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# Controlled Release of Isonicontinic Acid Hydrazide from the Membrane-Coated Tablet

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**Abstract** □ Membrane-coated tablet of isonicotinic acid hydrazide (INAH) which releases INAH at the zero-order kinetics was developed. It consisted of a soluble tablet core surrounded by a porous membrane which controls the diffusion rate. Tablet cores were prepared by compressing granules of INAH and polyvinyl pyrrolidone (PVP). The cores were coated by polyvinyl chloride (PVC) dissolved in methyl ethyl ketone in which micronized sucrose were suspended. Diffusion rate of INAH from the tablet through the membrane was constant until the loaded INAH in the core was almost released. The rate was independent of pH of the dissolution medium. Water-soluble sucrose particles behaved as a poreproducing material in the water-insoluble PVC film coat. The pH independency of the rate was probably due to the high solubility of INAH in the water of wide pH range. The diffusion rate of INAH could be controlled by changing the composition of the membrane or the coat weight. This membrane-coated INAH tablet seemed to be a powerful candidate for the controlled release drug delivery system (DDS) of INAH or other highly watersoluble drugs.

**Keywords** □ Membrane-coated tablet, Isonicotinic acid hydrazide, Controlled release, Diffusion rate, Drug delivery system, Zero order kinetics.

The concept of the controlled release of drugs has attracted much interest, and numerous drug delivery systems (DDS) are commercially available. The aim of controlled DDS is to obtain drug release kinetics meeting therapeutic need. Since a constant plasma level is adequate in many forms of therapy, a zero-order release of a drug from the dosage form is often desirable. Among DDS, those based on a diffusion-controlled release through a polymeric membrane have appeared to be reliable in order to achieve a zero-order release[1-5].

Isonicotinic acid hydrazide (INAH) is rapidly and completely absorbed in man after oral administration[6-10]. The rate of elimination of INAH in the body is an individual characteristic, highly variable from person to person and known to be under genetic control[11-20]. This hereditary trait is attributable mainly to differences in drug metabolizing polymorphic N-acetyltransferase activity located in the liver. An attempt to overcome the deficiency of rapid acetylator by increasing the dose of INAH has failed, largely because of the active toxic manifestations which may occur at high drug level. The best solution then appeared to be the development of a slow-release INAH preparation which would enable rapid acetylators to attain blood levels comparable to those of slow acetylators[20-22].

Membrane-coated tablet of INAH was prepared according to the method of Källstrand and Ekman[5], which based on the solution-diffusion through a rate-controlling microporous membrane. Membrane coating involves coating a tablet with a porous, water-permeable membrane, which is insoluble in the GI tract. The gastric juices penetrate the tablet through the

pores and dissolve drugs (Fig. 1).

Polyvinyl chloride (PVC) was selected as a membrane material because it is widely used in the areas from stomach tubes to polymeric matrix[23,24]. Its devices have been shown to be highly reliable and have a low risk to benefit ratio. This polymer is water-insoluble, has low toxicity and good mechanical resistence[5]. Micronized sucrose was used as a pore-producing material in the water insoluble PVC film coat.

## EXPERIMENTAL METHODS

*Materials*

Isonicotinic acid hydrazide(INAH, A-Ju), polyvinyl chloride(PVC, Lucky Chem.), sucrose(Sam Yang), polyvinyl pyrrolidone(PVP, Chin Hwa), magnesium stearate(Shimakyu), methyl ethyl ketone(Kokusan), potassium chloride(Shimakyu), sodium hydroxide(Shimakyu), potassium biphthalate(Shimakyu), potassium phosphate monobasic(Wako) and ethyl alcohol (Merk) were used and reagent grade.

*Apparatus*

Tablet machine(Erweka), mill machine (Alpine), homomixer(Tokushu Kika Kogyo, HV-M811062), viscometer(Rion, VT-04), particle size analyzer (Seishin), UV-spectro-photometer (LKB), pH-meter(Corning), KP-sieve, hardness tester (Monsanto) were used.

*Preparation of Tablet Core*

INAH powder was screened through 45-mesh sieve and granulated with a 15% solution of PVP in ethanol. A 25 g volume of the solution was mixed with 1,000 g of INAH. The wet granulation was screened through 18-mesh sieve and dried in forced-air oven at 55°C for 2 hrs. The dried granules were mixed with 5 g of magnesium stearate. Circular, biconvex tablets with a 13-mm diameter were compressed to a hardness of 8 kg/cm$^2$. The disintergration time in pH 7.4 phosphate buffer solution at 37°C was less than 10min. The tablet weight was 515.25±1.21 mg, of which 500±0.56 mg was INAH.

*Preparation of Membrane-coated Tablets*

The polymeric film coatings were applied to the tablets in batch sizes of 1,600 in a conventional coating pan rotaing at 20 rpm. Coating solutions consisted of 4.5% PVC in methyl ethyl ketone, and were stirred in 50°C water-bath for 10 min. Because of their high viscosity (~160cps), it was not possible to use more concentrated solutions. Different amounts of micronized sucrose (particle size $<50$ $\mu$m) were suspended in the polymer solution. Coating was achieved by spraying the suspension on the moving bed of tablets intermittently. Coating was continued until the weight of the coat on each tablet was reached.

*Drug Diffusion Studies*

Diffusion studies were performed using 900ml of dissolution medium in 1,000 ml three-necked round bottomed flask at 37±0.5°C with the tablet held in 40-mesh stainless steel basket according to USP-XX rotating-basket method. Rotating speed was 150 rpm and buffer solutions of pH 1.2, 3.0, 5.2 and 7.4 were used as dissolution media. Aliqouts of samples were periodically withdrawn from the outlet and immediately same aliqouts of buffer solution were added to dissolution medium. Samples were analyzed for drug dissolution mass by contrast with blank buffer solution by UV-spectrophotometer at 263 nm.

## RESULTS AND DISCUSSION

*Characteristics of the Membrane Coating*

The coating membrane consists of a water-

insoluble polymer and dispersed water-soluble pore-creating substance. When a membrane-coated tablet is swallowed, the gastric juice will dissolve the pore forming substance and the dissolved INAH will diffuse out through the pores in the membrane (Fig. 1). Scanning electron microscopy shows porosity of the membrane after dissolution of sucrose particle, a pore-forming substance (Fig. 2). Micronized sucrose seemed to be suitable for the pore-forming substance with regard to toxicity and solubility. The degree of polymerization of PVC was 1,000. It was suitable in mechanical properties and transparancy. The external appearance of the tablet was not changed even after the dissolution of INAH from the tablet was completed. No ruptures of the membrane were found after the dissolution. The main factor influencing shell hardness was found to be the thickness of the membrane.

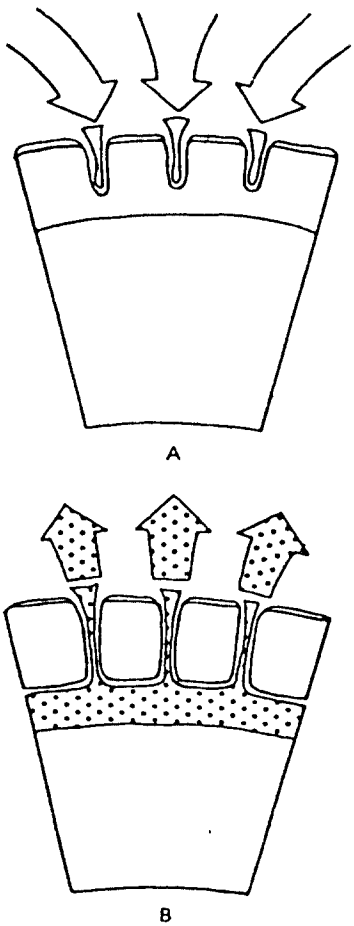
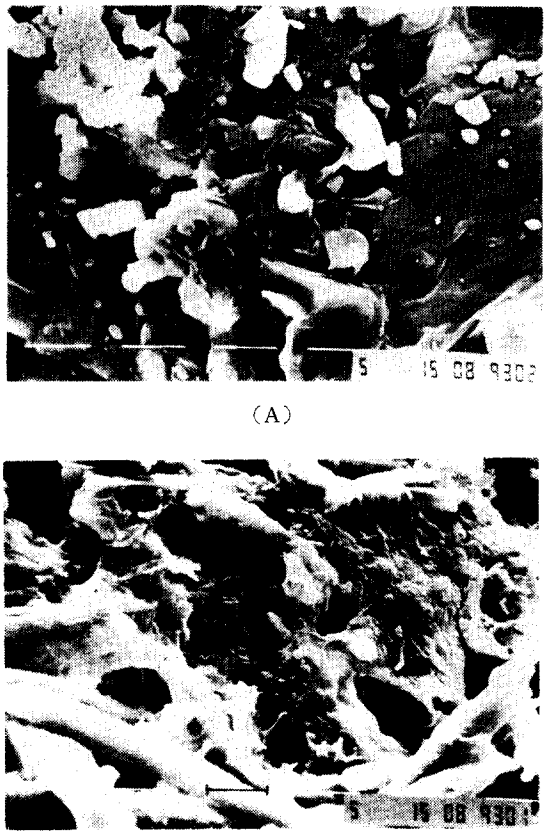



**Fig. 1**: Segment of membrane-coated tablet: (A) liquid penetrating into the membrane, dissolving the sucrose particles and (B) drug solution diffusing the membrane (transferred from reference 5).



(A)

(B)

**Fig. 2**: Scanning electron microphotographs of the membrane coat of INAH tablets: (A) membrane with suspended sucrose crystals and (B) the membrane after dissolution of the crystals. The bar indicates 5um.

*Drug Diffusion Studies*

The diffusion of dissolved INAH from the

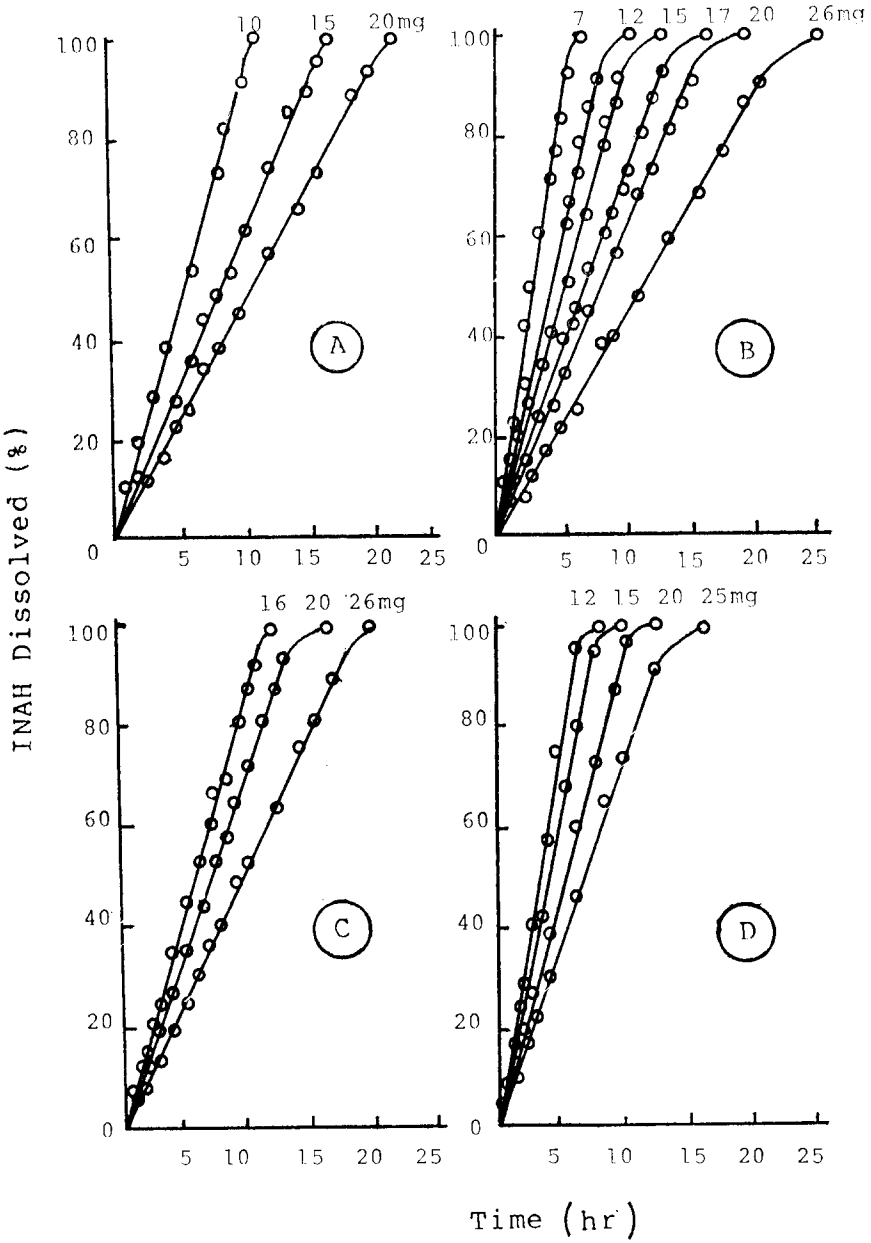



**Fig. 3**: In vitro release of INAH from the membrane-coated tablets using the rotating basket method. Dissolution test was performed at 37°C, 150 rpm and pH of the dissolution medium was 7.4. Numbers in the figures indicate the weight (mg) of the coat. The sucrose/PVC ratios of A, B, C and D were 2.0, 2.5, 2.75 and 3.0 respectively.

tablet through the pore can be calculated by using Fick's first law of diffusion

$$\frac{dM}{dT} = D \cdot (Cs - Cu) \frac{A}{h} \qquad \text{(Eq. 1)}$$

where $dM/dT$ is the rate of diffusion, $D$ the diffusion constant, $A$ the surface area, and $h$ the thickness of the diffusion layer. As long as the membrane coating tablet contains a saturated solution together with solid drug substance, the concentration inside the coating shell, $Cs$, is much higher than the concentration outside the coating shell, $Cu$. For INAH, $Cs$ was 12.5 %, while $Cu$ in our dissolution studies was maximally 0.06 %. Thus, the diffusion could be regarded as to take place during sink conditions (which means $Cu$ is neglible compared with $Cs$) and Eq. 1 is reduced to:

$$\frac{dM}{dT} = D \cdot S \cdot \frac{A}{h} \qquad \text{(Eq. 2)}$$

where $S$ means $(Cs - Cu)$ when $Cu$ is negligible compared with $Cs$. This implies that the diffusion should proceed at a constant rate (zero-order process). At the point where no solid substance is left within the membrane coating tablet, the rate of diffusion declines with decreasing concentration (first-order process).

*Release Pattern of INAH*

The release pattern of INAH from a membrane-coated tablet in pH 7.4 buffer solution is shown in Fig. 3. As the sucrose particles in the membrane were dissolved, the release of INAH began. The release rate increased sharply to a maximum in a few minutes, and maintained constant until above 90% of INAH was released. After 90% of content was released, the rate decreased slowly and linearly. At this point, there was no solid INAH left in the shell and the rate accordingly decreased.

*Effect of the Coat Weight on Release Rate*

The release rate of INAH from the tablet

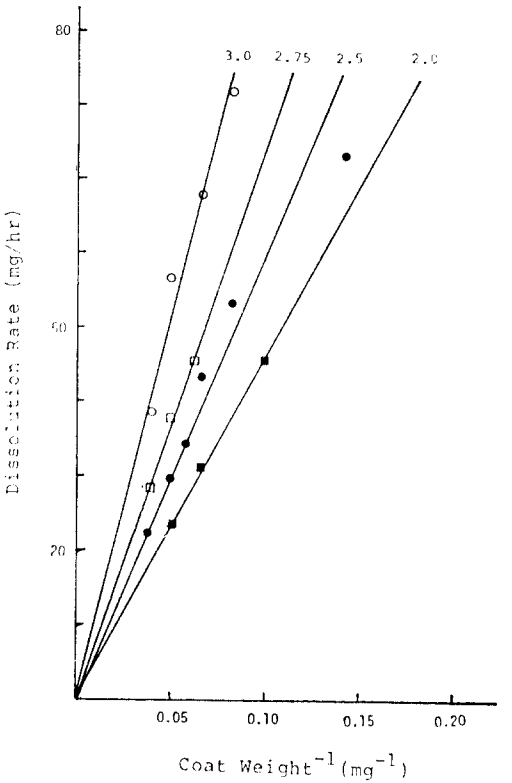



**Fig. 4**: Plots of the dissolution rate of INAN against the reciprocal of the coat weight of the tablets (pH 7.4, 37°C, 150 rpm). Numbers in the figure indicate the ratio of sucrose/PVC.

was proportional to the reciprocal of the coat weight (Fig. 4). Eq. 2 implies the proportional relationship between the release rate and the reciprocal of the thickness of the diffusion layer. The linear relationship in Fig. 4, therefore, seems to be due to rough proportionality of the coat weight to the thickness of the diffusion layer.

*Effect of Membrane Composition on the Release Rate of INAH*

The ratio of the soluble component to the insoluble polymer (sucrose: PVC) in the membrane influenced the release rate (Fig. 5). The

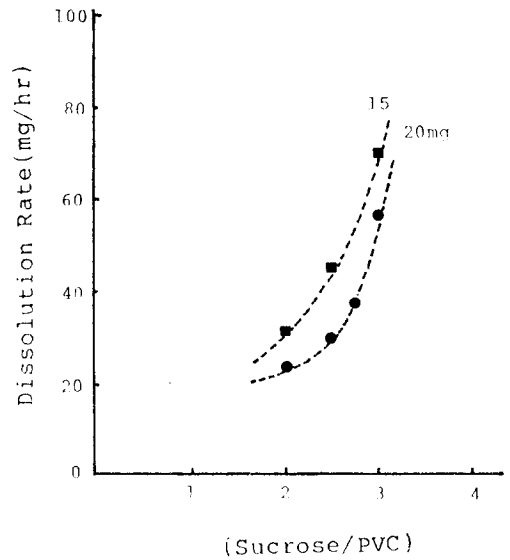



**Fig. 5**: Effect of the sucrose/PVC ratio on the dissolution rate of INAH from the tablets (pH 7.4, 37°C, 150 rpm). Numbers in the figure indicate the coat weight (mg).

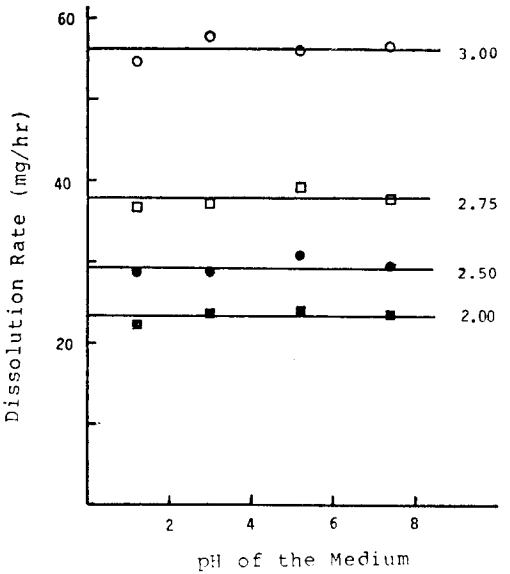



**Fig. 6**: Effect of pH on the dissolution rate of INAH from tablets. The sucrose/PVC ratios(numbers in the figure) were varied from 2 to 3, but the coat weights were kept constant at 20mg.

release rate increased as the ratio of sucrose/PVC increased, probably because it gives a high porosity coating. Desired release rate was achivable by controlling this ratio.

*Effect of pH of the Dissolution Medium on the Release Rate of INAH*

Fig. 6 shows that the release rate is independent of the medium. This may be due to pH-irrespective solubility character of INAH. INAH is very highly soluble in pH ranges examined in this study. It could make $S$ in Eq. 2 constant and therefore, constant release of INAH was achivable in a pH-independent manner. This implies the possibility of constant release of INAH from the tablet in the gastrointestinal tract, where pH varies from 1 to 8 or more. Constant release of INAH in vivo also implies the possibility of constant absorption and constant blood level of INAH subsequently.

## CONCLUSION

Membrane-coated tablets of INAH were prepared to develope a controlled release drug delivery system and the release characteristics were studied. Tablet core was prepared by compressing granules of INAH and PVP and was coated by spraying the suspension of PVC and micronized sucrose in methyl ethyl ketone. Water-soluble sucrose behaved as a pore-producing material in the water-insoluble PVC film coat. The release of INAH from the tablet was zero-order rate process. The release rate increased as the ratio of sucrose/PVC (w/w) increased and decreased as the coat weight increased. The release rate could be controlled by varing the sucrose PVC ratio of the coating suspension. The release rate did not depend on the pH of the dissolution medium. This pH-independency of the release rate implies the possibility of

constant release of INAH in vivo strongly, in which pH varies in the wide range (from 1 to 8 or more). Therefore, this membrane-coated INAH tablet seemed to be a powerful candidate for the controlled release drug delivery system of INAH. Plasma level of INAH after administration of this tablet must be checked in vivo and now be in process in our laboratory.

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