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Research paper

Alginate-based pellets prepared by extrusion/spheronization: A preliminary study on the effect of additive in granulating liquid

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Abstract

The aim of this study was to investigate the possibility of producing alginate-based pellets by extrusion/spheronization and also to improve the formation of spherical alginate-based pellets by investigating the effect of additive in granulating liquid on characteristics and drug release from resulting pellets. Two types of sodium alginate (30%) were evaluated in combination with theophylline (20%), microcrystalline cellulose (50%) and different granulation liquids. The pellets were then prepared in a basket extruder, then spheronized and dried. The final products were characterized by morphological examination and drug release study. Different additives in the granulating liquid influenced the ability of the extruded mass to form pellets (the processability) with this technique. However, different sodium alginate types responded to shape modifications to a different extent. Long, dumbbell-shaped pellets were obtained with viscous granulating liquids. However, short, nearly spherical pellets were obtained with watery granulation liquid with calcium chloride that reduced the swelling ability of sodium alginate. Improvements in the pellet characteristics were also dependent on the sodium alginate type employed. Most of pellet formulations released about 75–85% drug within 60 min and showed a good fit into both Higuchi and Korsmeyer–Peppas equations. Higher amount of 3% calcium chloride, as a granulating liquid, in the formulation showed higher mean dissolution time resulting from the cross-linking properties of calcium ions to the negative charges of alginate molecules.

Keywords: Alginate; Granulating liquid; Pellets; Extrusion; Basket extruder; Spheronization

1. Introduction

Extrusion/spheronization is an established technique in pharmaceutical industry which results in spherical pellets in a typical size range between 0.5 and 2 mm. These pellets possess high density, small particle size distribution, and regular shape. They are usually used for the production of multiple-unit dosage forms because of their advantages over single-unit dosage forms, for example, they maximize drug absorption, reduce peak plasma fluctuations and minimize potential side effects [1]. Pelletization of a hydrophilic polymer without pretreatment of the polymer or admixture of an extrusion aid by the extrusion/spheronization technique has not been successfully reported. Law and Deasy [2] have produced pellets from spray-dried mixtures of hydrophilic polymers (e.g., sodium carboxymethylcellulose (sodium CMC), hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC)) and microcrystalline cellulose (MCC) by extrusion/spheronization. They found that adhesive polymers (sodium CMC and HPMC) was less suitable for pelletization by this technique. Recently, Tho and coworkers [3,4] have produced pellets from polysaccharide pectin by extrusion/spheronization and identified

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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 [5] demonstrated that the chitosan pellets could be prepared by extrusion/spheronization using diluted acetic acid solution as granulating liquid.

In order to understand more about the behavior of a swelling hydrocolloid in the extrusion/spheronization process, alginate was selected as an example because of abundant availability and its wide use in pharmaceutical application. Alginate is a linear unbranched polysaccharide, which contains 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. These homopolymeric regions of M and G blocks are interspersed with regions of alternating structure (MG blocks) [6,7]. The composition and extent of the sequences and the molecular weight determine the physical properties of the alginates. Alginate has been studied in several drug delivery systems, for example, matrix tablets [8] and film coatings [9–11]. Several reports have been published on alginate in multiple-unit dosage forms, mainly on hydrogel beads produced by ionotropic gelation of alginate in the presence of calcium ions (e.g., [12,13]).

The objective of this study was to investigate the possibility of producing alginate-based pellets by extrusion (i.e., using a basket extruder) and spheronization. In the future, such pellets could be used for oral drug delivery. Chatchawalsaisin et al. [14] reported the use of sodium alginate alone (up to 16%) or in combination (4%) with chitosan to produce pellets by ram extruder. As no earlier studies regarding extrusion of sodium alginate have been reported with basket extruder, this study represents the first steps in identifying some of the factors influencing the process of sodium alginate extrusion and the characteristics of the resulting product. Theophylline has been chosen as a model drug. It has been widely used 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 (see Table 1) were the generous gift from ISP (Thailand)

Table 1
Typical properties of sodium alginate used[a]

Code	Product	Alginate type	Particle size (μm)	Viscosity[b] (mPa s)	Composition (%)		M/G ratio[c]
					M	G	
MG	Manugel® DMB (batch no. 991131)	Sodium alginate (high G)	106	300	37	63	0.59
MC	Manucol® DMF (batch no. 951111)	Sodium alginate (high M)	106	300	61	39	1.56

[a] Size, viscosity, M/G ratio are specified and reported by the manufacturer.
[b] 1% as is viscosity. Viscosity is generally measured using a Brookfield LV viscometer at 60 rpm with a no. 2 spindle.
[c] Mannuronic acid (M) to guluronic acid (G) ratio.

Table 2
Characteristics of alginate-based pellets prepared by extrusion/spheronization using different granulating liquids

Granulating liquid[a]	Pellet characteristics	
	MC	MG
Water	Dumbbell-shaped	Dumbbell-shaped
5% PVP in water	Dumbbell-shaped	Dumbbell-shaped
10% PVP in water	Dumbbell-shaped	Dumbbell-shaped
10% PVP in 5% ethanol	Spherical + rod-shaped	Spherical + rod-shaped + fine
10% PVP in 10% ethanol	Irregular + fines	Irregular + fines
10% PVP in 15% ethanol	Irregular + fines	Irregular + fines
10% Acacia	Dumbbell-shaped	Dumbbell-shaped
5% Pectin USP	Dumbbell-shaped	Dumbbell-shaped
2% HPMC	n/a[b]	Dumbbell-shaped
2% Sodium CMC	Dumbbell-shaped	Dumbbell-shaped
2% MG	Dumbbell-shaped	n/a
2% MC	n/a	Dumbbell-shaped
2% Citric acid	Dumbbell-shaped	n/a
1% Calcium chloride	Dumbbell-shaped + spherical	Dumbbell-shaped + spherical
2% Calcium chloride	Spherical + fines	Spherical + fines
3% Calcium chloride	Spherical	Spherical
4% Calcium chloride	Spherical	Spherical

[a] PVP, polyvinylpyrrolidone; HPMC, hydroxypropylmethylcellulose; sodium CMC, sodium carboxymethylcellulose.
[b] n/a, not applicable.

Co., Thailand. Theophylline (Lot number 99360-A) was obtained as a gift sample from BASF (Thai) Limited, Thailand. Microcrystalline cellulose (Avicel PH101, Batch number 6521, FMC Corp., USA) was used as received without further purification. All other chemicals were of reagent or food grade and used as supplied.

2.2. Manufacture of pellets by extrusion/spheronization

One hundred grams of theophylline (TPL) (20%), sodium alginate (30%) and microcrystalline cellulose (50%) was mixed in a planetary mixer (Model K5SS, Kitchen Aid, USA) for 20 min. Various amounts of different granulating liquids (water, ethanol, acacia, alginate, pectin, HPMC, sodium CMC, polyvinylpyrrolridone (PVP), citric acid and calcium chloride solution (in water)) were added slowly to the powder blend, which was then mixed until a homogeneous, 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. Spheronization was performed in a spheronizer (Model 250, Caleva, England) with a rotating plate of regular cross-hatch geometry, 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.

Fig. 1. Shape, size and size distribution of alginate (MC) pellets using (a) water, and 10% PVP in (b) water, (c) 5% ethanol, (d) 10% ethanol, (e) 15% ethanol as a granulating liquid (35–37 g/100 g powder mass).

2.3. Characterization of pellets

Morphological examination of the pellet shape was carried out using a digital camera (Model S602Zoom, Fujifilm, Japan) equipped with Super-EBC Fuji Nonlens (6×) optical zoom. Pellet imaging was performed on each batch of pellets. The pellets were spread over a flat surface by spatula and were photographed by digital camera. Under the same optical conditions, an image of a linear scale was used to calibrate.

The particle size distribution of spherical pellets (formulations that used 3% calcium chloride as a granulating liquid) was determined using a set of test sieves (600–2360 microns 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 percentage of weight retained was plotted against the mean size of pellets in each fraction.

2.4. Dissolution studies

To examine the effects of investigated factors on drug release, the dissolution studies were carried out using USP dissolution apparatus I (Erweka, Germany) equipped with baskets which was operated at the speed of 100 rpm. Nine hundred milliliters of simulated gastric fluid

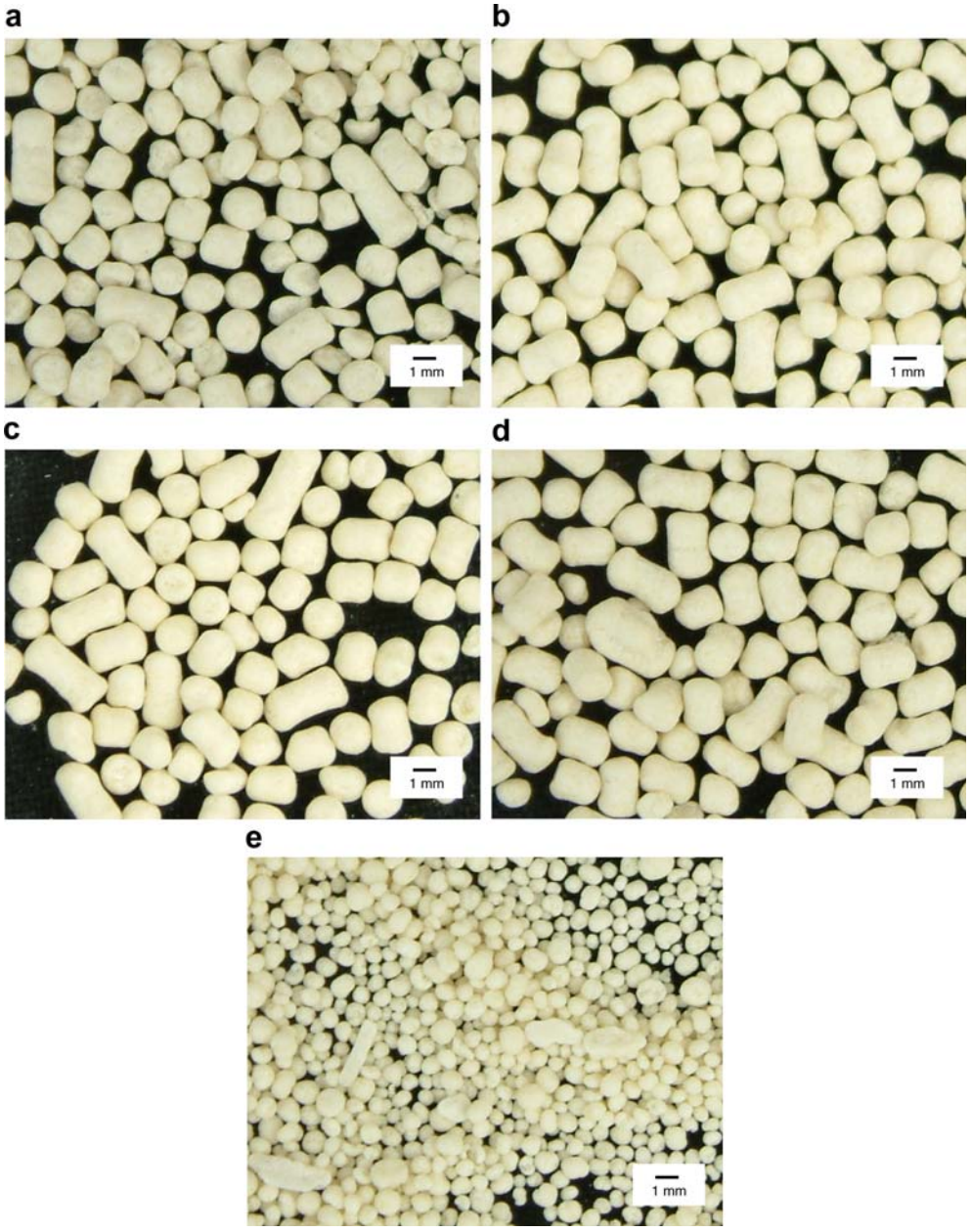

Fig. 2. Effect of the amount of granulating liquid (10% PVP in 5% ethanol) on shape, size and size distribution of alginate (MC) pellets; (a) 28 g, (b) 30 g, (c) 36 g, (d) 40 g, (e) 43 g of granulating liquid per 100 g of powder mass.

(USP27) without pepsin (SGF), as the dissolution medium, was placed in the glass vessel, the apparatus assembled, and the dissolution medium equilibrated 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, Wellesley, MA) at 270 nm. Each dissolution study was performed in triplicate. Mean dissolution time (MDT) was calculated from dissolution data and has been used for comparison. To study the release kinetics from matrix pellets, the release data were fitted to Higuchi and Korsmeyer–Peppas models.

3. Results and discussion

3.1. Pelletization

The preliminary trials of pelletization by (basket) extrusion/spheronization with the MCC and sodium alginate (MC or MG), using water as the granulating liquid, were successful only in the case of using MCC due to its unique water absorbing and retaining characteristics [15]. MC and MG could not be extruded/spheronized because the materials turned into a tacky mass, even in the amount of 10%, due to their solubility in water. The viscous granulating liquids containing hydrophilic polymer (e.g., PVP in water, acacia, HPMC, pectin, alginate or sodium CMC in water) yielded the long, dumbbell-shaped pellets (Table 2).

In order to avoid the tackiness, water was substituted by alcohol (ethanol) or hydro-alcoholic mixture as the granulating liquid, similar to previous reports [4,16]. This was done initially because the alginate was practically insoluble in alcohol and therefore did not cause tackiness. Using 10% PVP in 5% ethanol gave the more spherical shape with some rod-shaped pellets (Table 2 and Fig. 1). Figs. 1 and 2 demonstrate the shape, size and size distribution of alginate-based pellets (MC) using water, and 10% PVP in various concentration of ethanol as a granulating liquid and the effect of its amount on shape, size and size distribution. Increased concentration of ethanol, when used as a solvent for PVP, resulted in a reduction in the pellet length for both alginates used. The massive production of fines at high concentration of ethanol in granulating liquids supports the theory of reduced entanglements as the contact points between sodium alginate particles in the extrudate are reduced. This is in agreement with Schroder and Kleinebudde [17] who reported a faster disintegration of pellets prepared using higher amount of isopropanol than those using smaller amount of isopropanol. It was attributed to the decreased particle–particle bonding with increasing levels of propanol. Moreover, the rapid evaporation characteristic of ethanol may also affect the fine particles' formation.

As calcium ions are capable of cross-linking G units of alginate, addition of calcium chloride to the granulating liquid reduced the pellet size and formed spherical pellets for both alginates (Table 2), in the same manner as low methoxy pectins previously reported by Tho et al. [4] It has been reported that carboxyl groups of G units (GG or alternate MG block of sodium alginate chains) form networks with calcium ions as shown in Fig. 3 [18], resulting in less swellable calcium alginate. Thus, it is likely that the cross-linking mechanism is important for the improved ability of the extruded mass to form pellets (the processability) of these alginate types. This is different from the case of chitosan pellets using diluted acetic acid as a granulating liquid [5], in which the chitosan was expected to be dissolved resulting in a gel-like wet mass.

Figs. 4 and 5 illustrate the photo-images of pellets made of MC and MG alginates, respectively. The effect of amount of granulating liquid (3% calcium chloride) on shape, size and size distribution of alginate-based pellets is also shown in these figures. It is obvious that higher amount of granulating liquid provided more spherical shape of pellets with a narrower size distribution (Fig. 6). Pellets that used lower amount of granulating liquid had a broader size distribution compared to fine particles presented. The spherical pellets made of MG alginate required smaller amount of a granulating liquid for pellet formation, compared to MC alginate (Table 3 and Figs. 4 and 5). This may be due to the high content of G units in MG, which is responsible for cross-linking with calcium ions [18]. Moreover, the pellets made of MG yielded the slower drug release and consequent higher MDT than those made of MC when the amount of 3% calcium chloride was used at the same level (see Table 3).

From the above results, it is possible to conclude that the different additives in the granulating liquid influenced the processability with this technique. Moreover, different chemical contents of alginate responded to modifications to a different extent.

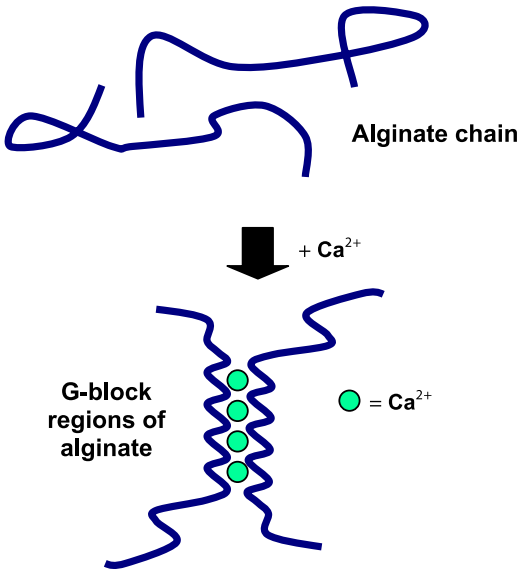

Fig. 3. The egg-box model for alginate gelation with calcium ions. Guluronic acid (G) blocks of alginate are held together by a number of calcium ions.

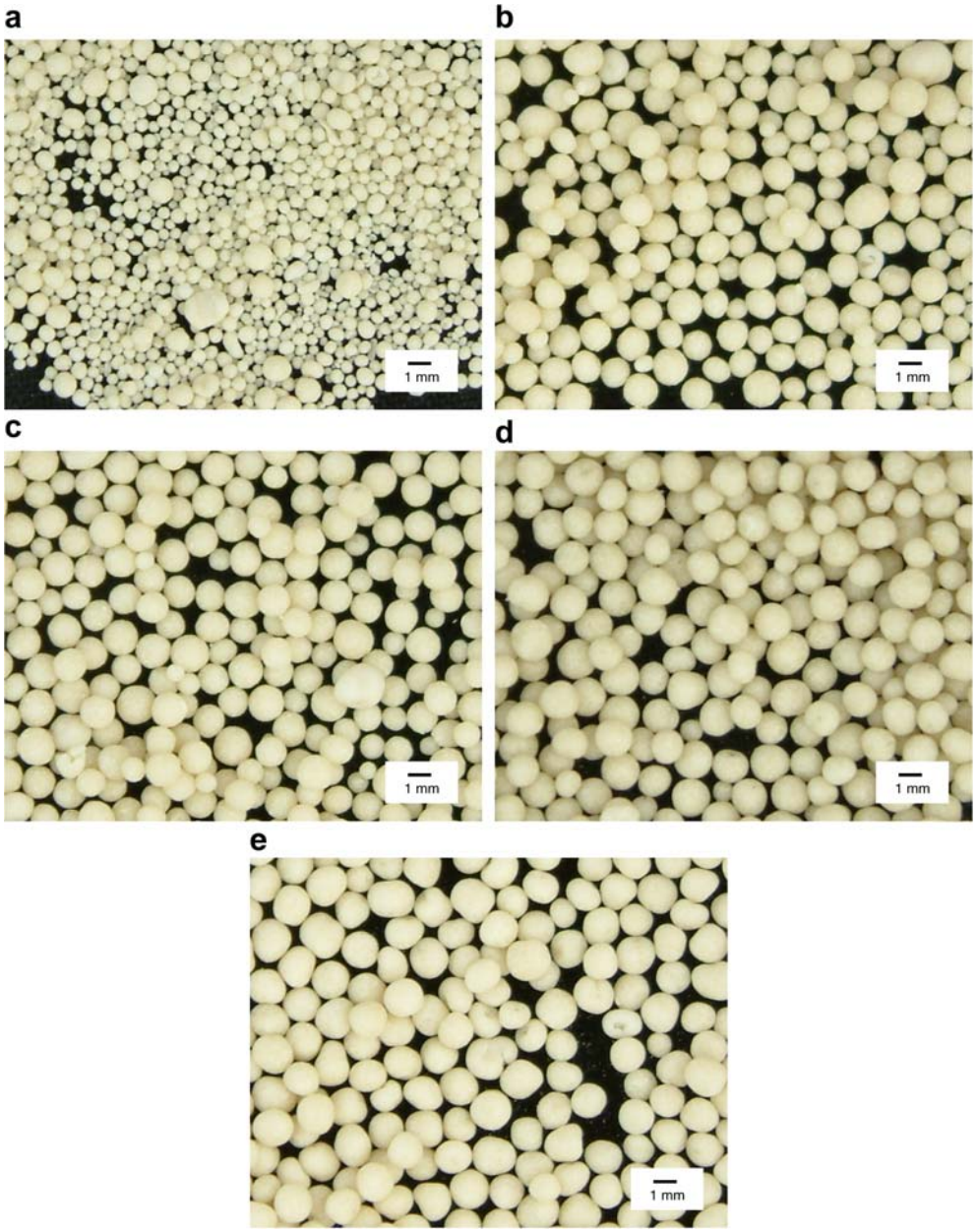

Fig. 4. Effect of the amount of granulating liquid (3% calcium chloride solution) on shape, size and size distribution of alginate (MC) pellets; (a) 50 g, (b) 55 g, (c) 60 g, (d) 65 g, (e) 67.5 g of granulating liquid per 100 g of powder mass.

3.2. Drug release studies and analysis of release data

Fig. 7 shows the results of dissolution tests of alginate-based pellets (made of either MC or MG) using different amounts of granulating liquid (i.e., 3% calcium chloride solution). Most of matrix pellet formulations released approximately 75–85% drug within 60 min. The exception is for the MC-based pellets using 3% calcium chloride of 50 g/100 g of powder mass which released faster (almost 100% drug released within 60 min). Lower amount of granulating liquid may contribute to the rapid drug release.

Generally, Higuchi and Korsmeyer–Peppas models were used for the analysis of the dissolution mechanism of matrix-type, alginate-based pellets. When these models are used and analyzed in the preparation, the rate constant obtained from these models is an apparent rate constant. The drug release patterns from pellets made of different alginates and different amounts of 3% calcium chloride were analyzed.

The release of drugs from the matrix pellets can be analyzed by release kinetics theories [19,20], as follows:

$$\text{Higuchi model}: \quad \frac{M_t}{M_f} = k \cdot \sqrt{t} \tag{1}$$

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 (a) the shape of the

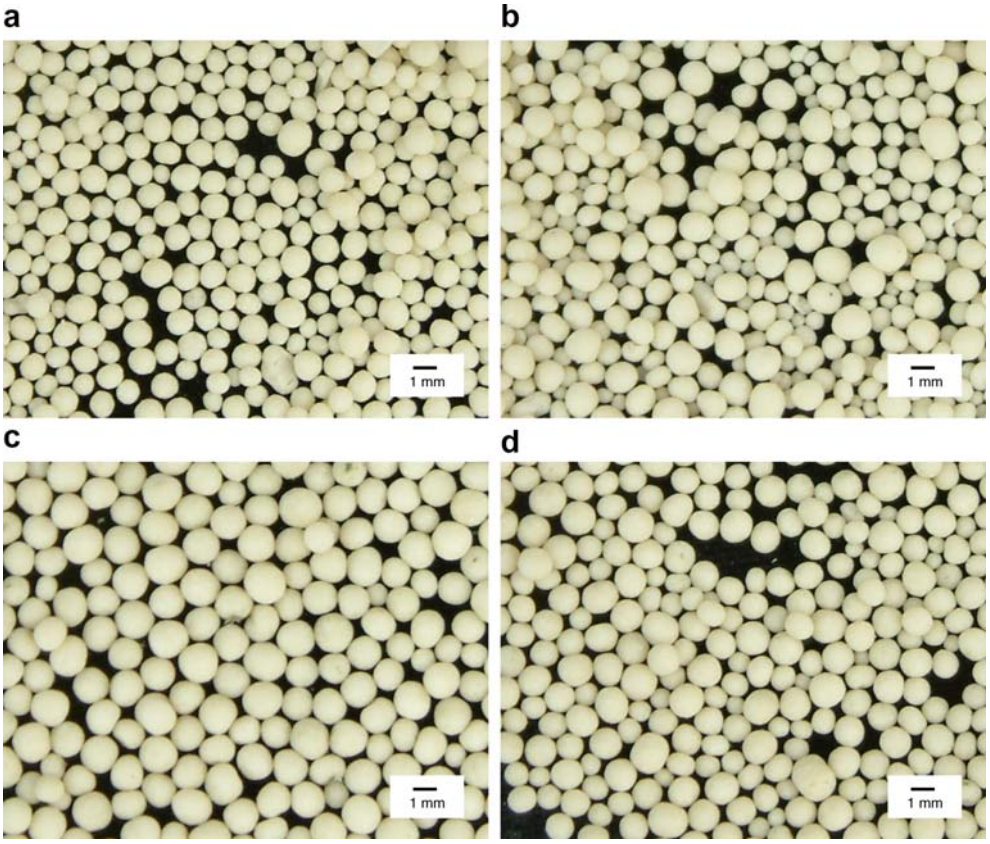

Fig. 5. Effect of the amount of granulating liquid (3% calcium chloride solution) on shape, size and size distribution of alginate (MG) pellets; (a) 47 g, (b) 50 g, (c) 53 g, (d) 57 g of granulating liquid per 100 g of powder mass.

matrix, (b) the internal structure of the matrix as it affects the tortuosity and porosity of the matrix and (c) the drug concentration and solubility.

$$\text{Korsmeyer–Peppas model}: \quad \frac{M_t}{M_f} = k' \cdot t^n \tag{2}$$

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, and M_t/M_f represents the drug dissolved fraction at time t. 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 [20]. To clarify the release exponent for different batches of spherical matrix pellets, the log value of percentage of drug dissolved was plotted against log time for each batch according to the following equation.

$$\log\left[\frac{M_t}{M_f}\right] = \log k + n \log t \tag{3}$$

A value of $n = 0.43$ indicates Fickian release (case I transport); $0.43 < n < 0.85$ for non-Fickian release (anomalous transport); $n = 0.85$ for case II transport; and $n > 0.85$ for super case II transport from spheres.

The release rate kinetic data for Higuchi and Korsmeyer–Peppas models are shown in Table 3. Drug release data of pellets using MC and MG showed good fit into both Higuchi and Korsmeyer–Peppas equations ($r^2 > 0.993$). 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 0.516 to 0.775, and the k' value ranged from 0.053 to 0.102 (Table 3).

Mean dissolution time or MDT is used to characterize drug release rate from a dosage form and indicates the drug release retarding efficiency of polymer. In this study, MDT was calculated from dissolution data using the following equation:

$$\text{MDT} = \frac{n}{n+1} \cdot k'^{\frac{-1}{n}} \tag{4}$$

where n is the release exponent and k' is the release rate constant. Pellets prepared with alginate, MC or MG, showed different MDT (Table 3). Higher amount of granulating liquid used (3% calcium chloride solution) in the formulation showed higher MDT value. This finding can be attributed to the binding properties of calcium ions to the negative charges of alginate molecules [18]. The alginate with high G content (i.e., MG) showed higher MDT value than MC alginate when the same amount of

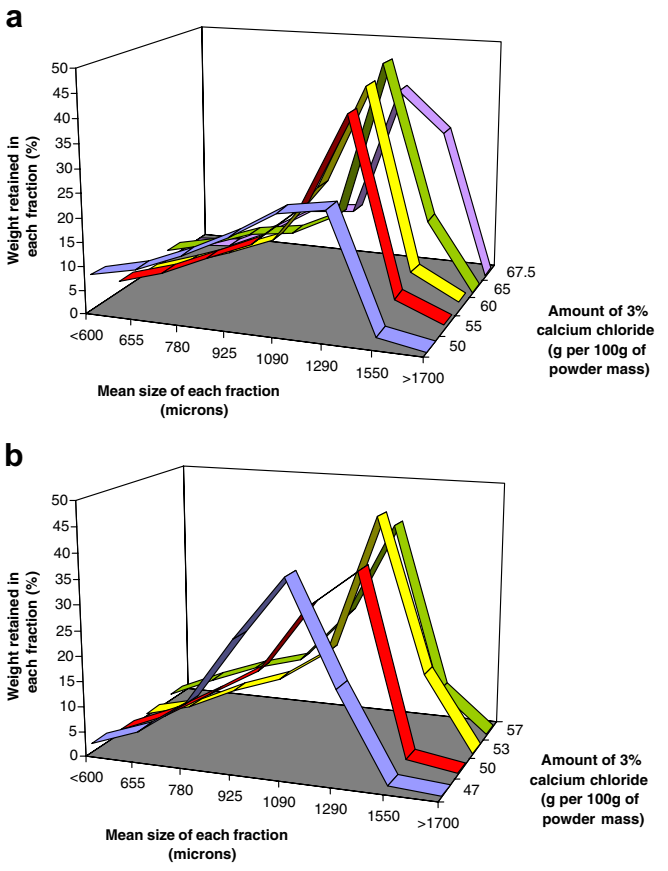

Fig. 6. Size distribution, as determined by sieve analysis, of alginate-based pellets prepared by extrusion/spheronization using different amounts of granulating liquid (i.e., 3% calcium chloride solution); (a) MC and (b) MG.

granulating liquid was used (e.g., 50 g per 100 g of powder mass). This is probably due to the greater calcium binding and consequently cross-linking properties of G blocks in MG alginate. The divalent calcium cation fits into the G block structure like eggs in an egg box. This binds the alginate polymers together by forming junction zones, resulting in gelation of the solution [18].

4. Conclusion

It was demonstrated that the ability of alginate to form pellets as well as the characteristics of the products can be influenced during the granulation process (e.g., adding substances to the granulation liquid, type of sodium alginate used, etc.). The viscous granulating liquids containing hydrophilic polymer yielded long, dumbbell-shaped pellets while the watery granulation liquids with calcium chloride, which reduced the swelling ability of sodium alginate, yielded short and nearly spherical pellets. Most of pellet formulations released about 75–85% drug within 60 min and showed a good fit into both Higuchi and Korsmeyer–Peppas models. Higher amount of granulating liquid

Table 3
Effect of amount of granulating liquid (3% calcium chloride) on the release kinetics and mean dissolution time (MDT) of alginate-based pellets prepared by extrusion and spheronization ($n = 3$)

Amount of 3% calcium chloride (g)	Higuchi model		Korsmeyer–Peppas model			Order of release	Mean dissolution time, MDT (min) (SD)
	Correlation coefficient (r^2)	Higuchi rate constant (k)	Correlation coefficient (r^2)	Kinetic constant (k')	Diffusional exponent (n)		
Manucol (MC)							
50[a]	0.9987	25.522	0.9940	0.092	0.775	Non-Fickian	18.5 (0.14)
55	0.9968	11.038	0.9981	0.077	0.587	Non-Fickian	37.4 (0.98)
60	0.9996	10.952	0.9968	0.067	0.626	Non-Fickian	39.2 (5.21)
65	0.9985	10.353	0.9950	0.068	0.598	Non-Fickian	40.9 (0.83)
67.5	0.9938	10.304	0.9636	0.086	0.557	Non-Fickian	37.2 (0.23)
Manugel (MG)							
47	0.9887	13.502	0.9697	0.053	0.759	Non-Fickian	32.6 (0.82)
50	0.9946	11.157	0.9868	0.071	0.634	Non-Fickian	35.5 (0.97)
53	0.9985	10.253	0.9994	0.102	0.516	Non-Fickian	35.9 (0.93)
56	0.9965	10.532	0.9979	0.069	0.599	Non-Fickian	41.3 (0.38)

[a] Gram of 3% calcium chloride per 100 grams of powder mass.

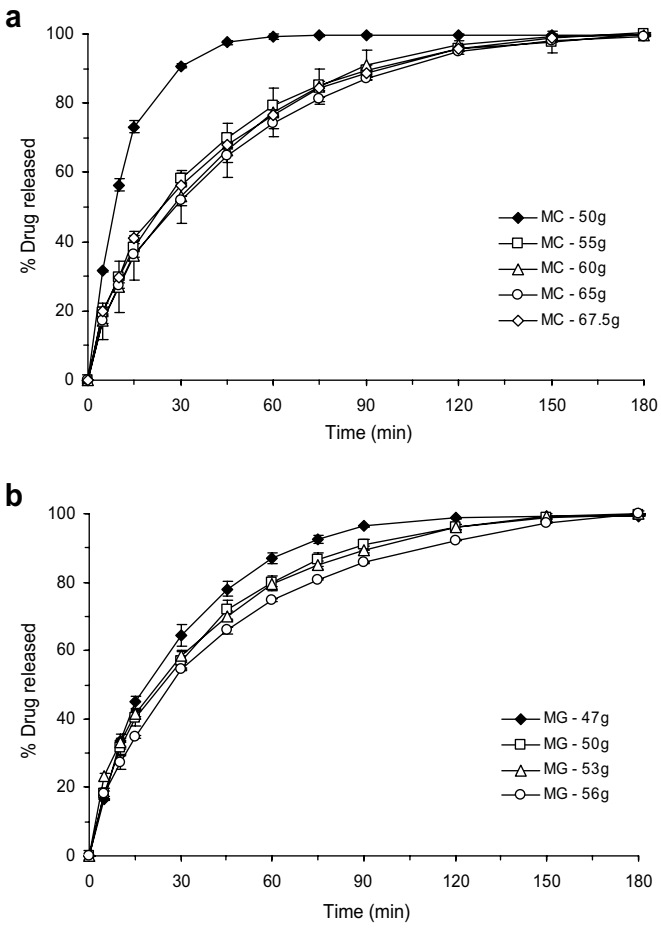

Fig. 7. Percentage of drug released, in simulated gastric fluid, from alginate-based pellets prepared by extrusion/spheronization using different amounts of granulating liquid (i.e., 3% calcium chloride solution); (a) MC and (b) MG, $n = 3$.

(i.e., 3% calcium chloride) in the formulation showed higher MDT value resulting from the binding properties of calcium ions to the negative charges of alginate molecules.

We are continuing our experiments with these systems in an attempt to: (1) increase the amount of sodium alginate in the pellet formulations and elucidate its effect on pellet characteristics, and (2) exert greater control over the release characteristics of the extruded/spheronized pellets using sodium alginate.

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