

Gastric Emptying Rate of Drug Preparations. III. Effects of Size of Enteric Micro-Capsules with Mean Diameters Ranging from 0.1 to 1.1 mm in Man

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The gastric emptying rates of three enteric micro-capsule preparations with mean diameters of 1.1 mm and less (1.1, 0.5 and 0.1 mm) were compared. The gastric emptying rate was evaluated by determining the pharmacokinetic parameters of pyridoxic acid, including V_{\max} (peak excretion rate) and T_{\max} (time to reach peak excretion rate) after oral administration of micro-capsules containing pyridoxal phosphate as a marker drug to five healthy subjects. When given under fasting conditions, the gastric emptying rates of these preparations, according to T_{\max} , differed significantly; the preparations with smaller particle sizes were emptied from the stomach at a faster rate than those with larger particle sizes. However, under non-fasting conditions the gastric emptying rates were virtually the same, regardless of particle size, and all the preparations were emptied from the stomach at a much slower rate than when administered under fasting conditions.

Keywords gastric emptying rate; enteric micro-capsule; healthy human subject; particle size; food; pyridoxal phosphate; bioavailability

Introduction

The gastric emptying rate of oral dosage forms is one of the most important determinants of drug bioavailability and is dependent upon various factors, such as the size and density of the preparations, dietary amount and content, disease state of the subject and coadministered drugs.¹⁻⁴⁾ Ideally, preparations for oral administration should be formulated so that the gastric emptying rate is virtually constant regardless of the subject's condition. The relationship between the size of the preparation and gastric emptying rate has been reported by many authors.⁵⁻⁹⁾ In studies which compared the gastric emptying rates of dosage forms, such as enteric-coated granules (1 mm diameter) and enteric-coated tablets (10 mm diameter),⁷⁾ enteric-coated granules (1, 4 and 8 mm diameter)⁸⁾ and plastic spheres (1, 2.4 and 3.2 mm diameter),⁹⁾ the smaller ones have been observed to be emptied faster under both fasting and non-fasting conditions, and liquid solutions of drugs also appear to be emptied rapidly under both conditions. There are few reports about the gastric emptying rates of solid dosage forms with diameters of less than 1 mm, probably because of the technical problems involved in their preparation. One of the authors has developed a new technique for preparing micro-capsules with diameters of less than 1 mm. This report describes the results of a study in which the gastric emptying rates of three solid dosage forms with mean diameters of 1.1 mm and less were compared in healthy subjects under fasting and non-fasting conditions.

Materials and Methods

Materials Pyridoxal phosphate and pyridoxic acid were obtained from Nakarai Chemicals, Ltd., Kyoto, and from Sigma, St. Louis, respectively. Dextrin (Amycol-5L) was obtained from Nippon Starch Refining Co., Ltd. All the other reagents used were of analytical grade.

Preparations of Pyridoxal Phosphate-Containing Enteric Micro-Capsules Pyridoxal phosphate was granulated with dextrin (20 w/w% in 45 v/v% ethanol), dried and sieved through different meshes, 80—105, 420—500 and 840—1000 μm . Three grams of the pyridoxal phosphate granules were dispersed¹⁰⁻¹²⁾ in 50 ml of an acetone solution of HP-55 (hydroxypropylethyl cellulose phthalate) and ethylcellulose (2:1 w/w). One hundred ml of cyclohexane was added gradually to the solution to

induce coaggregation. The micro-capsules were washed with a solution of ethyl acetate-cyclohexane (7:3 v/v) followed by washing with *n*-hexane, dried and sieved through different meshes to separate the sizes. The particle sizes, with density determined by a pycnometer and the pyridoxal phosphate content of each of the preparations, A (88—125 μm), B (420—590 μm) and C (840—1410 μm), used in this study are listed in Table I. The mean diameters quoted represent the middle value of the size range sieved.

Solubility of Pyridoxal Phosphate *in Vitro* The solubility of pyridoxal phosphate powder, *in vitro*, at pH 1.2 (the first fluid of the JP XI disintegration test), pH 4.5 (0.1 M acetate buffer), pH 5.5 (0.1 M acetate buffer) and pH 6.6 (0.1 M phosphate buffer) was determined at 37°C as described previously.¹³⁾

Dissolution Rate of Pyridoxal Phosphate from Micro-Capsules *in Vitro* The dissolution of pyridoxal phosphate from the micro-capsules, *in vitro*, was measured by the oscillating basket method¹⁴⁾ at 37°C. The dissolution media used were the first fluid (pH 1.2, disintegration test, JP XI) and 0.1 M acetate buffers (pH 5.5 and 4.5), and the concentration of the drug in the media at various times was monitored at 390 nm.

Bioavailability Study Each of the three preparations (A, B and C), which contained 10 mg of pyridoxal phosphate, were given orally to five subjects (two females and three males, aged 22—27 years and weighing 48—67 kg) with 100 ml of tap water under fasting and non-fasting conditions, according to a randomized cross-over design with a three-day washout between finishing one test period and taking the next preparation. Each subject gave informed consent for the study to be performed. None of the subjects received any medication for at least 2 weeks prior to taking the first oral preparation. For the fasting experiment, subjects were fasted overnight and for 4 h after ingestion of each of the preparations, after which a standard lunch (400 g rice and 200 ml miso soup) was consumed. Urine samples were collected for 28 h after administration and stored at -20°C until assayed. For the non-fasting experiment, the preparations were given orally 30 min after consumption of a standard breakfast (100 g bread, one boiled egg, 15 g butter, 35 g cucumber and 200 ml milk). The sampling and storage procedures were conducted as described for the fasting experiment.

The bioavailability of pyridoxal phosphate was evaluated using the

TABLE I. Characteristics of Enteric Micro-Capsules of Pyridoxal Phosphate

Micro-capsule	Particle size range	Density	Content (%)
A	88—125 (100) ^{a)}	1.113	53.9
B	420—590 (500)	0.989	64.5
C	840—1410 (1100)	1.053	68.9

a) Mean diameter.

following pharmacokinetic parameters, which were based on the urinary excretion of pyridoxic acid, one of its major metabolites: the excretion rate at the midpoint between urine sampling times, cumulative amounts excreted in the urine from 0 to 28 h (Am_{0-28}), peak urinary excretion rate (V_{max}) and time to attain the peak urinary excretion rate (T_{max}). Pyridoxic acid, which is a metabolite of intrinsic compounds, is excreted in the urine at a constant rate. However, as its basal excretion rate is relatively small compared with that observed after administration of pyridoxal phosphate, the observed values were used for pharmacokinetic analysis without subtraction of the basal values.

Assay of Pyridoxic Acid in Urine The concentration of pyridoxic acid in urine was determined by high-performance liquid chromatography (HPLC). The chromatographic system consisted of a pump (Shimadzu LC-6A), fluorescence detector (Shimadzu RF-530) set at 325 nm (excitation) and 410 nm (emission), reverse-phase column (Nucleosil C18, 5 μ m, 250 \times 4 mm) and a mobile phase (0.05 M phosphate buffer (pH 7.0): acetonitrile (77:23 v/v)). Twenty microliters of 50-fold diluted urine with purified water was injected onto the HPLC system and eluted at a flow rate of 1.0 ml/min. The lower limit of the assay for pyridoxic acid in urine was 10 ng/ml.

Statistical Analyses The pharmacokinetic parameters obtained from the urinary excretion data of pyridoxic acid were subjected to analysis of variance (ANOVA) and Tukey's multiple range test, if necessary. Differences at p values of less than 0.05 were considered to be significant.

Results

The solubility of pyridoxal phosphate powder, *in vitro*, was very high (12 mg/ml at pH 1.2, 101 mg/ml at pH 4.5, 163 mg/ml at pH 5.5 and 29 mg/ml at pH 6.5). Less than 10% of the pyridoxal phosphate in the micro-capsules had

dissolved after 2 h at pH 1.2 and 4.5, but at pH 5.5 they dissolved after a short lag time (t_{lag}) (2.1, 2.0 and 2.6 min for preparations A, B and C respectively), irrespective of particle size. As pyridoxal phosphate is a highly soluble drug, its pH-dependent dissolution from the micro-capsules can be ascribed to the dissolution characteristics of HP-55, the capsular material used.

Figure 1 shows the mean urinary excretion rates of pyridoxic acid obtained after oral administration of pyridoxal phosphate from the different-sized enteric micro-capsules. The peak time (T_{max}) to reach the maximum excretion rate (V_{max}) of pyridoxic acid tended to be longer in proportion to the size of the micro-capsules when administered under fasting conditions, and tended to be longer when administered under non-fasting conditions.

Figure 2 shows the relationship between the mean particle size of the enteric micro-capsules administered and the resultant pharmacokinetic parameters of pyridoxic acid. According to the Am_{0-28} values, the bioavailability of pyridoxal phosphate appeared to be the same, regardless of the preparation or administration conditions. When administered under fasting conditions, the T_{max} values of the preparations differed significantly, although none of the V_{max} values differed significantly. Under non-fasting conditions, however, neither V_{max} nor T_{max} of any of the

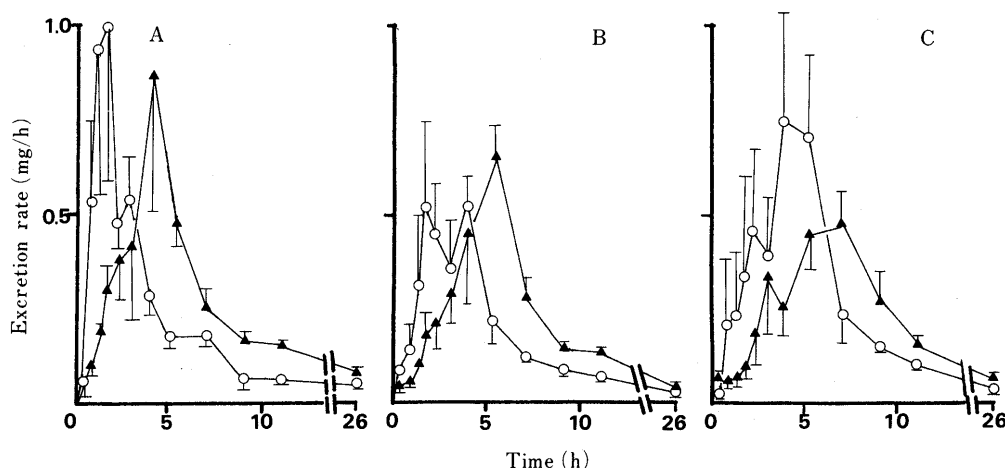


Fig. 1. Urinary Excretion Rate of Pyridoxic Acid after Administration of Enteric Micro-Capsules of Pyridoxal Phosphate with Three Different Mean Diameters under Fasting (○) and Non-fasting (▲) Conditions

A, micro-capsule A; B, micro-capsule B; C, micro-capsule C. $n=5$, mean \pm S.E.

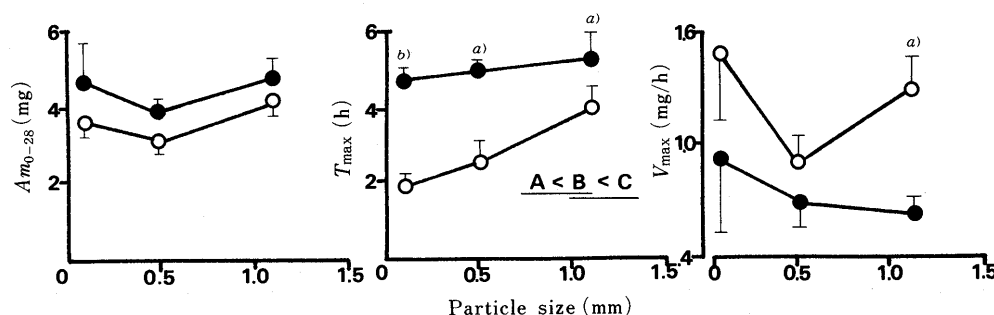


Fig. 2. Relation between Mean Diameter of Enteric Micro-Capsules and the Pharmacokinetic Parameters of Pyridoxic Acid after Oral Administration of Enteric Micro-Capsules Containing 10 mg of Pyridoxal Phosphate under Fasting (○) and Non-fasting (●) Conditions

$n=5$, mean \pm S.E. T_{max} showed significant differences between fasting and non-fasting conditions (a) $p < 0.05$, (b) $p < 0.01$) in all preparations tested, and between preparations under fasting conditions. The mean values for treatments not underscored by the same line differ significantly. The V_{max} of preparation C is significantly lower under non-fasting than under fasting conditions (a) $p < 0.05$).

preparations differed significantly. When these parameters were compared under fasting and non-fasting conditions, the T_{\max} values of all three preparations and V_{\max} of preparation C differed significantly.

Discussion

In this study we used enteric micro-capsules containing pyridoxal phosphate as a marker drug in order to compare the gastric emptying rates of preparations with mean particle diameters of 1.1 mm and less. As pyridoxal phosphate is highly soluble and is absorbed rapidly from the gastrointestinal tract,¹⁵⁾ it is reasonable to expect that it would appear in blood almost immediately after dissolution from the enteric micro-capsule. This method enables the relative gastric emptying rates of different preparations, or of identical preparations under different administration conditions, to be measured, although it does not provide a precise value of the absolute gastric emptying rate.

Pyridoxal phosphate was considered to be absorbed rapidly from the small intestine, regardless of the gastric pH of the subjects, when it was administered as an enteric-coated tablet from which the drug dissolved, *in vitro*, after a short lag time at pH 5.5 using the oscillating basket method, as shown previously.^{16,17)} In a previous study, we investigated the relationship between the gastric emptying rates of aspirin-containing enteric-coated preparations and the size of the preparations (1, 4 and 8 mm) by comparing the pharmacokinetic parameters of the resultant salicylates.⁸⁾ The parameters used to estimate the gastric emptying rate (t_{lag} , T_{\max} and mean absorption time (MAT)) increased, *i.e.* the relative gastric emptying rate decreased, as the size of the dosage form increased. In addition, food intake slowed the gastric emptying rate of the preparations tested, although the smaller preparations were affected to a lesser degree.

The T_{\max} values obtained indicate that the gastric emptying rates of preparations with diameters of 1.1 mm or less are affected by the particle size of the preparation when administered under fasting conditions (Fig. 2), although apparently somewhat less than those with diameters in excess of 1 mm.⁸⁾

The V_{\max} value, which is used often as a parameter of the rate of bioavailability, of the various preparations did not differ significantly. V_{\max} varies with changes in the rate of bioavailability and in the extent of bioavailability. The extent of bioavailability, reflected by the Am_{0-28} values, ranged from 3.2 to 4.4 mg under fasting and 4.0 to 5.0 mg under non-fasting conditions, although these values did not differ significantly. This may explain why the V_{\max} value of the preparations did not differ significantly, although the T_{\max} values did.

The effect of particle size on gastric emptying rate (T_{\max}) observed under fasting conditions was not observed under non-fasting conditions. In the non-fasting state, the gastric emptying rate (T_{\max}) was slower than that in the fasting state for all the preparations tested, regardless of size. As the gastric contractions after food intake are less powerful than those in the fasting state,^{18,19)} the larger preparations are believed to remain in the stomach longer

under non-fasting conditions. As demonstrated previously, the rate of bioavailability, represented by t_{lag} , T_{\max} and mean residence time (MRT), of powders and granules was affected less than that of tablets after postprandial administration.⁵⁾ In this study of microcapsules with a mean diameter of 1.1 mm or less, no effect of particle size on the gastric emptying rate (T_{\max}) was observed under non-fasting conditions.

In conclusion, even in preparations with a mean particle size diameter ranging from 0.1 to 1.1 mm, the gastric emptying rate, represented by T_{\max} , appeared to be affected significantly by particle size under fasting conditions, although to a lesser extent than has been observed with preparations with mean diameters in excess of 1 mm. However, under non-fasting conditions, no effect of particle size on the gastric emptying rate (T_{\max}) was observed, and it was reduced to the same extent for all the preparations tested, regardless of particle size.

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