Relationship Between Gelation Rate of Controlled-release Acetaminophen Tablets Containing Polyethylene Oxide and Colonic Drug Release in Dogs

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Purpose. We hypothesized that sufficient gelation of orally administered hydrophilic matrix tablets before they reach the colon could, as a result of continuous erosion of the gelated matrix, prevent the decrease in colonic drug release which normally occurs here. The purpose of this study was to elucidate the effect of gelation of hydrophilic matrices containing polyethylene oxide on colonic drug release in dogs using controlled-release (CR) acetaminophen tablets.

Methods. Two types of CR tablets were prepared, a slow gelling tablet (SG) and a rapid gelling tablet (RG) containing an extra highly water soluble filler. *In vitro* and *in vivo* performance were examined.

Results. SG and RG showed similar drug release behavior *in vitro*. In oral administration to dogs, the two formulations showed similar gastrointestinal transit, reaching the colon within 2–4 h after oral dosing. Further, they showed similar maximum plasma levels (Cmax) and time to Cmax (Tmax). In contrast, however, the two tablets produced different plasma levels from 2 h post-dosing, with plasma levels of RG higher than those of SG and with smaller individual variation. Directly observed colonic drug release behavior of RG was similar to *in vitro* drug release, whereas that from SG was suppressed.

Conclusions. Colonic drug release is closely related to the gelation of hydrophilic matrix, and rapid gelation provides continuous *in vivo* drug release.

KEY WORDS: controlled-release; gelation; colonic release; hydrophilic matrix.

INTRODUCTION

In recent years, many drugs have been developed as oral controlled-release (CR) dosage forms. For once-daily dosage forms of drugs with a short biological half-life, the key to maintaining effective drug levels in plasma throughout the day is continuous drug absorption over 24 hours. Generally, although most drugs themselves are well-absorbed from the lower gastrointestine (GI), including the colon (1), drugs in CR dosage forms are hardly absorbed after entry into the colon following oral dosing (2–4). Because residence time of tablets in the upper GI (stomach and small intestine) is only about 5–8 h in humans (5) and 2–3 h in fasted dogs (2, 6), it is difficult to maintain drug absorption for an extended period. We previously reported that the cause of low drug absorption from CR tablets in the colon is the suppression of drug release from the tablet (2).

Because of their simplicity and low cost, hydrophilic gel-forming matrix tablets are widely used as oral controlled-release dosage forms. Hydration of the polymer results in the formation of a gel layer which controls the release rate of drug (7). The rate-limiting step in this gel layer formation is water penetration. *In vitro* drug release of water-soluble drugs is controlled by diffusion out of the gel layer, whereas release for poorly soluble drugs is solely by erosion (7). Several other factors, namely drug/polymer ratio (7–9) and polymer viscosity (8, 10, 11), have also been found to affect *in vitro* drug release. *In vitro* drug release behavior, however, is not always reflected in *in vivo* performance, especially in the colon (2). One reason for this is the presumed difference in environment around matrices under *in vitro* and *in vivo* conditions. In *in vitro* drug release testing, the matrix is generally fully immersed in fluid up to the end of testing. In oral administration, in contrast, the amount of fluid around the matrix gradually decreases as it transits the GI tract.

To improve colonic drug release, we sought to develop an oral continuous absorption system. We hypothesized is that if hydrophilic matrices were sufficiently gelated during their stay in the stomach and small intestine, where digestive juices are abundant, continuous drug release in the colon could be assured due to gel erosion.

In this study, we prepared two type of CR tablets using acetaminophen (AAP) as a model drug and polyethylene oxide (PEO) as a hydrophilic gel-forming polymer, and investigated the effect of the gelation of PEO matrices on colonic drug release.

MATERIALS AND METHODS

Materials

AAP was purchased from Yoshitomi Pharmaceutical Industries Ltd. (Japan). PEO (Polyox WSR-303) of average molecular weight 7 million was purchased from Union Carbide Corp. (USA). Polyethylene glycol 6000 (PEG6000) was purchased from Sanyo Chemical Industries (Japan). Other reagents used were of analytical reagent grade.

Preparation of Tablets

PEO matrices without AAP: PEO and various fillers were mixed at a weight ratio of 1:1 and then directly compressed using 8-mm diameter round-faced (8 mmR) punches. The resulting tablets weighed 200 mg.

Slow gelling tablet (SG): AAP and PEO were mixed (1:2) in a mortar, and the mixtures were directly compressed using 8.5-mm diameter round-faced (8.5 mmR) punches. The resulting tablets weighed 300 mg and contained 100 mg of AAP.

Rapid gelling tablet (RG): AAP, PEO, and PEG6000 were mixed (1:3:4) in a mortar, and the mixtures were directly compressed using 9-mm diameter round-faced (9 mmR) punches. The resulting tablets weighed 400 mg and contained 50 mg of AAP.

In Vitro AAP Release Test

In vitro release of AAP from the CR tablets was determined using the dissolution apparatus no. 2 (paddle) of the JP XI at

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a rotation speed of 200 rpm. The test media were 500 ml of 1st fluid (pH 1.2), 2nd fluid (pH 6.8) for JP XI disintegration test or 0.1 M acetate buffer (pH 4.0). The release of AAP was determined spectrophotometrically at 280 nm.

Gelation Indexes

The tablet was immersed in JP XI 2nd fluid (pH 6.8) at 37°C. After a predetermined time, the tablet was removed from the medium and the diameter of gelated tablet (Dgel) was measured (Fig. 1). The gel layer was peeled off and the diameter of the non-gelated core (Dcore) was measured. The gelation index (GEI) was calculated from eq. 1 using the initial diameter of tablets (Dini) and Dcore.

$$GEI(\%) = (1 - Dcore^3/Dini^3) \times 100 \quad (1)$$

Pharmacokinetic Study

This experiment was conducted in adherence to the "Principles of Laboratory Animal Care", 1985 revision. Four male beagle dogs weighing 11.4 to 13.6 kg were fasted from 20 h before administration until the last blood sample was taken with free access to water. CR tablets at a dose of AAP 100 mg were administered orally with 30 ml water. Blood samples were collected at predetermined times. Plasma samples were immediately separated and frozen at −20°C until assay.

An aqueous solution of 60 μg/ml 2-acetaminophenol was prepared for use as an internal standard. Internal standard solution (0.1 ml) and 5 ml of ethyl acetate were sequentially added to 0.5 ml of plasma in a test tube. The tube was shaken for 10 min, and centrifuged for 5 min at 2000 rpm. The upper organic layer was transferred to a clean test tube, then evaporated. The dried residue was redissolved with 0.1 ml of mobile phase for HPLC assay.

AAP in plasma was determined by HPLC with UV detection according to a previously reported procedure (12). Separation on the octadecylsilane column (Nucleosil, 150 mm length × 4.6 mm diameter, 5 μm) was achieved at ambient temperature and a flow rate of 1 ml/min. The mobile phase contained water:acetonitrile:methanol (88:6:6). UV detection was at 254 nm.

Maximum plasma level (Cmax) and time to maximum plasma level (Tmax) were determined according to the standard procedure. The area under the plasma level-time curves (AUC) was calculated by the linear trapezoidal method. Mean residence time (MRT) was computed by moment analysis (13).

Necroscopy Study

This experiment was conducted in adherence to the "Principles of Laboratory Animal Care", 1985 revision. Three male beagle dogs weighing 11.4 to 13.6 kg were fasted for 20 h before first administration with free access to water. Tablets were labeled by the addition of 0.03–0.08 mg coloring agent in order to allow tracing in the GI tract. Both SG and RG were administered with 30 ml water to each of the three dogs at 6, 4 and 2 h before necroscopy. Six hours after first dosing, the dogs were then sacrificed and the entire GI tracts removed and opened. The CR tablets were immediately recovered from their GI tracts. By analyzing the residual amount of AAP in the tablets, the *in vivo* release of AAP was calculated as the difference between initial and residual contents.

RESULTS AND DISCUSSION

Effect of Filler on PEO Matrices Gelation

In order to obtain a rapid gelling formulation, the effect of fillers on the gelation of polyethylene oxide (PEO) matrix tablets containing various fillers with different water solubility was investigated. The gelation index (GEI) was defined as the percentage of the tablet which had undergone gelation after immersion. As shown in Table I, the diameter of the non-gelated core (Dcore) and GEI of various matrices after 2 h of immersion were related to the water-solubility of the filler used. Matrices contained lactose or mannitol, widely used to enhance drug release rate from hydrophilic matrices, showed GEI of less than 30%, a value almost the same as that without fillers. This finding suggests that fillers having a water-solubility of under 200 mg/ml have little effect in enhancing the gelation of PEO matrices. In contrast, GEI in matrices containing a highly water-soluble fillers markedly increased to over 80%. Water-soluble filler in the tablet dissolved immediately before a tight gel layer could form on the surface, allowing water to penetrate into the inner part of the tablet through water paths and thereby causing most of the tablet to be gelated. These highly water soluble fillers therefore enhance the gelation of PEO matrices.

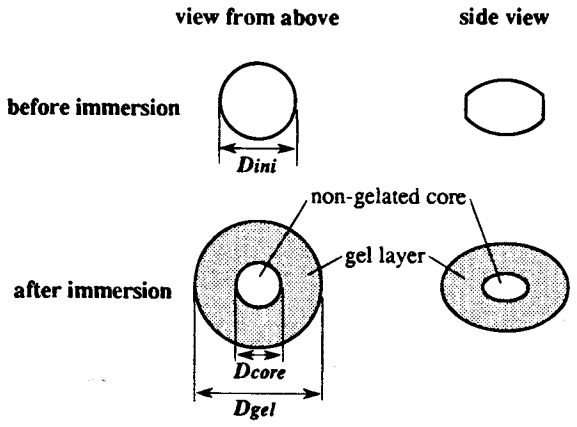

Fig. 1. Schematic diagram of gelling of polyethylene oxide matrix tablets.

Table I. Effect of Fillers on the Diameter of Non-gelated Core (Dcore) and Gelation Index (GEI) of PEO Matrix Tablets After 2 h Immersion in JP XI 2nd Fluid (pH 6.8). Each Result Shows Mean ± S.D. of Three Experiments

Filler	Water required for 1 g of solute	DCore (mm)	GEI (%)
none		7.11 ± 0.17	29.7 ± 5.0
Lactose	< 8 ml	7.29 ± 0.11	24.4 ± 3.3
D-Mannitol	< 6 ml	7.21 ± 0.11	26.8 ± 3.3
PVP K30	< 2 ml	4.48 ± 0.36	82.2 ± 4.3
PEG6000	< 1 ml	4.04 ± 0.04	87.1 ± 0.4
Sucrose	< 1 ml	3.07 ± 0.33	94.2 ± 1.9
D-Sorbitol	< 1 ml	2.48 ± 0.22	97.0 ± 0.8

Table II. Change in the Diameter of Non-gelated Core (Dcore), Gel Layer (Dgel), and Gelation Index (GEI) of CR Tablets After 2 h Immersion in JP XI 2nd Fluid. Each Result Shows Mean ± S.D. of Three Samples

Sample	Time (h)	Dcore (mm)	Dgel (mm)	GEI (%)
SG	0	8.5	8.5	0
	2	7.83 ± 0.43	12.15 ± 0.20	21.5 ± 13.2
	4	7.55 ± 0.16	13.48 ± 0.22	30.0 ± 4.3
	6	6.73 ± 0.19	14.39 ± 0.46	50.4 ± 4.2
RG	0	9.0	9.0	0
	2	5.58 ± 0.05	13.05 ± 0.32	76.2 ± 0.6
	4	3.08 ± 0.03	14.32 ± 0.30	96.0 ± 0.1
	6	0	15.47 ± 0.53	100

In Vitro Characteristic of CR AAP Tablets

Two types of controlled-release (CR) acetaminophen (AAP) tablets for the *in vitro* drug release test were prepared, a slow gelling tablet (SG) containing AAP and PEO and a rapid gelling tablets (RG) containing an extra highly water-soluble filler, polyethylene glycol 6000 (PEG6000). On the basis of previous results (2) showing that *in vitro* drug release pattern by the paddle method at 200 rpm was close to its *in vivo* drug release from hydrogel matrix tablets in fasted dogs, this paddle rotation speed was adopted. Fig. 2 shows the *in vitro* release profiles of AAP from the CR tablets. SG and RG were designed to show a similar *in vitro* drug release pattern at any test medium pH.

Table II shows changes in the diameter of the gel layer (Dgel), Dcore and GEI of AAP tablets after immersion in JP XI 2nd fluid. The Dgel of both tablets increased with time for up to 6 h, reaching approximately 1.7-fold the initial diameter before exposure to the fluid. The Dcore of RG, however, decreased faster than that of SG. The non-gelated core of RG had completely disappeared after 6-h immersion, whereas that of SG still comprised 78% of the initial diameter. This difference would be due to the presence in RG of the highly water-soluble PEG6000 as a gelation enhancement filler, which would enhance water penetration into the inner parts of the tablet compared to that of SG. Thus, the GEI of RG was 2–3 times greater than that of SG at each time point.

GI Transit of CR Tablets in Fasted Dogs

Individual GI transit of CR tablets in three fasted dogs is shown in Fig. 4. The location of both SG and RG varied widely at 2 h after dosing, with tablets found in the colon, stomach and ileum. Motility patterns in the GI tract of fasted animals and humans follow complex cyclical processes and several phases of interdigestive migrating contraction (IMC). Phase I is a quiescent period. Phase II consists of intermittent and irregular contractions that gradually increase in strength, culminating in a period of intense contractions during phase III of the IMC called the "housekeeper wave". These contractions play an important role in the emptying of drugs and preparations from the stomach. Single-unit dosage forms remain in the stomach until the phase III activity of IMC (14), which occurs about every 2 h in fasted dogs (15). The intersubject variation of location at 2 h after dosing would be explained by the appearance of this phase III in each dog.

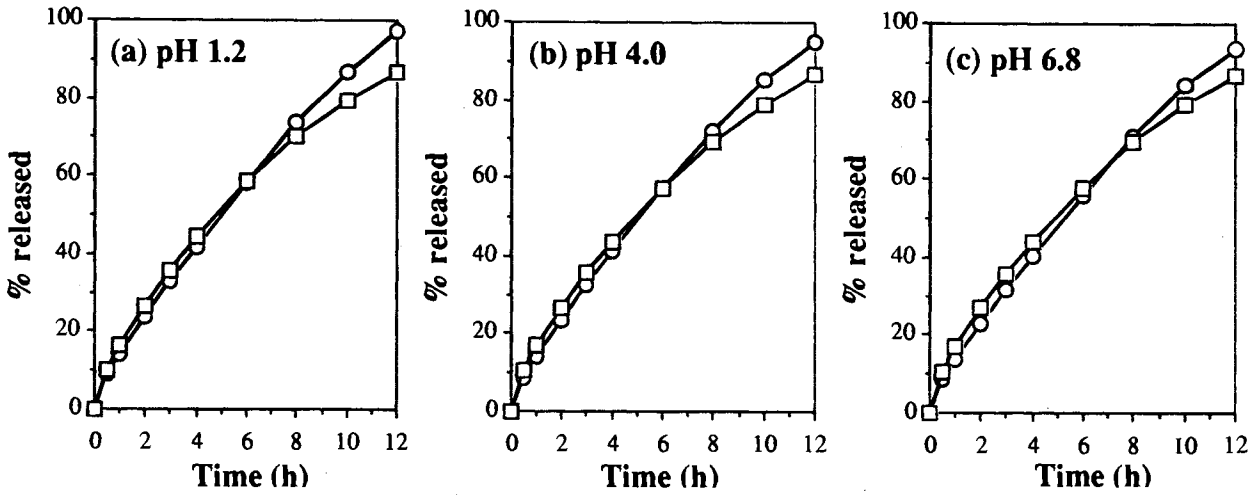

Fig. 2. Comparison of *in vitro* release of AAP from SG (□) and RG (○) using the paddle method at a rotation speed of 200 rpm in JP XI 1st fluid (a), 0.1 M acetate buffer (b) and JP XI 2nd fluid (c).

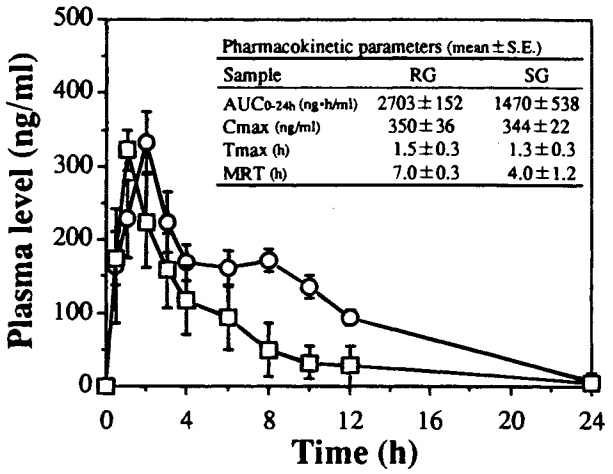

Fig. 3. Plasma levels of AAP after oral dosing of SG (□) and RG (○) to fasted dogs. Each result shows the mean ± S.E. of four dogs.

In all dogs, however, the tablets had reached the colon within 2–4 hours after dosing. This time is in accordance with other (6) and our (2) previous results, indicating that the GI transit of these tablets was not modulated, even though both tablets expanded up to 1.7-fold after 6-h immersion *in vitro*. Importantly, GI transit of SG and RG were equivalent in all dogs.

Pharmacokinetic Study in Dogs

Fig. 3 shows mean plasma levels and pharmacokinetic parameters after oral dosing of CR tablets to fasted dogs. As the two CR tablets provided similar GI transit and *in vitro* drug release behavior, they would be expected to show equivalent *in vivo* performance if gelation did not affect *in vivo* performance. From 2 h post-dosing, however, plasma level was higher with RG than SG. The area under the plasma level-time curve (AUC) and mean residence time (MRT) of RG were both 1.8 times greater than those of SG, while maximum plasma level (Cmax) and time to Cmax (Tmax) were both equivalent. These findings suggested that the *in vivo* behavior of CR tablets differs, especially in the colon. In addition, Fig. 3 also demonstrates that the intersubject variation in plasma levels of RG were smaller than those of SG.

The reason the two CR forms provided different plasma levels in fasted dogs in spite of equivalent GI transit and *in vitro* release patterns may be explained as follows. SG moves into the colon without having undergone fully gelation. Drug release here is remarkably suppressed due to the small volume of GI fluid and viscous colonic contents, which restricts fluid penetration into the tablet and retards further gelation and gel layer erosion. Further, plasma levels are also dependant on individual variation in residence time in the upper GI. RG, in contrast, is sufficiently gelated during its stay in the upper GI, and moves into the colon with its surface gel layer constantly eroded, maintaining similar drug release in the colon to that in the stomach and small intestine. This continuous drug release from RG results in an increase in AUC but no change in Cmax. Further, because RG release drug across much of the GI tract, individual variation in GI transit has less effect on drug release.

In Vivo Release from CR Tablets

To confirm the effect of gelation on colonic drug release, *in vivo* AAP release from the CR tablets was directly observed at necroscopy (Fig. 4). At 2 h after administration, *in vivo* drug release from both CR tablets was close to their *in vitro* release profiles, indicating that these tablets released AAP in the water-rich environment of the stomach and small intestine to result in a similar Cmax between them. In addition, this finding also suggests that, despite the enhancement of gelation of RG by the addition of water-soluble filler, RG does not disintegrate or undergo rapid erosion by the mechanical destructive force of GI motility. A hydrogel of PEO may therefore have sufficient strength for GI mechanical destructive forces.

From 2 h of post-dosing, however, *in vivo* drug release from SG in the colon was inhibited compared to its *in vitro* drug release. In contrast, *in vivo* AAP release from RG was close to its *in vitro* drug release profile, even in the colon where little water is available. Although the small number of dogs used

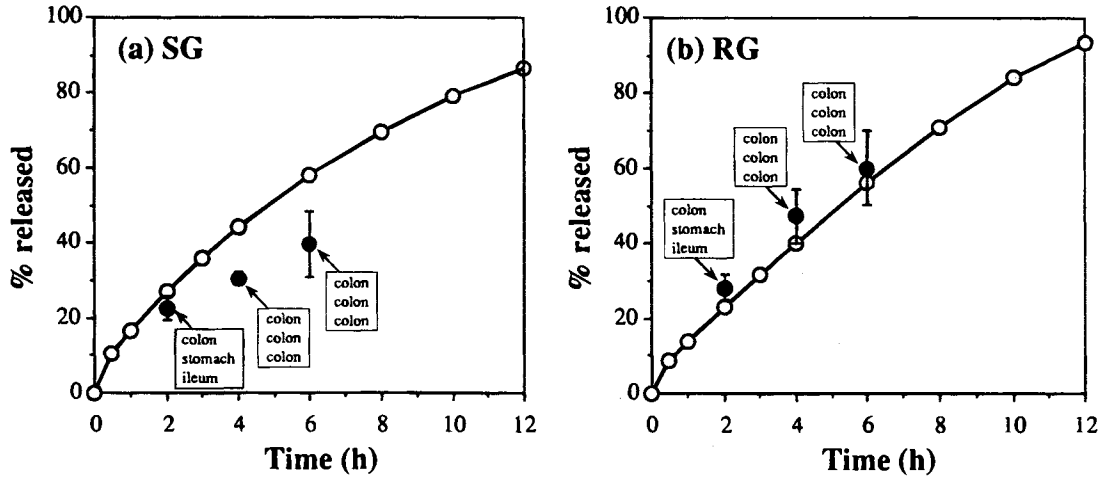

Fig. 4. *In vivo* AAP release (●) from SG (a) and RG (b) after oral dosing to dogs and *in vitro* release (○) determined by the paddle method at 200 rpm in JP XI 2nd fluid. Each result shows the mean ± S.E. of three dogs. Individual recovery locations are shown by an arrow.

for necroscopy limits statistical power, these results suggest that drug release in the colon is related to tablet gelation. Moreover, they also indicate that PEO matrices containing water-soluble fillers undergo sufficient gelation during their stay in the stomach and small intestine to prevent the suppression of drug release from tablets in the colon.

CONCLUSIONS

These studies have suggested that drug release in the colon is closely related to the gelation of hydrophilic matrices. For many drugs, continuous colonic drug release from CR dosage forms may allow continuous drug absorption without prolongation of gastric retention. Gelation control is an effective way to obtain an oral continuous absorption system of hydrophilic matrix. This simple technique may be useful in the design of once-daily oral formulations of drugs with short half-lives.

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