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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