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A Systematic Approach to Scale-Up the High-Shear Granulation Process for Mebendazole Tablets to Achieve a Scale-Independent Drug Release

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Abstracts

The optimized high-shear wet granulation process variables quantified on 1.5 kg batch were scaled up to 90 kg production scale for the manufacture of mebendazole tablets to achieve the scale invariant drug release. The matching granulation properties and dissolution profiles were obtained by the use of a constant impeller-tip velocity in all the high-shear scale-up mixers used. The resultant end point of granulation remained reproducible regardless of scale of manufacture.

Key words: Echinococcosis, high-shear granulation, scale-up, tip velocity, dynamic similarity, drug release

Introduction

Mebendazole is a widely used anthelmintic drug and is also recommended for the treatment of human echinococcosis (hydatid) for which systemic absorption of drug is mandatory (Kumar *et al.*, 1992). For this disease, caused by *Echinococcus granulosus*, the first line of treatment is surgery (Erdincler, 1997). The WHO informal working group on echinococcosis has suggested postoperative or/and preoperative chemotherapy with benzimidazole derivatives for a period of 3 months to few years (WHO, 1996). Mebendazole is a practically insoluble drug. To achieve optimum drug release from tablet dosage form, the United States Pharmacopoeia 2000 has first introduced the dissolution test for mebendazole tablets and no other pharmacopoeia still includes it. A good drug release with mebendazole tablets of 100 mg dose is not difficult to achieve. Attainment of a complete drug release in the same volume of dissolution fluid in the same specified time from the tablets of 500 mg dose (not found in the market) was considered for this task, as it would be more useful for severe alveolar and hepatic echinococcosis.

The advantage of a single-pot high-shear system is that premixing, wet massing and granulation are all performed in a short period of time in the same piece of equipment. But the dangers of this rapidity lie in a possibility of over granulation due to excessive wetting, thus producing less porous granules with occasional lumps. The main problem related to high-shear granulation is the end point control, which is a function of the impeller speed, amount of granulating fluid per tablet, rate of addition of granulating fluid and granulation time, all of which in turn vary with the scale of manufacture (Horsthuis, 1993). Compared to a laboratory high-shear granulator, the production scale high-shear granulator produces a very high shear force for the same impeller speed. Hence, the process parameters optimized in a small-scale high-shear granulator cannot be as such applied to a large scale high-shear granulator. In the scale-up of high shear

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granulation process, lack of reproducibility of granulation properties and drug release profile arise from poor in-process control or incorrect extrapolation from small-scale studies. American Association of Pharmaceutical Scientists (AAPS) has been conducting several workshops in this regard, cosponsored by FDA, from December 1991 onwards and the proceedings of these workshops are published in journals (Skelly, 1993). In practice, mostly this initial transfer to production scale still remains empirical or quiet often a costly try-it-and-see approach.

The purpose of this investigation was to transfer the already optimized granulation process for mebendazole tablets from the laboratory high-shear granulator to the production scale high-shear granulator by a systematic application of some reported engineering principles, without any compromise to the drug release profile of the resultant tablets.

Materials and Methots

Mebendazole USP (micronised) and all other materials of pharmaceutical or analytical grade were provided by Cadila Pharmaceuticals Ltd., Ahmedabad, India. Brand name/Grade details of tablet ingredients are given in Table 1.

Manufacture of tablets: Manufacture of tablets involves 7 steps *viz.*, 1. Delumping, 2. Premixing, 3. Wetting and Granulation, 4. Drying, 5. Dry milling, 6. Final mixing and 7. Compression. Table 1 shows the formula of mebendazole tablet and Table 2, the granulation processing parameters for the scale-up process in three different high-shear granulators, PMA 65, PMA 300 and PMA 600 (Niro-Fielder, Eastleigh, UK). The process parameters for these three scale-up mixers are the values extrapolated from the previously optimized values of a laboratory scale mixer (PMA 10, Niro-Fielder, UK). All the intragranular ingredients viz., mebendazole, calcium carbonate, sodium starch glycolate, cross carmellose sodium, pregelatinised starch had been passed through 60 mesh and premixed in the high-shear granulator for 4 minutes.

Table 1. Formula for the manufacture of mebendazole tablets

Ingredients	Grade/Brand	% w/w
Intragranular		
Mebendazole	USP (micronised)	50
Calcium carbonate	USP	32
Sodium starch glycolate	Primogel	3
Cross carmellose sodium	Ac-Di-Sol	2
Pregelatinised starch	National	5
Polysorbate 80	Tween 80	1
Color sunset yellow	FCF	0.03
Extragranular		
Sodium starch glycolate	Primogel	2
Starch	USP	2
Talc	USP	1
Sweet orange	Approved Flav.	0.97
Magnesium stearate	BP	1
Theoretical weight of each tablet = 1000 mg, each containing 500 mg of mebendazole USP		

Table 2: Granulation processing parameters for various pma high shear mixers

Parameters (Scale-up factors)	PMA 10*	PMA 65	PMA 300	PMA 600
Bowl volume (L)	10	65	300	600
Bowl diameter (m)	0.326	0.510	0.930	1.120
Batch size (kg)	1.5	10	45	90
Bowl volume/powder weight ratio	6.7	6.5	6.7	6.7
Scale of manufacture	1X	6.7X	30X	60X
Impeller speed (rpm)	300	200	110	90
Impeller-tip velocity (m/sec)	5.12	5.34	5.35	5.28
Chopper speed (rpm)	3000	3000	3000	3000
Granulating fluid volume (L)				
Calculated	--	3.6	15.9	31.8
Actual	0.530	3.6	17.2	34.4
Granulation time (min)				
Calculated	--	1.2	2.2	2.7
Actual	0.8	1.2	2.5	2.3

* Parameters for PMA 10 were optimized by trial and error.

Before spraying water (granulating fluid), polysorbate 80 and color sunset yellow were dissolved in one half of the volume of water for wet massing. This solution and the remaining water were sprayed successively from a pressurized stainless-steel vessel, using nozzle of appropriate diameter so as to finish the entire granulating fluid in approximately 3 minutes (impeller on; chopper off). Immediately after addition of granulating fluid, the chopper was turned on at 3000 rpm (impeller on; chopper on) for a period called granulation time as specified in the Table 2.

The theoretical volume of granulating fluid for any scale was calculated by using volume used for the lowest scale multiplied by the scale of manufacture. The theoretical granulation time was determined by using ratios of the impeller speeds multiplied by the time used for the lowest scale. The impeller-tip speed of all scale-up mixers was kept equal to that of the lowest scale mixer (PMA 10) for which the tip speed was optimized by trial and error method. Tip speed or impeller-tip velocity (V), the distance traveled by the impeller-tip per minute was calculated by using the formula $V = \pi nd$; where n is the revolution per second and d is the diameter (meter) of the bowl. To attain the same impeller-tip velocity, impeller speed was adjusted. Chopper speed remained same for all the batches.

The wet granular materials were transferred into the bowl of a Fluidized Bed Dryer (for 1.5 kg batch, model SD 01, Sreeji Chemicals and Equipments, Mumbai, Inida: for 10 kg batch, model KELFBD-10; and for both 45 and 90 kg batches, model KELFBD-60, Karnavati Eng. Ltd., Ahmedabad, India). Drying was performed at 50°C until the moisture content was reduced to 3.5–3%. The dried granules were oscillated through a 16 mesh screen (KELOG-8, Karnavati Eng. Ltd., Ahmedabad, Inida) and the larger aggregates were sized by using a multi mill equipped with sieve No.12 (Cad Mill model CMJ-8, Cadmach Mach. Ltd., Ahmedabad, India). The extragranular ingredients *viz.*, sodium starch glycolate, starch, talc and sweet orange passed through 60 mesh were blended with the dried preweighed granules for 10 minutes in a suitable twin shell blender (Unique mixers and Furnaces Pvt. Ltd., Mumbai, India) followed by mixing with magnesium stearate for 1 minute. Final blend was compressed into tablets using 10 station

rotary tablet press (RSB4-1 GMP, Karnavati Eng. Ltd., Ahmedabad, India) with 19.5 X 10 mm capsule shaped punches to produce tablets of 6.20±0.05 mm thickness and hardness of 8 – 9 kg/cm^2 for a weight of 1000 - 1020 mg. For compressing granules of batch size 1.5 kg, the press speed was 20 rpm and the larger ones were compressed at 40 rpm.

Study of granule properties: For Scanning Electron Microscopic (SEM) study, several representative granules from 1.5 and 90 kg batch were placed on a SEM sample stub and coated with conductive layer of platinum. Sample was observed in a Scanning Electron Microscope (model JSM-5610 LV, Jeol, Japan) using a voltage of 20 kV at 70 times magnifications for examination of the external morphology of dried granules. For viewing the internal structure, the following steps were preliminary. Numerous granules were placed under vacuum (25 psi) in aluminium weigh boats at 30°C for few hours for removing the residual moisture. The granules were submerged in liquid nitrogen for several minutes, fractured by direct pressure using the flat side of a temperature stabilized SEM sample stub and allowed to warm at room temperature. Using an ordinary microscope, several granules were selected for the study, mounted on SEM sample stub, granules were platinum coated and viewed using 20 kV in the SEM at 250 times magnifications. The representative images were recorded.

Granulation Particle Size Distribution (PSD) was determined using a RoTap sieve shaker equipped with a series of six screens. A 100 g sample was used and the apparatus was shaken for 10 min. The weight mean diameter of the –16/+100 mesh granulations was calculated using sieve analysis data. Moisture content was estimated (Karl Fisher Titrator, model AF 8, Mumbai, India) at the end of drying. Bulk density and tap density were also measured.

Study of tablet properties: Thickness (Digital vernier, BS-Mitutoyo, model CD-8", Japan), hardness (model Pfizer, Sreeji Chemicals and Equipments, Mumbai, Inida), Friability (Roche, Electrolab, EF 2 model, Mumbai, India) weight variation and disintegration tests (medium-water) (Electrolab ED-2L model, Mumbai, India) were conducted. Following the method given in USP 2000 monograph for mebendazole tablets, assay of mebendazole tablets was carried out. Dissolution test was performed according to the USP 2000 monograph using apparatus II (paddle) and 75 rpm with 900 ml of 0.1N hydrochloric acid containing 1% w/v sodium lauryl sulphate for maintaining sink condition. Percentage of drug released (Q) in 30, 60, 90 and 120 minutes was determined by HPLC method (Alliance; model – Waters 2690).

Results and Discussion

Figure 1 shows Scanning Electron Microscopic (SEM) photographs of the external surface of granules manufactured at lowest scale (1.5 kg) and the highest scale (90 kg). Figure 2 represents the internal structure of the granules. As far as the external morphology is considered, granules from the lowest scale of manufacture appeared to have relatively more porosity. However they displayed a compact internal core with a more loosely agglomerated smooth outer shell, having few or more larger voids. On the other hand, most of the granules manufactured on the highest scale, showed loosely packed particles with or without single larger void in the internal structure surrounded by a more compacted outer shell with evenly distributed smaller voids. Thus both the categories assume comparable apparent permeability to the dissolution fluid. Mercury intrusion technique may not be useful to identify this duality in porosity of mebendazole granules. Intragranular incorporation of calcium carbonate was to cause a reaction of the former with hydrochloric acid in the dissolution medium to evolve carbon-di-oxide and eventually making the granules more porous.

A comparison of the granulation samples obtained from various scale-up batches showed similar particle size distribution, including 10 – 12% of fines (Figure 3). The vibrational and frictional forces produced during sieve analysis may be assumed to address the granule strength. The strength of granules produced from various scale-up batches was considered to be almost similar as the quantity of fines produced by the RoTab sieve shaker was same. Earlier it

has been reported (Cutt *et al.*, 1986) that increased granule friability was observed when the substrate surface was changed from hydrophilic to hydrophobic. His finding supported the use of polysorbate 80 during wet massing stage for reducing the surface hydrophobicity and hence less friability of resultant granules, apart from increasing the wettability. Table 3 shows the geometric mean diameter (dg), density and Carr's index values, which are indirect means of measuring flow property, compressibility and drug releasing ability of the granules. All these properties were not affected by this method of scale-up. From the above facts it is concluded that all the dimensional properties of the granules were comparable regardless of the scale of manufacture.

Table 3. Granule and tablet characteristics

Batch Size (Kg)	Granules				Tablets					
	dg (μm)	Density (g/ml)		Carr's Index (%)	Weight ± 10 (mg)	Assay (%)	Thickness ± 0.05 (mm)	Hardness (kg/cm^2)	Friability (%)	DT (min)
		Bulk	Tap							
1.5	290(09)	0.45	0.55	18	1010	100.7	6.20	8-9	0.18	4.0 ± 0.3
10	308(10)	0.47	0.56	16	1010	102.2	6.20	8-9	0.27	3.5 ± 0 5
45	295(12)	0.46	0.55	16	1010	103.1	6.20	8-9	0.20	4.0 ± 0.5
90	322(08)	0.48	0.58	17	1010	101.5	6.20	8-9	0.24	4.5 ± 0.2

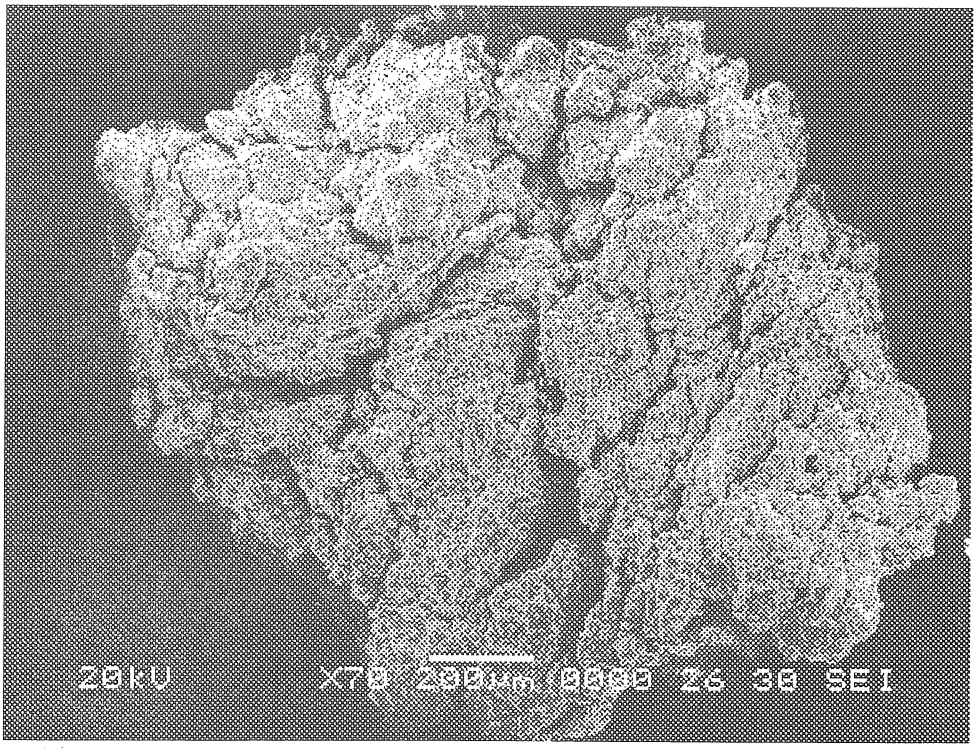
dg = median granule diameter(Figures in parentheses are standard deviations)

Table 4. Dissolution of mebendazole from tablets manufactured in various scales

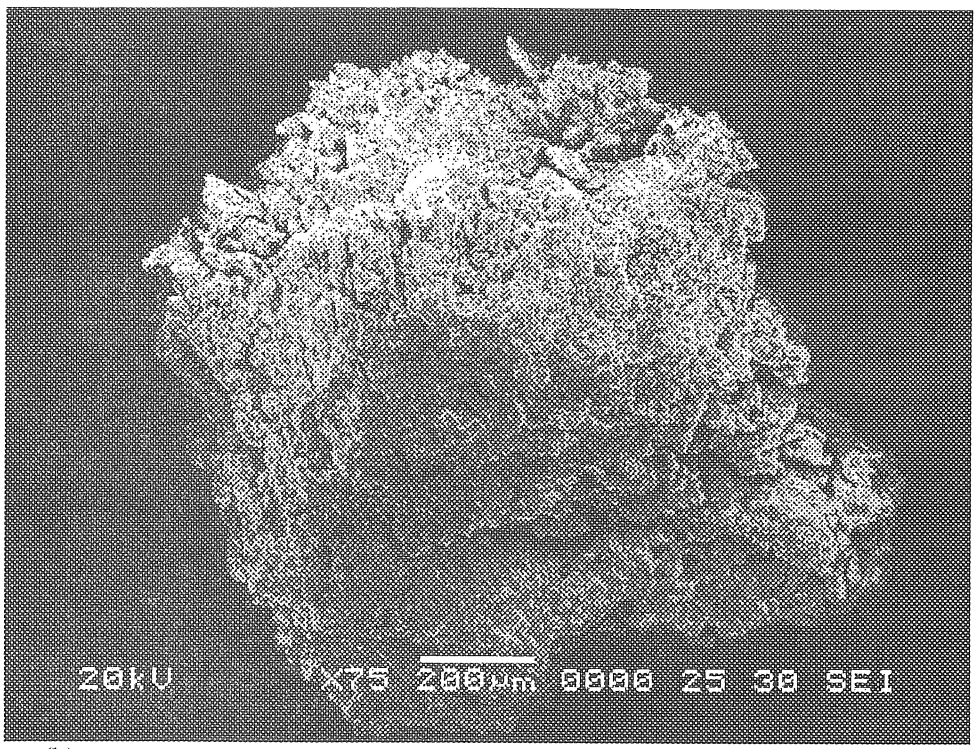
[k] Figures in parentheses are coefficient of variation (%) values

Batch Size (kg)	Mean % of mebendazole dissolved				Dissolution Efficiency		K_1X10^{-3} (min^{-1})
	30 min	60 min	90 min	120 min	DE_{60} (%)	DE_{120} (%)	
1.5	63.2	86.2	94.3	97.2	53.1	73.2	33.33 (4.6)[k]
10	57.3	81.1	91.1	95.0	48.3	69.0	28.39 (3.0)
45	58.8	83.4	92.4	96.1	49.9	70.6	29.55 (3.6)
90	55.6	79.7	90.6	94.6	47.2	68.1	27.04 (2.5)

It is to be stressed here that according to the principle of equifinality, actual end point of granulation can be represented in terms of desired mean particle size or size distribution curve. Once it is achieved, all the other granule properties and subsequent tablet properties remain the same regardless of the impeller speed, binder addition rate etc. (Emory, 1997).

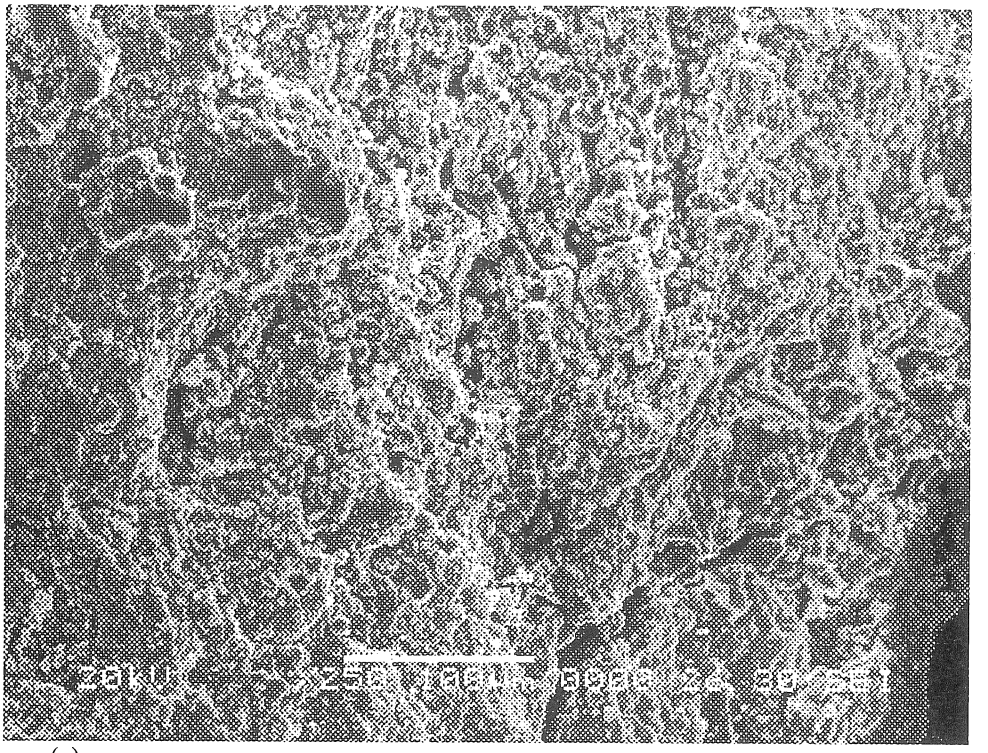


(a)

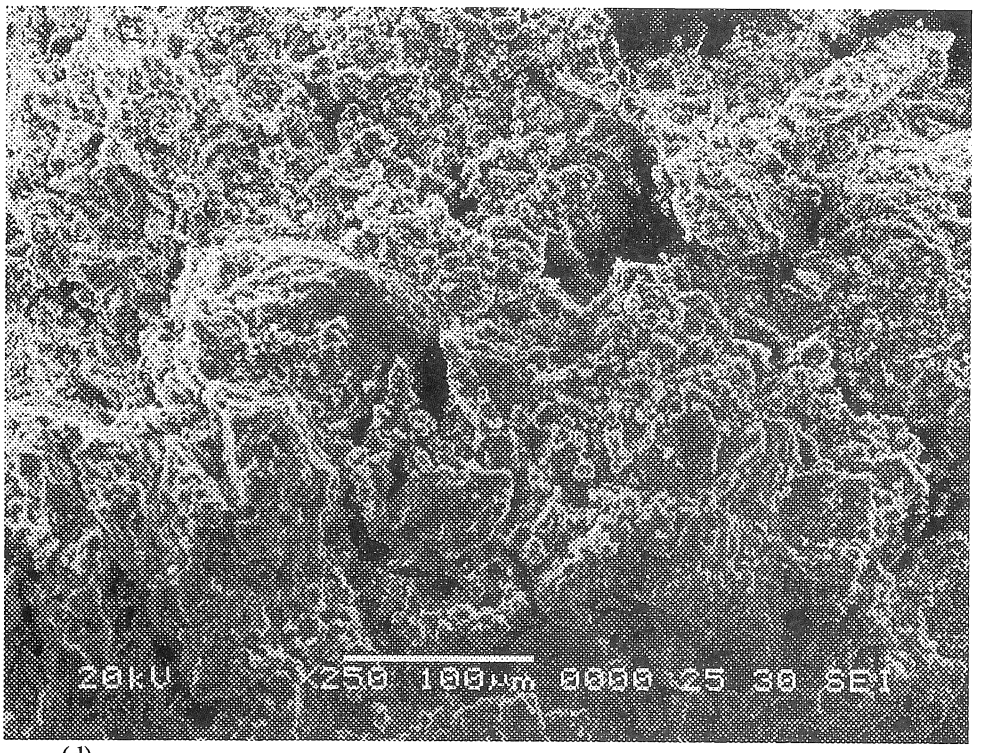


(b)

Figure 1: SEMs (70X) of external surface of mebendazole granules:
a) batch size 1.5 kg, b) batch size 90 kg.



(c)



(d)

Figure 2: SEMs (250X) of internal (cryofractured) surface of mebendazole granules: c) batch size 1.5 kg, d) batch size 90 kg.

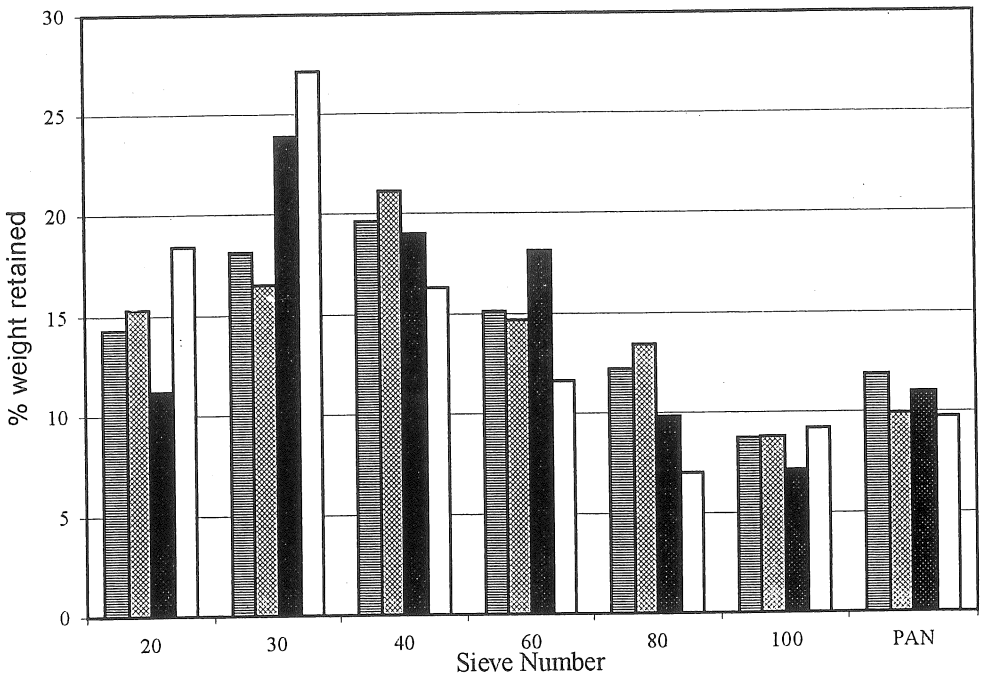


Figure3: Particle size distribution of high-shear granulations of various scales of manufacture: 1.5 kg; 10 kg; 45 kg; 90 kg;

The tablet crushing strength values were between 8 and 9 kg/cm^2 (Table 3), disintegration time (DT) and friability values were also similar in all the cases regardless of the scale of manufacture. Tablets from all the batches passed in the weight variation test and they met USP 2000 monograph specifications for mebendazole tablets. Tablets manufactured in different scales showed nearly super imposable dissolution characteristics, validating the appropriateness of this method of scale-up (Table 4). The fit factors for the dissolution profiles were calculated (Moore *et al.*, 1996) and the values were found to be more than 50, indicating the similarity in drug release behavior of the tablets of various scales. The dissolution rate constant (K_1) and dissolution efficiency values (DE_{60} and DE_{120}) were calculated according to the method of Khan (Chowdary *et al.*, 2000). All these values were sufficiently similar and reproducible with low coefficient of variations. Samples of tablets from 10, 45 and 90 kg batch size, packed in aluminium foils into strips have been stored at 25°C and 60% RH (real time study as per ICH guidelines). The 12 month-stability reports as on date showed a little or no change in assay and dissolution profiles.

Thus, all the process parameters quantified at the lowest scale could be easility extrapolated to the production scale when the impeller-tip velocity was kept constant. The constant tip speed could establish kinematically as well as dynamically similar conditions. According to the modeling theory (Leuenberger, 1983), two processes may be considered similar if there is a geometrical, kinematic and dynamic similarity. Two systems are geometrically similar if they have same ratio of linear dimensions. Two geometrically similar systems are kinematically similar if they have same ratio of velocities between corresponding points. Two kinematically similar systems are dynamically similar when they have the same ratio of forces between corresponding points.

The engineering designs of the four scales of PMA high-shear mixers involved in this study were geometrically similar. The fraction of bowl volume filled by powder particles in the mixers was also kept same in all the mixers used (adjustment of batch size according to the

bowl volume) to avoid disturbances to such geometric similarity. Kinematic similarity was achieved by maintaining the same impeller-tip speed (radial velocity) for all PMA mixers. In addition, the constant tip speed is believed to produce dynamically similar conditions or similar shear forces, regardless of impeller size (Poska, 1991).

Impeller-tip speed corresponding to shear force has been used as a scale-up parameter in fluid mixing (Oldshue, 1985). However there are some conflicting reports. For example, the processing of lactose granulations in Gral mixers (Horsthuis, 1993) showed that the same tip velocity did not result in the same end point (in terms of particle size distribution). These findings were contradicted by a later study (Rekhi *et al.*, 1996) indicating that a successful scale-up was possible when the wet massing time was inversely proportional to the impeller speeds. Hence, the granulation time was increased while the impeller speed was decreased. No correction factor was taken into account in calculating the volume of water per kg of powder materials. This is because it been reported to be scale invariable provided that the binder was mixed in as a dry powder and water was added separately during wet massing (Leuenberger, 1983). To achieve the wet mass of desired (similar) consistency, the actual volume of used water slightly exceeded the calculated quantity. However the deviation was within the range specified ($\pm 20\%$) in AAPS/FDA workshop (Skelly, 1993). As the chopper speed does not produce any significant variation in the end point of granulation (Holm *et al.*, 1984), no adjustment was made to it. The resultant scale-up parameters obtained by extrapolation from the parameters of the lowest scale of manufacture are shown in table 2. As seen in the table there was good agreement between the actual and calculated values when the impeller-tip velocity was kept constant. In conclusion, a virtually successful scale-up was possible with constant impeller-tip velocity when the volume of water addition during wet massing was proportional to the batch size and wet massing time was related to the ratio of impeller speeds. This method of scaling-up the factors influencing the end point control on high shear wet granulation process for mebendazole tablets would therefore reduce the cost of the process compared to the conventional try-it-and-see approach.

References

Chowdary, K.P.R., Nalluri, B.N. (2000). Nimesulide and β-cyclodextrin inclusion complexes; physicochemical characterization and dissolution rate studies. *Drug Dev. Ind. Pharm.* 26:1217-1220.

Cutt, T., Fell, J.T., Rue, P.J., Spring, M.S. (1986). Friability and fracture strength of granules of glass beads and PVP. *Int. J. Pharm.* 33: 81-85.

Emory, H. (1997). Prospective validation of high-shear wet granulation process by wet granule sieving method. *Drug Dev. Ind. Pharm.* 23: 203-215.

Erdincler, P. (1997). The role of mebendazole in surgical treatment of central nervous system hydatid disease. *Br. J. Neurosurg.* 11: 116-120.

Holm, P., Schaefer, T. (1984). Granulation in high speed mixers, Part II; Effect of process variables during kneading. *Pharm. Ind.* 46: 97-101.

Horsthuis, G.J.B. (1993). Studies on up-scaling parameters of the Gral high-shear granulation process. *Int. J. Pharm.* 92: 143-150.

Kumar, A., Chattopadhyay, T.K. (1992). Management of hydatid disease of the liver. *Postgrad. Med. J.* 68: 853-856.

Leuenberger, H. (1983). Scale-up of granulation processes with reference to process monitoring. *Acta Pharm. Technol.* 20: 64-74.

Moore, J.W., Manner, H.H. (1996). Mathematical comparison of dissolution profiles. *Pharm. Technol.* 20: 64-74.

Oldshue, J.Y. (1985). Mixing Process (A. Bisio and L. Kabel, eds.), Published by Wiley, New York, pp. 162-171.

Poska, R. (1991). Integrated mixing, granulating and microwave drying; A development experience. *Pharm. Eng.* 11: 9-13.

Rekhi, G.S., Carcicofe, R.B., Parikh, D.M. (1996). A new approach to scale-up of a high-shear granulation process. *Pharm. Tech.* Yearbook: 58-67.

Skelly, J.P. (1993). Workshop Report: Scale-up of immediate release oral solid dosage forms. *Pharm. Res.* 10: 313-316.

Skelly, J.P. (1993). Workshop Report: Scale-up of extended release oral solid dosage forms. *Pharm. Res.* 10: 1800-1805.

United States Pharmacopoeia (2000). Published by United States Pharmacopoeial Convention, Rockville, MD, pp. 1941-1943.

WHO Informal Working Group on Echinococcosis (1996). Guidelines for treatment of cystic alveolar echinococcosis in humans. *Bull WHO.* 74: 231-242.

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