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# Inter-subject variation in oral absorption of ketoprofen from controlled-release granules in rabbits

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## Summary

Three kinds of controlled-release granules of ketoprofen were prepared. The release rate of granules A was controlled by ethylcellulose (EC) and was increased with increasing the pH value in the medium. The release rates of granules B and granules C were controlled by EC, hydroxypropyl methylcellulose (HPMC) and Eudragit E100. Granules B released the drug rapidly at pH 5 and 6 in the medium, while the release from granules C was less influenced by the pH value in the medium than those from granules A and granules B.

We used gastric-acidity-controlled rabbits to evaluate the variation in the absorption after oral administration of these granules. Plasma levels after administration of 3 kinds of controlled-release granules to the non-treatment group were prolonged compared with those of the commercial capsule. There were no statistically significant differences in $AUC_{0\text{-}24h}$ between each granular formulation and the commercial capsule. There were statistically significant differences in $C_{max}$ or $T_{max}$ between the high and the low gastric acidity groups after administration of granules A or granules B, while there were no statistically significant differences in $C_{max}$, $T_{max}$ and $AUC_{0\text{-}24h}$ between high and low gastric acidity groups after administration of granules C. It was indicated that pH-independent controlled-release granular formulation would be one of the useful dosage forms which could potentially reduce the inter-subject variations in absorption.

## Introduction

It is important that an orally controlled-release product have the same extent of bioavailability as the conventional one. It is also desirable that a controlled-release product have a small intra- and inter-subject variation in absorption. Furthermore, the relationship between the physiological factors and the release characteristics of the drug from the dosage form should be considered in the preparation of controlled-release products.

It is well known that gastric emptying time, intestinal motility, variation of gastric pH, surface area, specific absorption site, blood flow and first-pass metabolism are the physiological factors

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that may influence bioavailability after administration of controlled-release products. In the present study we concentrated on the gastric pH.

Solubilities of many drugs are dependent upon the pH. While passing through the GI tract, an orally administered drug is subjected to pH values from 1 to 7. It was reported that the gastric pH can be changed from about 1 to 7 by the physiological condition and the presence of food (James and Pickering, 1949; Finholt and Solvang, 1968; Moore and Englert, 1970; Fordtran and Walsh, 1972; Meldrum et al., 1972; Malagelada et al., 1976). Moreover, drugs taken orally stay for varying periods in the individual parts of the GI tract. It was also reported that the absorption of drugs from the GI tract greatly depends upon the retention time (Levy and Jusko, 1966; Nimmo et al., 1973; Bates et al., 1974) and the pH value (Ogata et al., 1982, 1985, 1986) in the stomach.

Thus it is extremely difficult to obtain even approximately the same release rate from controlled-release formulations everywhere in the GI tract. Also it is expected that the release rate from such dosage forms could vary with different gastric pH values.

Gastric emptying of a single-unit dosage form may be characterized by an essentially random process with an inherently large intra- and inter-subject variation. However, the influence of gastric emptying time and intestinal motility on intra- and inter-subject variations in the rate and the extent of availability can be largely avoided by the use of multiple-unit, controlled-release dosage forms (Bogentoft et al., 1978; Bechgaard et al., 1982; Bechgaard, 1982).

Thus, we tried to prepare a formulation that was less influenced by gastric pH and gastric emptying, namely pH-independent controlled-release granules. There are few publications which discuss the pH-independent release products. In a recent study, Bechgaard and Baggesen (1980) dealt with intra- and inter-subject variation in the rate of availability from multiple-unit controlled-release propoxyphene products with pH-dependent and pH-independent drug release. We also reported that pH-independent release granules of nifedipine, a neutral drug, reduced the inter-subject variation in absorption (Kohri et al., 1986, 1987). In the present study we formulated an acidic drug, ketoprofen, into a pH-independent release dosage form. The mechanism of drug release from the pH-independent controlled-release granules is different from that of pellets reported by Baggesen and Bechgaard (1980). Furthermore, we administered the pH-independent controlled-release granules to gastric-acidity-controlled rabbits and compared the plasma drug profiles from this formulation with those of pH-dependent controlled-release granules.

## Materials and Methods

### *Materials*

Ketoprofen (Sigma Chemical Co., St. Louis, MO), ketoprofen commercial capsules (Orudis, Rhone Poulenc), ethylcellulose (EC, 100 cps; Wako Pure-Chemical Industry, Osaka), hydroxypropyl methylcellulose (HPMC, 50 cps; Sigma Chemical Co., St. Louis, MO), Eudragit E100 (Röhm Pharma) and distilled diethyl ether were used. Fenbufen which was used as an internal standard was extracted from Napanol tablets (Lederle) with methanol. All other chemicals were reagent grade.

### *Preparation of controlled-release granules*

Ketoprofen and polymers were dissolved in ethanol/dichloromethane (1 : 1), and then corn starch was added with agitation by a magnetic stirring bar in a jacketed beaker connected to a thermostated water bath. A slurry with suitable toughness was obtained by evaporating the solvent

TABLE 1

*Composition of granules*

| Granules | Ketoprofen (%) | EC [a] (%) | Eudragit E100 (%) | HPMC [b] (%) | Corn starch (%) |
|---|---|---|---|---|---|
| A | 6.7 | 23.3 | – | – | 70.0 |
| B | 6.7 | 23.3 | 13.3 | 6.7 | 50.0 |
| C | 6.7 | 23.3 | 6.7 | 13.3 | 50.0 |

[a] Ethylcellulose.

[b] Hydroxypropyl methylcellulose.

while maintaining the water bath at 70 °C. The slurry was forced through a 24-mesh sieve. The resultant cylindrically shaped materials clung to the sieve surface even after passing through the pore. After drying the embryonic materials at 50 °C, the cylindrically shaped materials were scraped with a spatula. A fraction of granules with a size between 20- and 28-mesh was obtained. The composition of each controlled-release granular formulation is shown in Table 1.

*Content of drug in granular formulation*

Thirty mg of granules were dissolved in 20 ml of ethanol/dichloromethane (1 : 1) by shaking for 30 min. After centrifugation at $1500 \times g$ for 5 min, the supernatant was appropriately diluted with the same solvent and spectrophotometrically analyzed against a blank at 260 nm. Triplicate runs were made on each granule.

*In vitro release studies*

The paddle method in JP-XI was employed for investigating the release rates from the granules. The releasing vessel in a constant temperature water bath is cylindrical. The paddle was assembled at a depth of $25 \pm 2$ mm from the bottom. Seventy-five mg of the granules were dispersed in 500 ml of various pH media: pH 1.2 (0.1 N HCl), pH 3 (0.1 M $CH_3COONa$–0.1 N HCl), pH 5 (0.1 M $CH_3COONa$–0.1 M $CH_3COOH$), pH 6 (0.05 M $Na_2HPO_4$–0.05 M $KH_2PO_4$), pH 7 (0.05 M $Na_2HPO_4$–0.05 M $KH_2PO_4$) at $37 \pm 0.5$ °C. Ionic strength of each medium was adjusted to 0.11 M with NaCl. The shaft of the paddle was rotated at 150 rpm. Five ml samples were removed at predetermined intervals and filtered through the membrane filters with a pore size of 0.45 $\mu$m (Toyo Roshi Co.). Five ml of fresh medium was added to the dissolution vessel immediately to maintain the original volume. The solutions were analyzed spectrophotometrically against a blank at 260 nm. Triplicate runs were made on each study.

*Preparation of gastric-acidity-controlled rabbits*

Gastric-acidity-controlled rabbits were prepared by the method of Takahashi et al. (1983). Male rabbits, weighing 2–3 kg, were fed the special solid diet (Clea Diet No. 001 CR-3, Nihon Clea Co., Tokyo) for a week. After that, rabbits were fasted for 24 h, but had free access to water. After fasting, rabbits were fed 100 g of the special soft diet (CR-3/water, 2 : 3) per day for 2 days. During these days rabbits were prevented form coprophagy in cangue. On the day of the oral administration 50 g of diet I (CR-3/0.5 N HCl, 2 : 3), diet II (CR-3/Tomix-S Granular [Tomita Pharmaceutical Co.]/water, 20 : 2 : 30) or the special soft diet was fed to rabbits to prepare the high acidity, the low acidity or the non-treatment group, respectively. Essentially, the rabbit gastric pH values corresponding to high acidity and low acidity were controlled with hydrochloric acid and antacid, respectively.

*Measurement of intragastric pH*

About 1 ml of gastric content was aspirated by a catheter at 0.5, 1.5, 3, 4 and 5 h after feeding each diet. After centrifugation of the gastric content, the pH value of the supernatant was measured by pH meter (Horiba, Kyoto) or pH test paper (Toyo Roshi Co.).

*Oral administration of ketoprofen formulations to rabbits*

Controlled-release granules in a hard gelatin capsule (JP XI, No. 3) or a commercial capsule containing an oral dose of 3.3 mg/kg weight of ketoprofen was administered to the gastric-acidity-controlled rabbits at 10 min after feeding the diet.

Each formulation was inserted into the stomach of the rabbit with a plastic catheter attached to a syringe. The plastic catheter was threaded through a hole in a wooden stick holding the mouth open, and into the stomach. The capsule was pushed to the open end of the plastic catheter with 20 ml of water. No water was given for the first 4 h and no food allowed until the absorption study was over. About 1.5 ml of blood was drawn from the marginal ear vein before administration (time 0) and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 and 24 h post-dosing. Plasma samples were stored at −20 °C for a few days until the drug concentrations were assayed.

*Assay of ketoprofen in plasma*

Ketoprofen plasma concentrations were assayed by HPLC. 0.1 ml of methanol and 2 ml of acetonitrile were added to 0.5 ml of plasma. After the mixture was vortexed for 10 s and centrifuged at $1000 \times g$ for 5 min, 1 ml of 0.05 M phosphate buffer (pH 9) (0.05 M $Na_2HPO_4$–0.05 M $KH_2PO_4$) and 4 ml of distilled diethyl ether were added to 2 ml of the supernatant. The mixture was shaken for 15 min. After centrifugation, 1 ml of an aqueous layer was acidified by addition of 0.5 ml of 0.1 N HCl, and the mixture was, further, shaken with 4.5 ml of diethyl ether for 15 min. After centrifugation, 4 ml of organic layer was taken and evaporated to dryness in vacuo. The residue was reconstituted with 200 $\mu$l of methanol containing the internal standard (fenbufen), and 10 $\mu$l of the solution was injected into HPLC system.

A liquid chromatograph (Hitachi 635A) equipped with a high pressure sampling valve (638-0801, 1–150 $\mu$l) was used. For the stationary phase, a reverse-phase column (ERC-ODS-1161, 6 mm i.d. $\times$ 10 cm; Erma Optical Works) was used; the column was warmed to 55 °C using a constant-temperature water bath circulator. The mobile phase consisted of 0.05 M acetic acid/acetonitrile (60 : 40). The flow rate was 0.9 ml/min and the pressure was approximately 40 kg/cm$^2$. Detection was at 260 nm using a variable wavelength UV monitor (Hitachi 638-41) at 0.005 a.u.f.s. The retention times for ketoprofen and an internal standard are 7 and 9 min, respectively. The peak height ratio gave a linear relationship when plotted against the ketoprofen plasma level ranged from 20 ng/ml to 5 $\mu$g/ml. The lower limit of the assay was 20 ng/ml of ketoprofen in plasma. Reproducibility studies on replicates containing 20 ng, 0.5 and 5 $\mu$g/ml of plasma yielded coefficient of variation 1.3% ($n = 9$), 4.9% ($n = 9$) and 2.5% ($n = 9$), respectively.

*Pharmacokinetic analysis and statistics*

The peak plasma level ($C_{max}$) and the time to the peak plasma level ($T_{max}$) were determined from the individual curves. The area under the plasma level versus time curve from 0 to 24 h ($AUC_{0\text{-}24h}$) were calculated by the trapezoidal rule. The pharmacokinetic parameters for the commercial capsule and each controlled-release granular formulation were compared using one-way analysis of variance. Equality of variances and statistical differences between the high and the low acidity groups after administration of controlled-release granular formulations were tested by the $F$ and $t$ tests, respectively.

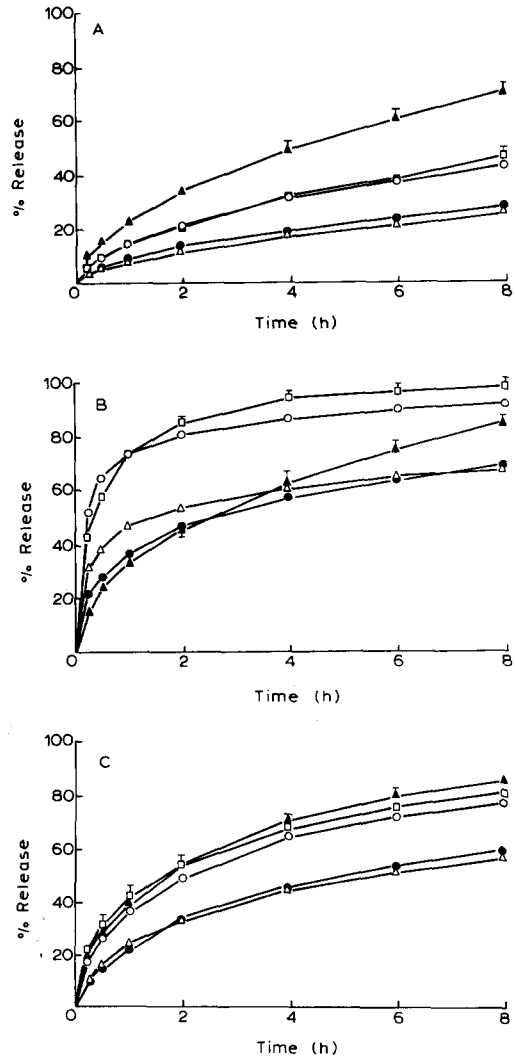


Fig. 1. Release profiles of granules A (plot A), granules B (plot B) and granules C (plot C) in various pH media. Key: ●, pH 1.2; △, pH 3; ○, pH 5; □, pH 6; ▲, pH 7. Each result is mean ± S.D. ($n = 3$).

## Results

*In vitro release study*

The release rate of ketoprofen from granules A, the release of which was suppressed by EC, increased with increasing pH, as shown in Fig. 1. Granules B, whose release rate was controlled by EC, HPMC and Eudragit E 100, rapidly released ketoprofen in the media at pH 5 and 6, while in the media at pH 1, 3 and 7 similar release patterns were observed (Fig. 1). Granules C, which was composed of the same polymers as granules B, but the portion of HPMC to Eudragit E 100 was different from granules B, released ketoprofen at similar rates in the media at pH 5, 6 and 7, while slower release was noted at pH 1 and 3 (Fig. 1). The release rate of granules C was less influenced by the variation of the pH in the medium over the range of 5–7 than the other two granular formulations.

*Gastric pH profile after ingestion of diet*

Gastric-acidity-controlled rabbits were used to examine the relationship between absorption and gastric pH.

The profiles of gastric pH versus time were shown in Fig. 2. The high acidity group which ingested diet I showed the low pH values (1–2) from 0.5 to 5 h after ingestion. The low acidity group which ingested diet II showed a gastric pH of about 5 at 0.5 h after ingestion, but the pH value decreased to about 2 at 5 h after ingestion. The non-treatment group which ingested the special soft diet showed the gastric pH between the high and the low acidity groups.

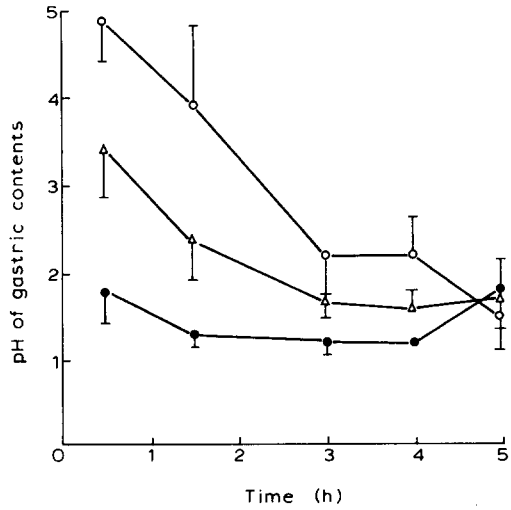


Fig. 2. Gastric pH profiles of gastric-acidity-controlled rabbits. Key: ●, high acidity group ($n = 4$); △, non-treatment group ($n = 3$); ○, low acidity group ($n = 6$). Each result is mean ± S.D.

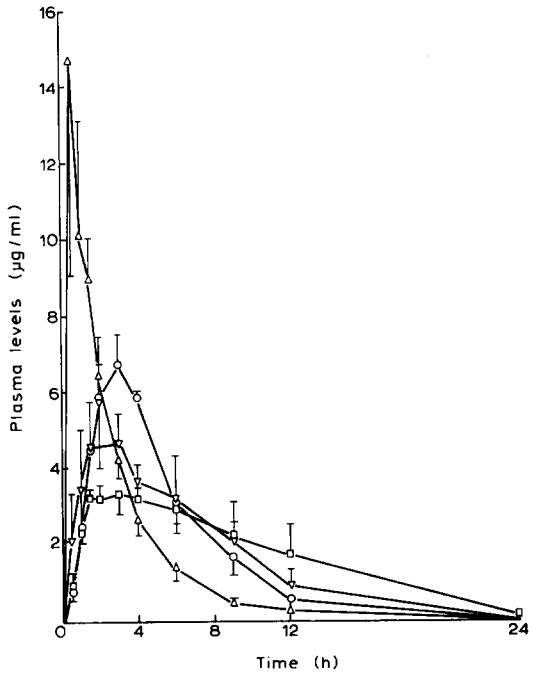


Fig. 3. Plasma levels after oral administration of commercial capsule and three kinds of granular formulations to non-treatment group. Key: △, commercial capsule; ○, granules A; ▽, granules B; □, granules C. Each result is mean ± S.E.M. ($n = 4$).

*Oral administration of ketoprofen formulations to rabbits*

We administered a commercial capsule and 3 kinds of controlled-release granules of ketoprofen to the gastric acidity-controlled rabbits.

Fig. 3 shows mean plasma levels after oral administration of these formulations to rabbits which were fed the special soft diet. The plasma level after oral administration of a commercial capsule increased rapidly and disappeared quickly. In the case of 3 kinds of granules, lower $C_{max}$, longer $T_{max}$ and more extended plasma profiles

TABLE 2

*Pharmacokinetic parameters of ketoprofen after oral administration of commercial capsule and three kinds of controlled-release granules to non-treatment group*

Each result is mean ± S.E.M. ($n = 4$).

| Parameter | Commercial capsule | Granules A | Granules B | Granules C |
|---|---|---|---|---|
| $C_{max}$ (μg/ml) [b] | 15.6 ± 5.18 | 7.0 ± 0.50 | 6.8 ± 1.18 | 4.0 ± 0.27 |
| | NS [a] | | | |
| | NS | | | |
| | $P < 0.05$ | | | |
| $T_{max}$ (h) [b] | 0.9 ± 0.24 | 3.3 ± 0.25 | 4.0 ± 1.6 | 6.0 ± 1.23 |
| | NS | | | |
| | NS | | | |
| | $P < 0.05$ | | | |
| $AUC_{0\text{-}24h}$ (μg · h/ml) [b] | 36.2 ± 5.82 | 41.0 ± 5.87 | 40.7 ± 3.07 | 42.2 ± 8.61 |
| | NS | | | |
| | NS | | | |
| | NS | | | |

[a] Not significant at $P > 0.05$.

[b] Statistically significant differences among the 4 formulations as indicated by one-way analysis of variance.

(after 4 h) were observed. Results of one-way analysis of variance are shown in Table 2. There was no significant difference in $AUC_{0\text{-}24h}$ between the commercial capsule and each granular formulation (Table 2). There was a statistically significant difference in $C_{max}$ and $T_{max}$ between the commercial capsule and granules C ($P < 0.05$).

As shown in Fig. 4 and Table 3, plasma levels of ketoprofen after administration of granules A (release rate was controlled by only EC) to the low acidity group showed a statistically significantly higher $C_{max}$ and shorter $T_{max}$ than when administered to the high acidity group. No significant difference in $AUC_{0\text{-}24h}$ was noted for the two groups.

The difference between mean plasma levels after administration of granules B to the high and the low acidity groups was shown in Fig. 4. The gastric pH of the low acidity group initially showed about 5 after ingestion of diet II (Fig. 2) and granules B rapidly released ketoprofen in the medium at pH 5 and 6 (Fig. 1), which resulted in a much higher $C_{max}$ and a shorter $T_{max}$ after administration to the low acidity group than to the high acidity group. There was a statistically significant difference ($P < 0.02$) in $C_{max}$ as shown in Table 3, but no significant difference in $T_{max}$ and $AUC_{0\text{-}24h}$ between the high and the low acidity groups. It should be noted, however, that $T_{max}$ of the high acidity group was somewhat longer and exhibited a wider range. This is reflected by the

TABLE 3

*Pharmacokinetic parameters of ketoprofen after oral administration of 3 kinds of granular formulations to rabbits*

Each result is mean ± S.E.M. ($n = 4$–6).

| Granules | Gastric acidity | $C_{max}$ (μg/ml) | $T_{max}$ (h) | $AUC_{0\text{-}24h}$ (μg·h/ml) |
|---|---|---|---|---|
| A | High | 2.7 ± 0.30 | 4.0 ± 0.71 | 35.2 ± 2.01 |
| | Low | 5.2 ± 0.22 | 0.8 ± 0.33 | 35.4 ± 7.10 |
| | *t*-test | $p < 0.01$ | $p < 0.02$ | NS [a] |
| | *F*-test | E.V. [b] | E.V. | E.V. |
| B | High | 4.2 ± 0.68 | 5.5 ± 2.77 | 32.5 ± 4.19 |
| | Low | 9.5 ± 1.51 | 1.3 ± 0.60 | 35.5 ± 1.35 |
| | *t*-test | $p < 0.02$ | NS | NS |
| | *F*-test | E.V. | U.E.V. [c] | U.E.V. |
| C | High | 4.7 ± 0.98 | 3.3 ± 0.80 | 43.5 ± 2.73 |
| | Low | 6.1 ± 0.41 | 1.8 ± 0.28 | 42.5 ± 6.06 |
| | *t*-test | NS | NS | NS |
| | *F*-test | E.V. | E.V. | E.V. |

[a] Not significant at $P > 0.05$.

[b] Equal variances at $P > 0.05$.

[c] Unequal variances at $P < 0.05$.

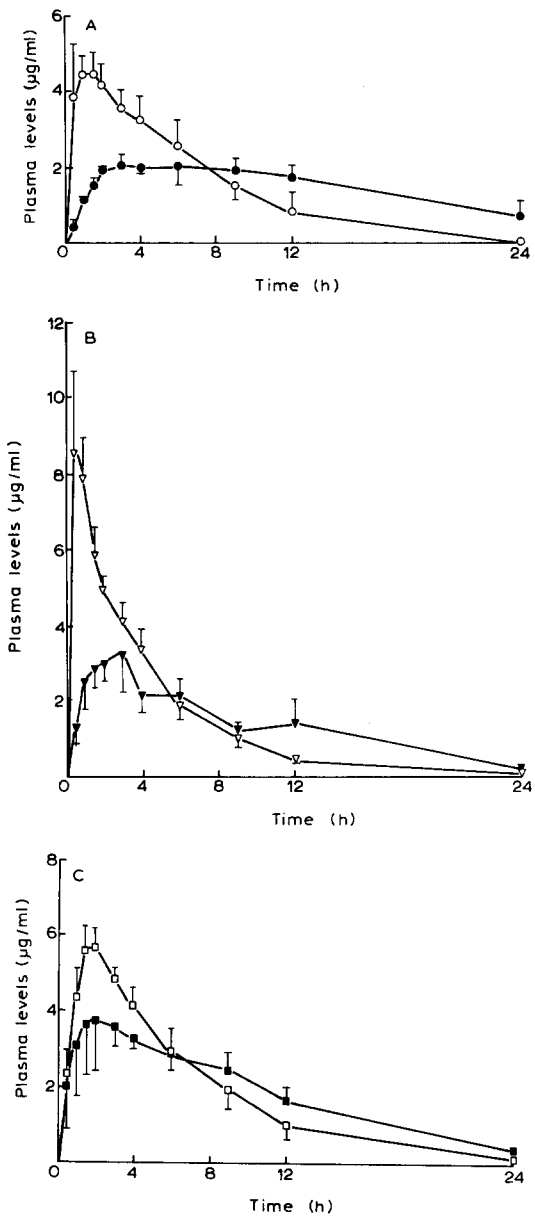


Fig. 4. Plasma levels after oral administration of granules A (plot A), granules B (plot B) and granules C (plot C) to high (●, ▼, ■) and low (○, ▽, □) acidity groups. Each result is mean ± S.E.M. ($n = 5$–6).

unequal variances between the high and the low acidity groups. The large variances observed could be explained by the gastric emptying time. When $C_{max}$, $T_{max}$ and $AUC_{0\text{-}24h}$ were tested for statistical significance between the high and the low acidity groups after administration of granules C, no significant differences were found, as shown in Fig. 4 and Table 3. The variances in $C_{max}$, $T_{max}$ and $AUC_{0\text{-}24h}$ were also not significantly different between the high and the low acidity groups.

## Discussion

It has been reported that there are large intra- and inter-subject variations in gastric pH up to about a pH of 7 (James and Pickering, 1949; Finholt and Solvang, 1968; Moor and Englert, 1970; Meldrum et al., 1972) resulting from various physiological conditions. Stomach fluids in man are normally within the range of 1–3. It has also been reported that gastric pH increases after food consumption (James and Pickering, 1949; Fordtran and Walsh, 1973; Malagelada et al., 1976) or antacid administration (Barr et al., 1971). Moreover, the orally administered drug stays for varying lengths of time in the individual parts of GI tract which leave various pH values. Solubility and absorption greatly depend upon the retention time and the pH value in the stomach. This undoubtedly contributes to intra- and inter-subject variations in bioavailability.

We use the gastric-acidity-controlled rabbit as a model animal in absorption. Gastric pH of the high and the low acidity groups showed about 1 and about 5 at 0.5 h after ingestion, respectively. Gastric pH of low acidity group returned to the normal gastric pH in about 5 h after ingestion of diet II. The pH values in the stomach of gastric-acidity-controlled rabbits were also reported by Takahashi et al. (1983). They showed that the pH value after ingestion of diet II was maintained at about 5–6 even at 3 h after ingestion. This discrepancy in pH value for the low acidity group would be ascribed to the method by which the gastric content from rabbits were sampled. Our method which used aspiration by catheter would extensively strain the rabbits, which could cause the pH in the stomach to decline to the acidic condition more rapidly.

We prepared 3 kinds of granular formulations which have typical release characteristics as follows. Type 1: the release rate is suppressed by a hydrophobic polymer in all pH media (granules A). Type 2: the release rate is controlled to burst at pH 5 and 6 based on the gastric pH of the low acidity group (granules B). Type 3: the release rate is less influenced in various pH media. The release mechanism from these granular formulations would be shown as follows. A plot of release from granules A which contain EC as a binder of the granules against the square-root of time shows the relationship to the linear at all pH buffer solutions (not shown). Release from granules A would therefore be expected to occur by a diffusion-controlled process as described by Higuchi (1963).

Granules B and C were composed of EC, HPMC and Eudragit E100. The release rate of these was different from that of granules A. Since ketoprofen is an acidic drug, it dissolves more rapidly on increasing the pH value in the medium. However, addition of Eudragit E100 in the preparation of the granules made the release rates of ketoprofen increase at pH 1, 3, 5 and 6, since the property of Eudragit E100 to be soluble in the acidic medium (Lehman, 1968) resulted in the enhancement of ketoprofen release in these media. The slower release rate of granules B at pH 7 than at pH 5 and 6 would result from the suppression by Eudragit E100 at pH 7 since Endragit E100 dissolves less with increasing the pH in the medium to more than about 5 (Lehman, 1968). Eudragit E100 is an acrylic resin which is a cationic polymer based on dimethylaminoethyl and neutral methacrylic acid esters. The ratio of HPMC-to-Eudragit E100 of granules C is smaller than that of granules B. The release rate of ketoprofen from granules C was least influenced by the variation of the pH value in the medium among these 3 kinds of granular formulations. In the case of granules B and C, plots of release against the square-root of time did not show the relationship to be linear (not shown). The mechanism of drug release from granules B and C would be eroding types which could be explained by the fact that the formation of a hydrated and gelled zone on the surface act as a barrier to the further penetration of the liquid into the matrix interior (Huber et al., 1966). As the gelled zone of HPMC slowly dissolves in the medium, a fresh surface is exposed to the liquid, with subsequent formation of a new gelled zone. Drug is liberated from this zone through a combination of diffusion and attrition processes. Part of the drug is diffused through the swollen area while the remainder is liberated when the hydrated zone is dissolved. The dissolution of Eudragit E100 would accelerate the release of ketoprofen in the medium below pH 6. EC would suppress the release rate in the medium at all pH values.

We examined the release of the commercial capsule in various pH media. This formulation showed rapid release, more than 90% of ketoprofen in 30 min, even in the acidic medium though the solubility of ketoprofen in the neutral medium is much larger than in the acidic medium (not shown). The commercial capsule may be prepared to rapidly release ketoprofen even in the acidic medium. It is not considered that a large variation of absorption will be observed after administration of this formulation to high and low acidity groups.

Firstly, we administered these 3 kinds of granular formulations and a commercial capsule to rabbits which ingest the special soft diet (non-treatment group). The plasma levels after oral administration of a commercial capsule is similar to that observed after oral administration of the same product to humans (Houghton et al., 1984). Plasma levels after administration of all three kinds of granular formulations were significantly prolonged longer than that of commercial capsule (Fig. 3, Table 2). There was no significant difference in $AUC_{0\text{-}24h}$ among 4 ketoprofen formulations which were examined in the present study. Secondly, these granules were administered to gastric-acidity-controlled rabbits. Pharmacokinetic profiles after administration of granules A or B were varied largely with the difference of gastric acidity (Fig. 4, Table 3). The greater reproducibility of the rate of availability after administration of granules C were obtained because of the lower sensitivity to the surrounding pH with respect to drug release (Figs. 1, 4, Table 3). It seems that the absorption of ketoprofen from these granules in different gastric acidity groups are expected from their release studies in vitro. In the present study,

we found that the variation of plasma level profile after administration of granules C, the release rate from which was less influenced by various pH values, was smaller than that after administration of granules A and B to the high and the low acidity test groups.

In conclusion, pH-independent controlled-release granules could be a useful tool in controlled-release dosage forms to potentially reduce inter-subject variation in drug absorption.

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