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Sustained Release of Theophylline from Hydroxypropylcellulose Tablets

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Abstract □ Compressed tablets were prepared from theophylline and hydroxypropylcellulose. Effects of the viscosity grades of the polymer, the mixing ratios of two polymers with different viscosity grades, and the polymer contents in the tablets on release patterns of theophylline were examined *in vitro*. Release rate was decreased with increasing viscosity designation and polymer contents in the tablets. In salivary level profiles of theophylline following oral administration of sustained-release tablets to five human volunteers, a low but sustained level was noted indicating sustained release of the drug from the tablets *in vivo*.

Keyphrases □ Theophylline—hydroxypropylcellulose tablets □ Hydroxypropylcellulose—viscosity grades, mixing ratio, contents □ Compressed tablets—sustained release *in vitro*, oral administration □ Salivary levels—reverse-phase high-performance liquid chromatography

Since most of the commercially available water-soluble cellulose derivatives (1) are considered to be stable against microbial attack and safe when ingested orally, it appeared to be worthwhile to evaluate them as suitable materials for sustained-release preparations.

Although several studies have reported the sustained release of drugs from compressed hydrophilic matrices prepared from cellulose derivatives (2–8), few have examined the relationship between release rates *in vitro* and drug concentration profiles in body fluids (7).

Following the examination of representative viscosity grade polymers of methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, and hydroxypropylcellulose, hydroxypropylcellulose was selected for further studies, since it exhibited release patterns suitable for a sustained-release preparation.

In the present study, modification of the release rate of theophylline from compressed hydroxypropylcellulose tablets was examined by changing viscosity grades of the polymer, mixing ratios of two polymers with different viscosity grades, and changing polymer contents in the tablets. Theophylline was used as a representative drug, since sustained-release formulations are desirable because of the short elimination half-life in humans, especially in children (9). To evaluate body fluid level profiles of theophylline in volunteers, saliva levels were measured, since correlation of serum and saliva theophylline concentrations after administration of a sustained-release preparation has been reported (10).

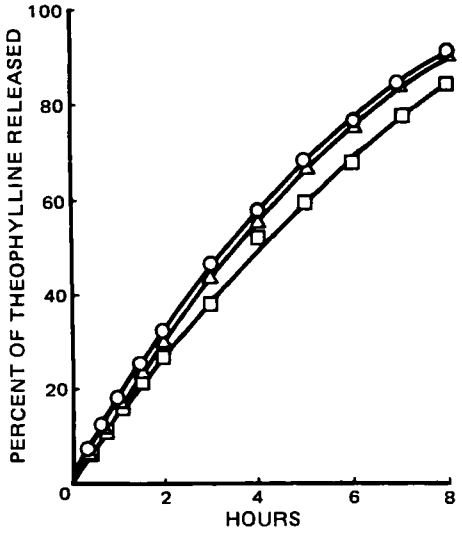

Figure 1—*Release profiles of theophylline from tablets prepared from 1:1 mixture of theophylline (250 mg) and hydroxyproylcellulose (1:1 mixture of low- and medium-viscosity grades) by compressing the drug–polymer mixture for 5 sec (○), 30 sec (△), or 120 sec (□). Average of three determinations.*

EXPERIMENTAL

Materials—Three viscosity grades of hydroxypropylcellulose[1] were used. Theophylline (anhydrous) and 7-(2-hydroxyethyl)theophylline were used as supplied [2]; and all other chemicals were of reagent grade.

Preparation of Tablets—Flat-faced tablets (500 mg, 13-mm diameter, and ~3-mm thickness) were prepared by compressing mixtures of theophylline and hydroxypropylcellulose directly under 180 kg/cm^2 for 30 sec using a potassium bromide tablet die and a hydraulic press[3].

To examine the effect of compression pressure on drug release, pressures of 60, 180, or 540 kg/cm^2 were applied to the drug–polymer mixture for 30 sec. To examine the effect of compression periods on drug release, a compression pressure of 180 kg/cm^2 was applied to the drug–polymer mixture for 5, 30, or 120 sec.

Release Studies—A tablet was suspended by means of a polyethylene net in a 200-ml release medium in a wide-mouthed bottle. Since the release rate of theophylline from hydroxypropylcellulose tablets is not very dependent on the pH values of the medium, a 0.2% NaCl solution, ad-

[1] HPC-L, M, and H from Nihon Soda Co., Tokyo. Viscosity ranges of 2% aqueous solutions at 20° are 6–10, 150–400 and 1000–4000 cps, respectively.
[2] Tokyo Kasei Kogyo Co., Tokyo.
[3] Shimadzu potassium bromide press, Shimadzu Manufacturing Co., Kyoto.

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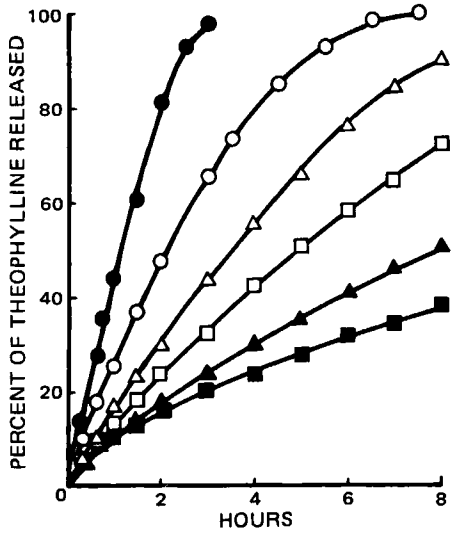

Figure 2—*Release profiles of theophylline from tablets prepared from 1:1 mixture of theophylline (250 mg) and hydroxypropylcellulose of various compositions. Average of three determinations. Key: Viscosity grades of the polymer: (●) low; (▲) medium; (■) high-viscosity grade polymer, and (○) (3:1) (△), 1:1, and (□) 1:2 mixtures of low- and medium-viscosity grade polymers.*

justed to pH 1.2 was used as a release medium. The medium was kept at 37° and stirred with a magnetic stirrer. At predetermined intervals, 1-ml portions of the medium were pipetted for the spectrophotometric determination of the theophylline concentration at 272 nm after dilution with 0.2 *M* acetate buffer, pH 5.0.

Measurement of Salivary Levels in Human Volunteers—Five healthy volunteers, two males and three females (23–31 years of age), participated in the study. To eliminate ingestion of theophylline from other sources and possible formation of theophylline *in vivo* following intake of caffeine (11), the subjects were told to abstain from any drinks containing caffeine. Blank saliva samples were collected a few minutes before administering the preparation. After overnight fasting, a single 250-mg dose of theophylline powder (as a fast-dissolving preparation) or a hydroxypropylcellulose tablet (as a sustained-release preparation) containing the same amount of the drug was administered, with 100-ml water, wrapped in a wafer sheet to eliminate possible contact of the drug with mucosa of the mouth. Saliva samples were collected at appropriate intervals up to 24 hr. A small amount (~10 mg) of citric acid, a salivary flow stimulant, was put on the tongue and held in the mouth for 1–2 min, then a 2-ml sample of the saliva was collected in a test tube and kept frozen until analysis. No food was taken for 4 hr postdose. A crossover design was used and a minimum interval of 1 week was allowed between trials.

Analysis of Theophylline Levels in Saliva—Reverse-phase high-performance liquid chromatography for theophylline in saliva (12) was employed using 7-(2-hydroxyethyl)theophylline as an internal standard. A liquid chromatograph[4] equipped with UV detector set at 270 nm and a reverse-phase-type column (Zorbax ODS, 4.6 ϕ × 0.25 m) was used.

RESULTS AND DISCUSSION

Effect of Compression Pressure and Compression Period on Drug Release—Figure 1 shows the release patterns of theophylline from tablets prepared by compressing the drug–polymer mixture for various periods. Only a slight decrease in release rate was observed with 6- and 24-fold increases in compression period.

In the examination of the effect of compression pressure on release rate, three pressure levels covering a ninefold change in pressure were applied to the mixture. Release patterns (not shown) of theophylline from tablets thus prepared were practically superimposable. Thus, compression pressure and compression period are not important factors in modifying the release pattern of the drug.

Effect of Viscosity Grades of the Polymer—Figure 2 shows the release patterns of theophylline from tablets with 250 mg of theophylline and 250 mg of one of three viscosity grades of hydroxypropylcellulose.

[4] Model LC-3A, Shimadzu Manufacturing Co., Kyoto.

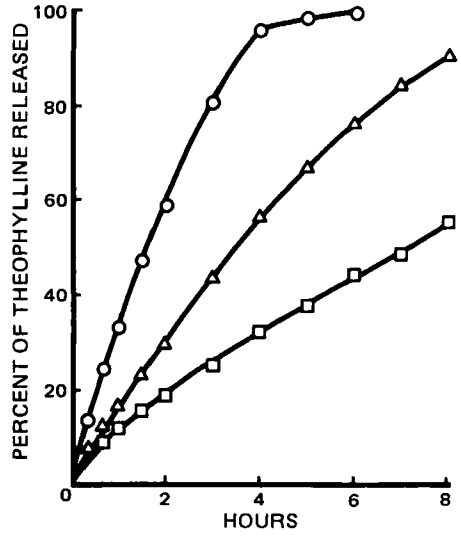

Figure 3—*Release profiles of theophylline from tablets prepared from (○) 1:1/3, (△) 1:1 and (□) 1:3 mixtures of theophylline (250 mg) and hydroxypropylcellulose (1:1 mixture of low- and medium-viscosity grade polymers). Average of three determinations.*

The drug release rate was fast from the tablets made of the low-viscosity grade polymer, while the release rate was slow from tablets made of the polymers of medium- and high-viscosity grades. Therefore, tablets made from mixtures of low-viscosity grade polymer and medium-viscosity grade polymer in the mixing ratios, as shown in Fig. 2, were examined to obtain an appropriate release rate. With an increase in the contents of the medium-viscosity grade polymer, the release rate was decreased. Therefore, the drug release rate can be modified by changing the mixing ratio of two polymers with different viscosity grades depending on the required sustained period.

To examine a release mechanism of theophylline from compressed hydrophilic tablets, the amount of the drug released was plotted (not shown) against square root of time according to the Higuchi equation (13). The lines obtained were upward curves, indicating a different release mechanism from that expected from the Higuchi equation for release of drug from solid matrices. The tablet expanded as water penetrated forming a layer of gel on the surface of the tablet, but it gradually eroded afterward. Thus the following processes are likely to operate: penetration of water through matrices to form a gel in the outer layer, dissolution of a drug in the gel, permeation of the drug through the gel, release of the drug from the gel to a release medium, and slow dissolution of the gelled polymer in the outermost layer in the release medium.

Effect of Polymer Contents—Figure 3 shows the release patterns of theophylline from three tablets containing the same amount of the drug

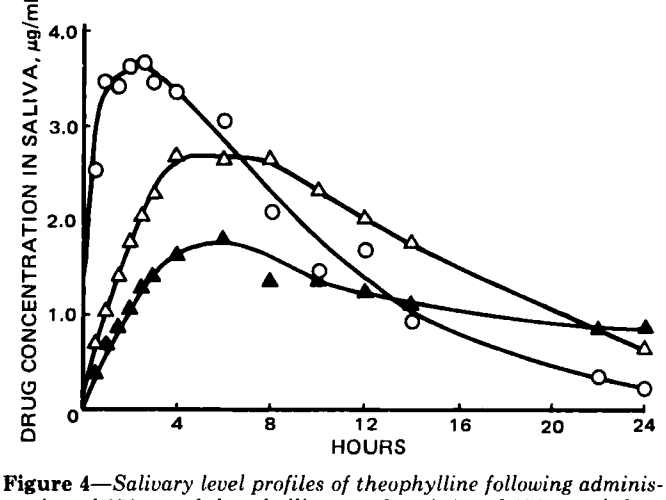

Figure 4—*Salivary level profiles of theophylline following administration of 250 mg of theophylline powders (○) and 250 mg of theophylline–250 mg of hydroxypropylcellulose [1:1 mixture of low- and medium-grade polymers (△) or medium-viscosity grade polymer alone (▲)] tablets to volunteers. Average of five subjects.*

but different amounts of the polymer. The polymer mixture used in the test was a 1:1 mixture of the low-viscosity grade polymer and the medium-viscosity grade polymer. As expected, the drug was released from tablets more slowly with an increase in polymer contents; therefore, the release rate of the drug can be modified by changing the polymer contents in the tablets.

Salivary Levels Following Oral Administration—In Fig. 4, the average salivary levels of theophylline following oral administration of two kinds of sustained-release tablets were compared with those of fast-dissolving powders. After the administration of the tablets, salivary levels were lower at earlier hours but higher afterward compared with salivary levels following administration of powders. The lowest salivary levels observed after administration of the tablet prepared from the medium-viscosity grade polymer reflect a slow release rate, as shown in Fig. 2, demonstrating that different drug level profiles in body fluids are obtainable by modifying the release patterns of drug. Although it is shown that the rate of bioavailability is decreased with a decrease in release rate *in vitro*, the effect of release rate on the extent of bioavailability has to be examined by extending sampling periods to 36–48 hr.

The present study demonstrated that the release of theophylline from compressed tablets prepared from hydroxypropylcellulose can be modified by changing viscosity grades of the polymer, mixing ratios of two polymers with different viscosity grades, and changing polymer contents in the tablets. Sustained-release *in vitro* is reflected in drug level curves after oral administration of sustained-release tablets.

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Characterization of Spray Patterns of Inhalation Aerosols Using Thin-Layer Chromatography

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Abstract □ The spray pattern of an inhalation aerosol was characterized using photography and by observing the impaction pattern on a TLC plate. The aerosol plume was conical in shape, and its cross section increased with increasing distance from the actuator. Three puffs of the aerosol, at a distance of 3 cm between actuator and the TLC plate, produced a spot that had approximately the same diameter as the cross section of the aerosol plume at that distance from the actuator. The TLC technique with these parameters was selected to develop an assay characterizing the spray pattern of an inhalation aerosol because of its specificity, simplicity, and speed.

Keyphrases □ Aerosols, inhalation—spray pattern characterizations using photography and TLC □ TLC—characterization of spray patterns for inhalation aerosols □ Spray patterns—of inhalation aerosols, characterized by TLC and photography

Pressurized inhalation aerosols are generally used for drug administration into the lower respiratory tract. Only a minor part of the dose administered reaches the lung directly (1–3). Recently, using an *in vivo* radioactive technique, it was estimated directly that an average 8.8% of the administered dose was deposited in the lungs with 80% deposited in the mouth (4). The remainder of the drug (9.8%) was either exhaled or deposited in the aerosol actuator. Various test methods for the control of aerosol products have been developed (5–7). These include tests for net contents, medication delivered per dose, particle size distribution, valve delivery, vapor pressure, leakage rate, moisture contents, and spray pattern.

One of the important objectives in developing an aerosol product is to obtain the spray pattern best suited for the intended application. Various factors can affect the spray pattern. These factors are the design of the valve and the actuator, the pressure in the container, and its content composition (8, 9). The spray pattern is affected by the size and shape of the actuator orifice as well as by the valve (10). Therefore, characterization of spray patterns is important for evaluating the valve and actuator performances. In addition to its pattern, other tests generally used to characterize the spray are particle size distribution of the drug substance delivered and spray angle (11).

Several methods have been devised to record and compare the spray pattern of aerosol products. One method is based on the impingement of the spray on a piece of paper, glass, silica gel, or paper that has been treated with a dye–talc mixture (12, 13). Photographic (14) and laser holographic[1] methods also have been used. Miszuk *et al.* (15) recently described a technique that utilizes two orthogonal video images. These methods are best suited for solution aerosols in which the active ingredient is dissolved

[1] Laser Photographic Laboratories, Arlington Heights, Ill.

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