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Research paper

Extended release of a large amount of highly water-soluble diltiazem hydrochloride by utilizing counter polymer in polyethylene oxides (PEO)/polyethylene glycol (PEG) matrix tablets

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ABSTRACT

The purpose of this study was to evaluate the feasibility of using a counter polymer in polyethylene oxide (PEO)/polyethylene glycol (PEG) polymeric matrices for the sustained release of a large amount of highly water-soluble drug. PEO/PEG matrix tablets (CR-A) containing four drugs with different water solubilities were prepared to investigate the effect of drug solubility on the drug-release and diffusion properties of PEO/PEG matrices. Cross-linked carboxyvinyl polymer (CVP)/PEO/PEG matrix tablets (CR-B) containing a water-soluble drug, diltiazem hydrochloride (DTZ), were also prepared, and their *in vitro* characteristics were compared with those of CR-A. Their *in vitro* drug release properties were evaluated using a dissolution test, and the polymeric erosion and drug diffusion properties of the matrices were also calculated. Drugs with higher solubility in water were released faster for the CR-A. The drug-release rate also increased with the amount of drug loaded. CR-A containing 50% DTZ (by weight) extended drug release by only 6 h. This confirms the difficulty experienced when trying to formulate PEO/PEG matrices for the sustained release of a large amount of highly water-soluble drugs due to large drug diffusion. In an attempt to control this issue, a polymer bearing a charge opposite that of the drug was used to effectively decrease the diffusion of DTZ, resulting in sustained release for 24 h or longer. These results suggested that including counter polymer in the PEO/PEG matrix tablet is a useful tool for achieving the sustained release of a large amount of highly water-soluble drug.

1. Introduction

Oral-controlled release technologies have been developed in an attempt to improve patients' quality of life (QOL) by reducing the inconvenience caused by the frequent dosing of conventional tablets. Monolithic polymeric matrix tablets composed of drug and gel-forming polymers are commonly used because they are easy to manufacture and inexpensive. Among the various hydrophilic polymers used as drug-release controlling agents, hydroxypropylmethylcellulose (HPMC) is the most common due to its safety, applicability, and compatibility with many drugs. Many researchers have extensively investigated the drug release characteristics of HPMC matrices. It has been reported that the molecular weight of a drug, drug solubility, drug to polymer ratio, tablet shape, and viscosity of HPMC affect *in-vitro* drug release [1–7].

Recently, polyethylene oxides (PEOs) have been proposed as alternatives to HPMC for the controlled polymeric matrix system [8,9]. They have the following characteristics: high water solubility, high gelation ability, and low toxicity [10–12]. It has been reported that PEO matrix tablets can release drugs *in vitro* stably over a long period. On the other hand, it has also been demonstrated that a matrix tablet consisting of drug and PEO failed to release the drug sufficiently *in vivo*, even though it successfully achieved extended release *in vitro* [13]. This was due to a difference in water conditions which affected the formation of hydrogel. Abundant water is available for the formation of PEO hydrogel in the *in-vitro* dissolution test, but the water content in the gastrointestinal (GI) tract varies by site, i.e., there is ample water in the upper GI tract (stomach and small intestine), but little water is available in the lower GI tract including colon. The discontinuous *in-vivo* drug release from the PEO matrices was caused by the insufficient PEO hydration due to its slower swelling rate. It was found that only 22% of polymer in the preparations became hydrated within 2 h. Maggi et al. reported that PEO matrices absorb water gradually to reach maximum swelling at about 8 h [14], which is much longer than the interval of time that the preparations stayed in the upper GI tract, where digestive juice is abundant [15–16]. Sako et al. demonstrated that a

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combination of PEG and PEO was useful as an oral controlled absorption system (OCAS). PEG used as a hydrophilic agent promoted water uptake into the tablets (hydrogel), which underwent complete gelation within a few hours. As a result, OCAS enabled the stably sustained release of the drug throughout the GI tract, including the colon, where available water is limited [13]. In addition, OCAS allowed for stable drug release in the GI tract without any drug burst caused by disintegration because the hydrogel of PEO-based matrices was more robust and resisted stronger stresses than HPMC matrices, [17].

Highly water-soluble drugs diffuse through the gel-layer rapidly after water has penetrated the tablet; therefore it is difficult to extend the drug release from the preparations. Due to this, it is necessary to control the drug release. Especially, there is a high dose of the water-soluble drug included, leading to the larger size of the matrix tablet. There is a concern that large preparations may lead to poor patient compliance, especially for elderly patients and/or those who have difficulty in swallowing. The influence of water solubility on the release of drugs from HPMC-based matrix tablets has been investigated [3], but there are only a few reports that deal with PEO-based matrices. Kim formulated PEO matrix tablets that achieved the sustained release of diclofenac Na (solubility: 25 mg/mL in water) for over 12 h [9]. However, Maggi et al. reported that PEO tablets containing 49% (by weight) of the highly water-soluble drug, i.e., diltiazem hydrochloride (solubility: >100 mg/mL in water) extended drug release for only 8 h [18]. So far, no articles have been reported to quantitatively assess the contribution drug diffusion and polymeric erosion to the release process of PEO-based matrices. In addition, there have been no reports of any PEO-based matrix tablets that have achieved the sustained release of a large amount of highly water-soluble drug for 24 h. So far, acetaminophen is the only drug to be incorporated into a PEO/PEG matrix [13]. No attempts have been made using any other drugs with different solubilities. As mentioned above, PEO/PEG matrix tablets have the key features of rapid water uptake and the resulting complete gelation of its polymeric excipients within a few hours. Accordingly, the solubility of a drug may affect the ability of the release from PEO/PEG matrix, especially in the case of a highly water-soluble drug, because it may easily dissolve and diffuse throughout the matrix.

The objective of this study is to develop PEO-based matrix system that enables the sustained release of a large amount of a highly water-soluble drug for 24 h. For this purpose, the effect of drug solubility on the release from PEO/PEG matrix tablets and on the contribution of drug diffusion and polymeric erosion to the release process was quantitatively evaluated in order to clarify the capability of OCAS in terms of drug applicability and loading ability. The release property of PEO/PEG matrix tablets containing different percentages (10–75% by weight) of different drugs was evaluated and compared. In addition, the feasibility of using counter polymer, which has the opposite charge as the drug, was evaluated as a tool for the decrease in diffusion of a large amount of highly water-soluble drug. DTZ, which is a basic compound, was used as a model drug with high solubility, and cross-linked carboxyvinyl polymer (CVP) was used as a model counter polymer. It was hypothesized that the electrostatic charges of a counter polymer and a highly water-soluble drug would interact, which would theoretically restrict drug diffusion in PEO/PEG matrix tablets. To demonstrate this hypothesis, the effect of the counter polymer incorporated into PEO/PEG matrix tablets on the drug release, diffusion, and polymeric erosion was evaluated.

2. Materials and methods

2.1. Materials

Nifedipine hydrochloride (NIF, mean particle size: 10.9 μm), nicardipine hydrochloride (NIC, mean particle size: 30.2 μm), acetaminophen (AAP, mean particle size: 103.2 μm), and DTZ (mean particle size: 50.9 μm) were used as model drugs with different solubilities in water. NIF and AAP were purchased from Sagami Chemical Industries (Tokyo, Japan) and API Corporation (Osaka, Japan), respectively. NIC was manufactured in-house. Diltiazem hydrochloride (DTZ) was donated by Divi's Laboratories, Ltd. (Andhra Pradesh, India). Sodium benzoate (SBE) purchased from Kanto Chemical (Tokyo, Japan) was used as a model of anionic drug with high water solubility. Cross-linked carboxyvinyl polymer (CVP), Carbopol 971 P NF obtained from Noveon, Inc. (Calvert, KY, USA), was used as a counter polymer bearing charges opposite to those of DTZ. Polyox WSR 303 (mean particle size: 115.5 μm), a polyethylene oxide (PEO) with an average molecular weight of 7 million, was purchased from Dow Chemical (Piscataway, NJ). Macrogol 6000 (mean particle size: 143.0 μm), a polyethylene glycol (PEG) with an average molecular weight between 7300 and 9300, was purchased from Sanyo Chemical Industries (Kyoto, Japan). All other reagents were of analytical reagent grade.

2.2. Preparation of test tablets

Polymeric matrix tablets without CVP (CR-A) were prepared as follows. The formulation of each tablet is shown in Table 1. All materials were passed through a sieve (355 um) before mixing them to avoid aggregations. The ratio of PEO and PEG was fixed at 1:1, based on weight. Drugs were manually mixed with PEO and PEG in a mortar for 5 min, and the resultant mixture was compressed into 400-mg tablets in an oil press using 9.8 kN in applied force. Round-faced 9.5-mm diameter tooling was used. For the preparation of DTZ tablet with CVP (CR-B), the drug was mixed manually with CVP, PEO, and PEG in a mortar and compressed into 400 mg tablets under the same conditions as described above, with the exception of external lubrication with magnesium stearate. A die and punches were coated with a negligible amount of magnesium stearate by cotton swab, which had little effect on drug release (data not shown). In this study, the total tablet size was fixed at 400 mg, and the drug load ranged from 40 mg (10% by weight) to 300 mg (75% by weight).

2.3. Evaluation of drug release from the matrix tablets

Dissolution experiments were used to evaluate the *in-vitro* drug release property of the matrices. These studies were carried out using Japan Pharmacopeia XIV (referred to as "JP" hereafter) Dissolution Test Method 2 (paddle method) at a paddle speed of 200 rpm in 900 ml of dissolution medium ($n = 3$). Drug release was evaluated with JP Disintegration Test Fluid 2 (referred to as "JP2 fluid" hereafter), pH 6.8. For the NIF and NIC dissolution tests, an appropriate amount of Tween 80 was added to the medium to achieve the appropriate sink conditions. At predetermined time

Table 1
The formulations of CR-A with different drug content

	CR-A10	CR-A25	CR-A50	CR-A60	CR-A75
Drugs	40	100	200	240	300
PEO	180	150	100	80	50
PEG	180	150	100	80	50
Total (mg)	400	400	400	400	400

intervals, a sample was withdrawn from the dissolution vessel and assayed using a UV–vis spectrophotometer. The UV–vis wavelengths for NIF, NIC, AAP, and DTZ analysis were 340, 357, 280, and 250 nm, respectively. The NIF and NIC samples were shielded from light during assessment, due to their instability when exposed to light.

2.4. Calculation of drug diffusion from matrix tablets

Using JP2 fluid, the erosion property of the polymeric components was evaluated using an *in-vitro* dissolution apparatus (paddle method) at a paddle speed of 200 rpm in 900 ml of test medium ($n = 3$). The matrix tablets of CR-A50 and CR-B50 containing 50% drug/50% excipient (by weight) were used in this experiment. The matrix tablet becomes hydrogel after water penetration, and a part of hydrogel was dissolved in the dissolution medium and the other part remained as hydrogel layers on the non-gelated core. Percentage erosion (E_{2h}) used in this study was defined as the ratio of the gelated polymers dissolved into the dissolution medium, except the hydrogel layers of the tablets. The contribution of polymeric erosion and drug diffusion changes to function of time, however, in order to avoid the extra hydration of polymer matrix and accurately calculate the resultant drug diffusion, 2 h was selected as a sampling time point. Two hours after test initiation, the tablets were taken out and dried at 40 °C for 4 days in a circulation dryer, followed by drying at 40 °C for 3 days under reduced pressure. The weight of the resultant samples was measured (W_{2h}), and the percentage erosion was calculated for each of the polymeric components (E_{2h}), using Eq. (1).

$$\text{Percentage erosion of polymers}(E_{2h}, \%) = (W_{\text{initial}} - W_{2h} - R_{2h} \times \text{drug loading})/W_{\text{initial}} \times 0.5 \times 100 \quad (1)$$

- W_{2h}: The weight of the dried preparation after the dissolution test
- W_{initial}: The weight of the preparation before initiation of the test
- R_{2h}: The percentage of drug dissolution for 2 h after initiation of the test

Because the drug loaded was the same as the amount of polymeric excipient (200 mg), the percentage of drug release caused by diffusion (D) of the formulation was calculated by subtracting the percentage of matrix erosion from the percentage of drug released for 2 h after initialization of the dissolution test, using Eq. (2).

$$\text{Percentage drug diffusion}(D_{2h}, \%) = R_{2h} - E_{2h} \quad (2)$$

3. Results

3.1. Effect of drug solubility and drug-loaded amount on the in-vitro characteristics of PEO/PEG matrix tablets (CR-A)

The thickness of CR-A with NIF, NIC, AAP, and DTZ were 5.6 ± 0.1 mm, 5.7 ± 0.1 mm, 5.7 ± 0.1 mm, and 5.6 ± 0.1 mm, respectively. The hardness of CR-A with four drugs was 160.3 ± 12.0 N, 168.0 ± 14.9 N, 164.0 ± 6.6 N, and 157.0 ± 5.3 N, respectively, which indicated no significant differences in characteristics of the matrix tablets independent of the drug applied. The release property of PEO/PEG matrix tablets comprising different drugs was evaluated. Fig. 1 shows the release profiles of 4 drugs from PEO/PEG matrices containing 50% drug (by weight) (CR-A50). All formulations showed sustained drug the release patterns. The duration of the extended release varied, depending on the species of the drug incorporated. The release rate for the drugs increased in this order: NIF < NIC < AAP < DTZ. The CR-A50 with NIF showed, sustained release for over 12 h, while that with DTZ completed the release within about 8 h. The T_{50} value, the time at which 50% of the drug has been released from a matrix tablet into dissolution medium, of each drug was calculated from the drug release profiles and plotted against the solubility of the drugs. The T_{50} values for CR-A50 containing NIF, NIC, AAP, or DTZ were 6.7 h, 5.5 h, 4.2 h, and 3.1 h, respectively. Drugs with higher solubility had smaller T_{50} values (Fig. 2), which clearly indicated that the drug solubility affects the rate of release from the PEO/PEG matrix.

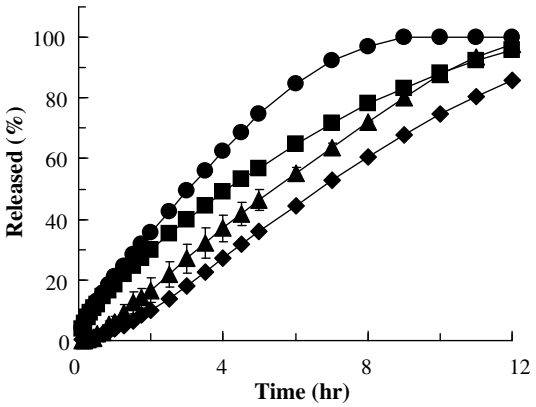

Fig. 1. Drug release profiles of CR-A50 (drug content: 50% by weight, based on total tablet size; diamond: NIF, triangle: NIC, square: AAP, and circle: DTZ).

The drug release from CR-A10 and CR-A25, which contained 10% and 25% active ingredients (by weight), respectively, was similarly evaluated. The T_{50} values for CR-A10 containing NIF, NIC, AAP, or DTZ were 8.5, 5.7, 5.0, and 4.0 h, respectively. For all drugs, the matrices with larger amount of drug loaded had smaller T_{50} values (Fig. 2). The results suggested that it becomes more difficult to prolong the release period as the amount of drug loaded and/or solubility increases.

With respect to DTZ, the drug with the fastest release rate, the effect of drug content on release behavior, was evaluated further. The drug release properties of CR-A10, CR-A25, CR-A60, and CR-A75, which contained 10%, 25%, 60%, and 75% DTZ (by weight), were measured. When the CR-A T_{50} values were plotted against

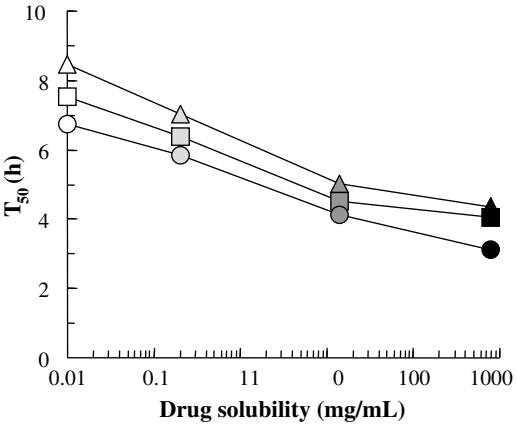

Fig. 2. Effect of drug solubility and amount loaded on the T_{50} values of CR-A (drug content: 10% by weight (triangles), 25% by weight (squares) and 50% by weight (circles), based on total tablet size; open symbols: NIF, light gray symbols: NIC, dark gray symbols: AAP, and closed symbols: DTZ).

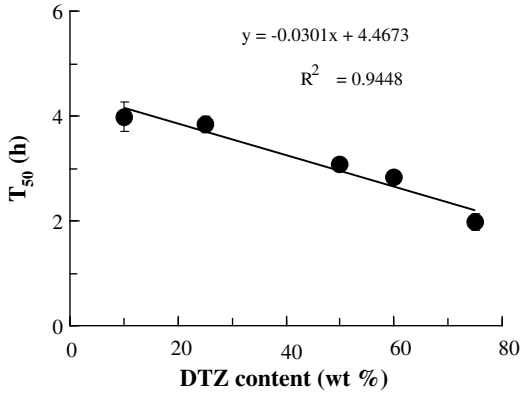

Fig. 3. Effect of the amount of DTZ loaded on the T_{50} values of CR-A.

the DTZ content (Fig. 3), there was a correlation between them, and the T_{50} values decreased with the DTZ content. These results confirmed the difficulty in extending the release of tablets containing highly water-soluble drugs with a high drug content.

In order to clarify the reasons for the varying release rates observed for the different drugs, the contribution to the release process made by the polymeric erosion and the drug diffusion was evaluated. The erosion property of CR-A50 was measured, and the results are shown in Table 2. The polymeric erosion of CR-A50 containing NIF, NIC, AAP, or DTZ at the 2-h time point during the dissolution test was 16.6%, 16.6%, 19.2%, and 16.5%, respectively. The results indicated that drug solubility affected the polymeric erosion of the tablets only marginally. This was probably due to the homogeneity of the matrix tablets in formulations containing the same amount of polymeric excipients. On the contrary, the drugs with higher solubility showed faster drug release caused by diffusion. The drug diffusion of CR-A50 containing AAP and DTZ at the 2-h time point was 10.8% and 19.1%, respectively, while that of CR-A50 containing NIF and NIC was almost negligible. These results suggested that highly water-soluble drugs could easily diffuse out through PEO/PEG matrices, resulting in faster drug-release rates than those of poorly water-soluble ones such as NIF and NIC.

3.2. The effect of CVP inclusion on the in vitro characteristics of PEO/PEG matrix tablets (CR-B) with DTZ

As described above, the control of drug diffusion through the matrices was important for achieving the sustained release of a highly water-soluble drug. In this report, utilization of a counter polymer in the PEO/PEG matrix tablets was proposed as an approach. In this experiment, DTZ was used as a highly water-soluble model drug. As DTZ is a basic compound, anionic polymer, CVP, was used as a counter polymer. The CR-B50, which contained 50% DTZ (by weight), was prepared by replacing half the amount of polymeric excipients (PEO/PEG: 1/1) with CVP (Table 3). The release property of CR-B50 was evaluated under the same conditions

Table 2
Contribution of polymeric erosion and drug diffusion to the release of drugs from the CR-A50 (drug content: 50% by weight, based on total tablet size; data from the 2 h time point after the dissolution test began)

CR-A50	Drug			
	NIF	NIC	AAP	DTZ
Drug released (%)	10.0 ± 0.4	16.7 ± 3.8	29.9 ± 0.3	35.6 ± 0.5
Drug released caused by polymeric erosion (%)	16.6 ± 0.7	16.6 ± 1.0	19.2 ± 3.2	16.5 ± 0.2
Calculated drug diffusion (%)	−6.6	0.1	10.8	19.1

Table 3
The formulations of matrix tablets containing DTZ

	CR-A50	CR-B50	CR-C50	CR-D50	CR-E50
DTZ	200	200	200	200	200
CVP	–	100	–	–	50
PEO	100	50	200	–	50
PEG	100	50	–	–	50
HPMC	–	–	–	200	–
i-carrageenan	–	–	–	–	50
Total (mg)	400	400	400	400	400

as CR-A. CR-B50 showed a sustained DTZ release pattern for 24 h, and the release was much slower than that of CR-A50 (Fig. 4). The T_{50} value of CR-B50 was 12.9 h, which was 4.2 times longer than that of CR-A50. As a reference, SBE was used as a model of anionic compound, and the drug release from CR-A and CR-B was evaluated. It was not observed the remarkable effect on the extended release by counter polymer in the case of SBE. The T_{50} value of CR-B50 containing SBE was 3.2 h, which was much smaller than that of a cationic drug, i.e., DTZ (12.9 h). The results suggested that the counter polymer, CVP, effectively delayed the DTZ release from the PEO/PEG matrices.

The polymeric erosion property of CR-B50 was measured at 2 h time point after the dissolution test. The resultant drug diffusion was also calculated and compared with that of CR-A50 (Fig. 5). At the 2-h time point, 8.2% of polymer in CR-B50 had eroded and half the amount to be eroded from CR-A50 (16.5%). It is interesting that only 3.6% of the drug in CR-B50 was released via the diffusion process, which is one-fifth of that of CR-A50 (19.1%). The results demonstrate that CVP decreased drug diffusion through the matrix to a remarkable degree. The polymeric erosion rate for CR-B50 was also found to be the dominant factor in the release of DTZ because it restricted the drug diffusion process.

4. Discussion

In general, the drug release from the hydrogel matrix tablet is classified broadly into four processes, water penetration into a tablet, the drug dissolution, the drug diffusion through the matrix, and the erosion of polymeric excipient(s). Because highly water-soluble drugs dissolve easily when water penetrates into a matrix tablet, the dissolution of a drug cannot be a rate-limiting step in the release process. It was reported that *in vitro* drug release from HPMC

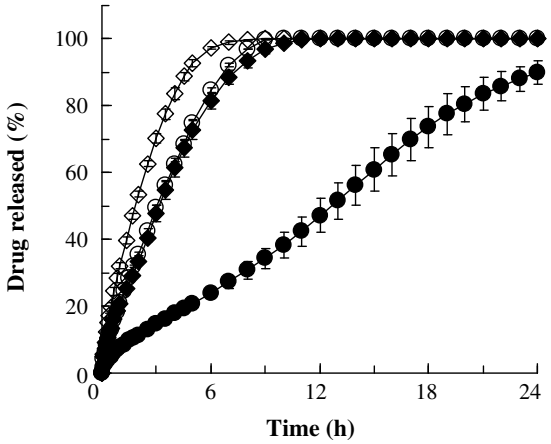

Fig. 4. The effect of incorporating CVP into the PEO/PEG matrix (CR-B) on the release of DTZ (circle symbols) and SBE (diamond symbols) (drug content: 50% by weight, based on total tablet size; open symbols: CR-A50 and closed symbols: CR-B50).

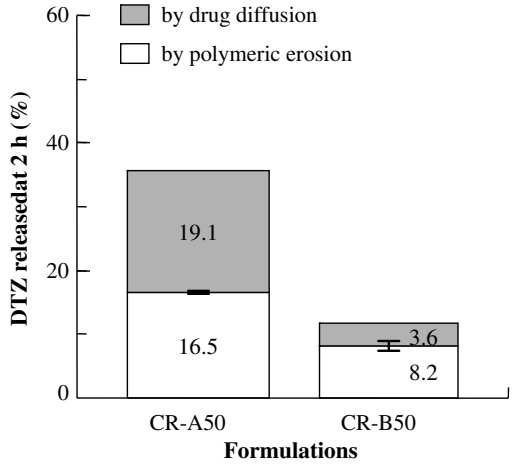

Fig. 5. The contribution of drug diffusion (gray columns) and polymeric erosion (open columns) to DTZ release from CR-A50 and CR-B50 (drug content: 50% by weight, based on total tablet size).

matrix tablets containing highly water-soluble drugs was accompanied by drug diffusion, and those containing poorly water-soluble ones by the erosion of polymeric excipients [19–20]. Maggi et al. reported that the hydration rate was faster for PEO matrices than for HPMC [14]. It was also reported that hydrophilic substances such as PEG enhanced the water uptake of PEO-based matrix tablets [13]. The water uptake and/or swelling property of the preparations depends on the polymeric characteristics. Consequently, the polymeric excipients may affect the release property, particularly for highly water-soluble drugs.

In this study, the ratio of T_{50} values for NIC (solubility in water: 0.2 mg/mL) to DTZ (600 mg/mL) in CR-A50 was 0.56. In other words, the release rate in the PEO/PEG matrices led to 1.8-fold, while the drug solubility led to 3000-fold (0.2–600 mg/mL). Kim reported that the release of diclofenac Na (DIC; solubility: 25 mg/mL) from the PEO (molecular weight of 4,000,000) matrices was faster than that of salfathiazole (Sul; 0.59 mg/mL), which was consistent with the trend of results in the current study [9]. However, the ratio of T_{50} values for DIC to Sul was calculated to be about 0.32, which indicated that the release rate increased only 3.1 times as against 42.4 times that the drug solubility increased (0.59–25 mg/mL). As current CR-A results could not be compared directly with Kim's due to different drug content and dissolution test conditions, the comparison of the effect of drug solubility on the release from PEO/PEG matrix tablets and PEO matrix ones was conducted. The drug release property of PEO matrix tablets (CR-C50) without PEG (drug/PEO = 200 mg /200 mg) was evaluated using HPMC tablets (CR-D50; drug/HPMC = 200 mg/ 200 mg) as a reference. The ratio of T_{50} values of NIC to DTZ in these tablets was 0.53 for CR-C50 and 0.55 for CR-D50 (data not shown), respectively. There was no significant difference in the ratio between CR-A50 (0.56) and CR-C50. From the results, it was confirmed that PEG, which acted as a hydrophilic agent to enhance water uptake ability and achieved the stable *in-vivo* drug release, did not accelerate the change in the drug-release rate, affected by drug solubility.

In a previous report, it was demonstrated that a PEO/PEG matrix tablet containing 12.5% AAP (by weight) achieved sustained release over a 12-h period [13]. In this study, the periods of extended release decreased slightly when the amount of AAP load increased to 50% (by weight). More than 80% of AAP was released within 8 h (Fig. 1). In addition, for a highly water-soluble drug, 80% DTZ (by weight) was released within 6 h. As shown in Fig. 2, there was a correlation between the T_{50} values and the solubility of the drug. In addition, the drug release increased with the increase in drug load. These results helped to elucidate the difficulty to control the release of a large amount of highly water-soluble drug in PEO/PEG matrices. One possible explanation is that the decrease in the concentration of polymeric components (Table 1) acts as a barrier to drug diffusion, which leads to the early hydration of the matrices when they are subjected to the mechanical stress of paddle agitation. Several researchers have evaluated drug release from HPMC matrices with different ratios of drug to polymer. They found that the drug-release rate enhanced as the relative drug proportions increased [2,7,12,20–21]. This agrees with the current observations.

In addition, the quantitative assessment of the contribution of drug diffusion and polymeric erosion to the drug release indicated that the release of NIF and NIC were relied solely on the polymeric components, while DTZ was released mainly by diffusion (Table 2). These results demonstrated that the faster release observed for the highly water-soluble drug was attributable to enhanced diffusion through the matrices. The larger content of DTZ promoted the hydrophilicity of the preparation, thereby allowing more rapid water penetration into the tablets, which resulted in greater diffusion than would normally be expected. Polymeric erosion was also confirmed to be a dominant factor in the release of poorly water-soluble drugs from PEO/PEG matrices, while the contribution of drug diffusion increased with increasing the drug solubility. Generally, the particle size of drug and compatibility affects the drug release property. However, there were similar tablet characteristics independent of the drug applied. In addition, because poorly water-soluble drugs such as NIF and NIC had the smaller particle size than DTZ, and DTZ was expected to be dissolved easily in the matrix after water penetration, it was considered that solubility of the drugs dominantly affected the drug diffusion and release property.

The amount of polymeric erosion (16.6%) was greater than the amount of drug released (10.0%) in CR-A50 containing NIF, even though the ratio of drug to polymeric excipient was in a weight ratio of 1:1. In the case of the dissolution test for NIF, appropriate amount of surfactant (Tween 80) was added to the medium to make a sink condition. As the medium was kept clear during the dissolution test, it was less likely that the some hydrogel clusters were peeled from the surface of the tablets and the drug could not be released from the resultant hydrogel clusters. Both PEO and PEG are more hydrophilic than NIF, having poor water solubility. Therefore, the polymeric components may have absorbed water preferentially, which resulted in a swollen hydrogel that peeled off before the drug could be dissolved. Actually, the dried test tablets (NIF) after dissolution test for 2 h was patterned indented surface, while that with other drugs (NIC, AAP, DTZ) had smooth surface. The results suggest that drug dissolution for poorly water-soluble drugs is a rate-limiting process. However, the contrary is true, as the solubility of the drug increases, the hydrophilicity of the preparation also increases. In particular, it is expected that highly water-soluble drugs such as DTZ would rapidly and easily dissolve in the matrices. The drugs' higher dissolving ability would lead to diffusion out of the tablet prior to the point where the swollen hydrogel would peel off, which would enhance the drug release rate.

These results suggest that a system that could restrict the drug diffusion in PEO/PEG matrices would be able to achieve the sustained release of a larger amount of highly water-soluble drug. To test this hypothesis, CVP in PEO/PEG matrix was used as an experimental system. As a result, CVP significantly extended the release of DTZ, which suggested a decrease in drug diffusion through the matrix. It was interesting that sustained DTZ release lasting 24 h or longer was achieved, even with a high drug content (e.g., 50% by weight). The preparation with CVP was also able to restrict the diffusion of DTZ that was observed in the CR-A50 without

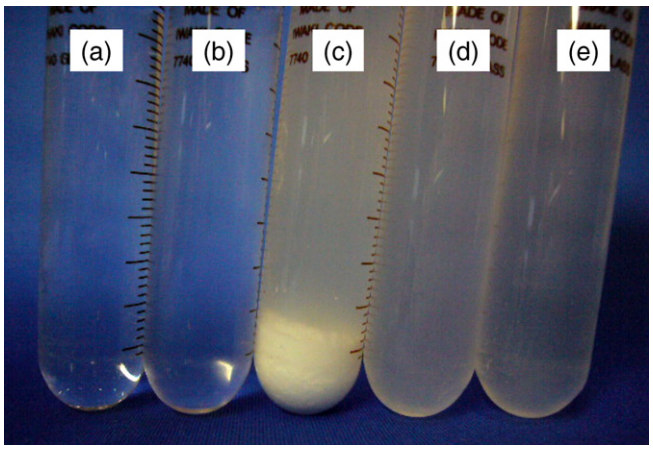

Fig. 6. Photographs of appearance of (a): DTZ solution (20 mg/mL) prepared with JP2 fluid, (b): CVP gel (10 mg/mL) prepared with JP2 fluid, (c): mixture of (a) and (b) (1/1, v/v), (d): addition of 1 N hydrochloric acid to (c), and (e): CVP gel after addition of 1 N hydrochloric acid.

counter polymer (Fig. 5). The amount of DTZ diffusion from CR-B (3.6%) was one-fifth that from CR-A50 (19.1%). As a consequence of restricted drug diffusion, polymeric erosion became a dominant factor in the drug release from CVP/PEO/PEG matrices. The results suggested that a counter polymer would be effective for controlling a large amount of highly water-soluble drug.

The carboxyl groups in CVP molecule were ionized in JP2 fluid (pH 6.8) due to pK_a of acrylic acid as 4.25 [22]. A basic drug DTZ, whose pK_a is above 7.7 [23], has a nitrogen atom in the molecule that becomes a cation at that pH. The carboxyl groups in the polymers can interact with drug moieties with opposite charges. These cooperative interactions may have formed the ionic complex, and decreased the liberty and/or solubility of the drug, which led to decreased drug diffusion in the matrix tablets. It is believed that the drug release occurs when the charge of the polymer is neutralized by protons at the border of matrix tablet and dissolution medium, thereby disrupting the cooperative interactions.

In order to confirm our hypothesis, the following two experiments were conducted. At first, DTZ solution (20 mg/mL, Fig. 6a) and CVP gel (10 mg/mL, Fig. 6b) were prepared using JP2 fluid (pH6.8), respectively. When they were mixed each other at the same volume, the white coarse precipitates generated (Fig. 6c). These precipitates disappeared after the addition of 1 N hydrochloride, and the system marginally became suspending state (Fig. 6d). As a negative control, CVP gel (10 mg/mL) and JP2 fluid without DTZ were mixed, followed by the addition of 1 N hydrochloride, which resulted in the similar state to marginal suspending state (Fig. 6e) as mentioned above. Suspending state shown in 6-e was considered to be caused by dissociation of CVP in acidic circumstances due to PKa of acrylic acid as 4.25. Accordingly, it was confirmed that that DTZ and CVP formed the complex which can be reversibly dissociated by the addition of hydrochloride, which suggested the involvement of electrostatic interactions between these molecules in the extended release from CR-B. In addition, it was confirmed that the T_{50} value of CR-B50 containing an anionic compound, i.e., SBE, was 3.2 h, which was much smaller than that of a cationic drug, i.e., DTZ (12.9 h). From these results, it was suggested the involvement of electrostatic interactions between these molecules in the extended release from CR-B50.

In this study, the release of DTZ from CR-B50 in simulated gastric fluid, JP Disintegration Test Fluid 1 (JP1 fluid, pH 1.2), could not be controlled well (T_{50} value: 5.6 h). It was reasonable that the interactions between DTZ and CVP do not occur in an environment with low pH like JP1 fluid (pH 1.2) because of the difficulty in ionizing the carboxylic group inducing hydration. The result, again, confirmed that the extended drug release of DTZ by CVP was attributed to the electrostatic interactions between two components. However, this was remedied by the combination of counter polymers based on the same mechanism. When CVP (100 mg) used in CR-B50 formulation was substituted to CVP (50 mg) and *iota*-carrageenan (50 mg), T_{50} values of resultant matrix tablets (CR-E50; consisting of DTZ (200 mg), CVP (50 mg), *iota*- carrageenan (50 mg), PEO (50 mg) and PEG (50 mg)) in JP1 and JP2 fluids were 8.6 and 10.4 h, respectively, which demonstrated the achievement of extended drug release not only in JP2 (pH6.8) fluid but also in JP1 (pH1.2) one. The T_{50} value of CR-E50 in JP1 fluid was increased 1.5-fold as compared to that of CR-B50 (5.6 h). It was estimated that the strongly acidic polymer, e.g., carrageenan, would effectively restrict the drug diffusion irrespective of pH of the medium applied because the sulfate groups in the polymer molecules can be ionized even in an environment with low pH, such as in gastric fluid (pH 1.2) [24]. Accordingly, the ratio of T_{50} values in JP2 to that in JP1 was 1.2 for CR-E50, while that was calculated as 2.3 for CR-B50 (T_{50} value in JP1: 5.6 h and that in JP2: 12.9 h), which also demonstrated the extended release of DTZ with less pH dependency by the combination of CVP and carrageenan.

5. Conclusion

In this study, drugs with higher water solubilities were released faster from the PEO/PEG matrices. The drug-release rate also increased as the amount of drug content increased. PEG, which enhances polymeric gelation, was used as a hydrophilic agent but did not facilitate the drug release rate of highly water-soluble DTZ. These results illustrate the difficulty with using PEO/PEG matrix tablets for the sustained release of a large amount of a highly water-soluble drug, due to the significant diffusion of the drug. The utilization of a polymer bearing a charge opposite that of the drug effectively restricted the diffusion of DTZ. As a result, the drug was released mainly by matrix erosion, which led to an extended release of 24 h or longer, even with a high drug content (e.g., 50% by weight). The results suggest that incorporating counter polymer(s) into PEO/PEG matrices is an effective way to achieving the sustained release of a large amount of highly water-soluble drugs with less pH dependency.

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