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Preparation of Furosemide Retard Tablets Using Hydroxyethylcellulose as Matrix Forming Material

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히드록시에칠셀룰로오스를 겔상 메트릭스로 사용한 서방성 푸로세미드정제의 제조

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Furosemide retard tablets were prepared using hydroxyethylcellulose(HEC) as a matrix material. Dissolution of furosemide from this tablet was retarded significantly comparing with conventional tablets and greatly dependent on HEC concentration and pH of the dissolution medium. The mechanism of retarded release was supposed to be due to HEC gel formation and drug diffusion through the gel matrix.

Furosemide is one of a series of anthranilic acid derivatives which is commonly used as a potent diuretic, the major use of which is in acute or chronic renal failure, congestive heart failure and liver cirrhosis[1-3]. Regardless of chemical structure and mechanism of action, diuretic agents produce an antihypertensive effect in proportion to their diuretic and saluretic activity[4-5]. In the treatment of hypertension, diuretics are used in combination with other hypotonic agents and its treatment has often to be carried out over several months[6-8]. In this case, short and potent diuretic action of furosemide causes the rapid onset of the effect of furosemide immediately after administration, which always means the intensified diuresis to the patient. It is therefore desirable to modify the activity of furosemide by means of suitable preparation which prevents an undesired diuresis peak over a prolonged period of time[9-12].

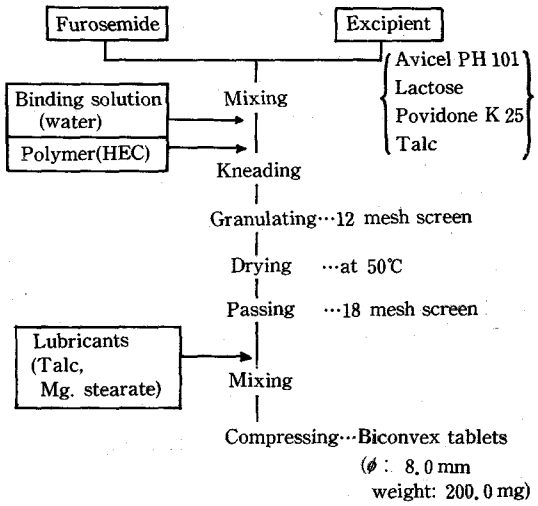
This study was designed to develop a suitable preparation having a desired release, the manufacturing method of which was not so difficult as those reported[9-12]

Hydroxyethylcellulose(HEC) or hydroxypropylmethylcellulose(HPMC) was used as a matrix material in our study since they provided a sustained release properties over a reasonable length of time[13-15].

EXPERIMENTAL

Raw Materials and Reagents

Furosemide was provided from Han Dok Remedia Ind., Korea, and other raw materials used were of pharmaceutical grade. The reagents and solvents in this work were of reagent grade.



Scheme 1—Preparation of furosemide retard tablets by wet granulation method.

Apparatus

Single punch machine(Manesty), impact fine mill(Alpine), UV visible spectrophotometer(Varian), hardness tester(Erweka), friability tester(Erweka), dissolution tester(Jasco), flow-through cell dissolution tester(Desaga), jolting volumeter(Jel) and test screening machine(Jel) were used.

Preparation of Tablets

The experimental tablets were prepared by wet granulation technique as shown in Scheme 1. The substances of furosemide, Avicel, lactose, povidone and talc were homogeneously mixed, kneaded with water, while adding HEC(EC, HPMC), and then processed into granules. Lubricants were evenly mixed with the granules. The mass was then compressed on a single punch machine into biconvex tablets having a diameter of 8mm and a final weight of ca. 200 mg. The hardness of tablets was in the range of 70-90 N.

Determination of Angle of Repose

Angle of repose was measured by dropping the material through vibrating screen above the horizontal plate, using controlled mechanical means.

Granule Distribution Analysis

Granule distribution was measured, using sieves with different mesh openings.

Compressibility Test

Compressibility was calculated by the following equation.

$$C=100(P-A)/P$$

where P is packed bulk density(Packed bulk density was measured using automatic tapping device. Tapping was made 100 times), and A is loose density.

Friability Test

Friability was measured by running the test tablets in the friability drum for 4 minutes at 25 rpm and then checking the weight loss.

Dissolution Test

The *in vitro* dissolution profiles of various retard tablet formulations were determined by the following two dissolution test methods.

Automated U.S.P. rotating basket method -900 m*l* of phosphate buffer(pH 5.8 or pH 6.8) or artificial gastric fluid(pH 1.2) was placed in the vessel, and the dissolution medium was equilibrated to 37±1℃. One tablet in the basket was placed in the apparatus and the apparatus was operated immediately at 50 rpm. Samples of 10 m*l* were taken at given time intervals. The same volume of the fluid removed was replaced with fresh buffer. Withdrawn samples were diluted with the buffer used to yield

Table I—*Composition of Experimental Tablets.*

Formula No.	Composition (mg/tab.)					
	Furosemide	HEC[1]	EC[2]	HPMC[3]	HPMC[4]	Excipient
Group I						
A-1	60.0	20.0	–	–	–	120.0
A-2	60.0	10.0	–	–	–	130.0
A-3	60.0	5.0	–	–	–	135.0
A-4	60.0	3.0	–	–	–	137.0
Group II						
B	60.0	–	20.0	–	–	120.0
C-1	60.0	–	–	20.0	–	120.0
C-2	60.0	–	–	–	20.0	120.0

[1] HEC: Natrosol 250 HHX, [2] EC 7 cps, [3] HPMC 50 cps, [4] HPMC 15 cps.

5-10 mg/m*l*, and then the absorbance was measured at the wavelength of ca. 277 nm, using a double beam spectrophotometer. As furosemide is sensitive to light, all samples were protected from light prior to analysis. In advance, a calibration curve was constructed over the range of 2.0-12.0 μg/m*l*(r>0.9999).

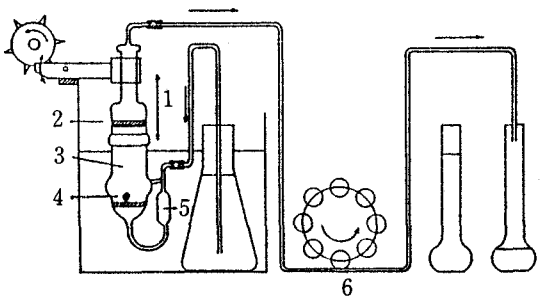
A cumulative correction was made for the previously removed samples in determining the total amount dissolved.

$$Cn.\ Corr = Cn.\ meas + \frac{10}{900}\sum_{s=1}^{n-1} Cs.\ meas \cdots \quad \text{Eq. 1}$$

were *Cn. meas* denotes the spectrophotometrically measured concentration, while *Cn.Corr* is the concentration of the n-th sample expected in the medium if previous samples had not been removed.

Flow-through dissolution cell method[16]-the dissolution studies were started in pH 1.2 artificial gastric fluid for one hour and continued for additional one hour in pH 5.5 phosphate buffer, and finally the dissolution medium was exchanged with pH 7.5 phosphate buffer. Desaga flow cell 147060 shown in Scheme 2 was used. The temperature and flow rate of the dissolution medium were maintained at 37±1℃ and 100 m*l*/hr, respectively.

After 1, 2 and 4 hours, each fraction was collected(Fraction I, II, III) and assayed spectrophotometrically. Samples of fraction I was diluted with methanol and the absorbance was measured at the wavelength of ca. 343 nm. Samples of fraction II and III were diluted with 0.1 N NaOH solution and the absorbance was measured at the wavelength of ca. 334 nm.



Scheme 2—Flow-through cell dissolution apparatus.

1, pendulum movement; 2, filtering device; 3, Desaga flow cell 147060 ; 4, test sample; 5, served as bubble trapping, 6, peristaltic pump.

Table II—*Physical Characteristics of the Tablets and Granules.*

Formula No.	Friability of tablets, %	Granules		Distribution, % (<0.3 mm) of diameter
		Repose Angle (°)	Compressibility	
A-1	0.07	40	14.6	25.0
A-2	0.11	38	14.6	28.8
A-3	0.12	41	16.9	35.0
A-4	0.09	40	15.9	37.8
B	0.19	40	15.7	23.4
C-1	0.20	39	15.0	24.0
C-2	0.17	40	14.7	25.2

RESULTS AND DISCUSSION

Physical Properties of Granules and Tablets

As shown in Table II, seven formulations didn't differ significantly in their physical properties. Very small values of friability (<1.0%) and compressibility (<20%) indicate that the tablets prepared are not susceptible to capping, laminating and bridge formation in the process of tableting.

Dissolution Behaviours

In consequence of furosemide solubility[17], the dissolution rate of furosemide formulation increased sharply with the increase of the pH.

Fig.1 shows that 10% of furosemide was dissolved at pH 1.2 buffer, 30% at pH 5.8 buffer, and 70% at pH 6.8 buffer after 10 hours from formula A-1, respectively.

Fig.2 shows that among cellulose derivatives, HEC retarded the release of furosemide .

Retarded release might be due to the formation of gel matrix in the dissolution medium[18].

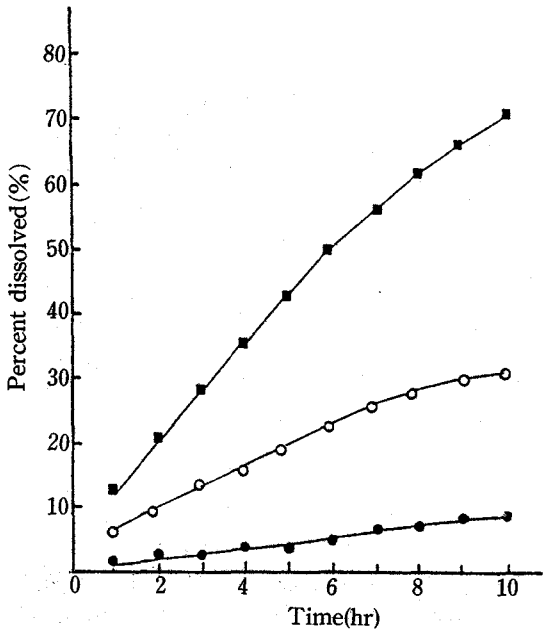


Figure 1—*In vitro* dissolution profiles of furosemide from formula No.A-1 in pH 1.2, 5.8 and 6.8 buffers at 37℃, using U.S.P. rotating basket apparatus at 50 rpm.
Key: ●, pH 1.2 buffer; ○, pH 5.8 buffer; ■, pH 6.8 buffer

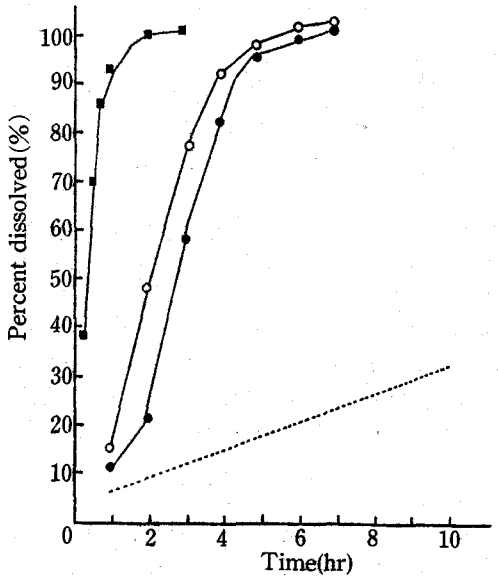


Figure 2—*In vitro* dissolution profiles of furosemide retard formulations in pH 5.8 phosphate buffer at 37℃, using U.S.P. rotating basket apparatus at 50 rpm.
Key: ···, Formula A-1; ●, Formula C-1; ○, Formula C-2; ■, Formula B.

On the other hand, the tablets formulated with EC or HPMC failed to form a gel and disintegrated rapidly in the dissolution medium. EC or HPMC of higher viscosity might retard the release.

In order to determine the proper concentration of HEC, the furosemide tablets formulated with HEC in various concentrations were prepared and the dissolution test was carried out, using two dissolution methods. The dissolution profiles obtained from the test in the flow-through cell dissolution system are shown in Fig.3. In the dissolution method using flow-through dissolution cell, the dissolution medium can be changed at certain time intervals, which is thought to simulate the pH change encountered as oral preparations move along the gastrointestinal tract[19].

In tablets formulated with HEC(Formula A-1~A-4), the release of furosemide measured in the flow-through cell was in the claimed

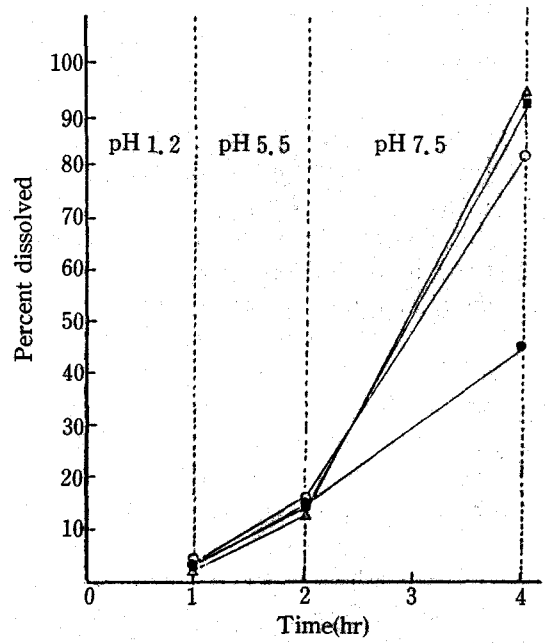


Figure 3—*In vitro* dissolution profiles of furosemide retard formulations in the flow-through cell system. The pH of the dissolution medium was continuously changed from 1.2 to 5.5, and finally to 7.5.
Key: ●, Formula A-1; ○, Formula A-2; ■, Formula A-3; △, Formula A-4.

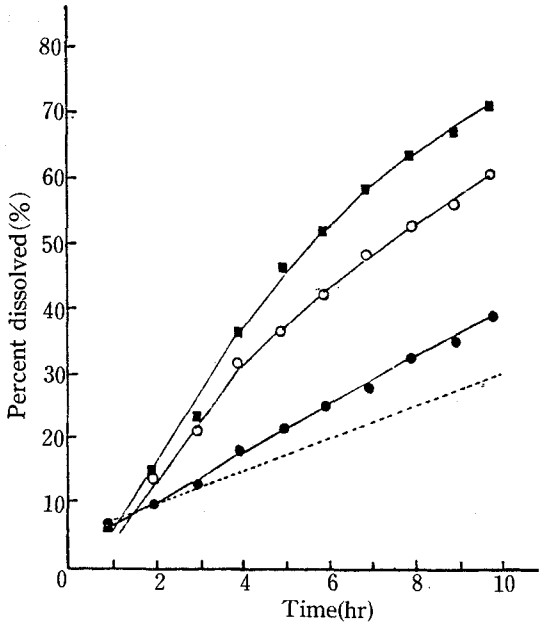


Figure 4—*In vitro* dissolution profiles of furosemide retard formulations in pH 5.8 phosphate buffer at 37℃, using U.S.P. rotating basket apparatus at 50 rpm.
Key: ···, Formula A-1 ; ●, Formula A-2 ; ○, Formula A-3 ; ■, Formula A-4.

range, regardless of the concentration of HEC. But the tablets formulated with 3-5 mg of HEC per tablet(Formula A-3, A-4) were thought to be unsuitable as the retard formulations, as the tablets dissolved rapidly in the dissolution medium. In regard of this assessment, the dissolution target range should be established first, and then justifiable evaluation would be obtained. The dissolution profiles for the above tablets obtained from U.S.P. dissolution method are shown in Fig.4. The dissolution rate decreased with the increase of HEC. This implies that the HEC is the major factor for the retarded release.

The dissolution data were treated by following mechanical equations.

$\log m = K_1 t + a$(first-order kinetics)·····Eq.2

$100^{1/3} - m^{1/3} = Kt$(cube root relationship)···Eq.3

$100 - m = Qt^{1/2}$(diffusion controlled model)··· Eq.4

Where m represents the percentage of drug

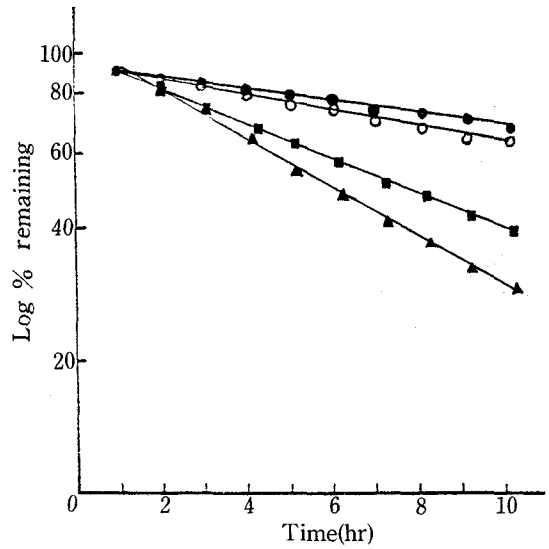


Figure 5—Plot of dissolution data according to Eq.2. Data were taken from Fig 4.
Key: ●, Formula A-1 ; ○, Formula A-2 ; ■, Formula A-3 ; ▲, Formula A-4.

undissolved at time t, K_1 is the apparent first-order rate constant, a is a constant, K is the cube root relationship rate constant, and Q is the Higuchi constant. The curves plotted

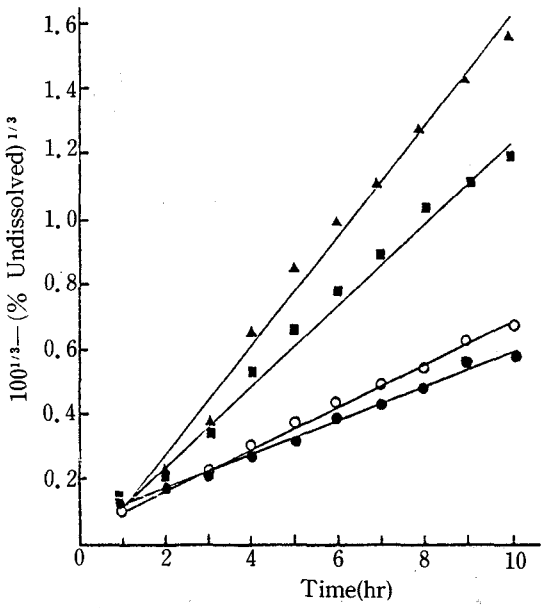


Figure 6—Plot of dissolution data according to Eq.3. Data were taken from Fig. 4. For symbols, see Fig. 5.

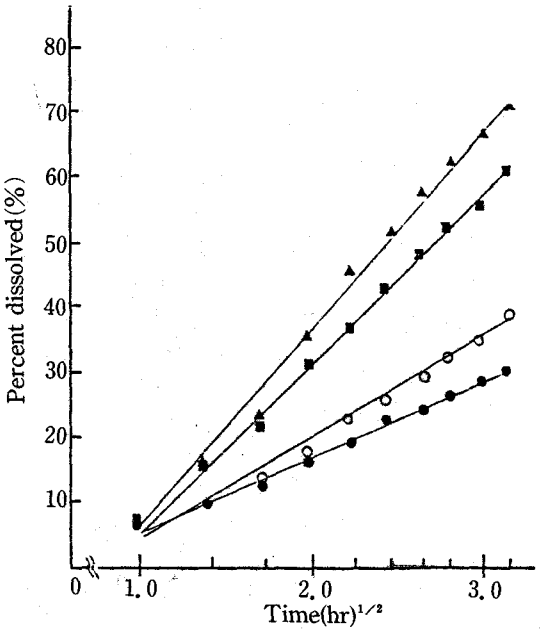


Figure 7—Plot of dissolution data according to Eq.4. Data were taken from Fig 4. For symbols, see Fig 5.

according to these equations are shown Figs. 5-7.

The "goodness of fit" was evaluated by a linear regression analysis and is summarized in Table III. The data for the tablets formulated with HEC(A-1~A-4) followed a first-order kinetic process(Eq.2), suggesting that the rate of release from the formulation is proportional to the amount of drug remaining in the tablet. They also followed Eq. 3 and Eq. 4, suggesting that the actual dissolution and the penetration of dissolution medium through the porous matrix were the major rate-determining factors in the drug release mechanism[20-23].

Table III—*Comparison of Fits of Dissolution Data Using a Linear Regression Analysis*

Equation	Correlation coefficient (r)			
	Formula A-1	Formula A-2	Formula A-3	Formula A-4
First-order kinetics ($\log m = K_1 t + a$)	−0.9992	−0.9986	−0.9982	−0.9977
Cube root relationship ($100^{1/3} - m^{1/3} = Kt$)	0.9988	0.9988	0.9962	0.9948
Diffusion controlled model ($100 - m = Qt^{1/2}$)	0.9963	0.9906	0.9966	0.9936

For abbreviations, see text.

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