Defining Scaling Criteria in High Shear Granulation

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INTRODUCTION

Mandated changes in the way pharmaceutical manufacturers are developing products are being ushered by the Food and Drug Administration (FDA) for new drug applications and generic ANDAs. Prior to the phasing in of pharmaceutical quality assessment systems for submission review (chemistry, manufacturing and controls (CMC)) targeting implementation in 1Q2007 [1], development of solid products by granulation was and is still by and large an empirical, 'look, touch and feel' exercise. Barriers to progress in this area lay in the reluctance by industry to embrace new methods that may not be readily accepted by the FDA (the perception being that old proven methods were more likely to be accepted by the regulators); but barriers also existed and still exist because of the limited fundamental understanding of the complex materials behaviours and the many mechanisms at work in granulators. Pharmaceutical development requires an understanding of scale up behaviours in manufacturing processes based on predictive characterization of the way granules form via wetting and nucleation, the way granules grow viz a viz consolidation and coalescence and the way they break by attrition. This understanding, however, is in its naissance as the different mechanisms in play need to be separated and studied individually. Scale-up of high shear granulation, therefore in the pharmaceutical industry, has been approached in a number of ways [1-7]. Typically, impeller tip speeds were kept constant as a scale-up parameter (kinematically similar criterion). Froude number was also suggested a scale-up parameter (as a for dynamic similarity criterion) even for geometrically dissimilar granulators [4].

In this study, the critical process parameters to define the scale up criteria of a typical pharmaceutical high shear granulation process were examined within a defined design space boundary. The high-shear wet granulation process was studied from laboratory to pilot/production scale by (1) keeping the granulation solution to powder mass ratio, the bowl loading, granulation time and the Froude number constant and (2) using the optimal granulation conditions collected at a bench-top scale using a face-centered-central composite design. Pharmaceutically significant attributes of dried granules, and tablets were evaluated to describe a manufacturing control strategy.

EXPERIMENTAL

Materials

Microcrystalline cellulose (MCC; FMC Avicel PH101), lactose monohydrate, (Foremost #310), polyvinyl pyrrolidone (ISP; Povidone K29-32), croscarmellose sodium (FMC) and magnesium stearate (Mallinckrodt) were purchased from commercial suppliers. Purified water USP was produced in-house.

Preparation of table top scale batches (0.38 kg scale)

A face-centered-central-composite design (9 run plus a replicated center point) was applied to optimize the table top scale granulation process of the tablet formulation (Table 1). The factors studied were water addition (30 to 43% w/w) and massing time (30 to 120 sec). The responses were granule flow, crushing strength and friability. The experimental design is shown in Table 2. A statistical software package (SAS JMP version 5.1) was employed for data analysis. Duplicate small scale confirmation batches were also prepared and the predicted and observed parameters were compared.

Table 1: Composition of Model Tablet Formulation

Ingredient	Function	mg/tablet	Wt %
Intragranular			
Microcrystalline cellulose	Filler	18.48	73.92
Lactose	Filler	4.74	18.95
Povidone	Binder	0.78	3.13
Purified Water	Granulation liquid	--	--*
Intergranular			
Croscarmellose Na	Disintegrant	0.875	3.50
Mg stearate	Lubricant	0.125	0.50
Total		25.0	100.0

*Water was removed during processing.

Table 2: Face-centered-central-composition for optimization of table top scale granulation process of model formulation

Run #	Pattern of Design	Water Content (g)	Massing Time (s)
1	+ +	*165*	*120*
2	a 0	*115*	*75*
3	0 A	*140*	*120*
4	- -	*115*	*30*
5	A 0	*165*	*75*
6	0 a	*140*	*30*
7	0 0	*140*	*75*
8	0 0	*140*	*75*
9	- +	*115*	*120*
10	+ -	*165*	*30*

Granulation: MCC, lactose and Povidone (total of 385 g) were mixed in a bench-top high-shear granulator (Key KG-5, 3 L) for 2 minutes at an impeller speed of 688 rpm. Then water was sprayed onto the powder bed at 27 g/min, with the impeller and chopper speeds set at 688 and 3000 rpm, respectively. After spraying, the mixture was wet massed for a period defined by the experimental design. Power consumption was recorded during dry mixing and wet granulation with a Labview data acquisition system.

Drying: The wet granules were sieved through a 10 mesh screen, and dried in a fluidbed dryer (Aeromatic S-1), with an inlet air temperature of 50^{o}C and an air flow rate of 110 m^3hr^{-1} until the targeted loss-on-drying (Mettler Toledo moisture balance) of the dried granules reached 1.5 to 2 %.

Blending and Lubrication: The dried granules were blended with Croscarmellose sodium in a V-shell blender (Patterson-Kelly Yoke blender, 1 qt) at a rotation speed of 25 rpm for 20 minutes, and then lubricated with magnesium stearate for 3 minutes at the same speed.

Compression: The lubricated blend was compressed at a target tablet weight of 25 mg using a rotary tablet press (Piccola, B10) equipped with 2 sets of 3 mm round shallow concave, plain tooling. The turret rotation speed was set 20 rpm. Compression profiles of compression forces from 2 to 9 kN were collected.

The wet and dried granules were observed under an optical microscope (ZEISS Axioskop). Particle size distribution (ATM sonic sifter), bulk and tapped density measurements (Vankel density meter), and flow properties (Flowdex flow tester) of the dried granules were determined. Weight uniformity, crushing strength, friability, and disintegration time of the tablets were also collected.

Preparation of scale up batches

The high-shear wet granulation process was scaled up to 1.15 and 7.46 kg in a PMA1 (GEA, 10 L bowl) and a PMA65 (GEA, 65 L bowl) high shear granulator, respectively. To keep the Froude number constant, the impeller speed was set at 597 rpm for the PMA1, and 435 rpm for the PMA65. The water spray rate of the scale-up batches was increased as a linear function of to the batch size (Table 4). Portions of wet granules obtained from these batches were used for downstream processing (fluidbed drying and compression) which was identical to that of the small scale batches. Responses of these batches were measured and compared with those of small scale confirmation batches.

RESULTS AND DISCUSSION

Process optimization of model granulation at 0.38 kg scale

The particle size distribution, flow properties, weight variation, crushing strength, friability and disintegration time for the small scale granulation batches are presented in Table 3. The results show that the wet granulation improved the flow properties in parallel with a loss in compactability, characterized by decreasing crushing strength and increases in friability (Figure 1). Increasing either water content or massing time had negative effects on granule compactibility. This finding is consistent with reports concerning wet granulation of formulations composed mostly of MCC. [8, 9] It was reported that the decrease in MCC compactability is associated with the changes in MCC crystallinity, surface properties and porosity as a result of hydration and drying. [8]

Table 3. Test Results of Responses for the Small Scale Granulation Batches

Run #	Pattern of the design	D_{50} (µm)	D_B (g/ml)	D_T (g/ml)	Flowdex (mm)	Weight variation (%RSD)	Crushing strength* (kP)	Friability* (%wt loss)	Disint. time* (sec)
1	+ +	73	0.629	0.794	14	1.95	1.57	1.33	4
2	a 0	58	0.539	0.702	18	0.81	3.29	0.50	42
3	0 A	66	0.594	0.736	16	2.61	2.19	0.69	11
4	- -	55	0.527	0.668	16	1.63	3.20	0.13	49
5	A 0	89	0.671	0.833	14	2.63	2.09	0.59	7
6	0 a	63	0.540	0.701	16	2.55	2.74	0.04	33
7	0 0	61	0.584	0.739	16	3.13	2.34	0.37	29
8	0 0	62	0.573	0.711	16	3.98	2.40	0.57	29
9	- +	55	0.553	0.710	20	1.15	3.17	0.19	55
10	+ -	88	0.568	0.725	14	3.35	2.43	0.47	22
Control **		62	0.370	0.484	24	1.68	6.32	0.08	124

*Tablets compressed at a target compression force of 5 kN.

**Results from a dry blend of the same formulation.

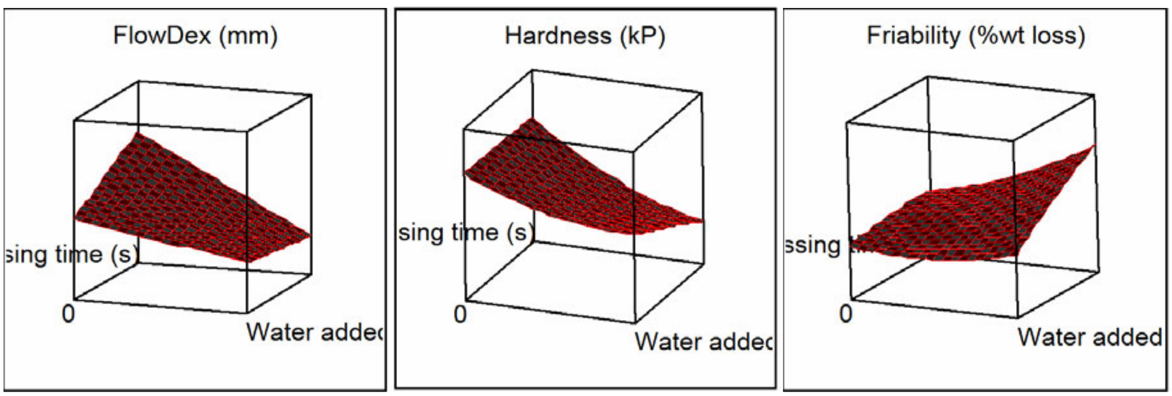

Figure 1: Contour plot of flow properties, hardness and friability in the experimental design space.

Three criteria were used for the optimization of the granulation process: (1) Flowdex value (FV) of granules ≤ 16 mm (indicating satisfactory flow properties); (2) Crushing strength (CS) ≥ 2.6 kP; and (3) friability (FR) ≤ 0.3%. The water content level and massing time required for an optimized process are shown in Figure 2. The results indicate that the area of the optimized parameter combinations in the water amount - massing time plane is small, favouring low to median levels of water and short massing times. The results also suggest that increasing granulation time and granulation fluid level will reduce the compactability of the granulation. This is not unexpected because of the changes of materials properties as a result of the hydration and dehydration of microcrystalline cellulose.

Under the optimized conditions, wet powder could not coalesce to form strong granules; rather, loose agglomerates were formed preferentially. The loose agglomerates could be dissociated during fluid bed drying.

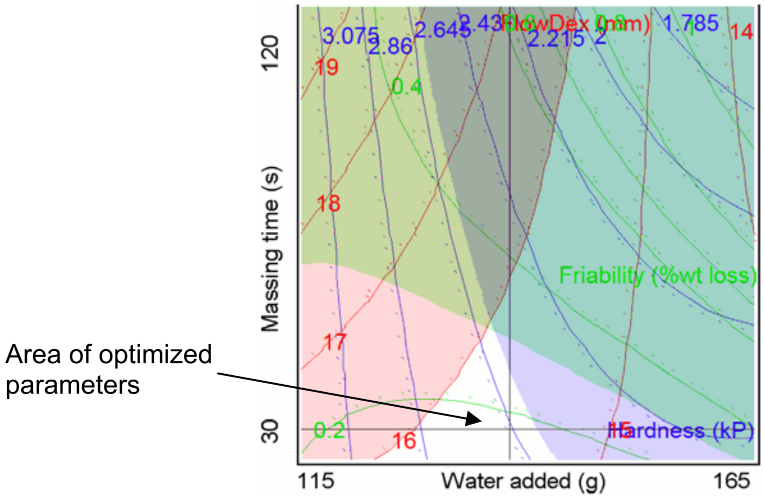

Figure 2: The area of optimized parameter levels for small scale batches (385 g dry powder).

A granulation fluid level of 35.8% w/w along with a massing time of 36 seconds was chosen for confirmation table top batches, and scale up batches.

Scale-up of model granulation

The dimensionless number *Fr* is a function of the impeller diameter (d), impeller speed (*N*), and the acceleration of gravity (g).

$$Fr = N^2 d/g \qquad \text{Equation 1}$$

Scale-up of the high-shear wet granulation process from KG-5 to PMA1 and PMA65 was conducted by keeping Froude number (*Fr*) at 2.714. As the size of the three granulators was different, the speed of the impeller was adjusted in to keep *Fr* constant. The processing parameters are listed in Table 4.

Table 4: Granulation and scale up parameters for model granulation

	KG-5, 3L	PMA1, 10L	PMA65
Impeller diameter (m)	0.202	0.269	0.506
Impeller speed (rpm)	688	597	435*
Impeller speed (s^{-1})	11.47	9.94	7.25
Froude number	2.714	2.714	2.714
Impeller tip speed (ms^{-1})	7.3	8.4	11.5
Dry powder weight (kg)	0.38	1.15	7.46
Loading level in bowl (%)	34.5	34.5	34.5
Water content (% of dry powder weight)	35.8	35.8	35.8
Spray rate (g/min)	27.0	80.6	523
Wet massing time (s)	36	36	36

* PMA65, impeller speed II. This speed is fixed, not adjustable.

Evaluation of wet granules using optical microscopy

Optical micrographs of wet granules obtained from three different granulation scales are shown in Figure 3. The wet granules were similar in appearance across the manufacturing scales. In agreement with the short granulation time, the granules appear as loose agglomerates of less than 200 µm. The particle size distribution of these granules by optical microscopy is not determined because of potential sample-to-sample variations. The presence of loose granules suggests the potential for attrition in down stream operations.

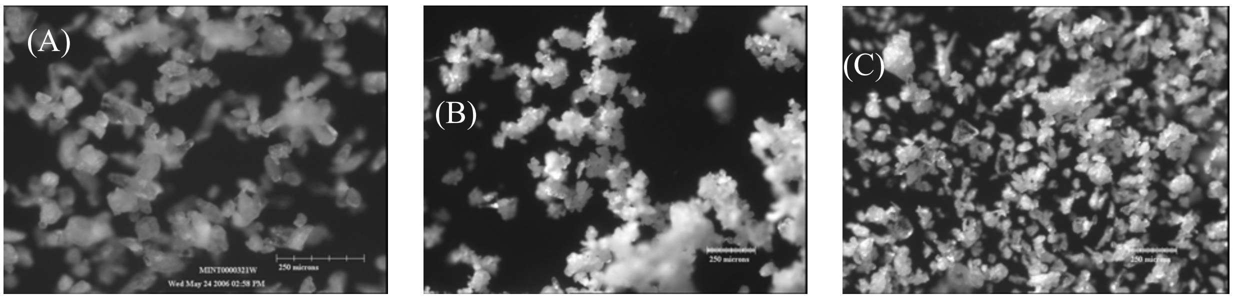

Figure 3: Microscopic images of wet granules obtained from different granulators (A) KG-5, 10×; (b) PMA1, 5×; and (C) PMA65, 5×

Physical Properties of Model Granulation

The physical properties of dried granules from the table-top model confirmation batches and the scale-up batches were studied and the results are provided in Table 5. The differences in flow, bulk/tapped density and particle size distribution are small and therefore may not significantly affect unit processes such as flow and blending. The bulk density (0.545± 0.014 g/mL), tapped density (0.689±0.021 g/mL), and flowability (Flowdex = 16 mm) of the dried granules are comparable across the scale ranges evaluated. The particle size of the dried granules from equipment of identical design configuration (PMA 1 and PMA65) are similar (D_{50} = 80 and 83 µm), but larger than that obtained using the KG-5 granulator (D_{50} = 70 µm) (Figure 4). The granule sizes also correlate with the rank order of the impeller speed and granulator scale.

Table 5: The Properties of Dried Granules Compared with Model Predictions

	D_{50} (µm)	Bulk density (g/mL)	Tapped density (g/mL)	Flowdex (mm)
Model prediction	63	0.543	0.691	16
KG-5, 3L, batch 1	70	0.535	0.698	16
KG-5, 3L, batch 2	69	0.549	0.694	16
PMA1, 10L	80	0.532	0.658	16
PMA65	83	0.563	0.706	16

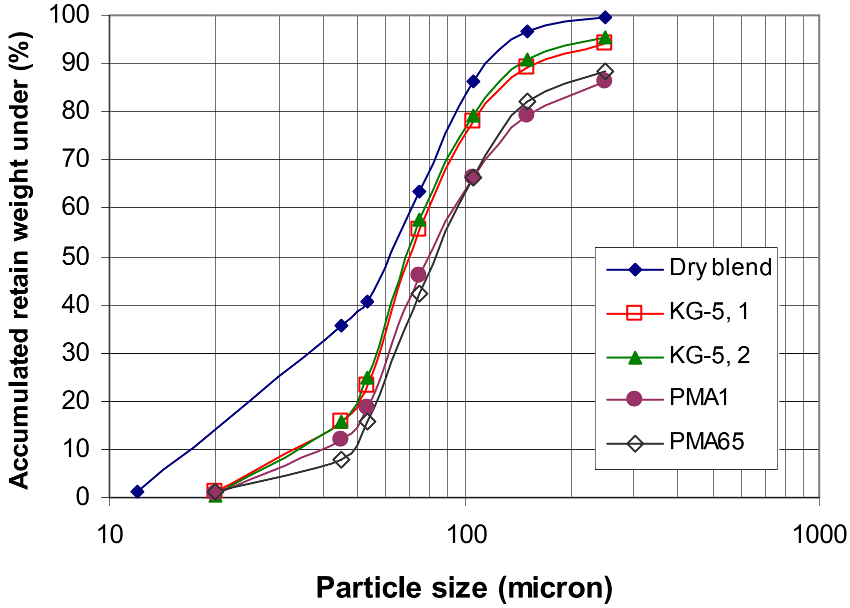

Figure 4: Particle size distribution of dry blend and dried granules formed in different granulators.

There is an increase of particle size by granulation (compared with the dry blend; Figure 4), but the changes are small because the granules are weak. Since the D_{50} values for the dried granules are only slight larger than that of the input dry blend (D_{50} = 62 μm) and larger wet granulation sizes were observed by optical microscopy (Figure 3), the results suggest significant agglomerate attrition during fluid bed drying.

Evaluation of Physical Properties of Tablets

The weight uniformity, crushing strength, friability and disintegration time of the tablets from granulations of batch sizes ranging from 0.38 to 7.46 kg are shown in Table 6.

Table 6: Properties of Tablets of the Batches Using Different Granulators

Batch size	Granulator	Weight Uniformity (%RSD)	Crushing Strength* (kP)	Friability* (%wt loss)	Disintegration Time* (second)
0.38 kg, #1	KG-5, 3L	1.48	1.46	0.76	8
0.38 kg, #2	KG-5, 3L	2.10	2.29	0.30	60
1.15 kg	PMA1, 10L	1.61	3.08	0.28	15
7.46 kg	PMA65	1.55	1.84	0.44	15

* Tablets compressed at a target compression force of 5 kN.

The weight uniformity of tablets (RSD 1.69 ± 0.28%) is comparable across the scales suggesting satisfactory flow properties of the granules. However, the mean crushing strengths (hardness) of tablets by wet granulation (1.46-3.08 kP) were variable and were significantly lower than those obtained from direct compression blend (6.32 kP; Figure 5). This is related to the loss of tensile strength after hydration and drying of a specific direct compression excipient (e.g. MCC) as documented in the literature. [8, 10, 11] This observation is confirmed by the poor compression behavior of an over-granulated batch of the same formulation processed within the PMA 65.

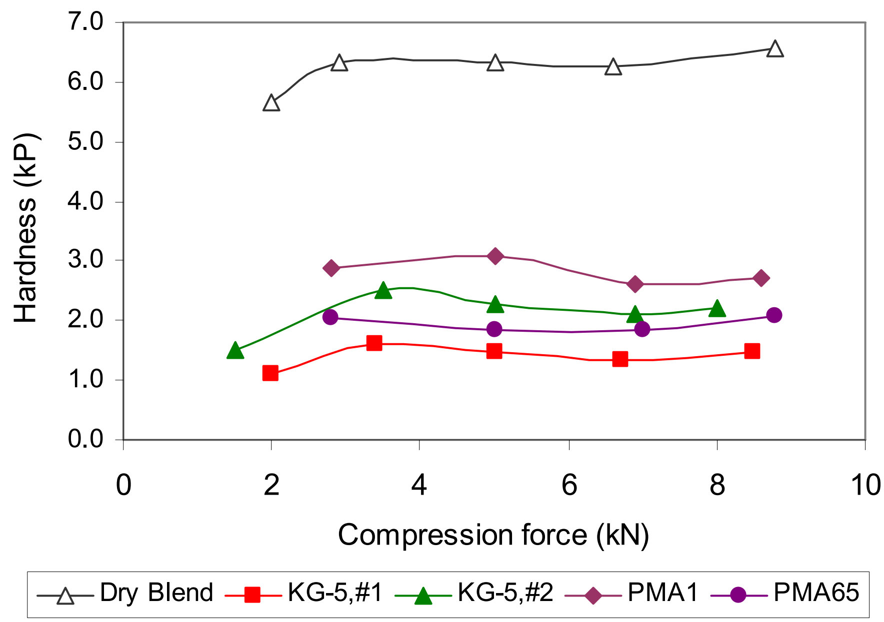

Figure 5: The profiles of hardness with compression force.

It was noticed that the compaction behavior of different batches varied significantly (regardless of scale). Factors not evaluated during granulation and downstream processing might be attributed to variations of granule compactability, resulting in different crushing strength, friability and disintegration time.

Power consumption has been examined for granulation batches with KG-5 granulator. Granulation endpoints however could not be discerned from power curves using the existing formulation and processing

CONCLUSIONS

Wet granulation is generally used for enhancing drug distribution, powder flow or compaction. In this study, critical process parameters of a typical wet granulation were mapped using a statistical design of experiment (DOE) to produce tablets with satisfactory compaction behaviour. The optimised process parameters together with a constant Froude number were used successfully to produce tablets with acceptable characteristics.

The DOE results suggest that a lightly granulated process is needed to produce the desired tablet properties. A different design space will likely to be required should different acceptance criteria be needed for processing reasons (e.g. stronger granules, larger granules for better flow properties). The presence of loose agglomerates is problematic when considering down stream processing and may segue into issues such as particle size reduction. Indeed, the lack of reproducibility chiefly on the compaction profiles and tablet characteristics may be associated with the changes of material properties of MCC during granulation and the granule attrition in the down stream processes.

The results suggest that the design space should be tailored to the specific priority of the processing (ie. variation in parameter ranges and expected responses when prioritizing tableting behaviour vs. flow vs. content uniformity). To ensure that the needed attributes are built into the drug product for consistent manufacture with high quality for its intended use, further understanding is needed of the key physical material properties which may change due to variability in lot to lot of input material. Parameters for wetting and binder distribution are needed in addition for control and an improved scale-up design. Linking processing controls across the scales and across the unit operations ranging from blending, milling, granulation, drying and tabletting is the ultimate target in delivering in a quality by design paradigm.

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REFERENCE

1. Nasr, Moheb M., A new pharmaceutical quality assessment system (PQAS) for the 21st century – why is it needed, what does it mean, and how do we get there?, and Buehler, Gary, Incorporating the concepts of QbD in the assessment of generic drugs. AAPS Workshop presentations. North Bethesda, MD USA 05 October 2005.
2. Achanta AS, Adusumilli P, James KW. Endpoint determination and its relevance to physicochemical characteristics of solid dosage forms. Drug Dev. Ind. Pharm. 23(6):539-546, 1997.
3. Ameye, Dieter; Eseldin Keleb, Chris Vervaet, Jean Paul Remon, Erwin Adams, Desire L. Massart, Scaling-up of a lactose wet granulation process in Mi-Pro high shear mixers, European Journal of Pharmaceutical Sciences 17: 247–251, 2002.
4. Bock, Thomas K.; Kraas, Ulrike. Experience with the Diosna mini-granulator and assessment of process scalability, European Journal of Pharmaceutics and Biopharmaceutics 52(3): 297-303, 2001.
5. Holm, P.; High shear mixer granulators. In: Parikh, D.M. (Ed.), Handbook of Pharmaceutical Granulation Technology. Marcel Dekker, New York, pp. 151–204, 1997.
6. Horsthuis GJB; van Laarhoven, H.A.H. ; van Rooij, R.C.B.M. and Vromans, H. ; Studies on upscaling parameters of the Gral high shear granulation process. Int. J. Pharm. 92:143, 1993.
7. Wehrle, P.; Nobelis, P.; Cuine, A.; Stamm, A.; Scaling-up of wet granulation—a statistical methodology. Drug Dev. Ind. Pharm. 19 (16):1983–1997, 1993.
8. Badawy, S.I.F.; Gray, D.B.; Hussain, M.A.; A study of the effect of wet granulation on microcrystalline cellulose particle structure and performance. Pharmaceutical Research, 23 (3): 634-640, 2006.

9. Gustafsson, C.; Lennholm, H.; Iverson, T.; Nystrom, C.; Evaluation of surface and bulk characteristics of cellulose I, powders in relation to compaction behaviour and tablet properties. Drug Dev. Ind. Pharm. 29 (10): 1095-1107, 2003.
10. Westermarck, S; Juppo, AM; Kervinen, L; Yliruusi, J, Microcrystalline cellulose and its microstructure in pharmaceutical processing, Eur. J. Pharm. and Biopharm. 48(3); 199-206, 1999.
11. Bashaiwoldu, AB; Podczeck, F; Newton, M, A study on the effect of drying techniques on the mechanical properties of pellets and compacted pellets Eur. J. Pharm. Sci. 21(2 - 3); 119-129, 2004.