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Sustained-Release Formulation of Buformin Hydrochloride[1,2]

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Using buformin hydrochloride, a highly water-soluble drug, as a model drug, a sustained-release dosage form was developed. Six granule formulations were prepared from corn starch–lactose, synthetic aluminum silicate, ethyl cellulose, and polymethylmethacrylate, and five tablet formulations were prepared from corn starch–lactose, calcium hydrogen phosphate, crystalline cellulose, ethyl cellulose, and sodium polyacrylate. These formulations were subjected to dissolution tests for *in vitro* screening of potential retard forms. It was found that incorporation of sodium polyacrylate was very effective in reducing the release rate. Two formulations incorporating sodium polyacrylate were selected as the most successful retard forms in an *in vitro* study. They were orally administered to beagle dogs for *in vivo* evaluation. It was concluded that this material is one of the most promising excipients for a sustained-release dosage form which contains an extremely water-soluble drug.

Keywords——sustained-release; buformin hydrochloride; highly water-soluble drug; sodium polyacrylate; dissolution; urinary excretion

An important target of research in the pharmaceutical field has been to formulate a sustained-release preparation for highly water-soluble drugs, for which it is difficult to control the release rate.[4] Buformin hydrochloride is clinically used as an antidiabetic agent. However, the biological half-life in humans is 1.8 h,[5] and the drug must be administered 3—4 times a day. It would be preferable to have a sustained-release preparation which could be administered only once or twice a day. In this study, buformin hydrochloride was selected as a model drug, and a model experiment to develop a sustained-release dosage form was performed. Six granule formulations were prepared from corn starch–lactose, synthetic aluminum silicate, ethyl cellulose, and polymethylmethacrylate, and five tablet formulations were prepared from corn starch–lactose, calcium hydrogen phosphate, crystalline cellulose, ethyl cellulose, and sodium polyacrylate. These formulations were subjected to dissolution tests for the *in vitro* screening of potential retard forms. Additionally, the formulations incorporating sodium polyacrylate, *i.e.*, the most successful ones in the *in vitro* study, were subjected to an animal study for *in vivo* evaluation.

Experimental

Materials——Buformin hydrochloride was purchased from Sanwa Chemical Co., Ltd. Glease® tablets containing 50 mg of buformin hydrochloride per tablet from Yamanouchi Pharmaceutical Co., Ltd. were also used. The following excipients were used: sodium polyacrylate (PANA), whose degree of polymerization was 22000—66000, from Nihon Kayaku Co., Ltd., polymethylmethacrylate (PMMA) of low molecular weight from Aldrich Chemical, Inc., ethyl cellulose (EC), whose viscosity was 9—10 cP at a concentration of 5% in (ethanol + toluene) at 25 °C, from Tokyo Kasei Co., Ltd., corn starch of JP X, lactose of JP X, synthetic aluminum silicate (SAS) of JP X, and crystalline celluloe (MCC) of JP X marketed as Avicel PH-102. Vitachange (activated) was purchased from

Wako Pure Chemical Co., Ltd. All other materials were of reagent grade, and were used without further purification.

Determination of Saturation Solubility of Buformin Hydrochloride——Three ml of water, JP X disintegration medium No. 1 (pH 1.2), or J.P. IX disintegration medium No. 2 (pH 7.5) was poured onto 3 g of buformin hydrochloride in a test tube. The solution was heated on a water bath at 80 °C for 5 min, then the test tube was transferred to a reciprocating shaker thermostatted at 37 °C and kept at 44 rpm until the concentration of the solution reached equilibrium. The solution was withdrawn through a membrane filter of pore diameter 0.8 μm, and the filtrate was diluted with pH 7.0 Clark–Lubs buffer solution and analyzed for buformin hydrochloride by the ultraviolet absorption method at 232.5 nm using a Hitachi 124 spectrophotometer. Experiments were repeated three times and the mean value was calculated.

Preparation of Buformin Hydrochloride Granules——A mixture of corn starch–lactose (3 : 7) or SAS was used as the excipient. EC or PMMA was used as the binder. Chloroform was used as the granulation solvent. Granules were prepared by the following two methods.

Single Granulation Method: Buformin hydrochloride and excipients were poured into binder solution in a mortar. After being kneaded in the mortar, the mixture was passed through an 18-mesh sieve, and dried for 4 h at 40 °C. Granules of the 18- to 32-mesh fraction were used in this study.

Double Granulation Method: Buformin hydrochloride was dissolved in a 10% chloroform solution of EC in a mortar. After sufficient kneading in the mortar, the mixture was dried for 4 h at 40 °C, then ground and passed through a 12-mesh sieve. The film-like granules and the excipient were granulated in 10% chloroform solution of EC in a mortar again. After being kneaded in a mortar, the mixture was passed through an 18-mesh sieve, and dried for 4 h at 40 °C. Granules of the 18- to 32-mesh fraction were used in this study. Six formulations tested in the study are listed in Table I.

Preparation of Buformin Hydrochloride Tablet——Flat-faced tablets 13 mm in diameter were prepared by compressing the given amount of powder directly under 700 kg/cm^2 for 3 min in a Shimadzu hydraulic press. Five formulations tested in the study are listed in Table II. Formulations J and K were prepared by a two-step method. Buformin hydrochloride granules were made by the single granulation method with MCC as the excipient, EC as the binder and ethyl acetate as the granulation solvent, then the mixture of the granules and PANA was subjected to direct compression as described above.

Table I. Formulations of Buformin Hydrochloride Granules

	Formulation					
Component (mg)	A	B[a)]	C	D[a)]	E	F
Buformin hydrochloride	50	50	50	50	50	50
Corn starch	30	15				
Lactose	70	35				
SAS			100	50	100	
EC	50	100	50	100		
PMMA					50	100
Total	200	200	200	200	200	150

a) Doubly processed granules.

Table II. Formulations of Buformin Hydrochloride Tablets

	Formulation				
Component (mg/tablet)	G	H	I	J	K
Buformin hydrochloride	50	50	50	50	50
Corn starch	60				
Lactose	140				
Calcium hydrogen phosphate		450	100		
MCC				338	338
EC				62	62
PANA			100	300	550
Total	250	500	250	750	1000

Dissolution Rate Study by JP X Dissolution Test Method I——Dissolution of buformin hydrochloride was tested in a JP X dissolution test apparatus (method I; rotating basket method) in 500 ml of water at an agitation speed of 100 rpm at 37 °C. A preparation containing 50 mg of buformin hydrochloride was subjected to the test. Five ml of sample solution was withdrawn at appropriate intervals through a membrane filter of pore diameter 0.8 μm (it was immediately replaced with an equal volume of the test medium) and analyzed for buformin hydrochloride by the ultraviolet absorption method at 232.5 nm using a Hitachi 124 spectrophotometer. Experiments were repeated three times and the mean value was calculated.

Dissolution Rate Study by JP X Dissolution Test Method II——Dissolution of buformin hydrochloride was tested in a JP X dissolution test apparatus (method II; paddle method) in 500 ml of JP X disintegration medium No. 1 at an agitation speed of 150 rpm at 37 °C. Except for the use of pH 7.0 Clark–Lubs buffer solution for dilution, the same procedure as described above was adopted for the test.

***In Vivo* Absorption Study**——Formulation J and K and Glease® tablets each equivalent to 100 mg buformin hydrochloride were orally administered to four male dogs of 10—14 kg body weight, fasted for 12 h before and after administration, by the three-way cross-over method. Urine was collected at 0, 3, 6, 9, 12, 24 and 36 h following the administration.

Determination of Buformin Hydrochloride in Urine——Buformin hydrochloride in urine was determined according to the modified method reported by Beckmann *et al.*[5] After activated Vitachange had been washed with deionized water several times, it was soaked in 20% NaCl solution for about 8 h. Then it was washed with deionized water until no chloride ion was detected, and used for determination. Two ml of urine was diluted with deionized water to 20 ml, and the diluted sample was passed through an activated Vitachange column (1.3 × 20 cm). The column was washed with 100 ml of 2.5% NaCl solution. The absorbance of eluate at 232.5 nm was read, then 0.05 ml of 4 N HCl was added to the eluate in a cell and the absorbance at 232.5 nm was read again. Buformin was determined from the difference of absorbance at 232.5 nm before and after addition of 4 N HCl.

Results and Discussion

Saturation Solubility of Buformin Hydrochloride

The saturation solubility of buformin hydrochloride in various solutions at 37 °C is listed in Table III. It is considered to be very difficult to develop a satisfactory long-acting formulation for buformin hydrochloride because it is extremely soluble in water, but the results listed in Table III clearly indicate the importance of controlling the release rate in the physiological pH range.

Dissolution Rate Study

The dissolution of buformin hydrochloride from granules in water at 37 °C as determined by the rotating basket method at an agitation speed of 100 rpm is shown in Fig. 1. Formulation A consists of singly processed granules and B consists of doubly processed ones with less corn starch, lactose and binder, EC. Irrespective of the granulating process and the quantities of excipients and EC, about 95% of buformin hydrochloride was dissolved in 30 min when corn starch–lactose was used as the excipient (formulation A and B); this result can be attributed to the water solubility of lactose and swelling characteristics of corn starch in water. When a water-insoluble diluent, SAS was used as the excipient (formulation C and D), significant retardation of release was observed in formulation D (double granulation with EC). This suggests that double granulation of buformin hydrochloride with water-insoluble SAS and EC significantly suppresses the dissolution of the drug. The above result was confirmed by using water-insoluble synthetic resin, PMMA, as demonstrated in the dissolution profiles of formulations E and F. Formulation F was doubly processed with PMMA

Table III. Saturation Solubility Values of Buformin Hydrochloride at 37 °C

Medium	Saturation solubility (g/ml)
Water	0.258
J.P. X disintegration medium No. 1	0.490
J.P. IX disintegration medium No. 2	0.319

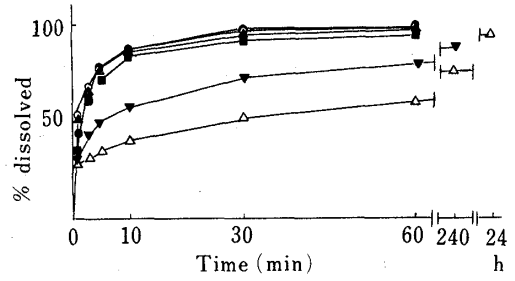

Fig. 1. Dissolution of Buformin Hydrochloride from Granules in Water at 37 °C as Determined by the J.P. X Rotating Basket Method (100 rpm)

Symbols: formulations A (●), B (▲), C (■), D (▼), E (○) and F (△).

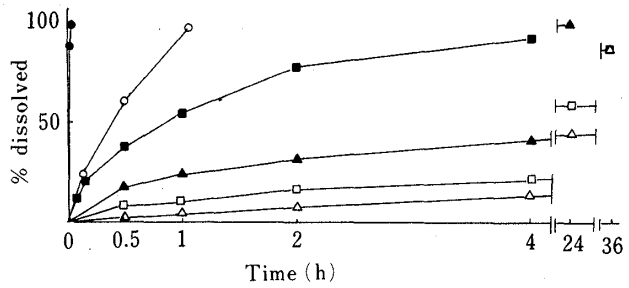

Fig. 2. Dissolution of Buformin Hydrochloride from Tablets in Water at 37 °C as Determined by the J.P. X Rotating Basket Method (100 rpm)

Symbols: formulations G (●), H (■), I (▲), J (□), K (△) and Glease® (○).

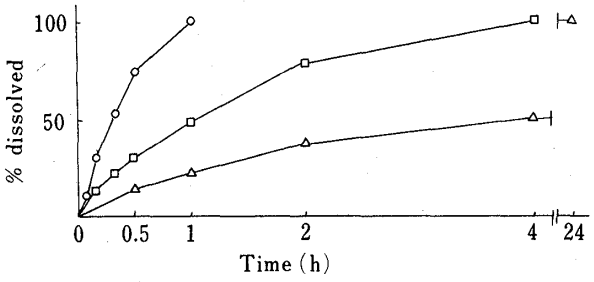

Fig. 3. Dissolution of Buformin Hydrochloride from Tablets in J.P. X Disintegration Medium No. 1 at 37 °C as Determined by the J.P. X Paddle Method (150 rpm)

Symbols: formulations J (□) and K (△) and Glease® (○).

and the dissolution rate was reduced to about half of that formulation E.

The dissolution of buformin hydrochloride from tablets in water at 37 °C as determined by the rotating basket method at an agitation speed of 100 rpm is shown in Fig. 2. Dissolution of buformin hydrochloride from corn starch–lactose tablet, formulation G, was completed within 3 min, and Glease® tablets showed next fasted dissolution. All the tablets intended to give sustained release gave smaller dissolution rates than that of Glease® tablets. When a water-insoluble diluent, calcium hydrogen phosphate, was pressed with buformin hydrochloride (formulation H), the dissolution rate of the drug was decreased almost to half of that of Glease®. However, it still took only 2 h to reach a plateau. A highly viscous polymer, PANA, was incorporated into the tablets to reduce further the rate of dissolution. PANA has been used as a vehicle for transdermal drug absorption from ointments and plasters. A little work has been done on its use for oral long-acting formulations; some patent applications have described oral dosage forms containing PANA. By incorporation of PANA, prolonged retention of specific drug in dog stomach was attempted, in order to achieve prolonged local action.[6] PANA was also used in formulations to retain drugs in the buccal or nasal cavity for topical applications.[7] There has been a study evaluating PANA in pharmaceutical preparations, but the results were limited to manufacturing procedures and *in vitro* testing.[8] The viscosity of aqueous PANA solution is greatly dependent on the pH of the solution. With increase in pH, the viscosity increases about one hundred times over the physiological pH range. In developing a sustained-release formulation for an extremely water-soluble drug, this peculiar physical characteristic can be an advantage for suppressing excessive drug dissolution at such high physiological pHs as 6.8 and 7.5. As shown in Fig. 2, formulations I, J and K gave significantly retarded dissolution of the drug.

The dissolution of buformin hydrochloride from formulations J and K and Glease® tablets in JP X disintegration medium No. 1 at 37 °C as determined by the paddle method at an agitation speed of 150 rpm is shown in Fig. 3. Dissolution of the drug from Glease® tablets

reached equilibrium in 1 h both in water and in artificial gastric juice. This suggests that the dissolution of the drug from Glease® tablets was fast enough to eliminate the effect of the difference in saturation solubility. However, the dissolution from formulations J and K was greatly reduced in water, which reflects the lower agitation speed and lower saturation solubility, which is about twice as much in JP X disintegration medium No. 1 as in water (Table III). This difference increased the dissolution rate of buformin hydrochloride about two-fold. In addition, solution pH affected the viscosity of the PANA solution. The viscosity of aqueous PANA solution was reported to be reduced with decrease of solution pH.[9]

Based on the above results, formulation J and K were selected as potential candidates for a sustained-release formulation, and were subjected to a bioavailability study in comparison with the conventional dosage form, Glease® tablets.

In Vivo Absorption Study

Buformin hydrochloride excretion per hour in beagle dogs following oral administration of formulations J and K and Glease® tablets is shown in Fig. 4. Glease® tablets showed maximum excretion (25% of dose) during 3—6 h after the administration, with a sharp decrease after 6 h, and very little was excreted after 12 h, whereas formulations J and K showed a more gradual decrease, and even during 24—36 h about two-thirds (2/3) of the excretion obtained in the case of tablets during 12—24 h was found, as shown in Fig. 4. Excretion in the case of formulation J was significantly smaller than that in the case of Glease® tablets during 3—6 h ($p<0.05$). A similar trend was observed for formulation K, although the cumulative amount excreted was slightly lower. The significantly different excretion behavior during 3—6 h correlates well with the rapid dissolution characteristic of Glease® tablets, and the significant difference between Glease® tablets and formulations K and J during 12—24 h ($p<0.05$) resulting from the retarding effect of PANA found in the *in vitro* dissolution tests.

Cumulative urinary excretion of buformin hydrochloride in beagle dogs following oral administration of formulation J and K and Glease® tablets is shown in Fig. 5. The excretion

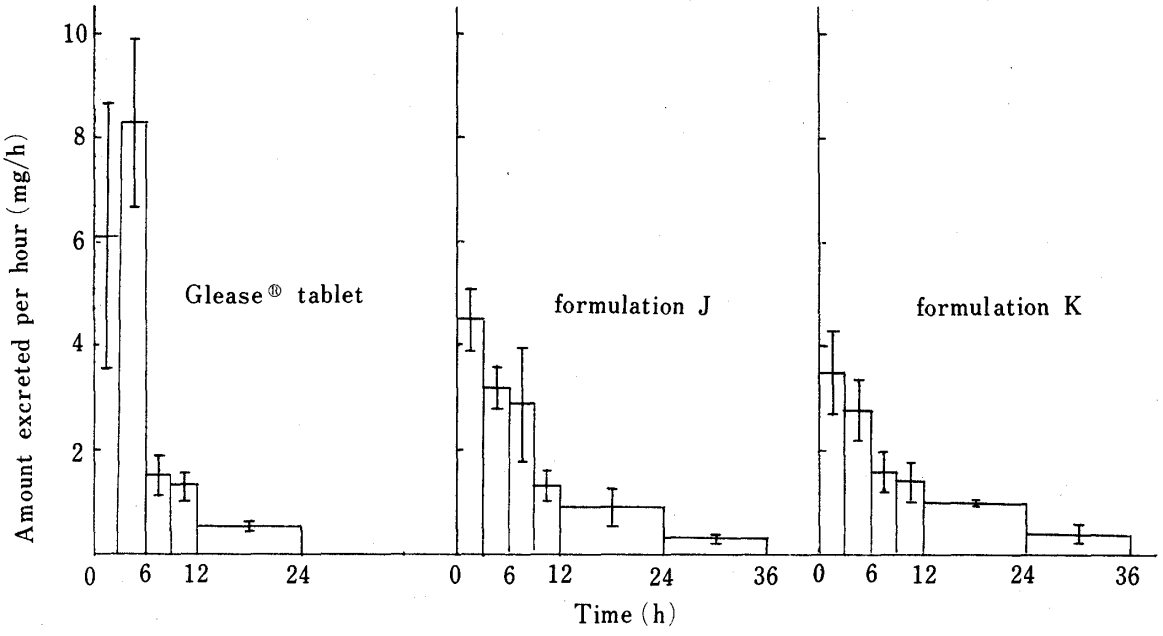

Fig. 4. Urinary Excretion of Buformin Hydrochloride in Beagle Dogs Following Oral Administration of 100 mg of Buformin Hydrochloride Sustained-Release Preparations

Each value is the mean ± S.E. of four determinations.

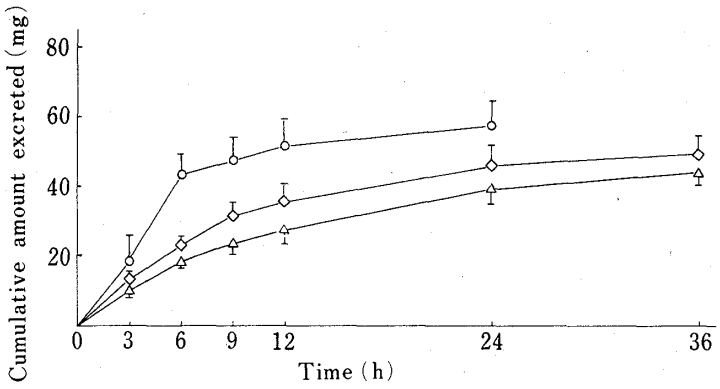

Fig. 5. Cumulative Urinary Excretion Curves of Buformin Hydrochloride in Beagle Dogs Following Oral Administration of 100 mg of Buformin Hydrochloride Sustained-Release Preparations

Symbols: formulations J (◇) and K (△) and Glease® (○).
Each symbol represents the mean ± S.E. of four determinations.

curve in the case of the Glease® tablets leveled off at 24 h, which indicates that the excretion of drug is essentially completed at 24 h after the administration. Significant differences in cumulative excretion of buformin hydrochloride were observed at 6, 9 and 12 h between formulation K and Glease® tablets, while a significant difference was observed only at 6 h between formulation J and Glease® tablets at the 0.05 level of significance. Further, at 24 h the cumulative excretions of buformin hydrochloride after administration of formulation J and K and Glease® tablets were not significantly different, which suggests that the total amount of drug of drug excreted in 24 h is essentially the same after administration of all three dosage forms. Figure 5 also suggests that formulation K is preferable, as regards sustained-release characteristics, to formulation J, although no significant difference in drug excretion was found. These results indicate that PANA is a very promising excipient for a sustained-release preparation of a highly water-soluble drug such as buformin hydrochloride.

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References and Notes

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