Interaction between Polyethylene Films and Bromhexine-HCl in Solid Dosage Form. III. Prevention of Drug Sorption by Improving Manufacturing Processes

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The interaction between polyethylene containers and bromhexine-HCl solid dosage forms prepared by different methods was studied. It was found that bromhexine-HCl tablets prepared by the wet method (kneading) had more drug remaining than those prepared by the dry method. The sorption of drug to polyethylene was influenced by the kneading solvents used, and the most effective solvent in preventing sorption was methanol, which has high solubility for bromhexine-HCl. A ground mixture of bromhexine-HCl with crystalline cellulose was effective in inhibiting the sorption of bromhexine to polyethylene. This was explained in terms of the monomolecular dispersion of bromhexine molecules within the network of cellulose molecules in the ground mixture.

Keywords bromhexine-HCl; polyethylene; sorption; ground mixture; kneading; content decrease; solid dosage form

In a previous paper, 1 we reported that the decrease of bromhexine-HCl content in granules and tablets was due to the sorption of bromhexine-HCl to the polyethylene film of packaging materials. In the present paper, the effect of the manufacturing method on the amount of bromhexine-HCl remaining in tablets was studied using a direct compression method and a wet granulation method.

It is known that the co-grinding method 2 of drugs with additives is useful to enhance the dissolution rate of drugs, 3 to prevent sublimation of the components, 4 and to accelerate the chemical reactions 5 by a mechanochemical effect. 6 In order to investigate the effect of co-grinding on the prevention of the sorption, comparisons were made between physical mixtures, ground mixtures, and kneaded granules.

Experimental

Materials Bromhexine HCl (JP XI) was obtained from Boehringer Ingelheim Pharmaceutical, Inc. Crystalline cellulose (JP XI) obtained from Asahi Chemical Industry Co., Ltd. was dried at 60°C in a vacuum. 3-5 Solvents used were methanol, ethanol, and isopropanol, all special reagent grade from Kokuken Chemical Co., Ltd. A mixed solvent (weight ratio; water: isopropanol = 1:1) was also used. The packaging material of polyethylene film (Duapinnon Printing Co., Ltd.) was the same as used previously. 5

Preparation of Physical Mixture Powder The physical mixture powder was prepared by simple blending of bromhexine-HCl and crystalline cellulose in a mill (Yariya Type No. I). The mixing ratio of bromhexine HCl to crystalline cellulose was 1:249 in weight. The d-mannitol physical mixture was prepared by simple blending of bromhexine-HCl and d-mannitol (weight ratio = 1:249).

Preparation of Kneading Powder The kneading powder was prepared by kneading 100 g of the physical mixture powder with kneading solvent using a mortar and pestle. The kneading solvents were ethanol (10, 30, 60 g), distilled water (60 g), methanol (60 g), or the mixed solvent (60 g). After kneading, each sample was dried at 60°C for 2h. After this, here, this kind of powder is referred to as kneading powder (A). Other kneading powders (B) were prepared by mixing 60 g of bromhexine-HCl solution containing 400 mg bromhexine-HCl and 100 g of crystalline cellulose, kneading and drying at 60°C for 2h.

Preparation of Ground Mixture The ground mixture of bromhexine-HCl with crystalline cellulose was prepared by grinding the physical mixture with a mortar and pestle (Yamato, Labomill UT-21) for from 30 min to 20h. The total weight of specimen was 20.0 g.

Preparation of Tablets The tablets (diameter: 2.0 cm, thickness: 4.0 mm) were compressed directly by the tableting machine as reported previously. 15 Formulations of tablets are listed in Tables I—IV.

Storage Each tablet was packed with polyethylene film and stored at 65±1°C.

Measurement of Bromhexine-HCl The remaining amount of bromhexine-HCl in each tablet was determined as a function of time using high performance liquid chromatography (HPLC) as described previously. 15

Solubility Study An excess amount of bromhexine HCl was added to 5 ml of each solvent at 25°C, and the suspension was shaken constantly for 7h. After filtration, the bromhexine-HCl concentrations were determined by HPLC.

Powder X-Ray Diffractometry Powder X-ray diffraction patterns were measured using a Rigaku Denki RAD-3C diffractometer using a scintillation counter. The measurement conditions were as follows: target, Cu filter; Ni; voltage, 30 kV; current, 40 mA; scanning speed, 4°/min.

Dissolution Test The dissolution rates of bromhexine-HCl from the physical mixture powder, the kneading powders (A and B), and the ground mixture were tested by the JP XI dissolution test (method 2). Test conditions were as follows: rotating speed, 100 rpm; test fluids, methanol, isopropanol, or JP XI 1st fluid; volume of fluid, 400 ml; temperature, 37±0.5°C. At appropriate intervals, an aliquot solution was withdrawn and filtered by means of a membrane filter (0.45 μm). The concentrations of bromhexine-HCl were determined by HPLC.

Results and Discussion

Effect of Amount of Solvent Used in Kneading Powder (A) on the Sorption of Bromhexine-HCl to Polyethylene Film

The amounts of bromhexine-HCl remaining in tablets after packaging in polyethylene film were determined by using tablets which were prepared from the kneading powder (A). The formulations for kneading powder (A) are listed in Table I. The weight of ethanol was varied from 100 to 600 mg for each tablet.

The amount of bromhexine-HCl remaining in each tablet are shown in Fig. 1. The amount of bromhexine-HCl remaining in the tablet increased with an increase of ethanol. No degradation of bromhexine-HCl was found during storage as was reported in the previous paper. 15 It was concluded that the decrease of bromhexine-HCl from the tablet was due to the sorption to polyethylene film, and that the use of a large quantity of kneading solvent prevented the sorption of bromhexine-HCl to the film.

Effect of Kneading Solvent on the Sorption of Bromhexine-HCl to Polyethylene Film

The effect of the kneading solvent on the sorption was studied for methanol, ethanol, distilled water, and mixed solvent (mixing weight ratio of water to isopropanol = 1:1).

The tablets, of which formulations are shown in Table II, were packaged in polyethylene film and stored at 65°C. The remaining bromhexine-HCl was determined, and the
results are shown in Fig. 2, with the result of physical mixture as the reference. Great variations in the remainder were observed among the tablets prepared from different kneading solvents. Those prepared from kneading powder (A) which were kneaded by methanol showed the highest remainder of bromhexine·HCl. The effect of the solvent on the remaining bromhexine·HCl was in decreasing order, methanol > the mixed solvent > ethanol > distilled water.

**Solubility of Bromhexine·HCl in Various Solvents** It was found that the amount and kind of solvents exerted influence on the sorption behavior of bromhexine·HCl to the polyethylene film. The solubility of bromhexine·HCl in each solvent was measured at 25°C, and results are shown in Fig. 3. The greatest solubility of bromhexine·HCl was observed in methanol: 38.5 µg/ml at 25°C. The order of solubility of the solvents was in decreasing order, methanol > the mixed solvent > ethanol > distilled water. A close relationship between the solubility of bromhexine·HCl in a solvent and the amount remaining in the tablets prepared from that solvent was observed; the powder kneaded with a high solubility solvent showed strong prevention of the sorption of bromhexine·HCl to polyethylene film as shown in Fig. 2. The results indicate that the dissolution process of bromhexine·HCl to the kneading solvent during kneading has an important role in preventing the sorption of bromhexine·HCl to polyethylene film.

**Effect of Kneading Powder (B) on the Sorption of Bromhexine·HCl to Polyethylene Film** Another kneading method was used to investigate the effect of the dissolution step on the drug sorption. The formulation of kneading powders (B) is listed in Table III. The weight of each solvent was enough to dissolve the total amount of bromhexine·HCl contained. In method (B), bromhexine·HCl was first

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**TABLE I. Formulation of Tablets**

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<td>Weight of tablet (mg)</td>
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**Fig. 1. Effect of Amount of Ethanol Used for Kneading on the Amount of Bromhexine·HCl Remaining in Tablets after Storage in a Polyethylene Package at 65°C**

- Weight of ethanol: ○, 600 mg/tablet; □, 300 mg/tablet; Δ, 100 mg/tablet.

**TABLE II. Formulation of Tablets**

<table>
<thead>
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<td>Water</td>
<td>Mixed solvent</td>
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<td>4</td>
<td>4</td>
<td>4</td>
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<tr>
<td>Crystalline cellulose (mg)</td>
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<td>996</td>
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<tr>
<td>Weight of solvent (mg)</td>
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<td>Weight of tablet (mg)</td>
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</table>

*a* Water: isopropanol = 1:1.

**Fig. 2. Effect of Kneading Solvents on the Amount of Bromhexine·HCl Remaining in Tablets after Storage in a Polyethylene Package at 65°C**

- ▲, physical mixture. Kneading solvent: ○, methanol; □, mixed solvent; Δ, ethanol; ■, distilled water.

**Fig. 3. Solubility of Bromhexine·HCl in Each Solvent at 25°C**

- A, mixed solvent (water:isopropanol = 1:1); B, ethanol; C, distilled water; D, isopropanol; E, methanol.

**TABLE III. Formulation of Tablets**

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>Solvent</td>
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<td>Mixed solvent</td>
<td>EtOH</td>
<td>Water</td>
</tr>
<tr>
<td>bromhexine·HCl (mg)</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
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<tr>
<td>Crystalline cellulose (mg)</td>
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<td>Weight of tablet (mg)</td>
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*a* Water: isopropanol = 1:1.
dissolved in each solvent. The amount remaining in tablets was then determined after storage in polyethylene film at 65°C. The results are shown in Fig. 4. Using kneading powders (B), the transfer of bromhexine·HCl to polyethylene film was prevented. The amount remaining in the tablets was especially significant for distilled water or ethanol, as compared with the results shown in Fig. 2, in which tablets were made of kneading powders (A). The remainder of bromhexine·HCl in the tablets kneaded by methanol or the mixed solvent was almost the same as that shown in Fig. 2.

From Figs. 2 and 4, it is apparent that the complete dissolution of bromhexine·HCl in the kneading solvents improved the drug sorption to the polyethylene film. This means that intact bromhexine·HCl crystals had a high trend for the change from a solid dosage form to polyethylene film, while most of that deposited on the additives remained in the tablets. In Fig. 4, however, there was a small variation among the samples in their ability to retain bromhexine·HCl in tablets. It was assumed that an other property of the kneading solvent could be related to this difference in retention ability.

**Effect of Grinding on the Sorption of Bromhexine·HCl**

Great sorption of bromhexine·HCl to polyethylene film took place with tablets made of the physical mixture powder (Fig. 2). In order to investigate the effect of the dispersing state of molecules within crystalline cellulose on this sorption, the co-grinding method was studied. The physical mixture powder of bromhexine·HCl (0.4%) with crystalline cellulose was ground in an automatic mortar for a definite time, and the ground mixture powder was compacted by direct compression method. The amount of bromhexine·HCl remaining in the tablets was determined after packaging in polyethylene film and storage at 65°C (Fig. 5).

The remainder of bromhexine·HCl in the tablets increased with an increase of grinding time. The results indicate that co-grinding was effective to prevent the sorption of bromhexine·HCl to polyethylene film.

Figure 6 shows X-ray diffraction patterns of the ground mixture (ground for 20h), the methanol kneading powder (A), and the physical mixture powder. The samples were prepared in various bromhexine·HCl concentrations from 0.4% to 5.0%. In the physical mixture of bromhexine·HCl concentration of 0.4%, no diffraction peaks due to bromhexine·HCl crystals were observed. At concentrations of 2.5% and 5.0%, however, X-ray diffraction peaks due to these crystals were observed. In the ground mixture, the peaks of bromhexine·HCl crystals were not observed, indicating that the drug molecules were dispersed monomolecularly in the matrix as reported previously. In the case of methanol kneading powder (A), the peaks of these crystals disappeared in low concentration samples,
while small peaks were still observed in the 5.0% sample.

**Change of Sorption Behavior with the Addition of Sodium Bicarbonate to the Tablet** In a previous paper,\(^7\) we reported the effects of the excipients in preparations on the sorption of bromhexine·HCl to polyethylene film. The addition of acids (citric acid and tartaric acid) prevented the sorption of bromhexine·HCl to polyethylene film, while the addition of sodium bicarbonate accelerated the sorption. In previous experiments, tablets were made by the physical mixture of bromhexine·HCl, crystalline cellulose, and additives, it was assumed that the additives dispersed within the tablets acted directly with bromhexine·HCl, and that the sorption behavior was affected. Sodium bicarbonate addition to the tablets was carried out and the amount of bromhexine·HCl remaining was measured for each sample to investigate the effect of the molecular state of bromhexine·HCl in the ground mixture and in methanol kneading powder (A) on the sorption behavior.

Tablets were compacted from two kinds of powders: one prepared with 1000 mg of the ground mixture powder and 50 mg of sodium bicarbonate, and the other prepared with 1000 mg of methanol kneading powder (A) and 50 mg of sodium bicarbonate. The formulations are listed in Table IV (2 and 4). As a reference, tablets were prepared from the D-mannitol physical mixture powder as shown in Table IV (5 and 6). The amount of bromhexine·HCl remaining in the tablets after packaging in polyethylene film and storage at 65 °C is shown in Fig. 7. The remainder did not change before and after the addition of sodium bicarbonate, in the cases of the ground mixture and methanol kneading powder (A). However, in the physical mixture with crystalline cellulose, the remainder with sodium bicarbonate was smaller than that without. The addition of sodium bicarbonate accelerated the sorption of bromhexine·HCl to the polyethylene film as reported previously.\(^7\) The D-mannitol physical mixture (Table IV-5) prevented the sorption of bromhexine·HCl, however, the addition of sodium bicarbonate to the D-mannitol physical mixture (Table IV-6) accelerated the sorption.

It was reasonable to consider that the sorption was accelerated by the direct effect of sodium bicarbonate on bromhexine·HCl in the physical mixture powders. On the other hand, in the ground mixture and methanol kneading powder (A), no effect of sodium bicarbonate addition on the sorption was observed. This fact was ascribed to the monomolecular dispersions of the bromhexine·HCl molecules within the network structure of crystalline cellulose molecules in both substances.

**Dissolution Test** The dissolution rates of bromhexine·HCl were measured for the ground mixture and the methanol kneading powder (A). Both samples prevented the sorption of bromhexine·HCl to polyethylene film. The test fluids used were JP XI 1st fluid, methanol, and isopropanol. As a reference, the physical mixture powder was studied (Fig. 8).

In JP XI 1st fluid, a high dissolution rate of bromhexine·HCl was observed for the physical mixture powder, the
methanol kneading powder (A) and the ground mixture. In methanol, the dissolution from the physical mixture powder and the methanol kneading powder (A) were fast, while it was slow from the ground mixture. The dissolution rate in isopropanol from the physical mixture powder remained fast but the rates from the ground mixture and the methanol kneading powder (A) were slow.

The low dissolution rate of bromhexine·HCl in isopropanol from the ground mixture and the methanol kneading powder (A) was attributed to the molecular state of bromhexine·HCl in the matrix, that is, each drug molecule was dispersed within the hydrogen bonding network structure of crystalline cellulose and the isopropanol was not polarized enough to break this structure. The dissolution of bromhexine·HCl from methanol kneading powder (A) in methanol media was rather fast. In this matrix, bromhexine·HCl molecules were thought to be dispersed within the network of the cellulose molecules in the amorphous region\(^8\) which were extended by methanol at the kneading process, resulting in fast dissolution in the fluid of methanol. The high dissolution rate of bromhexine·HCl into water from all powders was due to the great polarity of water molecules.

**Conclusion**

A manufacturing method in which bromhexine·HCl molecules are dispersed within the network of cellulose molecules effectively prevents the sorption of bromhexine·HCl to polyethylene film, even in the presence of sodium bicarbonate.

**References**