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Low shear granulation of pharmaceutical powders: Effect of formulation on granulation and tablet properties

H. Ma[a], G.P. Andrews[b], D.S. Jones[b], G.M. Walker[a,*]

[a] School of Chemistry and Chemical Engineering, Queen's University Belfast, Belfast BT9 5AG, Northern Ireland, UK
[b] School of Pharmacy, Queen's University Belfast, Belfast BT9 5AG, Northern Ireland, UK

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ABSTRACT

Low shear granulation, which is a form of wet granulation, is an important unit operation in the pharmaceutical, detergent and food industries. The granulation mechanisms for wet granulation include wetting and nucleation, consolidation and growth and attrition and breakage. In an experimental study the influence of process parameters on the low shear granulation was investigated using lactose and starch as model pharmaceutical powders and CMC solution as a model binder. Four parameters: binder viscosity; binder content; ratio of starch to lactose; and shear rate, were investigated at granulation times of 1 and 12 min using a factorial design technique. The data indicated that increased mass mean diameter and was found using higher viscosity binders and high liquid-solid ratio. In general, lower mass mean diameters were found at longer granulation times, which may suggest that granule breakage has a significant influence on this particular low shear agglomeration process. Moreover, three different size ranges of granules taken from the low shear granulation processes under various processing conditions were subsequently pressed into tablets using tablet press. Standard pharmaceutical hardness and disintegration analyses were performed on the tablets. These analyses indicated that the formulation (i.e., starch–lactose and liquid–solid ratios) rather than granulation process parameters had a stronger influence on the mechanical properties of the tablets.

1. Introduction

1.1. Pharmaceutical granulation and tabletting

Fine particles are difficult to handle, transport, feed and store and are therefore often agglomerated into required sizes and shapes. This is an important step in many industries such as pesticides, pigments and pharmaceuticals, which require the particle to be finally divided for processing but were improper granulation, can cause problems with downstream tabletting [1].

The agglomeration of individual particles to each other or solid surfaces is controlled by the competition between volume and surface forces. In order for these for these short-range physical forces to become active external effects must bring the particles together.

The pharmaceutical industry has tried to control granulation, where an extremely small amount of finely divided active must be mixed uniformly with a large amount of inert filler. While controls are put in place to try and achieve the desired results there is currently no method of measuring the homogeneity of the granulated particles on line. Homogeneous distribution of the active pharmaceutical ingredient is necessary to meet expectations of dosage unit uniformity. The homogeneity of functional excipients is necessary for consistent product performance. In recent years a greater understanding of granulation processes is occurring due to the development of Stokes deformation number and regime map analyses [2–5]. However, the importance of a uniform distribution within pharmaceutical granulation cannot be under estimated as it affects the final product uniformity and therefore the quality, safety, and efficacy of the product [6,7].

A large variety of techniques are available for granulation and the selection of the correct piece of equipment is currently based on which parameters are critical to the process or required in the product. Recent studies on wet granulation have investigated experimental variables such as liquid to solids ratio [8] and applied the regime map approach proposed by Litster et al. [3] and Iveson et al. [4]. The effect of binder viscosity and its effect on granule strength and breakage have also been investigated in a number of pharmaceutical systems [9–11] Moreover, the complex interactions involved in wetting, nucleation and growth are now

* Corresponding author at: School of Chemistry and Chemical Engineering, Queen's University Belfast, David Keir Building, Stranmillis Road, Belfast BT9 5AG, Northern Ireland, UK. Tel.: +44 2890 974253.
E-mail address: g.walker@qub.ac.uk (G.M. Walker).

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Table 1
Investigated variables.

X_i (i = 1,2,3,4) Coded variable	Z_1 Impeller speed (rpm)	Z_2 Starch–lactose	Z_3 CMC–water (%)	Z_4 Liquid–solid
+1	250	0.30	1.5	0.16
−1	150	0.16	0.5	0.12
0	200	0.23	1	0.14
$+\alpha$ = 1.414	300	0.33	1.7	0.17
$-\alpha$ = −1.414	100	0.13	0.3	0.11

increasingly being applied to wet granulation pharmaceutical systems [12].

In the tabletting compression cycle of pharmaceutical powders several processes may be involved: initial packing and rearrangement of particles; formation of temporary structures; elastic deformation; plastic deformation; breakage of particles; bond formation; consolidation, followed by elastic recovery during the decompression process [13]. In general, however, when compacting pharmaceutical powders the volume of the compact decreases rapidly at first and then more slowly with increasing pressure. The mathematical description of this empirical relationship, which effectively describes the complex process, has been attempted by numerous researchers [14,15].

The aim of this work is to investigate some of the fundamental properties of pharmaceutical formulations and processing parameters in a low shear mixer. In addition, by using a Factorial Design technique we aim to predict the granulation properties of various formulations. The work also addresses the influence that the formulation and processing parameters have on the properties of tablets pressed from the low shear granules.

2. Materials and methods

2.1. Materials/equipment

In each low shear granulation experiment, starch (National Starch and Chemical, AB) of the fraction (<75 um) and lactose (Davidson and Hardy, Fisher Scientific, UK) of the fraction (<180 um) were used as primary powder and carboxymethyl cellulose (CMC) sodium salt (Sigma–Aldrich, Germany) which was dissolved in distilled water was used as binder. Kenwood apparatus was used for low shear granulation at a fixed impeller speed.

2.2. Parameters investigated

These experiments were aimed at investigating the influence of process parameters on low shear granulation. To determine the effect of operating conditions on the process, a single parameter was varied with other parameters remaining constant. Four process parameters investigated, shear rate (impeller speed Z_1), hydrophobicity of primary powder (starch to lactose ratio Z_2), viscosity of binder (CMC to water ratio Z_3) and binder amount (liquid to solid ratio Z_4) (see Table 1). Two responses were chosen to characterise the granulation: the mean size of granules at 1 min (Y_1) (to determine extent of nucleation and initial granule growth); the mean size of granules at 12 min (Y_2) (to determine extent of further granule growth and/or granule breakage); the standard deviation of binder fraction at 1 min (Y_3); the standard deviation of binder fraction at 12 min (Y_4) (Table 2). Regression analysis of the data was carried out within the statistical design package ('Design-Expert' version 5.0.0, Stat Ease, Inc.), using a quadratic model of Central Composite Design with interactions:

$$Y = b_0 + \sum_i b_i X_i + \sum_{ij} b_{ij} X_{ij} \quad (1)$$

With i,j = 1,2,3,4, where Y is the calculated response, X_i is the coded independent process variable (−1 = low level, 0 = central level and +1 = high level) and the coefficient b_0, b_i, b_{ij} characterise, respectively, the constant, the linear and quadratic effects of the variable X_i and the interaction between X_i and X_j.

To characterise these coefficients, the second level in every variable, X_i, was set to be $+\alpha$ = 1.414 and $-\alpha$ = −1.414. The design was restricted to 28 granulation experiments aimed to give quantitative information about the effect of process parameters on the granule responses. The complete model was based on the simultaneous variation of four factors varied at five levels (see Tables 1 and 2).

The $l_{4,3}$ mean size was calculated by the mass mean length of number distribution which is ratio of the fourth moment over the third moment, defined by Eq. (2):

$$l_{4,3} = \frac{m_4}{m_3} = \frac{\int_0^\infty l^4 n(l)\ dl}{\int_0^\infty l^3 n(l)\, dl} \quad (2)$$

where l represents length of granules, $n(l)$ is number based distribution.

2.3. Granulation experimental methods

A typical experiment was undertaken using the following procedure:

(i) *Primary powder addition:* Starch and lactose were weighed on electronic balance, accurate to ±0.02 g, depending on the starch to lactose ratio set for each experiments.
(ii) *Premix:* The impeller was started at the speed of 200 rpm for 1 min to achieve a uniform distribution of primary powder before adding binder.
(iii) *Binder preparation:* The binder is prepared by dissolving CMC powder in distilled water, the ratio was defined as: CMC–water, i.e., mass of CMC powder/mass of distilled water.
(iv) *Method of binder addition:* Binder was manual added to the mixer by a spray-on binder addition method. The impeller was rotated at a speed of 100 rpm and the binder sprayed onto a dynamic powder bed within 30 s after premixing. The

Table 2
Response function.

Response	Units	Name	
Y_1	Mean size of granules at 1 min	$l_{4,3}$ (1 min)	μm
Y_2	Mean size of granules at 12 min	$l_{4,3}$ (12 min)	μm
Y_3	Standard deviation of binder fraction at 1 min	STD_b (1 min)	–
Y_4	Standard deviation of binder fraction at 12 min	STD_b (12 min)	–

Table 3
Process variables investigated and mean granule size/binder SD obtained.

Standard order (StO)	Z_1 impeller speed	Z_2 starch–lactose	Z_3 CMC–water	Z_4 liquid–solid	Mean size 1 min, μm	Mean size 12 min, μm
1	2.6	0.16	0.5	0.12	838	598
2	5.4	0.16	0.5	0.12	821	541
3	2.6	0.3	0.5	0.12	769	563
4	5.4	0.3	0.5	0.12	741	393
5	2.6	0.16	1.5	0.12	933	764
6	5.4	0.16	1.5	0.12	924	695
7	2.6	0.3	1.5	0.12	913	758
8	5.4	0.3	1.5	0.12	886	667
9	2.6	0.16	0.5	0.16	856	656
10	5.4	0.16	0.5	0.16	985	790
11	2.6	0.3	0.5	0.16	699	595
12	5.4	0.3	0.5	0.16	712	487
13	2.6	0.16	1.5	0.16	1144	821
14	5.4	0.16	1.5	0.16	1061	799
15	2.6	0.3	1.5	0.16	1040	821
16	5.4	0.3	1.5	0.16	993	773
17	2	0.23	1	0.14	981	83
18	6	0.23	1	0.14	755	57
19	4	0.13	1	0.14	953	647
20	4	0.33	1	0.14	796	500
21	4	0.23	0.3	0.14	772	496
22	4	0.23	1.7	0.14	1121	997
23	4	0.23	1	0.11	806	492
24	4	0.23	1	0.17	911	634
25	4	0.23	1	0.14	850	532
26	4	0.23	1	0.14	876	548
27	4	0.23	1	0.14	872	546
28	4	0.23	1	0.14	859	53

mass of binder as calculated was metered by the spraying device.

(v) *Binder viscosity:* The viscosity of binder was altered by using different CMC to water ratios.

(vi) *Sampling and drying:* The impeller was stopped and granules were removed and dried at a temperature of 40 °C in a vacuum oven for 6 h.

(vii) *Sample analysis:* Granules sample after drying were characterised by size distribution and mass mean particle size. Six grades of sieves were employed (2000, 710, 500, 355, 250, and 180 μm).

2.4. Tablet pressing experimental methods

Formulations for the tablet pressing were chosen to investigate the effect of: powder hydrophobicity (starch–lactose ratio was varied from 0.16 to 0.30, w/w); binder viscosity (binder CMC content was varied from 0.5 to 1.5%, w/w); binder content (liquid–solid ratio was varied from 0.12 to 0.16, w/w). A Riva SA Minipress MII was used for the tablet pressing employing a 5 tonne compression force. After low shear granulation, three size fractions of each granulation trial were chosen for the tablet pressing (2000–710, 710–500 and 500–355 μm). The hardness of 10 tablets of each formulation were analysed in a COPLEY Model 5Y Tablet Hardness Tester. Tablet disintegration on the formulations was performed COPLEY tablet disintegration Tester using purified water at 37 °C and three tablets samples.

3. Results and discussion

Table 3 lists the results of mass mean granule size for all 28 experiments, which were conducted in a fully randomized order at both 1 and 12 min. For comparison, they are sorted by standard order. Reproducibility can be tested by comparison of repeated batches. Experiments 25–28 all run at impeller speed of 200 rpm, starch to lactose ratio 0.23, CMC to water ratio 0.01 and liquid to solid ratio 0.14.

3.1. The effect of time on size distribution of granules

It can be seen from Table 3 that the mass mean granule size at 12 min is generally lower than at 1 min. More than half of granules (size > 180) produced at 1 min have a size > 710 μm, but the mass of granules >710 μm decreases at 12 min meanwhile an increasing in mass of granules which have the size between 500 and 180 μm is evident. Thus, the arithmetic mean size in each case shows an obvious decreasing, which indicates that granule breakage dominates the process as this stage.

3.2. The effect of impeller speed on size distribution of granules

Fig. 1a–c illustrates a plot of cumulative mass fraction of granules versus granule size for variation in impeller speed. The data indicate that initially an increase in impeller speed increases the extent of agglomeration (1 min); over 12 min particles decrease in size due to attrition (little difference in equilibrium mass mean particle size).

Fig. 1a and b shows the size distribution of impeller speed of 100, 200 and 300 rpm at 1 min with other parameters remain constants simultaneously. Higher impeller speed produce more granules in lower size fractions and lower impeller speed produces more granules in higher size fractions. Thus with increasing of impeller speed from 100 to 200 rpm and to 300 rpm, the mean size of granules decreases from 981 to 850 and to 755, respectively. Also, the amount of ungranulated powder increased with increasing of impeller speed.

3.3. The effect of starch to lactose ratio on size distribution of granules

It can be seen from Table 3 that for Exp. 1 to Exp.16, increasing of starch to lactose ratio results in a decrease in the mass mean granule size. Fig. 2a–c shows size distribution of starch to lactose ratio of 0.33, 0.23 and 0.13 at 1 min with other parameters remaining constant. Although the data are similar, generally a higher starch to lactose ratio produces more granules in the lower size fractions,

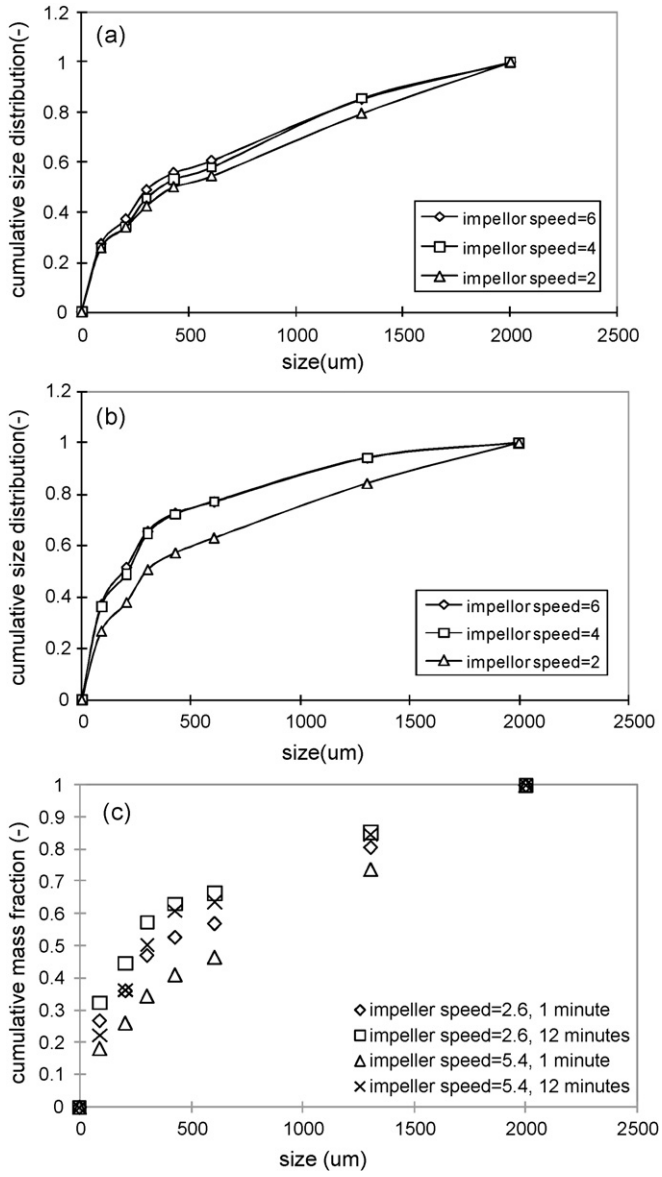

Fig. 1. Effect of impeller speed: (a) $t = 1$ min; (b) $t = 12$ min; (c) on low shear granulation with variation in time (experimental runs 3 and 8).

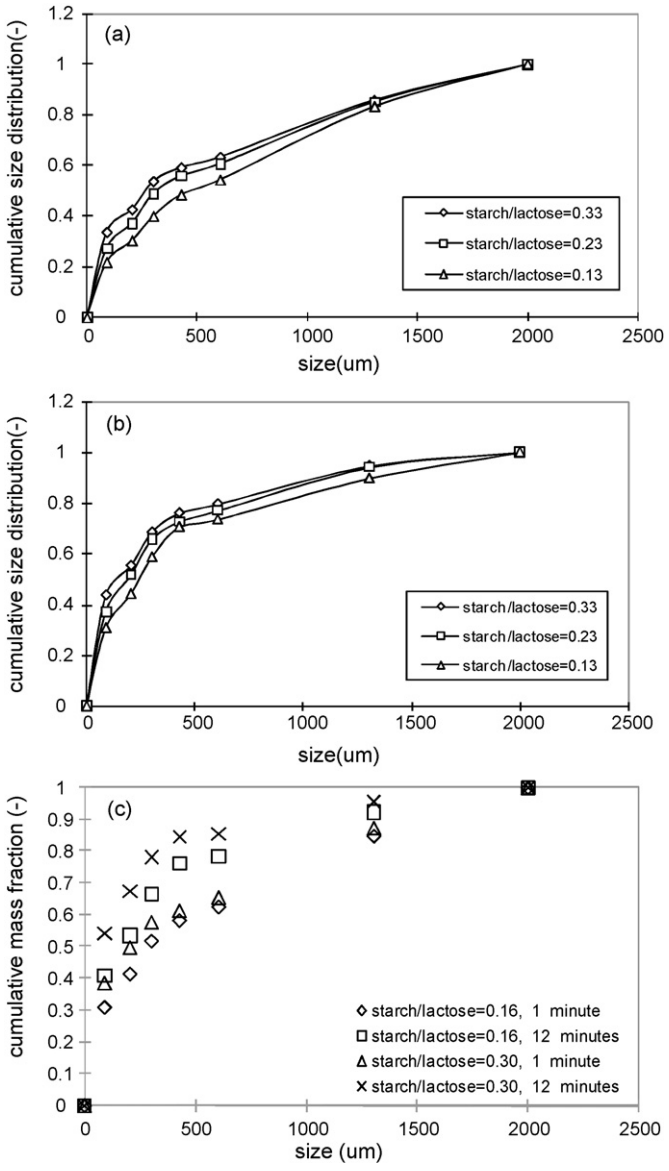

Fig. 2. Effect of starch–lactose ratio: (a) $t = 1$ min; (b) $t = 12$ min; (c) on low shear granulation (experimental runs 6 and 12).

with higher starch to lactose ratios resulting in more granules in the higher size fractions. Thus with decreasing of starch to lactose ratio from 0.33 to 0.23 and to 0.13, the mean size of granules increased from 796 to 850 and to 953. Moreover, an increase in ungranulated powder was found with increase in starch to lactose ratio.

3.4. The effect of viscosity of binder solution

From Table 3 it can be seen for Exp. 1 to Exp. 16 that the general the mean granule size increased with increasing binder viscosity. Fig. 3a–c shows granule size distributions with CMC to water ratio of 0.003 (4 cPs) 0.01 (60 cPs), 0.017 (300 cPs) at 1 and 12 min, respectively (other parameters remaining constant). The data indicate that CMC to water ratio (and thus the binder viscosity) has a significant influence to size distribution with an increase in binder viscosity resulting in an increase in larger size granules and and an overall increase in mean granule size.

3.5. The effect of binder to powder ratio (liquid to solid ratio)

It can be seen from Table 3 that for Exp. 1 to Exp.16, increasing of the liquid to solid ratio results in an increase in the mass mean granule size. Fig. 4a–c shows the size distribution of liquid to solid ratio of 0.11, 0.14 and 0.17 at 1 and 12 min, respectively, with other parameters remaining constant. Although the data are similar, overall an increase in binder content results in an increase in larger sized granules resulting in an increase mean granule size. Higher quantties of binder also decreased the amount of ungranulated powder in the system.

3.6. Factorial design and granulation

The over all influence of the granulation variables are detailed in Table 4 on the granulation coefficent at both 1 and 12 min. The data indicate that most influential factor is the viscosity of binder X_3. The role of binder viscosity has attracted considerable attention in recent years, due to its complex role in influencing: (i) the distribution of binder and thus the extent of granulation and (ii)

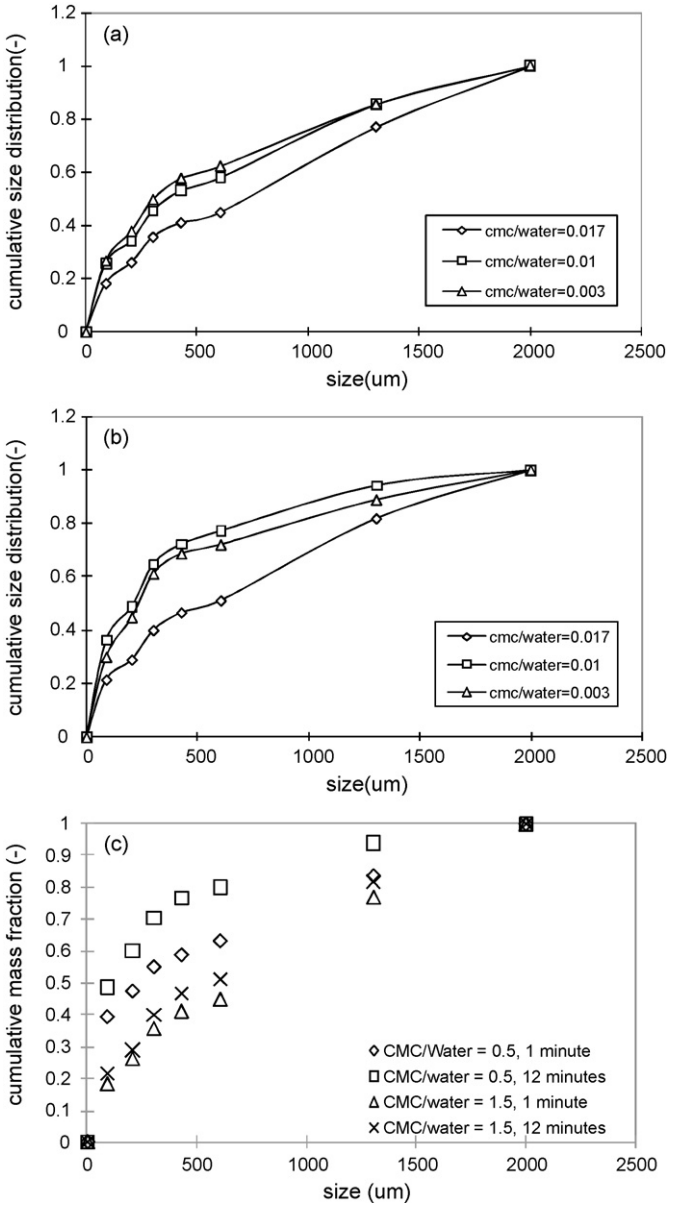

Fig. 3. Effect of binder viscosity: (a) $t = 1$ min; (b) $t = 12$ min; (c) on low shear granulation (CMC–water 0.5% = 8 cPs; CMC–water 1.5 = 200 cPs) (experimental runs 1 and 2).

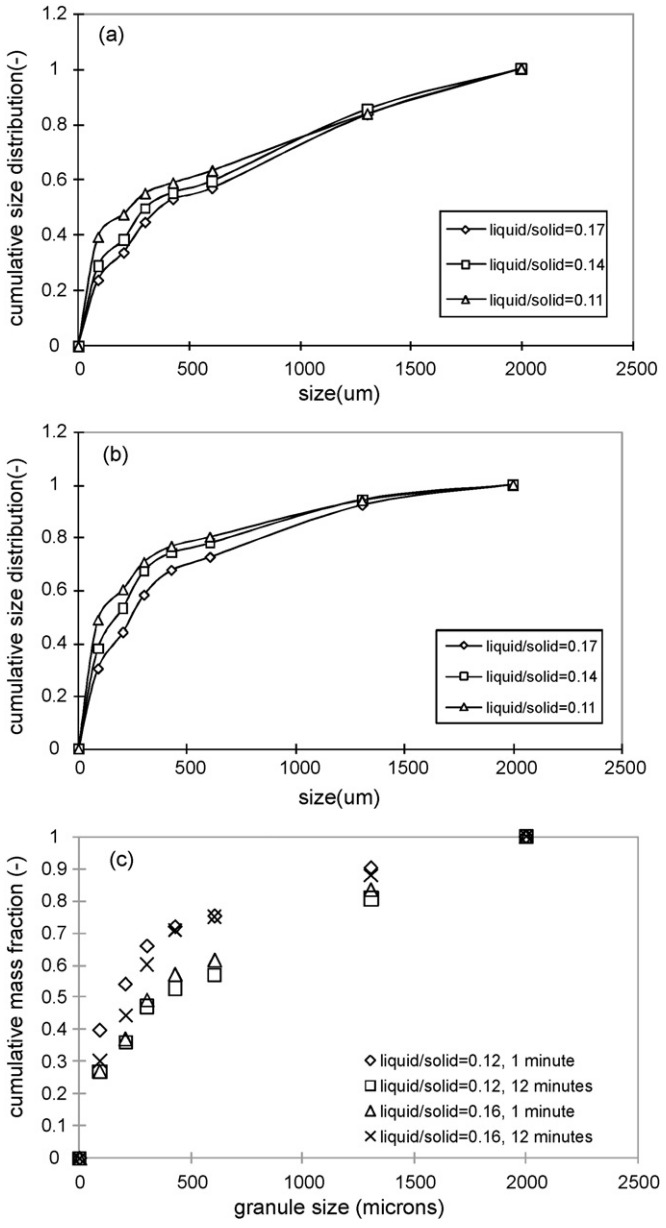

Fig. 4. Effect of binder–powder ratio: (a) $t = 1$ min; (b) $t = 12$ min; (c) effect of liquid–solid ratio on low shear granulation (experimental runs 14 and 15).

the strength of agglomerates and breakage [16]. These contradictory influences have been highlighted in a recent study on wet granulation phramaceutical systems, whereby granules produced using low viscosity binders (<1 Pa s) showed incraesed breakage; granule breakage decreased with higher viscosity binders (>1 Pa s); and granulation proved limited for very high viscosity binders (viscosity > 30 Pa s) due to poor binder distribution [10]. Another stufyindicated that low liquid viscosity favours the achievement of high liquid transfer coefficient and a greater extent of granulation [11]. The phenomena of increaesed granule with binder viscosity are also evident in this present study illustrated by the high response to the variable in the factorial design.

The liquid to solid ratio (L/S) X_4 was also found, as expected, to be highly signifcant; indeed several authors have shown this to be the most important variable in wet granulation systems. A recent study on the granulation of pharmaceutical excipients concluded that the effect of L/S ratio is of paramount importance and usually determines the growth behaviour [8].

The coefficents in Table 4 indicate that the impeller speed, X_1, has the lease influence of the four major variables investigated. As with binder viscosity, impeller speed can increase both granule growth [11] and breakage [17,18] depending on the mecahnical properties of the agglomerates. A recent study on wet granulation has shown that the effect of impeller speed is influenced by the L/S ratio [8], this is also found in this present study with coefficents for this combination of variables (L/S and impleller speed), X_1X_4, demonstrating higher variance than combinations of other varaibles.

The effect of starch–lactose ratio, X_2, also shows a moderate variance in this system, with formulations containing higher startch–lactose ratios demonstrating a higher extetnt of granulation. These surface wetting interations are again complex with nucleation and subsequent granule growth dependent upon the liquid–solid contact angle, powder particle size and binder surface tension and viscosity. These relationships are commonly described

Table 4
Model of coded variables for granulation.

Coefficient (12 min)	Coefficient (1 min)	Variable
598.124	868.9	Intercept
−43.8368	−34.0916	X_1
−47.2095	−48.6816	X_2
93.889	83.7947	X_3
49.9857	52.4816	X_4
41.6936	−1.09961	X_1^2
−23.7512	2.27641	X_2^2
104.538	51.2662	X_3^2
−29.2779	−4.77572	X_4^2
−10.9875	−3.43125	X_1X_2
5.4625	2.28125	X_1X_3
15.1125	−8.96875	X_1X_4
40.6875	19.4437	X_2X_3
−19.9375	−26.2313	X_2X_4
−9.1875	14.3812	X_3X_4

X_1 = impeller speed; X_2 = starch–lactose ratio; X_3 = CMC–water ratio; X_4 = liquid–solid ratio.

by the Washburn equation [19]:

$$l = \sqrt{\frac{Kt\gamma_{L/V}\cos\theta}{2\mu}} \quad (3)$$

where t = wetting time (s); l = capillary length (m); $\gamma_{L/V}$ = interfacial free energy at the liquid–vapour interface (N m^{-1}); θ = the angle created between the liquid, vapour and solid interface (°); K = a size factor which accounts for the complex path formed by the channels between particles (m); μ = viscosity of the liquid (Pa s).

In the present experimental system, the lactose particles are more hydrophilic than lactose which would tend to increase wetting and nucleation. However, the over-riding factor in the surface wetting of this particular system would be the particle size of the powder, i.e., formulations with a higher starch content would have a lower particle size (thus an increase in K from Eq. (3)), which should in turn promote, increased capillary action, wetting, nucleation and growth. These phenomena were also reported in recent study on the granulation of phramaceutical powders where controlled growth was found to be highest in readily wettable APIs (powders) [12].

3.7. Pharmaceutical analysis

The aim of this section is identify and analyse effects of process parameters from the granulation step on subsequent tablet pressing. Analysis of the tables was all undertaken at least 24 h after compression to allow elastic recovery.

Process parameters of each tablet pressing formulation are detailed in Table 5. However, during tablet pressing process, granules of Exp. 4 and Exp. 7 were quite difficult to tablet. This was due to: the high hydrophilicity of granules from Exp. 4; and of excessive binder content for Exp. 7, making them too adhesive for flow in the hopper prior to being pressed.

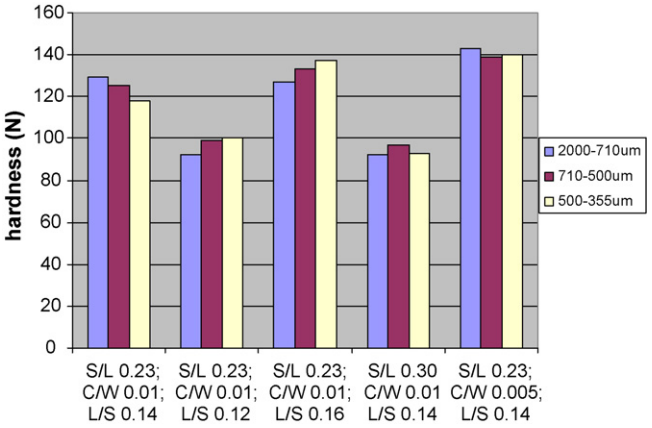

Fig. 5. Tablet hardness under various process parameters and granule size.

Fig. 5 illustrates the effect of variation in process parameters and granule size on tablet hardness. The data indicate that tablet hardness largely independent of granule size. In terms of process parameters, an increase in liquid–solid ratio from 0.12 to 0.14 to 0.16 resulted in an increase in tablet hardness of approximately 35%. This may be attributed to stronger liquid bridges and capillary adhesion between granules. However, an increase in starch–lactose ratio from 0.23 to 0.30 decreased tablet hardness by approximately 21% which may be due to a decrease in hydrophilicity within the formulation. Increases in CMC–water ratio from 0.005 to 0.010 resulting in a viscosity increase from 8 to 60 cPs decreased tablet hardness by approximately 12%. For lower viscosity binder this may be attributed to more liquid expelled to granule surface under pressure in the tablet press and thus more capillary adhesion between granules.

Fig. 6 illustrates the effect of variation in process parameters and granule size on tablet disintegration time. In general more rapid disintegration was found with larger granule sizes, which may be attributed to decreased tablet density found using larger granules. The data also indicate that an increase in liquid–solid ratio from 0.12 (and 0.14) to 0.16 increases the disintegration time by approximately 13%, this correlates with the significant increase in tablet hardness found with increase in liquid–solid ratio with harder tablets requiring longer time to disintegrate. The data indicate that increase in starch–lactose ratio from 0.23 to 0.30 increases the disintegration time by approximately 15%. Furthermore, increases in CMC–water ratio from 0.005 to 0.010 decreases disintegration time (≈15%), which again correlates with the increase in tablet hardness found with lower viscosity binders.

Fig. 7 illustrates the relationship between tablet hardness and disintegration time for the variables under investigation. From this analysis a number of conclusions regarding the effect of formulation variables can be drawn: (i) the tablets with the high

Table 5
Tablet pressing formulations.

Process parameters/formulation No.	Impeller speed (rpm)	Starch–lactose	CMC–water (%)	Liquid–solid
1	200	0.23	1	0.14
2	200	0.23	1	0.12
3	200	0.23	1	0.16
4[a]	200	0.16	1	0.14
5	200	0.30	1	0.14
6	200	0.23	0.5	0.14
7[a]	200	0.23	1.5	0.14

[a] Tablets not able to be produced.

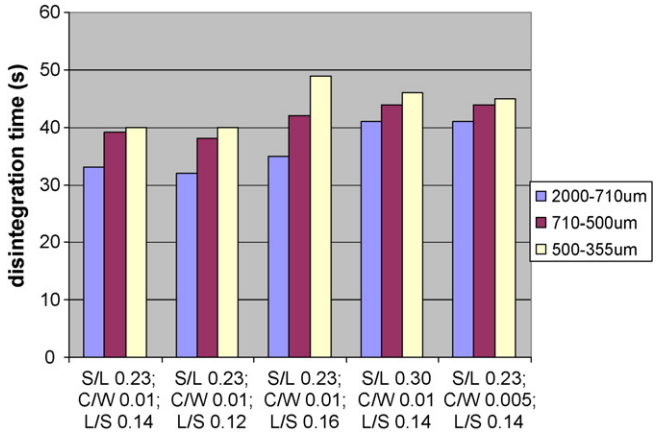

Fig. 6. Tablet disintegration time under various process parameters and granule size.

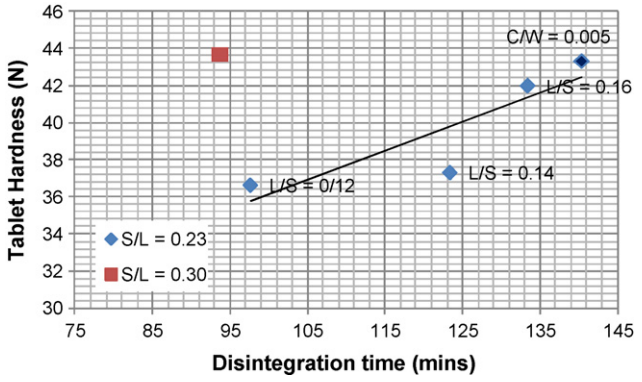

Fig. 7. Tablet hardness versus disintegration time (based on mean from three particle sizes): liquid–solid, L/S ratio = 0.14 unless stated; CMC–water C/W ratio = 0.01 unless stated.

starch–lactose ratio disintegrated more rapidly due to the increased hydrophilic content, rather than any reduction in tablet hardness; (ii) the three batches of tablets with constant L/S and C/W ratios increased in tablet hardness and disintegration time with increase in liquid–solid, L/S ratio; (iii) the tablets with the low CMC–water ratio (C/W = 0.005) followed the same trend (i.e., increasing disintegration time with tablet hardness), however, further tablet hardness and associated disintegration time was induced due to the low CMC–water ratio (i.e., a low viscosity binder in the granulation process).

4. Conclusions

Four parameters: binder viscosity; binder content; ratio of starch to lactose; and shear rate, were investigated at granulation times of 1 and 12 min. The data indicated that increased mass mean diameter and was found using higher viscosity binders. However, increasing the impeller speed also resulted in increased mass mean diameters suggesting, which may suggest that granule breakage does not have a significant influence on this particular low shear agglomeration process. Overall, from the tablet analysis, the data indicate that disintegration time increases with decreasing of size of granules. This phenomenon is consistent with previous work which indicated, that for a given compaction pressure, smaller sized granules increase the relative density and thus increase fracture stress of the tablet [16].

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