Pharmacokinetics of Acetaminophen from Rapidly Disintegrating Compressed Tablet Prepared Using Microcrystalline Cellulose (PH-M-06) and Spherical Sugar Granules

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The aim of the present study was to evaluate the bioavailability of a drug from rapidly disintegrating tablets prepared using fine spherical crystalline cellulose (PH-M-06) and spherical sugar granules (Nonpareil, NP). Rapidly disintegrating tablets containing acetaminophen as the model drug in combination with a mixture of NP-108 (purified D-mannitol) and PH-M-06 were prepared. Plasma concentration profiles and pharmacokinetic parameters of acetaminophen in rabbits were investigated after oral administration of the prepared tablets. No significant difference in $C_{\text{max}}$ and $AUC_{0-\infty}$ of acetaminophen between rapidly disintegrating tablets and conventional tablets was observed after direct administration of these tablets into the stomach of rabbits. However, $t_{\text{max}}$ (15 min) of acetaminophen from rapidly disintegrating tablets was significantly ($p<0.05$) shorter than that from conventional tablets (130 min). The same $t_{\text{max}}$ was observed for rapidly disintegrating tablets and solution. When suitable excipients such as fine spherical microcrystalline cellulose (PH-M series) and spherical sugar granules (NP series) were used, rapidly disintegrating tablets could be prepared by the conventional direct compression method. According to the results of moment analysis, the mean residence time (MRT) obtained between both rapidly disintegrating and conventional tablets indicates that the mean absorption time (MAT) from these tablets is approximately 60 and 90 min, respectively. This difference in MAT between the two tablets may be caused by the difference in the sum of the mean dissolution time (MDT) and the mean disintegration time (MDIT) of these tablets. Rapidly disintegrating tablets allow rapid absorption of the drug compared with conventional tablets.

Key words acetaminophen bioavailability; rapidly disintegrating tablet; fine microcrystalline cellulose; spherical sugar granule; rabbit

In our previous paper, we reported that tablets with the characteristic of rapid disintegration by saliva in the mouth (rapidly disintegrating tablets) can be prepared by the direct compression method using spherical sugar granules (water-soluble sugar granules, Nonpareil®, hereafter abbreviated as NP) in combination with fine microcrystalline cellulose (PH-M-06, mean particle size, 7 μm) as the binder to decrease the sensation of roughness in the mouth after disintegration. Such tablets (compressed at 3 kN) had sufficient crushing tolerance (force required to break the tablet, 3 kg) and short disintegration time (within 15 s) in the mouth. We also found that the use of crystalline cellulose with a water-insoluble material of small particle size is better than that with a water-insoluble material of large particle size in terms of the sensation of roughness after disintegration of the tablet in the mouth. Although the particles of NP, a spherical sugar granules, are large, it does not give a feeling of roughness in the mouth because it is well dissolved by saliva. These technical achievements led us to investigate whether the bioavailability of a drug from this type of tablet might be equivalent to that of conventional preparations for oral administration.

The aim of the present study was to evaluate the bioavailability of a drug from rapidly disintegrating tablets prepared using fine spherical crystalline cellulose (PH-M-06) and spherical sugar granules (NP). Rapidly disintegrating tablets containing acetaminophen as the model drug in combination with a mixture of NP-108 (purified D-mannitol) and PH-M-06 were prepared. Plasma concentration profiles and pharmacokinetic parameters of acetaminophen in rabbits were investigated after oral administration of the prepared tablets.

**Experimental**

**Materials** Acetaminophen (JP XIII) was purchased from Maruish Seiyaku Co., Tokyo, Japan. As spherical sugar granules, purified D-mannitol spheres (Nonpareil-108®, Friend Industry Co., Tokyo, Japan) were used. Fine microcrystalline cellulose (Avicel PH-M-06®) was a gift from Asahi Chemical Industry Co., Tokyo, Japan. All other reagents were of analytical grade.

**Preparation and Evaluation of Tablets** Rapidly disintegrating tablets were prepared by the direct compression method as described in a previous report. The crushing tolerance of the prepared tablets (200 mg, flat-faced, 8 mm diameter) by diametrical compression was measured with a digital crushing tolerance measuring machine (TS-50N®, Okada Seiko, Tokyo, Japan). Determination of the disintegration time in the mouth was carried out according to the method described in our paper. Administration of Tablets in Rabbits For oral administration experiments, male rabbits (Japan White) weighing 2.8–3.1 kg were used. They were housed individually in cages under environmentally controlled conditions (23 ± 2°C; 55 ± 5% relative humidity, 12 h light/dark cycle). Prior to each experiment, the rabbits were starved for 24 h according to the method of Maeda et al. with slight modification, and were allowed free access to tap water only. Rapidly disintegrating tablets (100 mg) were directly administered into the stomach of rabbits. Tablets (flat-faced, 5 mm diameter) containing 50 mg of acetaminophen each were prepared and administered using a gastric intubation tube (made of silicone rubber) with one tablet set on the tip of tube. Conventional tablets (100 mg) or solution (3 ml) containing 50 mg (same dose as that of rapidly disintegrating tablets) acetaminophen were administered orally. For intravenous injection, saline solution containing acetaminophen (50 mg/3 ml) was administered into the marginal ear vein.

**Pharmacokinetic Analyses** Plasma acetaminophen concentration was assayed by high-performance liquid chromatography (HPLC), as reported by Ameer et al. The peak acetaminophen concentration ($C_{\text{max}}$) and the time to reach $C_{\text{max}}$ ($t_{\text{max}}$) were obtained from individual plasma acetaminophen concentration-time curves. The statistical moments for the plasma acetaminophen concentration-time curves are defined by the following equations:

\[ C(t) = \frac{A}{2} \left( 1 + \frac{t}{t_D} \right) e^{-\frac{t}{t_D}} \]

\[ A = \text{area under the plasma concentration-time curve} \]

\[ t_D = \text{time of drug elimination} \]

\[ t_{\text{max}} = \text{time of maximum plasma concentration} \]

\[ C_{\text{max}} = \text{maximum plasma concentration} \]

\[ AUC_{0-\infty} = \int_0^{\infty} C(t) \, dt \]

\[ AUMC_{0-\infty} = \int_0^{\infty} t \cdot C(t) \, dt \]

\[ T_{\text{max}} = \text{time of maximum plasma concentration} \]

\[ t_{\text{lag}} = \text{lag time} \]

\[ t_{\text{rise}} = \text{rise time} \]

\[ t_{\text{fall}} = \text{fall time} \]

\[ t_{\text{half}} = \text{time to half-maximum concentration} \]

\[ t_{\text{MRT}} = \text{mean residence time} \]

\[ t_{\text{MDT}} = \text{mean dissolution time} \]

\[ t_{\text{MDIT}} = \text{mean disintegration time} \]

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Results and Discussion

Crushing Tolerance and Disintegration Time of Acetaminophen Tablets Prepared Using Microcrystalline Cellulose and Spherical Sugar Granules (NP-108) Although many kinds of spherical sugar granules (NP) are commercially available, NP-108, which consists of D-mannitol, was chosen to avoid the interaction between sugar and drug, such as Maillard’s reaction. Tablets (200 mg) containing acetaminophen were prepared using PH-M-06 mixed with NP-108 (mixing ratio, PH-M-06 : NP-108 = 7:3) as excipients. Fig. 1 shows the relationships between compression force and crushing tolerance (A) or disintegration time (B) of tablets containing acetaminophen of various concentrations. When a mixture of acetaminophen (concentration 10%) and excipients consisting of PH-M-06 and NP-108 was compressed at 4—6 kN, the prepared tablets (indicated by closed circles in Fig. 1) had crushing tolerance exceeding 3 kg and disintegration time in the mouth within 15 s. In the case of tablets containing 25% acetaminophen (indicated by closed triangles), a higher compression force (6—10 kN) was required to achieve the same levels of crushing tolerance (>3 kg) and disintegration time (<15 s). The prepared tablets containing 50% acetaminophen (indicated by closed squares) disintegrated within 15 s. However, crushing tolerance did not exceed 3 kg when the mixture of drug and excipients (PH-M-06 and NP-108) was subjected to a maximum compression force of 10 kN. Therefore, the rapidly disintegrating tablet disintegrates optimally at the maximum acetaminophen concentration of approximately 30%. Generally, as the compression force (or pressure) used to prepare a tablet increases, the disintegration time increases. We noted a good relationship between compression force and disintegration time in this study. Probably, NP-108, a water-soluble excipient, accelerates disintegration after the penetration of water into the tablets due to the dissolution of NP-108.1)

Pharmacokinetic Analyses of Acetaminophen following Administration of Prepared Tablets into Stomach of Rabbits To evaluate the difference in the pharmacokinetic parameters between acetaminophen in rapidly disintegrating tablets and that in conventional tablets, these two types of tablets were directly administered into the stomach of rabbits due to difficulty in spontaneous oral administration, as stated in Experimental. However, because one dose (500—800 mg) of acetaminophen is generally used in humans, it was difficult to administer the same tablet prepared for humans to rabbits due to the large size of the tablet. Therefore, acetaminophen tablets (100 mg) containing acetaminophen 50 mg, lactose 49 mg and magnesium stearate 1 mg were prepared as reference, for rapidly disintegrating tablets that contained acetaminophen 50 mg together with PH-M-06 (35 mg) and NP-108 (15 mg), prepared with a compression force of 5 kN. The crushing tolerance and the disintegration time of these rapidly disintegrating tablets were 3.2 kg and 10 s, respectively.

Figure 2 shows plasma acetaminophen concentration–time curves after administration of the rapidly disintegrating tablet, the conventional tablet or the solution into the stomach of rabbits. The pharmacokinetic parameters of acetaminophen for these preparations were calculated by linear trapezoidal integration to a nonexponential equation, and were compared with those of the orally administered solution.

\[
AUC_{0-\infty} = \int_0^\infty C \, dt, \quad (1)
\]

\[
MRT = \frac{\int_0^\infty t(C) \, dt}{\int_0^\infty C \, dt}, \quad (2)
\]

\[AUC_{0-\infty}\] is the total amount of area under the plasma acetaminophen concentration–time curve up to an infinite time, and \[MRT\] is the mean residence time in the body. \[AUC_{0-\infty}\] and \[MRT\] were calculated by linear trapezoidal integration to a nonexponential equation. For statistical evaluation, one-way analysis of variance and Dunnett’s test were used. A \(p\) value of less than 0.05 was considered to denote a significant difference.

| Table 1. Pharmacokinetic Parameters of Acetaminophen (Dose 50 mg) after Administration into Stomach of Rabbits |
|------------------------------------------------|-----------------|--------------|--------------|---------------|-------|
| Dosage form | \(t_{\text{max}}\) | \(C_{\text{max}}\) | \(AUC_{0-\infty}\) | \(MRT\) | \(BA\) |
| --- | (min) | (\(\mu g/ml\)) | (\(\mu g/ml\)·min) | (min) | (%) |
| Rapidly disintegrating tablet | 15±0* | 4.8±0.7 | 327±22 | 89±20 | 59±4 |
| Conventional tablet | 130±26 | 3.1±0.7 | 385±14 | 121±12 | 70±2 |
| Solution | 15±0 | 7.2±3 | 421±31 | 51±6 | 76±6 |

Each value represents the mean±S.E. of three to five experiments. Statistically significant differences: *, \(p<0.05\) in rapidly disintegrating tablet vs. conventional tablet.
minophen are summarized in Table 1. No statistical difference in $C_{\text{max}}$ and $AUC_{0-\infty}$ between the rapidly disintegrating tablet and the conventional tablet was observed. Interestingly, the $t_{\text{max}}$ (15 min) of the rapidly disintegrating tablet was significantly ($p<0.05$) shorter than that of the conventional tablet (130 min). The same value of $t_{\text{max}}$ between the rapidly disintegrating tablet and the solution was observed. A low value (30 min shorter than that of conventional tablet) of $MRT$ (approximately 90 min) of the rapidly disintegrating tablet suggests that rapid disintegration took place in the gastrointestinal tract. Rapid disintegration of the tablets obviously influences the pharmacokinetics of the drug. These results suggest that the bioequivalence between the rapidly disintegrating tablet and conventional preparations should be evaluated carefully.

Acetaminophen or ascorbic acid tablets can be prepared using NP-108 spherical d-mannitol granules and PH-M-06 (fine spherical microcrystalline cellulose), at a low compression force (4—8 kN). Such tablets with good texture have sufficient crushing tolerance (exceeding 3 kg) and short disintegration time (within 15 s) in the mouth. It is possible to prepare tablets (drug concentration of approximately 25%) with NP-108. When suitable excipients such as fine spherical microcrystalline cellulose (PH-M series) and spherical sugar granules (NP series) are used, rapidly disintegrating tablets can be prepared by the conventional direct compression method.

According to results of the moment analysis,8) values of $MRT$ obtained for the intravenous injection and the solution form indicate that the mean absorption time ($MAT$) from the solution in the gastrointestinal tract is approximately 20 min. On the other hand, values of $MAT$ for both rapidly disintegrating and conventional tablets are estimated to be approximately 60 and 90 min, respectively. This difference in $MAT$ values between these two tablets may be caused by the difference in the sum of the mean dissolution time ($MDT$) and the mean disintegration time ($MDIT$) of these tablets. Probably, the difference in $MDIT$ values plays an essential role in the difference in $MRT$ between rapidly disintegrating and conventional tablets. Consequently, it was found that rapidly disintegrating tablets allow rapid absorption of the drug compared with conventional tablets.

Acknowledgements The authors wish to thank Freund Industrial Co., Tokyo, Japan, and Asahi Chemical Industry Co., Ltd., Tokyo, Japan, for generously supplying Nonpareil® series and Avicel® PH-M series, respectively.

References and Notes