International Journal of Pharmaceutics 431 (2012) 70–77

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Preparation and evaluation of granules with pH-dependent release by melt granulation

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ARTICLE INFO

Article history:
Received 13 September 2011
Received in revised form 27 March 2012
Accepted 9 April 2012
Available online 15 April 2012

Keywords:
Melt granulation
Aminoalkyl methacrylate copolymer E
pH-dependent release behavior
Granules properties

ABSTRACT

This study had two objectives: (1) to prepare, by melt granulation in a high-shear mixer, granules containing acetaminophen (APAP) as a model drug and aminoalkyl methacrylate copolymer E (AMCE) as a pH-sensitive polymer that readily dissolves at pH values lower than 5, and (2) to investigate the effects of AMCE loading (5–15%) on granule properties and the *in vitro* release profile of drug from the granules. Compared with polymer-free granules, the granules containing 5% and 10% AMCE were found to have higher median diameters and wider particle size distributions. For the formulation containing 15% AMCE, on the other hand, the diameters and distribution were similar to those for polymer-free granules. From compression testing, load–displacement curves revealed that AMCE enhanced particle strength at ambient temperature and induced plastic strain, while suppressing fragmentation of the granules. In addition, from dissolution testing using media with pH 4.0 and pH 6.5, granules containing AMCE, except 15% AMCE loading, exhibited drug release with significant pH dependence. When the pH 4.0 and pH 6.5 dissolution profiles were further compared by calculating the difference factor (f_1), the 5% AMCE granules showed the strongest pH dependence of drug release among all formulations in this study. Large cracks and breakage were observed on the surface of 10% AMCE granules after they were used in dissolution testing. The obtained results are attributed to the plastic strain properties of AMCE above its glass transition temperature, and to the irregular distribution of AMCE within granules. Hence, this study has demonstrated for the first time that the combination of melt granulation and AMCE incorporation enables the formulation of novel functional granules that exhibit pH-dependent release of the active ingredient.

1. Introduction

Incorporation of functional polymers, such as those with hydrophilic or pH-sensitive properties, into pharmaceutical dosage forms is an essential technique in designing novel formulations with sustained release, taste masking, and/or enteric delivery. Toward this end, numerous studies using functional polymers have been conducted, and functional polymers are considered especially useful for coating techniques (Kramar et al., 2003; Siepmann et al., 2008; Kranz and Gutsche, 2009). However, a major disadvantage of such coating techniques is that organic solvents are typically used to dissolve the polymers. Consequently, potential toxicity of residual solvents, environmental pollution caused by liquid waste, and high manufacturing costs are matters of concern. Recently, aqueous-based coating systems, where polymers are dispersed in aqueous solvents rather than organic ones, have been developed. However, the drying process is time-consuming when aqueous solvents are used because of their low volatility (Cerea et al., 2004). Against this background, development of a novel solvent-free technique is highly desirable.

As a solvent-free alternative to conventional coating techniques, melt granulation has attracted attention in pharmaceutical research. This technique utilizes a binding material with a low melting or softening point; after melting, the material acts as a binding liquid. The binder congeals at room temperature to yield a solid dosage form, suggesting that this technique can be adapted to moisture-sensitive active ingredients. In addition, since a drying process is unnecessary, melt granulation is considered more economical and environmentally friendly. Meltable binders (MBs) often used in melt granulation include polyethylene glycols (Schaefer et al., 1990; Cheng and Hsiau, 2010), waxes (Zhou et al., 1996, 1997), stearic acids (Voinovich et al., 2001; Grassi et al., 2003), and surfactants (Krošelj et al., 2008; Bukovec et al., 2009). Therefore, the chemical and physicochemical properties of MBs provide flexibility in the properties of the pharmaceutical dosage form.

Abbreviations: APAP, acetaminophen; AMCE, aminoalkyl methacrylate copolymer E; GM, glyceryl monostearate; MC-wax, microcrystalline wax; MB, meltable binder; DCPD, dibasic calcium phosphate dihydrate; SEM, scanning electron microscope.

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http://dx.doi.org/10.1016/j.ijpharm.2012.04.031

Thomsen et al. (1993, 1994) have previously shown the possibility of using melt granulation in a high-shear mixer to combine different types of hydrophobic MBs with drugs and thereby prepare pellets with prolonged release properties. Hamdani et al. (2002) reported on using a high-shear mixer to prepare prolonged release matrix pellets containing Compritol 888 and Precirol ATO5 as MBs. To develop granules or pellets with controlled or sustained release properties, previous studies have focused on the optimal selection of MBs. However, to the best of our knowledge, little information has been reported about the incorporation of functional polymers into formulations, prepared by melt granulation, which contain MBs and active ingredients. Specifically, the incorporation of functional polymers into melt granulation would facilitate the development of granules with various desired functionalities including taste masking, oral disintegration, and colonic delivery.

In the present study, aminoalkyl methacrylate copolymer E (AMCE; Eudragit EPO) was selected as a functional polymer. AMCE is a cationic copolymer based on dimethylaminoethyl methacrylate and neutral methacrylic esters, and dissolves at a pH below 5 (Xu et al., 2008). Owing to the pH-dependent properties of AMCE, it is suitable for taste masking, without lowering drug bioavailability, in formulations that retain undissolved active ingredients in the buccal cavity and release them quickly in the stomach (Shiino et al., 2010). Because of the high plasticity of AMCE, it has been used to prepare solid dispersions by hot melt extrusion (Chokshi et al., 2005; Qi et al., 2008; Gryczke et al., 2011) and wax matrices by spray congealing (Yajima et al., 1996). Since AMCE has been widely used in other hot-melt processes, this polymer is considered suitable for the present study.

The purpose of this study was to develop novel matrix granules, prepared by melt granulation, which have pH-dependent properties and contain acetaminophen (APAP)—a widely used analgesic and antipyretic agent for infants and children—as a model drug, glyceryl monostearate (GM) and microcrystalline wax (MC-wax) as MBs, and AMCE. Furthermore, the effects of AMCE loading on granule properties and the *in vitro* release profile of APAP from the granules were investigated.

2. Materials and methods

2.1. Materials

APAP was kindly provided by Iwaki Pharmaceutical Co. Ltd. (Shizuoka, Japan), dibasic calcium phosphate dihydrate (DCPD) was provided by Kimura Sangyo Co. Ltd. (Tokyo, Japan), and MC-wax was provided by Nippon Seiro Co. Ltd. (Tokyo, Japan). AMCE was purchased from Röhm Degussa (Darmastadt, Germany), and GM was purchased from Taiyo Chemical Industry Co. Ltd. (Saitama, Japan). All the reagents used were of the highest grade available from commercial sources.

2.2. Melt granulation

Size reduction of APAP and DCPD was carried out using a sample mill (TI-300, Cosmic Mechanical Technology Co. Ltd., Fukushima, Japan), and the milled compounds were then passed through a 149 μm sieve (Tokyo Screen Co. Ltd., Tokyo, Japan). Granulation was conducted with a high-shear mixer (MECHANOMiLL, Okada Seiko Co. Ltd., Tokyo, Japan) equipped with a rubber heater and temperature sensor (Fig. 1A). The batch size was 150 g for all formulations, and specifications for the formulations are summarized in Table 1.

To manufacture granules, the jacket temperature was fixed at approximately 85 °C, and the experiments were conducted at an impeller speed of 1200 rpm. After the product temperature reached

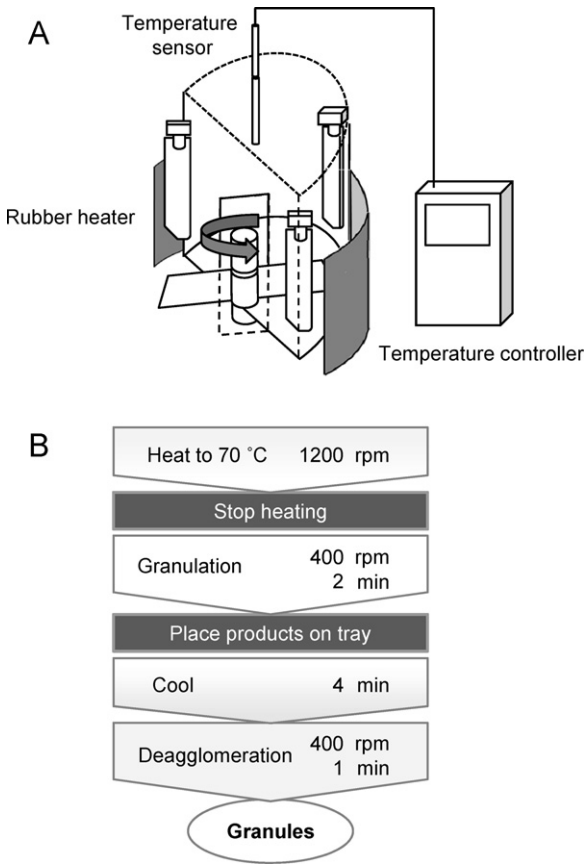

Fig. 1. Schematic representation of (A) MECHANOMiLL apparatus and (B) granulation process flowchart.

70 °C, the rubber heater was turned off and the impeller speed was lowered to 400 rpm. Mixing was then stopped after 2 min, and the lid was removed. To cool the obtained product, the mixture was ejected from the bed of the mixer, spread into thin layers on metal trays, and allowed to stand for 4 min. After this, the mixture was once more transferred to the mixer and additional granulation was performed for 1 min at 400 rpm. This granulation process is summarized in the flowchart in Fig. 1B.

2.3. Characterization of granules

2.3.1. Particle size distribution and median diameter

The size distribution of granules was evaluated by sieve analysis using 10 standard sieves (Tsutsui Scientific Instruments Co. Ltd., Tokyo, Japan) with aperture sizes ranging from 125 to 1700 μm. The percent passing against the sieve opening size on a log scale was displayed by plotting and the plotted points were connected with a straight line referred to as a grain-size distribution curve. The median diameter of granules, d_{50}, was obtained from the half percent of accumulative size distribution curve.

Table 1
Formulation of granules prepared by melt granulation.

Formulation	APAP (%)	AMCE (%)	GM (%)	MC-wax (%)	DCPD (%)
Polymer-free	10	0	8	8	74
AMCE 5%	10	5	8	8	69
AMCE 10%	10	10	8	8	64
AMCE 15%	10	15	8	8	59

2.3.2. Yield and useful yield

The total yield of the final product (%, w/w) was calculated by dividing the mass of the product by that of the initial materials, multiplied by 100. According to the general rules for preparations in 15th Japanese Pharmacopoeia, an appropriate granule size is defined as being approximately 355–1400 μm in diameter. Therefore, obtained granules that passed through a 1000 μm sieve, but not through a 425 μm sieve, were defined as the useful fraction in this study. The useful yield (%, w/w) was calculated by dividing the mass of the useful fraction by that of the starting material, multiplied by 100.

2.3.3. Determination of drug content

Granules (100 mg) with diameters in the 425–1000 μm range were dissolved in 200 mL of distilled water, and the drug content of the granules was determined by UV spectroscopy at 243 nm (UVmini-1240, Shimadzu Co., Kyoto, Japan).

2.3.4. Compression analysis of granules

The compression fracture strength of 500–710 μm granules was found with a particle hardness tester (Grano, Okada Seiko Co. Ltd., Tokyo, Japan). Granules with particle sizes ranging from 500 to 710 μm were used to directly compare the effect of composition in each formulation, because broad particle size distribution affects the compression fracture strength of granules. The deformation behavior and fracture strength of granules were assessed by individually testing 10 granules from each batch by diametral compression between two horizontal stainless steel plates at a velocity of 100 μm/s. The analysis was performed at 25 °C (T_{25}) and at 70 °C (T_{70}), which are representative of ambient and granulation process temperatures, respectively. For the analysis at 70 °C, granules were heated on a hotplate equipped with a temperature sensor before compression.

2.3.5. Roundness

Ten granules with diameters in the 425–1000 μm range were chosen randomly for this analysis. After that, the images of their granules were captured using an Olympus BHS microscope connected to a digital imaging camera, and were then analyzed with WinROOF image analysis software (Version 5.5, Mitani Co. Ltd., Fukui, Japan) to determine the exact diameters and shapes of granules. The shapes of the granules were defined by their roundness (Pt/Pr), where Pt is the theoretical perimeter length of a perfectly spherical granule having the same area as the one under analysis, and Pr is the actual perimeter length.

2.3.6. Scanning electron microscopy

The surface morphology of 425–1000 μm granules was assessed by scanning electron microscopy (SEM; JSM-5310LV, JEOL, Tokyo, Japan). Samples were placed on double-sided adhesive tape, one side of which had been applied to an aluminum stub. Excess granules were removed, and the samples were sputter-coated with platinum under argon gas before imaging.

2.4. Dissolution testing

The release behavior of APAP from 425 to 1000 μm granules of each formulation was examined in accordance with the paddle method listed in the Japanese Pharmacopoeia (16th edition). The test medium was 900 mL of either pH 4.0 acetate buffer solution or pH 6.5 phosphate buffer solution, and the medium was heated to 37 ± 0.5 °C. The paddle rotation speed was 50 rpm. At 2.5, 5, 7.5, 10, 15, 20, 30, 45, 60, 90, and 120 min, 5 mL aliquots of the test solutions were withdrawn and replaced with an equal volume of buffer solution, and the samples were passed through a membrane filter (0.45 μm). The amount of APAP released into the medium was quantitatively determined by UV spectroscopy at 243 nm.

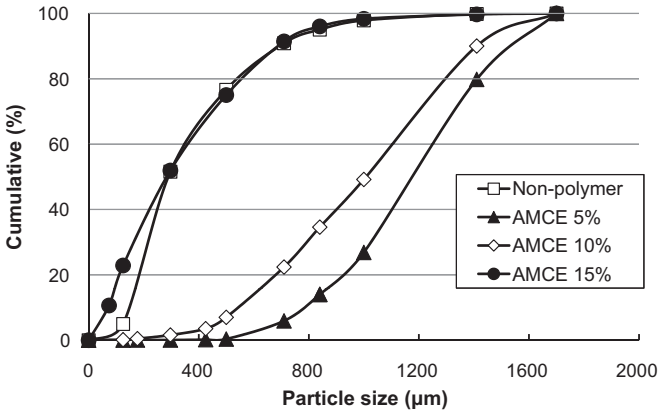

Fig. 2. Effect of AMCE loading on size distribution of granules.

The difference factor (f_1) was used to evaluate pH-dependent release patterns of APAP from the granules. f_1 is calculated from the percent (%) differences between the dissolution profile at pH 4.0 and pH 6.5 for each time point:

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} \times 100, \quad (1)$$

where n is the number of time points, R is the dissolution value of the reference (pre-change) batch at time t, and T is the dissolution value of the test (post-change) batch at time t as described above (Moore and Flanner, 1996). According to the FDA's guidance, dissolution data time points below 85% drug release and only one sampling time point above 85% were used to calculate f_1.

2.5. Statistics

Statistical analyses were performed by using Student's t-test, where a probability value of $p < 0.05$ was considered to indicate statistical significance.

3. Results and discussion

3.1. Effect of AMCE loading on granule characteristics

In this study, the conditions for preparing granules were derived from preliminary thermal analysis experiments and previous reports by Thomsen et al. (1993, 1994). The melting range or glass-transition temperature (T_g) of the MBs was examined by differential scanning calorimetry (DSC; DSC-100, Seiko Instruments Inc., Japan). GM and MC-wax melted at peak temperatures of 70 °C and 58 °C, respectively. In addition, AMCE deformed plastically at a peak temperature of ~55 °C (data not shown). Thomsen et al. (1993, 1994) reported the relationship between the process parameters of the high-shear mixer—such as product load, jacket temperature and massing time—and the yield when using GM and MC-wax as MBs. Based on the preliminary results and the previous reports, the granulation process was set as shown in Fig. 1B.

Fig. 2 shows plots of cumulative percentage mass fraction *versus* granule particle size, and Table 2 lists the yield, useful yield, d_{50}, drug content, and roundness for each formulation. When 5% and 10% AMCE were incorporated into the formulation, broad particle size distributions were observed; the median diameters of granules containing 5% and 10% AMCE were 1180 and 1010 μm, respectively, a 3-fold increase in comparison with polymer-free granules. This result might be attributable to the plastic strain

Table 2
Technological and physicochemical properties of granules.

Formulation	Yield (%)	Useful yield (%)	d_{50} (μm)	Drug content (%)	Roundness
Polymer-free	92.0	29.9	290	9.14 ± 0.13	0.916 ± 0.037
AMCE 5%	65.7	26.3	1180	9.90 ± 0.18	0.883 ± 0.041
AMCE 10%	70.1	32.1	1010	9.66 ± 0.06	0.884 ± 0.040
AMCE 15%	72.1	31.8	280	8.20 ± 0.15	–

properties of AMCE being affected by the jacket's temperature at 70 °C, which is above T_g (=55 °C) for AMCE. Therefore, AMCE that melted during the granulation process appears to act as a binder that enabled agglomeration and growth in granule formation. However, when 15% AMCE was incorporated into the formulation (Fig. 2 and Table 2), the particle size distribution overlapped with that of polymer-free granules, and the median granule diameter for this formulation was approximately equal to that for the polymer-free formulation. In addition, about 23% of the 15% AMCE granules were found to have particle size of less than 125 μm. This result suggests that AMCE could not act as a binder at higher loading, and an optimal proportion of AMCE exists for formulations prepared by this melt granulation process. Differences in the particle size distribution of granules containing lower and higher AMCE contents might also be explained by the differences of its adherence to the inner walls of the high-shear mixer. The temperature of the inner surface is easily raised by the rubber heater accessory that covers the outside of the high-shear mixer, and the plastic strain of AMCE powders are affected by this heating. In addition, particle sizes of AMCE powder are small (d_{50} < 50 μm), and would be strongly affected by the granulation conditions. Thus, an increase in the adherence of AMCE to the inner walls of the mixer will occur as the AMCE loading is increased. Table 2 also lists each formulation's drug content, which closely agreed with the theoretical value when 5% or 10% AMCE was incorporated. However, the drug content was slightly lower for the 15% AMCE formulation than for the others. This result might also reflect the fraction of granules with particle size of less than 125 μm, which would contain higher APAP content (Fig. 2).

Fig. 3 shows SEM images of granules. Polymer-free granules were spherical and smooth (Fig. 3A), but 5% and 10% AMCE granules had slight surface asperity (Fig. 3B and C). Table 2 lists the roundness of each granule: polymer-free granules were slightly more spherical than granules incorporating AMCE. These differences in the SEM images and in the calculated roundness suggest that plastic deformation of AMCE could induce agglomeration of granules. However, the 15% AMCE granule image (Fig. 3D) shows the presence of a primary particle on the granule surface and indications of insufficient liquid saturation. This confirmed that the ratio between amounts of MBs and AMCE was involved in particle growth. Furthermore, the roundness of 15% AMCE granules could not be measured accurately, because the granules were flat. Such flat granules might be formed by a globule adhering on the inner wall of the high-shear mixer as the mixer shaved the granules with its shear blade.

3.2. Growth mechanism of AMCE granules

Fig. 4A and B shows typical granule strength profiles until fracture at ambient temperature (T_{25} = 25 °C) and granulation process temperature (T_{70} = 70 °C), respectively. The peaks in the plots indicate that granules are divided by their cross-sectional area. Granule strengths were calculated from the plots by Hiramatsu's equation (Hiramatsu and Oka, 1966) (Table 3). Fig. 4A and B shows clear differences in the peaks of the load–displacement curves between polymer-free and 10% AMCE granules. The load–displacement curve of polymer-free granules is convex upward. In contrast, the load–displacement curve of 10% AMCE granules is more smooth, suggesting that the granules were not differentiated and merely deformed. Moreover, 5% AMCE granules also displayed a load–displacement curve similar to that for 10% AMCE granules (data not shown). This difference between polymer-free and AMCE granules might depend on the characteristics of AMCE; namely, AMCE granules acquire greater toughness and flexibility. This characteristic change is supported by the results shown in Table 3, where an AMCE loading-dependent increase in particle strength at T_{25} was also observed. Although similar trends in the load–displacement curves were found at T_{25} and T_{70} (recall T_{70} is assumed to be the temperature during the granulation process), the particle strength at T_{70} was rarely lower than that at T_{25} (Fig. 4 and Table 3).This result indicates that, although AMCE did not affect the deformability of granules during the granulation process, incorporation of AMCE strengthened the granules after cooling.

Wet granulation is one of comparative granulation techniques, and the following two mechanisms have been reported to be involved in the agglomerate formation and growth of granules (Schæfer and Mathiesen, 1996; Schæfer, 2001): the MB distribution mechanism and the MB immersion mechanism. However, for the melt granulation process using a high-shear mixer in the present study, the distribution mechanism might be promoted by a smaller particle size and lower viscosity of MBs and by a higher impeller rotation speed. Therefore, we hypothesize that the particle growth mechanism consistent with our obtained results and previous reports is as summarized schematically in Fig. 5. On the one hand, Fig. 5A shows a typical distribution mechanism and agglomerate growth for polymer-free granules. In agglomerate growth, coalescence and breakage gradually occur for the spherical granules and particle size is increased until equilibrium is established. On the other hand, Fig. 5B shows a different agglomerate growth method for granules containing AMCE; specifically, after the nucleation phase, plastic deformation of AMCE—which is irregularly located due to the viscous behavior of AMCE—prevents breakage of agglomerate. Based on these growth mechanisms, particle size for AMCE granules might be larger than that for polymer-free granules, as shown in Fig. 2.

3.3. Release patterns of APAP from granules prepared by melt granulation

Fig. 6 shows the results on the release behavior of APAP from each type of granule at pH 4.0 and pH 6.5. Any significant changes between release profiles of APAP from polymer-free granules were not observed under both pH conditions (Fig. 6A). In contrast, 5% and 10% AMCE granules exhibited pH-dependent release patterns; fast release of APAP from granules was observed at pH 4.0, owing to the pH-sensitivity of AMCE, whereas the release of APAP at pH 6.5 was prolonged (Fig. 6B and C). However, the release of APAP

Table 3
Compression data for granules.

	Granule strength (mN/mm^2)		
	Polymer-free	AMCE 5%	AMCE 10%
Ambient temperature (T_{25})	205 ± 85	329 ± 62*	433 ± 159*
Granulation temperature (T_{70})	10.4 ± 2.9	14.0 ± 3.4	13.3 ± 3.5

* P < 0.05 as compared with polymer-free granules.

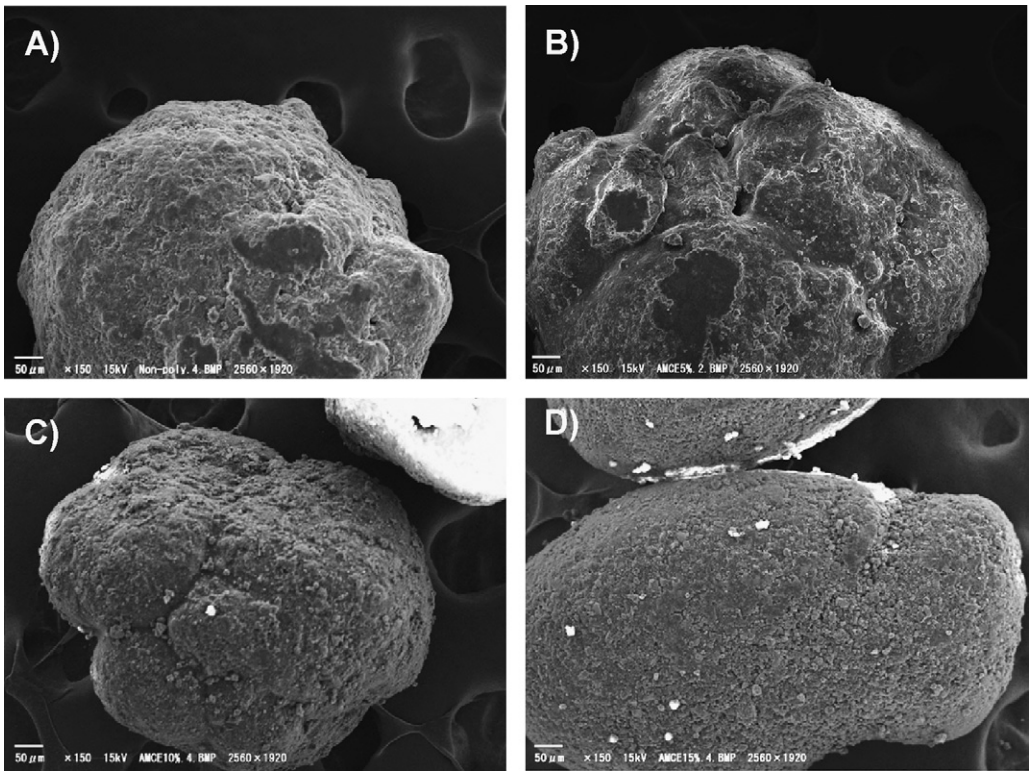

Fig. 3. SEM images of granules: (A) polymer-free; (B) 5% AMCE; (C) 10% AMCE; and (D) 15% AMCE.

from 15% AMCE granules under both pH conditions did not exhibit pH-dependent behavior and fast release of APAP was observed in both cases (Fig. 6D). From the SEM image of 15% AMCE granules (Fig. 3D), the presence of a primary particle on the granule surface was found to be observed due to the insufficient liquid saturation. Taken together, we infer that higher AMCE loading caused an insufficient MBs-coating to drug particles, MBs-uncoated drug particles existed on the surface of granules, and consequently fast release of APAP would be observed in both pH conditions (Fig. 6D).

The difference factor (f_1), which is proportional to the average difference between the two pH profiles, is recommended in the U.S. Food and Drug Administration's guidance for industry for comparing dissolution profiles (FDA, 1997). According to that document, f_1 values up to 15 (0–15) generally indicate the equivalence of two curves, and values over 15 indicate a significant difference between two curves. Therefore, we regarded an $f_1 > 15$ as an indication of pH-dependent release in the present study. Calculating each f_1 value for the granule formulations, we found that f_1 for polymer-free granules was 7.60, suggesting that the release behavior was the same at pH 4.0 and pH 6.5, but we found that f_1 values for granules containing AMCE were over 15 in all cases, thus indicating pH-dependent release behavior. In particular, since the f_1 value for 5% AMCE granules was the largest (57.5), this formulation was found to exhibit drug release behavior with the strongest pH dependence among the formulations in this study. However, according to the FDA's guidance, when comparing dissolution profiles by means of f_1, all profiles should be conducted on at least 12 individual dosage units. In addition, to allow use of mean data, the percent coefficient of variation at the earlier time points (*e.g.*, 15 min) should not be more than 20%, and at other time points should not be more than 10%. In this study, the dissolution profiles in each

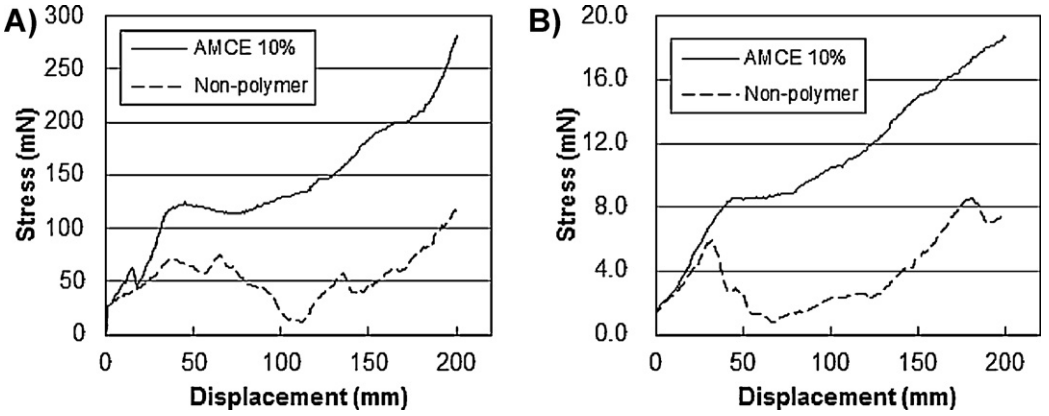

Fig. 4. Typical compressive force profiles for polymer-free and 10% AMCE granules at (A) ambient temperature (25 °C; T_{25}) and (B) granulation temperature (70 °C; T_{70}).

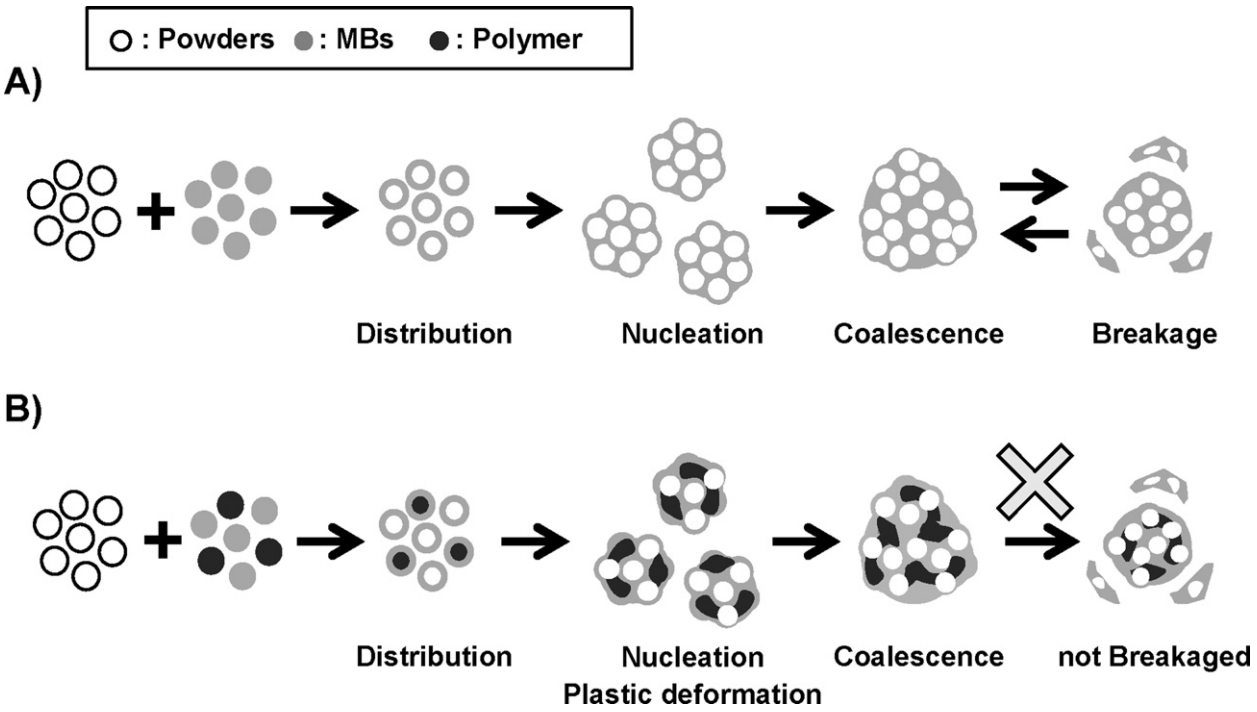

Fig. 5. Hypothesized agglomerate formation mechanisms in melt granulation: (A) polymer-free granules and (B) granules containing AMCE.

formulation were performed in only triplicate and time intervals at which the test solutions were withdrawn were determined by only the preliminary experiments. Therefore, further dissolution studies would be desired to calculate the precise f_1 values.

Finally, to confirm the influence of AMCE on the APAP amount released from granules, SEM images of granules that were dried after being used in dissolution testing under pH 4.0 (Fig. 7) were taken. These images show that numerous micro-pores formed on

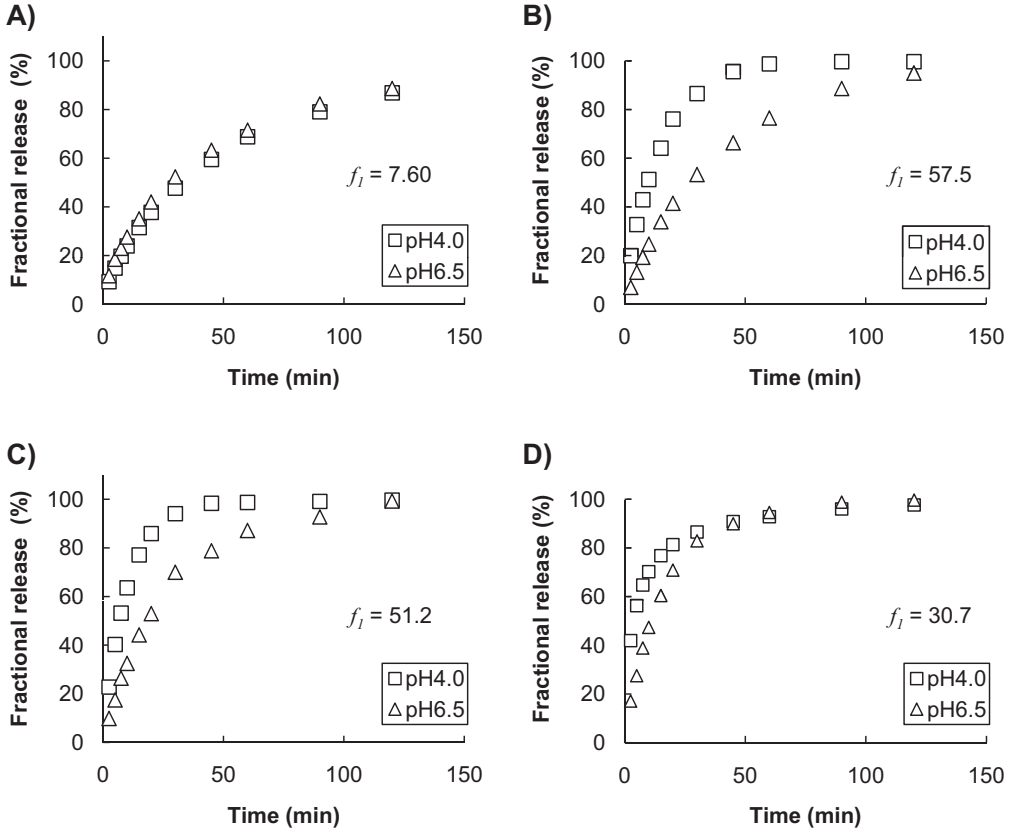

Fig. 6. Release patterns of APAP from granules prepared by melt granulation at pH 4.0 and pH 6.5: (A) polymer-free; (B) 5% AMCE; (C) 10% AMCE; and (D) 15% AMCE Each point represents the mean ± S.D (n = 3).

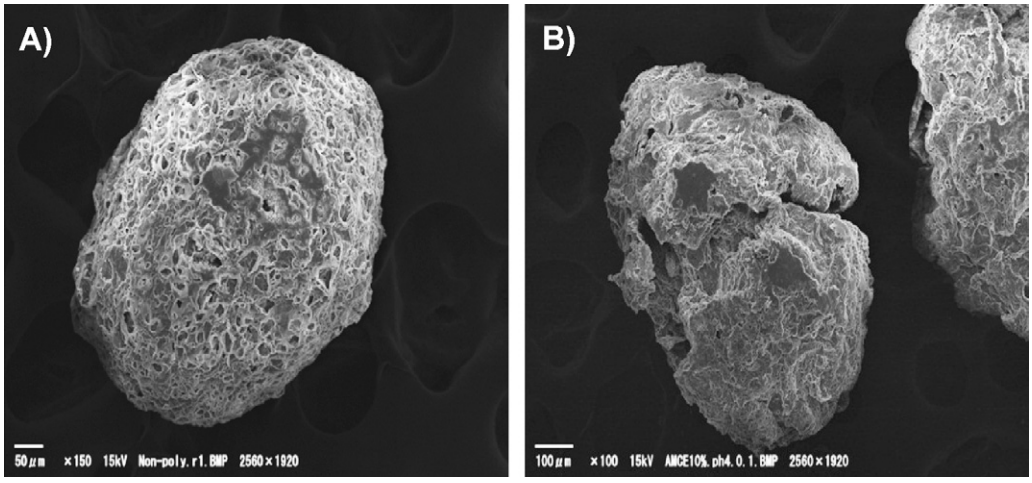

Fig. 7. SEM images of granules after release study: (A) polymer-free and (B) 10% AMCE.

the surface of polymer-free granules; this pore formation might be a consequence of the dissolution of APAP from the surface of granules. Furthermore, the granules kept a shape consistent with that before the dissolution testing (Fig. 7A). Conversely, SEM images of 10% AMCE granules showed substantial cracks and breakage on the surface of granules (Fig. 7B). Such a considerable change in surface morphology might be a consequence of the dissolution of APAP and AMCE, which has been irregularly distributed on the surface of the granules, as mentioned in Section 3.2.

4. Conclusions

In the present study, we prepared granules containing pH-sensitive AMCE polymer by melt granulation with a high-shear mixer, in order to investigate the effects of AMCE loading on granule properties and on *in vitro* drug release profiles from granules. The median diameter was found to be higher and the particle size distribution was found to be wider, for granules containing 5% and 10% AMCE, whereas values for granules containing 15% AMCE were comparable with those for polymer-free granules. From the load–displacement curves obtained by compression testing, AMCE enhanced particle strength at ambient temperature and induced plastic strain, while suppressing fragmentation of the granules. In addition, from dissolution testing using media at pH 4.0 and pH 6.5, incorporation of AMCE, especially 5% AMCE, showed significant pH dependence in the release profile. Therefore, the present study has demonstrated for the first time that the combination of melt granulation and AMCE incorporation enables the development of novel functional granules that exhibit pH-dependent release of the active ingredient.

Acknowledgments

The authors thank the following companies for kindly providing reagents used in this study: Kimura Sangyo Co. Ltd., Nippon Seiro Co. Ltd., and Iwaki Seiyaku Co., Ltd.

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