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Evaluation of sodium alginate as drug release modifier in matrix tablets

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Abstract

Alginates are useful natural polymers suitable for use in the design of pharmaceutical dosage forms. However, the effects of particle size, viscosity and chemical composition of alginates on drug release from alginate matrix tablets are not clearly understood. Hence, 17 grades of sodium alginate with different particle size distributions, viscosities and chemical compositions were used to prepare matrix tablets at various concentrations to screen the factors influencing drug release from such matrices. Particle size was found to have an influence on drug release from these matrices. Sodium alginate was subsequently classified into several size fractions and also cryogenically milled to produce smaller particle size samples. Cryogenic milling could be successfully applied to pulverize coarse alginate particles without changing the quality through degradation or segregation. This study showed the significance of each alginate property in modulating drug release: particle size is important in initial alginic acid gel barrier formation as it affected the extent of burst release; higher alginate viscosity slowed down drug release rate in the buffer phase but enhanced release rate in the acid phase; high M-alginate might be more advantageous than high-G-alginate in sustaining drug release; and, the effect of increasing alginate concentration was greater with larger alginate particles. This can serve as a framework for formulators working with alginates. Furthermore, the results showed that sodium alginate matrices can sustain drug release for at least 8 h, even for a highly water-soluble drug in the presence of a water-soluble excipient.

Keywords: Alginate; Particle size; Viscosity; Cryogenic milling; Controlled release

1. Introduction

In recent years, the biomedical and pharmaceutical industries have shown much increased interest in the use of biopolymers, particularly alginates (Shilpa et al., 2003). The naturally occurring alginate polymer has long been used in the food and beverage industries as thickening, gel-forming and colloidal-stabilizing agents. They are also used as binders and disintegrants in tablet manufacture. In addition to being a widely used food additive, alginate possesses several characteristics that make it a potential biopolymer suitable for the development of controlled-release systems. Hydration of an alginate matrix leads to the formation of a gelatinous layer which can act as a drug diffusion barrier. Crosslinking of alginate can also be initiated by polyvalent cations such as calcium and barium, forming insoluble alginate with the anionic polymer.

Commercial alginates are extracted primarily from marine algae such as *Laminaria hyperborea, Ascophyllum nodosum* and *Macrocystis pyrifera* (Gombotz and Wee, 1998). Alginates are linear unbranched polysaccharides containing varying proportions of β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues. The M and G monomers are 1 → 4 linked by glycosidic bonds, forming homopolymeric MM or GG blocks, which are interspersed with heteropolymeric MG or GM blocks. Molecular variability in this polymer depends on the source of marine algae, tissue from which alginates are extracted, and also the season of crop harvesting. The composition, sequence of polymer blocks and molecular weight of alginates are important as these factors determine the physical properties of the gel formed.

Oral polymeric matrices are commonly employed to achieve controlled-release of drugs. When a hydrophilic matrix is placed in an aqueous medium, the hydrophilic colloid component swells to form a gelatinous surface layer. This then controls the diffusion of water into the matrix. Release of drugs from such a system is governed by two mechanisms (Alderman, 1984): (i) diffusion of a water-soluble drug through the gel layer and (ii) release of a water-soluble or water-insoluble drug by erosion

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of the outer gel layer as it becomes well-hydrated. Within the hydrated surface layer of the matrix, the core remains dry, acting as a non-releasing reservoir of drug and polymer.

Matrix tablets containing sodium alginate as the release-retarding agent have been prepared by direct compression (Timmins et al., 1992; Hodsdon et al., 1995; Efentakis and Buckton, 2002; Moroni and Drefko, 2002; Holte et al., 2003), granulation (Howard and Timmins, 1988; Sirkiä et al., 1994; Bayomi et al., 2001) and compression coating (Sirkiä et al., 1994; Kaneko et al., 1998) or spray coating (Kaneko et al., 1997). Some of these studies have demonstrated the feasibility of preparing alginate matrix tablets industrially. For example, alginate matrices could be produced by compaction of alginate granules (Timmins et al., 1992) as well as by direct compression (Holte et al., 2003). However, work done on alginate matrix tablets is still limited. Many different grades of sodium alginate are commercially available and these grades vary in their particle size, molecular weight and chemical composition. These variations may have an impact on drug release behavior, and yet there has been no substantial study to determine the influence of a wide range of alginate grades on the drug release properties of alginate matrix tablets. Furthermore, previous research work had shown the importance of polymer particle size in influencing drug release performance from certain hydrophilic matrices (Mitchell et al., 1993; Aldrete and Robles, 1997; Velasco et al., 1999; Heng et al., 2001). It is hypothesized that alginate particle size can be employed to modify drug release from alginate matrix tablets. In addition, alginate viscosity might play a role in influencing drug release pattern from alginate matrices. Hence, this study began with the screening of 17 commercially available grades of sodium alginate to elucidate their effects on drug release. This was followed by a more intensive examination using selected alginates to examine the effects of alginate particle size and viscosity on drug release. The effect of matrix porosity on drug release was also determined. This study was geared towards gaining further insight on how the properties of commercially available alginates influence drug release from alginate matrices, from a mechanistic perspective.

2. Materials and methods

2.1. Materials

Seventeen grades of sodium alginate (ISP-Alginates Industries, USA) were used. These can be classified into two groups, M- and G-rich alginates. M-rich alginates consist of approximately 60% mannuronic acid and 40% guluronic acid while the G-rich alginates have typical values of about 37% mannuronic acid and 63% guluronic acid (Lawson, 2003). The M-rich alginates used were Keltone HVCR, Keltone LVCR, Kelvis, Kelcosol, Manucols (LB, LF, DH, LKX, SS/LL and DMF); G-rich alginates used were the Manugels (LBA, LBB, GHB, GMB, DJX, DMB and DPB). The Manucol alginates are known to be richer in mannuronic acid while the Manugel alginates have relatively higher proportions of guluronic acid.

Chlorpheniramine maleate (BP grade, China), a water-soluble model drug, was milled prior to use (median particle size ~30 μm) while lactose (Pharmatose 200M, DMV, The Netherlands) and magnesium stearate (Merck, Germany) were used as supplied.

2.2. Particle true density determination

The true volumes of material used for tableting were measured using a helium pycnometer (Penta-pycnometer, Quantachrome, USA) according to the USP method. The powders were oven-dried and cooled in a desiccator prior to carrying out measurements. The measurements were repeated until three consecutive readings did not vary by more than 0.1%. The true density of a powder is obtained by dividing the sample mass taken after pycnometric measurement by the sample true volume.

2.3. Sieving

Sodium alginates (Manucol LB and Manucol SS/LL) were classified into different size fractions using sieves (Endecotts, UK) vibrated at an amplitude of 1.5 cm for 20 min.

2.4. Cryogenic milling

Cryogenic milling of sodium alginate (Manucol LB) was carried out using an impact pulverizer mill with a 0.3 mm mesh (Goblin, Nara, Japan) at about −60 °C with liquid nitrogen. Milling speeds of 7500, 10 000, 12 500 and 15 000 rpm were used and milling was performed in duplicates for each milling speed.

2.5. Preparation of matrix tablets

The formulations of the matrix tablets used were 5, 10, 30 or 50% (w/w) sodium alginate, 40 mg of chlorpheniramine maleate per tablet, 1% (w/w) magnesium stearate and lactose as diluent to adjust tablet weight to 350 mg. The batch weight of each formulation was 35 g. The weighed amounts of drug, sodium alginate and lactose were premixed geometrically using a spatula and subsequently randomly mixed in a bag for 10 min. The lubricant, magnesium stearate was then added, followed by mixing for another 2 min. The resultant powder mixture was individually weighed and electrically compressed into matrix tablets weighing 350 ± 5 mg using a single punch tableting machine (Manesty F3, UK) with 9.5 mm diameter flat punches. Matrix tablets with porosities of 0.15 ± 0.05 were made. The tablets were stored in a desiccator for at least 3 days to allow for tablet relaxation before use.

2.6. Drug release studies

Drug release from matrix tablets was evaluated using USP Method A at 50 rpm and 37 ± 0.5 °C for up to 8 h using paddles (USP Apparatus II, Vankel, USA). Dissolution test was first carried out in 750 ml of 0.1N hydrochloric acid (pH 1.2) for 2 h and pH of the medium was then adjusted to 6.8 by adding 250 ml of 0.2 M sodium phosphate solution, preheated to 37 °C. Either

2 M hydrochloric acid or 2 M sodium hydroxide was used for minor adjustment of the pH of the dissolution media when necessary. At suitable time intervals, samples were collected and assayed spectrophotometrically (Shimadzu, UV-1201, USA) at 266 and 262 nm for samples in acid and buffer, respectively, using the appropriate Beer's plots. For each formulation, at least triplicate dissolution runs were carried out and the averaged results reported. The dissolution parameters used to analyze the drug release studies were $T_{25\%}$ and $T_{75\%}$. These values represent the time taken in minutes to achieve 25 and 75% drug release, respectively.

The mechanism of drug release from the matrix system was studied by fitting the dissolution data to the following equations: zero order, first order, Higuchi square root and the modified Korsmeyer-Peppas (Lindner and Lippold, 1995).

2.7. Particle size determination

The particle size distribution was determined by laser diffractometry (Coulter LS 230, USA) using the dry powder module in at least duplicates and the median particle size was used to represent the particle size of the alginate powders.

2.8. Viscosity determination

The kinematic viscosities of 1% (w/w) solutions of the different alginate grades were determined at 37 °C using suspended-level viscometers. Kinematic viscosity, v, was calculated from the equation $v = Kt$, where t is the flow time in seconds and K is the nominal viscometer constant. The alginate solutions were prepared one day in advance and equilibrated to the required temperature for 30 min before taking measurements. The average of not fewer than three readings was taken as the flow time of the solution being examined, provided that consecutive readings did not differ by more than 1%.

2.9. Statistical analysis

Data obtained were subjected to correlation analysis and ANOVA at a significance level of $\alpha = 0.05$. Dissolution profiles were compared using similarity factor, f_2, and the profiles were significantly different if $f_2 < 50$.

3. Results and discussion

3.1. Effect of matrix tablet porosity

The primary aim of determining the effect of matrix tablet porosity on drug release was to establish the stable range of matrix tablet porosity that did not influence drug release from alginate matrices. Matrix tablets containing 10, 30 and 50% Manucol LB were compressed at different pressures to produce tablets of porosities ranging from 0.08 to 0.2. Attempts to produce matrix tablets with porosities below the abovementioned range resulted in tablet capping upon ejection from the die. Drug release studies showed that there was no significant difference in the drug release profiles of tablets with the same alginate concentration but different porosities (Fig. 1). The formation of a gel barrier around the matrix tablet controls the drug release behavior of the tablet. Hence, drug release is expected to be more closely related to the porosity of the hydrated gel layer, which is independent of the dry matrix porosity.

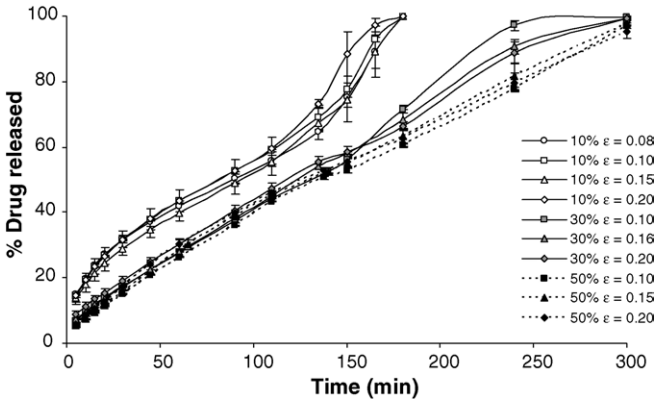

Fig. 1. Effect of matrix tablet porosity on drug release from alginate matrix tablets containing different amounts of Manucol LB. ε denotes theoretical tablet porosity calculated by $\varepsilon = 1 - \rho_A/\rho_T$, where ρ_A is the apparent tablet density and ρ_T is the tablet true density.

Other investigators (Timmins et al., 1992; Velasco et al., 1999; Rekhi et al., 1999; Bettini et al., 1994) had also reported that changes in compression force only had minimal effect on drug release from matrix tablets once a critical hardness is achieved. It can be assumed that variation in compression force is closely related to changes in the porosity of the matrix tablets. An increase in drug release was only observed when the tablets were too soft (about 3 kp) and this could be due to the lack of powder compaction or consolidation (Rekhi et al., 1999). Sodium alginate matrices prepared at three compression force levels over the range 1500–5000 kg were found to produce overlapping dissolution profiles, indicating that compression force over the stated range did not affect drug release (Timmins et al., 1992). Other studies using HPMC matrices showed similar findings (Velasco et al., 1999; Bettini et al., 1994).

3.2. Screening the performance of 17 grades of sodium alginate

3.2.1. Performance of sodium alginate as sustained-release carrier

Dissolution studies showed that some alginate matrices can sustain drug release for at least 8 h, particularly at 50% alginate content, even for a highly water-soluble model drug, chlorpheniramine maleate, in the presence of a water-soluble excipient, lactose (Fig. 2). Chlorpheniramine maleate was used as it has high aqueous solubility that is relatively similar at both acidic and neutral pH (650 and 584 g/L at pH 1.2 and 6.8, respectively); this would ensure that drug release is primarily dependent on the properties of the matrix and not on drug solubility.

3.2.2. Influence of sodium alginate concentration

In general, dissolution $T_{25\%}$ and $T_{75\%}$ values increased when alginate concentration was increased from 10 to 30% (Fig. 3).

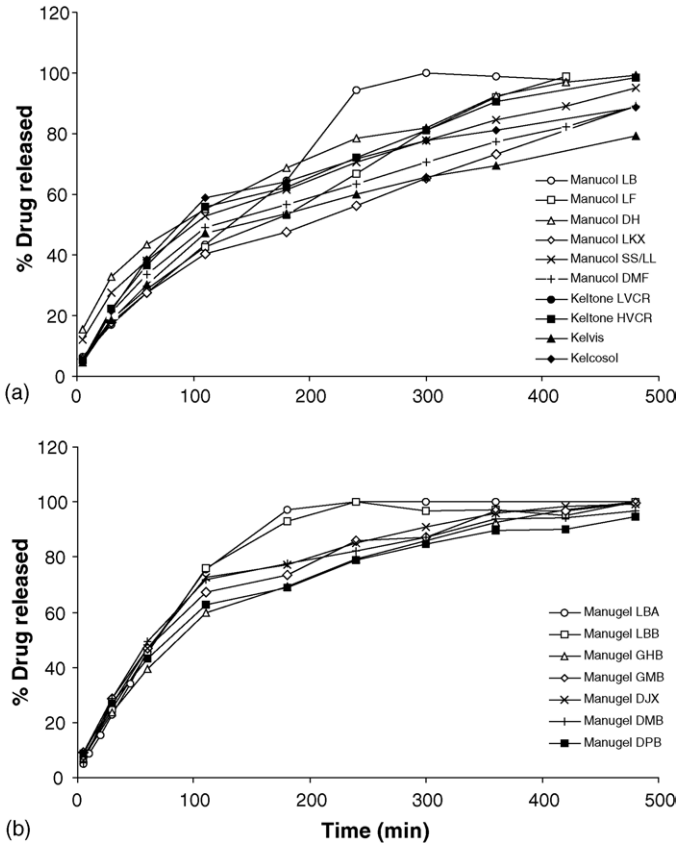

Fig. 2. Dissolution profiles of matrices containing 50% of (a) M-rich alginates and (b) G-rich alginates.

The comparatively lower $T_{25\%}$ and $T_{75\%}$ values shown by 10% alginate matrices could be attributed to the formation of a less effective diffusion barrier due to fewer polymer particles available for the formation of a continuous and resistant gel barrier. In contrast, higher polymer concentration gave rise to a more effective diffusion barrier to further augment the $T_{25\%}$ and $T_{75\%}$ values. Further increase in polymer concentration from 30 to 50% reduced the release-retarding effect of the polymer but only in half of the cases (Fig. 3). Other profiles showed a decrease in $T_{25\%}$ or $T_{75\%}$ values while some showed minimal changes in these values with higher concentrations of alginate.

The effect of polymer concentration on drug release had been widely reported for HPMC matrices (Alderman, 1984; Rekhi et al., 1999; Gao et al., 1996; Skoug et al., 1993). The most common reason used to explain the effect of polymer content on drug release was that an increase in polymer content resulted in increased viscosity of the gel matrix, causing a reduction in the effective diffusion coefficient of the drug (Skoug et al., 1993). Likewise, Gao et al. (1996) correlated the reduction in drug release rate with increasing HPMC content to a reduction in drug diffusivity with an increase in polymer concentration. However, a change in diffusion coefficient could not fully explain the difference in drug release rate. Skoug et al. (1993) noted that the extent of modulation in drug release rates was not proportional to the changes in formulation composition. In another study, it was observed that drug release rate decreased with an increase in HPMC content up to 20% polymer content. Further increase in polymer content had marginal influence in retarding drug release (Wan et al., 1993). Given the complexity of swellable matrices,

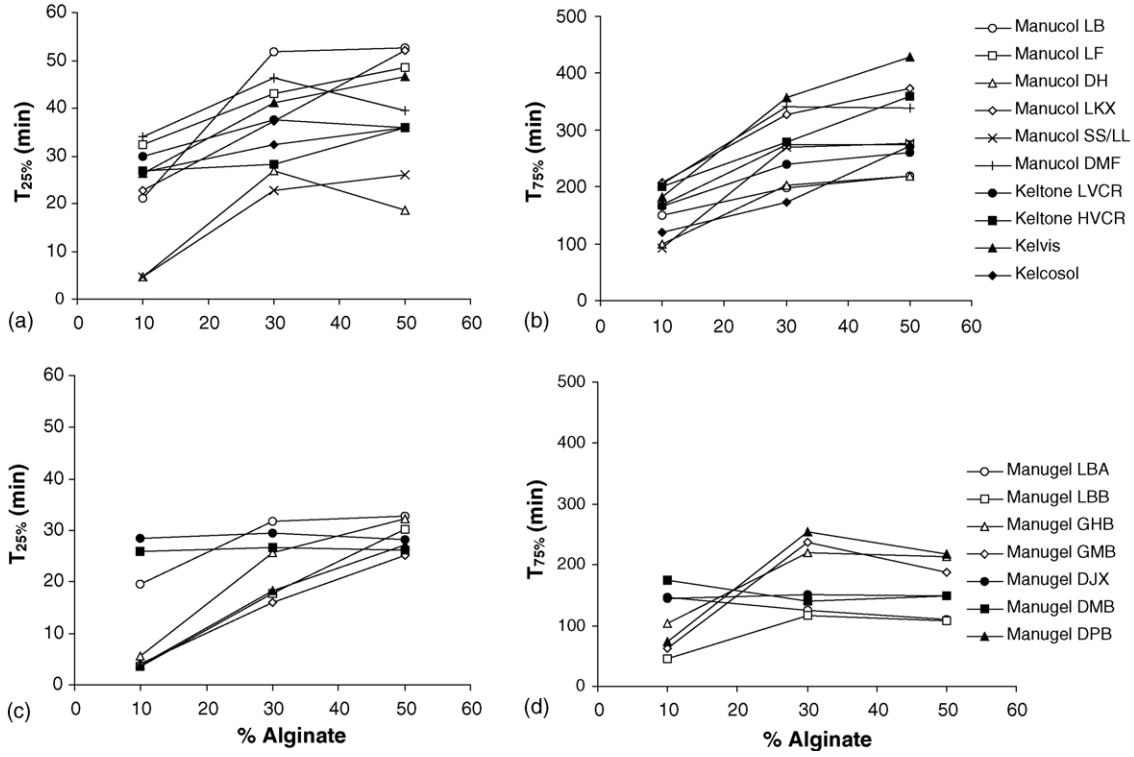

Fig. 3. The influence of alginate concentration on $T_{25\%}$ and $T_{75\%}$ for (a and b) M-rich alginate and (c and d) G-rich alginate.

it is unlikely that a change in diffusion coefficient is entirely responsible for the change in drug release rate. Other factors, such as differences in water penetration rate, water absorption capacity and swelling, which result from changes in polymer content could have played a part in modulating drug release (Skoug et al., 1993). This can be illustrated by the following observation made in this study.

Close examination of the alginate matrix tablets showed that the integrity of the matrices was adversely affected during the dissolution study. Varying patterns of deformation, depicted by the presence of surface cracks, grooves and lamination were observed. The extent of deformation was greater at higher alginate concentrations. As alginate content increased, the extent of matrix swelling increased due to greater liquid imbibition. The latter caused pressure built-up within the matrix which could be released by matrix deformation. In the acidic medium, the conversion of sodium alginate to insoluble alginic acid which could swell without generating surface stickiness could further contribute to the inability of the matrices to maintain their integrity. These effects might have compromised the gel barrier developing around the matrix and exposed greater surface area to the dissolution medium. Hence, the resultant drug release parameters were affected by these various compounding factors.

3.2.3. *Influence of sodium alginate particle size and viscosity*

The degree of association between sodium alginate particle size or viscosity and drug release parameters, $T_{25\%}$ or $T_{75\%}$ was determined using correlation analysis. Table 1 shows the Pearson correlation coefficient between the dissolution parameters used and the polymer variables investigated.

Correlation analysis for all 17 grades of sodium alginate showed that only particle size could be correlated well with the dissolution parameters at 10% sodium alginate concentration. The relationship among these variables was further investigated using surface plots (Fig. 4). The surface plots of 10% alginate matrices showed that drug release was strongly associated with alginate particle size. In general, as the particle size decreased, $T_{25\%}$ and $T_{75\%}$ increased. However, the relationship between particle size and drug release was not a strongly linear one. Curve fitting studies revealed that the data fitted a quadratic model better than a linear model, as shown by the higher R^2 values obtained with a quadratic model (Table 1). Hence, a plateau for $T_{25\%}$ and $T_{75\%}$ was observed as particle size decreased further. The particle size value beyond which $T_{25\%}$ or $T_{75\%}$ leveled-off was around 100 μm.

Alderman (1984) reported that smaller particles hydrated faster, leading to quicker gel barrier formation and hence slower drug release. Contrary to Alderman's theory, Mitchell et al. (1993) reported that larger HPMC particles showed higher initial hydration rates compared to smaller particles. Thus, it was postulated that the higher release rates observed for matrices with larger HPMC particles was due to the relative lack of polymer particles and not the particle size per se. For the same amount of alginate, a reduction in particle size is accompanied by an increase in the number of particles and an enhancement in the polymer surface area. Hence, the use of smaller alginate particles would favor interparticulate contact, contributing to better polymer particle coalescence and create a less

Table 1
Correlation between drug release parameters and alginate particle size or viscosity, and curve-fitting values for both linear and quadratic models describing the relationship between drug release and particle size at 10% alginate content

Alginate grade	Sample size	Dissolution parameter	Alginate content (%, w/w)	Pearson correlation coefficient, r		Curve fit, R^2	
				Particle size	Viscosity	Linear	Quadratic
All grades	17	$T_{25\%}$	10	−0.825[a]	0.182	0.681	0.8435
			30	−0.466	0.035		
			50	−0.382	0.018		
		$T_{75\%}$	10	−0.790[a]	0.010	0.624	0.6757
			30	−0.218	0.125		
			50	−0.481	0.369		
High M	10	$T_{25\%}$	10	−0.666[a]	0.195	0.4433	0.8515
			30	−0.371	−0.039		
			50	−0.327	−0.063		
High G	7		10	−0.963[a]	0.071	0.928	0.938
			30	−0.549	−0.263		
			50	0.133	−0.614		
High M	10	$T_{75\%}$	10	−0.723[a]	0.060	0.5229	0.5728
			30	−0.426	−0.138		
			50	−0.735	0.294		
High G	7		10	−0.799[a]	−0.024	0.638	0.677
			30	0.449	0.609		
			50	0.476	0.598		

R^2 values represent the goodness-of-fit between the variables $T_{25\%}$ or $T_{75\%}$ and particle size for both linear and quadratic models.
[a] Correlation is significant at the 0.05 level (two-tailed).

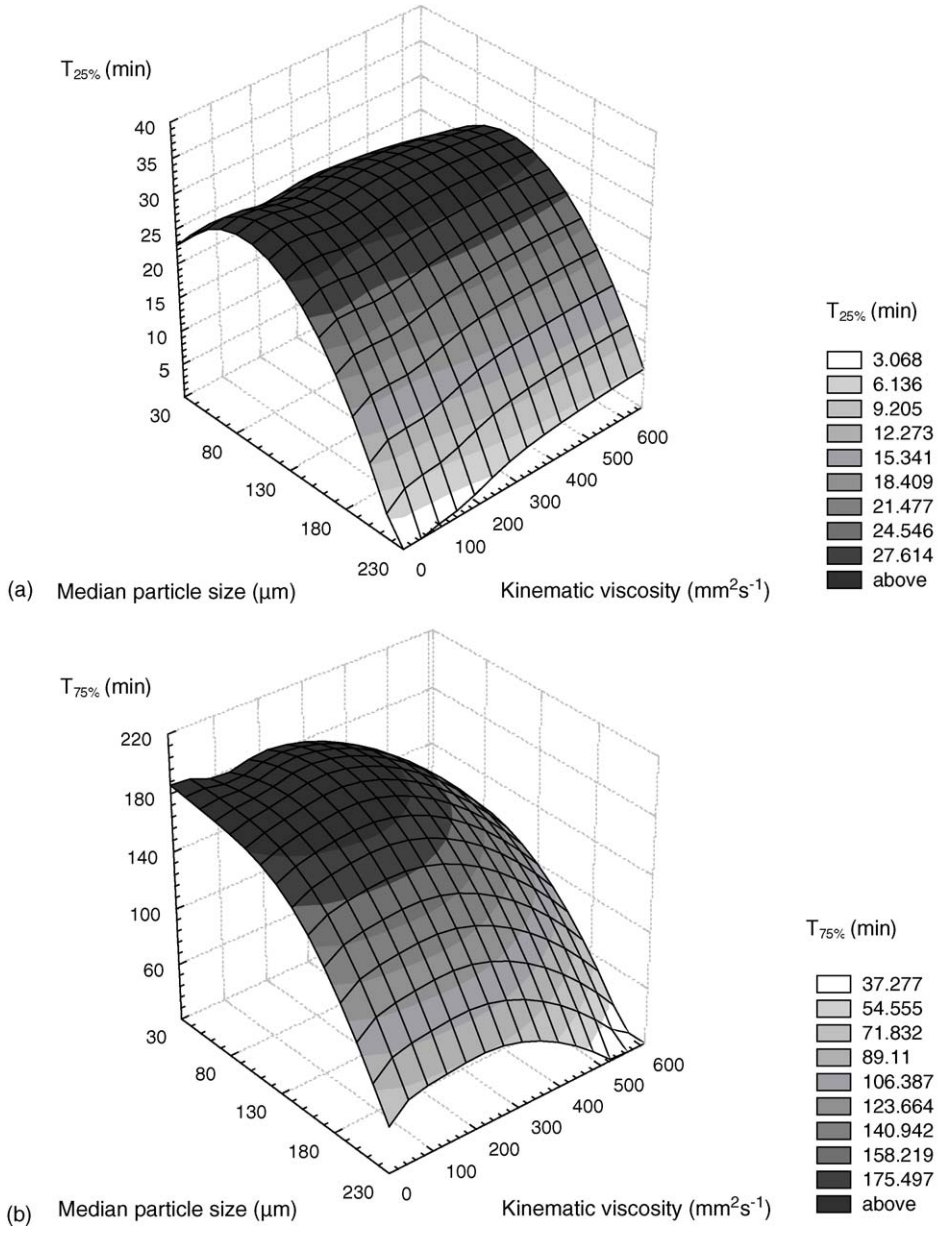

Fig. 4. Response surface plots for (a) $T_{25\%}$ and (b) $T_{75\%}$ of 10% alginate matrices.

permeable gel barrier for more effective retardation of drug diffusion.

It was interesting to note that drug release was more sensitive to a change in alginate concentration when alginate particles were larger. Fig. 5 shows that the effect of alginate concentration on drug release was most noticeable for matrices containing larger sodium alginate particles when alginate content was increased from 10 to 30%. The increase in $T_{25\%}$ and $T_{75\%}$ values when alginate content was increased from 10 to 30% was more than 100% for alginates with median particle sizes of about 200 μm and above [Manugels (LBB, GHB, GMB and DPB) and Manucols (DH and SS/LL)]. In addition, these matrices showed pronounced burst release at 10% polymer content. On the contrary, increasing the concentration of alginates with smaller particle sizes from 10 to 30% did not augment $T_{25\%}$ and $T_{75\%}$ to that extent. The relative lack of alginate particles when larger particles were used resulted in areas on the tablet surface where there was an absence of polymer as noted by Mitchell et al. (1993) while working with HPMC matrices. Dissolution medium would enter through these areas and cause a burst release of drug before a protective barrier could be formed. Increasing polymer concentration would provide more particles to cover the tablet surface and reduce the polymer-free areas. With smaller particles, a sufficiently complete gel barrier was formed before significant burst release could occur, even at 10% alginate content. The extent of increase in surface coverage would be greater for larger particles than for smaller ones with the addition of more polymer, leading to a greater enhancement in drug retardation observed with larger particles when alginate concentration was increased from 10 to 30%.

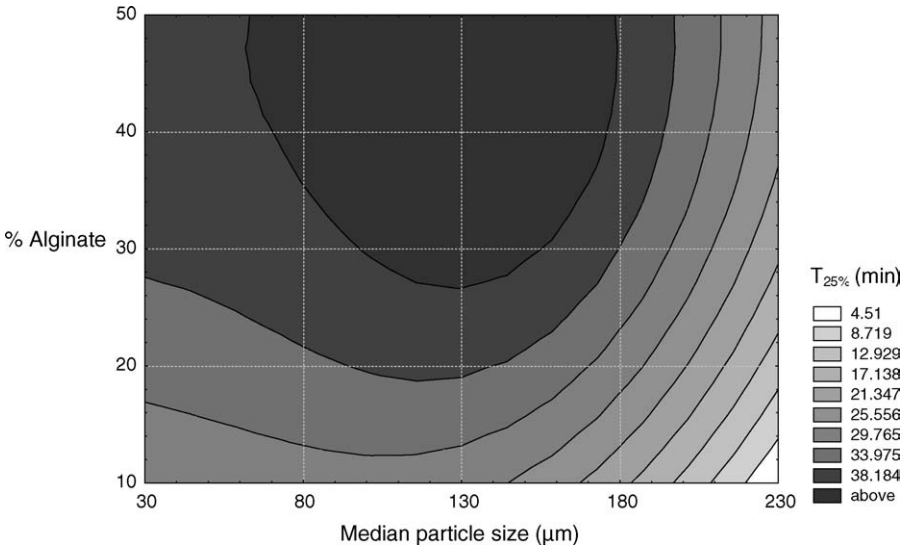

Fig. 5. Contour plot showing the influence of particle size on the extent of change in $T_{25\%}$ with an increase in alginate concentration.

At 30 and 50% sodium alginate levels, the influence of particle size was not apparent. With 10% alginate concentration, the extent of tablet surface coverage by alginate particles depended largely on the relative number of alginate particles present in the system. For the same amount of alginate, smaller particles would translate into relatively greater number of particles per unit weight, and hence, greater extent of tablet surface coverage. It follows that the porosity of the gel barrier formed would depend mainly on the relative number of alginate particles on the tablet surface. Therefore, at low alginate concentration, drug release is sensitive to particle size effect because at this concentration, the porosity of the gel barrier is highly dependent on the relative abundance of particles available on the tablet surface. At higher alginate concentration, there are adequate particles to form a stable gel barrier. Hence, drug release from these matrices is modulated by factors other than particle size. These factors include differences in liquid uptake, swelling, as well as matrix deformation during dissolution as observed for alginate matrices in this study. The masking of particle size effect by the concentration effect at higher alginate content was in agreement with other research findings carried out with HPMC (Mitchell et al., 1993; Velasco et al., 1999; Heng et al., 2001).

When the alginates were grouped according to their composition as either high M- or high G-alginates, similar results as those described for all 17 grades were obtained (Table 1). This showed that the influence of particle size on drug release was not affected by the chemical composition of sodium alginate.

On the other hand, the influence of alginate viscosity was not apparent from the surface plots (Fig. 4) and correlation analysis did not indicate clear association between drug release and alginate viscosity (Table 1). Nonetheless, the results of this screening study may be more affected by the influence of the more dominant factor, particle size, especially at low alginate concentration. In an attempt to estimate the influence of viscosity, alginates with similar particle size distribution but different viscosities were chosen for comparison. The dissolution profiles of these alginates did not show any significant difference between the different viscosity grades. However, when the release profiles in the buffer phase were compared (Fig. 2), lower-viscosity matrices showed faster drug release compared to higher-viscosity alginate matrices. Further investigations were carried out to ascertain the relative contributions of viscosity in drug release from alginate matrices.

3.2.4. Influence of mannuronic and guluronic acid content in sodium alginate

Grades of sodium alginate with different M/G content but similar median particle sizes and viscosities were compared to determine the effect of M/G content on drug release (Table 2). Comparison of dissolutions profiles (Fig. 6) using similarity factor showed that the profiles of Manucol LB and Manugel LBA as well as Manucol DMF and Manugel DMB were significantly different at 30 and 50% alginate levels ($f_2 < 50$). However, the profiles for Manucol DH and Manugel DMB at 30 and 50% were statistically similar ($f_2 > 50$). The profiles were similar at 10% alginate level for all three pairs of alginates ($f_2 > 50$). This shows that M/G content influenced drug release behavior of alginate matrices and this effect could only be observed at 30 and 50% alginate concentration. To determine whether pH affected the influence of M/G content on drug release, the release rates in the acid and buffer phases were determined from curve-fitting studies using the Higuchi and zero order equations, respectively ($R^2 > 0.99$) (Table 2). Exceptions were made for the release in acid for 30 and 50% Manucol LB and Manugel LBA matrices, which showed better fit to the zero order equation. Results showed that M-rich alginates gave lower drug release rates in acid while G-rich alginates gave lower drug release rates in buffer. Comparison of profiles in acid or buffer phases using similarity factor showed that the release rates were significantly different only for 30 and 50% alginate matrices for Manucol LB-Manugel LBA and Manucol DMF-Manugel DMB groups.

It appeared that M-rich alginates hydrated faster under acidic condition and built up the diffusion barrier more rapidly, resulting in slower release in the acid phase. On the other hand, G-rich

Table 2
Drug release rate constants for matrices containing 10, 30 and 50% of M- and G-rich alginates

Alginate grade	Viscosity ($mm^2\ s^{-1}$)	Median particle size (μm)	Rate constant					
			10% alginate		30% alginate		50% alginate	
			Acid	Buffer	Acid	Buffer	Acid	Buffer
Manucol LB	2.8	164	4.95	0.75	0.35*	0.35	0.38*	0.29
Manugel LBA	2.5	155	6.32	NA	0.60*	NA	0.68*	NA
Manucol DH	28.0	207	6.24	0.26	4.68	0.20	4.76	0.13
Manugel GHB	30.4	224	6.37	0.21	5.48	0.13	6.41	0.13
Manucol DMF	89.6	96	5.53	0.21	4.77	0.14	5.41	0.11
Manugel DMB	115.4	82	6.63	0.14	7.74	0.08	8.10	0.09

Drug release rate constants in the acid phase and buffer phase are expressed as $\%/min^{0.5}$ and %/min, respectively, except for values denoted with (*), which are expressed as %/min. The rate constants in buffer were not calculated for Manugel LBA due to insufficient data points.

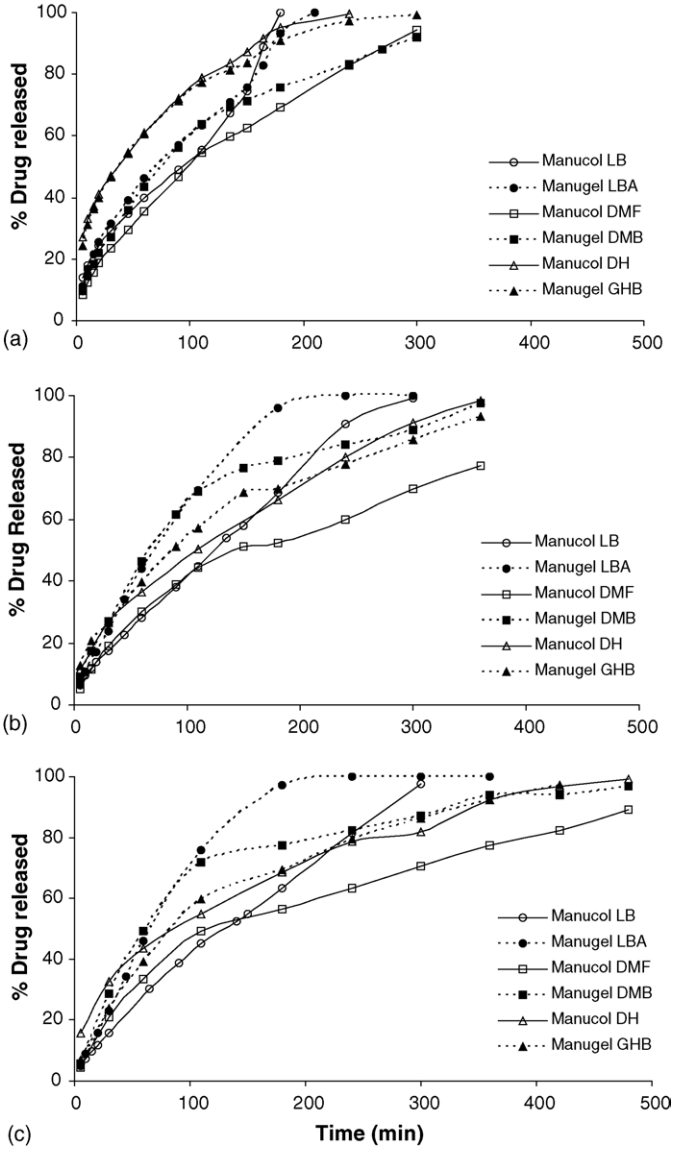

Fig. 6. Effect of MG content on drug release from alginate matrices for (a) 10%, (b) 30% and (c) 50% alginate concentration.

alginates slowed down drug release more than the M-rich alginates in the buffer phase. The observation in the buffer phase is in agreement with other researchers' findings (Veski and Marvola, 1993; Sirkiä et al., 1994) where pH 7.2 buffer systems were used for dissolution studies. At near-neutral pH, G-rich alginates formed more rigid gels upon hydration than M-rich alginates (Veski and Marvola, 1993), which may be less prone to erosion and thus constitute a more effective barrier to drug release. However, when alginate matrices were subjected to acidic conditions prior to dissolution at pH 6.8, the overall release rates were enhanced (Fig. 6).

3.3. Investigation of particle size effect using Manucol LB

3.3.1. Investigation using sieved fractions of sodium alginate

Screening study has shown that drug release from sodium alginate matrices were influenced by the median particle size of the various grades of sodium alginate. However, the effect of particle size alone could not be clearly ascertained since the various grades of alginate also differed in their viscosity and composition. Hence, further investigation into particle size effect was carried out using a grade of sodium alginate (Manucol LB).

Manucol LB was sieved into fractions of 180–250 μm, 125–180 μm, 90–125 μm and <90 μm and each size fraction was incorporated into matrix tablets at 5 and 10% alginate concentration. The release profiles of these tablets were subsequently determined (Fig. 7). Particle size effect was observed at both alginate concentrations used, but the distinction between the size fractions was clearer at 5% alginate content. The trend obtained supports the observation from the screening study: the smaller the particles, the slower the drug release. It was also noted that the extent of initial burst release diminished with smaller polymer size fractions. Burst release was defined as the *y*-axis intercept extrapolated from the initial curvature of the dissolution profile. Burst release of 25, 20, 10 and 5% were observed with 5% alginate matrices with decreasing alginate size fraction, while initial bursts of 25, 14, 6 and 4% were observed for matrices containing 10% alginate with diminishing particle size fractions.

Burst release is often observed prior to or during the development of a diffusion barrier capable of controlling the penetration

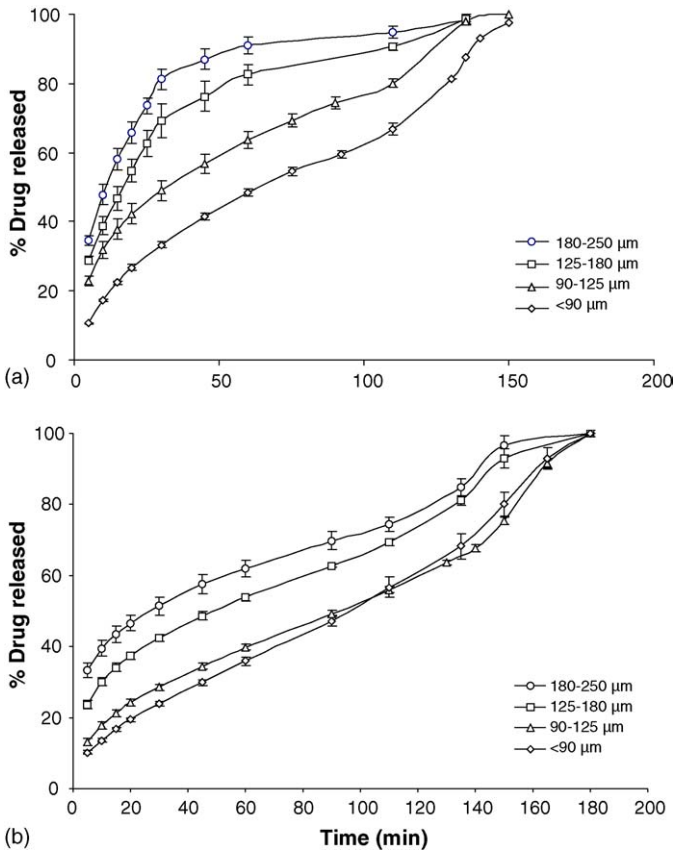

Fig. 7. Dissolution profiles of matrices containing (a) 5% and (b) 10% Manucol LB sieved fractions (mean ± standard error of mean; $n \geq 3$).

of dissolution medium and drug diffusion (Huang and Brazel, 2001). Once the gel barrier formed, drug release slowed down and this was reflected by a change in the slope of the dissolution profiles. During the initial phase, surface erosion from the matrix was observed. This could indicate that the alginate particles were not yet sufficiently hydrated to coalesce with neighboring particles to form a continuous barrier. Surface erosion was further aggravated by the relative scarcity of alginate particles to bind with neighboring particles upon hydration, particularly when larger alginate particles were used.

The dissolution curves were triphasic: initial burst release, followed by a slower release phase in the acidic medium, and finally, a faster release phase which occurred after dissolution media pH-change. Multiphasic release was more obvious for 10% alginate matrices and was not apparent for 5% alginate matrices containing alginate size fractions of 180–250 μm and 125–180 μm since drug release from these matrices was almost completed within 2 h in the acidic phase. The release profiles were modeled to determine the mechanism of drug release. Only the second release phase was used for kinetic modeling. For 10% alginate matrices, the data points in the second phase showed the best fit to the first order kinetics model ($R^2 > 0.99$) except for the smallest size fraction, <90 μm which fitted best with the zero order model. It was noted that the R^2 value increased with a decrease in alginate particle size fraction when the data points were fitted to the zero order model. Further modeling using the modified Korsmeyer–Peppas model (Lindner and Lippold, 1995) revealed that the n value, which is indicative of the drug release mechanism, increased with decreasing particle size fraction; the n values obtained were 0.5038, 0.503, 0.5924 and 0.6939 for alginate size fractions of 180–250 μm, 125–180 μm, 90–125 μm and <90 μm, respectively ($R^2 > 0.99$). This suggests a gradual evolution of release mechanism towards zero order release. It was reported that zero order kinetics prevailed if $n > 0.66$ for hydrocolloid matrices (Mockel and Lippold, 1993).

The trend observed for release mechanism from 10% alginate matrices was not observed for 5% alginate matrices (Fig. 7), implying that alginate concentration could also affect release mechanism. For 5% matrices containing 180–250 μm and 125–180 μm fractions, drug release occurred rapidly in a zero-order manner until 70–80% of drug was released, after which the release profiles gradually leveled-off. The faster release rate observed with 5% matrices containing the two larger size fractions could be due to the disintegrating action of isolated alginic acid particles. For 90–125 μm and <90 μm fractions, curve fitting studies showed the best fit to the first order kinetic model. The n values derived from the modified Korsmeyer–Peppas equation were 0.8104, 0.9563, 0.4817 and 0.593 for 5% matrices containing alginates in order of decreasing particle size fraction. The first two n values were more than 0.66 and fitted the zero order model ($R^2 > 0.99$).

The change in pH from 1.2 to 6.8 resulted in a change in the gel barrier properties due the re-conversion of alginic acid to sodium alginate. This conversion produced an apparent change in the release profile as well as a morphological transformation of the matrices. The rough and porous outer layer slowly became smooth and viscous following pH-change and drug release became faster as the matrices showed gradual erosion. The matrices completely dissolved at the end of the dissolution process. Hence, it is postulated that the alginic acid gel is more resistant to erosion compared to the sodium alginate gel. The higher rate of erosion explains the faster release in the buffer media. The data points collected after pH-change were not curve-fitted due to lack of data points.

Other investigations have shown that particle size effect is masked at higher polymer concentration (Mitchell et al., 1993; Aldrete and Robles, 1997; Velasco et al., 1999; Heng et al., 2001). Nevertheless, matrices containing 30 and 50% Manucol LB were made using size fractions of 180–250 μm and 90–125 μm to examine whether particle size effect could still be observed at higher alginate concentration. Interestingly, results showed that the dissolution profiles were still dissimilar, albeit to a lesser extent relative to matrices containing lower concentrations of alginate (Fig. 8). The profiles of different size fractions showed a more pronounced difference in the initial portion of the dissolution curve. Increase in alginate concentration generally reduced the extent of burst release from matrices of both size fractions. At 30% alginate, triphasic dissolution profile was only observed with the larger size fraction, 180–250 μm, while the 90–125 μm size fraction gave rise to a zero order release profile with slight initial burst release. The higher release during the third (buffer) phase observed with the larger size fraction could suggest that the ionic gel barrier formed from larger particles was weaker and more readily erodable. At 50% alginate

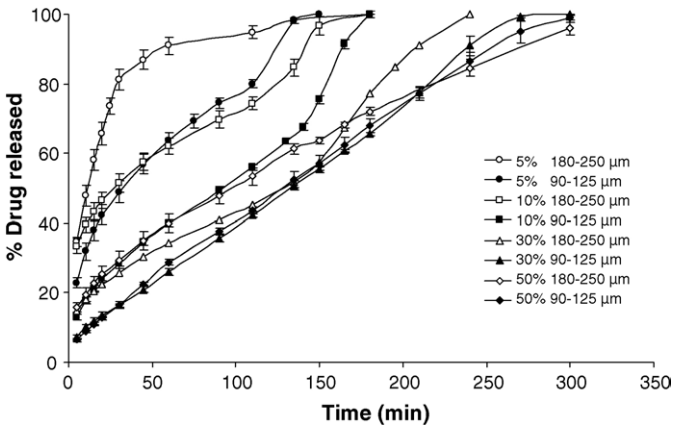

Fig. 8. Dissolution profiles showing the influence of alginate concentration on the manifestation of alginate particle size effect (mean ± standard error of mean; $n \geq 3$).

concentration, both curves did not show any apparent phase transition and dissolution followed zero order kinetics for release between 20 and 80%. Zero order kinetics could imply that drug diffusion occurred through a gel layer of constant thickness with respect to time attributed to the synchronization of alginate swelling and alginate gel layer erosion rates.

3.3.2. Investigation on the homogeneity of alginate sieved fractions

Blending of alginates with different viscosity is commonly employed to produce a product with the required viscosity (Draget, 2000). With this in mind, the viscosities of the sieved fractions were determined using 1% (w/w) alginate solutions. It was found that the sieved fractions had significantly different viscosities (Table 3) and the viscosity values decreased as the particle size fraction decreased. This implied that the alginate sieved fractions were not homogeneous in terms of molecular weight distribution and probably chemical composition as well. In order to eliminate the possible confounding effects due to differences in molecular weights or chemical composition, and to investigate whether alginates having particles smaller than the smallest sieved fraction would further retard drug release from the matrices, comminution of sodium alginate was carried out to produce milled fractions of different particle sizes and yet homogeneous in their chemical content and average molecular weight.

Table 3
Median particle size and kinematic viscosities of sieved and milled Manucol LB

	Mesh size (μm)	Median particle size (μm)	Kinematic viscosity ($mm^2 s^{-1}$)
Control		164	2.8
Sieved fractions	180–250	241	3.3
	125–180	183	3.0
	90–125	138	2.7
	<90	82	2.4
Cryomilled fractions		88	2.8
		60	2.8
		44	2.7
		41	2.7

3.3.3. Comminution of sodium alginate

Attempts to comminute sodium alginate using impact mills at ambient temperature were unsuccessful. The highly plastic nature of sodium alginate presented considerable resistance to fracture. Furthermore, alginate is heat-sensitive and might be subjected to degradation when ground using conventional mills which are usually associated with considerable heat generation. The alternative comminution method considered was the use of cryogenic milling where material temperature was reduced to sub-zero levels to increase its brittle behavior and to provide a temperature-controlled environment for size reduction.

Manucol LB was cryogenically milled at four different speeds, 7500, 10 000, 12 500 and 15 000 rpm and alginate batches with median sizes of 88, 60, 44 and 41 μm were produced, respectively. The extent of particle size reduction increased linearly with milling speed up to 12 500 rpm, beyond which the particle size leveled off. This was because as particles became smaller, they were more difficult to mill since fewer flaws were present in the finer particles for crack propagation, which led to particle fracture.

Viscosity measurements carried out on the 1% (w/w) solutions of the milled fractions showed that the viscosity was not significantly different among the milled fractions and from that of the unmilled alginate (Table 3), implying that the milled fractions were homogeneous in terms of molecular weight and chemical composition. The lack of change of solution viscosity also indicated that cryogenic milling did not contribute to alginate polymer degradation.

The milled fractions were subsequently incorporated in matrix tablets and dissolution studies carried out. Drug release from matrix tablets containing these milled fractions did not differ significantly compared to those containing sieved fraction of <90 μm at alginate concentrations of 5 and 10% (Fig. 9). This meant that the particle size threshold had been reached, below which there will be no significant difference in drug release. This critical threshold value falls around 80–90 μm (Table 3). This

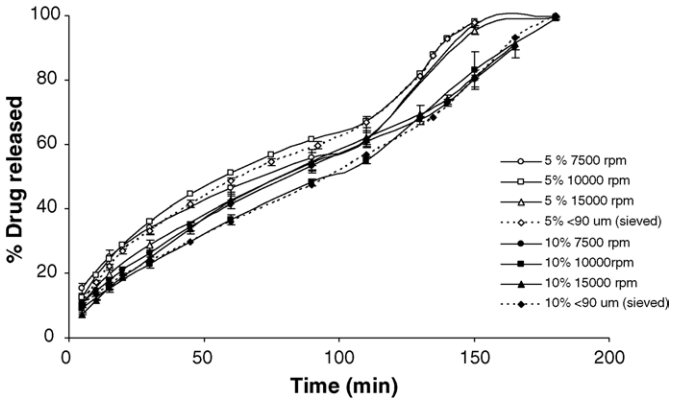

Fig. 9. Drug release profiles of matrices containing cryomilled Manucol LB at 5 and 10% alginate content compared with those containing <90 μm sieved fraction (mean ± standard error of mean; $n \geq 3$).

value agrees closely with the threshold value of about 100 μm obtained from the screening study.

3.4. Investigation on the effect of alginate viscosity using two viscosity grades of alginate

Screening studies using 17 grades of alginate did not show any clear trend between viscosity and drug release. Nevertheless, visual observations showed that alginate viscosity had an effect on matrix behavior. Furthermore, viscosity has been widely reported to affect drug release from hydrophilic matrices (Alderman, 1984; Wan et al., 1992; Aldrete and Robles, 1997) and a more critical investigation of this factor is warranted. More importantly, sodium alginate becomes insoluble at acidic pH and it would be interesting to determine if alginate viscosity plays a role in drug release during the acid phase of the dissolution process. Further investigation on alginate viscosity effect was carried out using two M-rich alginate grades, Manucol SS/LL and Manucol LB, with kinematic viscosities of 3 and 81 $mm^2\ s^{-1}$, respectively. These alginates were sieved to obtain similar size fractions and the release profiles of matrix tablets at 10, 30 and 50% alginate content were determined. The kinematic viscosities of the sieved Manucol SS/LL fractions were similar to the unsieved alginate ($P > 0.05$).

It was interesting to note that alginate viscosity influenced drug release in a contrasting manner depending on the dissolution medium (Fig. 10). When dissolution proceeded in the acidic medium, drug release was slower from matrices containing lower viscosity alginate, compared to matrices of higher viscosity alginate. Upon changing the pH of the dissolution medium to 6.8, drug release became faster for low-viscosity alginate matrices relative to high-viscosity alginate matrices and this pattern was observed at all three alginate concentrations. The faster release from a high-viscosity alginate matrix in the acid phase is somewhat surprising since many have reported that polymers with higher viscosities retarded drug release to a greater extent than lower-viscosity polymers (Alderman, 1984; Wan et al., 1992; Aldrete and Robles, 1997). The amount of burst release was higher for Manucol SS/LL compared to Manucol LB for each corresponding size fraction (Fig. 10). Observations made during the dissolution study revealed the possible mechanism behind the greater burst rate and release rate in the acid phase produced by matrices with higher viscosity alginate. Manucol SS/LL matrices swelled immediately when wetted during the dissolution test, forming loose, porous and friable outer gel layer that was easily eroded. Manucol LB matrices also showed initial surface erosion but the matrices did not show appreciable swelling. Pronounced matrix swelling in the acidic phase probably resulted in the higher drug release rate due to enhanced mobility of macromolecules, causing greater diffusivities of water and drug as observed with HPMC matrices (Siepmann et al., 1999). It is also possible that swelling of the gel layer in acid increased its porosity. More importantly, higher alginate viscosity could have reduced the rate of alginate particle hydration, which is essential for rapid formation of a protective gel barrier. Hence, increased matrix swelling and reduced rate of alginate particle hydration with higher viscosity alginate

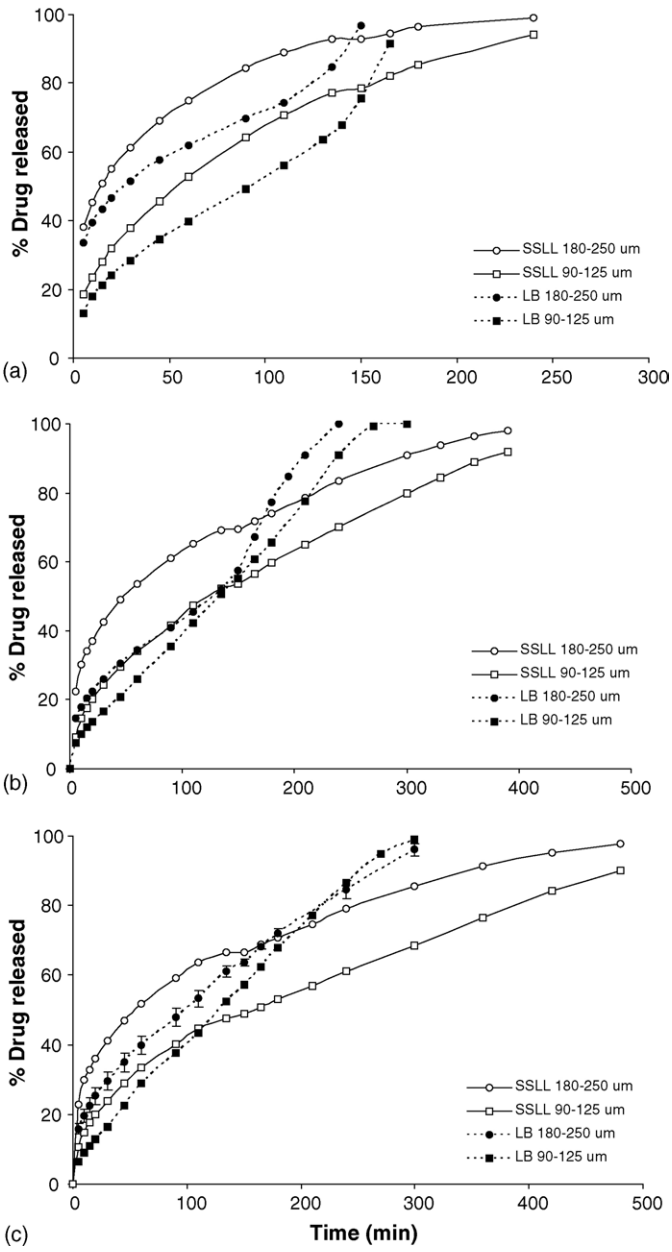

Fig. 10. Drug release profiles from matrices containing sieved fractions of Manucol SS/LL (high-viscosity) or Manucol LB (low-viscosity) at (a) 10%, (b) 30% and (c) 50% alginate concentration.

resulted in greater drug release rate in the acid phase. In a study on alginate matrices by Efentakis and Buckton (2002), faster drug release was also observed for high-viscosity alginate matrix tablets in acid but the reason given was that the high-viscosity alginate tablets showed more extensive lamination relative to low-viscosity alginate tablets. In the case of Manucol SS/LL matrices, no apparent matrix deformation such as lamination was observed during dissolution in the acid phase. Conversely, the slower drug release in the buffer phase observed for high-viscosity alginate matrices could be due to the formation of a more viscous and erosion-resistant ionic gel barrier. It was observed that Manucol SS/LL matrices eroded at a slower rate relative to Manucol LB matrices in the buffer phase.

At all three alginate concentrations, Manucol SS/LL matrices showed similar release patterns. Drug release started with an initial burst, followed by a gradually retarding release in the acid phase which followed either a first order or Higuchi model, and an even slower release phase showing zero order kinetics. On the other hand, drug release pattern for Manucol LB matrices was found to depend on particle size and alginate concentration used, as described earlier. This probably indicates that drug release mechanism from matrices containing alginates with relatively low viscosity depends more on particle size and alginate content, relative to higher viscosity alginates. This shows that drug release pattern can be governed by alginate viscosity besides particle size and this should be borne in mind during formulation design.

The profiles of Manucol SS/LL matrices showed a plateau region between the first two sampling time points (135 and 150 min) after pH change. No such pattern was observed for Manucol LB matrices. This plateau region occurred immediately after the conversion of alginic acid gel to sodium alginate gel. This indicated that Manucol SS/LL formed a sufficiently viscous gel barrier that drug release was impeded temporarily upon complete formation of the ionic barrier, after which drug was released in a controlled manner by diffusion and matrix erosion.

In addition, it was noted that alginate viscosity influenced the manifestation of particle size effect. Fig. 10 shows that the influence of particle size was more conspicuous at 30 and 50% alginate concentration for Manucol SS/LL matrices than it is for Manucol LB matrices. The higher alginate concentration did not seem to mask the particle size effect of higher-viscosity alginate.

4. Conclusion

Sodium alginate can be used to modify the release of highly water-soluble drugs. The industrial aspects of alginate matrix preparation have been investigated by other researchers (Timmins et al., 1992; Holte et al., 2003). Judicious selection of alginate grade is important in designing modified-release dosage forms. In general, a reduction in alginate particle size resulted in slower drug release and diminished the initial burst effect from alginate matrices, up to a threshold level of about 80–100 μm. Alginate viscosity effect could be seen as being double-edged since high viscosity enhanced, rather than diminished release rate in the acidic phase, but gave rise to more viscous and erosion-resistant gel barrier which slowed release more effectively in the buffer phase relative to low viscosity alginate. Hence, retardation of drug release in the acid phase can be best achieved using alginate with small particle size, low viscosity and probably one with a high M/G content. However, once the alginate matrix gets into the buffer phase, a high-viscosity alginate would retard drug release more effectively. Nevertheless, further retardation of drug release can be achieved by increasing the amount of alginate incorporated in the matrices. It was also noted that alginate particle size, viscosity and concentration affect not only the rate of drug release, but also the release mechanism. The pH-sensitivity and ability to form a gel barrier in both acidic and near-neutral environment is a unique feature of sodium alginate that can be utilized in formulation design. This study also demonstrated that alginate particle size can be reduced using cryogenic milling without degrading the polymer. Further work to elucidate alginate matrix hydration behavior, such as swelling and erosion, is ongoing.

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