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Research paper

Alginate-based pellets prepared by extrusion/spheronization: Effect of the amount and type of sodium alginate and calcium salts

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Abstract

Pellets containing microcrystalline cellulose (MCC), a model drug (theophylline) and a range of levels of sodium alginate (i.e., 10–50% w/w) were prepared by extrusion/spheronization. Two types of sodium alginate were evaluated with and without the addition of either calcium acetate or calcium carbonate (0, 0.3, 3 and 10% w/w). The effects of amount and type of sodium alginate and calcium salts on pellet properties, e.g., size, shape, morphology and drug release behavior, were investigated. Most pellet formulations resulted in pellets of a sufficient quality with respect to size, size distribution and shape. The results showed that the amounts of sodium alginate and calcium salts influenced the size and shape of the obtained pellets. However, different types of sodium alginate and calcium salt responded to modifications to a different extent. A cavity was observed in the pellet structure, as seen in the scanning electron micrographs, resulting from the forces involved in the spheronization process. Most of pellet formulations released about 75–85% drug within 60 min. Incorporation of calcium salts in the pellet formulations altered the drug release, depending on the solubility of the calcium salts used. The drug release data showed a good fit into both Higuchi and Korsmeyer–Peppas equations.

Keywords: Alginate; Calcium salts; Pellets; Extrusion; Spheronization

1. Introduction

Alginates, a group of anionic polysaccharides, are linear polysaccharides extracted from brown seaweed. They contain varying amounts of (1–4)-linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues. The residues may vary widely in composition and sequence and are arranged in a pattern of blocks along the chain. The homopolymeric regions of M and G blocks are interspersed with regions of alternating structure (MG blocks) [1,2]. The composition and extent of the sequences and the molecular weight determine the physical properties of the alginates. One of the most important and useful properties of alginates is the ability to form gels in the presence of some multivalent metal ions such as calcium. The controlled addition of these ions technically leads to insoluble alginate gel formation. The affinity of alginates for calcium ions and their gel forming properties is mainly related to the overall fraction of G residues, the molecular weight of the polymer, and the calcium ion concentration at the time of gelation. When two G residues are adjacent in the polymer, they form a binding site for calcium [3]. Alginates are of pharmaceutical interest because of their non-toxicity, biodegradability and biocompatibility [2,4]. Alginate hydrogels have the potential to be used as either controlled release membrane or matrix systems for therapeutic drugs. In the membrane system, alginates could be applied as a coating material

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on the solid units (e.g., [5–7]). Matrices incorporating alginate salts or a combination of alginate with other polymers have been employed to successfully control the release of many drugs (e.g., [8–13]).

The focus of the present paper was to produce pellets as a multi-particulate system by extrusion/spheronization. The extrusion/spheronization is an established technique that enables the formation of spherical pellets with advantages of regularity of shape and size, smooth surface characteristics which are ideal for the application of a release retarding membrane [14]. Generally, these spheres have low friability and have few fines. So far, microcrystalline cellulose (MCC) has been used as a universal filler and binder for the extrusion/spheronization process. However, it has distinct disadvantages, such as lack of disintegration and a limited capability for controlled drug release. Alternative materials, especially hydrophilic polymers, are being investigated for the purpose to substitute or reduce the use of MCC. For example, Law and Deasy [15] have produced pellets from spray-dried mixtures of MCC and hydrophilic polymers (e.g., sodium carboxymethylcellulose (sodium CMC), hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose) by extrusion and spheronization. They found that adhesive polymers (sodium CMC and HPMC) were less suitable for pelletization by this technique. Recently, Tho and coworkers [16,17] have produced pellets from polysaccharide pectin by extrusion/spheronization and identified factors influencing the process and the characteristics of the resulting product. They found that spherical pellets could be obtained by using ethanol as granulating liquid. Steckel and Mindermann-Nogly [18] demonstrated that the chitosan pellets were successfully prepared by extrusion/spheronization using diluted acetic acid solution as granulating liquid. Thommes and Kleinebudde [19,20] proposed the use of κ-carrageenan as an alternative pelletization aid to MCC in the extrusion/spheronization process. Chatchawalsaisin et al. [21] reported the use of sodium alginate alone (up to 16% w/w) or in combination (4% w/w) with chitosan to produce pellets by ram extruder. On the other hand, the spherical pellets with a maximum fraction of 60% w/w chitosan could be produced when 1.25–2.5% w/w sodium alginate was included in the formulations with no MCC [22].

Sodium alginate has been used as pelletization aid because of its abundant availability and its wide use in pharmaceutical application. It could be also used to modify the drug release. In the previous paper [23], we have described the possibility of producing alginate-based pellets (the content of sodium alginate in the formulation was 30% w/w) by extrusion (i.e., using a basket extruder) and spheronization process and the influence of additive in the granulating liquid on characteristics of and drug release from resulting pellets. In order to understand more about the behavior of alginates in the extrusion/spheronization process, we have further investigated the feasibility of their pelletization by extrusion/spheronization in this study. The effects of the amount and type of sodium alginate and calcium salts on the physical properties, such as particle size, shape, surface morphology and drug release characteristics, were studied. Theophylline was chosen as a model drug because of its ready availability, relatively low cost, ease of assay, and chemical stability.

2. Materials and methods

2.1. Materials

Two types of sodium alginate with different M/G ratios (i.e., 0.67 for Manucol® DMF (MC), Batch No. 951111, and 0.43 for Manugel® DMB (MG), Batch No. 991131) were the generous gift from ISP (Thailand) Co., Ltd., Thailand. Anhydrous theophylline (Lot number 99360-A) was obtained as a gift sample from BASF (Thai) Co., Ltd., Thailand. Microcrystalline cellulose (Avicel PH101, Batch No. 6521, FMC Corp., USA), calcium acetate (Batch No. 0525/01/04, Polskie Odczynniki Chemiczne S.A., Belgium), and calcium carbonate (Lot No. 02010, Riedel-de Haën, Germany) were used as received without further purification. All other chemicals were of reagent or pharmaceutical grade and used as supplied.

2.2. Manufacture of pellets by extrusion/spheronization

One hundred grams of theophylline (20% w/w) and various amounts of sodium alginate (MC or MG, 10–50% w/w) and microcrystalline cellulose (30–70% w/w) was mixed in a planetary mixer (Model K5SS, Kitchen Aid, USA) for 20 min. Various amounts of a granulating liquid (3% w/v calcium chloride) were added slowly to the powder blend (see Table 1), which was then mixed until a homogenous, cohesive, plastic mass was obtained. The resulting wet mass was extruded at a speed of 60 rpm (Model 25, Caleva, England), through perforations 1.5 mm in diameter and 1.5 mm in length. Spheronization was performed in a spheronizer (Model 250, Caleva, England) with a rotating plate of regular crosshatch geometry (diameter of 370 mm), at a speed of 600 rpm for 30 min. Pellets were then dried on a tray in an air dryer (Yeo Heng, Thailand) at 50 °C for 2 h.

To study the effect of incorporated calcium salts in the pellet formulations on the pellet characteristics, the formulations of powder blends were modified. Some portions of MCC in the formulations were substituted by different amounts (i.e., 0.3%, 3% and 10% w/w) of calcium salts (calcium acetate or calcium carbonate, Table 2). The amounts of theophylline and sodium alginate (MC or MG) were kept constant at 20% and 30% w/w, respectively. Other parameters were the same as mentioned above.

2.3. Characterization of pellets

2.3.1. Pellet size and shape

The image analysis was performed on each sample using image analysis software (IQmaterials version 2, Media

Table 1
The mean Feret diameter, shape factor and aspect ratio of alginate-based pellets prepared by extrusion/spheronization

Formulation[a]	Code	Amount of 3% $CaCl_2$[b]	Mean Feret diameter (mm ± SD)	Shape factor ± SD	Aspect ratio ± SD
No sodium alginate	MCC pellets	38.0	0.952 ± 0.220	0.86 ± 0.10	1.11 ± 0.06
MC 10%	MC10	34.1	0.832 ± 0.190	0.82 ± 0.10	1.09 ± 0.08
		37.0	0.834 ± 0.205	0.85 ± 0.10	1.09 ± 0.10
		40.1	0.939 ± 0.152	0.90 ± 0.09	1.10 ± 0.06
MC 20%	MC20	41.1	1.039 ± 0.194	0.83 ± 0.08	1.17 ± 0.11
		44.1	0.910 ± 0.201	0.81 ± 0.12	1.14 ± 0.12
		47.1	0.851 ± 0.190	0.80 ± 0.11	1.13 ± 0.10
MC 25%	MC25	53.3	1.045 ± 0.464	0.84 ± 0.20	1.20 ± 0.24
		56.6	0.972 ± 0.369	0.81 ± 0.14	1.15 ± 0.20
		59.6	0.816 ± 0.379	0.82 ± 0.17	1.16 ± 0.16
MC 30%	MC30	52.2	0.950 ± 0.230	0.82 ± 0.11	1.21 ± 0.19
		55.2	1.351 ± 0.614	0.84 ± 0.16	1.20 ± 0.18
		58.3	1.094 ± 0.430	0.80 ± 0.15	1.20 ± 0.15
		64.9	0.874 ± 0.274	0.71 ± 0.15	1.21 ± 0.21
		67.8	1.075 ± 0.469	0.74 ± 0.16	1.15 ± 0.16
MC 40%	MC40	62.7	0.836 ± 0.614	0.76 ± 0.24	1.36 ± 0.32
		68.4	0.884 ± 0.640	0.70 ± 0.25	1.36 ± 0.31
		74.3	0.874 ± 0.571	0.82 ± 0.22	1.28 ± 0.23
MC 50%	MC50	69.6	1.207 ± 0.416	0.77 ± 0.18	1.26 ± 0.25
		88.6	0.632 ± 0.583	N/A	N/A
MG 10%	MG10	40.8	0.667 ± 0.403	0.81 ± 0.18	1.16 ± 0.16
		45.5	0.585 ± 0.304	0.86 ± 0.16	1.15 ± 0.19
		48.0	1.080 ± 0.475	0.87 ± 0.14	1.11 ± 0.11
		50.6	1.058 ± 0.452	0.89 ± 0.11	1.07 ± 0.07
MG 20%	MG20	53.5	0.708 ± 0.269	0.83 ± 0.12	1.12 ± 0.09
MG 25%	MG25	33.1	1.105 ± 0.191	0.84 ± 0.09	1.13 ± 0.06
		36.9	0.917 ± 0.313	0.85 ± 0.14	1.16 ± 0.11
		40.1	0.823 ± 0.289	0.82 ± 0.12	1.15 ± 0.13
		47.5	0.760 ± 0.301	0.86 ± 0.17	1.12 ± 0.15
		54.9	0.807 ± 0.390	0.79 ± 0.14	1.14 ± 0.13
MG 30%	MG30	46.8	0.794 ± 0.343	0.85 ± 0.13	1.22 ± 0.16
		49.8	1.055 ± 0.292	0.89 ± 0.10	1.15 ± 0.13
		53.2	0.934 ± 0.265	0.87 ± 0.12	1.13 ± 0.09
		56.6	0.899 ± 0.382	0.85 ± 0.18	1.21 ± 0.25
MG 40%	MG40	62.8	0.557 ± 0.300	0.84 ± 0.19	1.22 ± 0.19
		67.5	0.538 ± 0.368	0.82 ± 0.19	1.23 ± 0.21
		72.8	0.634 ± 0.427	0.83 ± 0.19	1.21 ± 0.19
		82.8	0.936 ± 0.397	0.76 ± 0.15	1.20 ± 0.19
MG 50%	MG50	68.7	N/A	N/A	N/A

N/A, not applicable.
[a] MC, Manucol DMF; MG, Manugel DMB.
[b] Grams of 3% w/v calcium chloride solution per 100 g of powder mass.

Cybernetics, USA). The pellets were spread over a flat surface by spatula and a digital image (Model S602Zoom, Fujifilm, Japan) was collected. Under the same optical conditions, an image of a linear scale was used to calibrate the image analysis software. The data taken from the pellet images ($n \geqslant 200$) were the Feret diameter, aspect ratio (the ratio of length to width of each particle) and shape factor. The Feret diameter of a pellet is defined as the average of 36 caliper measurements around the particle employing a 5° angle of rotation. The shape factor, a number indicating the degree of roundness of each particle, was calculated by the software according to Eq. (1) [24] where A is the area and P is the perimeter. A value of "1" indicates a particle that is perfectly round.

$$\text{Shape factor} = \frac{4\pi A}{P^2} \quad (1)$$

2.3.2. Particle size distribution

The particle size distribution of spherical pellets was determined using a set of the British standard test sieves (600–2000 μm with $2^{0.25}$ progression) and a sieve shaker (Octagon Digital, Endecotts, England) operated for 5 min at a frequency of 50 Hz and an amplitude of 1 mm. The weight retained in each fraction was determined by analytical balance (model AG204, Mettler-Toledo, Greifensee, Switzerland) and the percentage of each fraction was calculated.

2.3.3. Pellet morphology

Morphological examination of the surface and internal structure of the dried pellets was carried out using a scanning electron microscope (Model Maxim-2000, CamScan Analytical, Cambridge, England) equipped with back-scattered

Table 2
The mean Feret diameter, shape factor and aspect ratio of extruded/spheronized pellets made of different types and amounts of sodium alginate and calcium salts

Formulation[a]	Code	Amount of 3% $CaCl_2$[b]	Mean Feret diameter (mm ± SD)	Shape factor ± SD	Aspect ratio ± SD
MC 30% + $CaCO_3$ 0.3%	MC30/CC0.3	63.2	1.072 ± 0.706	0.67 ± 0.22	1.29 ± 0.33
		66.2	0.976 ± 0.538	0.65 ± 0.18	1.26 ± 0.26
		69.2	1.036 ± 0.549	0.70 ± 0.19	1.27 ± 0.33
MC 30% + $CaCO_3$ 3%	MC30/CC3	62.0	0.903 ± 0.570	0.75 ± 0.20	1.23 ± 0.30
		65.4	0.970 ± 0.567	0.72 ± 0.21	1.25 ± 0.23
		68.3	1.679 ± 1.209	0.63 ± 0.24	1.25 ± 0.27
MC 30% +$CaCO_3$ 10%	MC30/CC10	63.6	1.050 ± 0.421	0.75 ± 0.14	1.17 ± 0.16
MC 30% + CaAc 0.3%	MC30/CA0.3	57.5	0.890 ± 0.390	0.82 ± 0.13	1.13 ± 0.13
		59.6	1.089 ± 0.687	0.77 ± 0.20	1.16 ± 0.22
		65.0	0.940 ± 0.453	0.74 ± 0.16	1.16 ± 0.13
MC 30% + CaAc 3%	MC30/CA3	50.9	0.842 ± 0.343	0.82 ± 0.16	1.16 ± 0.16
		55.9	0.854 ± 0.310	0.71 ± 0.16	1.20 ± 0.19
		61.8	1.461 ± 0.566	0.74 ± 0.15	1.18 ± 0.22
MC 30% +CaAc 10%	MC30/CA10	44.8	1.542 ± 0.798	0.86 ± 0.14	1.09 ± 0.09
MG 30% + $CaCO_3$ 0.3%	MG30/CC0.3	54.9	0.898 ± 0.278	0.89 ± 0.11	1.11 ± 0.08
		63.0	0.972 ± 0.273	0.83 ± 0.10	1.09 ± 0.08
		68.6	1.648 ± 0.365	0.83 ± 0.11	1.10 ± 0.15
		68.7	1.207 ± 0.376	0.80 ± 0.15	1.10 ± 0.11
MG 30% + $CaCO_3$ 3%	MG30/CC3	51.0	0.814 ± 0.360	0.82 ± 0.15	1.16 ± 0.11
		53.9	1.101 ± 0.451	0.85 ± 0.19	1.18 ± 0.22
		53.9	0.860 ± 0.491	0.84 ± 0.18	1.19 ± 0.21
MG 30% + $CaCO_3$ 10%	MG30/CC10	52.9	0.929 ± 0.296	0.91 ± 0.11	1.08 ± 0.09
		55.9	1.065 ± 0.376	0.91 ± 0.11	1.09 ± 0.08
		58.9	0.911 ± 0.389	0.82 ± 0.17	1.10 ± 0.06
MG 30% +CaAc 0.3%	MG30/CA0.3	49.9	0.891 ± 0.401	0.88 ± 0.17	1.15 ± 0.13
		52.9	0.909 ± 0.218	0.89 ± 0.11	1.19 ± 0.09
		55.9	0.810 ± 0.414	0.85 ± 0.17	1.13 ± 0.10
MG 30% + CaAc 3%	MG30/CA3	49.8	0.799 ± 0.578	0.90 ± 0.14	1.11 ± 0.12
		52.9	0.981 ± 0.358	0.90 ± 0.13	1.10 ± 0.12
		53.8	1.568 ± 0.343	0.91 ± 0.09	1.06 ± 0.04
MG 30% + CaAc 10%	MG30/CA10	45.1	0.991 ± 0.294	0.89 ± 0.12	1.07 ± 0.08

[a] Grams of 3% w/v calcium chloride solution per 100 grams of powder mass.
[b] MC, Manucol DMF; MG, Manugel DMB; $CaCO_3$, CC, calcium carbonate; CaAc, CA, calcium acetate.

electron detector at an accelerating voltage of 25 keV [25]. The samples were not coated with gold, so that the difference in atomic number of elements (i.e., the difference between calcium and carbon) could be detected by back-scattered electron detector [25]. The internal structure of the pellets was examined by cutting them in half with a steel blade.

2.4. Drug release studies

To examine the effects of investigated factors on drug release, the drug release studies were carried out using USP dissolution apparatus I (Erweka, Germany) equipped with baskets which was operated at the speed of 100 rpm. One liter of simulated gastric fluid (USP27) without pepsin (SGF), pH 1.2, as the dissolution medium, was placed in the glass vessel, assembled the apparatus, and equilibrated the dissolution medium to 37 °C. The amount of drug release from pellets (100 mg of pellets in the size fraction of 1.00–1.18 mm) was measured at the suitable time interval and was then determined spectrophotometrically (model Lambda 2, Perkin-Elmer, USA) at the maximum wavelength (λ_{max}) of 270 nm. Each dissolution study was performed in triplicate.

Higuchi and Korsmeyer–Peppas models were used for the analysis of the drug release mechanism of matrix-typed, alginate-based pellets, as previously described [23]. The release of drugs from the matrix pellets can be analyzed by release kinetics theories [26,27], as follows:

$$\text{Higuchi model}: \quad M_t/M_f = Kt^{1/2} \tag{2}$$

where M_t is the amount of drug release at time t; M_f is the amount of drug release after infinite time and K is the Higuchi release rate constant which reflects the shape and the internal structure of the matrix as well as the drug concentration and solubility.

$$\text{Korsmeyer–Peppas model}: \quad M_t/M_f = K't^n \tag{3}$$

where K' is a constant incorporating the structural and geometric characteristics of the matrix pellets, n is the release exponent, indicative of the drug release mechanism. This model is generally used to analyze the release of which mechanism is not well known or when more than one type of release phenomena is involved [27]. The drug transport mechanism from spherical matrices is by Fickian diffusion (case I transport) when $n = 0.43$, if $0.43 < n < 0.85$, it indicated anomalous (non-Fickian) transport and for values of

$n = 0.85$, Case II or zero-order release kinetics was indicated. Case II relates to polymer relaxation, while non-Fickian release is described by two mechanisms, the coupling of drug diffusion and polymer relaxation. Occasionally, values of $n > 0.85$ for release from spheres have been observed, which has been regarded as Super Case II kinetics.

Mean dissolution time (MDT) was used to characterize drug release rate from a dosage form and indicated the drug release retarding efficiency of polymer. It is calculated from dissolution data using the following equation [28]:

$$\mathrm{MDT} = \left(\frac{n}{n+1}\right) \cdot K'^{(-1/n)} \quad (4)$$

3. Results and discussion

3.1. Pelletization

Two different types of sodium alginate with different M/G ratios were investigated in this study, i.e., MC (M/G ratio of 0.67, high M alginate) and MG (M/G ratio of 0.43, high G alginate). Our previous report [23] demonstrated that pellets could be prepared by (basket) extrusion and spheronization with the MCC and sodium alginate (MC or MG), using various granulating liquid. The addition of calcium chloride to the granulation liquid reduced the solubility and swelling ability of sodium alginate and consequently allowed successful spheronization process [23]. Based on this finding, calcium chloride solution seems to be the most suitable granulating liquid for extrusion/spheronization of alginate-based pellets and was therefore used in this study.

In this study, different amounts of granulating liquid (3% calcium chloride) were used depending on the formulations (Table 1). This also influenced the shape and size of the obtained pellets (discussed later). The pellets made of MG alginate required smaller amount of granulating liquid for pellet formation, compared to MC alginate. Improvements in the pellet characteristics were also dependent on the type of sodium alginate employed. In this study, we have further investigated the effects of type and concentration of sodium alginate and calcium salts on the

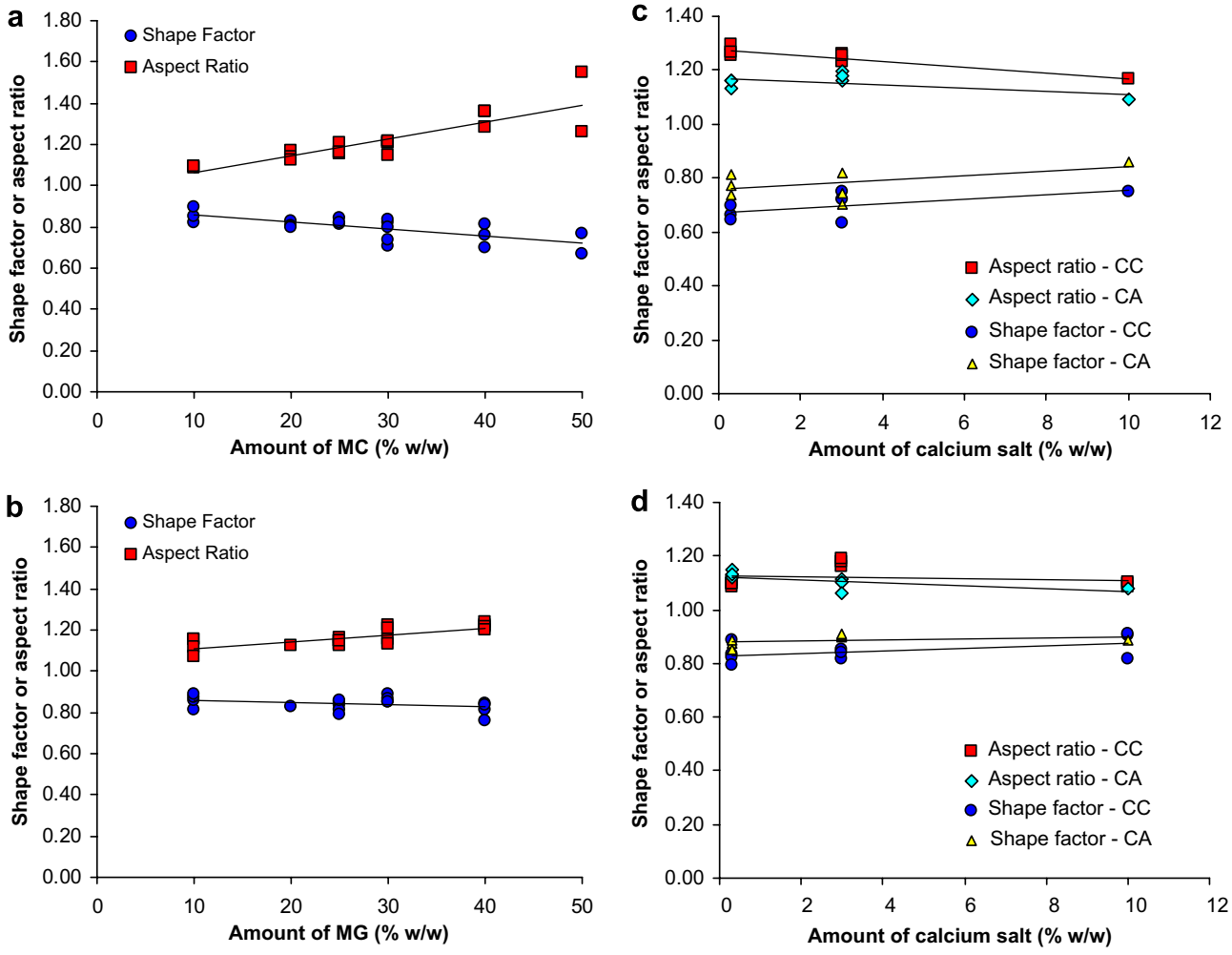

Fig. 1. Effect of the amount of sodium alginate (a and b) and calcium salts (c and d) on the shape factor and aspect ratio of the obtained pellets; (a) pellets containing various amounts of MC, (b) pellets containing various amounts of MG, (c) MC pellets containing various amounts of calcium salt, and (d) MG pellets containing various amounts of calcium salt. Linear lines according to the linear regression analysis are shown. (*Note*: The different data points represent data from each formulation using various amounts of granulating liquid.)

physical characteristics as well as drug release behavior. Pellets with 10–50% of MC (or MG) in powder mixture were produced (Table 1). It is possible to produce spherical pellets in the whole range of alginate investigated (discuss later). However, fine particles (size less than 710 μm) were obtained during spheronization of formulations with high amount of sodium alginate (e.g., 50% MG). This also reduced the yield of the obtained pellets. The addition of sodium alginate (MC or MG) of more than 50% made the extrusion (by basket extruder) more difficult and made the spheronization impossible. The incorporation of calcium salts (calcium acetate or calcium carbonate) was in relation to the importance of calcium ions to the alginate gelling mechanism. In fact, the ionic interactions between G blocks of alginate and calcium ions determine the formation of a cross-linked gel. Adding calcium salts would then influence the physical and drug release properties of the pellets (discussed later).

3.2. Physical properties of pellets

Table 1 shows the mean Feret diameter, shape factor and aspect ratio of the alginate-based pellets prepared by extrusion/spheronization. It is demonstrated that with an increasing amount of granulating liquid (3% calcium chloride), the differences in size and shape of extruded/spheronized pellets were observed. Considering each formulation, the mean particle size (Feret diameter) tended to decrease with increasing amount of granulating liquid, resulting from the ability of calcium ions to cross-link the G units of alginate [23]. On the other hand, the increased amount of MC or MG caused the increase in the mean pellet size. The mean Feret diameter of pellets was in less significantly ($P > 0.05$) changed after the calcium salts were incorporated in the pellet formulations (Table 2). The pellet size distribution for the pellets containing MC or MG, with or without calcium salts, was comparable, had a mode of 1.00–1.40 mm (data not shown). The formulations with higher amount of granulating liquid demonstrated a narrower size distribution. However, some formulations using lower amount of granulating liquid produced the pellets with a mode of smaller size (or fines) with a broader size distribution. This is probably due to the insufficient binding ability of the granulating liquid to bind the powder blends or to form the homogenous wet mass.

The sphericity of pellets, as described by shape factor and aspect ratio, is given in Tables 1 and 2, and also illustrated in Fig. 1. On the shape factor scale of 0.0–1.0, a shape factor of 0.0 indicates a cylinder object and 1.0 indicates a perfect sphere [29]. An aspect ratio of 1.0 indicates a perfect sphere. However, an aspect ratio of lower or equal to 1.1 has been considered good for pharmaceutical pellets [19]. Pellets of a mean aspect ratio above 1.2 were regarded insufficient. This specification was not achieved by most of the formulations. All products were nearly spherical with the shape factor ranging between 0.65 and 0.92, and the aspect ratio varying between 1.07 and 1.36. Increasing the amount of sodium alginate yielded less pellet sphericity, e.g., decreased shape

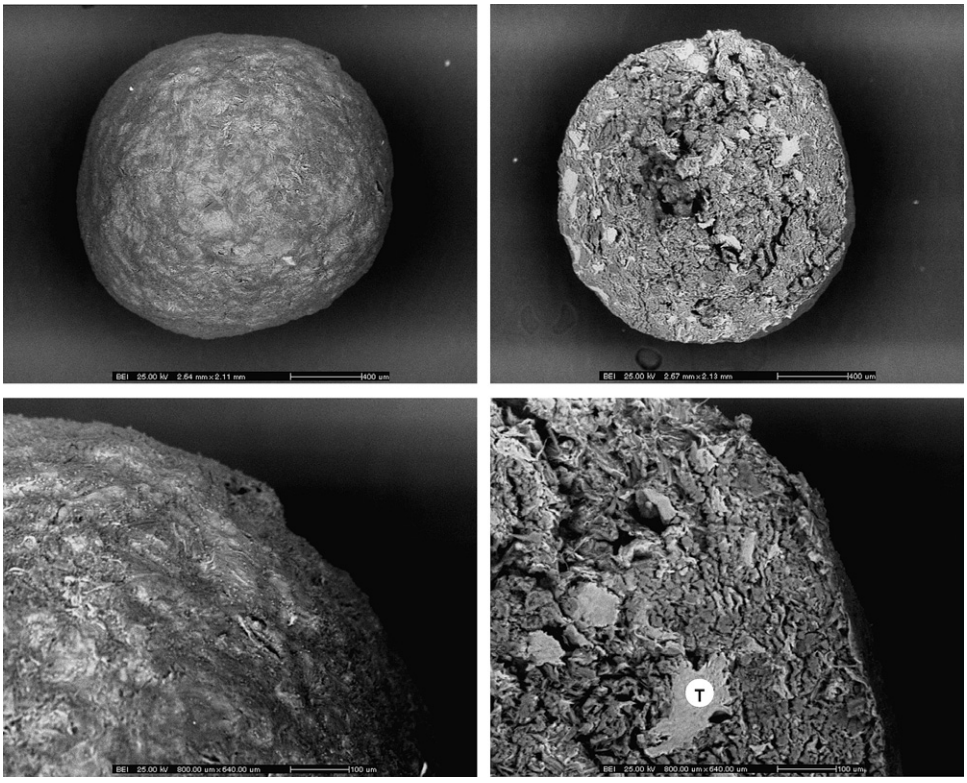

Fig. 2. Scanning electron micrographs of the pellets containing 30% (w/w) MC, showing the surfaces and internal structure. The brighter area (labeled as T) in the internal structure demonstrates the drug (theophylline) particles.

factor and increased aspect ratio (Table 1, Fig. 1a and b). Varying the amount of granulating liquid in each formulation also influenced the sphericity of pellets. Incorporation of calcium salts insignificantly influenced the sphericity of obtained pellets (Table 2). However, the increased amount of calcium salt tended to increase the shape factor and decrease the aspect ratio of pellets containing MC (Fig. 1c). It seemed that the sphericity of MG pellets, as shown in Fig. 1d, was less sensitive to the amount of calcium salt than MC pellets. It is probable that calcium ions cross-linked G units of MG alginate, resulting in less swellable calcium alginate during pellet manufacture [23].

3.3. Pellet morphology

Back-scattered electron imaging, unlike secondary electron imaging, uses high-energy elastic electrons to detect differences in atomic number. Higher atomic number elements reflect or highly deflect more electrons along the primary electron axis. Lower atomic number elements absorb more electrons and appear dark on electron micrographs, for example, the brightness of some elements (C, N and Ca) on the micrographs is $C < N < Ca$. Images are the result of atomic number contrast [25]. Figs. 2–4 show the back-scattered electron images of theophylline-loaded alginate-based pellets (30% MC) containing different amounts of calcium acetate. By using back-scattered electron imaging, the distribution of theophylline (nitrogen-contained drug) could be observed, i.e., brighter particles spreading all over the internal structure of pellet (Figs. 2 and 3). Materials with a larger atomic number will give off more back-scattered electrons. Calcium has a much higher atomic number than carbon and nitrogen atoms of drug molecule and excipients and therefore gave off many more electrons.

The appearance of the pellets containing 0% and 0.3% w/w calcium acetate showed nearly the same surface texture (Figs. 2 and 3). White clusters were observed on the pellet surface (Fig. 4). During slow drying in the tray dryer, some calcium acetate may dissolve and then migrate nearer the pellet surface. The presence of white clusters on the pellet surface was not obvious when the amount of calcium acetate was 0.3% w/w (Fig. 3). The higher amount of calcium acetate may allow a greater tendency to form clusters when dried. The migration of soluble components in extruded pellets during drying has been demonstrated [30]. Using water-insoluble calcium salt (e.g., calcium carbonate), however, the recrystallization of calcium on

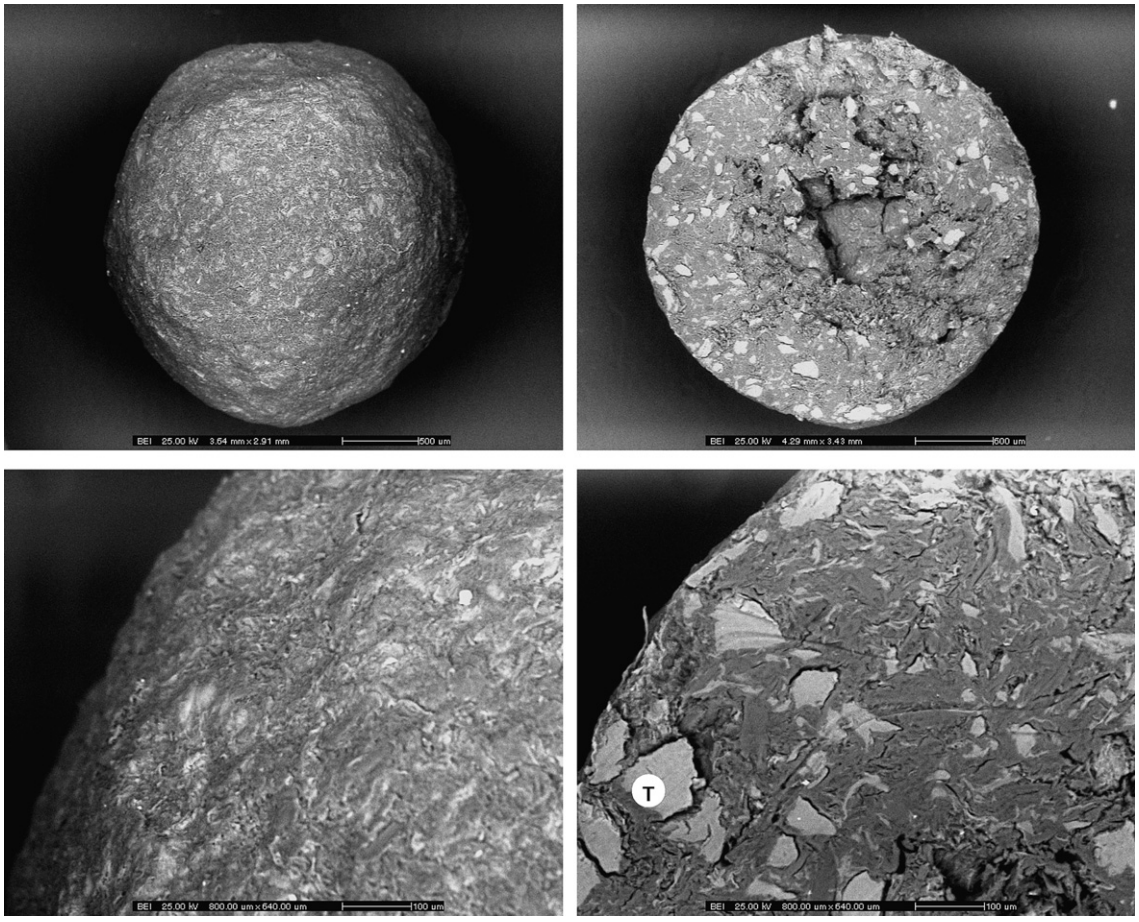

Fig. 3. Scanning electron micrographs of the pellets containing 30% (w/w) MC and 0.3% (w/w) calcium acetate, showing the surfaces and internal structure. The brighter area (labeled as T) in the internal structure demonstrates the drug (theophylline) particles.

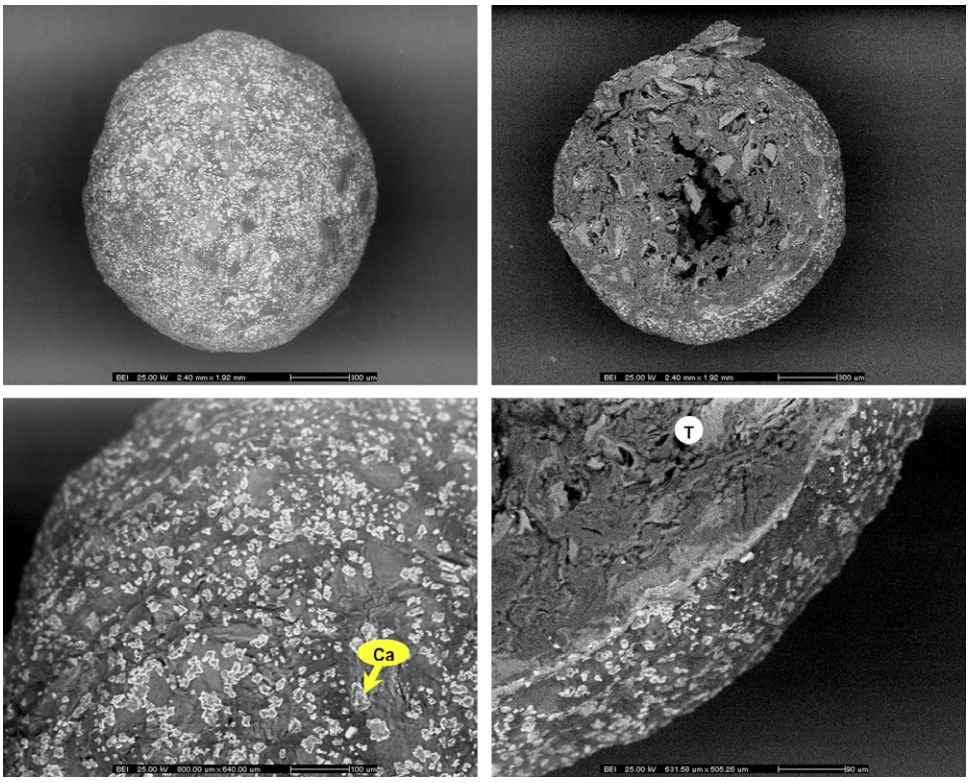

Fig. 4. Scanning electron micrographs of the pellets containing 30% (w/w) MC and 3% (w/w) calcium acetate, showing the surfaces and internal structure. The brighter area (labeled as T) in the internal structure demonstrates the drug (theophylline) particles. The calcium signal is much more intense, and in this figure the calcium ions appear brighter (labeled as Ca) than drug particles, mostly on the outer surface.

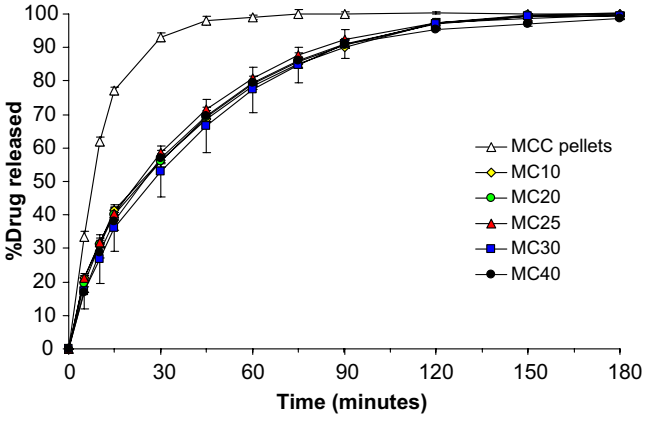

Fig. 5. Percentage of drug released from alginate-based pellets prepared by extrusion/spheronization using different amounts of MC, $n = 3$.

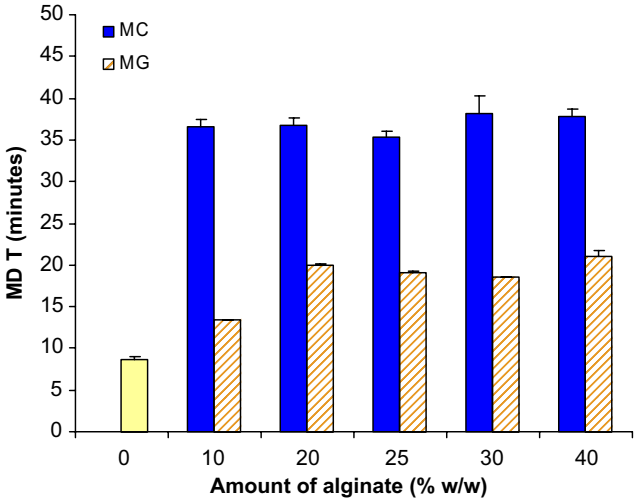

Fig. 6. Effect of the amount of sodium alginate (MC and MG) on the mean dissolution time (MDT) of alginate-based pellets, $n = 3$.

the surface was not seen (data not shown). The presence of water-soluble or -insoluble calcium salts in the pellet formulations would influence the drug release behavior of the obtained pellets (discussed later in Section 3.4). Additionally, the internal structure of the extruded/spheronized pellets revealed the cavity inside the pellets (Figs. 2–4). It is likely that, due to the rotational and the frictional forces involved in the spheronization process, the edges of the flat side fold together like a flower forming the cavity observed in the pellets as suggested by Baert and Remon [31].

3.4. Drug release studies and analysis of release data

Drug release studies were carried out in gastric fluid, i.e., SGF. Theophylline was used as a model drug. The drug release profiles were presented by plotting the amount of theophylline released against time. Fig. 5 shows the results of release test of alginate-based pellets using different amounts of MC, compared to MCC pellets without sodium alginate. Theophylline was released more rapidly from

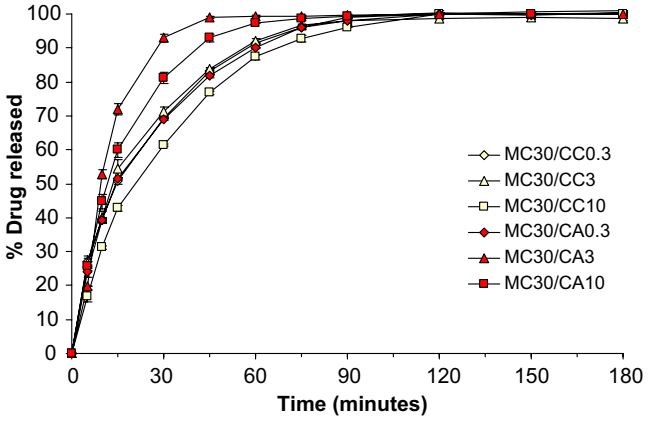

Fig. 7. Percentage of drug released from alginate-based pellets prepared by extrusion/spheronization using MC and different types and amounts of calcium salts, $n = 3$.

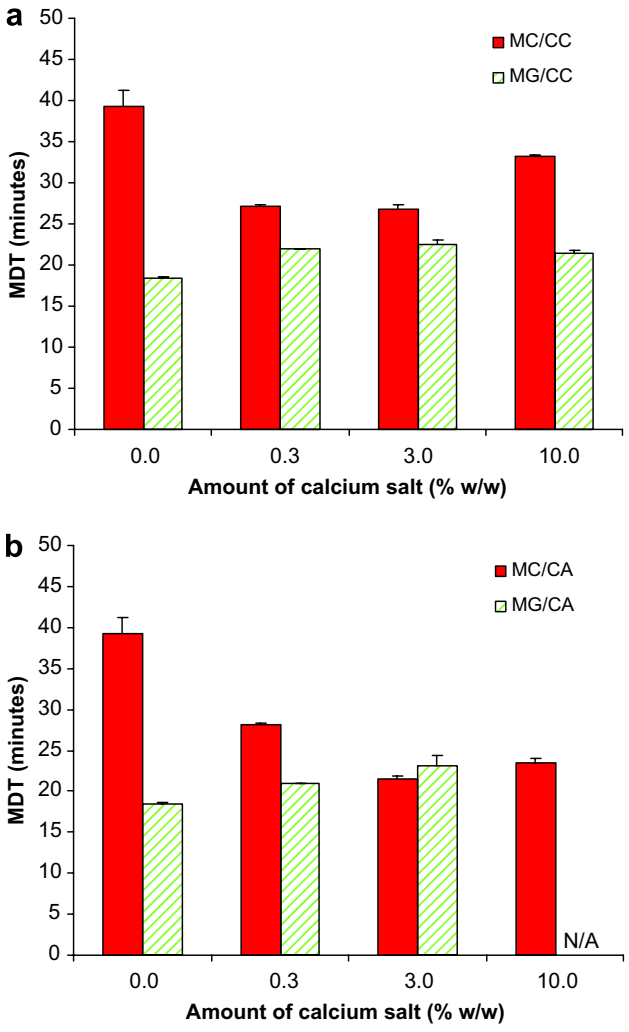

Fig. 8. Effect of the amount of calcium salts on the mean dissolution time (MDT) of alginate-based pellets; (a) calcium acetate, and (b) calcium carbonate, $n = 3$. *Note*: The data for 0% of calcium salts in (b) were repeated from those in (a) for comparison purpose.

MCC pellets and the release was complete (100%) within 45 min. Most of matrix pellet formulations released approximately 75–80% drug within 60 min. The formulations containing 50% of MC or MG were not tested since most of the obtained pellets were fine particles. Increased amount of sodium alginate insignificantly influenced the drug release characteristics and showed a similar MDT (Fig. 6). The exception is for pellets containing 10% of MG which released faster with the lowest value of MDT. It is thought that a low amount of MG (i.e., 10% MG) was insufficient to form gel and could form only a thin barrier around pellets. The effect of type of sodium alginate on the MDT is also shown in Fig. 6. A higher MDT (i.e., slower drug release) from MC pellets than from MG pellets, in acidic medium, was observed. It is possible that MC hydrated faster and built up the diffusion barrier more rapidly, resulting in slower release. These results are in good agreement with previous reports [10–12], in which the more advantages of MC alginate in sustaining drug release from matrix tablets have been investigated.

The incorporation of calcium salts in the pellet formulations (both MG and MC pellets) significantly influenced the drug release in acidic medium (Fig. 7) as well as their MDT values (Fig. 8). A slightly slower drug release was observed for MG pellets when the calcium salts were incorporated. The increased amount of calcium carbonate demonstrated a comparable drug release (i.e., similar MDT values). However, increasing the amount of calcium acetate slightly slowed drug release (i.e., increase in MDT). Similar results have previously been reported [12,13]. Increasing amount of calcium led to a greater degree of cross-linking and aggregation of the initial dimers giving higher gel strength and results in the slower drug release pattern.

Addition of more soluble calcium salt (i.e., calcium acetate) in the formulations slightly enhanced the drug release from MC pellets (Fig. 8). More pronounced effect on increased drug release was seen when the calcium amount was increased. This might be due to the pore formation from the excess of the soluble calcium salt (as also evidenced by SEM images in Fig. 4) in the pellet structure. Similar results were reported for sodium alginate matrix capsules containing calcium gluconate; the faster drug release in acidic medium may be caused by channeling effect of the soluble calcium salt [32]. Incorporation of calcium carbonate, which is insoluble at neutral pH, revealed the less pronounced effect. This is probably due to the limited concentration of free calcium ions in the presence of calcium carbonate. Although calcium carbonate could dissociate in acidic condition of the release study, the rate of dissociation would be limited by the rate of water diffusion into the pellets. However, the drug release may be modified by altering the microenvironment inside the matrix pellets. Sriamornsak and coworkers [13] reported that the maintenance of a constant and basic microenvironment created the most favorable conditions for calcium alginate gel formation. Therefore, the drug release in acidic condition was more extended in the formulations containing both

Table 3
The release kinetics of alginate-based pellets prepared by extrusion/spheronization ($n = 3$)

Formulation code	Amount of 3% $CaCl_2$[a]	Higuchi model		Korsmeyer–Peppas model		
		r^2	Higuchi rate constant, K	r^2	Kinetic constant, K'	Diffusional exponent, n
MCC pellets	38.0	0.9899	26.725	0.9859	0.099	0.769
MC10	34.1	0.9933	11.879	0.9945	0.094	0.528
MC20	47.1	0.9926	12.442	0.9901	0.081	0.571
MC25	59.6	0.9709	12.046	0.9992	0.086	0.566
MC30	58.3	0.9853	12.464	0.9977	0.067	0.626
MC40	74.3	0.9883	13.319	0.9919	0.060	0.664
MC50	69.6	N/A	N/A	N/A	N/A	N/A
MG10	48.0	0.9543	19.355	0.9825	0.170	0.593
MG20	53.5	0.9844	18.625	0.9935	0.094	0.736
MG25	54.9	0.9956	16.173	0.9999	0.138	0.591
MG30	56.6	0.9874	20.828	0.9940	0.092	0.775
MG40	82.8	0.9877	22.255	0.9927	0.055	0.946
MG50	68.7	N/A	N/A	N/A	N/A	N/A
MC30/CC0.3	66.2	0.9858	13.827	0.9955	0.117	0.530
MC30/CC3	65.4	0.9996	13.783	0.9949	0.095	0.638
MC30/CC10	63.6	0.9912	14.463	0.9816	0.057	0.721
MC30/CA0.3	65.0	0.9950	14.669	0.9841	0.098	0.590
MC30/CA3	55.9	0.9785	26.078	0.9811	0.030	1.196
MC30/CA10	44.8	0.9942	17.069	0.9993	0.770	0.770
MG30/CC0.3	54.9	0.9890	20.283	0.9942	0.066	0.869
MG30/CC3	53.9	0.9732	25.105	0.9821	0.053	1.001
MG30/CC10	52.9	0.9969	24.520	0.9973	0.047	1.023
MG30/CA0.3	52.9	0.9613	22.283	0.9768	0.056	0.954
MG30/CA3	52.9	0.9997	17.473	0.9951	0.124	0.645
MG30/CA10	35.1	N/A	N/A	N/A	N/A	N/A

Means of the r^2, rate constants and n values are shown.
N/A, not applicable.
[a] Grams of 3% w/v calcium chloride solution per 100 g of powder mass.

calcium acetate and sodium bicarbonate, compared to those containing calcium acetate alone or those without additive [13].

Table 3 shows the release kinetics data for Higuchi and Korsmeyer–Peppas models (Eqs. 2 and 3). Drug release data of pellets using MC and MG showed a good fit into Korsmeyer–Peppas equation ($r^2 > 0.99$), while those of the formulations containing both sodium alginate and calcium salts fitted well with Higuchi equation. Higuchi model is applicable if the release of drug is largely governed by diffusion through water-filled pores in the matrix. A good fit to Korsmeyer–Peppas equation indicated combined effect of diffusion and erosion mechanisms for drug release. The value of release exponent 'n' determined from various pellet formulations ranged from 0.528 to 1.196, and the K' value ranged from 0.047 to 0.138 (Table 3). The value of 'n' and K' was found to vary with the type of alginate and addition of calcium salts. The release exponents for some formulations released rapidly are not shown because there were insufficient data points on the release profiles between 10% and 60% release to provide accurate values. The pellets containing sodium alginate (MC or MG) without calcium salts and those containing MC and calcium salts exhibited an anomalous (non-Fickian) diffusion controlled release. In cases of pellets containing MG and calcium salts, the drug release demonstrated a Super Case II transport. It is evident that dissolution or erosion of the alginate (MG) matrices, those cross-linked with calcium ions, would account for the increasing values of 'n'. This type of transport has also been reported in literatures [12,33].

4. Conclusions

Two types of sodium alginate with different chemical compositions (MC and MG) were evaluated with and without the addition of either calcium acetate or calcium carbonate in the formulations for extruded/spheronized pellets. Most pellet formulations resulted in pellets of a sufficient quality. The results demonstrated that the amounts of sodium alginate and calcium salts influenced the size and shape of the obtained pellets. However, different types of sodium alginate and calcium salts responded to modifications to a different extent. Pellets containing MC showed a slower drug release compared to those containing MG. This is probably due to the rapid formation of gel barrier around the pellets. Incorporation of calcium salts in the pellet formulations altered the drug release, depending on the solubility of the calcium salts used. The slightly slower drug release was observed for pellets containing MG when the calcium salts were incorporated. The increased amount of calcium carbonate, which is insoluble at neutral pH, demonstrated a comparable drug release. However,

increasing the amount of a more soluble salt of calcium (i.e., calcium acetate) slightly slowed the drug release. For pellets containing MC, addition of calcium acetate in the formulations slightly enhanced the drug release. More pronounced effect on increased drug release was seen when the calcium amount was increased. Incorporation of calcium carbonate, however, revealed the less pronounced effect. The drug release data showed a good fit into both Higuchi and Korsmeyer–Peppas equations.

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