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Crosslinking of drug–alginate granules Part 2. Effect of granule preparation and composition on granule properties

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Abstract

Paracetamol–alginate (Keltone HVCR) (1:1) granules were prepared by a wet granulation process followed by crosslinking of dried granules in calcium chloride solution. The effect of shear (planetary (low), Brabender (high)), binder quantity (1:2, 1:1 water:powder) and drug particle size (PS 98, 275 μm) were studied using a factorial design. Supporting studies were carried out varying binder quantity and alginate grade (viscosity). In the pre-treated granules, drug entrapment was mainly influenced by drug PS, where the smaller particles showed better embedding. After crosslinking, drug particle size continued to be the most important factor influencing drug recovery. All factors influenced early stage release where high shear, high binder, small drug PS granules showed least release and the low shear, low binder and large drug PS granules showed greatest release. Some significant two-factor interactions were found. Granule consolidation (shown by SEM) and particle embedding increased with binder quantity and reduced as the alginate viscosity was increased. Crosslinking, as shown by Na and Ca contents was >90%. The impact of granule consolidation on drug entrapment and recovery was relatively small (<10%) when compared to its effect on early stage drug release (>60%) which may be important if these granule systems are to be used for taste improvement.

Keywords: Shear rate; Binder quantity; Drug particle size; Alginate viscosity; Granule crosslinking; Granule properties

1. Introduction

Failure to embed drug particles inside polymeric matrix systems can lead to uncontrolled release of drug from the formulation (Hwang and Brazel, 2001), including an initial burst release. Burst release from a drug formulation may be unwanted as it can cause patient compliance problems owing to the early release of an unpalatable drug from the formulation. Wet granulation is commonly used in the industry to manufacture drug polymeric particulates or tablets or hard gelatine capsules prepared with particulates. During wet granulation the process parameters and the materials used to prepare the granules are known to affect granule porosity which has the potential to affect the drug particle embedding process as well. The important granule processing parameters that can affect granule porosity include the shear rate and the binder quantity (Badawy et al., 2000; Carstensen, 2001; Ohno et al., 2007) while the critical granule composition parameters include the particle size of the drug and the grade of inert matrix material (commonly a polymer) used to control the rate of drug release. The smaller the drug particle size the more it is likely to be embedded inside the inert granule matrix. The type of polymer used to prepare the inert matrix affects granule porosity as often it constitutes a significant portion of the matrix (>20%) (Kibbe, 2000). This becomes very critical if the polymer used to prepare the granules is soluble in the granulating solvent thus affecting the wet mass characteristics during wet mixing.

In order to circumvent some practical problems posed by the method of preparation of drug–alginate beads a rapid scalable method for preparing crosslinked drug–alginate granules has been developed which uses only small quantities of water (Mukhopadhyay et al., 2005). The method consists of dipping (crosslinking treatment) dried granules (prepared by a wet granulation process) into an aqueous calcium chloride solution

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instead of dropping hydrated drug–alginate dispersion into a calcium chloride bath as is used traditionally for bead preparation. In this published study the effect of treatment conditions on the crosslinked granules was studied using a factorial approach keeping the process of preparation of granules and the drug particle size and the type of polymer constant.

In the current study, the effect of two important stock granule preparation process factors (shear rate and binder quantity) and changes in drug particle size (each at two levels) on the granule properties (before and after crosslinking) was investigated keeping the crosslinking process constant. These factors were hypothesized to influence drug particle embedding and hence affect granule properties. Additional studies involving different grades of alginate and binder quantity used (during wet granulations) at three levels was also carried out to further investigate the drug particle embedding process. The important granule properties studied here include drug entrapment/recovery and early stage drug release. Early stage release was of particular interest as a reduction in this could lead to a taste-masking effect.

2. Materials and methods

2.1. Materials

Keltone HVCR (sodium alginate, 400 cps, milled fine PS, Medium G), Keltone LVCR (sodium alginate, 50 cps, milled fine PS, Medium G) and Kelcosol (sodium alginate, 1300 cps, milled fine PS, Medium G) were from ISP Alginates, USA.

Paracetamol, as obtained from the supplier, was passed through a BSS 100 mesh (150 μm) sieve; the fraction below BSS 100 mesh was used in the study as low and the faction retained above the mesh (i.e. 150–500 μm) was used as high. The weight mean diameters of these two fractions were 98 and 275 μm.

All other materials used were of analytical grade unless mentioned.

2.2. Design of the study

2.2.1. Factorial study

A complete factorial study using three factors (shear, binder quantity and drug particle size) each at two levels ($2^3 = 8$ batches) was carried out. Paracetamol–alginate granules were prepared with Keltone HVCR (Table 1).

2.2.2. Additional studies

2.2.2.1. Alginate study. To investigate the effect of alginate viscosity grade on granule properties an additional study was carried out using three types of alginates (Keltone LVCR, Keltone HVCR, and Kelcosol) keeping the preparation process (shear rate and binder quantity) and drug particle size constant.

2.2.2.2. Binder study. To investigate the effect of the binder (water) quantity on granule properties the binder quantity was varied keeping the preparation process, alginate grade (Keltone HVCR) and drug particle size constant.

All batches were prepared in duplicate and the drug to alginate polymer weight ratio (1:1) was kept constant.

Table 1
Details of the factorial study

Factors	Low (1)	High (2)
Shear rate (shear)	Kenwood	Brabender
Binder quantity (ml/g)[a]	0.55	1.05
Particle size (μm)[b]	98	275

Trial number	Shear	Binder (ml/g)	Particle size (μm)
1	Kenwood	0.55	98
2	Brabender	0.55	98
3	Kenwood	1.05	98
4	Brabender	1.05	98
5	Kenwood	0.55	275
6	Brabender	0.55	275
7	Kenwood	1.05	275
8	Brabender	1.05	275

[a] The volume (ml) of water (binder) used to granulate 1 g of dry powder.
[b] The weight mean particle size of drug used.

2.3. Preparation of different types of stock granules

2.3.1. Factorial study

A uniform dry mix (1:1) of paracetamol and sodium alginate (Keltone HVCR) was granulated as per the process conditions (Table 1). The low shear batches were prepared using a planetary mixer (Kenwood Chef; Model A 703C; Australia) for 5–6 min using the different quantities of binder. The high shear batches were prepared from the drug–polymer dry mix by first granulating in the planetary mixer for 2 min and then mixing in a screw extruder (Brabender Twin Screw Extruder DSE 25 with attached software; Germany) for 4 min at 50 rpm.

2.3.2. Additional studies

2.3.2.1. Alginate study. Paracetamol (98 μm) and sodium alginate of different viscosities (Keltone LVCR, Keltone HVCR and Kelcosol) were granulated in the Kenwood mixer (water/dry powder: 0.73 ml/g) for 5–6 min. Twenty-four batches were prepared; 12 for subsequent crosslinking and the remaining 12 for plastogram analysis.

2.3.2.2. Binder study. Paracetamol (98 μm) and Keltone HVCR were granulated in the Kenwood mixer for 5–6 min using three different quantities of binder (water/dry powder: 0.55, 0.88 and 1.05 ml/g). Four batches were prepared; two for subsequent crosslinking and the remaining two for plastogram analysis.

After granulation, each wet mass was dried at 55–60 °C for 12–15 h, size reduced, de-dusted and a size fraction of 0.8/1.0 mm was separated and stored in a desiccator over silica gel prior to crosslinking. The moisture content of the granules was determined as indicated previously (Mukhopadhyay et al., 2005).

2.4. Plastograms of wet mass of untreated granules

The maximum and stabilized shear forces (torque) of the high shear batches (factorial study, Table 1) were determined from the plastograms as recorded by the Brabender plasticorder

attached to the Brabender mixer in the process of mixing the wet mass. Additionally, the maximum and stabilized torques for the alginate and binder studies were recorded as above. It is to be noted that these lots were not used for any further study.

2.5. The crosslinking (treatment) process

Aliquots of dried granules (containing 3 g drug) from trials 1 to 8 (Table 1) and the binder study were treated using 60 ml 100 mg/ml $CaCl_2 \cdot 2H_2O$ solution, at 25 °C, for 5 min with 4 min under stirring at 240 rpm and 30 s holding time at the beginning and end of the treatment process. In the alginate study, the amounts of granules and treatment solution used were half the amounts used in the factorial and the binder study.

After treatment, the crosslinked granules were filtered through a G1 sintered glass funnel under suction for 60 s. The crosslinked granules were dried as before. The granules were stored over silica gel until evaluation.

2.6. Characterization of crosslinked granules

Water uptake, moisture content and yield of the granules were determined as indicated previously (Mukhopadhyay et al., 2005).

Drug entrapment as percentage before crosslinking (DE(UT)) and drug recovery after crosslinking (DE(T)) were determined spectrophotometrically (Mukhopadhyay et al., 2005) as:

- DE(UT) (%) = 100 × (drug quantity per g of dried untreated granules)/(input drug quantity per g of dried untreated granules).
- DE(T) (%) = 100 × (drug content of treated granules × yield obtained in g)/(drug content of untreated granules × amount of granules taken for treatment in g).

Calcium and sodium content were determined as described previously (Mukhopadhyay et al., 2005).

Early stage paracetamol release into water (25 °C) in the first 10 s (R10) and subsequent 50 s (R50) was determined using the early stage drug release apparatus (Mukhopadhyay and Tucker, 2003) and conditions described earlier (Mukhopadhyay et al., 2005).

Crosslinked granules were sputter coated with a thin gold–palladium layer (BioRad SEM coating, UK) and investigated with a Cambridge Stereoscan S360 scanning electron microscope (SEM, Cambridge, UK) operated with an acceleration voltage of 10 kV.

2.7. Data analysis

Balanced ANOVA was performed (on percentage released) using MINITAB Release 12.1, PA, USA (at $p = 0.05$ for the factorial study). For the alginate and binder studies one way ANOVA and Tukeys pair-wise comparison at $p < 0.05$ were performed.

3. Results

3.1. Water uptake during treatment, yield and moisture content of the treated granules

Yield and moisture content of the granules from the factorial batches (Table 1) remained fairly constant and ranged from 93 to 95% and 5.5 to 8.0%, respectively. Water uptake varied slightly more (71–88%) and depended on the drug polymer composition of the granules undergoing treatment. Batches showing higher drug loss during initial processing (those with large drug particle size, low shear and low binder) lost drug as a result of poor particle embedding, thereby yielding granules with a higher proportion of polymer. These granules took up more water during treatment than the granules from batches with better particle embedding.

3.2. Drug entrapment and drug recovery of granules

In the factorial study smaller drug particle size significantly increased both drug entrapment and drug recovery from the granules (Fig. 1a and b) ($p = 0.000$). The binder quantity affected drug entrapment and drug recovery of the treated granules slightly ($p = 0.000$). However, shear influenced drug recovery more than it affected drug entrapment (Fig. 1a and b). Although there were some significant two-factor interactions (shear × binder ($p = 0.000$) and binder × particle size ($p = 0.000$)) and one three-factor interaction ($p = 0.000$) affecting DE(UT) they were of no practical significance.

In the alginate study, the drug recovery was influenced by the alginate grade to a small degree (Kelcosol 78.8%; Keltone HVCR 80.1% and Keltone LVCR 82.6%). Similarly, in the binder study the binder quantity had a significant but small effect on drug recovery (81.6% (low binder) to 83.8% (high binder)).

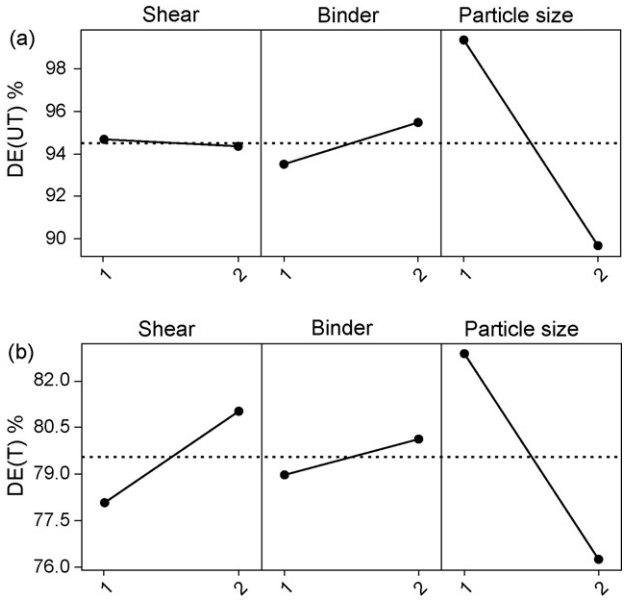

Fig. 1. Effect of shear, binder quantity used during preparation and drug particle size on (a) drug entrapment (DE(UT)) and (b) drug recovery (DE(T)). Data are treatment means.

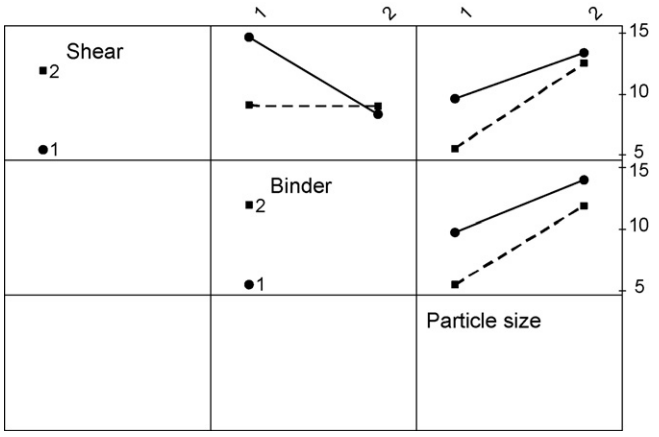

Fig. 2. Interaction plots showing the effect of shear, binder quantity and drug particle size on 60 s drug release (R10 + R50) (right axis) from treated granules. For example '*' marks cell 1 and 2 which shows the shear rate × binder quantity interaction and indicates that binder quantity affected R60 of low shear granules but had no effect on high shear granules.

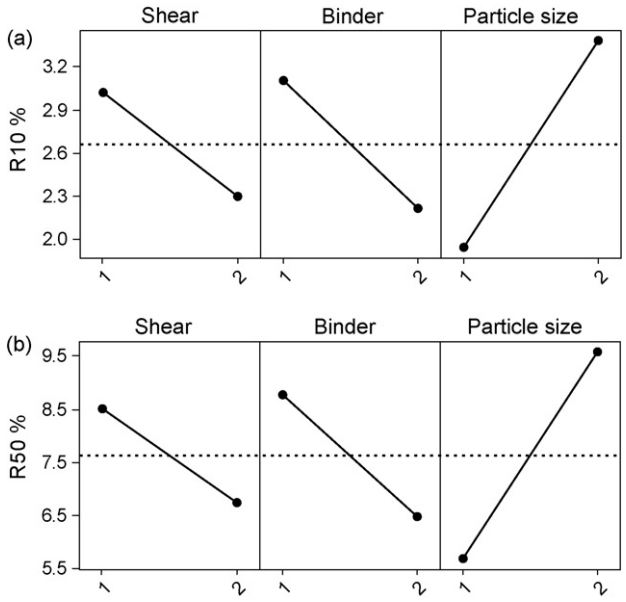

Fig. 3. Effect of shear, binder quantity and drug particle size on (a) 10 s drug release (R10) and (b) 50 s drug release after 10 s (R50) from treated granules.

3.3. Early stage drug release

3.3.1. Factorial study

The interaction plot (Fig. 2) shows there is a significant shear × binder interaction ($p = 0.000$). Binder quantity had no effect on early stage release in 60 s (R10 + R50) when the granules were prepared under high shear but significantly affected drug release from the low shear granules (Fig. 2, cells 1 and 2). Alternatively, the level of shear was not important when high binder was used as high binder itself helps in the consolidation of granule mass thus encouraging drug particle embedding. The effect on R10 and R50 was similar (data not shown). Other two-factor interactions were also significant ($p = 0.000$) but relatively small compared to the shear × binder interaction and the main effects. The three-factor interaction was significant ($p = 0.000$) but small compared to the main effects.

High levels of shear and binder decreased early stage drug release significantly. However larger drug particles led to higher early stage drug release (R10 and R50) (Fig. 3a and b). The effect of particle size on early stage drug release was greater than the effects of shear and binder quantity.

3.3.2. Additional studies

3.3.2.1. Alginate study. Early stage drug release (R10 and R50) was increased as the viscosity grade of the alginate used was increased (Fig. 4a) ($p = 0.000$).

3.3.2.2. Binder study. A decrease in the early stage drug release from the treated granules was observed as the binder quantity used for the wet granulation was increased (Fig. 4b) ($p = 0.000$).

3.4. Calcium and sodium contents of the treated granules

High levels of calcium and low levels of sodium were observed in general for all the batches and the lowest calcium and highest sodium contents of the polymer fraction of the granules were 10.3 and 1.37%, respectively. Before treatment, calcium and sodium contents of the polymer were 0.20% and 11.4%, respectively and these metals were not detected in the paracetamol. The above results suggest that all factorial batches were highly crosslinked (>90%) and granule crosslinking was unaffected by the independent factors studied here.

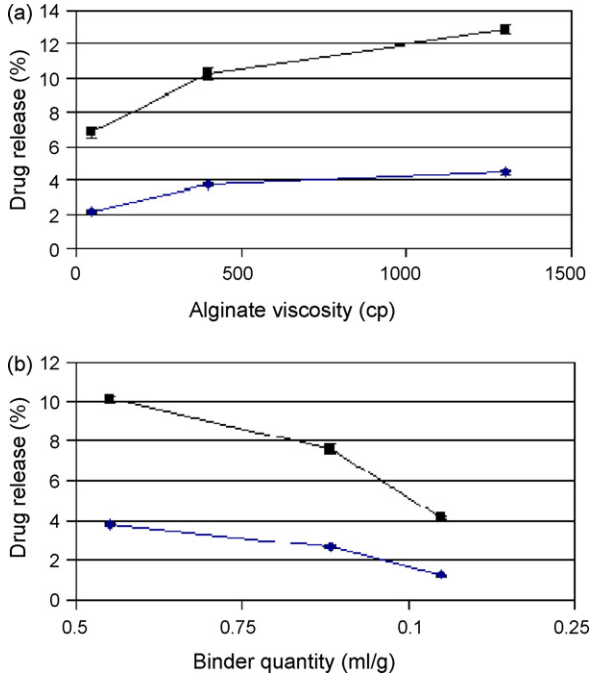

Fig. 4. (a) Alginate study: effect of alginate viscosity grade (Keltone LVCR, Keltone HVCR and Kelcosol) on R10 (♦) and R50 (■). (b) Binder study: effect of binder (low, intermediate and high) quantity on R10 (♦) and R50 (■). Points are means ($n = 2$).

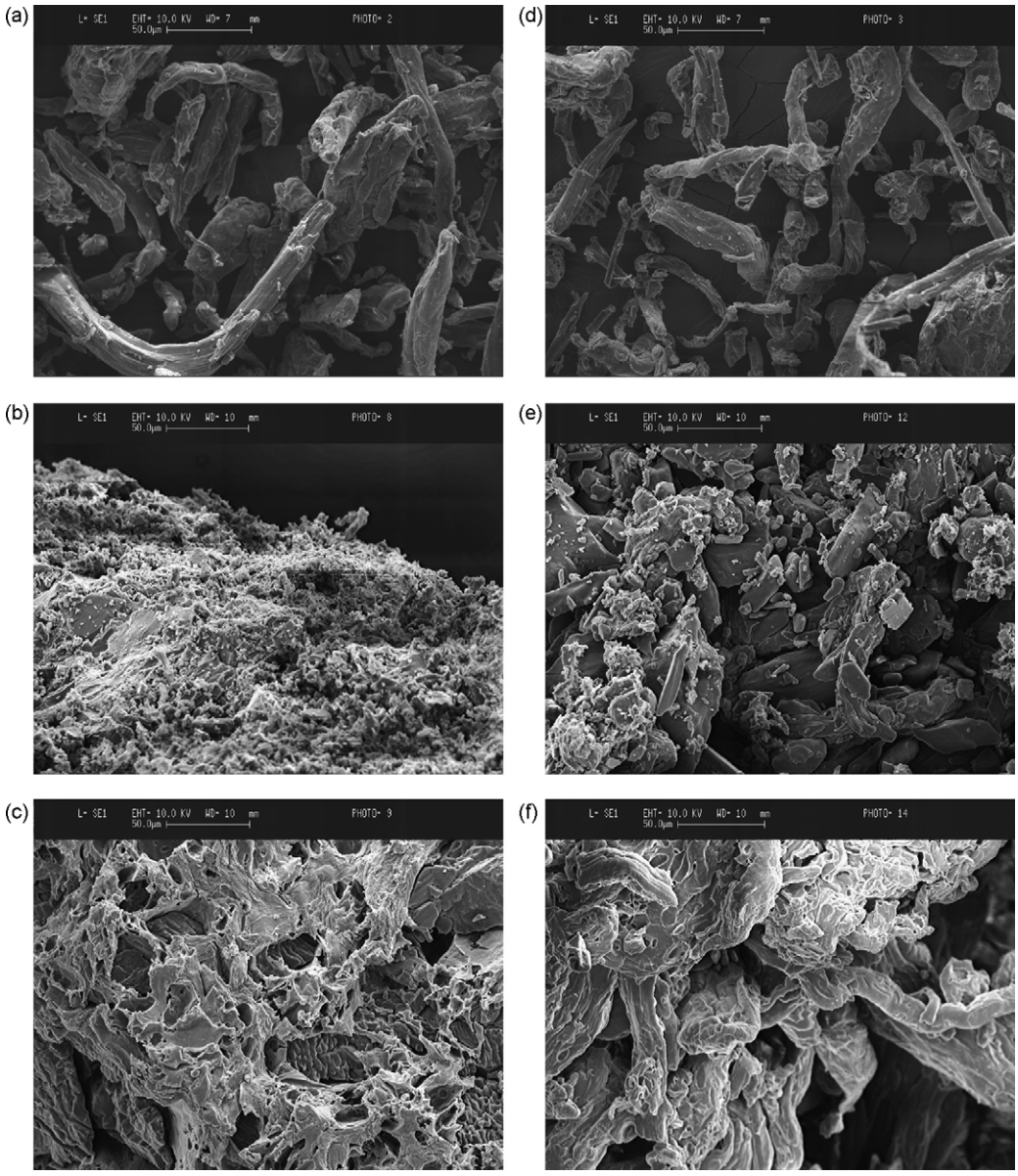

Fig. 5. Scanning electron micrographs of different types of sodium alginate powder: (a) Keltone LVCR and (d) Kelcosol used in the alginate study. In addition, drug–Keltone LVCR and drug–Kelcosol granules before treatment [(b) and (e)] and after crosslinking [(c) and (f)].

3.5. Scanning electron microscopy (SEM)

There was considerable variation in porosity of the granules in the batches, with high shear and high binder levels producing less porous granules as seen from the granule surface (data not shown).

In the alginate study, SEM suggested that the porosities of the Kelcosol granules both before and after treatment were greater than the porosities of Keltone LVCR granules (Fig. 5).

3.6. Plastogram study

From the plastogram, the maximum initial torque (MT) followed by the stabilized torque (ST) (expressed in Nm) were obtained. Both MT and ST depended on the quantity of water used during the wet granulation step (factorial study) and on the type of alginate used (alginate study). In the alginate study the MT and ST were lowest when the low viscosity grade sodium alginate was used and increased as the viscosity grade of the alginate was increased (Fig. 6a). Additionally, in the binder study, with low quantities of water, the MT and ST were 12.5 and 10.8 Nm and decreased to 4.8 and 4.4 Nm as the amount of binder quantity was increased (Fig. 6b).

4. Discussion

It was thought that drug particle embedding, which is directly related to the degree of matrix consolidation and thus inversely related to granule porosity, is the key factor that could affect the drug entrapment both before and after crosslinking and early stage drug release, since embedding reduces contact of the drug particles with fluid (either during the treatment process or dur-

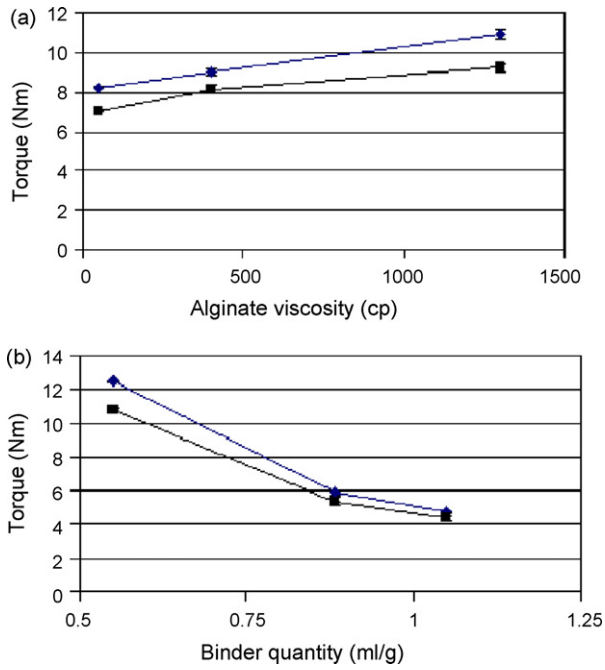

Fig. 6. (a) Alginate study: effect of alginate viscosity grade (Keltone LVCR, Keltone HVCR and Kelcosol) on maximum initial torque (♦) and stabilized torque (■). (b) Binder study: effect of binder quantity (low, intermediate and high) on maximum initial torque (♦) and stabilized torque (■). Points are means ($n = 2$).

ing exposure to release medium). Drug loss on contact with fluid diffusing into the granule matrix is facilitated by drug dissolution from the particle surface, either dissolving particles completely or else loosening particles within the matrix and promoting matrix erosion and thereby, particle loss. In the present study the effects of varying the key granule preparation process parameters and granule compositional factors were studied using a combination of a factorial study and additional studies.

4.1. Drug entrapment and drug recovery

Compared to the small drug particles (98 μm), the large drug particles (275 μm) were not properly embedded inside the polymer mass during the wet mixing and fell off readily during the de-dusting step leading to higher initial drug loss and hence low DE(UT) (Fig. 1a). During crosslinking, large particles continued to be lost more easily than small particles (DE(T); Fig. 1b)). However, when micronized drug particles were used (particle size <40 μm) (data not shown) neither DE(UT) nor DE(T) improved significantly compared to when drug particles having a mean size 98 μm were used. Thus there appears to be no advantage in using micronized (<40 μm) paracetamol instead of paracetamol with 98 μm particle size. For other sparingly/less soluble drugs (of similar solubility to paracetamol) a similar pattern of drug loss would be expected if large drug particles were used (i.e. 275 μm) compared to small drug particles (size <98 μm). However, the extent of loss would be influenced by the drug solubility since the lower the solubility, the slower the dissolution rate leading to reduced drug loss, either from direct dissolution or from particle loss accompanying matrix weakening and erosion.

Both shear and binder quantity affected drug recovery but drug entrapment was affected only by the binder quantity (Fig. 1a and b). It is understandable that both shear and binder quantity significantly affect drug recovery owing to their effect on matrix consolidation. The degree of consolidation influences drug particle embedding so that when the granules are exposed to the crosslinking solution the particles that are not well embedded are lost. The lack of effect of shear on DE(UT) could occur because, while these pre-treatment granules have been subjected to the same sieving and de-dusting procedure as the post-treatment granules, they have not been exposed to the treatment solution which was further able to remove loose drug during the process of granule hydration and swelling combined with partial dissolution of paracetamol particles.

As expected, better drug particle embedding takes place in the granules containing smaller drug particles leading to higher drug recovery. The same phenomenon is also evident from the main effects plot (Fig. 1b) where it can be seen that the effect of shear on DE(T) is significant whereas the effect of shear on DE(UT) is not significant. However, the effect of high shear and binder on the overall increase in DE(T) is small (<5%) when compared to the effect of drug particle size on DE(T) (9%).

From the plastogram studies it can be seen that the wet mass exerts different MT depending upon the viscosity grade of the alginate used (alginate study; Fig. 6a). Although the torque reduced and stabilized (ST; 2–3 min) with time the extent of reduction (MT → ST) also depended on the viscosity grade of the alginate used. From the SEM data (Fig. 5) it appears that Keltone LVCR (50 cps) granules become consolidated during the wet mixing step. However, the Kelcosol granules appear porous with occasional alginate polymer particles (fibre-like) becoming visible. A reduction in MT and ST was also observed when the binder quantity was increased in the binder study (Fig. 6b) owing to the increase in the softness of the wet mass during granulation with the increase in the binder quantity. SEM data of the high binder quantity granules showed that the granules became consolidated even when the wet mixing was carried out in a low shear mixer (data not shown). As a result, an increase in the drug recovery due to an increase in binder quantity was observed and this was comparable to that of trial 4 (factorial study) where, in addition to high binder quantity, high shear was also used (difference being <2%).

The above results suggest that the granule consolidation and hence drug particle embedding during wet granulation depends on all three factors: the viscosity grade of alginate, the shear rate applied and the binder quantity used especially if a low shear mixer, e.g. a planetary mixer is used.

4.2. Early stage drug release (R10 and R50)

Drug particle size had much larger effect on early stage drug release compared to the other two factors, i.e. shear rate and binder (factorial study Table 1; Fig. 2a and b). An increase in the shear rate and binder quantity led to a substantial decrease in early stage drug release (R10: >30% reduction and R50: >24%

reduction) (factorial study; Fig. 3). Although the smaller drug particles had greater surface area, granules containing smaller drug particles showed less drug release in 10 s as well as in 50 s due to better drug particle embedding inside the polymer matrix exposing fewer drug particles to the external medium during release studies. This higher drug embedding shown by the granules containing small drug particles compared to those containing large drug particles further supports our initial hypothesis. The relatively non-porous morphology of the high shear granules compared to that of the low shear batches provides evidence for the reduction in drug release being caused by the reduction in granule surface porosity.

In the alginate study (where the drug particle size was kept constant), the early stage drug release (R10 and R50) decreased as the viscosity grade of the alginate was decreased (Fig. 4a). As the binder quantity (water) used in the study was fixed, differences in consolidation or reduction in the granule porosity (Fig. 5) was caused by the use of different alginate grades. The low shear mixer (Kenwood; planetary mixer) was not able to consolidate the wet mass containing Kelcosol (1300 cps) as effectively as the wet mass containing Keltone LVCR, a low viscosity polymer (50 cps). Similarly, in the binder study, as the binder quantity was increased the matrix became more consolidated (decreased porosity) during wet mixing (Fig. 4b). As a result, early stage drug release also decreased with increased binder quantity. However, in the alginate and binder studies it can be seen that increased matrix consolidation increased drug entrapment only slightly (by <5%) but decreased early stage drug release considerably (by >50%; for R10 and R50) (Fig. 4a and b). Since better drug embedding reduces the early stage drug release considerably this may be relevant for taste improvement of granules or uncoated tablets prepared using the granules.

5. Conclusions

The current investigation showed that drug entrapment and early stage drug release from crosslinked granules composed of alginates depends (to different extents) on two granule preparation process parameters, shear rate and binder quantity. These factors affect the granule properties by affecting the drug particle embedding process which occurs as a result of drug–polymeric matrix consolidation (or porosity reduction) during the wet granulation step. The study also provides evidence that drug particles in the size range of <98 μm are adequate for the proper embedding of paracetamol particles. Also while granule porosity affected the granule properties, especially early stage drug release, it did not affect the extent of crosslinking when 100 mg/ml $CaCl_2 \cdot 2H_2O$ treatment solution was used for crosslinking the granules for 5–6 min time frame.

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