Utility of Mixture of Commercially Available Polymers as Constituents of Sustained-Release Microcapsules Containing Cefadroxil or Theophylline[1)]

Takahiro UCHIDA,* Takuji YASUTAKE and Shigeru GOTO

Faculty of Pharmaceutical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812, Japan. *Received July 2, 1991*

Hydroxy propyl methyl cellulose acetate succinate high grade (AS-HG) and ethyl cellulose (EC) mixture microcapsules containing cefadroxil or theophylline were prepared by a solvent evaporation method in liquid paraffin dissolved sorbitan tristearate as a dispersing agent, and their sustained-release properties were evaluated. The microcapsules prepared with AS-HG : EC (in a 2 : 5 weight ratio) mixture containing 20% of cefadroxil or theophylline exhibited apparent zero-order releasing pattern in pH 6 to 8, at 50 rpm and 37 °C (paddle method). These microcapsules were administered orally to beagle dogs and the plasma concentrations of cefadroxil or theophylline were measured periodically. As a result of *in vivo* investigation, a satisfactory sustained-release plasma pattern and an apparent zero-order process in the gastrointestinal absorption were confirmed by deconvolution analysis of both drugs.

Keywords microencapsulation; cafadroxil; theophylline; ethyl cellulose; hydroxy propyl methyl cellulose acetate succinate; sustained-release; zero-order process; beagle dog

Intense interest has been shown recently in the development of multiple-particulate sustained and controlled-release systems. In our search for these systems, we have investigated the microencapsulation of orally active drugs using commercially available polymers.[2)] Piretanide, a diuretic acting on the loop of Henle, was previously microencapsulated by a hydroxy propyl cellulose and ethyl cellulose (EC) mixture, and the evidence of sustained-release was obtained from pharmacokinetic and pharmacodynamic aspects using beagle dogs.[3)]

In the present investigation, cefadroxil and theophylline were adopted as model compounds. Cefadroxil, an oral cephem antibiotic, has been used in the treatment of various infectious diseases, but frequent administration is essential because of its rapid elimination from the body. A sustained-release preparation of cefadroxil therefore seemed advantageous. A sustained-release preparation of theophylline as an antiasthmatic agent was also thought to be beneficial in order to avoid its severe side effect in clinical therapy.

The purpose of the present study was to investigate the advantage of mixture of commercially available polymers for microencapsulation of cefadroxil or theophylline and thereby obtain pharmacological improvement.

Experimental

Materials Hydroxy propyl methyl cellulose acetate succinate (three grades of AS: AS-HG, AS-MG and AS-LG) and hydroxy propyl methyl cellulose phthalate (two grades of HP: HP-55 and HP-55S) were kindly supplied by Shin-etsu Chemical Co., Tokyo, Japan. Cefadroxil was provided by Towa Pharmaceutical Co., Osaka, Japan. Theophylline and EC (100 cps grade) were purchased from Tokyo Kasei Co., Tokyo, Japan. All drug powders used were passed through a 270 mesh (53 μm). Other reagents were all of special reagent grade.

Preparation of AS-HG and EC Mixture Microcapsules A solvent evaporation process in liquid paraffin containing sorbitan tristearate as a dispersing agent was employed as described previously.[4)]

Dissolution Experiments The procedure and the apparatus were the same as described.[4)] Microcapsules corresponding to 10 mg of drug powder were used in the dissolution experiment and dissolved cefadroxil or theophylline was analysed for drug concentration using high performance liquid chromatography (HPLC).

Electron Scanning Microscopy The microcapsules were coated with pure gold using an Eiko engineering coater 1B-3 type under a high vacuum (0.1 Torr) and at high voltage (800—1500 V) and 8 mA. The microcapsules obtained by this procedure were examined with a scanning electron microscope (Hitachi S 510, Tokyo, Japan) at 25 kV.

Animals Male beagle dogs weighing 14.5—16.1 kg were fasted overnight and used for the experiments. They were allowed free access to water, but no food was given until the last blood sample had been taken.

Single Intravenous Administration Cefadroxil (125 mg) dissolved in 0.3 ml of 1 N NaOH and 5 ml of isotonic NaCl solution, or aminophylline for injection solution (5 ml, 20 mg/ml potency, Eisai Co., Tokyo, Japan) were administered intravenously *via* the cephalic vein. Blood samples were withdrawn from the cephalic vein with a heparinized syringe up to 12 h after the administration, and the collected blood was centrifuged at 3000 rpm for 15 min to obtain the plasma.

Oral Administration Special hard gelatin capsules (1/80 oz, J type, Kasho Co., Tokyo, Japan) were filled with drug powders or microcapsules. Double oral administrations of cefadroxil powder (125 mg × 2) at 0 and 6 h, and single oral administration of microcapsules corresponding to 250 mg of cefadroxil at 0 h, were made with 30 ml of water. For the preparations of theophylline, two commercially available sustained-release tablets, Theodur[5)] and Theolong,[6)] theophylline powder and AS-HG and EC mixture microcapsules containing theophylline were used. Single oral administrations of these preparations corresponding to 200 mg of theophylline at 0 h were made with 30 ml of water.

Measurement of Plasma Level of Cefadroxil or Theophylline The plasma concentration of cefadroxil was determined by the reported procedure,[4)] and the plasma theophylline concentration was determined by HPLC which modified Kester's method[7)] as follows: To 1 ml of plasma, 20 μl of the internal standard (1 mg/ml cephalexin solution) and 1 ml of 10% trichloroacetic acid were added, and mixed by shaking for 15 min. After centrifugation at 3000 rpm for 15 min, 1 ml of the upper layer was taken. One hundred μl of this layer was injected into the HPLC apparatus (Shimadzu LC-6A, Kyoto, Japan) equipped with ultraviolet detector (Shimadzu SPD-6A), an integrator (Shimadzu C-R6A) and reversed-phase octadecyl silica column (6.0 × 150 mm, Shim-pack CLC-ODS). The mobile phase employed was acetonitrile : sodium acetate (10 mM): acetic acid (180 : 2500 : 7) and the flow rate was 2.0 ml/min. The wavelength of 270 nm was selected. Column temperature was maintained at 40 °C.

Pharmacokinetic Analysis The deconvolution[8)] program established by Hanano[9)] was adopted and % of cumulative drug absorbed was calculated based on the data obtained after oral and intravenous administrations.

Results and Discussion

Dissolution of Cefadroxil or Theophylline from Hydroxy Propyl Methyl Cellulose Phthalate and Hydroxy Propyl Methyl Cellulose Acetate Succinate Microcapsules, and These Polymers and EC Mixture Microcapsules Figure 1 shows the dissolution patterns of cefadroxil from microcapsules prepared using two types of hydroxy propyl methyl cellulose phthalate (HP-55 and HP-55S) and three types of hydroxy propyl methyl cellulose acetate succinate (AS-LG, AS-MG, and AS-HG) in pH 6.8 phosphate buffer at 37 °C, and rotation speed of 50 rpm (paddle method).

However, the dissolution rates were very fast in all cases and their patterns were found to have failed to anticipate the constant release and the sustained-release of cafadroxil.

To obtain the constant release characteristics of cefadroxil, the incorporation of EC into hydroxypropyl and acetate succinate was examined. Although many microencapsulation trials using various combination ratios of EC to enteric polymers were repeated, the combination of AS-HG and EC led exclusively to the production of the satisfactory microcapsules as summarized in Table I.

Microcapsules prepared with different weight ratios of AS-HG and EC and containing 20% cefadroxil or theophylline were prepared successfully and without drug loss during the process as shown in Table II. Typical scanning electron micrographs of an AS-HG and EC mixture microcapsule containing 20% of drug are illustrated in Fig. 2, and it is obvious that the microcapsule was spherical and its surface almost smooth.

Figures 3 and 4 show dissolution patterns of cefadroxil or theophylline from microcapsules prepared with different weight ratios of AS-HG and EC, in pH 6.8 at 37 °C, and rotation speed of 50 rpm. The dissolution rates of both drugs increased with the decrease in EC contents in supported materials of microcapsules. In these dissolution patterns, the AS-HG and EC mixture (2 : 5 weight ratio) microcapsule showed constant dissolution rates of cefadroxil over 0—3 h and of theophylline over 0—4 h. Constant dissolution rates were also obtained in pH 6.0 and 8.0 at 37 °C and 50 rpm.

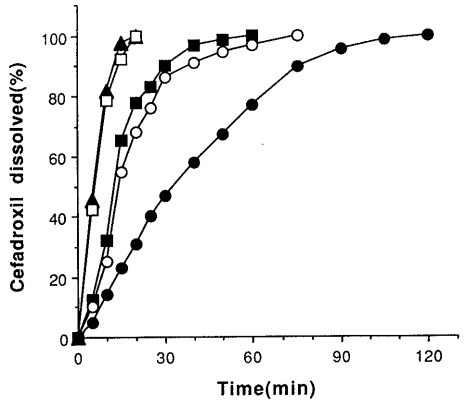


Fig. 1. Dissolution Curves of Cefadroxil from HP-55 (▲), HP-55S (□), AS-LG (■), AS-MG (○), and AS-HG (●) Microcapsules Containing 20% of Cefadroxil at 37 °C, 50 rpm and pH 6.8

***In Vivo* Evaluation of AS-HG and EC Mixture Microcapsules Containing Cefadroxil or Theophylline** The AS-HG : EC mixture (1 : 1) microcapsule was a failure, that is, the maximum plasma concentration of cefadroxil was larger than that of the first dosing of powder, and the slope of the declining phase was almost the same as that of the powder. This suggested that the absorption rate was uncontrollable. On the other hand, the plasma cefadroxil level after a single oral administration of an AS-HG : EC mixture (1 : 4) microcapsule remained at a lower level and showed more incomplete absorption than other preparations. Among the three preparations, the AS-HG : EC mixture (2 : 5) microcapsule showed the most favorable sustained-release property.

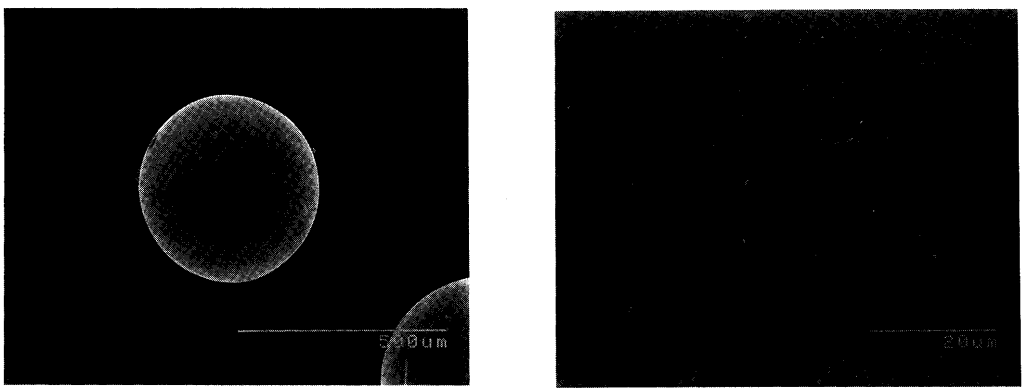
Table I. Possibility of Preparation of Several Commercially Available Enteric Polymers and EC Mixture Microcapsules

Enteric polymer : EC	Enteric polymer				
	HP-55	HP-55S	AS-LG	AS-MG	AS-HG
1 : 1	—	—	○	○	○
1 : 2	—	—	△	○	○
2 : 5	—	—	—	△	○
1 : 3	—	—	—	—	○
1 : 4	—	—	—	—	○

○, possible to prepare (completely); △, possible to prepare (not completely); —, impossible to prepare.

Table II. Components, Stirring Rates with the Propeller for Preparation of AS-HG and EC Mixture Microcapsules Using the Solvent Evaporation Process in Liquid Paraffin, Yield and Contents of Cefadroxil or Theophylline in Products

		Treatment No.				
		1	2	3	4	5
AS-HG (g)		3.0	2.0	1.71	1.5	1.2
EC (g)		3.0	4.0	4.29	4.5	4.8
Drug (g)		1.5	1.5	1.5	1.5	1.5
Stirring rate (rpm)		200	220	220	220	220
Yield (%)	Cefadroxil	92	91	88	90	92
	Theophylline	90	87	93	92	91
Drug content (%)	Cefadroxil	19.6	20.2	20.6	20.2	19.5
	Theophylline	20.1	19.5	20.1	19.4	19.7



×60 ×1500

Fig. 2. Scanning Electron Micrograph of AS-HG and EC Mixture (Weight Ratio 2 : 5) Microcapsule Containing 20% of Cefadroxil

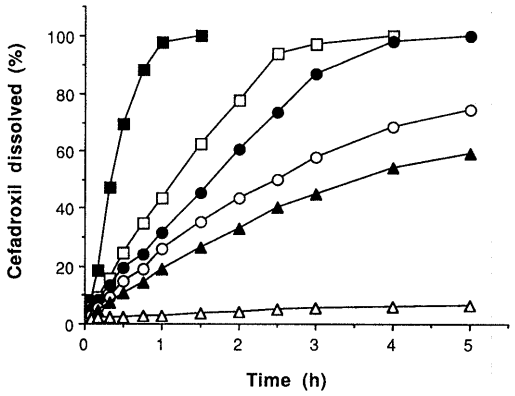


Fig. 3. Dissolution Curves of Cefadroxil from Various AS-HG and EC Mixture Microcapsules (Weight Ratio: 1:1, ■; 1:2, □; 2:5, ●; 1:3, ○; 1:4, ▲; 0:1, △) Containing 20% of Cefadroxil at 37°C, 50 rpm and pH 6.8

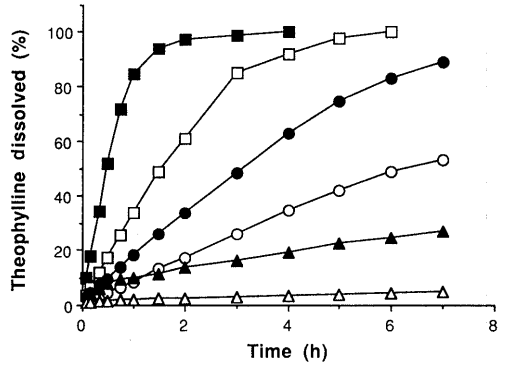


Fig. 4. Dissolution Curves of Theophylline from Various AS-HG and EC Mixture Microcapsules (Weight Ratio: 1:1, ■; 1:2, □; 2:5, ●; 1:3, ○; 1:4, ▲; 0:1, △) Containing 20% of Theophylline at 37°C, 50 rpm and pH 6.8

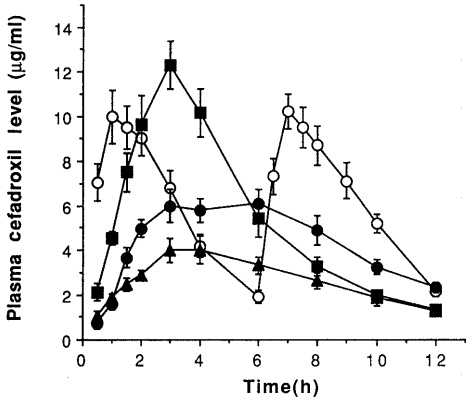


Fig. 5. Plasma Cefadroxil Level after a Single Oral Administration of AS-HG and EC Mixture Microcapsules (Weight Ratio: 1:1, ■; 2:5, ●; 1:4, ▲) Containing 250 mg and Double Oral Administration of 125 mg of Cefadroxil Powder (○) in Beagle Dogs

Each point represents a mean of four beagle dogs and vertical lines indicate the standard deviation.

In order to obtain a more precise pharmacokinetic index related to the absorption rate and extent of bioavailability, an analysis was made by the deconvolution method. The absorption process may be complicated as stated above, however, the deconvolution method seems advantageous for estimating properties of absorption process. The results of cumulative absorption %–time curves are shown in Fig.

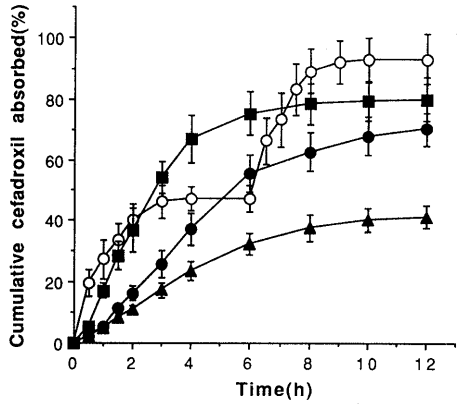


Fig. 6. Cumulative Absorbed %–Time Plots after a Single Oral Administration of AS-HG and EC Mixture Microcapsules (Weight Ratio: 1:1, ■; 2:5, ●; 1:4, ▲) Containing 250 mg of Cefadroxil and Double Oral Administration of 125 mg of Cefadroxil Powder (○) in Beagle Dogs using Deconvolution Method

Each point represents a mean of four experiments and vertical lines indicate the standard deviation. The calculation was undertaken based on plasma concentration data obtained after intravenous injection and is represented by the following equation: $C_{i.v.} = 17.73 \times \exp(-0.525 \times t) + 28.50 \times \exp(-7.02 \times t)$

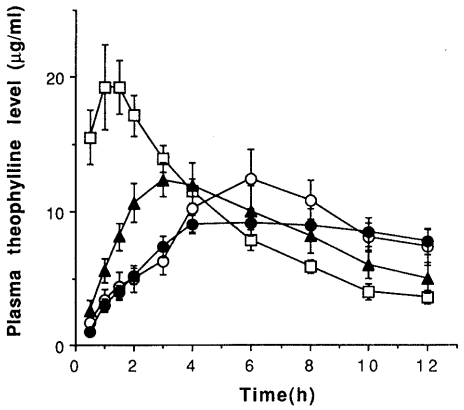


Fig. 7. Plasma Theophylline Levels after a Single Oral Administration of AS-HG of EC Mixture Microcapsule (Weight Ratio: 2:5, ●) Containing 200 mg of Theophylline, Theodur (○), Theolong (▲), and Theophylline Powder (□) in Beagle Dogs (200 mg/Body)

Each point represents a mean of four beagle dogs and vertical lines indicate the standard deviation.

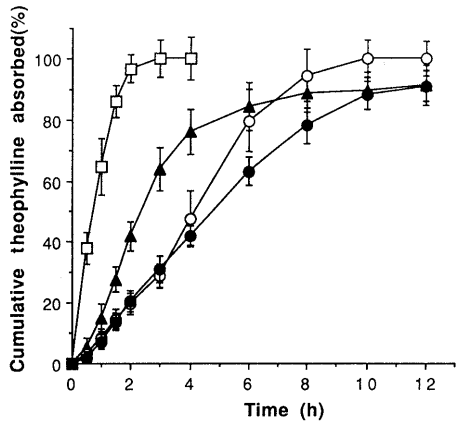


Fig. 8. Cumulative Absorbed %–Time Plots after a Single Oral Administration of AS-HG and EC Mixture Microcapsule (Weight Ratio: 2:5, ●) Containing 200 mg Theophylline, Theodur (○), Theolong (▲), and Theophylline Powder (□) in Beagle Dogs (200 mg/Body) Using Deconvolution Method

Each point represents a mean of four experiments and vertical lines indicate the standard deviation. The calculation was undertaken based on plasma concentration data obtained after intravenous injection and is represented by the following equation: $C_{i.v.} = 19.07 \times \exp(-0.14 \times t) + 127.52 \times \exp(-11.69 \times t)$

6. In the case of the AS-HG : EC mixture (2 : 5) microcapsule containing 20% cefadroxil especially, zero-order absorption was lengthened to 6 h. This may be closely related with the *in vitro* zero-order dissolution pattern of the drug.

To avoid severe side effects and achieve maximum therapeutic benefit, the plasma concentration should be precisely maintained within a narrow range. Sustained-release preparations of theophylline are thus very useful for maintenance therapy in chronic obstructive lung diseases.[10] The plasma theophylline level obtained after a single oral administration of theophylline powder in a conventional dosage form, AS-HG : EC mixture (2 : 5) microcapsule, and commercially available sustained-release preparations, Theodur and Theolong, are illustrated in Fig. 7. The microcapsule containing 20% theophylline showed the most favorable sustained-release pattern. The deconvolution analysis is shown in Fig. 8, and the absorption rate of theophylline in the AS-HG : EC mixture (2 : 5) microcapsule was maintained at a constant level up to 8 h, with the extent of absorption of the drug being almost the same as that of Theodur or Theolong. It is therefore obvious from several *in vitro* and *in vivo* evaluations that the AS-HG : EC mixture (2 : 5) microcapsule has desirable sustained-release properties. In future studies, we will examine whether a desirable sustained-release profile can also be obtained using AS-HG : EC mixture (2 : 5) microcapsules containing other drugs.

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References and Notes

1) This paper forms Part XXX of a series entitled "Evaluation of Microcapsules."
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