PERFORMANCE EVALUATION OF FOUR MILLING TECHNOLOGIES IN ROLLER COMPACTION FOR GRANULE PRODUCTION USING DESIGN OF EXPERIMENTS

T1430-04-23

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PURPOSE

Dry granulation is a complex process that offers several advantages, including a reduced risk of instability of drug and dosage form, and the elimination of the drying step, as no solvents are employed. Consequently, it can be more cost-effective and is particularly suitable for integration into continuous manufacturing processes. The aim of this study was to investigate the influence of selected process and formulation parameters in dry granulation, with particular focus on the roll compaction and milling stages, on the properties of the ribbons and granules generated in the respective unit operations. In particular, the performance of four different milling apparatuses was evaluated in view of their suitability for the manufacturing of different dosage forms.

OBJECTIVES

- To evaluate the impact of different process parameters on the quality of the final product
- To evaluate which mill design provide an advantage when the granulation is aimed at tableting or sachet filling

METHODS

PROCESS STEPS

Raw Materials → BLENDING → Powder Blend → COMPACTION → Ribbons → MILLING → Granules

Powder Blend → COMPACTION → Tablets

ANALYSIS PERFORMED

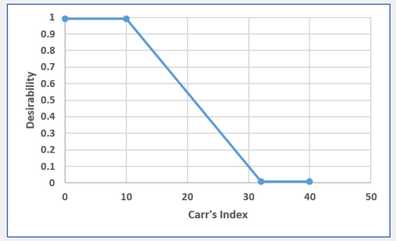
Raw Materials	Blends	Tablets	Ribbons	Granules
Flowability	Flowability	Friability	Mass	Flowability
PSD	Compactability	Mass	Thickness	PSD
		Height	Density	
		Diameter	Porosity	
		Crushing Strength	Fine Fraction	
		Cohesion Index	Fines PSD	
		Tensile Strength		
		Density		
		Solid Fraction		

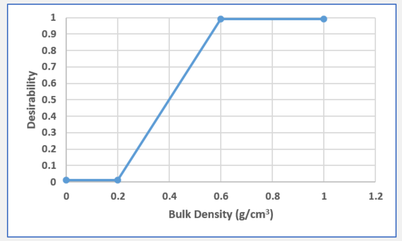
FACTORS EVALUATED IN THE DoE

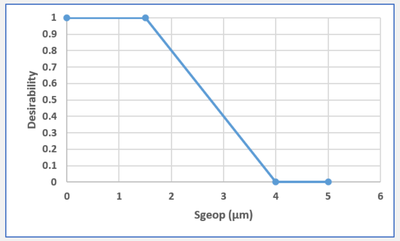
Critical Material Attributes	Critical Process Parameters	Mill Design
Lactose to MCC ratio	Screw Speed	Hammer Mill (HA)
	Compaction Force	Rotari Mill (RO
	Mill Speed	Rasping Mill (RA)
	Mesh Screen Opening	Oscillating Mill (OV)

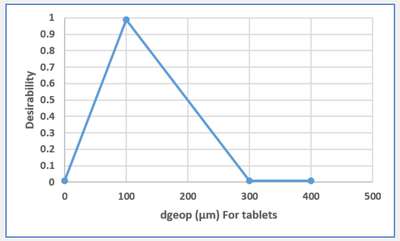
RESULTS

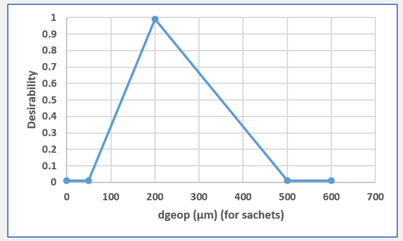
Desirability function graphs - Minitab 18 software (GMSL, Italy)











Coded Levels	Lactose:MCC, w:w	Screw Speed (rpm)	Compaction Force / Ribbon thickness ratio (N/mm)
-1	75:25	10	6.66
+1	25:75	33	13.33

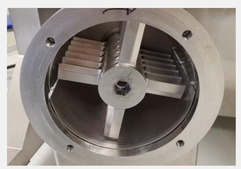
Mill	OV		RO		RA		HA	
Coded Levels	-1	+1	-1	+1	-1	+1	-1	+1
Screen Mesh Size (mm)	1	2	1.2	1.98	1.2	1.98	1.2	1.98
Mill Rotor Speed (rpm)	258	996	33	94	102	372	102	372

Mill	OV	RO	RA	HA
Factors	Optimized Levels			
Roller compaction for granules intended for tablet manufacturing				
Lac:MCC, w:w	25:75	75:25	75:25	66:33
Screw Speed (rpm)	10.00	10.23	21.00	10.00
F/t (N/mm)	5.03	5.03	6.44	6.44
Mesh (mm)	2	1.97	1.98	1.64
Rs (rpm)	258	76	102	102
Overall Desirability	0.8961	0.8773	0.8511	0.8171
Roller compaction for granules intended for sachet manufacturing				
Lac:MCC, w:w	75:25	75:25	75:25	75:25
Screw Speed (rpm)	10.00	29.09	33.00	10.00
F/t (N/mm)	13.73	5.03	5.99	5.99
Mesh (mm)	2.00	1.96	1.40	1.39
Rs (rpm)	996	94	102	102
Overall Desirability	0.7171	0.8534	0.7290	0.5584

- Two sets of DoE (full factorial design)
- 2^5-32 trials for each mill, for a total of 128 trials



FREUND GFC-220 GRANUFORCE™



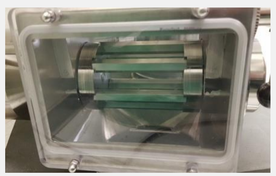
Hammer/Knife Mill



Rasping Mill (rotor)



Vertical Oscillating Mill



Rotary Mill

CONCLUSIONS

The relatively wide Design Spaces identified for both dosage forms are highly robust, even when different milling apparatus are used, highlighting their promising industrial applicability, particularly from a continuous manufacturing perspective.

- For tablet production, the different mill provided similar results, with the Hammer mill as the worst case, but still performing well.
- For sachets, the situation is different, the Rotary mill proved to be superior, followed by the Oscillating vertical and Rasping, which provided similar results, while the hammer mill lagged behind in performance, proving to be sub par.

In a subsequent phase of the study, it would be valuable to further investigate, in greater depth, the CQAs of granules intended for tablet manufacturing as a function of the levels of the factors considered.

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