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Letter to the Editor

Importance of Wet Mass Consistency in the Control of Wet Granulation by Mechanical Agitation: a Demonstration

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The technique of mixer-torque rheometry has been developed and used for several years to study the rheological behaviour of wet masses (Parker et al 1990a, b; Hancock et al 1992; Landin et al 1995). It has also been proposed that the wet mass consistency measured is a key parameter that can be used to scale-up wet granulation processes in pharmaceutical mixer–granulators (Cliff & Parker 1990; Rowe & Parker 1994; Landin et al 1996; Faure et al 1998).

To demonstrate that controlling the wet mass consistency enables the reproduction of the same quality of dry granules, two batches produced under completely different conditions but to similar levels of consistency were compared in terms of their downstream dry-granule properties. Batch 1 was produced in a pilot-scale high-shear mixer–granulator (Aeromatic Fielder PMA 100 L, Eastleigh, Hampshire, UK), whereas batch 2 was manufactured in a laboratory scale planetary mixer (Hobart AE240; The Hobart Manufacturing Co. Ltd, London, UK). The formulation was fixed at 55% w/w 450 mesh lactose (DMV International, Veghel, The Netherlands), 25% w/w microcrystalline cellulose (Avicel PH101, FMC, Cork, Ireland), 18% maize starch (National Starch and Chemical, Neustadt, Germany) and 2% w/w pregelatinized starch (National Starch and Chemical). Table 1 lists the conditions used for manufacture in both mixers, the levels of wet-mass consistency achieved by the two wet masses, and the properties of the downstream granules, produced and analysed as described below. The granule size distributions are also reported in Figure 1.

The consistency was determined by use of a mixer-torque rheometer (Caleva MTR, Sturminster-Newton, Dorset, UK) as previously described by Rowe & Parker (1994), run at a shaft speed of 50 rev min^{-1}. A baseline was recorded for 20 s, then wet sample (35 g) was introduced and mixed for 30 s, after which data were recorded for 30 s. The wet mass consistency of the sample was calculated as the mean torque value recorded with the sample in the mixer, less the mean torque value of the baseline recording.

Dry granules were obtained by identically processing the wet masses (approximately 1 kg each) which were wet-screened and then tray-dried at 40°C for 24 h. The fractions under 850 μm were analysed for size-distribution (by sieve analysis), apparent bulk density (aerated and tapped, to derive their Hausner ratio), flow (by use of an Aero-Flow; Amherst Process Instruments, Hadley, MA) based on an avalanching principle (Kaye & Gratton-Liimatainen 1995) and friability index (using a modified test-procedure in a Roche tablet friability-test apparatus). The densities were determined in a tapping apparatus similar to that described in the European Pharmacopoeia (second edition, V.5.5.4.). The Aero-Flow measures the time intervals between avalanches generated within a granule sample placed in the slow rotating drum of the apparatus. Compilation of the frequency and irregularity of these time intervals is then used to describe the flow behaviour of the sample. In the friability test, the Roche tablet friabilator was run for 5 min at 90 rev min^{-1} with a granular sample of 10 g and five small glass balls. The friability index was taken as 100 − x (%) where x is the percentage of the original sample fraction, 250–600 μm, retained by a 250-μm sieve after testing. Mechanically stronger granules have a lower friability index.

There were no differences between the characteristics of the two batches of granules that would

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Table 1. Comparison of batches of similar wet-mass characteristics but produced in different mixer–granulators.

		Batch 1	Batch 2
Conditions of manufacture	Mixer	High-shear mixer (Fielder PMA) 100 L bowl	Planetary mixer (Hobart AE240) 5 L bowl
	Batch size	27·4 kg	0·75 kg
	Moisture content*	47·5% w/w	47% w/w
	Speed setting	200 rev min^{-1}	300 rev min^{-1}†
Wet-mass characteristics (s.d.)		$\rho = 572\,kg\,m^{-3}$ $\mu = 0{\cdot}288 \pm 0{\cdot}026\,N\,m$	$\rho = 567 \pm 6\,kg\,m^{-3}$ $\mu = 0{\cdot}297 \pm 0{\cdot}010\,N\,m$
Granule size distribution <850 μm fraction	d_{25} (μm)	244	292
	d_{50} (μm)	370	424
	d_{75} (μm)	575	598
Bulk density <850 μm fraction	ρ aerated ($kg\,m^{-3}$)	455	476
	ρ tapped ($kg\,m^{-3}$)	559	597
	Hausner ratio	1·23	1·25
Flow behaviour <600 μm fraction	Strange attractor (s)	2·0	2·0
	Irregularity factor (s)	0·42	0·21
Friability index 250–600 μm fraction	Friability index (% ± s.d.)	16·7 ± 0·1	14·3 ± 0·8

*In percent water weight/weight of dry powder. † Blade rotational speed (not carousel speed).

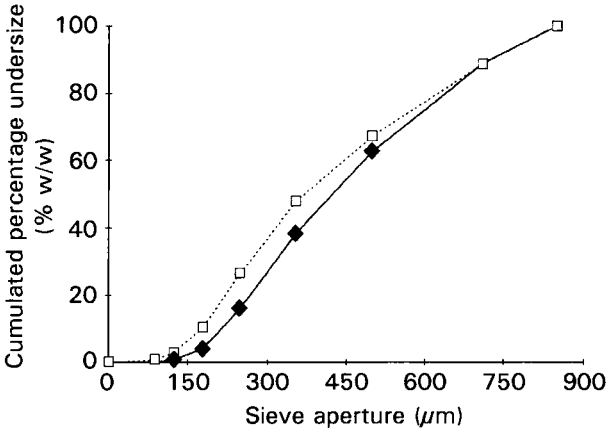

Figure 1. The granule-size distributions of batches 1 (◆) and 2 (□) produced from wet masses of identical dry composition and granulated to the same level of wet-mass consistency.

lead to variations in the quality of the tablets. These results therefore show that when wet-mass consistency is controlled, so is dry-granule quality. The conditions of manufacture of the intermediary wet mass are no longer relevant. The choice of granulation equipment and conditions of use remain crucial, of course, in determining what levels of wet-mass consistency can be achieved. In this example the Hobart planetary, i.e. low shear, mixer was used under extreme conditions (highest motor speed, reduced batch size) to achieve the same level of granulation as in the high-shear mixer.

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