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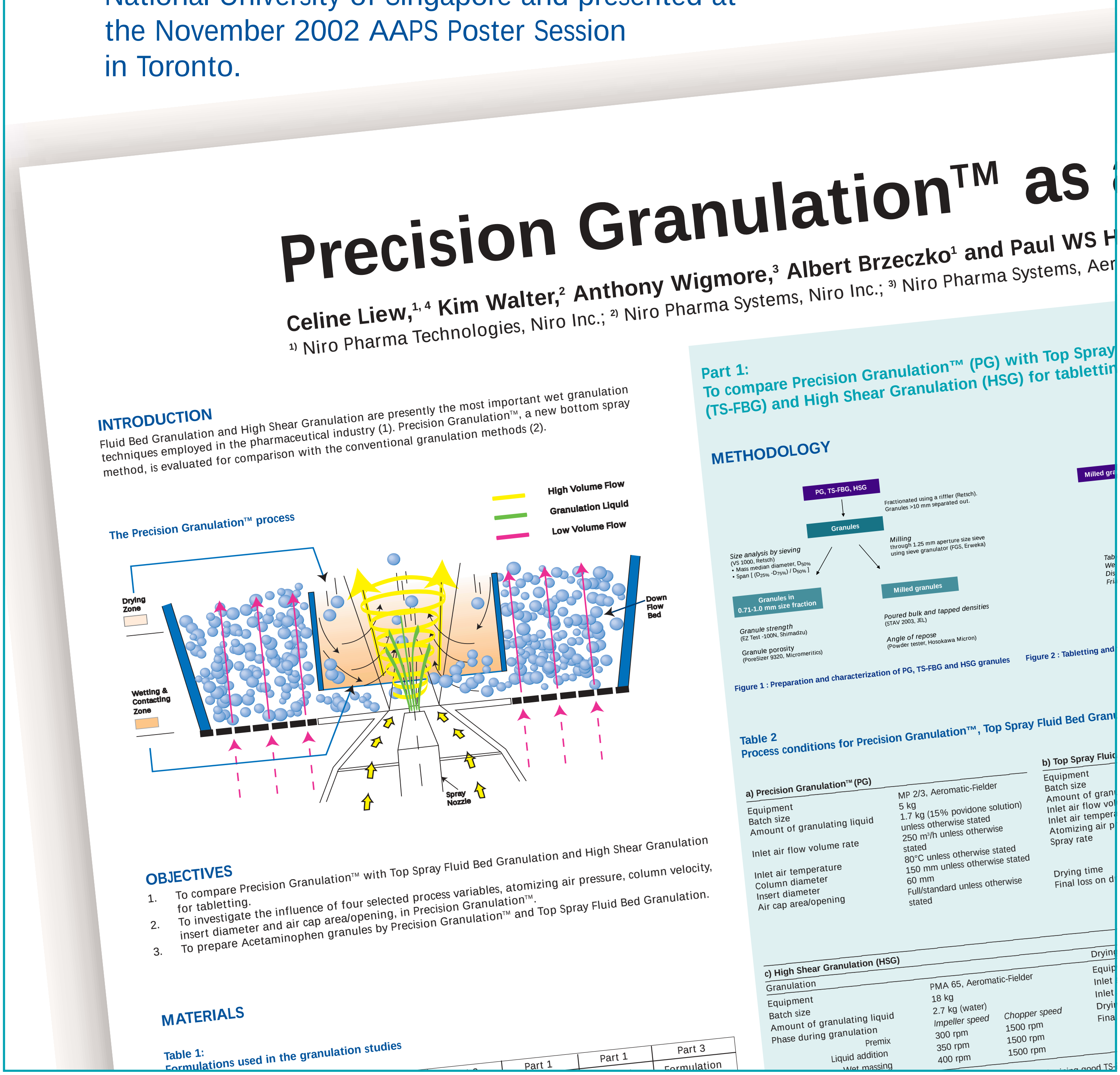
Precision Granulation™

A description of the work on Precision Granulation™ done by Niro Pharma Systems and the Department of Pharmacy of the National University of Singapore and presented at the November 2002 AAPS Poster Session in Toronto.



Precision Granulation™ as an Alternative Granulation Method

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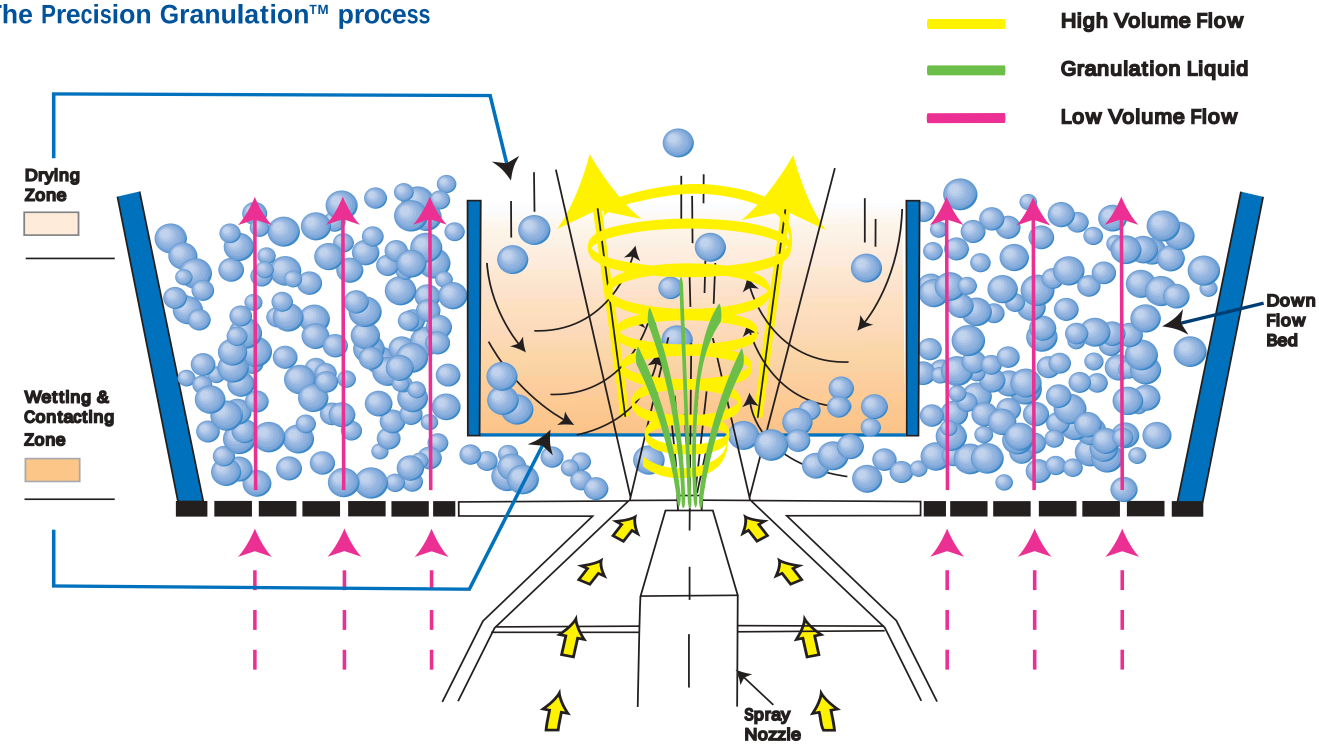
Niro Pharma Systems

National University of Singapore

Introduction

Fluid Bed Granulation and High Shear Granulation are presently the most important wet granulation techniques employed in the pharmaceutical industry (1). Precision Granulation™, a new bottom spray method, is evaluated for comparison with the conventional granulation methods (2).

The Precision Granulation™ process



Objectives

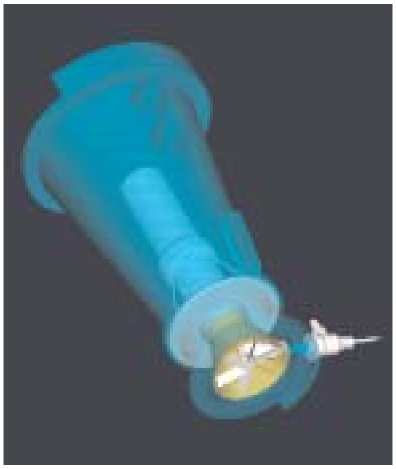
1. To compare Precision Granulation™ with Top Spray Fluid Bed Granulation and High Shear Granulation for tabletting.
2. To investigate the influence of four selected process variables, atomizing air pressure, column velocity, insert diameter and air cap area / opening, in Precision Granulation™.
3. To prepare Acetaminophen granules by Precision Granulation™ and Top Spray Fluid Bed Granulation.

Materials

Table 1
Formulations used in the granulation studies

Study	Part 1	Part 2	Part 1	Part 1	Part 3
Material	Formulation A1 (%)	Formulation A2 (%)	Formulation B (%)	Formulation C (%)	Formulation D (%)
Lactose 200M* (Pharmatose 200M, DMV)	88	88	-	-	-
Lactose 450M* (Pharmatose 450M, DMV)	-	-	88	-	-
Powdered sugar	-	-	-	88	-
Acetaminophen (Mallinckrodt)	-	-	-	-	88
Povidone / Polyvinyl pyrrolidone ([a]Kollidon 30, BASF; [b]Plasdone K29/32, ISP)	5[a]	5[b]	5[a]	5[a]	5[b]
Microcrystalline cellulose (Avicel PH-101, FMC)	5	5	5	5	5
Crospovidone (Polyplasdone XL10, ISP)	2	2	2	2	2

*From DMV product literature :
Lactose 200M - average particle size 0.040 mm; % <0.045 mm : 50-65
Lactose 450M - average particle size 0.020 mm; % <0.045 mm : minimum 90

Schematic diagrams of components of the Precision Granulator™

MP-1™ with Precision Granulation™ module

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1. O. Worts, Wet Granulation - Fluidized Bed and High Shear Techniques Compared, Pharm. Tech. Europe, 10(11), 27-28,30 (1998).
2. K.T. Walter, A Process for Granulation of a Particulate Material. European Patent 1064990 (2001).
3. T. Kawaguchi, H. Sunada, Y. Yonezawa, K. Danjo, M. Hasegawa, T. Makino, H. Sakamoto, K. Fujita, T. Tanino and H. Kokubo, Granulation of Acetaminophen by a Rotating Fluidized-Bed Granulator, Pharm. Dev. Tech., 5(2), 141-151 (2000).

Part 1:
To compare Precision Granulation™ (PG) with Top Spray Fluid Bed Granulation (TS-FBG) and High Shear Granulation (HSG) for tabletting

Methodology

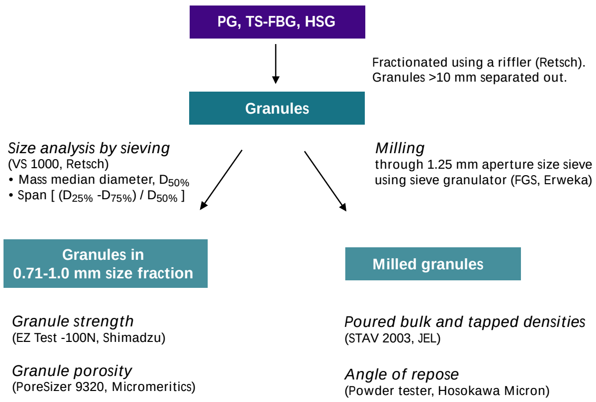


Figure 1 : Preparation and characterization of PG, TS-FBG and HSG granules

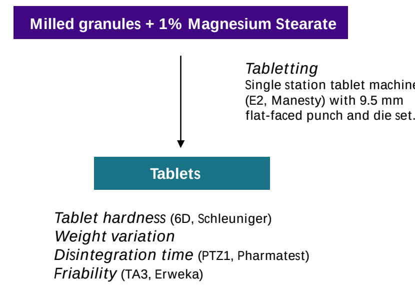


Figure 2 : Tabletting and tablet characterization of PG, TS-FBG and HSG batches

Table 2
Process conditions for Precision Granulation™, Top Spray Fluid Bed Granulation and High Shear Granulation trials

a) Precision Granulation™ (PG)

Equipment	MP 2/3, Aeromatic-Fielder
Batch size	5 kg
Amount of granulating liquid	1.7 kg (15% povidone solution) unless otherwise stated
Inlet air flow volume rate	250 m³/h unless otherwise stated
Inlet air temperature	80°C unless otherwise stated
Column diameter	150 mm unless otherwise stated
Insert diameter	60 mm
Air cap area/opening	Full/standard unless otherwise stated

b) Top Spray Fluid Bed Granulation (TS-FBG)

Equipment	MP 2/3, Aeromatic-Fielder
Batch size	12 kg
Amount of granulating liquid	4 kg (15% povidone solution)
Inlet air flow volume rate	300 m³/h
Inlet air temperature	70°C
Atomizing air pressure	1 bar
Spray rate	125 g/min; 162 g/min —> 120 g/min (start with fast spray rate and then reduce spray rate)
Drying time	8 min; 10.3 min
Final loss on drying (LOD)	2.3%; 2.1%

c) High Shear Granulation (HSG)

Granulation			Drying	
Equipment	PMA 65, Aeromatic-Fielder		Equipment	MP 2/3, Aeromatic Fielder
Batch size	18 kg		Inlet air flow volume rate	500 m³/h
Amount of granulating liquid	2.7 kg (water)		Inlet air temperature	70°C
Phase during granulation	*Impeller speed*	*Chopper speed*	Drying time	18 min
Premix	300 rpm	1500 rpm	Final loss on drying (LOD)	2.8%
Liquid addition	350 rpm	1500 rpm		
Wet massing	400 rpm	1500 rpm		

• Settings chosen for TS-FBG and HSG were fairly typical settings for obtaining good TS-FBG and HSG/drying processes

Table 3
Settings for the PG trial batches

a) Lactose 200M PG trials with povidone as a wet binder

PG batches	Atomizing air pressure (bar)	Column diameter (mm)	Inlet air temp. (°C)	Air flow volume rate (m^3/h)	Column velocity (m/s)	Spray rate (g/min)	Drying time (min)	Final LOD (%)
PG 19	0.5	150	80	250	3.9	130	no drying	4.9
PG 23	0.25	150	80	250	3.9	140	3.3	2.5
PG 24	0.25	150	80	250	3.9	140	3.4	2.1
PG 26	0.5	150	80	250	3.9	139	4	1.9
PG 30	0.25	100	50	300	10.6	79	4	2.0

b) PG trials with 2 grades of lactose and powdered sugar

PG batches	Material	Atomizing air pressure (bar)	Air cap area/ opening	Granulating liquid - water (kg)	Spray rate (g/min)	Drying time (min)	Final LOD (%)
PG 17	Lactose 200M	0.25	full/standard	2.53	109	3	2.8
PG 41	Lactose 450M	0.25	full/standard	3	118	2.7	2.6
PG 39	Lactose 450M	0.25	¼	3	119	5.3	3.0
PG 44	Powdered sugar	0.25	¼	1.5	81	2.4	2.2

Table 4
System for ranking the quality of the lactose 200M PG, TS-FBG and HSG tablet batches

Tablet characteristics	**Ranking system**
Weight variation	With "1" for batch with the smallest weight variation and "8" for batch with the largest weight variation.
Friability	With "1" for the least friable batch (i.e. with least % weight loss) and "8" for the most friable tablet batch.
Disintegration time	With "1" for batch with the shortest disintegration time and "8" for batch with the longest disintegration time.
Coefficient of variation for disintegration time	With "1" for batch with the smallest coefficient of variation and "8" for batch with the largest coefficient of variation.
Coefficient of variation for hardness	With "1" for batch with the smallest coefficient of variation and "8" for batch with the largest coefficient of variation.

- The 5 tablet characteristics were assigned equal weightage.
- For each tablet batch, ranks of the 5 tablet characteristics were summed to determine its composite rank.
- Tablet batches with the smallest and largest sum were assigned ratings of "1" and "8", respectively.
- The batch with the smallest composite rank was considered to be the most ideal batch, i.e. with the best overall tablet quality, within the group of 8 tablet batches.

Results

Granule characteristics

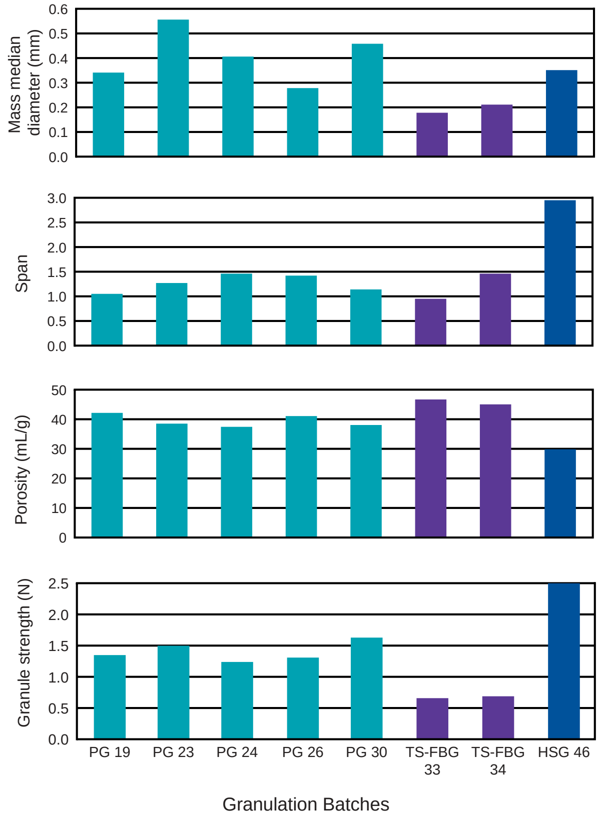


Figure 3: Size distribution, porosity and granule strength of the lactose 200M PG, TS-FBG and HSG batches

- HSG granules had the widest size distribution.
- Granule porosity increased and granule strength decreased for HSG, PG and TS-FBG.

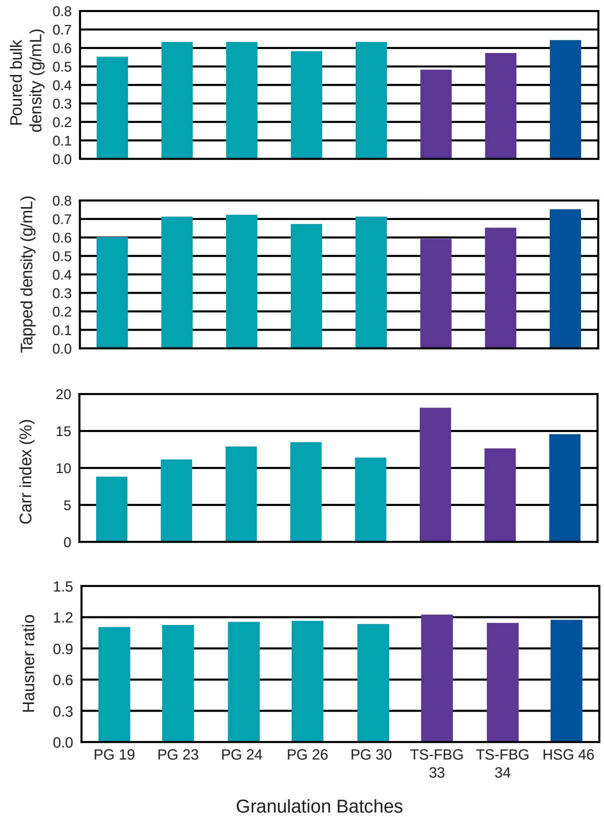


Figure 4: Poured bulk and tapped density, Hausner ratio and Carr index values of the lactose 200M milled PG, TS-FBG and HSG batches

- Poured bulk and tapped densities decreased for milled HSG, PG and TS-FBG.
- Angle of repose values for the granulation batches ranged from 32.5 to 35.6°.

Tablet characteristics

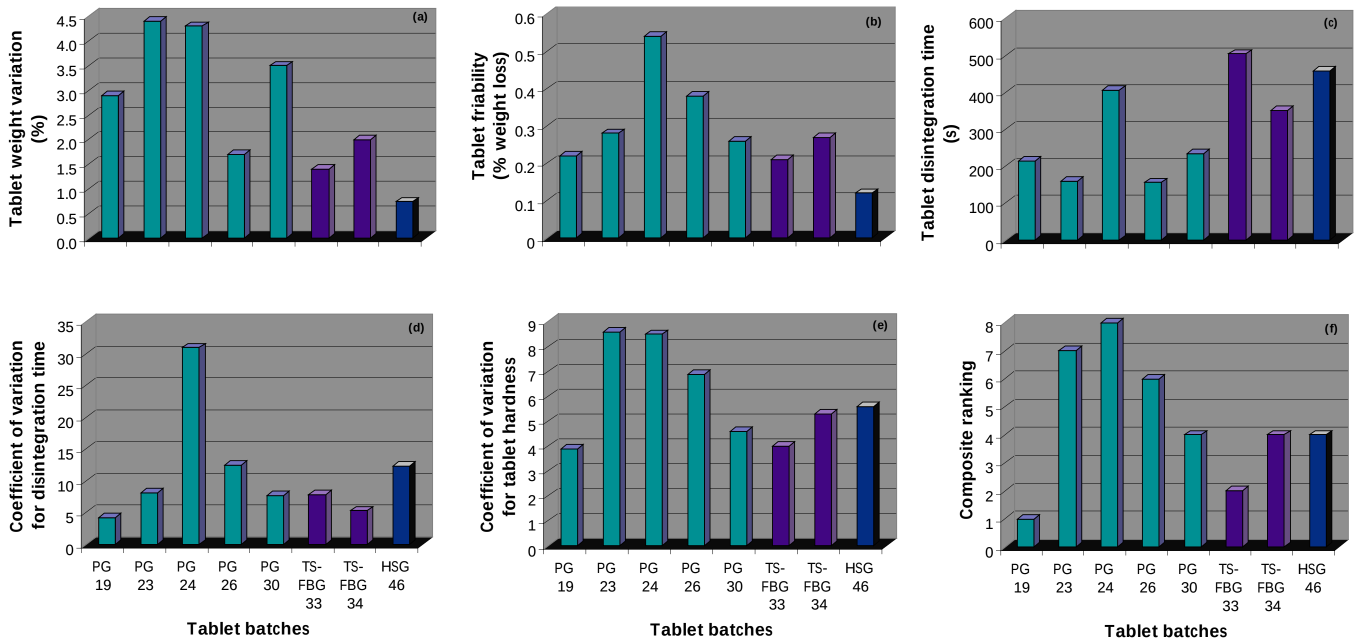


Figure 5: Tablet characteristics and composite ranking of the lactose 200M PG, TS-FBG and HSG batches

- Group mean hardness and weight of the 8 tablet batches : 105.9 (±15.1) N and 282.6 (±15.3) mg.
- PG 19 tablet batch ranked "1" in the composite ranking.
- TS-FBG 33 batch ranked "2". TS-FBG 34, HSG 46 and PG 30 tablet batches shared the same ranking of "4".

PG feasibility trials on fine particles (lactose 450M) and powdered crystalline material (powdered sugar) with poor flow properties

Table 5
Granule and tablet characteristics of lactose and powdered sugar PG batches

a) Granule characteristics

Granulation batches	Material	Mass median diameter $D_{50\%}$(mm)	Span	Porosity (mL/g)	Granule strength (N)	Poured bulk density (g/mL)	Tapped density (g/mL)	Carr index (%)	Hausner ratio	Angle of repose (°)
PG 17	Lactose 200M	0.496	1.16	42.80	0.87	0.55	0.59	5.83	1.06	33.2
PG 41	Lactose 450M	0.326	1.49	43.02	0.92	0.57	0.66	13.25	1.15	34.5
PG 39	Lactose 450M	0.419	1.20	43.77	0.73	0.55	0.61	9.75	1.11	32.2
PG 44	Powdered sugar	0.336	0.76	44.11	1.08	0.47	0.52	8.67	1.10	37.4

b) Tablet characteristics

Tablet batches	Material	Tablet weight (mg)	Weight variation (%)	Friability (%)	Disintegration time (s)	Coefficient of variation for disintegration time	Tablet hardness (N)	Coefficient of variation for hardness
PG 17	Lactose 200M	282.1	3.1	0.23	158	20.4	113.1	5.4
PG 41	Lactose 450M	268.5	1.8	0.40	529	7.6	98.9	7.8
PG 39	Lactose 450M	302	1.5	0.38	640	12.1	116.0	6.0
PG 44	Powdered sugar	279.2	2.2	0.42	332	4.8	116.0	6.4

- Both lactose 450M and powdered sugar could be granulated by PG.
- A greater amount of granulating liquid (water) was used for preparing lactose 450M PG granules.
- Tablets prepared from lactose 450M and powdered sugar PG granules with similar tablet weight and hardness had longer disintegration times than tablets made from the lactose 200M PG granules.

Part 2:
To investigate the influence of four selected process variables, atomizing air pressure, column velocity, insert diameter and air cap area/opening, in Precision Granulation™

Methodology

Process variables investigated in the experimental design

Factor	Low level (-)	Middle level (0)	High level (+)
Atomizing air pressure (bar)	0.3	1.2	2.0
Column velocity (m/s)	5	7	9
Insert diameter (mm)	24	30	40
Air cap area/opening	"¼"	"½"	"Full/standard"
Diameter (mm)	1.99	2.28	2.51

Response variables for evaluating the granulations :

- LOD after liquid addition, fraction of discharged yield > 2 mm, granule size distribution and friability (on unmilled granulations)
- Poured bulk and tapped densities, Hausner ratio, Carr index (on milled granulations)

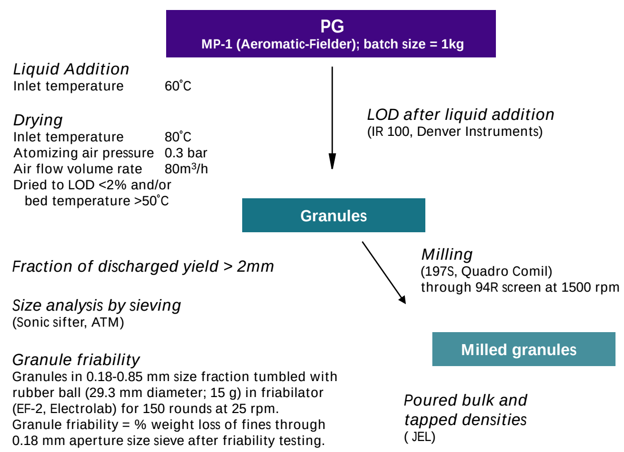


Figure 6 : Flow chart of granulation and granule characterization for the PG experimental design

Table 6
Experimental design*** for investigating the influence of 4 selected PG process variables

Run	Atomizing air pressure (bar)	Column velocity (m/s)**	Insert diameter (mm)	Air cap area/opening
1	-	+	0	+
2	+	+	-	0
3	-	+	+	-
4	-	-	+	-
5	0	0	-	+
6	-	-	-	+
7	-	+	+	0
8	+	-	+	-
9	+	-	0	+
10	-	-	-	0
11	+	+	-	-
12	+	+	0	+
13	+	-	0	0
2a*	+	+	-	0
6a*	-	-	-	+
4a*	-	-	+	-
2b*	+	+	-	0
1a*	-	+	0	+

* Indicates repeat runs. Data collected included in statistical analysis.

** Corresponding to column velocities at high, middle and low levels, binder spray rates set at 36, 28 and 20 g/min and air flow volume rates at 143, 111 and 80 m^3/h, respectively. Spray rates and air flow volume rates chosen for maintaining the same change in humidity between inlet and outlet conditions during binder liquid addition stage.

*** JMP Ver. 4 software (SAS Institute).

Table 7
Physical properties of lactose 200M powder mix for the experimental design study

Property	Value
Mass median diameter, $D_{50\%}$*	0.032 mm
Span *	1.48
Poured bulk density	0.547 (± 0.008) g/mL
Tapped density	0.808 (± 0.004) g/mL
Hausner ratio	1.48 (± 0.03)
Carr index	32.33 (± 1.33) %
LOD	1.91 (± 0.46) %

* Particle size analysis by laser scattering (LA-910, Horiba)

Results

Experimental design study - Granule characteristics

Table 8
LOD after liquid addition, discharged yield and fraction of yield > 2 mm

Run	LOD after liquid addition (%)	Discharged yield (%)	Fraction of discharged yield > 2 mm (%)
1	9.34	89.43	0.23
2	5.42	89.01	0.34
3	10.47	93.93	2.73
4	2.18	48.25	13.77
5	8.39	93.32	0.23
6	5.80	80.52	17.01
7	9.33	93.00	0.11
8	9.05	88.70	2.04
9	8.97	90.27	0.02
10	10.16	87.85	0.15
11	10.25	85.62	2.61
12	4.81	91.48	0.15
13	9.07	90.23	0.06
2a*	8.74	81.21	1.55
6a*	6.06	70.50	14.72
4a*	2.61	41.74	12.88
2b*	4.06	84.45	1.85
1a*	11.37	88.28	0.39

* Indicates repeat runs.

- Low LODs (about 2%) for runs 4 and 4a - due to non-homogeneous distribution of binder solution to powder mass. Overwetting in column resulted in formation of caked material around the spray nozzle. While the caked material was overwetted, material fluidizing outside the column (where sampling for LOD was performed) was underwetted.
- Most PG runs had discharged yields of 70-90% and gave granulations with < 3% w/w oversize particles (> 2 mm). Low discharged yields for runs 4 and 4a (42-48%) and relatively high proportions of oversize particles for runs 4, 4a, 6 and 6a (12-17%) - attributed to higher tendency for overwetting in column with combination of low column velocity (associated with low air flow volume) and low atomizing air pressure.

Table 9
Granule size distribution and friability

Run	$D_{50\%}$ (mm)	$D_{25\%}$ (mm)	$D_{75\%}$ (mm)	Span	Friability (%)
1	0.390	0.563	0.252	0.80	2.08
2	0.189	0.269	0.128	0.75	3.87
3	0.600	0.935	0.373	0.94	1.26
4	0.732	1.329	0.353	1.33	7.75
5	0.232	0.388	0.156	1.00	3.65
6	0.382	0.706	0.230	1.25	3.75
7	0.335	0.487	0.222	0.79	2.77
8	0.468	0.831	0.292	1.15	4.20
9	0.263	0.390	0.201	0.72	5.72
10	0.286	0.445	0.210	0.82	4.24
11	0.239	0.454	0.153	1.26	3.41
12	0.196	0.269	0.134	0.69	5.90
13	0.254	0.386	0.195	0.75	5.93
2a*	0.210	0.331	0.141	0.90	9.34
6a*	0.384	0.631	0.240	1.02	5.31
4a*	0.805	1.412	0.447	1.20	8.35
2b*	0.227	0.367	0.146	0.97	5.89
1a*	0.368	0.559	0.233	0.91	1.80

* Indicates repeat runs.

Table 10
Poured bulk and tapped densities, Hausner ratio and Carr index values of milled PG granules

Run	Poured bulk density (g/mL)	Tapped density (g/mL)	Hausner ratio	Carr Index (%)
1	0.524	0.616	1.18	14.98
2	0.515	0.612	1.19	15.86
3	0.527	0.614	1.17	14.27
4	0.505	0.597	1.18	15.34
5	0.491	0.589	1.20	16.65
6	0.478	0.572	1.20	16.49
7	0.479	0.571	1.19	16.11
8	0.456	0.532	1.17	14.29
9	0.435	0.525	1.21	17.20
10	0.462	0.554	1.20	16.60
11	0.546	0.649	1.19	15.97
12	0.491	0.590	1.20	16.73
13	0.437	0.528	1.21	17.18
2a*	0.529	0.629	1.19	16.00
6a*	0.476	0.566	1.19	15.85
4a*	0.498	0.582	1.17	14.47
2b*	0.520	0.626	1.20	16.98
1a*	0.531	0.620	1.17	14.41

* Indicates repeat runs.

- Poured bulk and tapped densities of milled granulations were lower than those of the original lactose 200M powder mix.
- Hausner ratio and Carr index values were also lower, indicating that the milled PG granules had better flow properties than the powder mix.

Statistical analysis

Table 11
P values from ANOVA and R^2 values from Summary of Fit data

Responses for granule characterization	Significance of process variables in ranges under investigation at 95% confidence interval	R^2
LOD after binder liquid addition (%)	Not significant (P = 0.1774)	0.5029
Fraction of discharged yield > 2 mm (%)	Not significant (P = 0.1226)	0.5448
Granule friability (%)	Not significant (P = 0.0467, i.e. 0.05)	0.6335
$D_{50\%}$	Significant (P <0.0001)	0.9272
$D_{25\%}$	Significant (P <0.0001)	0.9210
$D_{75\%}$	Significant (P = 0.0001)	0.8888
Span	Significant (P = 0.0401)	0.6453
Poured bulk density (g/mL)	Significant (P <0.0001)	0.9245
Tapped density (g/mL)	Significant (P <0.0001)	0.9324
Hausner ratio	Significant (P = 0.0022)	0.8037
Carr index (%)	Significant (P = 0.0092)	0.7388

- LOD after liquid addition, fraction of discharged yield >2 mm and granule friability responses were independent of the process variables.
- Granule size distribution and density responses were dependent on the process variables.

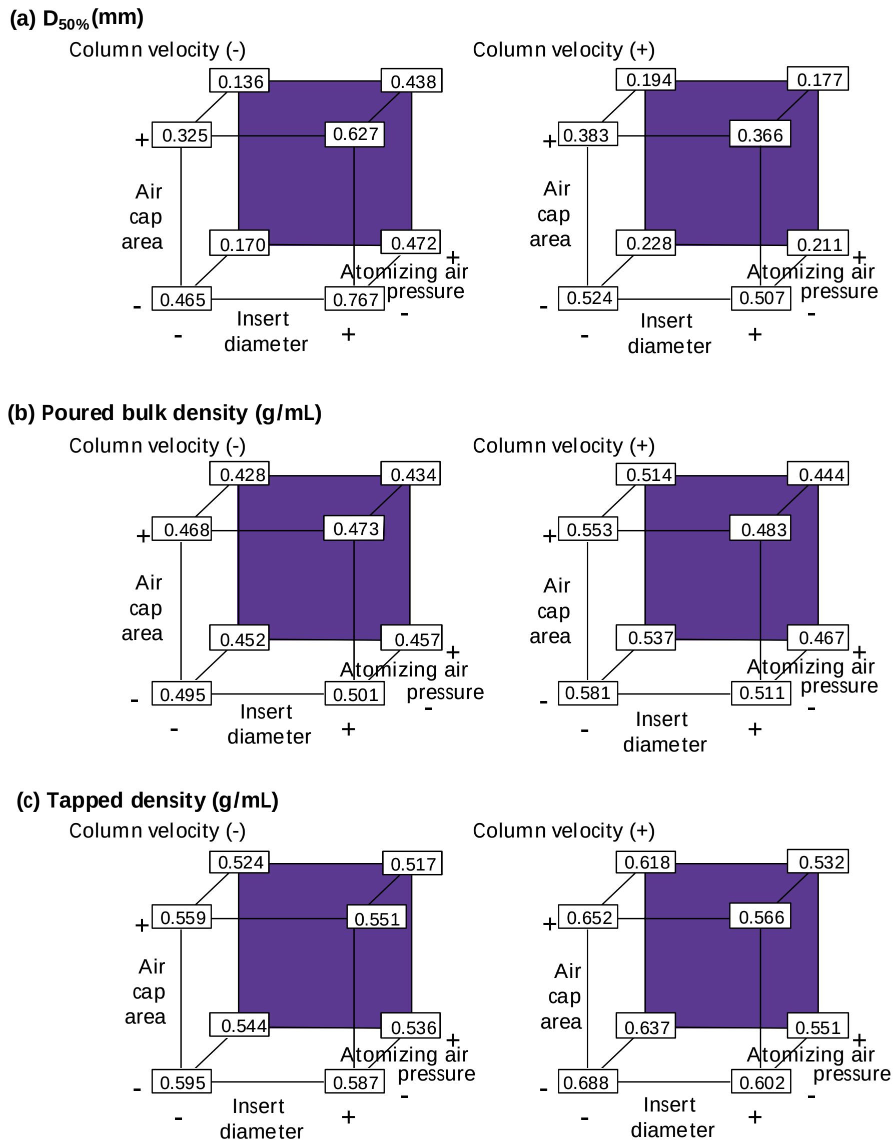
Table 12
Effects and interactions of the process variables on granule responses

Response	Process variables	P value	Effect/ Interaction
$D_{50\%}$			
	Atomizing air pressure	<0.0001*	-0.235
	Insert diameter X Column velocity	0.0058*	-0.160
	Insert diameter	0.0151*	0.143
	Column velocity	0.0637**	-0.063
	Air cap area/opening	0.0986**	-0.087
	Air cap area/opening X Atomizing air pressure	0.2251	0.054
Poured bulk density			
	Column velocity	<0.0001*	0.057
	Atomizing air pressure	0.0001*	-0.041
	Insert diameter X Column velocity	0.0011*	-0.038
	Insert diameter	0.0048*	-0.032
	Air cap area/opening	0.0154*	-0.026
	Air cap area/opening X Atomizing air pressure	0.7933	0.002
Tapped density			
	Column velocity	<0.0001*	0.063
	Atomizing air pressure	0.0002*	-0.042
	Insert diameter	0.0005*	-0.047
	Insert diameter X Column velocity	0.0013*	-0.039
	Air cap area/opening	0.013*	-0.028
	Air cap area/opening X Atomizing air pressure	0.3246	0.008

* Statistically significant (P< 0.05)
** 0.05 <P< 0.1

- For mean granule size, atomizing air pressure was the most important process variable while air cap area/opening was the least important.
- Column velocity had the most important effect on density responses of milled granulations while air cap area/opening was the least critical process variable.
- An interaction between column velocity and insert diameter was significant at P <0.05.
- Granule size increased with increase in insert diameter and decrease in atomizing air pressure, column velocity and air cap area/opening (Figure 7).
- Poured bulk and tapped densities of the milled granulations generally increased following an increase in column velocity and a decrease in atomizing air pressure, insert diameter and air cap area/opening (Figure 7).

Figure 7 :
Cube plots of predicted mean size and density responses at high (+) and low (-) levels of atomizing air pressure, column velocity, insert diameter and air cap area/opening



Part 3:
To prepare Acetaminophen granules by Precision Granulation™ and Top Spray Fluid Bed Granulation

Methodology

Preparation of Acetaminophen PG and TS-FBG granules

Table 13
Physical properties of the Acetaminophen powder mix

Property	Value
Mass median diameter, $D_{50\%}$ *	0.047 mm
Span *	1.55
Poured bulk density	0.335 (± 0.011) g/mL
Tapped density	0.589 (± 0.004) g/mL
Hausner ratio	1.76 (± 0.07)
Carr index	43.12 (± 2.08) %
LOD	1.08 (± 0.41) %

*Particle size analysis by laser scattering (LA-910, Horiba)

Model drug : Acetaminophen
Acetaminophen has been described as a cohesive powder that tends to agglomerate quickly during granulation to give large aggregates (3). Difficulties in granulating acetaminophen for producing tablets with good quality have also been reported.

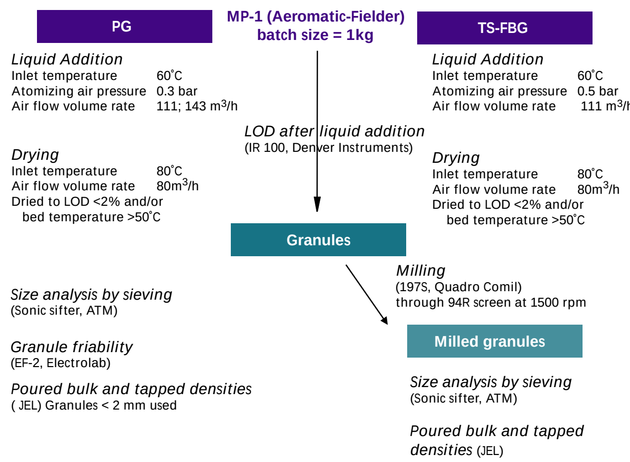


Figure 8: Flow chart of granulation and granule characterization of Acetaminophen PG and TS-FBG batches

Results

Table 14
LOD, discharged yield and size distribution of Acetaminophen granules prepared by PG and TS-FBG

Granulation batches	Granulation method	Column velocity (m/s)	Spray rate (g/min)	Binder solution (kg)	Concentration of Povidone binder solution (% w/w)	LOD after liquid addition (%)	Discharged yield (%)	Fraction of discharged yield >2 mm (%)	Mass median diameter, $D_{50\%}$(mm)	Span
TSAce01	TS-FBG	Not applicable	27 then reduce to 23	0.5	10	7.08	91	7.46	0.405	1.23
PGAce13	PG	7	28	0.5	10	9.47	86	0.96	0.291	1.29
PGAce09	PG	9	36	0.5	10	7.99	90	0.12	0.262	1.16
PGAce07	PG	7	30	0.333	15	7.39	91	0.07	0.244	1.30
PGAce10	PG	9	38	0.333	15	5.12	86	0.16	0.259	1.21

For PG :
With same amount of povidone, concentration of binder solution varied by changing proportion of water (e.g. 0.95 kg, 0.45 kg and 0.283 kg for 5%, 10% and 15% binder solutions, respectively) in binder solution. Spray rates adjusted to give the same rate of water addition to the powder mix.
For TS-FBG :
Spray rate and air flow adjusted accordingly to give a fairly typical TS-FBG granulation.

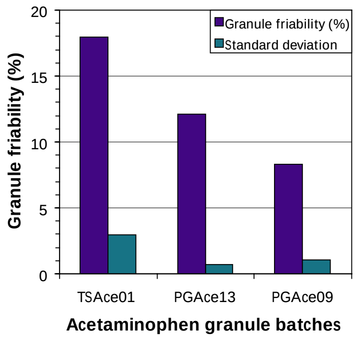


Figure 9: Friability of the Acetaminophen PG and TS-FBG granules

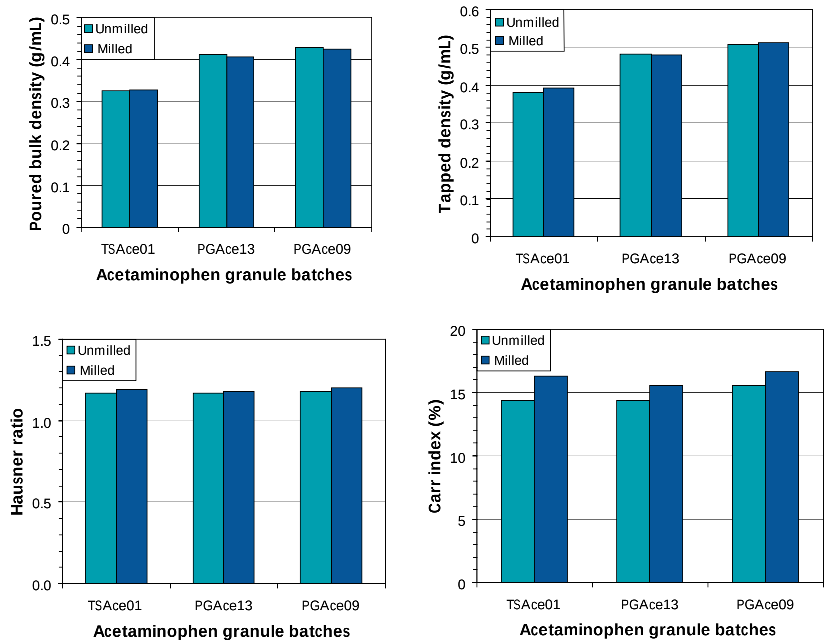


Figure 10: Poured bulk and tapped densities, Hausner ratios and Carr indices of the Acetaminophen PG and TS-FBG batches

Effect of concentration of binder solution on PG

- 10% and 15% binder solutions gave acetaminophen PG granules with similar mean sizes (0.24-0.29 mm).
- Batches prepared with 15% binder solution had lower LODs after liquid addition.
- In preliminary trials, 5% binder solution was also employed for PG. The greater net gain of solvent during liquid addition increased the weight of the powder mass and the tendency for the down flow bed to stop fluidizing. With column velocity fixed at a constant value (7 or 9 m/s), the set air flow volumes were insufficient for supporting the increasing weight of the powder mass towards the end of the liquid addition phase.

Influence of column velocity on PG

- For the same concentration of binder solution, higher column velocity (higher drying capacity associated with greater air flow volume rate) gave lower LODs after liquid addition.
- Material movement during liquid addition improved with higher column velocity. The resultant granulations had tighter size distributions (smaller span values).

Comparison of Acetaminophen PG and TS-FBG

- Higher spray rates can be used for PG compared to TS-FBG.
- TS-FBG granules had larger mean size, greater amount of discharged yield > 2 mm and were more friable than PG granules.
- Milling resulted in a greater change in size distribution for TS-FBG granules - due to presence of a greater proportion of larger size granules in the original unmilled granulation.
- Poured bulk and tapped densities of both unmilled and milled TS-FBG granules were lower than those of the PG batches. Hausner ratios and Carr indices of PG and TS-FBG granules were between 1.17-1.2 and 14.4-16.7%, respectively, indicating that the granulation processes improved the flow properties of the Acetaminophen powder mix.

Conclusion

Part 1: To compare Precision Granulation™ (PG) with Top Spray Fluid Bed Granulation (TS-FBG) and High Shear Granulation (HSG) for tabletting

- PG produced good quality granules with adequate flow and strength for tabletting. The quality of these tablets was comparable to those of tablets prepared from TS-FBG and HSG.

- Porosity, strength, bulk density and tapped density of PG granules were intermediate to those of HSG and TS-FBG granules. PG granules had the lowest Carr index and Hausner ratio values. For equivalent tablet weight and hardness, PG tablet batches showed faster disintegration times.

- Preliminary studies with the two grades of lactose and powdered sugar suggested that PG can offer an alternative to existing methods for investigating granulation of "difficult-to-granulate" materials.

Part 2: To investigate the influence of 4 selected process variables, atomizing air pressure, column velocity, insert diameter and air cap area/opening, in Precision Granulation™

- The statistical analysis indicated that PG size distribution responses and density responses of the milled granulations were dependent on atomizing air pressure, column velocity, insert diameter and air cap area/opening within the low and high levels investigated.

- For size distribution responses, atomizing air pressure appeared to be the most important factor while air cap area/opening was the least important. For poured bulk and tapped densities of milled granulations, column velocity was predicted to be the most critical factor while air cap area/opening was the least critical.

- Within the study range, mean granule size was predicted to increase with increase in insert diameter and decrease in atomizing air pressure, column velocity and air cap area/opening. Poured bulk and tapped densities of the milled granulations were predicted to increase with an increase in column velocity and a decrease in atomizing air pressure, insert diameter and air cap area/opening.

Part 3: To prepare Acetaminophen granules by Precision Granulation™ and Top Spray Fluid Bed Granulation

- Acetaminophen PG granules were less friable and had smaller mean size and relatively low proportion of oversize particles than the TS-FBG granules. These findings suggested that there may be a better distribution of the binder solution in PG. PG granules also had higher poured bulk and tapped densities. The PG and TS-FBG granules had comparable Hausner ratio and Carr index values.

- Higher spray rates (higher water/solvent addition rate) may be used in PG where binder solution is delivered in an upward direction co-current to the flow of material through the spray zone and column. In TS-FBG, binder solution addition and air flow are in a counter-current direction. Compared to TS-FBG, wetted particles in PG experience greater drying.

- Lower concentration of binder solution had the effect of increasing the solvent load delivered. Addition of a substantially greater amount of water to the powder mass increased the tendency for the down flow bed to stop fluidizing if spray rate and/or air flow were not re-adjusted accordingly during the liquid addition phase to compensate for the heavier solvent load.

- Material movement during PG improved with the use of a higher column velocity (associated with higher air flow volume rate). The greater drying capacity also supported higher spray rates for granulation.

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