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A DOE APPROACH TO STUDY THE INFLUENCE OF TSWG PROCESS PARAMETERS ON THE CHARACTERISTICS OF GRANULES AND TABLETS

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PURPOSE

The Twin Screw Wet Granulation (TSWG) is a manufacturing process gaining increased attention in the pharmaceutical industry for its advantages with respect to other batch-wise granulation approaches, especially the versatility, straightforward scale-up and the integration in a continuous manufacturing line [1-3].

At an early stage of a pharmaceutical development program, the available quantity of API is limited, and a twin-screw granulator can accommodate relatively small batch size. Moreover, larger campaigns, that are typically requested at later stages, can be conducted using the same equipment.

A DoE study was conducted in order to assess the influence of the main process parameters on the characteristics of granules and tablets. A leading formulation containing a soluble drug, namely Niacin, was used, and the factors evaluated in the DoE were the screw design, the screw speed, the Liquid/Solid ratio (L/S), the feed rate and the screen type to calibrate the size of the granules.

The responses evaluated were referring to the process (e.g. torque), the granules (e.g. particle size distribution (PSD), density and flowability) and the tablets (e.g. tensile strength, friability and disintegration time).

METHODS

The blends (10.5% w/w Niacin) were sieved and mixed in a blender (MB015, Pharmatech®) for 15 min at 17 rpm. Powders and demineralized water were added to a twin-screw granulator (Process 11, Thermo Scientific™) by using a volumetric feeder and a peristaltic pump, respectively. **A screening design using 2-level fractional factorial DoE** (2^{5-1}, six center points, resolution V, statistical power >80%), **was executed and analyzed using Design-Expert® v. 12. Twenty-two runs were randomly conducted** (Tab.1) **and the main factors and the two-way interactions were estimated independently. The model effects were selected using the AICc criterion with forward approach.**

The granules were dried in a fluid bed (Strea1, GEA) at LOD < 3% w/w and passed through a conical mill (Comil® U5, Quadro®) equipped with sieves (300 µm, 457 µm and 991 µm openings). The granules were characterized for PSD (sieve analysis), density, angle of repose and Hausner ratio using Ph.Eur. methods, and friability [3].

After mixing with extra-granular excipients, the blends were compacted with a single-punch press (EK-0, Korsch) equipped with a flat punch (diameter = 11.28 mm). The tablets (weight = 450 mg) were characterized by compendial methods for hardness, tensile strength, thickness, friability and disintegration time.

RUN	Factor A SCREW DESIGN*	Factor B SCREW SPEED (rpm)	Factor C L/S RATIO	Factor D POWDER FEED RATE (g/min)	Factor E SCREEN TYPE**
1	High shear	400	0.15	25	2
2	Low shear	700	0.35	10	2
3	High shear	550	0.25	17.5	1
4	High shear	700	0.35	25	2
5	High shear	550	0.25	17.5	1
6	High shear	700	0.15	25	0
7	Low shear	550	0.25	17.5	1
8	High shear	400	0.15	10	0
9	Low shear	400	0.15	25	0
10	Low shear	700	0.35	25	0
11	High shear	400	0.35	25	0
12	High shear	550	0.25	17.5	1
13	High shear	700	0.15	10	2
14	Low shear	700	0.15	10	0
15	Low shear	700	0.15	25	2
16	High shear	400	0.35	10	2
17	High shear	700	0.35	10	0
18	Low shear	550	0.25	17.5	1
19	Low shear	400	0.35	25	2
20	Low shear	550	0.25	17.5	1
21	Low shear	400	0.35	10	0
22	Low shear	400	0.15	10	2

*High shear = 2 mixing zones (block 3 and 7), *Low shear = 1 mixing zone (block 7), **0 = 300 µm (conidur); 1 = 457 µm (smooth); 2 = 991 µm (smooth)

Tab.1 - DoE factors, levels and runs

RESULTS

Model effects for each response were ranked by the magnitude of the factors (Tab. 2).
All statistical models were significant with $p < 0.05$ and a high level of goodness of fit (R^2) was observed for the majority of responses. Potential deviations from a linear effect were evaluated with curvature test.
A low L/S ratio (factor C) and high-shear screw design (factor A) as main effects increased the values of torque holding fixed all the other model factors.
The sieve type (factor E) influenced the PSD of the granules. Fine and medium size particles increased as the sieve opening became smaller.
By setting the largest sieve opening, the coarse fraction increased. The quantity of coarse particles also raised with the L/S ratio and low powder feed rate (Fig.3A).
The granule friability was acceptable (< 30% w/w) and impacted by the milling opening and screw design.
The flowability was between passable and excellent according to the Hausner ratio values (and excellent according to the angle of repose data).
The bulk and tapped density were impacted by the sieve opening and screw design as an interaction: higher response for a lowest opening sieve and high-shear screw design (Fig. 3B).
The tablet tensile strength (and hardness) were affected by the interactions AE, AC, DE and AB. Tensile strength was negatively affected by screw speed and positively affected by L/S ratio. The significant interaction AE highlighted an increase of tensile strength for a lowest opening sieve and low-shear screw design (Fig. 3C).

Response Name	Model	Effect	Curvature*	R^2
Torque (Nm)	p=0.0002	C; A; BD; B; D	S	0.79
Fine (<125µm)	p<0.0001	E; BC; C; CD; B; D	NS	0.90
Medium (125µm≤X<500µm)	p<0.0001	E; AB; CD; A; AE; AC; BD; BE; B; C; D	S	0.99
Coarse (≥500µm)	p<0.0001	E; CD; BD; AD; AB; A; BE; AE; D; B; C	S	1.00
Friability (%)	p=0.0065	E; A	S	0.53
Bulk density (g/cm³)	p=0.0008	AE; B; C; E; A	NS	0.71
Tapped density (g/cm³)	p<0.0001	E; AE; C; B; BE; A	NS	0.82
Hausner ratio	p=0.0009	E	NS	0.43
Tablet hardness (N)	p<0.0001	B; C; AE; E; D; AC; DE; AB; A;	S	0.97
Tablet tensile strenght (MPa)	p<0.0001	B; C; E; AE; D; AC; DE; AB; A	S	0.96
Tablet disintegratio n time (min)	p=0.0067	C; BC; BE; AE; AD; B; D; E; A	S	0.81
Tablet friability (%)	p<0.0001	B; C; BD; D; BC; A	S	0.95

***NS = not significant, S = significant; Green identifies positive effect. Red identifies negative effect**

Tab.2 - DoE responses and statistical models

The main interaction influencing the time of disintegration and friability was BC and BD, respectively. Longer disintegration time could be observed at low L/S ratio and screw speed whereas, at **high L/S ratio the disintegration time was faster regardless of the screw speed** (BC, Fig. 3D). Lower friability was observed at low screw speed despite of the powder feed rate and increased at high screw speed and low powder feed rate (BD).

CONCLUSIONS

A DoE study was successfully carried out, and the influence of the main process variables (and their interactions) on the process outcomes and the quality attributes of granules and tablets were identified. The high-shear screw configuration affected the torque (and the barrel temperature), probably due to the higher energy imparted by the two mixing zones, that resulted also in granules of higher density. Similarly, lower L/S ratio led to higher torque values likely due to water affecting the viscosity of the formulation.

The screen type influenced the granule PSD, friability and density also as an interaction with other factors. **Therefore, the selection of the sieve was critical for the granule attributes. All the tablets showed adequate hardness and friability. With low screw speed and high L/S ratio (as a main effects) harder tablets were obtained.** The disintegration time range was 4 – 21 min and **faster disintegration was achieved at high L/S ratio regardless of the screw speed. Generally, It appeared that the properties of the tablets were not correlated with the granule properties as different TSWG process parameters were varied.**

In conclusion, a screening design was implemented as a "model view" to evaluate the impact of key TSWG process parameters towards the properties of granules and tablets. It is envisaged to evaluate the analytical and physical properties of the prototypes (e.g. content uniformity, impurities, porosity), the process parameters and formulation composition (e.g. screw design and drug loading).

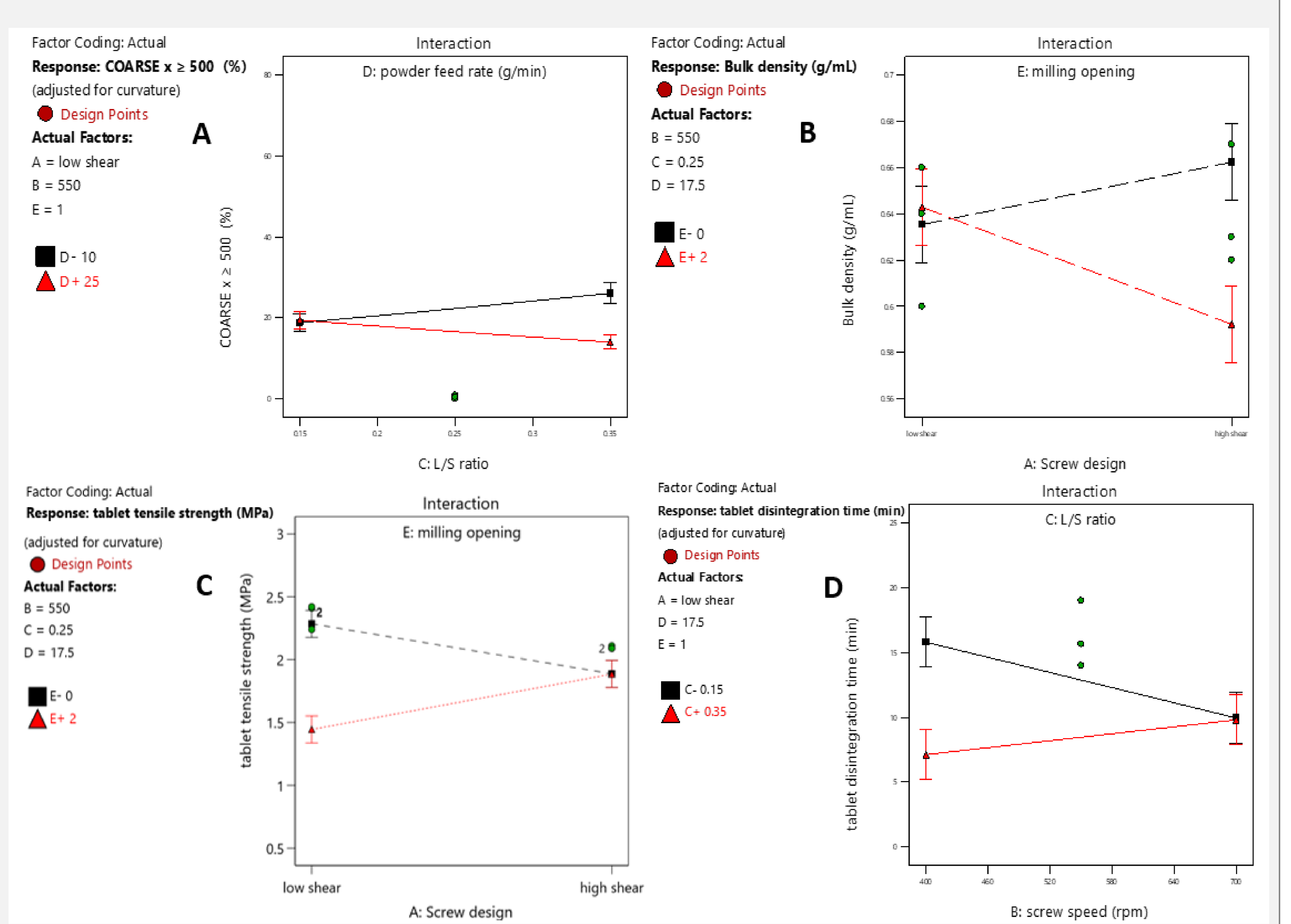

Fig.3 - Significant Interactions.

REFERENCES

[1] Portier et al, Pharmaceutics, 2021, 13, 668; [2] Keleb et al, Int J Pharm, 2002, 69; [3] Portier et al, Int J Pharm, 2020, 119004

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