Quality by Design of Continuous Wet Granulation

Functional characterisation of granules

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Introduction

Twin screw wet granulation has great potential for the pharmaceutical industry as it can allow continuous processing and manufacturing flexibility [1]. A formulation of ibuprofen 200 mg was evaluated using Quality by Design principles to:

- **Study the effect of Twin Screw Wet Granulation (TSWG) factors on granule quality;**
- **Characterise the final compressed tablet.**

The manufacture process produced granules which were tested for functional properties: flow, compressibility, tablet hardness, friability and disintegration.

DoE Methodology and Materials

A range of formulation and process parameters were considered (Figure 1). A preliminary risk assessment exercise was carried out to identify potential critical formulation and process parameters. Those chosen for this investigation are highlighted: solid feed rate, screw speed, compression force and % of disintegrant . The remaining factors were held constant .

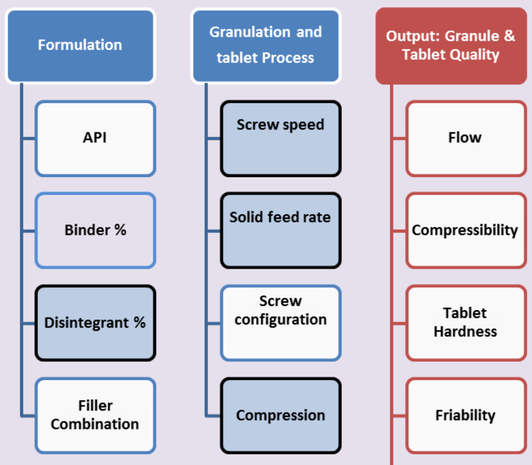


Figure 1 – Formulation and process factors considered for the twin screw wet granulation process.

Ibuprofen granules were produced using the Thermo Scientific 11mm twin screw extruder and a standard formulation of ibuprofen 200 mg immediate release.
Formulation and equipment variables are shown in Figure 1.

The quality of the granules and tablets were assessed by examining flow (Schulze Shear Cell), compressibility (Compaction Simulator), tablet hardness, friability and disintegration time.

Flowability: Shear cell

The shear cell test is useful to evaluate flowability characteristics of powders and granules. Flow was measured using a XSMV4 standard cell at 4000 Pa normal force and measured in duplicate.

The results show that all samples have an FFC of between 8.2 to 17 (Table 1). They are categorised between easy flowing to free flowing. FFC is good enough to predict acceptable flow on full scale tabletting equipment.

Table 1 – DoE parameters and the flowability results.

Solid feed Rate (g/min)	Screw speed (rpm)	Disintegrant (%)	Compression force (kN)	FFC Run 1	FFC Run 2	Flow category
5	250	3	Low	10	11	free-flowing
5	250	5	High	17	11	free-flowing
5	650	3	High	10	11	free-flowing
5	650	5	Low	9.8	16	free-flowing
6	450	4	Middle	9	8.6	easy-flowing
6	450	4	Middle	8.7	8.2	easy-flowing
7	250	3	High	8.7	9.8	easy-flowing
7	250	5	Low	13	13	free-flowing
7	650	3	Low	8.4	10	easy-flowing
7	650	5	High	11	10	easy-flowing

Design of Experiments – Factors and responses

The results for the tests were analysed using the JMP 11 software. The prediction profiler (Figure 2) shows the effects of factors on responses.

The red dotted line shows the mid-point conditions. The graphs show numbers attributed to the factors in X axis and the attributed to the responses in the Y axis. The continuous black line represents the correlation between lower and upper limit values of factors and their responses results.

In addition, the blue dotted lines represent the variation of the response values showing the effect of the changing compression force, solid feed rate, disintegrant level and screw speed on disintegration time, hardness and friability.

DoE Discussion of results

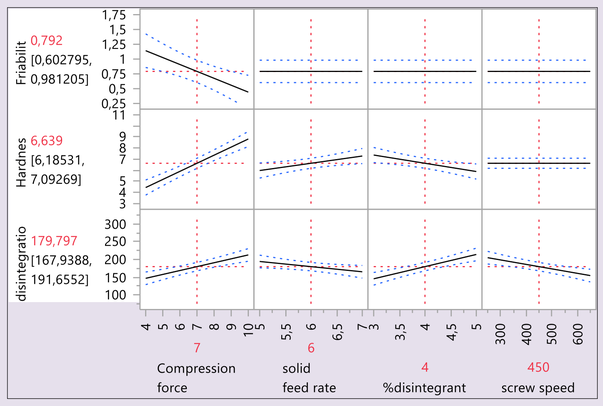


Figure 2 - Prediction profiler showing the effects of factors on responses

It is clear that the compression force is the most significant factor that influences the 3 responses. In hindsight, this factor was not appropriate to be studied as an input process factor and would have been better included as a quality output measurement.

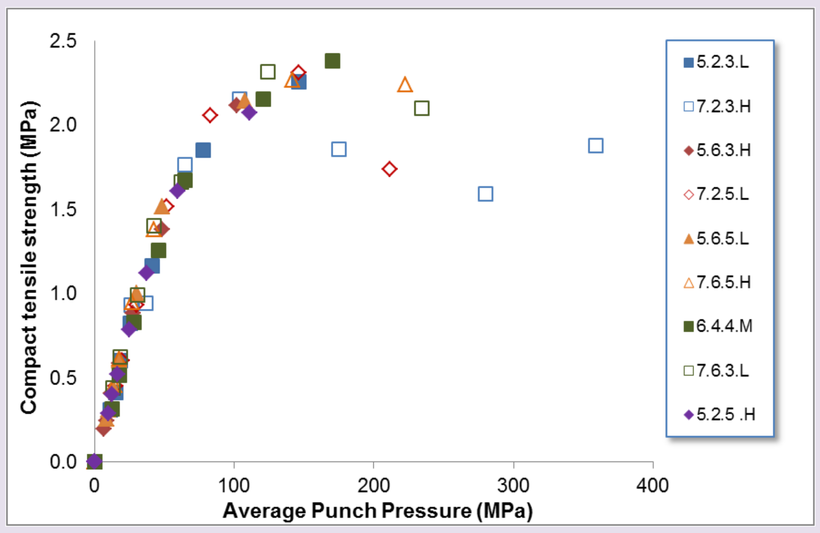
The tabletability of the granules was studied further to examine the formulation and process effects.

The results show:

- All factors affect disintegration time. As the time was extremely fast (12-54 seconds), in fact all would give an acceptable disintegration time.
- Compression force was the only variable to affect friability.
- Tablet hardness is improved by increasing compression force and solid feed rate, but decreases with an increase in disintegrant content.
- The only factor to influenced by screw speed was disintegration

Tabletability

The granules were compressed over a range of forces using a Phoenix hydraulic Compaction Simulator. The tablets were compressed using 10 mm diameter flat faced punches and the peak compression pressure was determined. The tablets were measured using calipers and the tablet hardness measured. Tensile strength was calculated[2] and the results plotted (Figure 3).



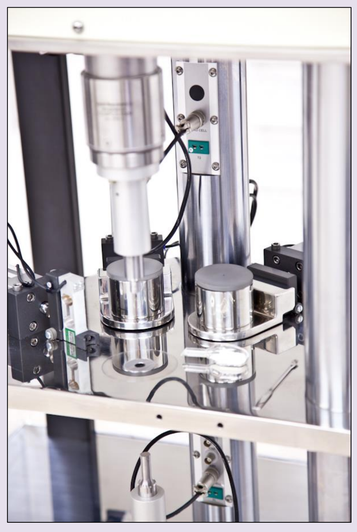


Figure 3 – Tabletability of the granules.

The results show that all of the formulation and process variants tested in the DoE investigation produced tablets that had very similar pressure versus tensile strength profiles. The tablet strengths are good, reaching a maximum of 2MPa before over-compression .

Conclusions

The results showed that granules could successfully be manufactured at all process conditions and had suitable flow properties for tabletting. The granules were compressible for all conditions tested.

Statistical analysis of the data showed that compression force had the greatest effect upon tablet quality and had perhaps masked the smaller effects of the process settings for this formulation. The formulation was surprisingly robust and would allow extension of the design space for future work.

References

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[2] J.Fell, J.M. Newton, Determination of tablet strength by diametral compression test. 1970 J. Pharm. Sci. 59: 688-691

Acknowledgments

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