Interaction between Polyethylene Films and Bromhexine HCl in Solid Dosage Form. IV. Prevention of the Sorption by Addition of Magnesium Aluminum Silicate

Takuya KUKITA,* Akemi YAMAGUCHI, Akihiko OKAMOTO and Masami NEMOTO

Research Center, Taisho Pharmaceutical Co., Ltd., Yoshino-cho 1–403, Omiya-shi, Saitama 330, Japan. *Received September 28, 1991*

The effects of magnesium aluminum silicate (MAS) addition on the sorption of bromhexine HCl to polyethylene film in tablets were studied. The addition of MAS prevented the sorption of bromhexine HCl to polyethylene film. In order to investigate the mechanism, the interaction between bromhexine HCl and MAS was studied by the powder X-ray diffraction method. It was observed that bromhexine HCl was preferentially adsorbed to the surface of MAS rather than to polyethylene film. The adsorption was accelerated at high temperature and reduced pressure conditions. The sorption of bromhexine base and bromhexine HCl to packaging material were compared using tablet dosage forms. The sorption of bromhexine base to polyethylene film was greater than that of bromhexine HCl.

Keywords bromhexine HCl; bromhexine base; magnesium aluminum silicate; sorption; polyethylene film; content uniformity; package

In previous papers,[1] we reported that the transfer of bromhexine HCl to polyethylene film took place when dosage forms containing bromhexine HCl were stored in polyethylene packages. This phenomenon was influenced by the dosage formula: the transfer was prevented by the addition of acidic materials (citric acid, tartaric acid), and accelerated by the addition of basic material (sodium bicarbonate) due to an effect of the additives on bromhexine HCl directly. Arisawa *et al.*, reported that the sorption of chlorpheniramine maleate to polyethylene was accelerated by the addition of precipitated calcium carbonate in granules.[2]

There are several reports of interactions between medicinals and adsorbents such as magnesium aluminum silicate (MAS) or anhydrous silicic acid.[3] In the present investigation, the effect of adsorbent addition to the dosage formulation on the sorption of bromhexine HCl to polyethylene film was studied using MAS which is an antacid agent similar to sodium bicarbonate and precipitated calcium carbonate.[4] The sorption of bromhexine base and the sorption of bromhexine HCl to polyethylene film from tablets were compared to investigate the effect of volatility.

Experimental

Materials Bromhexine HCl (JP XI) was obtained from Boehringer Ingelheim Pharm., Inc. Bromhexine base was obtained from bromhexine HCl by the method of Nishigaki *et al.*[5] Bromhexine base crystals were recrystallized from ethanol. The bromhexine base obtained was identified by elemental analysis. Crystalline cellulose (CC) (JP XI, Asahi Chemical Ind., Co., Ltd.) was dried at 60 °C *in vacuo*.[1c] MAS (Neusilin, Fuji Chemical Ind., Co., Ltd.) was dried at 110 °C *in vacuo*.[6] The packaging material used was a polyethylene film (Dainippon Printing Co., Ltd.), described previously.[1]

Preparation of Tablets The tablets (diameter; 2.0 cm, thickness; 4.0 mm, weight; 1000 mg) containing bromhexine HCl or bromhexine base were directly compressed with the physical mixture powders. The compression method was the same as reported previously.[1] Formulations of the physical mixture powders are shown in Table I.

TABLE I. Formulation of Physical Mixture Powder Containing Bromhexine HCl or Bromhexine Base with MAS (mg)

	A	B	C	D	E	F	G
Bromhexine HCl	4	4	4	4	4	—	—
Bromhexine base	—	—	—	—	—	4	4
CC	996	946	896	696	596	996	896
MAS	—	50	100	300	400	—	100

Sorption Study Tablets were stored in polyethylene film packages at 40, 50 and 65 °C. The amounts of drug remaining in the tablets were determined as a function of storage time by using high performance liquid chromatography (HPLC), as described previously.[1]

Preparation of Mixtures for Adsorption Study Bromhexine HCl was mixed with MAS in a mortar (mixing weight ratio = 5 : 95). The mixtures were stored under the following conditions in a desiccator containing calcium chloride anhydrate: (i) at 60 °C for a period between 4 and 24 h, (ii) at 80 and 100 °C for 4 h, and (iii) at 60 °C at a reduced pressure of about 10.0 mmHg for a period between 12 and 24 h. Bromhexine HCl was mixed with MAS and CC in a mortar (5% bromhexine HCl). MAS concentration was varied from 0% to 70%. The mixtures were stored at 60 °C at a reduced pressure of about 10.0 mmHg for 24 h. Bromhexine base was mixed with MAS in a mortar (mixing weight ratio = 5 : 95). The mixtures were stored at 40 °C for a period between 2 and 4 h.

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

Results and Discussion

Effect of MAS Addition on the Sorption of Bromhexine HCl to Polyethylene Film from Solid Dosage Form Tablets containing bromhexine HCl and MAS of varied concentrations were prepared. The amounts of bromhexine HCl remaining in the tablets were determined after packaging them in polyethylene film as a function of storage time at 65 °C. The tablets were prepared with the physical mixture powder which were shown in Table I (A—E). The

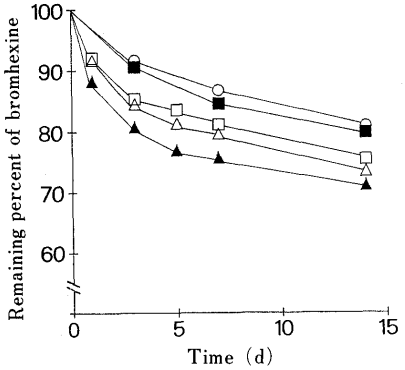

Fig. 1. Effect of MAS Addition on the Amount of Bromhexine HCl Remaining in Tablets in Polyethylene Film Package at 65 °C

MAS concentration: ○, 40%; ■, 30%; □, 10%; △, 5%; ▲, without MAS.

concentrations of MAS were varied from 0% to 40%.

The amounts of bromhexine HCl ramaining in each tablet are shown in Fig. 1. The remainder in the tablets increased with the increase of concentration of MAS. The results indicated that MAS in the tablets prevented the sorption of bromhexine HCl to polyethylene film. No degradation of bromhexine HCl was found during storage and analysis. In the previous papers,[1] we already reported that the content decrease of bromhexine HCl in tablets which were packaged with polyethylene film was due to sorption to the polyethylene film. In the case of MAS mixture, similar sorption of bromhexine HCl to the polyethylene film and the resulting content decrease was anticipated.

The addition of basic materials (sodium bicarbonate or precipitated calcium carbonate) accelerated the sorption of basic drugs in solid dosage form to plastic packaging materials.[1,2] In this case, however, the addition of MAS which was a basic antacid agent similar to sodium bicarbonate and precipitated calcium carbonate[3] inhibited the sorption of bromhexine HCl to polyethylene film. Large surface area and porous structure of MAS seemed to have great influences on the behavior of bromhexine HCl. In order to investigate the preventive role of MAS, we studied the interaction between MAS and bromhexine HCl.

Figure 2 shows the relationships between total release of bromhexine HCl from tablets (mg) and square root of storage time ($d^{1/2}$).[7] The results for containing various amount of MAS or sodium bicarbonate were shown. Linear relationships between the release of bromhexine HCl and the square root of storage time were observed. The release rate ($mg/d^{1/2}$) was determined from the slop of each line. It was found that the addition of MAS decreased the release rate of bromhexine HCl from tablets and that MAS inhibited the sorption of bromhexine HCl to polyethylene film. On the other hand, the addition of sodium bicarbonate to the tablets increased the release rate of bromhexine HCl from tablets and accelarated the sorption of bromhexine HCl to polyethylene film. The results indicated that the diffusion of bromhexine HCl in tablets was prevented by the addition of MAS.

Figure 3 shows the changes of powder X-ray diffraction patterns of the mixture of bromhexine HCl with MAS (mixing weight ratio = 5 : 95), stored at various temperatures and pressures. Curve (a) represents the diffraction pattern of the freshly prepared mixture, exhibiting diffraction peaks of bromhexine HCl crystals.[1c] Curves (b) and (c) represent

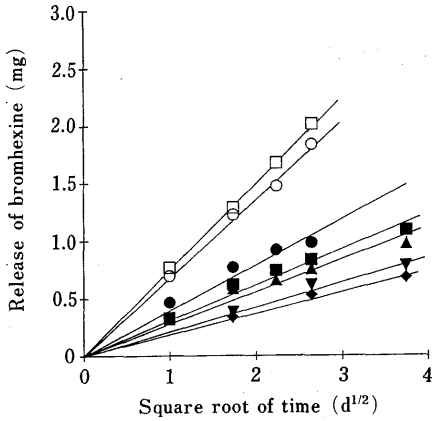

Fig. 2. Release of Bromhexine HCl from Tablets Containing Various Additives at 65 °C

●, without additives. Addition of MAS: ■, 5.0%; ▲, 10.0%; ▼, 30.0%; ◆, 40.0%. Addition of sodium bicarbonate: ○, 5.0%; □, 10.0%.

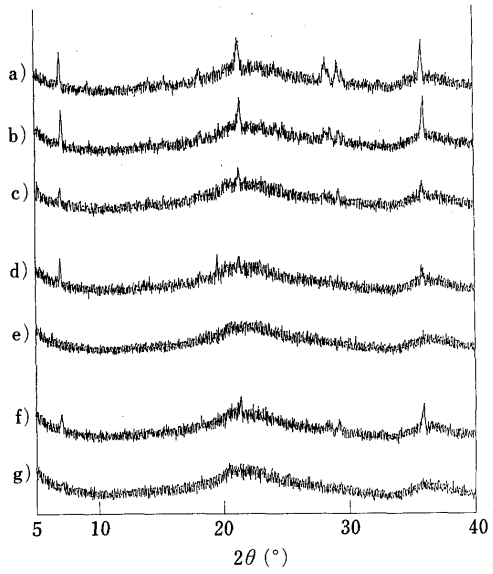

Fig. 3. Powder X-Ray Diffraction Patterns of Mixtures of Bromhexine HCl and MAS (5% Bromhexine HCl and 95% MAS)

a) Physical mixture, b) stored for 4 h at 60 °C, c) stored for 24 h at 60 °C, d) stored for 4 h at 80 °C, e) stored for 4 h at 100 °C, f) stored for 12 h at a reduced pressure and 60 °C, g) stored for 24 h at a reduced pressure and 60 °C.

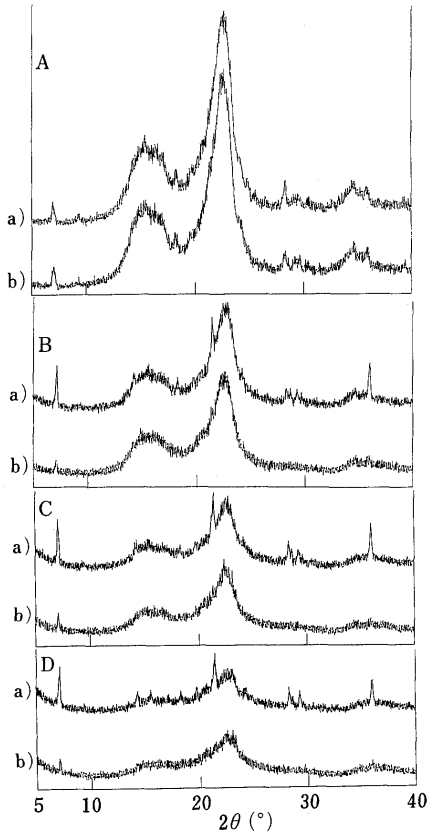

Fig. 4. Powder X-Ray Diffraction Patterns of Mixtures of Bromhexine HCl, CC and MAS (5% Bromhexine HCl)

A, MAS 0% and CC 95%; B, MAS 30% and CC 65%; C, MAS 50% and CC 45%; D, MAS 70% and CC 25%. a) Before storage, b) stored for 24 h at reduced pressure and 60 °C.

the diffraction patterns of the mixture after storage at 60 °C for 4 and 24 h. The diffraction peaks due to crystalline bromhexine HCl disappeared with the increase of storage time, but no content decrease of bromhexine HCl was observed. With increased storage temperature, the diffraction peaks disappeared indicating the conversion of bromhexine HCl to the amorphous state (curves d and e). At a reduced pressure (curves f and g), the diffraction peaks disappeared more rapidly than at an atmospheric pressure. The results indicated that bromhexine HCl crystals were changed to the amorphous state by the adsorption of bromhexine HCl on the surface of MAS. In the mixture containing adsorbent such as MAS, bromhexine HCl molecules were adsorbed on the surface of adsorbent and were sorbed to polyethylene film as well.

Nakai *et al.*, reported various interaction modes between medicinals and porous powders.[8] In the mixture of medicinals and porous powders, medicinal molecules were adsorbed on the surface of powders by sublimation. The vaporization of liquids and the sublimation of solids took place more rapidly at a reduced pressure than at an atmospheric pressure,[6] because the molecular mean free path was much longer than at atmospheric pressure. The results indicated that the phenomenon of amorphization of bromhexine HCl mixed with MAS took place *via* the gaseous phase, as the rate of amorphization of bromhexine HCl crystals at a reduced pressure was significantly fast.

Figure 4 shows the changes of powder X-ray diffraction patterns of the mixtures of bromhexine HCl with MAS and CC, stored for 24 h at reduced pressure and 60 °C. The concentrations of MAS varied from 0% to 70%.

In the case of the mixture without MAS (Fig. 4A), the intensities of the diffraction peaks did not changes after storage, indicating a stable bromhexine HCl cystalline state. However, in the cases of the mixture with MAS (Fig. 4B, C and D), the diffraction peaks of bromhexine HCl disappeared with storage time. With the increase of MAS concentration, the rate of diffraction peak disappearance increased significantly.

Bromhexine HCl crystals were changed to the amorphous state by the addition of MAS to the mixture.[1c] It was assumed that the sorption of bromhexine HCl to polyethylene film from tablets was prevented by the preferential adsorption of bromhexine HCl to the surface of adsorbent.

Effect of MAS Addition on the Sorption of Bromhexine Base to Polyethylene Film from Solid Dosage Form It is well known that the vapor pressure of organic bases is greater than that of HCl salts.[6] An evaluation of the rates of transfer of bromhexine base and bromhexine HCl to MAS is needed to clarify this phenomenon, since the transfer took place *via* the gaseous phase.

Figure 5 shows the changes of powder X-ray diffraction patterns of mixtures of bromhexine base (5%) with MAS (95%), stored at 40 °C. The bromhexine base diffraction peaks disappeared with increased storage time. The rate of disappearance of X-ray diffraction peaks of bromhexine base was greater than that of bromhexine HCl.

The sorption of bromhexine base to the polyethylene film from tablets was studied. Tablets were prepared by compressing physical mixtures of bromhexine base crystal and crystalline cellulose. The formulations of the physical

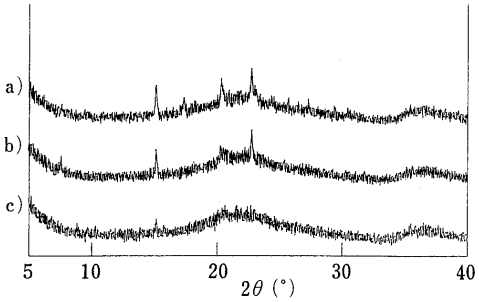

Fig. 5. Powder X-Ray Diffraction Patterns of Bromhexine Base and MAS Mixture (5% Bromhexine Base and 95% MAS)

a) Physical mixture, b) stored for 2 h at 40 °C, c) stored for 4 h at 40 °C.

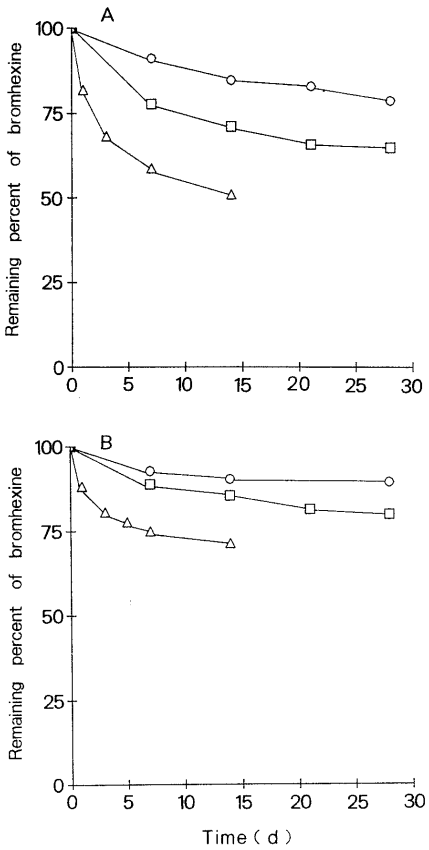

Fig. 6. The Amount of Bromhexine Base Remaining in Tablets during Storage in Polyethylene Film Package at Various Temperatures

A, bromhexine base; B, bromhexine HCl. ○, 40 °C; □, 50 °C; △, 65 °C.

mixtures are shown in Table I-F. The amounts of bromhexine base remaining in the tablets during storage in polyethylene package at 40, 50 and 65 °C are shown in Fig. 6A. Figure 5B shows the results of formulation A (Table I) as a reference.

The amounts of bromhexine base ramaining in tablets decreased as a function of storage time. A particularly rapid decrease was observed at high temperature. The content decrease of bromhexine base in the tablet was considered to be due to the sorption to the polyethylene film, similarly to the sorption of bromhexine HCl.[1,2] From the comparison of content decrease rates of bromhexine base and bromhexine HCl, it was found that the rates of content decrease of bromhexine base were higher than those of bromhexine HCl at all temperatures. This might be due to

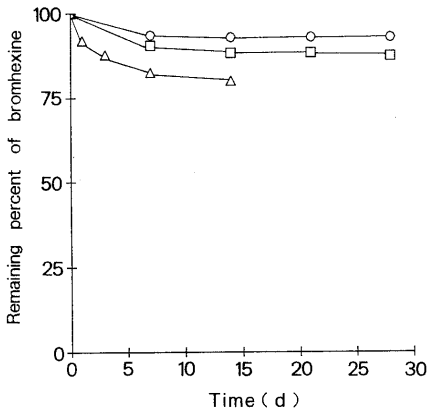

Fig. 7. Effect of MAS Addition on the Amount of Bromhexine Base Remaining in Tablets during Storage in Polyethylene Film Package at Various Temperatures

○, 40 °C; □, 50 °C; △, 65 °C.

the high volatility of bromhexine base.

Figure 7 shows the effects of 10% MAS addition on the amounts of bromhexine base remaining in tablets after storage at various temperatures. The formulation of the tablet is shown in Table I-G. A comparison of Fig. 6A with Fig. 7, revealed that the amount of bromhexine base remaining in the tablets with MAS was greater than that in tablets without MAS. The addition of MAS inhibited the sorption of bromhexine base and bromhexine HCl to polyethylene film from tablets similarly. Thus the above results indicate that bromhexine HCl and bromhexine base are preferentially adsorbed to the surface of MAS rather than to polyethylene.

Acknowledgement We are grateful to Dr. Y. Nakai and Dr. K. Yamamoto of Chiba University for their kind advice and encouragement.

References

1) *a*) T. Kukita, A. Yamaguchi, A. Okamoto, M. Nemoto, H. Yamaguchi, K. Yamamoto and Y. Nakai, *Yakugaku Zasshi*, **109**, 943 (1989); *b*) *Idem*, *ibid.*, **110**, 127 (1990); *c*) *Idem*, *Chem. Pharm. Bull.*, **39**, 1287 (1991).
2) M. Arisawa, M. Ishida, Y. Yokota and C. Eziri, *Toyama Yakuken Nempo*, **15**, 87 (1988).
3) *a*) D. C. Monkhouse and J. L. Lach, *J. Pharm. Sci.*, **61**, 1431 (1972); *b*) H. Yokoi, S. Enomoto and H. Takahashi, *Yakugaku Zasshi*, **98**, 418 (1978); *c*) K. Y. Yang, R. Glemza and C. I. Jarowski, *J. Pharm. Sci.*, **68**, 560 (1979); *d*) C. Liao and C. I. Jarowski, *ibid.*, **73**, 401 (1984); *e*) Y. Nakai, K. Yamamoto, K. Terada, T. Oguchi and M. Yamamoto, *Yakugaku Zasshi*, **107**, 294 (1987).
4) K. Tanaka (ed), "Gendai No Yakurigaku," Kinbara Shuppan, Tokyo, 1988.
5) S. Nishigaki, M. Ichiba, K. Owada, S. Takenobu, F. Kimita and K. Senga, *Jpn. J. Hosp. Pharm.*, **5**, 118 (1979).
6) *a*) T. Konno, K. Kinuno and K. Kataoka, *Chem. Pharm. Bull.*, **34**, 301 (1986); *b*) T. Konno and K. Kinuno, *ibid.*, **37**, 2481 (1989); *c*) T. Konno, *ibid.*, **38**, 1032 (1990); *e*) *Idem*, *ibid.*, **38**, 2003 (1990).
7) *a*) T. Higuchi, *J. Soc. Cosm. Chem.*, **11**, 85 (1960); *b*) *Idem*, *J. Pharm. Sci.*, **50**, 874 (1961); *c*) W. I. Higuchi, *ibid.*, **51**, 802 (1962).
8) *a*) Y. Nakai, K. Yamamoto, K. Terada and J. Ichikawa, *Chem. Pharm. Bull.*, **32**, 4566 (1984); *b*) *Idem*, *Yakugaku Zasshi*, **105**, 296 (1985); *c*) Y. Nakai, K. Yamamoto, K. Terada, T. Oguchi and S. Izumikawa, *Chem. Pharm. Bull.*, **34**, 4760 (1986); *d*) E. Yonemochi, T. Oguchi, K. Terada, K. Yamamoto and Y. Nakai, *ibid.*, **37**, 3083 (1989).