Release of Sodium Guaiazurene-3-sulfonate from Polymer Film Dosage Forms

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In vitro release tests were investigated in single-layered and double-layered film systems. Sodium guaiazurene-3-sulfonate (GAS) was chosen as the drug for local use. Hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose phthalate (HPMCP) and polyvinylacetaldiethylaminoacetate (AEA) were used to make films, and the tests were done with films made of various ratios of these two polymers.

The drug release from the HPC single-layered films was independent of pH, and showed a zero order release. The apparent release rate constants, k_a of the double-layered film varied according to the nature of the polymers and the drug as well as with the pH of the testing solutions.

The results suggest the possibility of sustained release from double-layered films.

Keywords film dosage form; sodium guaiazurene-3-sulfonate; hydroxypropylcellulose; single-layered film; double-layered film; oral mucosa; zero-order release; sustained release

In recent years, polymer films have been developed as a new type of controlled or sustained release dosage form for the local or systemic delivery of drugs. This form, used in various mucosal tissues, offers advantages for drugs which are subjected to high first-pass metabolism or are unstable in the gastrointestinal tract. Since the mouth has the most readily accessible mucosal membranes, it is a potential platform for local and systemic action.

Oral mucosal dosage forms of insulin have been investigated by Ishida.[1] Kurosaki[2] studied drug absorption from the oral cavity. Hui and Robinson[3] examined the ocular delivery of progesterone with a bioadhesive polymer film for delivering a mucosal dosage. Saito[4] has investigated the preparation and evaluation of oral mucosal adhesive film dosage forms.

Tablets of orally administrated dosage forms have been sold on the market,[5] but it caused a foreign body sensation when administrated to the oral cavity. We also studied the drug release from laminated polymer films, including a sodium guaiazurene-3-solfonate, as anti-inflammatory drugs.

Experimental

Materials Sodium guaiazurene-3-sulfonate (GAS; Konan Kagaku Kogyo Co., Ltd) was used as a model drug. The polymers used were hydroxypropyl cellulose (HPC, Mw, mean $= 6.0 \times 10^4$), hydroxypropyl methylcellulose phthalate (HPMCP, Mw, mean $= 4.5 \times 10^4$; both from Shin Etsu Kagaku Kogyo Co., Ltd.) and polyvinylacetaldiethylaminoacetate (AEA, Mw, mean $= 6.4 \times 10^4$; Sankyo Seiyaku Kogyo Co., Ltd.).

Preparation of Film Dosage Forms (a) Preparation of Single-Layered Film: Five grams each of HPC, HPMCP and AEA were dissolved in 100 ml of water/isopropyl alcohol (1:1), aceton and ethanol, respectively. Twenty-five milligrams of GAS were then added to 10 ml of 5% (w/v) HPC solution and mixed sufficiently. Ten mililiters of this mixed solution were molded in a teflon dish (10 cm diameter, 0.2 cm deep) and dried at room temperature. This procedure was repeated four times. The laminated sigle-layered films are uniform in 150—170 μm thickness.

(b) Preparation of Double-Layered Film: Double-layered film was prepared by covering the outer layer of film of HPMCP or AEA without GAS, which bonded with 5% (w/v) HPC solution, to the first film layer of HPC with GAS.

Procedure for Release Experiment (a) Release tests for polymer films were carried out with a JPXII dissolution test apparatus which used a paddle method that bonded one square centimeter of cut square film with double adhesion tape to the inside of a glass vessel with 500 ml of a medium at 37 ± 0.1 °C. A 100 rpm paddle rotating speed was used as the release medium was prepared with a buffered Clark-Labs solution, and the dissolved polymer films were determined by the weight of the surviving film after it had been dried for a fixed time. This procedure was repeated three times. (b) Release tests for GAS were carried out with a JP XII dissolution test apparatus employing the paddle method with 500 ml of medium at 37 ± 0.1 °C. A 100 rpm paddle rotating speed was used as the release medium was prepared with a buffered Clark-Labs solution and artificial saliva (Saliveht, Teijin Co., Ltd.), and the drug concentration was determined with a UV-spectrophotometer (Hitachi model 200-20) at 292 nm three times. The test films were in a square centimeter and were bonded with double adhesive tape to the inside of a glass vessel as shown in Fig. 1.

Results and Discussion

Drug Release Kinetics Drug release kinetics from a polymer film containing a dispersed drug could be changed from linearity with time (zero order) by laminating a membrane layer to the releasing surface. In the case of zero-order kinetics, the rate of drug release is a linear function of both the drug solubility (C_s) and membrane diffusivity (D) and is inversely proportional to the thickness of the membrane films, h.

Flynn[6] described the following equation at steady state:

$$Q = (DC_s/h)(t - h^2/6D) \tag{1}$$

where Q is the quantity released per unit of exposed area. For a given film in which the membrane remains constant, D, C_s, and h are constant through most of the
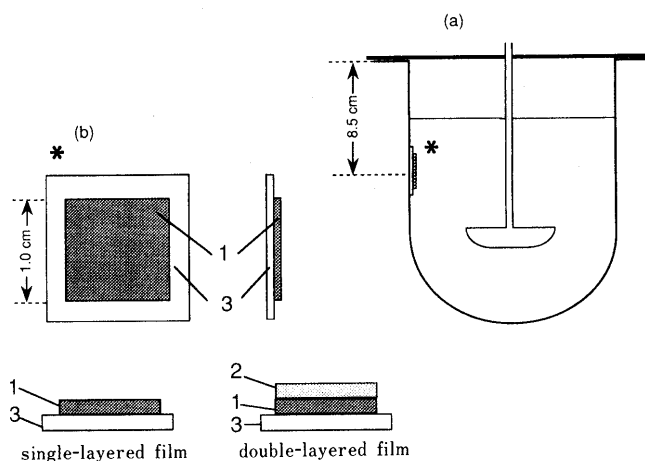

Fig. 1. Schematic Diagram of Polymer Films and Release Test Apparatus

(a) Release test apparatus; (b) polymer film dosage forms 1, HPC film with drug; 2, outer film layer without drug; 3, double-adhesive tape.

release, and the apparent zero-order rate constant may be defined as:

$$k_a = DC_s/h \tag{2}$$

and

$$Q = k_a t - k_a t_{lag} \tag{3}$$

$$t_{lag} = h^2/6D \tag{4}$$

The lag time, t_{lag}, is obtained by the intercept on the time axis when the steady state rate is extrapolated.

Effect of pH on the Dissolution of Polymer Films Figure 2 shows the apparent dissolution rates of the polymer films
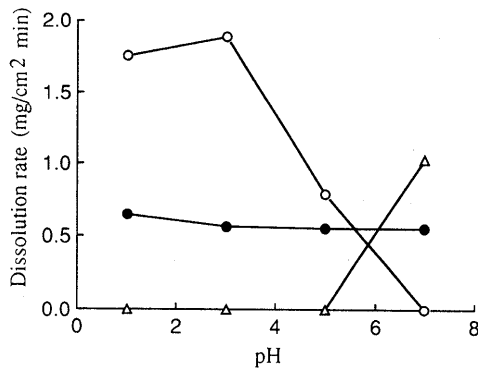

Fig. 2. Relationship between Dissolution Rate of Polymer Films and pH
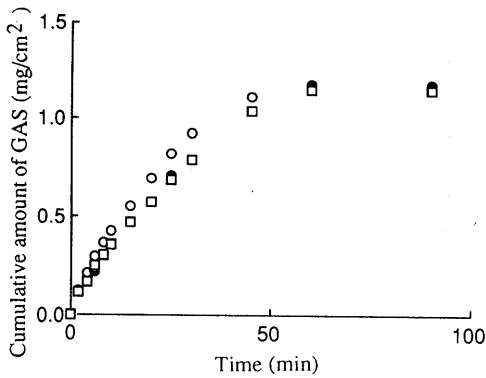
○, AEA; ●, HPC; △, HPMCP.

Fig. 3. Release Profiles of GAS from Single-Layered Films of HPC
○, pH 1.0; ●, pH 5.0; □, pH 7.0.

at various pH values. The apparent dissolution rate of HPC did not vary greatly with pH, whereas that of the AEA and HPMCP films did. The rate for the AEA film increased at lower pH values. However, that for the HPMCP film increased at higher pH values. These results reflect the presence of a diethylamino group in AEA and a carboxybenzoyl group in HPMCP.

Release of GAS from Single-Layered Films Figure 3 shows the release of GAS from the single-layered film dosage form. GAS release did not change with pH, since the dissolution of HPC film was independent of pH. These results show a zero-order drug release.

Release of GAS from Double-Layered Films Prepared for Sustained Release Double-layered films were prepared by bonding AEA or HPMCP films, in which the ratio of AEA and HPMCP was varied, onto the HPC film. Figures 4a, b and c show the release of drug from these double-layered films at pH 1, 5 and 7 respectively. For double-layered HPC and AEA films, there was no release at pH 7, since only a very small amount of AEA is dissolved in solutions at this pH values as shown in Fig. 2. As this is a double-layered film, the release profile has a lag time at pH 1 and 5. In the case of HPC and HPMCP double-layered films, drug release did not occur at lower pH values. When

TABLE I. Apparent Release Rate Constants (k_a) and Lag Times (t_{lag}) Obtained from Double Layered Films

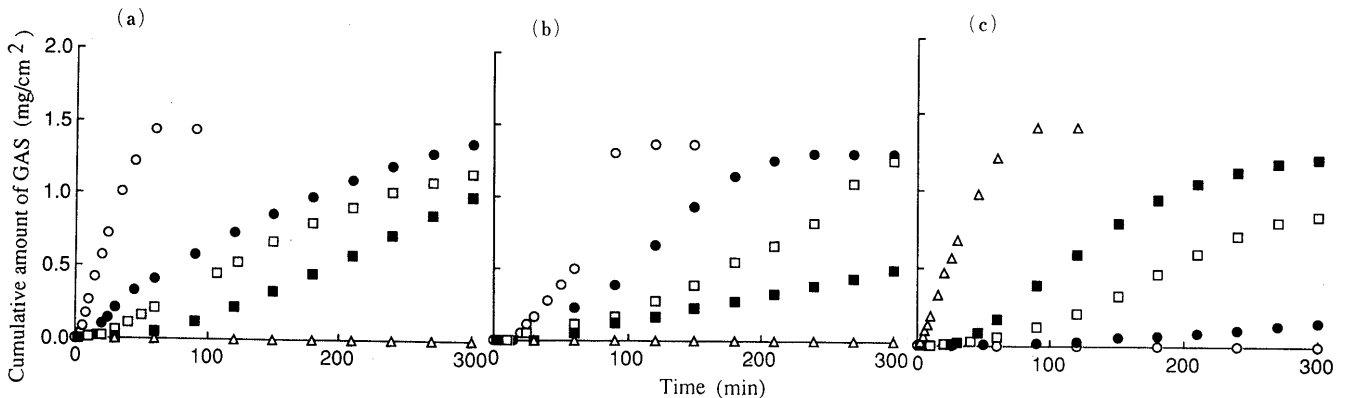| Ratio of AEA/HPMCP	k_a ($\times 10^{-2}\,mg\,cm^{-2}\,min^{-1}$)	t_{lag} (min)
	pH = 1.0	
1/0	2.93	1.5
2/1	0.74	6.2
1/1	0.49	16.4
1/2	0.38	57.3
0/1	0.0	0.0
	pH = 5.0	
1/0	1.10	15.0
2/1	0.74	31.5
1/1	0.44	56.8
1/2	0.18	25.2
0/1	0.0	0.0
	pH = 7.0	
1/0	0.0	0.0
2/1	0.06	57.8
1/1	0.38	56.4
1/2	0.61	27.4
0/1	2.30	1.2

Fig. 4. Release Profiles of GAS from Double-Layered Films
(a) pH 1.0, (b) pH 5.0, (c) pH 7.0. ○, AEA:HPMCP=1:0; ●, AEA:HPMCP=2:1; □, AEA:HPMCP=1:1; ■, AEA:HPMCP=1:2; △, AEA:HPMCP=0:1.
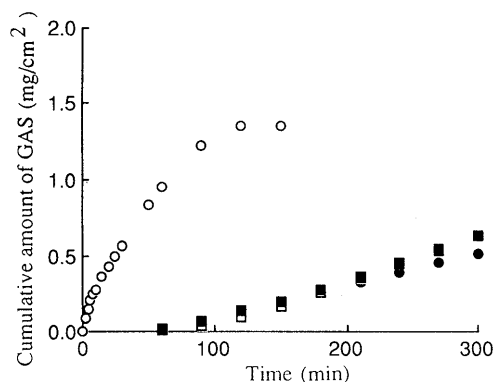
Fig. 5. Release Profiles of GAS from Single-Layered and Double-Layered Films in Artificial Saliva

○, HPC; ●, AEA:HPMCP=2:1; □, AEA:HPMCP=1:1; ■, AEA:HPMCP=1:2.

TABLE II. Apparent Release Rate Constants (k_a) and Lag Times (t_{lag}) Obtained from Fig. 5

Ratio of AEA/HPMCP	k_a ($\times 10^{-2}\,\mathrm{mg\,cm^{-2}\,min^{-1}}$)	t_{lag} (min)
HPC single layered film	1.36	0.0
2/1	0.22	62.7
1/1	0.29	86.2
1/2	0.28	73.2

the double-layered film contained a much greater amount of AEA than of HPMCP, drug release was high at lower pH values, but when the amount of HPMCP was much greater than that of AEA, drug release was high at higher pH values. These drug release profiles had a lag time and zero-order release. The zero-order relationship would be expected to break down before total drug release when the reservoir layer is no longer able to sustain C_s at the interface of the two layers. The apparent release rate constants, k_a and lag time, t_{lag} at steady state obtained from double-layered films are shown in Table I.

As shown in Table I, the apparent release rates were affected by the AEA–HPMCP ratio in the membrane layer. Increasing the AEA concentration from 0 to 100% increased the apparent release rate constant, k_a for pH 1 and 5. The other hand, k_a decreased with an increase in concentration of AEA in the membrane layer.

The lag times which showed a maximum value at the AEA–HPMCP ratio are 1/2, 1/1 and 2/1 for pH 1, 5 and 7 respectively.

We also examined drug release from double-layered films in artificial saliva, as shown in Fig. 5. The apparent release rate constants and lag time at steady state obtained from single-layered film and double-layered films for artificial saliva are shown in Table II.

The double-layered films containing a mixture of AEA and HPMCP showed a sustained release pattern and had a lag time, but no difference was observed between the drug release patterns of these various double-layered films. It was assumed that the release of GAS from these films was due to the inorganic ions present in artificial saliva and their influence on macromolecular electrolytes, and also to the very low solubility of AEA and HPMCP at pH 5.5.

These results suggest the possibility of sustained drug release from double-layered films; changing the macromolecular composites of the outer film layer offers the possibility of tailoring these films for particular drugs.

References and Notes

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