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Scale-up of a pharmaceutical granulation in fixed bowl mixer-granulators

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Abstract

Scale-up in fixed bowl mixer-granulators has been studied by applying the classical dimensionless numbers of Power, Reynolds and Froude to end-point prediction in a range of geometrically similar machines. The simple relationship of Power number/Reynolds number, as suggested by previous workers, has been found to be inappropriate for large-scale production machines where corrections have to be made for gross vortexing and powder bed height variation by the incorporation of the Froude number and a scaling factor. When corrections are made, data from 25-, 100- and 600-l machines all fall on the same curve allowing predictions of optimum granulation end-point conditions to be made for production-scale equipment from measurements on laboratory-scale equipment and vice-versa.

Keywords: Granulation; Mixer granulators; Scale-up

1. Introduction

Fixed bowl mixer granulators in which the mixing, densification and agglomeration of wetted materials are achieved through shearing and compaction forces exerted by a vertical impeller rotating at the bottom of the powder bed coupled with the cutting action exerted by a high speed chopper, are widely used in pharmaceutical granulation (Timko et al., 1990). Scale-up of formulations in this type of granulator poses many problems not least in attempting to keep the intragranular porosity and binder homogeneity constant (Schaefer, 1988) resulting, in some cases, in a high risk of overmassing due to short processing times. Whilst in-process monitoring of the load on the impeller has been used as a method of control, this technique suffers from the many factors which affect power-time profiles. Additionally laboratory end-point values are not easily transferred to the production scale.

Cliff and Parker (1990) have suggested an approach based on classical dimensionless power number/Reynolds number relationships used in liquid mixing systems for predicting the behaviour of plant-scale equipment from information generated from laboratory-scale apparatus. In their work, the fluid viscosity term required to quantify

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Reynolds number was taken from the torque value determined on a mixer torque rheometer (Rowe and Sadeghnejad, 1987) since this value has been shown to correlate directly with viscosity measured under controlled conditions of shear (Parker and Rowe, 1989). Results showed that the graphical relationship between Power number and Reynolds number obeyed a logarithmic relationship independent of the two mixers used. In this way a reference or master curve could be used to consider scale-up factors and define optimal end-point conditions on different scales on mixer granulators. This work extends the original work of Cliff and Parker (1990) to larger scale equipment.

2. Theoretical background

For an agitated mixer containing a liquid of density, ρ (kg/m^3) and viscosity, η (Pas), driven by an impeller of diameter, D (m), rotating at a speed of N (rev./s), three dimensionless numbers can be defined (McCabe et al., 1993):

(1) The Power number, N_P, which relates the drag force acting on a unit area of the impeller and the inertial stress and is given by:-

$$N_P = \frac{Pg}{\rho N^3 D^5} \tag{1}$$

where P is the power of the impeller motor (W) and g is the gravitational constant (ms^{-2}).

(2) The Reynolds number, N_{Re}, which relates the inertial force to the viscous force and is given by:-

$$N_{Re} = \frac{D^2 N \rho}{\eta} \tag{2}$$

(3) The Froude number, N_{Fr}, which relates the inertial stress to the gravitational force per unit area acting on the material. This is important in situations where there is gross vortexing or a significant wave motion on the surface of the material and is given by:-

$$N_{Fr} = \frac{N^2 D}{g} \tag{3}$$

For systems where there is geometrical similarity, i.e. all dimensions will have the same ratio, kinematic similarity where velocities at certain points will have the same ratio as those at other corresponding points and dynamic similarity where the ratios of the forces at certain points will be equal to those at other corresponding points:-

$$N_P = fn\,[N_{Re} \cdot N_{Fr}] \tag{4}$$

For systems where there is partial geometrical similarity, i.e. not all dimensions have the same ratio, shape factors, S, made dimensionless by dividing by the diameter of the impeller may be included. In these cases Eq. (4) needs to be modified to:-

$$N_P = fn[N_{Re}.N_{Fr}.S_1.S_2....] \tag{5}$$

It is interesting to note that this equation is not only applicable to Newtonian liquids but also to non-Newtonian liquids using an average apparent viscosity, η_a, calculated at an average shear rate (McCabe et al., 1993).

In previous work Cliff and Parker (1990) assumed geometrical similarity between a 25-l Diosna Pharma mixer and a 100-l Fielder PMA mixer and found a relationship for a pharmaceutical granulation independent of the mixer of the form:-

$$N_P \propto [N_{Re}]^{-2} \tag{6}$$

where the viscosity of the wet granulation was given by a torque value determined on a mixer torque rheometer (η^1), the density of the mix was given by the measured bulk density of the mix, (ρ^1) and the power was the differential power (i.e. the measured power of a specific mix less the power for the dry powder mix) ΔP. The work can be criticised on several counts (Kaminsky, 1994).

(a) The use of η^1 to define the viscosity term for the Reynolds number causes the latter not to be dimensionless. Recent work, however, has shown that η^1 is directly proportional to the kinematic viscosity of a wet mass (Landin et al., 1995) but the relationship between η^1 and η will vary with the formulation under test.

(b) Cliff and Parker (1990) did not make any corrections for the vortexing that occurs in such mixers and the variation in height of the mix as densification occurs on the addition of binder, i.e. they should have used Eq. (5) with a correction for the height of the bed of the form h/D.

(c) A solution of Eq. (6) shows that:-

$$\Delta P \propto \frac{(\eta^1)^2 ND}{\rho^1} \quad (7)$$

i.e. the differential power is proportional to the square of the viscosity (flow resistance) and inversely related to the bulk density but not a function of mixer volume (i.e. the exponent for D is less than 3). Intuitively this is contrary to physical laws, not only because of the bulk density term (for flow dominated by inertial forces the energy required is always proportional to the density of the material being moved) but also because of the lack of the volume term. This would imply that the relationship is unlikely to apply for large volume mixers even for comparable bulk densities.

The consequences of this theoretical analysis will be evaluated in this work using the same definitions for η^1, ρ^1 and ΔP as used by Cliff and Parker (1990).

3. Experimental

Three sizes of fixed bowl mixer granulators (Fielder PMA — Aeromatic Fielder Ltd) of nominal volumes 25, 100 and 600 l were used in this study. All were geometrically similar in all dimensions and while the 100- and 600-l machines have variable speed motors on both the impeller and chopper, the 25-l machine had two fixed speeds. Table 1 shows the impeller speeds used for each machine. In all cases the chopper speed was kept constant at 1500 rev./min.

A fixed formulation consisting of lactose (450 mesh, DMV International) 80% w/w, maize starch (National Starch and Chemical Co. Ltd.) 18% w/w and pregelled starch (National Starch and Chemical Co. Ltd.) 2% w/w was used with batch sizes in proportion to the volume of the mixer (Table 1). After the materials had been dry mixed for 2 min, the impeller power was noted and water was then sprayed on at a constant rate. Samples of wet mass were taken at specific times equivalent to different end points as given by the load on the impeller motor. The differential power ΔP was calculated for each sample. Due to the size of the bowl of the PMA 25 it was not possible to take multiple samples from a single mix and hence it was necessary to perform multiple experiments.

Table 1
Batch sizes and impeller speeds used in study

Mixer	Batch size	Impeller speeds (rev./min)		
	(kg)	Low	Medium	High
PMA 25L	7.5	287	—	572
PMA 100L	30.0	158	225	310
PMA 600L	180.0	74	—	173

The poured bulk density of the wet mass was determined as described by Cliff and Parker (1990) by weighing a loosely filled glass container of known volume.

The consistency (viscosity η^1) of the wet mass was measured using a mixer torque rheometer (Caleva MTR, Sturminster Newton) similar to that described in detail by Parker et al. (1990). The instrument was initially run empty at 52 rev./min for 20 s in order to generate a baseline torque value; 30 g of the sample of wet mass was then added and the instrument allowed to run for 30 s before initiating the data capture process (30 s). Each result was the mean of at least two measurements.

4. Results and discussion

Specimen results for both the 25- and 600-l mixers are shown in Table 2. It is interesting to note that the height of the powder bed during granulation in the 600-l mixer is approximately three times that in the 25-l mixer for comparable bulk densities. In addition it can be seen that ΔP is inversely related to the height of the powder bed, h, since this, in turn, is inversely proportional to the bulk density (ρ^1).

Power number/Reynolds number curves for all three mixers are shown in Fig. 1. Although the curves for the 25- and 100-l machines are superimposed, that for the 600-l machine is quite different with higher Reynolds numbers for the same Power numbers. Plotted on a log/log scale (Fig. 2) results in straight lines with high correlation coefficients (0.8662–0.9679). The lowest correlation

Table 2
Specimen results for the 25-l and 600-l mixer granulators with impellers rotating at 572 and 74 rev./min, respectively

D (m)	N (rev./s)	% Liquid	ΔP (W)	ρ^1 (kg/m^3)	η^1 (Nm)	h (m)
0.404	9.53	7.5	187	434	0.070	0.12
0.404	9.53	9.5	995	448	0.101	0.11
0.404	9.53	13.6	2100	525	0.107	0.10
0.404	9.53	17.4	2350	649	0.156	0.08
1.18	1.23	9.92	2100	460	0.103	0.38
1.18	1.23	14.88	2400	478	0.136	0.38
1.18	1.23	19.83	3400	546	0.152	0.35
1.18	1.23	24.79	4800	670	0.161	0.29
1.18	1.23	27.69	6500	747	0.261	0.27

coefficient (0.8662) for the 25-l machine can be attributed to the experimental procedure since, for this machine, every point was obtained from a different batch.

The slopes of the lines are approximately -2 (range 1.83–2.11) agreeing with those found by Cliff and Parker (1990) implying that the rate of change in the rheological behaviour of the wet mass with power input is similar for all machines. However, the different intercepts indicate that the effects of inertial and/or gravitational forces are not the same for all machines and need to be corrected for.

Power number curves plotted using Eq. (5) correcting for the changes in the height of the powder bed during granulation by the inclusion of the h/D term are shown in Fig. 3. Now the curves for all three machines are superimposed. Plotted on a log/log scale (Fig. 4) again results in straight lines with high correlation coefficients although, in this case, slightly lower than those in Fig. 2. This is due to the errors in the calculation of height of the powder bed from bulk density measurements. However, all three lines have similar intercepts and similar gradients (0.7–0.8). A graph for all the data points for all the machines is shown in Fig. 5 with regression analysis yielding an equation of the form:-

$$N_P = 7.96 \times 10^2 [N_{Re}.N_{Fr}.h/D]^{-0.732} \quad (8)$$

with a correlation coefficient of 0.7854 $n = 39$.

This relationship, implying an independence of the scale of mixer granulator used, can thus be used for predicting optimum end-point conditions on production-scale equipment. It must be re-

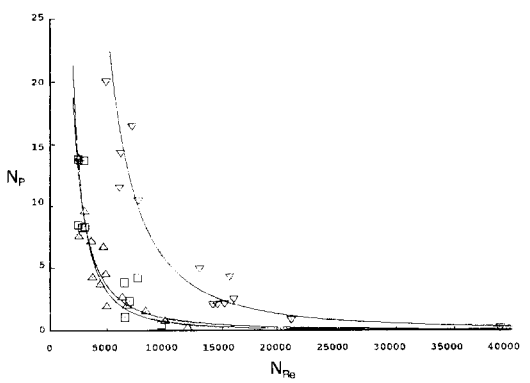

Fig. 1. Power number/Reynolds number curves for the PMA 25 (□), PMA 100 (△) and PMA 600 (▽) mixers.

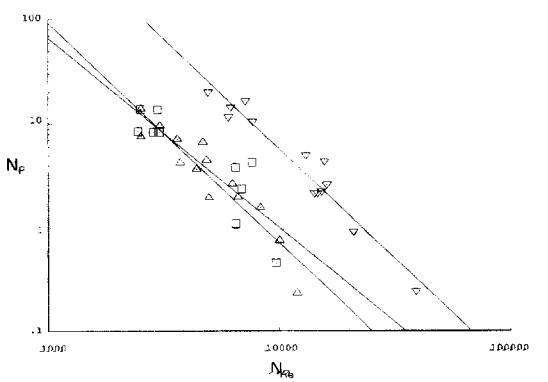

Fig. 2. Log. Power number/Log. Reynolds number relationships for the PMA 25 (□), PMA 100 (△) and PMA 600 (▽) mixers.

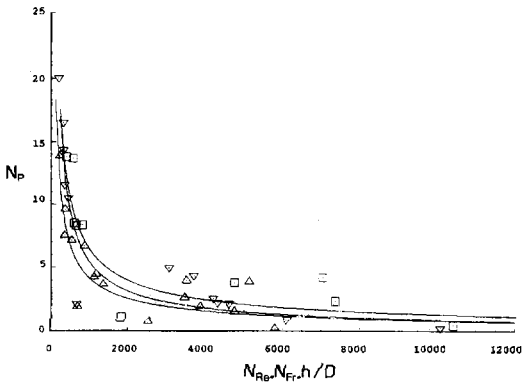

Fig. 3. Power number curves for the PMA 25 (□), PMA 100 (△), and PMA 600 (▽) mixers.

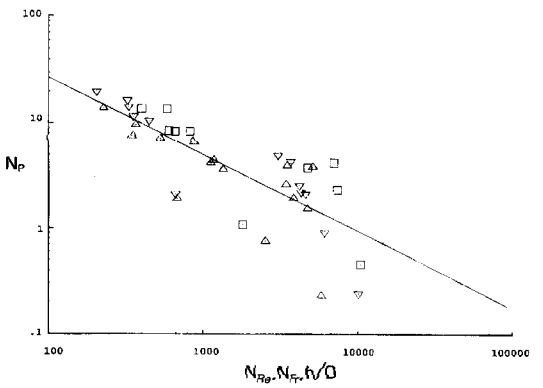

Fig. 5. Log. Power number relationship for all mixers.

alised, as demonstrated previously by Cliff and Parker (1990) that the numerical relationship given in Eq. (8) will be different for each formulation due to the fact that the relationship between the torque value measured by the mixer torque rheometer η^1, and the viscosity term, η, will be different. In addition the relationship given in Eq. (8) does not include any information on the relative rates of achieving the desired granulation end-points only the differential power on the impeller.

The universality of the concept of using dimensionless numbers to predict scale-up parameters for all types/designs of mixers used in pharmaceutical wet granulation will need to be evaluated. However, the results presented here would suggest that such an approach is viable especially where the wet mass is being mixed in such a high state of turbulence and behaving more like a concentrated suspension rather than a solid.

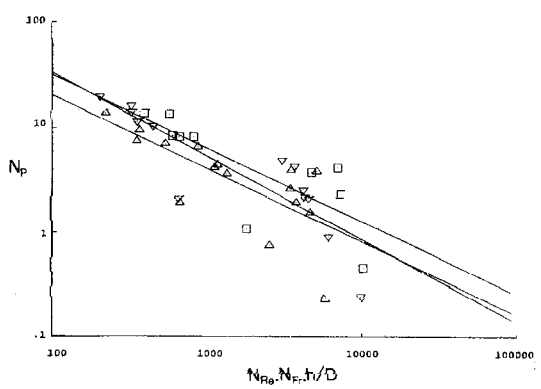

Fig. 4. Log. Power number relationships for the PMA 25 (□), PMA 100 (△), and PMA 600 (▽) mixers.

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