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Optimization of a novel wax matrix system using aminoalkyl methacrylate copolymer E and ethylcellulose to suppress the bitter taste of acetaminophen

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ABSTRACT

The purpose of the present study was to design and evaluate a novel wax matrix system containing various ratios of aminoalkyl methacrylate copolymer E (AMCE) and ethylcellulose (EC) as functional polymers in order to achieve the optimal acetaminophen (APAP) release rate for taste masking. A two factor, three level (3^2) full factorial study design was used to optimize the ratios of AMCE and EC, and the release of APAP from the wax matrix was evaluated using a stationary disk in accordance with the paddle method. The disk was prepared by congealing glyceryl monostearate (GM), a wax with a low melting point, with various ratios of polymers and APAP. The criteria for release rate of APAP from the disk at pH 4.0 and pH 6.5 were calculated to be more than 0.5017 μg/(ml·min) and less than 0.1414 μg/(ml·min), respectively, under the assumption that the particle size of spherical matrix should be 100 μm. In multiple regression analysis, the release of APAP at pH 4.0 was found to increase markedly as the concentration of AMCE increased, whereas the release of APAP at pH 6.5 decreased as the EC concentration increased, even when a high level of AMCE was incorporated. Using principle component analysis, it was found that the viscosity of the matrix affects the pH-dependent release of APAP at pH 4.0 and pH 6.5. Furthermore, using multiple regression analysis, the optimum ratio of APAP:AMCE:EC:GM was found to be 30:7:10:53, and the release pattern of APAP from the optimum wax formulation nearly complied with the desired criteria. Therefore, the present study demonstrated that the incorporation of AMCE and EC into a wax matrix system enabled the appropriate release of APAP as a means of taste masking.

1. Introduction

Drugs with an unacceptably bitter taste are generally difficult for patients to swallow, resulting in poor compliance and a subsequent reduction in their efficacy. Therefore, taste masking is used to mask the unpleasant taste of drugs and plays an important role in oral dosage forms, especially for drugs used by infants or elderly patients (Albertini et al., 2004; Kayumba et al., 2007).

Acetaminophen (APAP), which is often used as an analgesic and antipyretic agent for infants and children, has a bitter taste (Hansen et al., 1999; Suzuki et al., 2004; Zheng and Keeney, 2006). Numerous studies on masking the bitter taste of APAP have been conducted, and coating techniques using polymers were found to be useful (Pearnchob et al., 2003; Yoshida et al., 2009). However, a crucial disadvantage of these coating techniques is that organic solvents are often used to dissolve the polymers. Consequently, the potential toxicity of residual solvents in the body, the environmental pollution caused by liquid waste, and the high manufacturing costs are matters of concern. Recently, aqueous-based coating systems, in which the polymers are dispersed in aqueous rather than organic solvents, have been developed. However, removing the aqueous solvent during the drying process takes a long time due to the low volatility of the solvents used (Cerea et al., 2004).

In the present study, we examined a wax matrix system containing functional polymers as a means of suppressing the bitter taste of APAP. One of the advantages of this system is that none of the above-mentioned solvents or drying processes are required because it uses a wax with a low melting point that quickly congeals at ambient temperatures. In addition, as the solvent is not removed, this method produces a dense film without the empty spaces caused by other systems. Furthermore, since this system is cost-effective and easy to industrialize, we consider it to be more effective than coating technologies. Previously, Yajima et al. reported a wax matrix formula in which glyceryl monostearate (GM) was included as a wax with a low melting point and aminoalkyl methacrylate copolymer E (AMCE) was included as a functional polymer, in order to mask the bitter taste of clarithromycin (CAM) (Yajima et al., 1996). AMCE is a cationic copolymer based on dimethylaminoethyl methacrylate and neutral methacrylic esters and dissolves at <pH 5 (Xu et al., 2008). Due to the pH-dependent properties of AMCE, the wax matrix contain-

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ing CAM remained intact in the buccal cavity; i.e., at pH 6.5 for taste masking, and then the CAM was dissolved quickly from the wax matrix in the stomach; i.e., at pH 4.0, without lowering its bioavailability.

However, it is well known that the solubility of CAM differs under different pH conditions; namely, the solubility of CAM is quite high at pH 2.4 (10 mg/ml) or at pH 5.4 (5.5 mg/ml), whereas it is about negligible at pH 7.4 (Nakagawa et al., 1992; Salem and Duzgunes, 2003; Sharma, 2003). Therefore, the success described by Yajima et al. can probably be attributed to not only the effects of AMCE but also the pH-dependent solubility of CAM. In contrast, the solubility of APAP is about 20 mg/ml, which is much larger than that of CAM, and its solubility is not affected uniformly by all pH, suggesting that the incorporation of AMCE alone would not control the release of APAP as desired. Therefore, we next focused on ethylcellulose (EC) as a means of controlling the release of APAP from the wax matrix. EC polymers are widely known to be pH independent and water-insoluble materials. Recent evidence has suggested that the combination of EC and methacrylic polymers at different ratios is able to control drug release (Sanchez-Lafuente et al., 2002; Huang et al., 2006; Feng et al., 2008). Based on these reports, the authors speculated that the incorporation of EC into a wax matrix containing AMCE would control the release of APAP as desired, but little information is available regarding wax matrices composed of a combination of EC and AMCE.

The purpose of the present study was to design and evaluate a novel wax matrix containing APAP, AMCE, and EC at different ratios as a means of masking the bitter taste of APAP, and our goal was to optimize the ratio of AMCE and EC to ensure the appropriate release of APAP.

2. Materials and methods

2.1. Materials

Acetaminophen (APAP) was kindly provided by Iwaki Pharmaceutical Co. Ltd. (Shizuoka, Japan), aminoalkyl methacrylate copolymer E (AMCE; Eudragit® EPO) was from Röhm Degussa (Darmastadt, Germany), and glyceryl monostearate (GM) was from Taiyo Chemical Ind. Ltd. (Saitama, Japan). Ethylcellulose (EC; about 49% ethoxy) was purchased from Wako Pure Chemical Ind. Ltd. (Osaka, Japan). All of the reagents used were of the highest grade available from commercial sources.

2.2. Sensory test for the bitter taste of APAP

A sensory test for the bitter taste of APAP was carried out in 10 healthy human volunteers (seven men; three women; age range: 22–63 years). APAP solutions of varying concentration (15, 20, 25, 30, 35, or 40 μg/ml) were prepared by diluting the APAP with an adequate amount of water so that the difference between each concentration was identical. Each volunteer held 10 ml of 15 μg/ml test solution in his or her mouth for 10 s and then spat it out. After rinsing their mouth with distilled water, the bitterness of the test solution compared with that of the distilled water was then recorded as follows: −, did not detect any difference in taste between the test solution and the distilled water; +, detected some difference but was not able to be specific about the taste; ++, detected a bitter taste. The test solution with the next lowest concentration was then used, and the experiment continued like this in a stepwise manner. The threshold of bitterness of APAP was defined as the concentration at which more than half of the volunteers detected bitterness when holding the APAP in their mouth.

Table 1
Experimental design.

Formulation	APAP (%)	AMCE (%)	EC (%)	GM (%)	X1[a]	X2[b]
A	30	10	0	60	+1	−1
B	30	10	5	55	+1	0
C	30	10	10	50	+1	+1
D	30	5	0	65	0	−1
E	30	5	5	60	0	0
F	30	5	10	55	0	+1
G	30	0	0	70	−1	−1
H	30	0	5	65	−1	0
I	30	0	10	60	−1	+1

[a] Factor level of AMCE.
[b] Factor level of EC.

2.3. Experimental design

The formulation was designed using a two factor, three level (3^2)-full factorial design with two centre points, as summarized in Table 1. The ratio of APAP was fixed at 30% (w/w), and the ratios of AMCE (X1) and EC (X2) were changed as independent variables in each formula. The coded values of "+1", "0", and "−1" denote the proportions of 10%, 5%, and 0% of each variable in the formula, respectively. Each preparation was adjusted with GM to 100%.

2.4. Preparation of disk

First, GM was dissolved at 120 °C under agitation at 300 rpm, and then AMCE was added and allowed to dissolve in the melted GM. EC and APAP were then added to the melted mixture and suspended homogeneously. Subsequently, the suspensions were transferred to a cylindrical mold with an inner diameter of 2.5 cm and a height of 1.2 cm, and then left to cool. After the mass had solidified, one side of the disk surface was covered with epoxy resin so that only the other surface was available for the release study.

2.5. Measurement of viscosity

The viscosity of the suspensions containing GM, polymers, and APAP at 120 °C was measured with a rotational viscometer (TVB-10, Toki Sangyo Co. Ltd.).

2.6. In vitro drug release studies

The release of APAP from the disk was examined in accordance with the paddle method listed in the Japanese Pharmacopoeia (15th edition). The test solution was either 900 ml pH 4.0 acetate buffer solution or pH 6.5 phosphate buffer solution and was heated to 37.0 ± 0.5 °C. The paddle rotation speed was 50 rpm. At 5, 10, 15, 20, 25, and 30 min, aliquots of the solutions (4 ml) were withdrawn and replaced with an equal volume of buffer solution, and the samples were then filtered through a membrane filter (0.45 μm). The amount of APAP released into the medium was quantitatively determined by UV-spectroscopy at a wavelength of 243 nm (UV mini-1240, Shimadzu).

2.7. Measurement of wax matrix characteristics

Thermal analysis was carried out using a differential scanning calorimeter (DSC-100, Seiko Instruments, Inc.). The run was carried out in the temperature range of 20–300 °C at a heating rate of 5 °C/min under nitrogen flow (5 ml/min). Powder X-ray diffraction (PXRD) analysis was carried out with a Rigaku Rotaflex RU-200B

Table 2
Determination of the bitterness threshold of APAP.

Concentration (μg/ml)	Volunteers									
	1	2	3	4	5	6	7	8	9	10
15	–	–	–	–	–	–	–	–	–	–
20	–	+	–	–	+	–	+	–	–	–
25	+	+	–	+	++	+	–	–	+	–
30	+	+	+	+	+	+	+	–	++	+
35	+	++	+	+	++	++	++	–	++	++
40	+	++	+	++	++	+	++	+	++	++

powder X-ray diffractometer under the following conditions: target: Cu; current: 30 mA; scanning speed: 4°/min; and 2θ range: 2–40°.

2.8. Statistical analysis

The statistical analysis and optimization were performed using the computer programs ALCORA and OPTIM, which were donated by Kozo Takayama (Hoshi University) for use in Windows XP. The response surfaces were constructed using Excel 2003 (Microsoft Inc., USA). In addition, principal component analysis (PCA) was also performed using free software donated by Kimio Kanda to classify differences between the results, to detect trends, to define outliers, and to gain an overview of the data.

3. Results and discussion

3.1. Establishment of particle design for satisfactory taste masking

The fundamental objective of the present study was to prevent the preparation from easily dissolving in the mouth, while ensuring that the rapid release of APAP from the preparation was achieved in the stomach. However, the threshold concentration of APAP that causes a bitter taste in the mouth is unknown. Therefore, in order to determine the bitterness threshold for APAP, a sensory test was performed with various concentrations of APAP solution. As shown in Table 2, at 15–25 μg/ml of APAP, few volunteers detected any difference in taste between the test solution and the distilled water (represented as "–") although some detected a difference that they could not specify (represented as "+"). However, at 35 μg/ml, 60% volunteers detected a bitter taste caused by APAP (represented as "++"). Therefore, the bitterness threshold for APAP was determined to be 35 μg/ml. In the present study, the following criteria were established: pH 4.0 and pH 6.5 were used to simulate the lower pH conditions in the stomach and the higher pH conditions in the mouth, respectively.

(1) The unit dose of the spherical matrix with 100 μm should contain 200 mg of APAP so as to be bioequivalent to the conventional dosage form.
(2) Eighty percent of APAP should be released from the matrix within 30 min at pH 4.0.
(3) The release of APAP from the matrix should be less than 35 μg/ml when kept for 10 min at pH 6.5.

3.2. Determination of the release rate of APAP from the stationary disk

For the evaluation of the release rate of active ingredients from matrix systems, a stationary disk method using a cylindrical mold in which the wax suspension has been solidified is often used. Therefore, the release rates of APAP from such disks in pH 4.0 and pH 6.5 solutions were calculated as described by Yajima et al. (1996). In general, the release of a substance from a matrix is considered to proceed in proportion to time squared ($\sqrt{t}$) if the diffusion of the substance in the matrix is the dominant rate-limiting step. However, Yajima et al. reported that the release of the drug from the disk proceeded in proportion to time (t) at an early stage of dissolution because the disk itself may erode during the release of the drug (Yajima et al., 1996). In this case, Nernst's equation can be applied for the release from the matrix system as follows:

$$\frac{dC}{dt} = k \cdot \left(\frac{S}{V}\right) \cdot (Cs - C) \quad (1)$$

where k, S, V, Cs, and C are the intrinsic dissolution rate constants (cm/min), available surface area (cm^2), medium volume (ml), solubility (μg/ml), and dissolved amount at time t (μg/ml). Under sink conditions ($Cs \gg C$), Eq. (1) can be solved as follows:

$$C = k \cdot \left(\frac{S}{V}\right) \cdot Cs \cdot t \quad (2)$$

On the other hand, if Eq. (1) is applied to spherical particles under sink conditions, the particle size reduction rate (K), which is independent of the initial particle size, can be expressed as follows:

$$K = 2 \cdot k \cdot \frac{Cs}{\rho} \quad (3)$$

Then, K can be determined using the slope of the release rate from a disk (S = constant). Furthermore, if K can be determined, the slope of the % released in a mono-dispersion system with an original particle size of X_0 can be simulated as follows:

$$D = \frac{X_0^3 - (X_0 - K \cdot t)^3}{X_0^3} \cdot 100 \quad (4)$$

As mentioned above (Section 3.1), we established two release criteria; namely, that 80% of the APAP should be released from the matrix within 30 min at pH 4.0, and that the release of APAP from the matrix should be less than 35 μg/ml when kept for 10 min at pH 6.5. To meet these criteria, the K of spherical particles (ρ = 1 g/cm^3) with an X_0 of 100 μm should be more than 1.384 μm/min at pH 4.0 and less than 0.3900 μm/min at pH 6.5. In other words, the release rate of APAP from the disk should be more than 0.5017 μg/(ml·min) and less than 0.1414 μg/(ml·min) for pH 4.0 and pH 6.5 solutions, respectively.

3.3. Effect of AMCE and EC on the release of APAP from the stationary disk

The release of APAP from one surface of each matrix disk was evaluated in pH 4.0 and pH 6.5 buffer solutions in accordance with the paddle method (Fig. 1A and B). A linear relationship was obtained between the amount dissolved and time for each disk, and the slope of the line varied as the ratio of the ingredients changed. In particular, it was found that moderately rapid release was attained with formulation B, which was comprised of APAP (30%), AMCE (10%), EC (5%), and GM (55%), whereas the release rate of formulation G, which was comprised of APAP (30%) and GM (70%), was the slowest of all formulations in both buffer solutions. Using linear regression, the release rate of each disk was obtained as shown in Table 3, where Y1 and Y2 represent the release rate in pH 4.0 and pH 6.5 buffer solutions, respectively. In formulations A–F, which contained AMCE, the values of Y1 were significantly larger than those of Y2, whereas no differences between Y1 and Y2 were observed in formulations G–I, which contained no AMCE, indicating that the incorporation of AMCE induced the pH-dependent release of APAP.

Furthermore, to determine the significance of each factor as well as their interactions on the release of APAP at pH 4.0 and pH 6.5, multiple regression analysis was performed using the computer

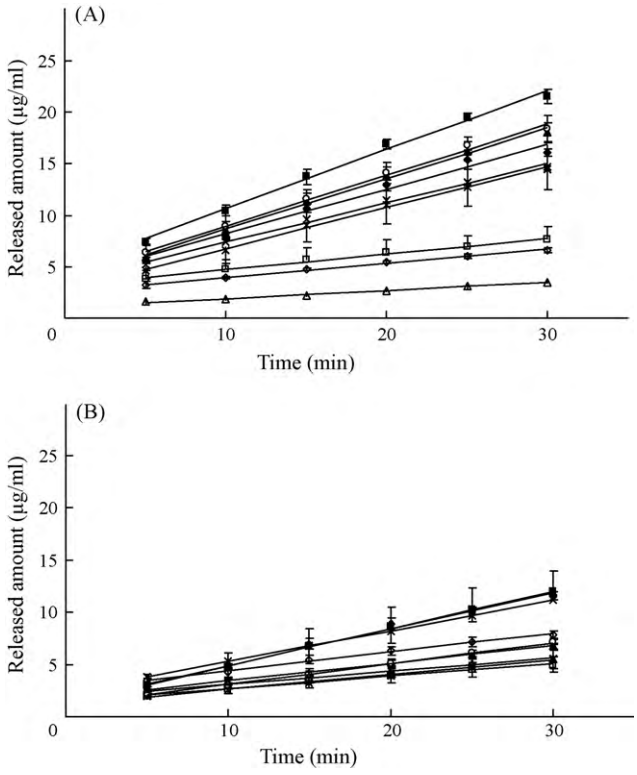

Fig. 1. Release rate of APAP from various disks obtained by two factor experimental design. (A and B) Release rate at pH 4.0 and pH 6.5, respectively. Each point represents the mean ± S.D. ($n = 3$). ♦, A; ■, B; ▲, C; ×, D; ✳, E; ○, F; △, G; ◊, H; □, I.

program ALCORA (Takayama et al., 1990). The relationships linking the main factors and their interactions with the response were determined and presented as quadratic equations of the general form in the following equation:

$$Y = \text{intercept} + \Sigma\,\text{main effect} + \Sigma\,\text{interactions}$$

The equation coefficients were calculated using the coded values; thus, the various terms can be compared directly regardless of their magnitude. The linear regression equations for Y1 and Y2 in terms of the coded factors were:

$$\begin{aligned} Y1 = {} & 0.44335 + 0.19262 \times X1 + 0.03705 \times X2 \\ & - 0.00844 \times X1X2 - 0.10961 \times X1^2 - 0.02807 \times X2^2 \\ & (R^2 : 0.92937, F : 69.4238, \text{Standard deviation} : 0.04710) \end{aligned} \quad (5)$$

Table 3
Experimental values of response variables.

Formulation	Y1[a] (μg/(ml·min))	R^2[b]	Y2[c] (μg/(ml·min))	R^2[b]
A	0.4546	0.9837	0.3514	0.9837
B	0.5766	0.9939	0.3592	0.9876
C	0.4923	0.9957	0.1688	0.9975
D	0.3814	0.9950	0.2875	0.9760
E	0.3986	0.9955	0.1434	0.9959
F	0.4956	0.9953	0.1998	0.9915
G	0.0817	0.9942	0.1276	0.9987
H	0.1363	0.9945	0.1814	0.9701
I	0.1515	0.9886	0.1217	0.9858

[a] Release rate at pH 4.0.
[b] Squared multiple correlation coefficient.
[c] Release rate at pH 6.5.

Table 4
ANOVA for the response surface reduced quadratic model.

Source	Y1	Y2
	p-Value	*p*-Value
Intercept	<0.05	<0.05
X1-AMCE	<0.05	<0.05
X2-EC	<0.05	<0.05
X1·X2	N.S.	<0.05
$X1^2$	<0.05	N.S.
$X2^2$	N.S.	N.S.
F[a]	<0.01	<0.01

[a] Observed *F*-value.

$$\begin{aligned} Y2 = {} & 0.22259 + 0.07478 \times X1 - 0.04603 \times X2 - 0.04418 \times X1X2 \\ & - 0.00812 \times X1^2 - 0.01851 \times X2^2 \\ & (R^2 : 0.66704, F : 11.4176, \text{Standard deviation} : 0.05371) \end{aligned} \quad (6)$$

where X1 and X2 were defined as the coded values for AMCE and EC, respectively. ANOVA of the screening design data (Table 4) suggested that the fit of the model to the data was significant (*F*-value for Y1: 69.4238, that for Y2: 11.4176, $p < 0.05$, respectively) and resulted in a good correlation (R^2 for Y1: 0.92937, that for Y2: 0.66704), indicating that the data were described adequately by the mathematical model. In particular, Y1 increased when AMCE (X1) increased (coefficient: 0.19262; $p < 0.05$) or EC (X2) increased (coefficient: 0.03705; $p < 0.05$) (Eq. (5)). In addition, Y2 increased when AMCE (X1) increased (coefficient: 0.07478; $p < 0.05$) or EC (X2) decreased (coefficient: −0.04603; $p < 0.05$). A slight negative interaction between AMCE and EC (X1X2; coefficient: −0.04418; $p < 0.05$) was also observed (Eq. (6)).

The effect of the formulation and variables on the response was also evaluated by studying the response plots for Y1 and Y2, respectively (Fig. 2A and B). As shown in Fig. 2A, Y1 markedly increased as AMCE (X1) increased, whereas EC (X2) had little effect on the increase in the value of Y1. By contrast, in Fig. 2B, while Y2 increased as AMCE (X1) increased, the increase in Y2 was suppressed as EC (X2) increased. Therefore, it was found that although AMCE enhanced the release of APAP from the disk in both the pH 4.0 and pH 6.5 buffer solutions, the incorporation of EC suppressed the effect of AMCE on the fast release of APAP from the disk at pH 6.5, without affecting the release of APAP at pH 4.0.

3.4. Effect of viscosity on the release of APAP from the wax matrix

The viscosity of the wax suspension in each formulation (A–I) was determined as the third response (Y3) because the viscosity was considered to be one of the factors affecting the release of the active ingredient from the wax matrix (Albertini et al., 2008). As shown in Table 5, while the lowest viscosity was observed in formulation G (1.757 P), which contained neither AMCE nor EC, the highest viscosity was observed in formulation C (21.54 P), which contained 10% AMCE and 10% EC. In addition, a comparatively high viscosity was also confirmed in formulations F (15.91 P) and I (10.15 P), both of which contained 10% EC, indicating that the incorporation of EC in the formulation enhanced the viscosity of the suspension.

To determine the involvement of viscosity in the release of APAP from the wax matrix, principal component analysis (PCA), which is able to simplify the response into latent variables as a means of explaining the main variance in the data (Haware et al., 2009), was performed (Fig. 3). Plots of the first two principal components showing their scores and loadings are shown in Fig. 3A and B, respectively. The first component (PC1) was responsible for 56.6%

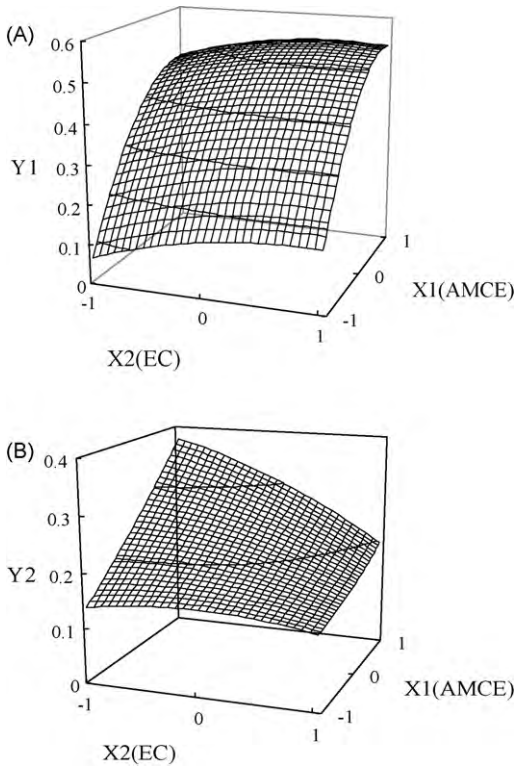

Fig. 2. The response surface plots for release rate induced by different ratios of AMCE and EC. (A and B) Response surface plots for Y1 and Y2, respectively.

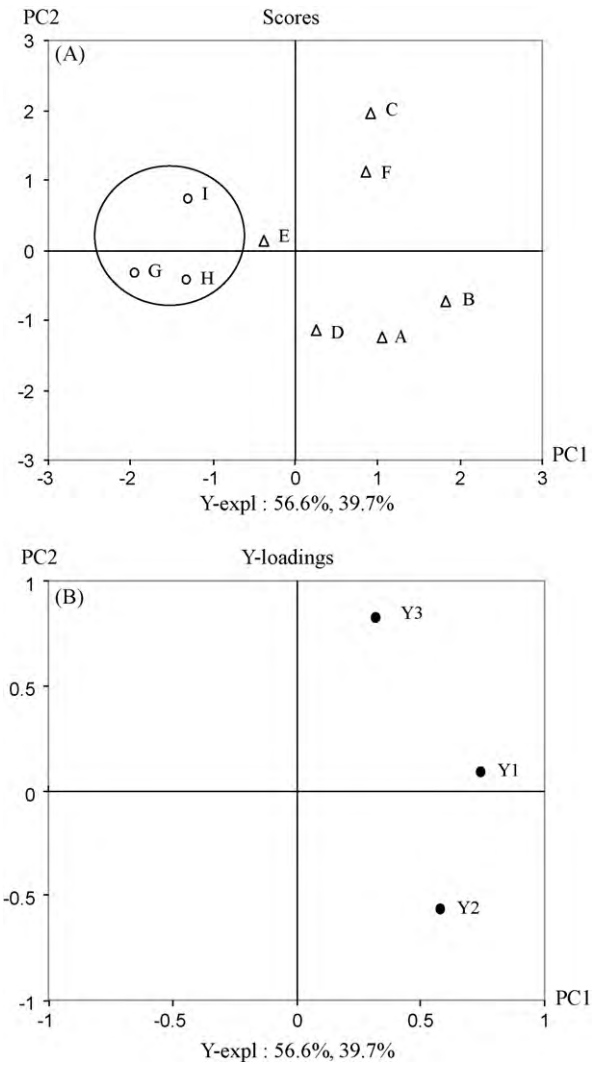

Fig. 3. (A) Score plots and (B) loading plots obtained by PCA of wax matrix responses (Y1, Y2, and Y3). The two displayed PC explain 56.6% and 39.7% of the data variance, respectively.

of the total variance in the data set while the second (PC2) was responsible for 39.7% of the total variance, thus representing 96.3% of the variation in the data. Generally, this score plot reveals the presence of outliers, as well as groups and patterns among formulations, and observations near to each other are more similar while those far away from each other are more dissimilar. As shown in Fig. 3A, no obvious groupings were observed, but formulations G, H, and I, which were plotted on the left, appeared to be different from the other formulations as they were located further away from them. It is clear that formulations G, H, and I contained no AMCE polymer and exhibited the slow release of APAP at pH 4.0 and pH 6.5 (Fig. 1). In addition, loading plots generally show relationships among variables, and variables near to each other are positively correlated, while those on opposite sides of the origin are negatively correlated, suggesting that variables close to the origin are less influential, while those further away from the origin are more influential. As shown in Fig. 3B, it was found that the release rate of APAP at pH 6.5 (Y2) was negatively correlated with the viscosity of the wax suspension (Y3), suggesting that increasing the viscosity of the formulation would suppress the release of APAP from the matrix at pH 6.5 without affecting the release of APAP at pH 4.0. In fact, formulations C and F, which had especially high viscosities (Table 5) and exhibited slow release of APAP from the disk at pH 6.5 (Table 3), were plotted on the upper section, as was Y3. This phenomenon might be partially explained by the uniformity and stable suspension conditions of APAP in the formulation due to the viscosity properties of EC. In addition, we also speculated that an increase of viscosity might lower the value of diffusion coefficient of acetaminophen in the wax matrix formulation because the diffusion coefficient is generally in inverse proportion to the viscosity. Therefore, at pH 6.5, the release of acetaminophen from wax matrix was significantly suppressed due to a low diffusion coefficient. On the other hand, under lower pH condition such as pH 4.0, AMCE highly dissolves. Therefore, since the release of acetaminophen was much higher at pH 4.0, the effect of a low diffusion coefficient might not be observed. Taken together, this result indicated that the incorporation of EC successfully enhanced the pH-dependent effects of AMCE on the release of APAP from the matrix.

3.5. Physical form of APAP in the wax matrix

Although the combination of AMCE and EC polymers was able to control the pH-dependent release behavior of APAP from the matrix at pH 4.0 and pH 6.5, the question of whether AMCE and EC

Table 5
Viscosity of wax suspensions in each formulation.

Formulation	A	B	C	D	E	F	G	H	I
Y3 (poise; P)	3.877	8.317	21.54	1.660	5.297	15.91	1.757	3.423	10.15
S.D.	0.103	0.130	0.620	0.092	0.287	0.647	0.100	0.042	0.252

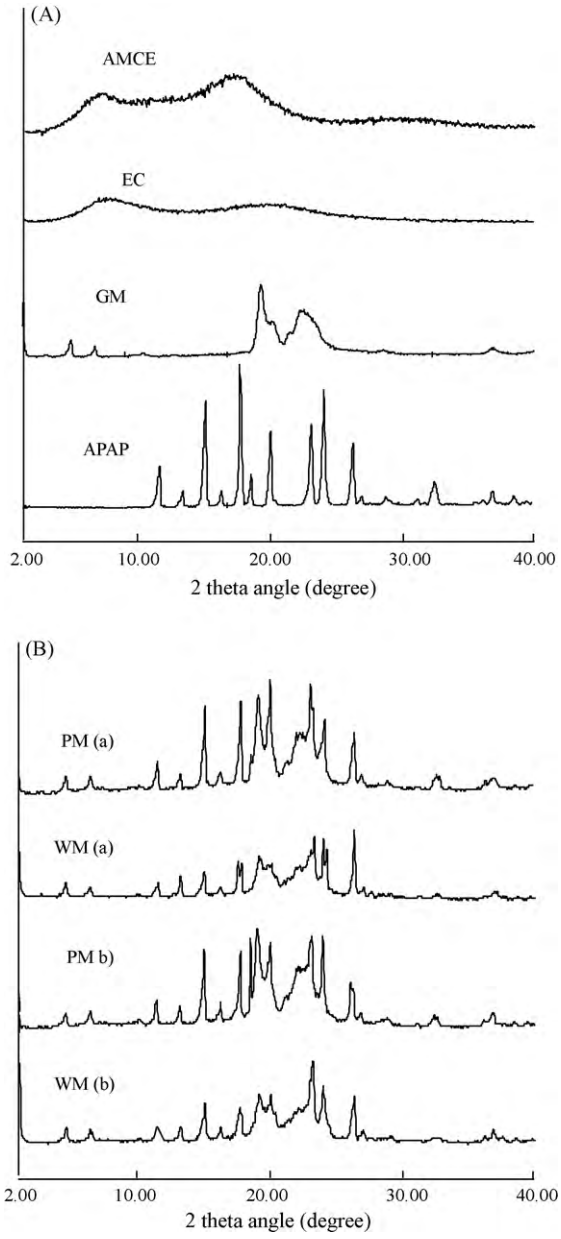

Fig. 4. X-ray diffraction patterns of AMCE, EC, GM, and APAP; their physical mixture (PM); and a wax matrix (WM) composed of them. PM (a) and WM (a) composed of APAP (30%), AMCE (10%), and GM (60%). PM (b) and WM (b) composed of APAP (30%), AMCE (10%), EC (5%), and GM (55%).

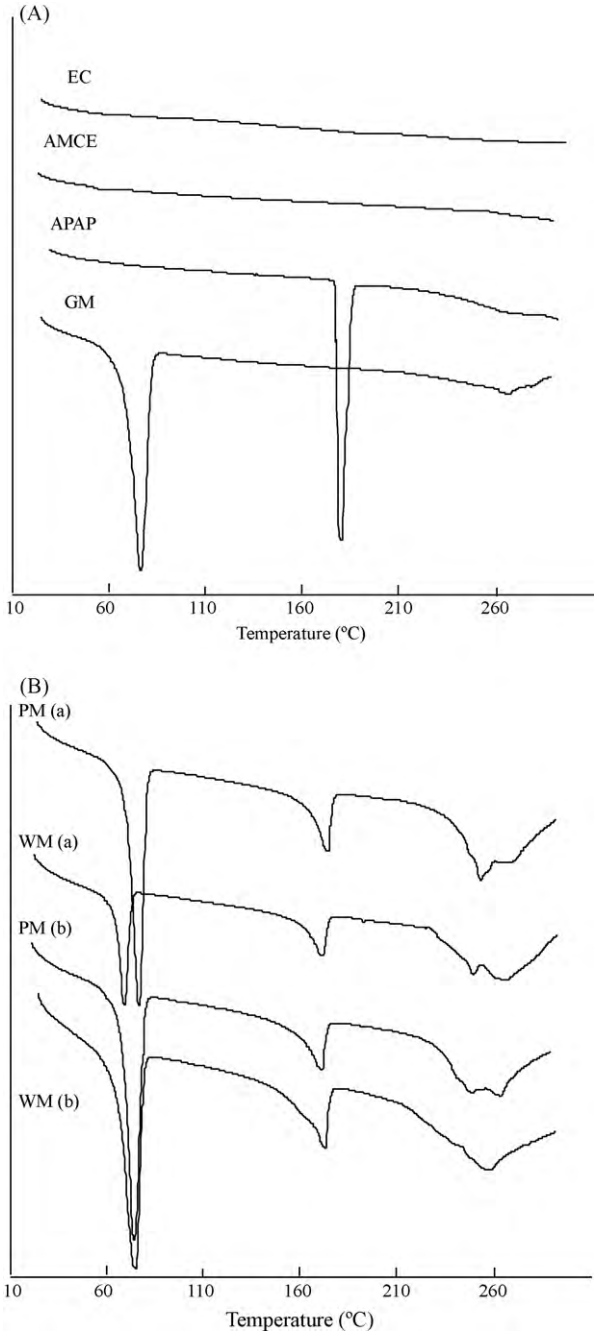

Fig. 5. Differential scanning calorimetry profiles of AMCE, EC, GM, and APAP; their physical mixture (PM); and a wax matrix (WM) composed of them. PM (a) and WM (a) composed of APAP (30%), AMCE (10%), and GM (60%). PM (b) and WM (b) composed of APAP (30%), AMCE (10%), EC (5%), and GM (55%).

had affected the crystalline form of APAP during the preparation of the matrix needed to be investigated. Therefore, powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC) were performed to confirm the crystalline states of APAP in the formulation. As shown in Fig. 4A, the PXRD patterns of AMCE and EC were hollow, and those of APAP and GM showed crystalline forms. The crystalline form of GM was considered to be the β-form, a generally stable form, as described by Yajima et al. (2002). The PXRD patterns of the physical mixture (PM) and wax matrix (WM) are shown in Fig. 4B. The peak intensity of WM (a) composed of APAP (30%), AMCE (10%), and GM (60%), was lower than that of PM containing the same components in the same proportions (b), indicating that the crystalline form of APAP had partially changed to the amorphous form in the WM formulation. However, a similar phenomenon was also observed in the PXRD patterns of PM (b) and WM (b) composed of APAP (30%), AMCE (10%), EC (5%), and GM (60%), suggesting that slight changes in the crystalline form of APAP did not affect the release of APAP from the matrix.

In addition, the DSC spectra of APAP, AMCE, EC, and GM are shown in Fig. 5A. As for AMCE and EC, no DSC spectrum peak was observed, whereas sharp melting peaks at 66.4 and 161.6 °C were observed for GM and APAP, respectively. When the DSC spectra of PM (a and b) and WM (a and b) (Fig. 5B) were compared, it was found that their peaks patterns were nearly identical. Therefore, although slight transition of the state of APAP from crystalline to amorphous was observed in the wax matrix, preparation conditions such as mixing the matrix with AMCE and EC polymers at a high temperature did not affect the pH-dependent release behavior of APAP.

Table 6
Experimental values of optimum matrix formulation.

	APAP:AMCE:EC:GM = 30:7:10:53 (X1 = 0.4, X2 = 1.0)		
	Experimental release rate (μg/(ml·min))	Predicted release rate (μg/(ml·min))	Objective release rate (μg/(ml·min))
Y1	0.5049	0.5086	0.5017
Y2	0.1425	0.1716	0.1414

3.6. Optimization of matrix formulation

After generating the polynomial equations relating the dependent and independent variables, the levels of X1 and X2 were optimized using the computer program OPTIM, and the optimal levels of AMCE (X1) and EC (X2) were found to be 0.4 (7%) and 1.0 (10%), respectively. A drug release study was then carried out using the optimized matrix formulation (Table 6). As a result, the release rates of APAP at pH 4.0 and pH 6.5 were found to be 0.5049 and 0.1425 μg/(ml·min), respectively, both of which nearly complied with the desired objective release rate of APAP.

4. Conclusions

While acetaminophen (APAP) is widely used as an analgesic and antipyretic, it has a bitter taste, resulting in poor compliance and a subsequent decrease in its efficacy. Therefore, to overcome this disadvantage of APAP, a novel wax matrix formulation containing a combination of AMCE and EC as functional polymers was designed and evaluated as a means of achieving appropriate release of acetaminophen (APAP) for taste masking. A two factor, three level (3^2) full factorial design was used to optimize the ratios of AMCE and EC, and the release rate of APAP from the wax matrix was evaluated using a stationary disk in accordance with the paddle method. As a result of multiple regression analysis and principal component analysis, the release rate of APAP at pH 4.0 markedly increased as the concentration of AMCE increased. Interestingly, while the release rate of APAP at pH 6.5 increased as the concentration of AMCE increased, the release of APAP at pH 6.5 was suppressed as the concentration of EC increased, demonstrating that the incorporation of EC was able to sensitively elicit pH-dependent AMCE behavior in the formulation. Furthermore, multiple regression analysis enabled the identification of the optimal formulation for achieving appropriate release of APAP for taste masking. In the present study, although GM was also used as a wax base to adjust each preparation to 100%, it was considered that GM might affect *in vivo* release of drug due to the presence of gastric or intestinal juice. Therefore, further studies would be required to evaluate the *in vivo* release of acetaminophen from the optimized matrix formulation. Taken together, the present study demonstrated that this novel wax matrix system is a useful technique for taste masking.

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