Gastric Emptying Rates of Drug Preparations. II. Effects of Size and Density of Enteric-Coated Drug Preparations and Food on Gastric Emptying Rates in Humans

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Enteric-coated granules with different densities and tablets of different sizes were prepared in order to study the effect of these physical properties of dosage forms on the gastric emptying rates in humans. The effect of food on the gastric emptying rate was also studied. Aspirin contained in an enteric-coated product as a marker drug was used to determine the gastric emptying rate by measuring salicylates excreted into the urine. The larger the size of the dosage form, the larger were the values of parameters for estimating the gastric emptying rate such as t<sub>lag</sub>, t<sub>max</sub> and the mean absorption time. There was a significant correlation between the gastric emptying rates and sizes of dosage forms. On the other hand, no effects of density of enteric-coated granules on the gastric emptying rate were observed. The gastric emptying of dosage forms of various sizes or densities tested were prolonged by food. However, the gastric emptying rate of granules was less affected by food than that of tablets.

Keywords — gastric emptying rate; enteric-coated granule; enteric-coated tablet; human; dosage size form; granule density; meal; aspirin

Introduction

In the previous report, the gastric emptying rates of three types of dosage forms (liquid, granules and tablet) were determined simultaneously in humans and beagle dogs using three different marker drugs contained in the dosage forms. The dosage form with a larger size was found to be more slowly emptied from the stomach, and the gastric emptying rate of granules was found to be less affected by food than those of the tablet and liquid. In order to study the effects of physical properties of dosage forms such as size and density and food on the gastric emptying rate more precisely, enteric-coated granules with different densities and enteric-coated tablets with diameters of 4 and 8 mm containing aspirin as a marker drug were prepared and the gastric emptying rates were determined under the fasting and nonfasting states in the same manner as previously reported.

Materials and Methods

Materials — Enteric-coated products of aspirin used were prepared as follows. Tablets-8: Plain tablets contained 20% aspirin (JP IX), 55% Lactose G® (Freund Ind., Co., Ltd.), 10% microcrystalline cellulose, 13% Perfiller 101® (Freund Ind., Co., Ltd.) and 2% lubricant. The plain tablets were coated with 8% (w/w) carboxymethylcellulose (CMEC). The diameter and the apparent density of the tablets were 8 mm and 1.32, respectively, and 127.5 mg of aspirin was contained in three tablets. Tablets-4: Plain tablet contained 20% aspirin, 68% Lactose G®, 10% microcrystalline cellulose and 2% lubricant and the tablets were coated with 15% CMEC. The diameter and apparent density were 4 mm and 1.39, respectively, and 110.0 mg of aspirin was contained in fifteen tablets. Granules-L: Plain granules contained 20% aspirin, 45% Nonparell® (Freund Ind., Co., Ltd.), 30% cornstarch and 5% low substituted hydroxypropylcellulose and were coated with 20% CMEC. The granules had spherical shapes of 1
mm diameter and their apparent density was 1.29. About 440 particles (total weight is 600 mg) contained 106.7 mg of aspirin. Granules-H: High density granules contained 21% aspirin, 17% Nonparell® , 31% barium sulfate, 29% cornstarch and 2% low substituted hydroxypropylcellulose, and were coated with 20% CMEC. The granules had the same shape and size as Granules-L. Their apparent density was 1.92 and 102.7 mg of aspirin was contained in 600 mg granules (about 300 particles).

All other chemicals were of reagent grade.

**Dissolution Rate** — The dissolution rate of aspirin from enteric-coated preparations was measured by an oscillating basket method using 900 ml of the first fluid of the disintegration test (JP X, pH 1.2) and 0.1 M acetate buffer of pH 5.6. One hundred and twenty mg of aspirin, a single dose in human study, were used for determination of the dissolution rate and 2 ml of the test solution was sampled periodically. The solution filtered through a membrane filter with a pore size of 0.8 μm was diluted with 0.1 N NaOH. The sodium salicylate in the solution was determined at 310 nm.

**Bioavailability** — Three Tablets-8, fifteen Tablets-4 and 600 mg of Granules-L and -H were separately administered to human subjects orally in the fasting and nonfasting states. In each treatment about 120 mg of aspirin was administered. A randomized block design for eight treatments was performed using six subjects. Urine was sampled at 0.5, 1.5, 2.5, 3.5, 4.5, 5.5, 6.5, 8, 10, 12, 14 and 22 h after drug administration. The other protocol of the test was the same as previously reported.

**Assay** — All salicylates excreted into urine were determined colorimetrically. Three ml of urine sample and 2 ml of conc. HCl were sealed in an ampule. The ampule was kept in an oil-bath at 100 °C for 17 h. The solution was transferred to a test tube containing 2 ml of water and 0.5 ml of 6 N HCl was added to the test tube. Then free salicylates were extracted into 4 ml of chloroform, and 3 ml of the organic phase were reextracted with 6 ml of Trinder’s reagent (4% Fe(NO₃)₃·9H₂O in 1 N HCl). The absorbance of salicylate-ferric ion complex in the aqueous phase was measured at 540 nm.

**Statistical Analyses** — The lag time (τₗₜ₃) in the appearance of metabolites in urine and the mean absorption time (MAT) were used as parameters for estimating the gastric emptying rate. τₗₜ₃ was calculated by fitting urine data to an apparent one compartment model with first-order absorption using PKM-MULTI, a non-linear least square program. MAT was calculated by subtracting the reciprocal of the elimination rate constant from the mean residence time. Because all dosage forms prepared contained the same drug, aspirin, and the elimination rate constant could be assumed to be constant in one subject throughout all treatments, the time taken to reach the peak excretion rate (τₜₚₓ) was also used as a parameter representative of the gastric emptying rate. These parameters were statistically subjected to analysis of variances (ANOVA) and the Tukey’s multiple range test was done if necessary.

**Results and Discussion**

The dissolution rates of aspirin from the formulations used are summarized in Table I. In the previous study, an enteric coated tablet with a critical dissolution pH of 5.5 (the lowest pH where an enteric coated tablet dissolves) was found to dissolve rapidly in subjects at any level

<table>
<thead>
<tr>
<th>Dosage forms</th>
<th>Diameter</th>
<th>Aspirin content/dose</th>
<th>Particle numbers/dose</th>
<th>Density</th>
<th>τₜₚₓ pH 6.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granules-L</td>
<td>1 mm</td>
<td>106.7 mg</td>
<td>ca. 440</td>
<td>1.29</td>
<td>24.0</td>
</tr>
<tr>
<td>Granules-H</td>
<td>1 mm</td>
<td>102.7</td>
<td>ca. 300</td>
<td>1.92</td>
<td>28.3</td>
</tr>
<tr>
<td>Tablets-4</td>
<td>4 mm</td>
<td>110.0</td>
<td>15</td>
<td>1.39</td>
<td>23.9</td>
</tr>
<tr>
<td>Tablets-8</td>
<td>8 mm</td>
<td>127.5</td>
<td>3</td>
<td>1.32</td>
<td>24.8</td>
</tr>
</tbody>
</table>
of gastric acidity once it was transferred into the intestine. Thus the enteric-coated preparations of aspirin were designed to release aspirin at pH values higher than 5.5 for determination of the gastric emptying rates of granules and tablets. All enteric-coated dosage forms prepared showed no dissolution of aspirin in the first fluid (JP X) within 2 h. Although the gastric emptying rate of various dosage forms did not correlate with each other in the previous study,\(^1\) it was found that the larger the particle size, the longer the gastric emptying rate. Therefore in this study, we investigated more precisely in humans the effect of size on the gastric emptying rates of dosage forms using 1, 4 and 8 mm diameter particles or tablets each containing the same marker drug, aspirin. The effects of density of dosage forms on the gastric emptying rate were also studied using granules of 1 mm diameter.

Since salicylic acid is eliminated linearly at dosages below 0.3 g,\(^7\) the linearity in the elimination was maintained after administration of 0.1 g of aspirin in this work. Although all salicy-

### Table II. Effect of Food on Gastric Emptying Rate of Dosage Forms

<table>
<thead>
<tr>
<th>Diameter</th>
<th>Parameter</th>
<th>Fasting</th>
<th>Non fasting</th>
<th>Tukey’s test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granules-L (1 mm)</td>
<td>(t_{\text{lag}}) (h)</td>
<td>1.28±0.72 (^a)</td>
<td>3.24±1.21</td>
<td>n.s. (^b)</td>
</tr>
<tr>
<td></td>
<td>(t_{\text{max}}) (h)</td>
<td>4.33±1.21</td>
<td>7.04±2.00</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>MAT (h)</td>
<td>3.32±1.06</td>
<td>4.64±0.70</td>
<td>n.s.</td>
</tr>
<tr>
<td>Granules-H (1 mm)</td>
<td>(t_{\text{lag}}) (h)</td>
<td>1.45±0.99</td>
<td>3.33±1.21</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>(t_{\text{max}}) (h)</td>
<td>4.17±1.17</td>
<td>8.04±3.21</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>MAT (h)</td>
<td>3.67±0.87</td>
<td>5.47±1.78</td>
<td>n.s.</td>
</tr>
<tr>
<td>Tablets-4 (4 mm)</td>
<td>(t_{\text{lag}}) (h)</td>
<td>1.66±0.58</td>
<td>4.70±1.44</td>
<td>(p &lt; 0.05)</td>
</tr>
<tr>
<td></td>
<td>(t_{\text{max}}) (h)</td>
<td>5.71±2.00</td>
<td>9.25±1.77</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>MAT (h)</td>
<td>4.22±0.58</td>
<td>6.38±0.97</td>
<td>(p &lt; 0.05)</td>
</tr>
<tr>
<td>Tablets-8 (8 mm)</td>
<td>(t_{\text{lag}}) (h)</td>
<td>2.96±1.04</td>
<td>5.99±1.65</td>
<td>(p &lt; 0.05)</td>
</tr>
<tr>
<td></td>
<td>(t_{\text{max}}) (h)</td>
<td>6.75±1.40</td>
<td>8.71±1.93</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>MAT (h)</td>
<td>5.05±0.91</td>
<td>7.23±1.74</td>
<td>(p &lt; 0.05)</td>
</tr>
</tbody>
</table>

\(^a\) Mean ± S.D. \(^b\) Not significant at \(p = 0.05\).
lates in the urine were determined concomitantly, the excretion rates-time curves followed an apparent one-compartment model with first-order absorption. Therefore the $t_{lag}$ and the differences of MAT between different dosage forms are considered to represent the lag time and the time differences only in the absorption phase.

**Effect of Diameter on Gastric Emptying Rate**

Figure 1 shows the average excretion rate-time profiles after administrations of the three dosage forms separately to six healthy volunteers post- or pre-prandially. The values of $t_{lag}$ and MAT of Granules-L and Tablets-8 in the fasting state (Table II) were a little larger than those of the granules and the tablet observed in the previous study,\(^1\) which might be caused by the fact that the dissolution rates of granules and tablets used and the subjects were different in the two studies.

The values of the parameters increased in all subjects except one as the diameters of the dosage forms increased (Fig. 2). The correlation coefficient between each parameter and the diameter was very high ($r = 0.975$ for $t_{lag}$, $r = 0.995$ for MAT and $r = 0.987$ for $t_{max}$). The result of this study show more clearly the effect of size of the dosage forms on the gastric emptying rate than the results of the previous study; that is, granules are emptied more rapidly than tablets. In the previous study, data for the small tablet were lacking and different marker drugs were used in dosage forms with various sizes.

**Effect of Density on Gastric Emptying Rate**

The nearly equal values of the parameters for Granules-L and -H were obtained (Table II), and were not significantly different. Bechgaard *et al.*\(^8\) reported that the gastrointestinal transit time of heavy pellets was longer than that of light pellets using ileostomy patients. Although granules of similar density used by Bechgaard *et al.*\(^8\) were used in this study, no effects of the density of the formulations were recognized. They measured the transit time of the pellets from the stomach to the end of the ileum, while, in this study, we concentrated mainly on the transit time of the granules from the stomach into the upper site of the intestine, although the observed transit time included the time for dissolution. This may be one of the reasons why such a discrepancy of results occurred between theirs study and ours. From our results, there does not seem to by any large differences in the transit rate between the heavy and light granules, at least until leaving the stomach.

**Effect of Food on the Gastric Emptying Rates of Drugs**

The delay in the gastric emptying caused by
Effect of Size on Gastric Emptying Rate

taking food before administration was recognized in this study (Table II). Gastric emptying of Granules-H was affected by food as was that of Granules-L (Table II). In the previous study, the gastric emptying rates was also found to be prolonged by food. However, the difference in the gastric emptying rates of granules between fasting and nonfasting states was smaller than that observed; that is, the differences of parameter values of Granules-L between both treatments were smaller than those observed in the other dosage forms tested and they were not statistically significant.

Bogentoft et al. reported that plasma level profiles of salicylic acid overlapped after administration of aspirin enteric-coated granules post- and prandially. Maekawa et al. pointed out that the drug absorption rate of enteric-coated granules was less affected by kinds of foods than that of enteric-coated tablets. These findings were also confirmed by our studies. Therefore, in the case of enteric-coated preparations, granules should be administered to obtain a clinical effect that is relatively unvaried by administration conditions such as feeding.

The good correlations between the parameters for estimating the gastric emptying rate and the diameter of the formulations still remained after administration in the nonfasting state except \( t_{\text{max}} \ (r = 0.993 \text{ in } t_{\text{lag}} \text{ and } r = 0.962 \text{ in MAT}) \). The peak excretion rates after preprandial administration of all drugs ranged between 14.7 and 17.0 mg/h, and those after postprandial administration between 14.1 and 16.2 mg/h. Recovery of salicylates in 22 h after preprandial administration of all drugs ranged between 94.5 and 104.9% and that of postprandial administration between 93.7 and 103.2%. These values did not differ significantly between drug administrations post- and pre-prandially. Thus delayed gastric emptying by food did not lead to a lower absorption amount of drugs from these preparations.

The relationship between the gastric residence time (GRT) of the Heidelberg capsule and \( t_{\text{lag}} \) of aspirin contained in an enteric-coated tablet was investigated in beagle dogs, and an excellent correlation was recognized (\( t_{\text{lag}} = 1.0 \times \text{GRT} + 1.95 \)). Also, a significant linear relationship (\( t_{\text{lag}} = 0.92 \times \text{MAT} - 1.52, p < 0.01 \)) was obtained between \( t_{\text{lag}} \) and MAT, and the value of the slope for this line was near 1. Thus, both parameters used in this work are recognized as suitable parameters for estimating the gastric emptying rate, although our method for determination of the gastric emptying rate of a formulation was an indirect method.

References