Performance Investigation of Twin Screw Granulation Process

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1. Purpose of the Study

Presently, bi-modal or tri-modal particle size distribution, irregular particle shapes, inadequate process control and lack of steady state have been observed when processing of wet granules is attempted using a continuous twin-screw granulator. Therefore, the effect of process parameters in twin screw granulation like screw speed, feed rate, fluid uptake and screw configuration on granule properties have been widely researched and published. The screw geometry, however, has potential of significant impact on process & product characteristics. Thus, there is a need to acquire a fundamental understanding of the nature of work carried out by the traditional bi-lobe (BL) / integer geometry (Fig 1) and the novel fractional lobe (FL) geometry (Fig 2) in terms of their effect on granulation process and granule attributes.

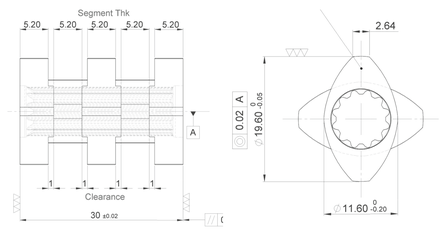

Figure 1. Bi-lobed Geometry

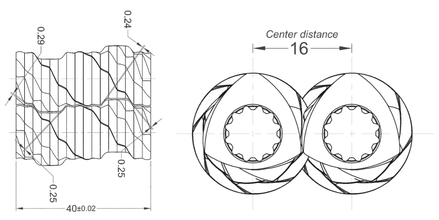

Figure 2. Fractional Lobed Geometry

2. Materials and Methods

Table 1. Composition for Metformin Hydrochloride granules

S.No.	Name of the Ingredients	% w/w
1	Metformin Hydrochloride	95
2	Povidone K30	5
3	Purified Water*	8

* Used as granulating fluid, removed in the process of drying

Granulation was performed using a 20 mm co-rotating twin screw processor (STEER) L/D of 9 and Do/Di of 1.71. Pre-wetted powder (8% w/w water) was fed using a feeder

The length of the kneading zone was kept constant at 30 mm for both elements in the Bi-lobe processor (BLP) and the Fractional lobe processor (FLP) (Fig. 3 and Fig. 4), the process was performed at 1000 rpm and at varying feed rate (30, 60 and 120g/min).

Figure 3. Screw Configuration for BLP

Figure 4. Screw Configuration for FLP

The wet granule mass was dried in a hot air oven at 50 °C until the LOD was less than 1.5% w/w. The dried granules were characterized for particle size, friability, morphology and porosity.

The granules were lubricated with 0.5% Magnesium Stearate and compressed into circular 11 mm tablets with an average weight of 525 mg. The physical properties of the tablets were evaluated.

Process Designation	Geometry	Feed Rate g/min
BLP1	Bi-lobe Geometry	30
BLP2	Bi-lobe Geometry	60
BLP3	Bi-lobe Geometry	120
FLP1	Fractional Lobe Geometry	30
FLP2	Fractional Lobe Geometry	60
FLP3	Fractional Lobe Geometry	120

Table 2. Investigation Summary

3. Results and Discussion

3.1 Process Characteristics

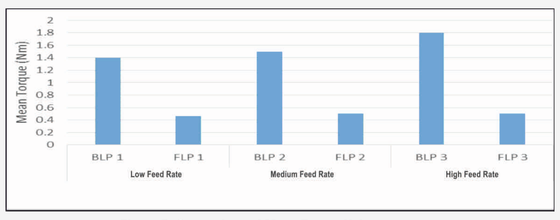

Figure 5. Comparison of Mean Torque Values

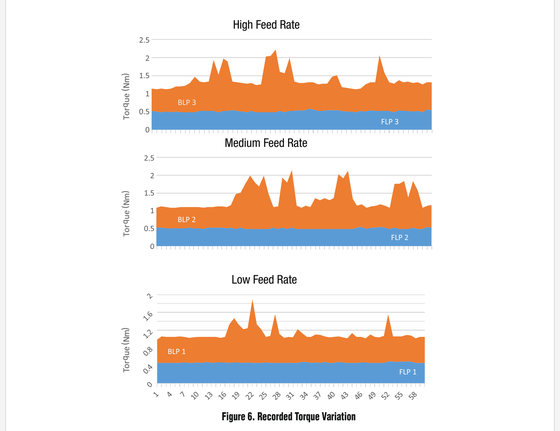

Figure 6. Recorded Torque Variation

The mean torque (Fig. 5) and torque profile (Fig. 6) with fractional lobe geometry at the three feed rates were found to be significantly lower compared to the bilobe geometry. It was observed that the steady state obtained with fractional lobe was more consistent without any sudden disturbances. The mean torque observed with fractional lobe geometry did not show any change with feed rate possibly due to no stagnation (absence of hot spots and dead spots). In order to understand this further, mathematical simulation for both geometries was performed to map the pressure field using finite element models.

Bi-lobe and Fractional lobe profiles of 10 mm thickness were considered for the numerical investigation forming the computational domain. These lobes were pivoted at the centers of two intersecting cylindrical bores which form the stationary walls in the modeling work. These lobes form the moving boundaries in the same direction about the pivoted point (co-rotation).

Steady state analysis was carried-out with the orientation between the lobes being 45° and 90° (Fig. 7). Numerical simulation (ANSYS 16), using finite volume method for the discretization of the conservation laws in three dimension and the local balance, was written on each discretized cell to establish the "control volume". The discretized cell was subjected to deformation using displacement diffusion equation.

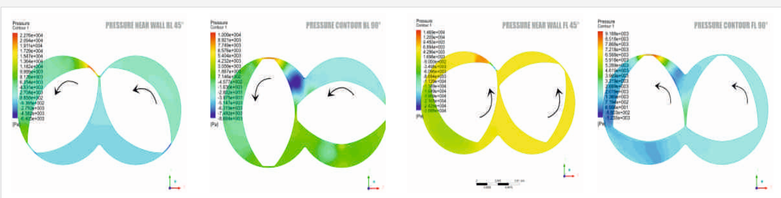

Figure 7. 45 and 90 orientation for the steady state analysis of Bi-lobe and Fractional lobe geometry

Wall shear stress and pressure fields in the form of color contours are shown in Fig. 7 for both geometry. It was observed that the wall shear variation was more pronounced in the case of Bi-lobe geometry, perhaps the cause for torque variation. The pressure contours show a significant asymmetry between the right and left sides. Further modeling (of the dynamic state) can reveal the impact on granule properties.

3.2 Granule Properties

Particle Size : It was observed that the mean particle diameter of granules produced using fractional lobe remained consistent and was not significantly affected by change in feed rate when compared to bilobe (Fig. 8).

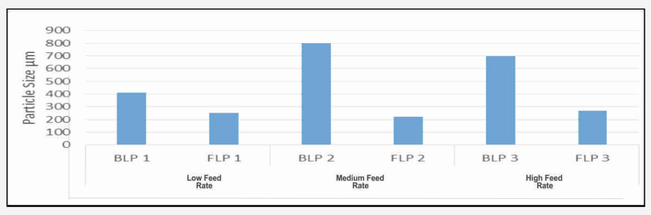

Figure 8. Comparison of the D50 Values for BLP and FLP

Granule Morphology

In order to check morphology of particles, photographs taken for particles greater than 850 µm were compared (Fig 9. & Fig 10). They clearly show that the fractional lobe produces symmetrical morphology closer to spheroid as compared to the elongated rod shape produced by bi-lobe.

Figure 9. Morphology of BLP Granules

Figure 10. Morphology of FLP Granules

Friability Test for Granules

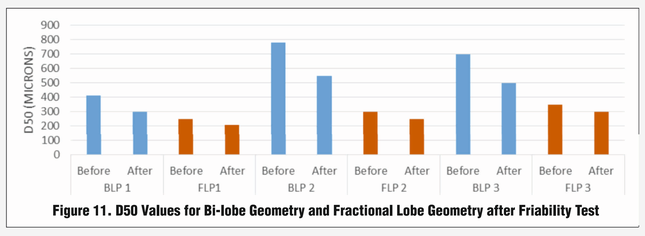

Figure 11. D50 Values for Bi-lobe Geometry and Fractional Lobe Geometry after Friability Test

The tensile strength of the granules was determined by perfoming the friability on granules using Friabilator (ELECTROLAB) and comparative sieve analysis before and after the test.

There was a 25 to 30% reduction in the D50 value for the BLP batches while in case of FLP the reduction was significantly lower (10 to 15% reduction). This may be attributed to the symmetrical shape of FLP particles giving rise to inherently higher tensile strength.

Flow Properties

	BLP1	BLP2	BLP3	FLP1	FLP2	FLP3
Angle of Repose	36	33	30	23	22	24

Table 3. Flow Properties of BLP and FLP Granules

The angle of repose results indicate better flow properties for FLP granules due to their spherical morphology.

Porosity

For determining porosity, BLP1 and FLP1 batches were selected. These two batches had a similar particle size distribution. The granules were sized through a #40 sieve and the fraction retained on # 60 sieve was subjected to porosity evaluation using the High pressure mercury porosity meter (Auto Pore IV 9500 V1.09 - MICROMERITICS).

The Median pore diameter (area) by 6 times, average pore diameter > 50% and apparent skeletal density >25% were found to be significantly higher in FLP compared to the BLP granules. The insignificant difference in % porosity needs further investigation to understand its relevance for differences observed with the granules' average pore diameter, skeletal density and median pore diameter.

Parameter	Units	BLP-#40-60 (420 to 250micron)	FLP-#40-60 (420to 250micron)
Total intrusion volume	mL/g	1.3931	1.3443
Total pore area	M2/g	0.237	0.141
Median pore diameter (volume)	nm	120815.5	102461.3
Median pore diameter (area)	nm	1347.5	9156.2
Average pore diameter4V/A	nm	23559.1	38083.3
Bulk density at 0.51 psia	g/mL	0.4719	0.5235
Apparent(Skeletal)Density	g/mL	1.3774	1.7673
Porosity	%	65.74	70.38

Table 4. Porosity of Granules

Tablet Properties

The FLP granules exhibited tighter control over the weight variation and friability as compared to BLP. This may be attributed to the better flow and larger pore diameter. However, the impact needs to be studied at a bigger scale and longer compression runs for further understanding

Tablet Thickness (mm)	Average Weight (mg		Weight Variation (%)		Hardness (N)		Friability (% w/w)		DT (minutes)	
	BLP1	FLP1	BLP1	FLP1	BLP1	FLP1	BLP1	FLP1	BLP1	FLP1
5.5	512	518	4.02	2.08	100 - 120	100 - 120	0.367	0.121	3 - 5	5 - 7

Table 5. Comparative Physical Properties of Tablets of BLP1 and FLP1 Granules

4. Conclusions

The machine parameters and the granule attributes for the Bi-lobe Processor and the Novel Fractional Lobe Processor indicate the following:

- FLP provides uniform torque, demonstrating steady state across much wider range of throughput.
- Mathematical simulation indicates that the inconsistent torque in the BLP is due to high wall pressure, indicating the presence of hot spots.
- Uniformity of work done has resulted in symmetrical shaped particles by FLP.
- Better symmetry of particles has resulted in desirable granule attributes such as flow and friability.
- Absence of hot spots during FL processing has resulted in improved pore diameter and skeletal density.
- Improved morphology and other physical attributes of granules have resulted in better control over weight uniformity and friability of tablets.

These results clearly demonstrate significant improvement in processing and performance of granules using Fractional Lobe geometry, resulting in the potential opportunity for a truly continuous process to be commercially realized. This is of immense importance due to minimal human intervention, reduced manufacturing footprint, greater quality compliance, greatly reduced waste and environmental burden. Continuous processing can open up hitherto unexplored vistas in Pharmaceutical Manufacturing through seamless integration of multiple operations. The introduction of a granulator based on Fractional Lobe Geometry offers an immense potential to design, optimize and manufacture different types of drug products with highly controlled process and improved physicochemical attributes, truly enabling "Quality by Design".

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