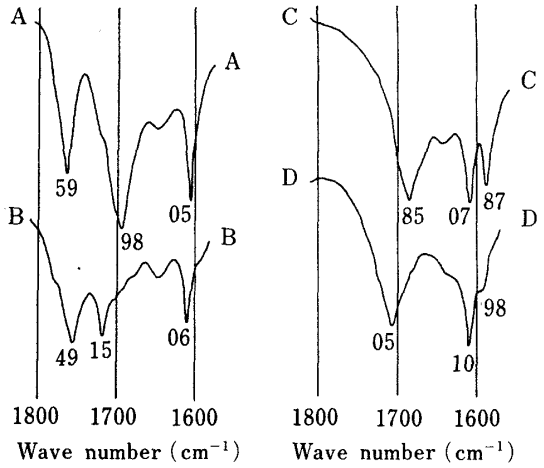

Fig. 3. IR Spectra of Mixtures of Aspirin and Methylparaben with Maltopentaose (Containing 10% Drug)

A—B, aspirin–maltopentaose system; C—D, methylparaben–maltopentaose system; A, physical mixture; B, mixture ground for 30 min; C, physical mixture; D, mixture ground for 60 min.

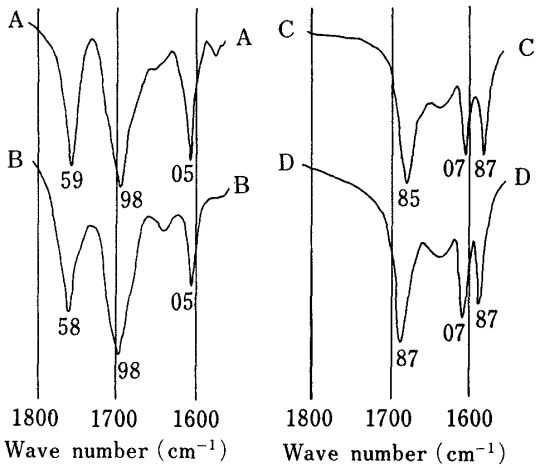

Fig. 4. IR Spectra of Mixtures of Aspirin and Methylparaben with Maltotriose (Containing 10% Drug)

A—B, aspirin–maltotriose system; C—D, methylparaben–maltotriose system; A, physical mixture; B, mixture ground for 60 min; C, physical mixture; D, mixture ground for 60 min.

crystals show two skeletal vibration bands of the benzene ring at 1607 and 1587 cm^{-1}. For the amorphous sample, the 1587 cm^{-1} band intensity was significantly decreased. The carbonyl band shift and the change of the skeletal vibration intensity indicate that drug molecules are dispersed monomolecularly in the ground mixture and are hydrogen-bonded with hydroxyl groups of maltoheptaose molecules.

ii) Grinding of Drug with Maltopentaose——Aspirin and methylparaben were each ground with maltopentaose. The powder X-ray diffraction and DTA results indicate that the drug was changed into an amorphous state within 30 min. Figure 3 shows the IR spectra of the aspirin–maltopentaose system and the methylparaben–maltopentaose system. In the aspirin ground mixture, the acetoxyl carbonyl and the carboxyl carbonyl bands were shifted to 1749 and 1715 cm^{-1}, respectively. In the ground mixture of methylparaben–maltopentaose (Fig. 3(D)), the carbonyl band was shifted about 20 cm^{-1} to higher frequency, and the 1587 cm^{-1} band (due to skeletal vibration of the benzene ring) disappeared. These IR data indicate that aspirin and methylparaben molecules are dispersed in the same manner as in the ground mixture with maltoheptaose.

iii) Grinding of Drug with Maltotriose——Aspirin and methylparaben were ground with maltotriose. It was clear from the powder X-ray diffraction and DTA measurements that both the aspirin–maltotriose and the methylparaben-maltotriose systems were in an amorphous state after 60 min of grinding. Figure 4 shows the IR spectra of both ground mixtures. The carbonyl bands and skeletal vibration were not changed in these systems. These results are significantly different from the results for ground mixtures of maltoheptaose–drug and maltopentaose–drug. The IR spectra of the ground mixture with maltotriose indicate that the drug molecules have no interaction with maltotriose, and that molecular-scale drug dispersion does not occur.

iv) Grinding of Drug with Maltose——Aspirin was ground with maltose. X-ray diffraction peaks due to aspirin and maltose decreased with increasing grinding time, but the diffraction peaks due to both crystals did not disappear even after 60 min of grinding. An endothermic peak due to the fusion of aspirin crystals was also observed in the mixture ground for 60 min, and the carbonyl bands and skeletal vibration band on IR were not changed. The same results were observed for the methylparaben–maltose system. These

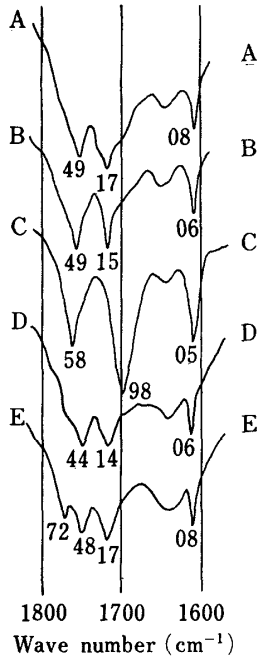

Fig. 5. Comparison of IR Spectra of Ground Mixtures of Aspirin with Maltoheptaose, Maltopentaose, Maltotriose, Microcrystalline Cellulose, and β-Cyclodextrin (Containing 10% Aspirin)

A, aspirin–maltoheptaose system; B, aspirin–maltopentaose system; C, aspirin–maltotriose system; D, aspirin–microcrystalline cellulose system; E, aspirin–β-cyclodextrin system.

results indicate that the crystalline drug is not changed into an amorphous state by grinding.

Comparison of IR Spectra of Ground Mixtures

Figure 5 shows the IR spectra of the ground mixtures of aspirin with maltoheptaose, maltopentaose, maltotriose, microcrystalline cellulose, and β-cyclodextrin. The IR spectra of aspirin with maltoheptaose and maltopentaose were nearly the same as that with microcrystalline cellulose. We have already reported that drug molecules were dispersed monomolecularly in hydrogen-bonded networks of microcrystalline cellulose in the ground mixture. A similar dispersed state of aspirin was assumed to exist in the ground mixtures with maltoheptaose and maltopentaose. On the other hand, when aspirin was ground with maltotriose, the IR spectrum did not change. It was suggested that drug molecules were in an amorphous state, but did not form a molecular dispersion because the molecular size of maltotriose was too small to form a complete hydrogen bonded network, which is indispensable for molecular dispersion.

As we have previously reported for some cyclodextrin and drug systems, the inclusion compound and the ground mixture showed nearly the same IR patterns.[8,9] Although maltoheptaose has the same molecular weight as β-cyclodextrin, it can not form an inclusion compound due to the linear shape of the molecule. When the IR spectrum of the ground maltoheptaose–aspirin system was compared with that of β-cyclodextrin–aspirin system, a significant difference was observed about the band at 1772 cm^{-1}. In the previous paper, the band at 1772 cm^{-1} was proposed to be due to the free acetoxyl carbonyl band, and the cavity of β-cyclodextrin was considered to have an important role in the appearance of this band. There is no band at 1772 cm^{-1} in the IR curve of the ground mixture with maltoheptaose. This result supports the occurrence of inclusion complex formation of aspirin with β-cyclodextrin during grinding.

References and Notes

1) This paper is part VII of "Effects of Grinding on the Physical and Chemical Properties of Crystalline Medicinals with Microcrystalline Cellulose." The preceding paper, part VI: Y. Nakai, K. Yamamoto, K. Terada, and K. Akimoto, *Chem. Pharm. Bull.*, **32**, 685 (1984).

2) Present address: *Kyowa Hakko Kogyo Co., Ltd., Shimotokari, Nagaizumicho, Suntogun, Shizuoka.*

3) Y. Nakai, E. Fukuoka, S. Nakajima, and K. Yamamoto, *Chem. Pharm. Bull.*, **25**, 3340 (1977).
4) Y. Nakai, E. Fukuoka, S. Nakajima, and Y. Iida, *Chem. Pharm. Bull.*, **26**, 2983 (1978).
5) Y. Nakai, S. Nakajima, K. Yamamoto, K. Terada, and T. Konno, *Chem. Pharm. Bull.*, **26**, 3419 (1978).
6) Y. Nakai, K. Yamamoto, K. Terada, and K. Akimoto, *J. Pharmacobio-Dyn.*, **5**, s-16 (1982).
7) R. M. Silverstein, G. C. Bassler, and T. C. Morill, "Spectroscopic Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, 1974.
8) Y. Nakai, K. Yamamoto, K. Terada, and K. Akimoto, *Chem. Pharm. Bull.*, **32**, 685 (1984).
9) K. Terada, K. Yamamoto, and Y. Nakai, *Labo-Pharma-Probl. Tech.*, **339**, 95 (1984).