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Application of Hydroxypropyl Cellulose to Peroral Controlled Release Dosage Forms[1]

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Intending to explore a new peroral controlled release dosage form using hydroxypropyl cellulose (HPC), an investigation was made on the disintegration and dissolution property of directly compressed tablets of *dl*-isoproterenol hydrochloride (IPH) held in a simple (PM) or spray dried (SDM) mixtures of HPC and lactose. A commercially available prolonged action preparation of IPH was also examined in comparison with the above preparations.

The hardness and disintegration time (dissolution time in the case of SDM tablet) increased with an increase in HPC. SDM was superior in molding property, but the tablet dissolved rapidly compared with PM tablet.

A double layer tablet of IPH held in 200 mg of SDM as the initial phase and 300 mg of PM as the depot phase afforded a suitable sustained release property without taking a strikingly rapid dissolution upon changing from No. 1 medium (acidic) to No. 2 (neutral), while the commercially available prolonged action preparation showed a rapid dissolution upon such the change of dissolution media. This sustained release property could be controlled by adjusting the ratio of the active ingredient in the respective layers. Accordingly, this double layer tablet seemed to be applicable to peroral prolonged action dosage forms on the basis of the consideration regarding the absorption, elimination and other properties of the active ingredient.

Keywords——hydroxypropyl cellulose; peroral controlled release dosage forms; *dl*-isoproterenol hydrochloride; spray dried mixture; disintegration test; dissolution test; double layer tablet

Most of prolonged action dosage forms are prepared in peroral ones and classified into various types.[3] Generally, a preparative procedure of these dosage forms is complicated to afford a highly controlled release property of active ingredients.

The authors reported in a previous paper[4] that hydroxypropyl cellulose (HPC) can be used as directly compressible vehicles for tablet making. Especially, the directly compressed tablets containing a large amount of HPC in addition to lactose or potato starch did not disintegrate completely within 60 min, collapsing into the caky aggregate parts which were covered with the gel-like layer of HPC. The size of these aggregate parts increased with an increase in the concentration of HPC. Additionally, it was found that the direct compression of a freeze dried mixture of HPC and lactose (1: 19—1: 4) was convenient for making a hard and gradually dissolving tablet which did not disintegrate.

Based on these findings, intending to explore a new peroral prolonged action dosage form, the present study was attempted to investigate the disintegration and dissolution property of directly compressed tablets of *dl*-isoproterenol hydrochloride (IPH) held in HPC and lactose as the simple powder mixture or the spray dried one. *dl*-Isoproterenol hydrochloride was chosen because some prolonged action preparations of this drug are commercially available.

1) This paper forms Part VIII of "Pharmaceutical Interaction in Dosage Forms and Processing." The preceding paper, Part VII: K. Takayama, S. Hasegawa, S. Sasagawa, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.* (Tokyo), **26**, 96 (1978).
2) Location: *Ebara-2-4-41, Shinagawa-ku, Tokyo 142, Japan.*
3) E.J. Ariens (ed.) "Drug Design," Vol. 4, Academic Press, Inc., New York, N.Y., 1973, Chapter 2.
4) Y. Machida and T. Nagai, *Chem. Pharm. Bull.* (Tokyo), **22**, 2346 (1974).

The spray dried mixture was used because of the low bulkiness and high fluidity compared with the freeze dried one. The investigation was extended to the double layer tablets prepared of the same vehicles and also a commercially available prolonged action preparation of IPH for comparison.

Experimental

Materials——Commercial *dl*-isoproterenol hydrochloride J. P. VIII (IPH) was used without further treatments. HPC-L (48—100 mesh), HPC-M (48—100 mesh) and lactose J. P. IX used were the same as in the previous paper.[4] HPC-H (48—100 mesh) was used after sieving in the same way as for HPC-L and HPC-M,[4] having the viscosity of 2744 centipoise in 2% aqueous solution when measured by a Tokyo Keiki BL type viscometer. The commercial prolonged action preparation used was supplied as the hard gelatin capsule filled with the three types of granules containing IPH and granules of pronase.

Preparation of Spray Dried Mixture of HPC-L[5] and Lactose (SDM)——The conditions of spray drying were as follows: Temperature of bulk solution: 35°, drying temperature: inlet-170°, chamber-120°, outlet-120°; dropping rate of bulk solution: 2.2 l/hr; concentration of bulk solution: 25%; revolution speed of atomizer: 14400 rpm; atmospheric pressure of chamber: 4 mmHg; spray dryer: Iwai Kikai Co. Ltd., rotating disk type. Concentrations of HPC-L were 5, 10, 15, 20, 25 and 30%.[6] Spray dried mixtures (SDM) were used after sieving by 60 mesh sieve.

Preparation of Tablet——1) Single Layer Tablet: 400 mg of powder was compressed directly in the same way as described in the previous paper.[4]

2) Double Layer Tablet: 300 mg of simple powder mixture of HPC and lactose (PM) was packed evenly in the die hole and 200 mg of SDM was stacked on the former, and then directly compressed under the pressure of 100 kg/cm^2 using the same apparatus as for the single layer tablet mentioned above. The content of IPH was 20 mg per tablet in each type of tablet.

Measurement of Hardness of Tablet——Hardness of tablet was measured using a Kayagaki Monsanto type hardness tester.

Disintegration Test——Disintegration test was done using a Toyama Sangyo T-2HS type disintegration tester according to the method in J. P. IX, but the attached disk was not used. The purified water was used as the disintegration medium.

Dissolution Test——1) J. P. Method: J. P. IX disintegration tester without the attached disk was used with 800 ml of the dissolution medium at 37°±2°. Dissolution medium used were described in J. P. IX as the disintegration media No. 1 (pH 1.2 for 120 min) and successively No. 2 (pH 7.5).[7] Five milliliters of solution was sampled out at appropriate time intervals and the resultant want of volume was compensated by adding the dissolution medium warmed at the same temperature. The concentration of drug was determined according to ultraviolet absorption method at 279 nm.

2) U. S. P. Method: Toyama Sangyo TR-5S3 U. S. P. dissolution tester was used on setting the revolution speed of the basket at 200 rpm. In addition to the media used in J. P. method, 0.01 N HCl was also used as the dissolution medium. Unless otherwise stated, the other testing conditions were the same as in J. P. method.

Results and Discussion

Influence of Concentration of HPC in the Vehicle on Hardness of Tablet

The relation between the hardness of tablet and the concentration of HPC in the vehicle is shown in Fig. 1. In the case of PM tablet containing HPC-L, HPC-M or HPC-H, the hardness of tablet increased with an increase in the concentration of HPC without depending on the degree of polymerization of HPC. The molding property in the direct compression seemed to have relation mainly to such physical properties of particles as the shape, plastic deformation and cohesive force, but not so much to the chemical structure. Therefore, it was considered possible that the degree of polymerization of HPC did not affect so much the hardness of directly compressed tablet compared with that of the tablet made by wet process. In the case of SDM tablets, the hardness was higher than PM tablets within the range of 5—30%

5) Only HPC-L was used because the others were too viscous to apply the spray drying method.
6) At the higher concentration of HPC, the solution was too viscous to apply the spray drying method.
7) IPH is known to be unstable in alkaline solution, but the maximum absorbance at 279 nm did not change with the lapse of time during this test, making possible the determination of the amount dissolved.

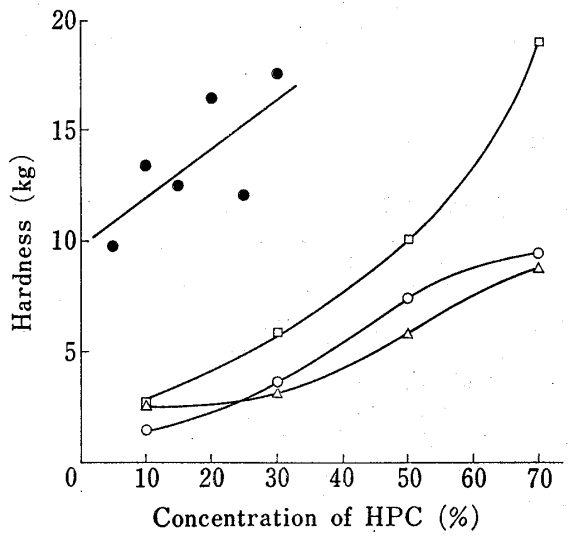

Fig. 1. Relation between Hardness of Tablet and Concentration of HPC inVehicle

Each symbol represents the mean of 5 determinations.
—●— : SDM tablet.
—○— : PM tablet (HPC-L).
—□— : PM tablet (HPC-M).
—△— : PM tablet (HPC-H).

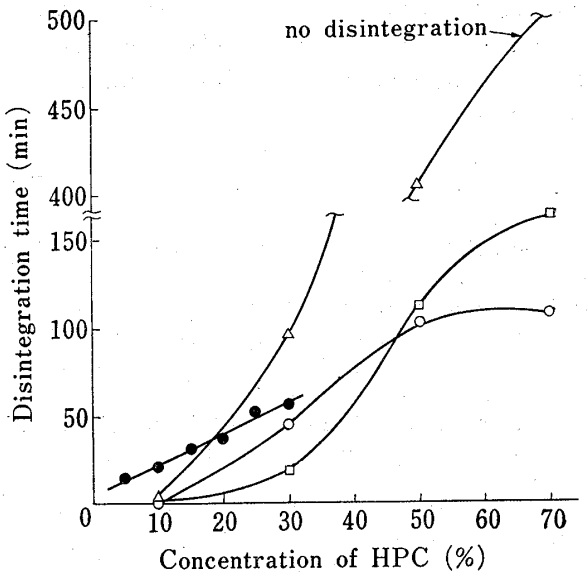

Fig. 2. Relation between Disintegration Time of Tablet and Concentration of HPC in Vehicle

Each symbol represents the mean of 6 tablets.
—●— : SDM tablet.
—○— : PM tablet (HPC-L).
—□— : PM tablet (HPC-M).
—△— : PM tablet (HPC-H).

HPC, similar to the result concerning the tablets of freeze dried mixture of lactose and HPC described in the previous paper,[4] but did not increase clearly with an increase in the concentration of HPC (correlation coefficient $r=0.723$, significant at 1% level by t-test). SDM is superior in fluidity to the freeze dried mixture because of the spherical form of the particle, and have a good molding property. Therefore, if several kinds of preparations of SDM thereby obtained are provided, they may afford useful directly compressible vehicles for the tablets. Moreover, these kinds of spray dried mixtures can be made containing sweeteners, which may be utilized as the vehicle for the troches.

Influence of Concentration of HPC in the Vehicle on Disintegration Time of Tablet

The disintegration time of tablet increased with an increase in the concentration of HPC, as shown in Fig. 2. Especially, an approximately linear relationship existed between the disintegration time of SDM tablets and the concentration of HPC (correlation coefficient $r=0.990$, significant at 1% level by t-test). In the case of PM tablets, the disintegration time increased with an increase in the degree of polymerization of HPC at the high concentration of HPC, while not in the concentration below 30%. PM tablets disintegrated rapidly at the low concentration of HPC, *e.g.*, at 10%, where the water may penetrate easily because of the large amount of lactose, *i.e.*, a water soluble substance. Then, it was considered that the particles of HPC in the tablet are dispersed immediately in water when disintegrated and thus the degree of polymerization of HPC does not affect the disintegration time of tablet at the low concentration. On the other hand, at the high concentration of HPC, the penetrating water may get viscous soon after the penetration because of the dissolution of HPC, supressing the further penetration into the inside of tablet to result in a delay of disintegration time, as may be related to the degree of polymerization of HPC. In the case of SDM, the tablet did not disintegrate in a regular style, but dissolved gradually. In this tablet, lactose and HPC were considered to be so homogeneously mixed in molecular level that the concentration of HPC might be related directly to the disintegration (or dissolution) time of SDM tablets.

Influence of Concentration of HPC in the Vehicle on Dissolution Rate of the Active Ingredient *dl*-Isoproterenol (IPH)

The dissolution property of each tablet was compared on the basis of half dissolution time (T_{50}). Figure 3 shows the relationship between the concentration of HPC and T_{50} of SDM tablets determined by U. S. P. method. An apparent linear relationship was observed between dissolution rate of IPH and the concentration of HPC (correlation coefficient $r=0.993$, significant at 1% level by t-test). IPH itself is readily soluble in water, and thus the disintegration (or dissolution) of tablet was considered to have relation to the dissolution of the active ingredient, as was proved by the result shown in Fig. 2. This linear relationship thereby found may be useful for controlling the dissolution property of the tablets to be prepared.

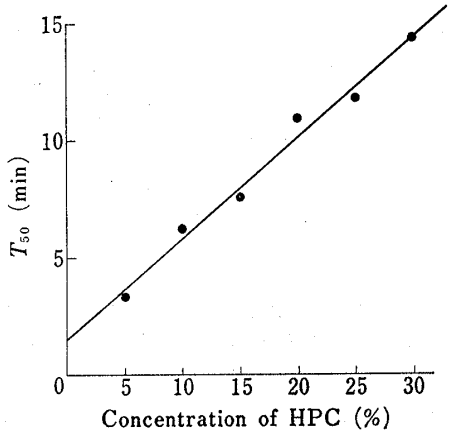

Fig. 3. Relationship between T_{50} in 0.01 N HCl determined by U. S. P. Method and Concentration of HPC in Vehicle of SDM Tablets

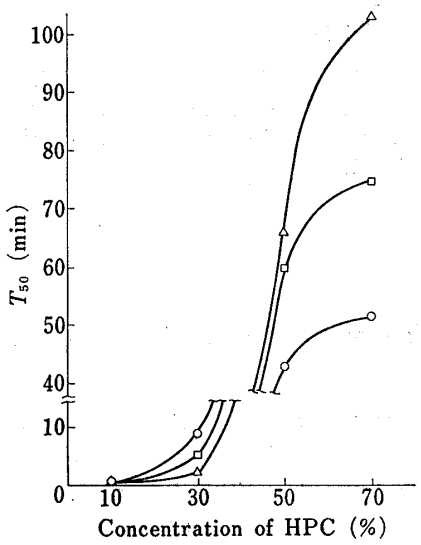

Fig. 4. Relation between T_{50} in 0.01 N HCl determined by U. S. P. Method and Concentration of HPC in PM Tablets
—○— : HPC-L. —□— : HPC-M.
—△— : HPC-H.

The relationship between the dissolution rate and the concentration of HPC in the cases of PM tablets was quite different from that of SDM tablets, as shown in Fig. 4. A comparatively fast dissolution of IPH was observed in the range below 30% HPC, but T_{50} arose dramatically in the range over this concentration.

The difference in dissolution property of IPH between SDM tablets and PM tablets corresponded to that in disintegration time or dissolution rate of the respective tablets shown in Fig. 2. Plotting T_{50} of SDM tablets against disintegration time, an approximately linear relationship was obtained, as shown in Fig. 5. (correlation coefficient $r=0.970$, significant at 1% level by t-test). Any similar relationship was not observed in the cases of PM tablets. This difference between SDM and PM tablets may also come from that in the mechanism of disintegration. In the case of SDM, the tablet dissolved gradually accompanying the simultaneous dissolution of IPH. Therefore, the disintegration time corresponded to T_{50}. On the other hand, in the cases of PM, the tablet containing less concentration of HPC disintegrated rapidly accompanying the simultaneous dissolution of IPH. However, in the tablet containing more concentration of HPC, the gel-like layer was formed to cover the tablet after the penetration of water, which might suppress the disintegration or dissolution. In this state, released IPH might have to diffuse through this gel-like layer and thus no linear relationship between the disintegration of tablet and dissolution of IPH might be observed.

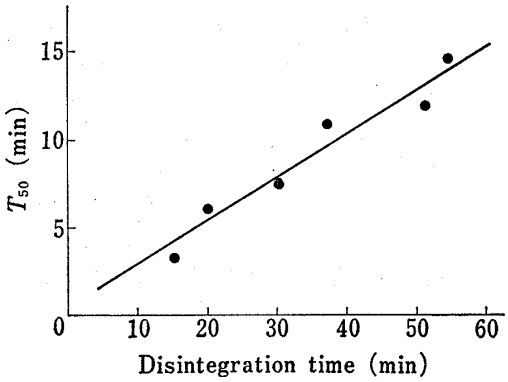

Fig. 5. Relationship between T_{50} in 0.01 N HCl determined by U. S. P. Method and Disintegration Time of SDM Tablet

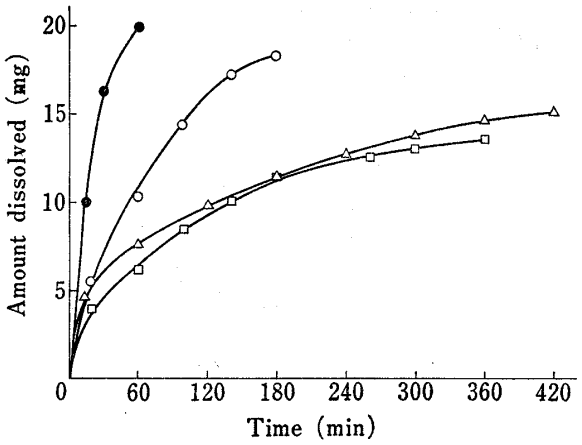

Fig. 6. Typical Dissolution Patterns of SDM Tablet and PM Tablet in 0.01 N HCl obtained by U. S. P. Method

—●— : SDM tablet (HPC-L, 30%).
—○— : PM tablet (HPC-L, 70%).
—□— : PM tablet (HPC-M, 70%).
—△— : PM tablet (HPC-H, 50%).

Evaluation of SDM and PM Tablets Regarding the Suitability as Prolonged Action Dosage Form

The typical dissolution patterns of SDM and PM tablets in 0.01 N HCl obtained by U.S.P. method are shown in Fig. 6. SDM tablets and PM tablets containing HPC-L were not suitable as the prolonged action dosage forms, because the time required for 100% release of drug (T_{100}) were 40 min and 180 min for the tablets containing 30% HPC-L and containing 70% HPC-L, respectively. On the other hand, T_{100} of PM tablets containing 70% of HPC-M and HPC-H were 266 min and 593 min, respectively. Therefore, it was concluded that PM tablets containing comparatively large amount of HPC-M or HPC-H may be used as peroral prolonged action dosage forms, when the concentration of HPC was adjusted under the consideration of physical and biological properties of the active ingredient.

Evaluation of the Double Layer Tablet Regarding the Suitability as Prolonged Action Dosage Form

As mentioned already, PM gave a sustained release property to the tablet. However, the amount of IPH dissolved at the early stage of the dissolution was very low compared with that of SDM tablets. Therefore, the tablet of PM alone seemed ineffective for an initial rise of blood concentration of drug after the administration, and a combination of SDM tablet seemed to give a good prolonged action dosage form. Then the tablets consists of two layers, *i.e.*, SDM layer (containing 20% HPC-L) as the initial phase and PM layer (containing 70% HPC-M) as the depot phase, as shown in Table I, were prepared and subjected to the dissolution

Table I. Double Layer Tablets Prepared and the Content of IPH in Initial and Depot Phases of Tablets

	Content of IPH (mg/tab)		
	Tablet A	Tablet B	Tablet C
SDM layer (initial phase)	2.5	5.0	7.5
PM layer (depot phase)	17.5	15.0	12.5

test by J. P. method and U. S. P. method. The dissolution patterns thereby obtained were discussed in comparison with commercially available peroral prolonged action preparation containing IPH, as follows.

i) Effect of Content of IPH in Initial and Depot Phases on Dissolution Rate——Prolonged action dosage forms should be designed so that the drug release is controlled throughout the gastro-intestinal tract. Therefore, it seemed more reasonable to examine the dissolution property in No. 1 and successively No. 2 media.

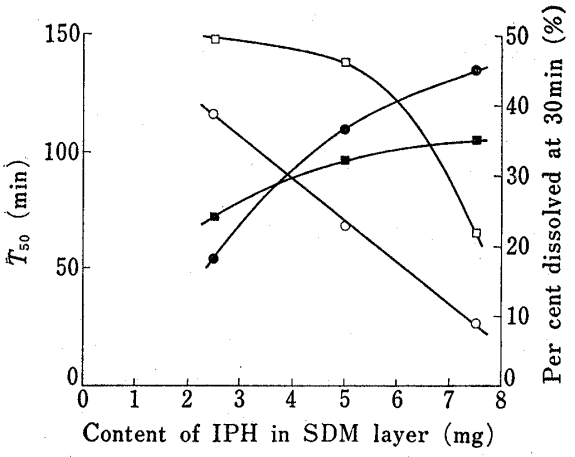

Fig. 7. Relation between T_{50} or Per Cent Dissolved of IPH at 30 min and Content of IPH in SDM layer of Double Layer Tablets

Each symbol represents the mean of 3 determinations.
—○— : T_{50} (J. P. method).
—□— : T_{50} (U. S. P. method).
—●— : per cent dissolved (J. P. method).
—■— : per cent dissolved (U. S. P. method).

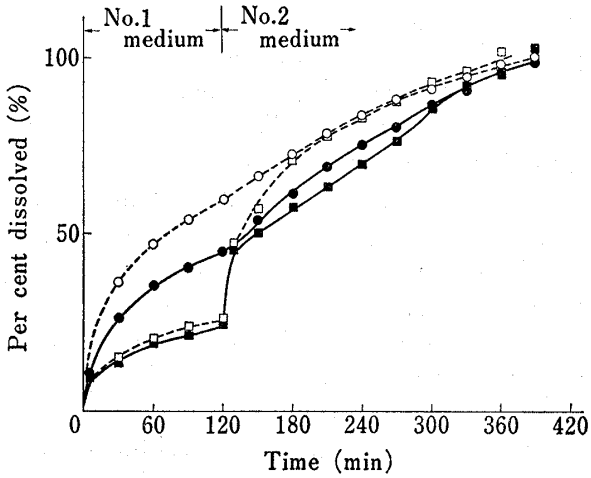

Fig. 8. Dissolution Profiles of Tablet B and Capsule D obtained by J. P. Method or U. S. P. Method

Each symbol represents the mean of 3 determinations.
···○··· : Tablet B (J. P. method).
···□··· : Capsule D (J. P. method).
—●— : Tablet B (U. S. P. method).
—■— : Capsule D (U. S. P. method).

Fig. 7 shows the T_{50} in No. 1 (for 120 min) and successively No. 2 media and the per cent dissolved at 30 min in No. 1 media of tablets A, B, C described in Table I. Apparently, T_{50} decreased and the amount dissolved increased with an increase of the content of IPH in SDM layer. An approximately linear relationship was observed between T_{50} determined by J. P. method and the content of IPH in SDM layer (correlation coefficient $r=-0.999$, significant at 1% level by t-test), while such a clearly linear relationship was not observed by U. S. P. method. The increasing tendency of the per cent dissolved at 30 min with an increase in the content of IPH in SDM layer was large in the result obtained by J. P. instrument compared with that by U. S. P. instrument. This difference seemed to come from the different stirring condition of both instruments. Essentially, it was indicated that the amount dissolved in the initial stage depends on the ratio of the active ingredient in SDM layer to that in PM one.

As a result, it may be concluded that the double layer tablet consists of the SDM layer and PM layer could be applicable to peroral prolonged action dosage forms by adjusting the ratio of the active ingredient in the respective layers on the basis of the consideration regarding the absorption, elimination and other properties of the active ingredient.

ii) Comparison of the Dissolution Property between the Double Layer Tablet and Commercially Available Prolonged Action Preparation——The double layer tablet prepared in this study (tablet B in Table I) was examined in comparison with a commercially available prolonged action capsule of IPH (capsule D). Capsule D contained the instant release granules (1 mg of IPH) and the sustained release granules in gastric juice (4 mg of IPH) and the sustained release granules in enteric fluid (5 mg of IPH). The dissolution profiles of both preparations are shown in Fig. 8. Generally, the release of IPH from tablet B was faster in

the test by J. P. method than by U. S. P. method, as mentioned already concerning Fig. 7. For example, the amount dissolved in No. 1 medium at 120 min of tablet B was given as 60% in J. P. method and 43.3% in U. S. P. method. On the other hand, in the case of capsule D, there was no difference in the per cent dissolved in No. 1 medium between both methods.

The sustained release property of tablet B (and also A and C) is considered to be based on the diffusion of drug through gel-like layer formed on the surface of the tablet. Therefore, the difference in the stirring condition of instrument seemed to give effect directly on the release of IPH. On the other hand, the sustained release property of capsule D is considered to be based on the release of drug from the three kinds of granules having different dissolution properties, and thus the release of IPH from this dosage form was not affected by the difference of the stirring condition of instrument.

However, a remarkable gap was observed in the dissolution curve of capsule D at 120 min, *i. e.*, the border of No. 1 and No. 2 media. This gap seemed due to a rapid dissolution of enteric granules in No. 2 medium. Such a gap was not observed on the dissolution curve of tablet B, keeping the former releasing tendency continuously. It is known that this type of release is preferable for some drug to a rapid dissolution upon changing from No. 1 medium to No. 2, *e. g.*, KCl preparations.[8]

The pH of gastro-intestinal fluid of individual persons is not identical and there are found a fairly large number of anacidity patients. Therefore, the release from the dosage forms based on the alteration in pH in gastro-intestinal fluid may sometimes be affected by the physiological difference among individuals. However, the peroral prolonged action dosage form in this study is not affected by the alteration in pH at gastro-intestinal tract, as may afford a merit. In addition of this merit, the presented dosage form can be easily prepared by the process of mixing and direct compression of bulk powder mixture.

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8) Y. Iwasaki, R. Sugiura, Y. Umemura, and T. Nagai, *The Clinical Report*, **8**, 2714 (1974).