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The effect of batch size on scale-up of a pharmaceutical granulation in a fixed bowl mixer granulator

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Abstract

The effect of two batch sizes of a pharmaceutical granulation processed in a fixed bowl mixer granulator has been evaluated using the classical dimensionless numbers, Power, Reynolds and Froude recently shown to apply to this type of mixer. Despite a correction for the differences in the heights of the powder bed the relationships were significantly different. This is thought to be due to the differences in the downward force acting on the impeller as a result of the changes in flow pattern as the powder bed contacts the sloping sides at the top of the mixer.

Keywords: Granulation; Mixer granulators; Scale-up; Batch size

1. Introduction

Fixed bowl mixer granulators in which the mixing, densification and agglomeration of wetted materials are achieved through shearing and compact ion forces exerted by a vertical impeller rotating at the bottom of a powder bed coupled with the cutting action exerted by a high speed chopper, are widely used in pharmaceutical granulation (Timko et al., 1990). In a recent paper Landin et al. (1996) have studied scale-up in these machines using the classical dimensionless numbers of Power (N_p), Reynolds (N_{Re}), and Froude (N_{Fr}) to predict granulation end point i.e. they found a relationship of the form:

$$N_p \propto \frac{1}{N_{Re} \cdot N_{Fr} \cdot h/D}$$

where

$$N_p = \frac{\Delta Pg}{\rho^1 N^3 D^5}$$

and

$$N_{Re} = \frac{D^2 N \rho^1}{\eta^1}$$

and

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Table 1
Specimen results on the two batch sizes processed at the fastest speed of 400 rev./min

Batch size kg	% Liquid added	ΔP(W)	ρ^1 (kg m^3)	η^1 (Nm)	h(m)
14.1	8.30	542.5	446	0.083	0.16
14.1	12.45	1372.5	448	0.126	0.15
14.1	16.60	2374.5	566	0.133	0.13
14.1	20.06	3105.0	664	0.170	0.11
19.5	9.30	810.0	454	0.090	0.21
19.5	13.90	2242.5	444	0.120	0.23
19.5	18.60	4357.5	570	0.138	0.18
19.5	21.70	5347.5	643	0.177	0.17

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

where

ΔP is the differential power (W) of the impeller motor (i.e. the total power less the power with a dry powder mix)

g is the gravitational constant (ms^{-2})

ρ^1 is the bulk density of the wet mass (kg/m^3)

N is the rotational speed of the impeller (rev./s)

h is the height of the powder bed (m)

η^1 is the consistency (viscosity) of the wet mass measured using a mixer torque rheometer (Nm).

The authors found a correlation independent of the size of mixer over the range 25–600 l. In order to maintain geometrical similarity (a necessary condition for the approach used) batch size in each mixer was kept in proportion to its volume and was not varied. The effect of this important variable is analyzed in this communication.

2. Methods

All work was carried out on a Fielder PMA 65 l mixer (Aeromatic-Fielder Ltd.). This has a power cell fitted to the AC motor driving the impeller allowing easy measurement of the power. The machine was run at three impeller speeds 200, 300 and 400 rev./min with two batch sizes of 14.1 kg and 19.5 kg. The chopper speed was kept constant at 1500 rev./min.

The formulation consisting of lactose (450 mesh, D.M.V.), 80% w/w, maize starch (National Starch and Chemical Co.) 18% and pregelled starch (National Starch and Chemical Co.) 2% w/w was dry mixed for 2 min after which water was sprayed on at a constant rate. Samples were collected every 3 min without stopping the experiment. The poured bulk density of the wet mass was determined by weighing a loosely filled glass container of known volume as described previously (Cliff and Parker, 1990; Landin et al., 1996). The consistency (viscosity) of the wet mass was determined 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 to generate a baseline torque value. 30 g of the sample was then added and the instrument allowed to run for 30 s before initiating the data capture process for 30 s. All reported values are an average of two measurements.

3. Results

Representative data on the two batch sizes processed at the fastest speed are shown in Table 1. Similar trends were shown at all other speeds.

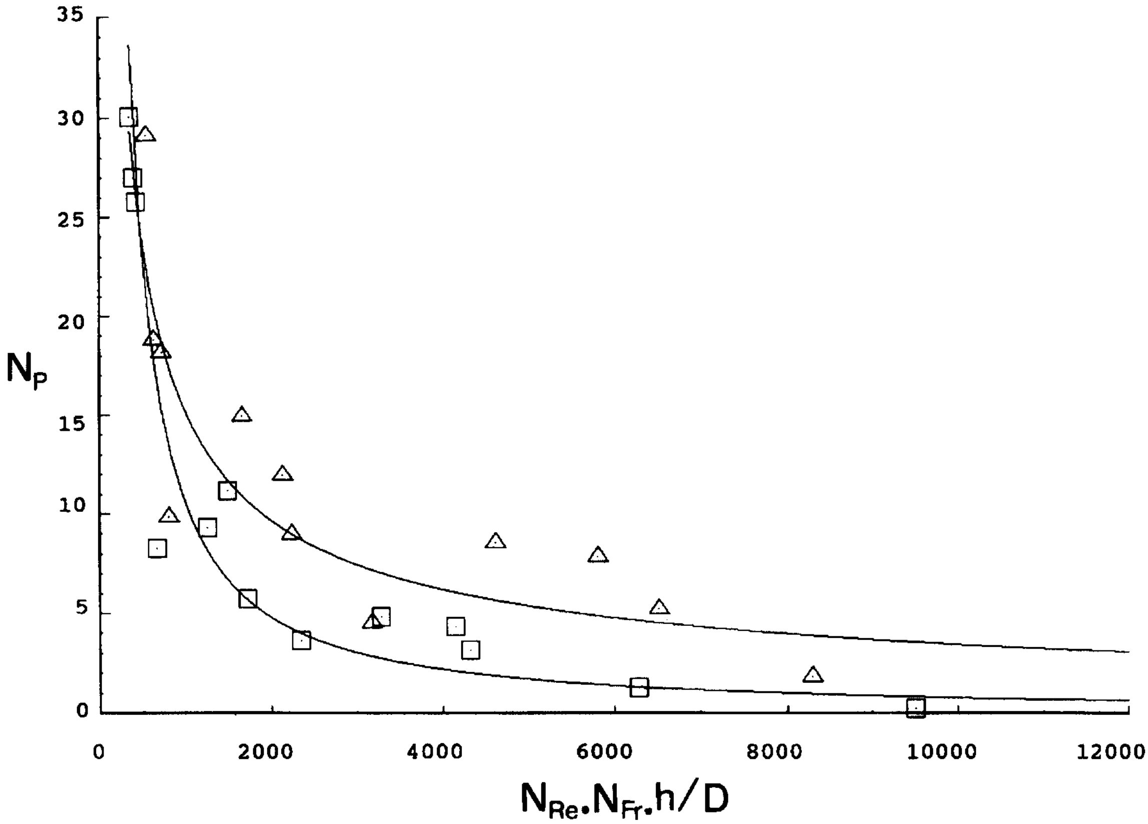

Fig. 1. Power number curves for the PMA 65 with batch sizes of 14.1 kg (□) and 19.5 kg (△).

Power correlations for the two are shown in Figs. 1 and 2. Statistical analysis of the data yields the following correlations:

for the 14.1 kg batch size:

$$N_p = 2.70 \times 10^4[N_{Re} \cdot N_{Fr} \cdot h/D]^{-1.14}$$

$r = 0.9152$ $n = 13$

for the 19.5 kg batch size:

$$N_p = 1.32 \times 10^3[N_{Re} \cdot N_{Fr} \cdot h/D]^{-0.65}$$

$r = 0.8432$ $n = 12$.

It can be seen that the two curves are not superimposed and that for the larger batch size more power is needed despite the fact that the differences in the mass and hence the height of the powder bed has been corrected for in the h/D ratio. This is thought to be due to the overall shape of the mixer which is parallel sided only to a height of 0.183 m at which point the sides slope inwards at a 60° angle. For all mixes involving the 14.1 kg batch size the height of the powder bed never exceeds 0.16 m while for the 19.6 kg load the height varies between 0.23 and 0.15 m with the lowest heights only being achieved with high water contents and high power numbers. For all mixes with bed heights in excess of 0.18 m there will be an increased downward force on the impeller due to more of the wet mass contacting the sloping sides resulting in an increased power requirement. In these cases the concept of geometric similarity is not applicable and hence the two curves for the two batch sizes are not superimposed.

It is important, therefore, when undertaking scale-up experiments in these type of mixers, to maintain geometric similarity of the powder bed by keeping the batch size in proportion to the overall shape of the mixer especially relative to the height of the parallel side.

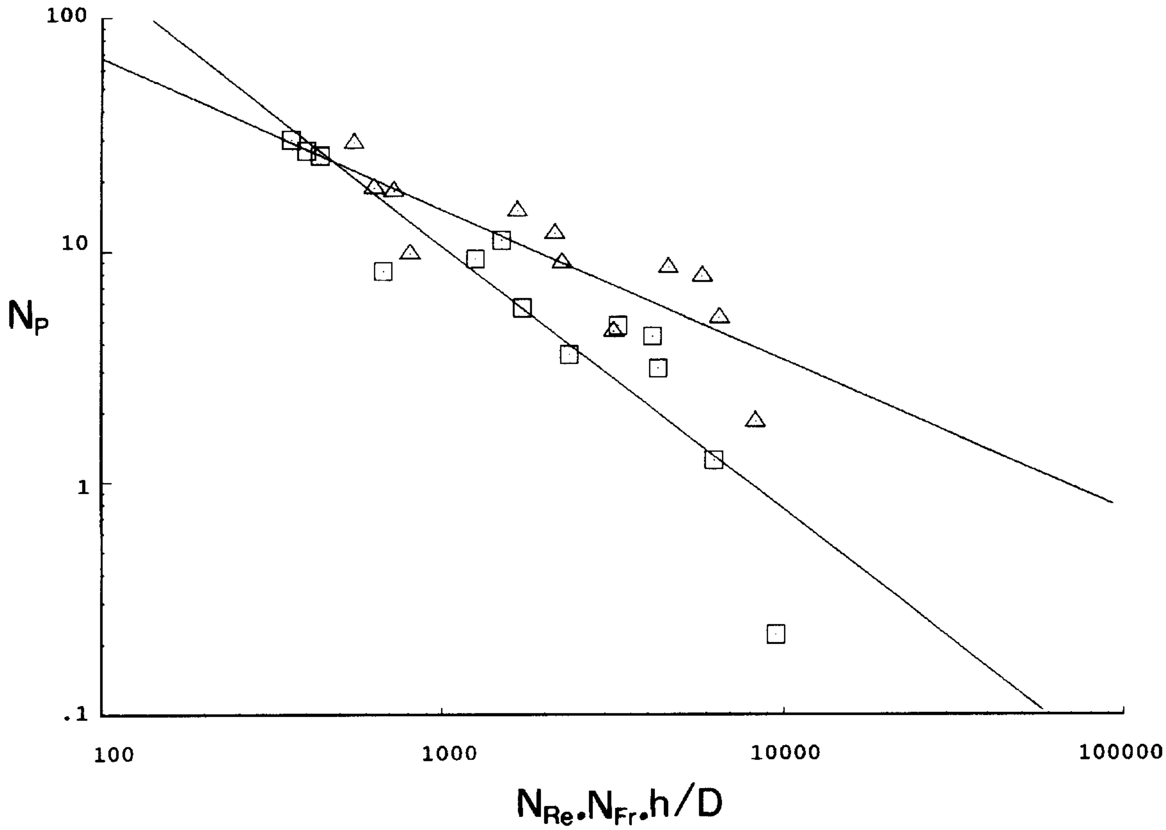

Fig. 2. Log Power number relationships for the PMA 65 with batch sizes of 14.1 kg (□) and 19.5 kg (△).

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