Optimization of a high shear wet granulation process using Quantisweb and JMP™

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Abstract

Purpose: To evaluate the use of a web-based optimization tool, Quantisweb, by comparing results to a commercially available DOE software, JMP™. The effect of formulation design on a wet granulation process was examined.
Methods: Wet granulation was carried out in a high shear granulator followed by drying in a fluid bed under constant operating conditions. A lactose-based placebo formulation was used in this investigation. Four parameters (p) investigated were lactose to avicel ratio, binder content, water content and binder addition time. Responses evaluated were granule particle size, granule flow, tablet hardness and ejection force. Quantisweb followed a design requiring a minimum of Np+1 experiments for optimization. JMP™ followed a half-fraction factorial design with two center points for optimization. For both cases, a two-level design was followed.
Results: Quantisweb provided an optimization based on the results obtained, a set of weighting factors, "Yj", and defined ranges for the parameters, "Xi", under investigation. JMP™ provided a model based on the results obtained from the two-level half-fraction factorial design. Confirmation of the Quantisweb optimization resulted in granule with an average particle size of 265 microns and a Carr Index of 19%. Under a compression force of 18 kN, tablets had an average hardness of 7.6 kp with an average ejection force of 180 N. Target tablet weight was 250 mg. The JMP™ optimization resulted in granule with an average particle size of 245 microns and a Carr Index of 15%. Tablets, compressed at a force of 18 kN, had an average hardness of 7.1 kp and an average ejection force of 154 N.
Conclusions: The Quantisweb optimization, using an Np+1 design, concurred with results obtained using a two level half-fraction factorial design. For this case, Quantisweb has provided similar results as traditional methods with a 50% reduction in the number of experiments and the amount of raw material required.

Introduction

The development of a solid dosage form undergoes various stages. The optimization of a product can involve evaluation and determination of several variables, including the formulation and the processing parameters used during the manufacturing process. An optimal formulation and process is key to maintaining final product integrity. There are several commercially available software that provide optimization analysis. The advantage to such software is the ability of the research scientist to collect and analyze data on their own, without the aid of a statistician. In this study, two different software were evaluated, comparing the experimental design suggested and the final optimization predicted.

Objective

To evaluate the use of a web-based optimization tool, Quantisweb, by comparing results obtained with that of a separate statistical software, JMP. A high shear wet granulation process was studied in the investigation.

Methods & Materials

Commercial Software Evaluated :

- Quantisweb v. 2.0.3 (Quantis Formulation Inc., Montreal, QC, Canada)
  - Web-based optimization tool
  - DOE required a minimum of Np+1
- JMP v. 5.0.1 - statistical software (SAS Institute Inc., Cary, NC, USA)
  - statistical software
  - followed a half-fraction factorial DOE

Equipment & Instruments Used :

Wet granulation: 25 L high shear granulator (Fielder-Aeromatic)
Fluid bed drying: Glatt GPCG1 (Glatt Air Techniques)
Milling: 50G rasp screen, square impeller, 1750 rpm (Quadro Engineering Incorporated)
Sieve mesh analysis: 10 min shaking time (Gilson Company, Inc.,)
Tap density: 1000 taps (VanKel Tapped Density Tester)
Compression: 11/32" round standard concave, 250 mg tablet weight, 40 rpm table speed (Korsch PH106)

Table 1: Summary of parameters investigated and factors evaluated

Parameters investigated	-1	0	+1	Factors evaluated
Lactose to avicel ratio (-)	1:2	1:1	2:1	Granule particle size (microns)
Binder content (%)	2	4	6	Carr Index (%)
Water content (%)	34	42	50	Tablet hardness (kp)
Binder addition time (min)	3:00	6:00	9:00	Ejection force (N)

Maintained constant operating parameters during processing:

Wet Granulation:
- 3 kg batch size, dry
- impeller & chopper speeds = 261/3600 rpm
- pre-mixing time = 5 min
- post-binder addition mixing time = 2 min
- binder added as solution, spraying time variable

Fluid bed drying:
- wet granule divided into 2 equal sections
- inlet air temperature = 65˚C
- gas velocity = 2 - 5 m/s
- final product temperature = 40˚C

* *Note: LOD measurements not taken on final dried granule; product temperature was used as end point determination*

Table 2a) Experimental design followed using Quantisweb

Experiment	L/A Ratio	% HPC	% Water	Spray Time [1] (m:ss)
DOE3	0.5	2	34	3:00 (2:57)
DOE9	0.5	6	50	9:00 (8:29)
DOE11	2.0	6	50	3:00 (3:59)
DOE13	2.0	6	34	9:00 (10:29)
DOE14	2.0	2	50	9:00 (9:19)

Table 2b) Experimental design followed using JMP (half fraction factorial)

Experiment	L/A Ratio	% HPC	% Water	Spray Time
[2]DOE1	0	0	0	0
[2]DOE2	0	0	0	0
DOE3	-1	-1	-1	-1
DOE5	-1	-1	+1	+
DOE6	+1	-1	+1	-1
DOE7	+1	-1	-1	+1
DOE8	+1	+1	+1	+1
DOE10	-1	+1	+1	-1
DOE12	-1	+1	-1	+1
DOE15	+1	+1	-1	-1

[1] values in parentheses are actual spray times

[2] DOE1 & DOE2 represent two center points

Results

Table 3a) Results obtained from the Quantisweb experimental design

Experiment	Carr Index (%)	dp, avg (microns)	Tablet [1] hardness (kp +/- %RSD)	Ejection Force (N)
DOE3	24	134	11.9 ± 1.9	136
DOE9	28	236	5.3 ± 2.9	124
DOE11	15	3064	4.2 ± 3.3	72
DOE13	14	258	7.7 ± 1.4	189
DOE14	10	252	7.4 ± 3.4	215

Table 3b) Results obtained from the JMP experimental design

Experiment	Carr Index (%)	dp, avg (microns)	Tablet [1] hardness (kp +/- %RSD)	Ejection Force (N)
DOE1	15	199	7.7 ± 1.9	165
DOE2	17	188	7.6 ± 3.5	170
DOE3	24	134	11.9 ± 1.9	136
DOE5	18	150	8.2 ± 2.9	135
DOE6	13	281	8.1 ± 3.3	227
DOE7	15	169	8.2 ± 2.3	190
DOE8	16	1254	9.3 ± 2.5	74
DOE10	14	225	7.0 ± 2.5	138
DOE12	20	166	10.5 ± 1.8	124
DOE15	14	274	8.3 ± 0.9	179

[1]Tablet hardness was that based on a compression force of 18 kN, %RSD values not used in data analysis

Overall summary of results:
- increasing the amount of lactose led to improved flow and decreased particle size
- increasing the amount of HPC improved flow, reduced ejection force and increased particle size
- increased water levels reduced tablet compressibility and ejection force values
- spray time had negligible effect on results

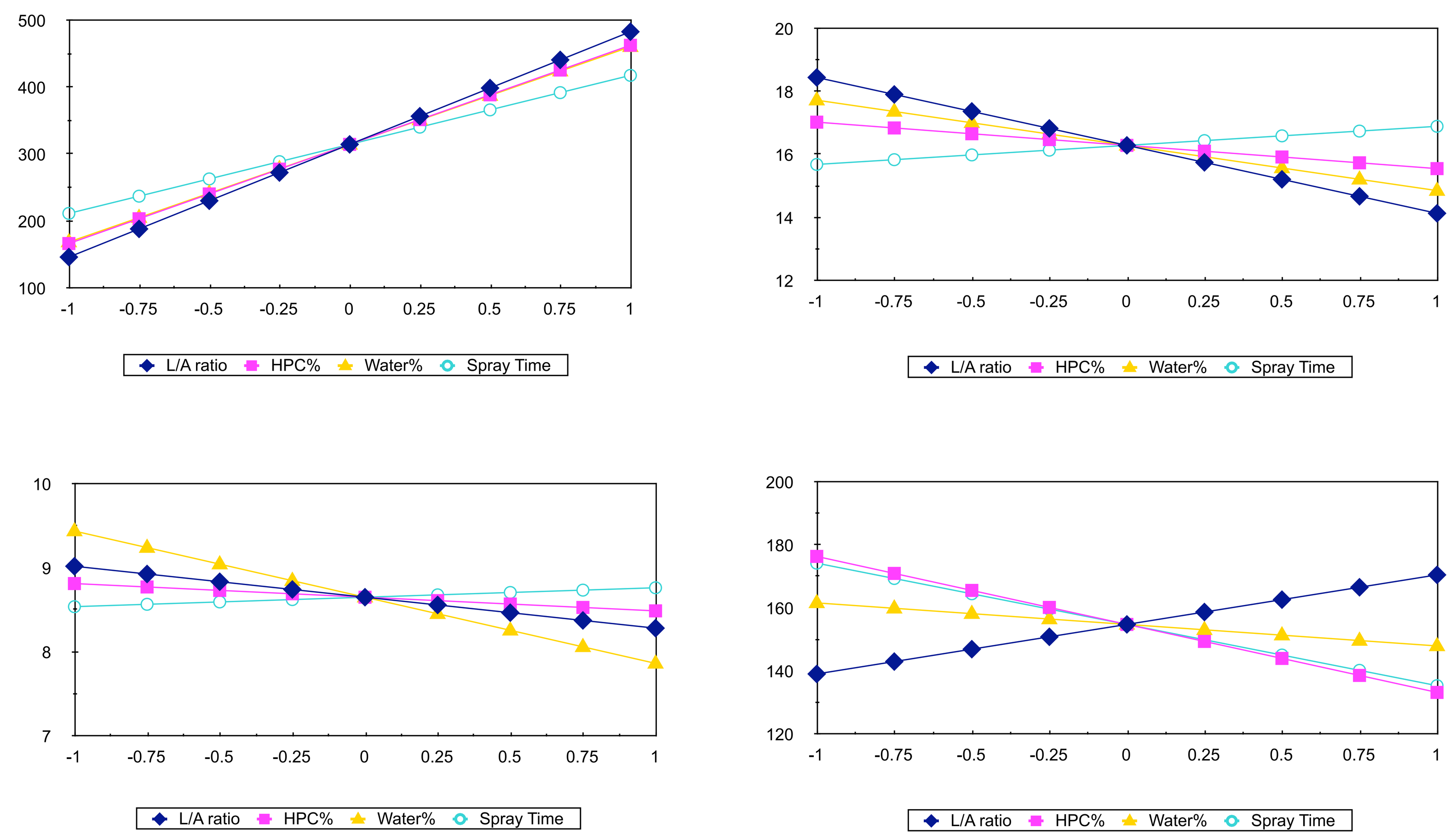

Figure 1: Effects of varying parameters: A) particle size distribution, B) Carr Index, C) tablet hardness and D) ejection force (based on the JMP analysis; half-fraction factorial)

Optimization: Data Analysis

Quantisweb Data Analysis:
Quantisweb provided an optimization based on three things: the actual results obtained from the DOE, a set of weighting factors, "Yj" (Table 4), and a defined range of ideal factor values acceptable for the parameters of interest, "Xi" (Table 5).
Based on these inputs, a set of multivariate equations are defined, known as behavioural laws. These laws provide an approximation of the impact of the parameters to the factors under consideration.
The optimization suggested by Quantisweb included an L/A ratio of 1:1, 4% HPC, 50% water and a spraying time of 4.5 minutes.

JMP Data Analysis:
JMP provided a model based on the actual results obtained from the two-level half-fraction factorial design, from which a set of optimal results could be determined. The optimal combination of variables, was obtained by fitting the values listed in Table 6 to the following equation :

$$\boldsymbol{A}X1 + \boldsymbol{B}X2 + \boldsymbol{C}X3 + \boldsymbol{D}X4 + Y = P$$

The optimization through model fitting in JMP suggested an L/A ratio of 1.8:1, 4.2% HPC, 42.5% water and a spraying time of 6.5 minutes.

Table 4: Weighting factors used in Quantisweb (Pair-wise comparison)

	Y1	Y2	Y3	Y4
Y1	1:1	1:3	1:4	3:1
Y2		1:1	1:2	5:1
Y3			1:1	6:1
Y4				1:1

Table 5: Ideal factor values for parameters of interest

	Description	Ideal Values	
		Min	Max
Level Y1	Particle size distribution (microns)	250	500
Level Y2	Carr Index (%)	5	20
Level Y3	Tablet hardness (kp)	6	9
Level Y4	Ejection force (N)	80	200

Table 6: Model obtained using JMP

X values ↓	P values →			
	PSD (microns)	Carr Index (%)	Tablet Hardness (kp)	Ejection Force (N)
	A	*B*	*C*	*D*
Intercept	315.222826	16.3032609	8.65543478	154.90212
L/A Ratio (X1)	168.342391	-2.156087	-0.3684783	15.7217935
HPC content (X2)	148.125	-0.7375	-0.1625	-21.58125
Water content (X3)	145.875	-1.435	-0.7875	-6.82875
Spray time (X4)	103.125	0.605	0.1125	-19.43875

Optimization: Results

Table 7: Optimization results using JMP and Quantisweb

Experiment		dp, avg (microns)	Carr Index (%)	Tablet hardness[1] (kp ± SD)	Ejection Force (N)
DOE16 (JMP)	Predicted	410	15	7.8	158
	Actual	245	15	7.1	154
DOE17 (Quantisweb)	Predicted	375	15	0.44	146
	Actual	265	19	7.6	180

[1] at a compression force of 18 kN

- Verification of the optimization work resulted in acceptable values, for both JMP and Quantisweb.
- Actual values obtained for particle size distribution were lower than those predicted by either software.
- The predicted value for tablet hardness by Quantisweb was below the acceptable value of 6-9 kp for a 250 mg tablet size.
- Additional work was completed with Quantisweb to evaluate the effect of varying the weighting factors and the ideal factor values. Results from this investigation showed minimal impact on the predicted factor values for optimization of the high shear wet granulation process.

Conclusions

- The Quantisweb optimization, using an Np+1 design, concurred with results obtained using a two level, half-fraction factorial design. For this case, Quantisweb has provided similar results as traditional methods with a 50% reduction in the number of experiments while reducing the amount of material required.
- Verification of the predicted optimization provided by Quantisweb and JMP produced granule and tablets of acceptable quality.
- The optimization as provided by Quantisweb predicted a tablet hardness of 0.44 kp. This prediction was based on the behavioural laws defined by all the inputs to the system, including the results of experiments, the defined ideal factor values and a set of weighting functions.

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