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Granulation monitoring in a high speed mixer/processor using a probe vibration analysis technique

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Granulations were prepared using the following formulation: maize starch 420 g; α-lactose monohydrate 3600 g; pre-gelatinized starch (Amigel), 300 g and water, approx. 700 ml according to experiment.

Granulation was carried out following pre-mixing of all constituent powders in the high speed mixer/granulator (type PMAV 25/2G, T.K. Fielder, Chandlers Ford, Hants, U.K.). A specially-constructed probe assembly was used and housed an accelerometer behind a target plate as shown in Fig. 1. The target used in most of the experiments reported here was a slightly concave plate attached to the accelerometer which was held in a rigid perspex mounting and allowed both the position and orientation of the probe target to be adjusted. In some experiments, the probe assembly was changed and used a shallow cone

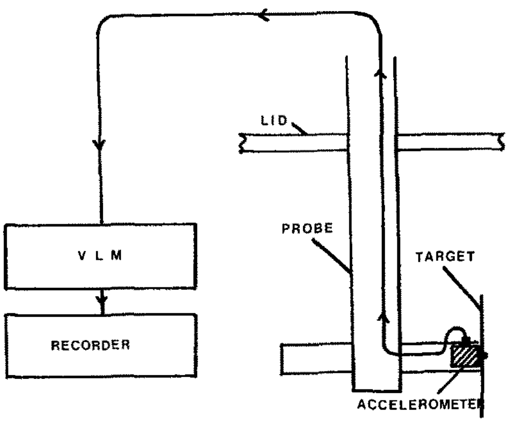

Fig. 1. Schematic diagram of probe assembly and vibration monitoring system.

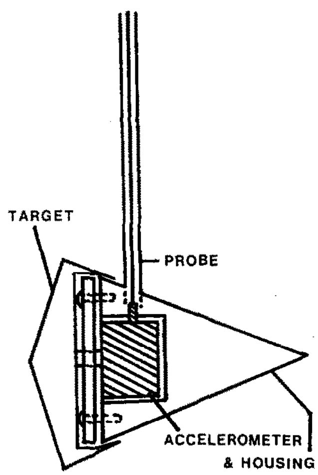

Fig. 2. Diagram of self-cleaning probe and target assembly.

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constructed in Dural as a self-cleaning target. The accelerometer housing was also made conical, to prevent build-up of powder or granular material (Fig. 2). In both designs, the probes were held rigidly to the lid of the mixer/granulator and the connecting cable taken out through the fluid addition port.

Initial experiments were carried out in order to obtain an approximate relationship between vibration signals and granulation conditions. In all the work reported here RMS acceleration was used to characterize changes occurring during granulation. It was considered that increasing granule size would increase the acceleration of agglomerates striking the probe target. During the dry mixing state, the probe position was adjusted to give maximum sensitivity. Granulation fluid was added in a single operation and the change in vibration profile with time was monitored on a chart recorder.

Initial experiments were carried out to determine the relationship between completion of granulation and end-point scale value. Fig. 3 shows a typical vibration profile and granulation was considered to have taken place between point 2 corresponding to a scale value of 15 and point 3 corresponding to a scale value of 20 (Table 1a). Continuation of granulation beyond point 3 produced granules which were too coarse and at point 4 (Fig. 3) corresponding to a scale value of 30, 21% of granules were found to have diameters greater than 1.7 mm (Table 1a).

It was therefore decided to consider the granulation end-point to coincide with a scale value of 15. Replicate experiments using this end-point value for acceleration provided granules with generally comparable particle size distributions, even though granulation time varied from 3.5 min to 5 min. However, in one experiment, the end-point scale value was not reached until 7 min granu-

TABLE 1
RELATIONSHIP BETWEEN GRANULATING CONDITIONS, GRANULATION END-POINT AND GRANULOMETRY

Batch no.	Scale value	Granulating Conditions				Oversize material (> 1.7 mm) (%)	Mass median diameter (μm)
		Time (min)	Fluid volume (cm^3)	Processor control			
				Chopper speed	Impeller (rpm)		
(a) Initial experiments							
1	30	9.5	700	Fast	400	21.0	N/A
2	25	8.5	700	Fast	400	N/A	N/A
3	2nd peak, 25	6.0	700	Fast	400	9.0	N/A
4	1st peak, 25	4.8	700	Fast	400	10.8	N/A
(b) End-point reproducibility							
5	20	7.5	700	Fast	400	4.4	292
6	20	5.0	700	Fast	400	5.0	286
7	15	3.5	700	Fast	400	5.6	302
8	15	7.0	700	Fast	400	7.3	358
(c) Fluid–volume effect							
9	15	4.5	700	Fast	400	5.1	297
10	15	6.25	680	Fast	400	5.5	292
11	15	7.75	660	Fast	400	5.1	278
12	15	11.41	640	Fast	400	4.0	298
13	–	–	620	Fast	400	Did not granulate	
(d) Process conditions effect							
14	15	3.0	700	Slow	400	4.6	300
15	15	4.5	700	Fast	400	5.6	265
16	15	4.7	700	Fast	300	2.5	215
17	15	12.5	700	Slow	300	5.8	270

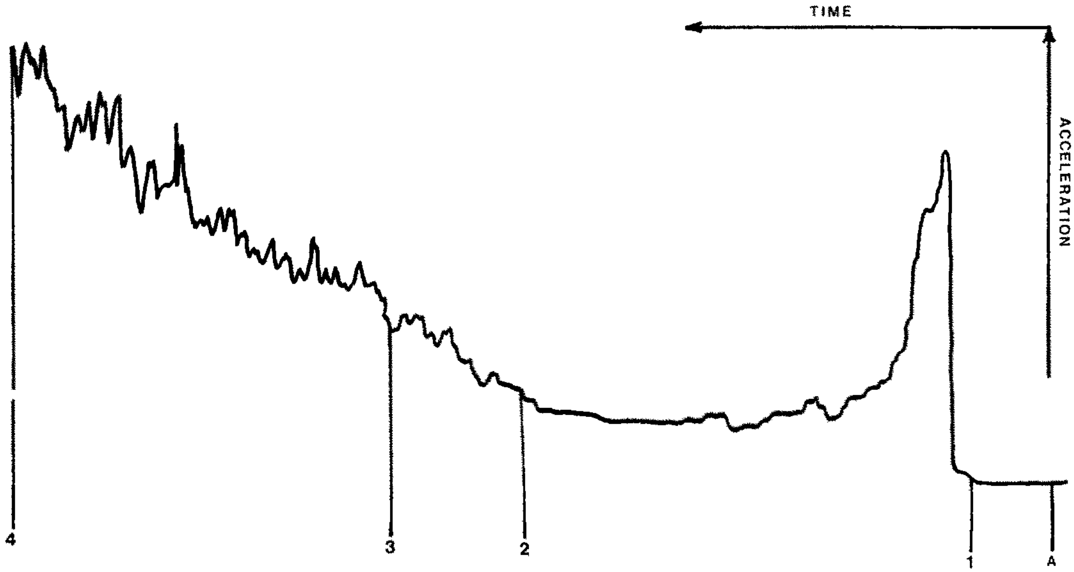

Fig. 3. Typical vibration profile. Key to acceleration levels: A = premixing of powders and setting target orientation to give maximum sensitivity; 1 = addition of water and chopper on; 2 = granulation just complete; 3 = granulation complete; 4 = V.L.M. re-scales-mass overwet.

lation time and in this case a slightly coarser product was obtained (Table 1b).

Further experiments were conducted using the end-point scale value of 15 to assess the effectiveness of use of end point monitoring as a method for evaluating formulation and process variations.

(i) Change on fluid volume. Previous granulations were performed using a granulating fluid volume of 700 ml and it was found that the end-point was reached over a period of between 3.5 min and 5 min. Reducing the volume of water added to 680 ml increased the time taken to reach the end-point to 6.25 min. A further reduction of volume to 660 ml of water, again increased the time taken to reach the granulation end-point (Table 1c). Although reducing the volume of water added to bring about granulation caused an increase in granulation time, the particle size distribution of the products was relatively constant (Table 1c). However, reduction of water volume below 640–620 ml caused so little particle agglomeration that the end-point scale value of 15 was not reached and it was found that the powder had not granulated (Table 1c). The range of granulation fluid volumes used corresponded to a reduction from 16% to 14.8% whilst still producing an acceptable product. Further reduction to 14.3% fluid caused insignificant agglomeration; this value being comparable with that of approx. 14% found by Holm (1984) for the minimum fluid volume for a lactose/Emcompress granulation.

(ii) Change of process variables. The fluid volume used in this experiment was 700 ml water. Using the slow chopper speed combined with an impeller speed of 400 rpm, the end-point scale value of 15 was reached after 3 min. Whereas using a fast chopper speed combined with the same impeller speed, granulation occurred after 4.5 min (Table 1d). The difference in these values could be considered within the limits of reproducibility.

A more marked difference was found between granule products and granulation end-points using an impeller speed of 300 rpm in combination with either slow or fast chopper speeds (Table 1d). It was found that granulation took over 12.5 min to complete using the slow chopper speed, although using the faster chopper speed, granules were produced with a reduced particle size (Table 1d).

It was considered that although the concave plate target provided a useful method of monitoring granulation and end-point control, there

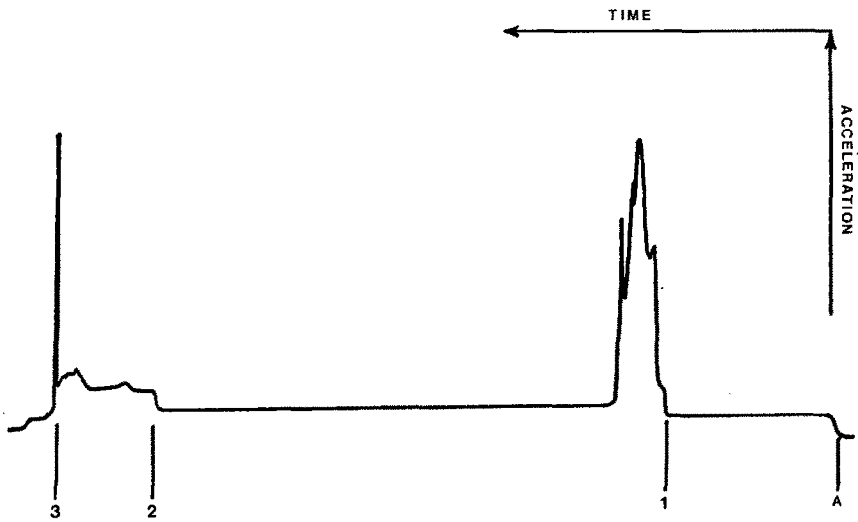

Fig. 4. Typical vibration profile obtained using self-cleaning probe. Key to acceleration levels: A = premixing of powders: 1 = addition of water; 2 = granulation just complete; 3 = granulation complete.

were problems resulting from build-up of powder and granules both behind the target plate and around the accelerometer output socket. For this reason it was decided to re-design the target as shown in Fig. 2 so that neither accelerometer housing nor target plate had surfaces on which material could accumulate. A series of granulations was carried out using a scale value of 5 above the stable base-line value obtained during pre-mixing. This enabled end-point control of granulation to be carried out as before, and a sample vibration record is shown on Fig. 4. Using this probe target, problems encountered due to build-up of powder and granules were overcome.

It was concluded that the use of an accelerator system had potential as a method of granulation monitoring and end-point control. Differences due to both granulation and process variables could be determined using vibration end-point control.

Reference

Holm, P., Granulation in Fielder PMAT 25 VG, Thesis, Department of Pharmaceutics, Royal Danish School of Pharmacy, Copenhagen, Denmark, 1984.