Interaction between Polyethylene Films and Bromhexine HCl in Solid Dosage Form. V. Effect of Packaging Materials on the Sorption of Bromhexine HCl

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A prevention method of the sorption of bromhexine HCl to plastic materials used in packaging was investigated. Four kinds of plastic packaging materials were used: Polyethylene (PE), polyethylene terephthalate (PET), polypropylene (PP) and polyacrylonitrile (PAN). Three polyethylenes having different densities were used. No effect of PE density on the sorption of bromhexine HCl from granules was observed. The effects of different kinds of plastics on the sorption of bromhexine HCl from solution and granules were studied. The sorption of bromhexine HCl to PAN, which had a high relative dielectric constant, was the most depressed among the four plastics. The sorption of meclizine HCl to PAN from the solution was also lowest, the same as bromhexine HCl.

Keywords bromhexine HCl; sorption; content decrease; relative dielectric constant; polyethylene; polypropylene; polyethylene terephthalate; polyacrylonitrile; polyethylene film; package

Introduction

The content decrease of drugs from the dosage form due to the drug sorption to plastic containers and intravenous administration sets has been reported for isosorbid nitrate,[1] nitroglycerin,[2] diazepam,[3] warfarin[4] and diltiazem.[5] This content decrease has caused the problem of a reduction of the expected pharmacological effect on patients. As packaging materials for dosage form, polyethylene (PE), polypropylene (PP) and polyvinyl chloride (PVC) are widely used.[6] Especially, polyacrylonitrile (PAN) has characteristic features in low gas permeability and high stability to organic solvents.[7] In the packaging of foods[8] and drugs, PAN is used in order to prevent the sorption of volatile compounds.

In previous papers,[9] we reported that the decrease of bromhexine HCl content in solid dosage forms and solution was due to the sorption of bromhexine HCl to the PE packaging materials and could be prevented by the improvement of manufacturing processes. In the present paper, in order to investigate the effect of plastics on sorption behavior, comparisons were made between PAN, PET (polyethylene terephthalate), PP and PE. The sorption of meclizine HCl to packaging plastic materials was also studied.

Experimental

Materials Bromhexine HCl (JP XI) was obtained from Boehringer Ingelheim Pharm., Inc.[9] Meclizine HCl was obtained from Kawakenfine Chemical Co., Ltd. Additives used were potato starch (Hokuren) and hydroxypropylcellulose (Nippon Soda Co., Ltd.). The packaging plastic materials used as films, beads and containers were high density polyethylene (HDPE), middle density polyethylene (MDPE), low density polyethylene (LDPE), PET, PP and PAN, all obtained from Dainippon Printing Co., Ltd.

Preparation of Granules The granules (total weight: 1000 mg) containing bromhexine HCl (4 mg), potato starch (976 mg) and hydroxypropylcellulose (20 mg) were prepared by using the rotary granulation method[9a] and were packed with each plastic film and stored at 65±1 °C.

Preparation of Bromhexine HCl Solution and Sorption Studies The solution of bromhexine HCl was prepared using buffer fluids (pH 5.0 phosphate buffer). The concentration of drug was 20 μg/ml. We used two methods for sorption studies. (i) The solution (20 ml) was shaken with respective PE beads (0.5 g, diameter is in the range of 3.5—4.5 mm) in a centrifuge tube at 25±1 °C. (ii) The solution was stored in respective plastic containers at 25±1 °C.

Preparation of Meclizine HCl Solution The solution of meclizine HCl was prepared and stored similar to bromhexine HCl.

Analytical Method of Drugs The amount of bromhexine HCl remaining in the granules and solutions were determined as a function of storage time using HPLC as described previously.[9] The amount of meclizine HCl remaining was determined using HPLC the same as in the condition of bromhexine HCl.

IR Absorption Spectroscopy JEOL JIR-6500 was used. The measurements were made according to the microscope transmittance method.

Results and Discussion

Effect of PE Density on the Sorption of Bromhexine HCl The relationship between the sorption and PE density has been reported for flavor compounds[8b,c] and phenylmercury salt preservatives.[10] The sorption of the flavor compounds and phenylmercury salt preservatives to LDPE was much greater than to HDPE. The effect of PE density on the sorption of bromhexine HCl from granules was studied using HDPE (0.95 g/cm^3, JIS K 6760), MDPE (0.94 g/cm^3) and LDPE (0.92 g/cm^3). The amount of bromhexine HCl remaining in the granules packed in each PE film was determined after storage at 65 °C. The results are shown in Fig. 1. Among three PE films, no significant difference was observed in the amounts of bromhexine HCl remaining in the granules. No degradation of bromhexine HCl was found during storage, the same as reported in previous papers.[9]

The density of PE depended upon the branching structure of polymer molecules. The differences in branching

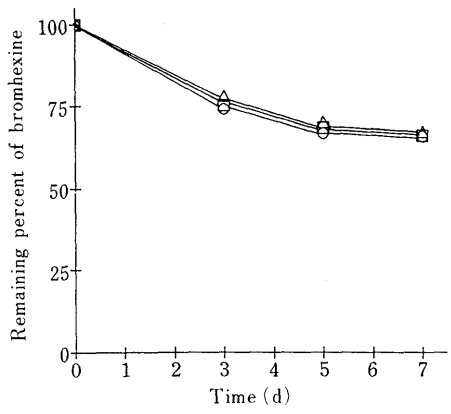

Fig. 1. Effect of PE Density on the Sorption of Bromhexine HCl to PE Films from Granules at 65 °C

□, HDPE; △, MDPE; ○, LDPE.

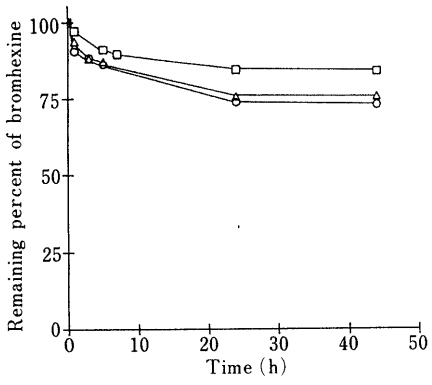

Fig. 2. Effect of PE Density on the Sorption of Bromhexine HCl to PE Beads from Solution at 25 °C

□, HDPE; △, MDPE; ○, LDPE.

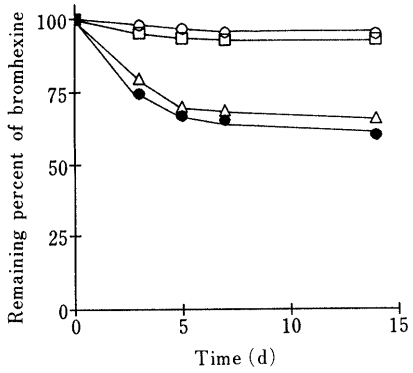

Fig. 3. Effect of Packaging Materials on the Sorption of Bromhexine HCl to Plastic Films from Granules at 65 °C

○, PAN; □, PET; △, PP; ●, LDPE.

TABLE I. Relative Dielectric Constants of Plastics[12]

	Relative dielectric constant (εr)
PAN	4.1 —4.8
PET	3.1
PP	2.1 —2.2
PE	2.25—2.35

structure were determined using IR spectrophotometry. The IR spectrum of LDPE was known to show the specific absorption bands near 1378 cm^{-1} due to the symmetric deformation vibration of the CH_3 group.[11] The three PE films used in this experiment showed different IR patterns near 1378 cm^{-1}, indicating varied structures among PE films. No dependency of sorption on the density could be explained by the slow release of bromhexine HCl from granules.

Figure 2 shows the sorption of bromhexine HCl to three kinds of PE beads from solution. Bromhexine HCl remained in solutions in the order of HDPE > MDPE > LDPE. The difference of sorption between the PEs was observed in the solution experiment. It was considered that in the solution experiment, the diffusion of adsorbate through PE was the rate determining step for the sorption. On the other hand, in the granules experiment, the slow releasing rate of bromhexine HCl from the granules was not enough to clearly distinguish the PE characteristics.

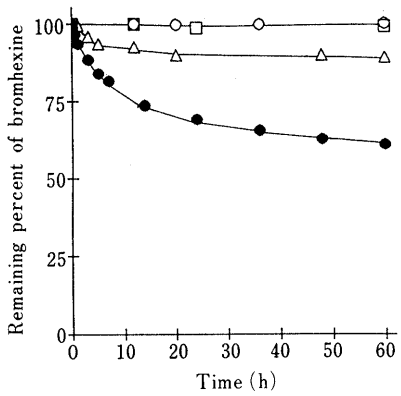

Fig. 4. Effect of Packaging Materials on the Sorption of Bromhexine HCl to Plastic Containers from Solution at 25 °C (Bromhexine HCl: 20 μg/ml, pH 5.0)

○, PAN; □, PET; △, PP; ●, LDPE.

TABLE II. Remaining Percent of Meclizine HCl in Buffer Solution after Storage in Various Plastic Containers for 48 h at 25 °C

	Remaining in solution
PAN	96.0%
PET	86.0%
PP	69.9%
LDPE	30.0%

Initial meclizine HCl concentration, 20 μg/ml; pH 5.0.

Changes of Sorption Behavior in Different Packaging Materials In order to investigate the effect of packaging materials on the sorption of bromhexine HCl to plastics, sorption studies were made using four kinds of plastics. Figure 3 shows the amount of bromhexine HCl remaining in the granules packaged in various plastic films after storage at 65 °C. Bromhexine HCl remained in granules in the order of PAN > PET > PP > LDPE. The difference of sorption behavior among plastic materials was considered based upon the plastic properties. The relative dielectric constants of these plastics already reported were listed in Table I.[12] From comparisons of relative dielectric constants, it was found that the sorption of bromhexine HCl increased when the relative dielectric constant decreased. As the relative dielectric constant represented the tendency of the polarity of the plastics, it was assumed that the decreased sorption of bromhexine HCl to PAN was due to an increased polarity in PAN.

Sorption of Drugs to Different Packaging Materials from Solution In order to investigate the effect of packaging materials on the sorption of bromhexine HCl from solution, the bromhexine HCl buffer solution (pH 5.0) was kept in various plastic containers at 25 °C. The results are shown in Fig. 4. The amounts of bromhexine HCl remaining in the solutions was in the order, PAN > PET > PP > LDPE. The results obtained in the solution study was in good agreement with the results obtained in the case of the granules storage study (Fig. 3). The sorption of bromhexine HCl to the packaging materials was prevented by using PAN and PET. Table II shows the remaining percentage of meclizine HCl in the buffer solution after storage in various plastic containers for 48 h at 25 °C.

Meclizine is a basic drug similar to bromhexine. The amount of meclizine HCl varied with the packaging materials, and the remaining amount was in the decreasing order of PAN > PET > PP > LDPE. The agreements were observed for the order of sorption of bromhexine HCl and meclizine HCl to different plastic materials. The results indicated that PAN packaging was the most effective method for preventing the sorption of bromhexine HCl and meclizine HCl.

In previous papers,[9b] we reported that the sorption of bromhexine HCl to the PE container from the solution depended on the apparent partition coefficients determined between various pH buffers and *n*-hexane. The increasing of the sorption of bromhexine HCl to PE was related to an increased ratio of nonionized molecules. From this study, it was found that, due to the high polarity, the sorption of even nonionized molecules was prevented by using PAN. The sorption to PE was greater than that to PP. But, the relative dielectric constants of PP and PE were about the same value. It was assumed that another property of plastic could be related to the sorption to PP and PE.

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