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Optimization of a Spray-Drying Process for an Amorphous Solid Dispersion via Experimental Design

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PURPOSE

The bio-enabling technological approach of an amorphous solid dispersion (ASD) via spray drying was utilised in the development of a solid oral dosage form of *Compound G*. Following preliminary feasibility studies and in an attempt to optimise the spray drying process for future scale-up, a Design of Experiments was constructed using a 2^4 full-factorial design. The process parameters of air temperature, nozzle size, nozzle pressure and solution feed-rate were investigated for their impact on the selected response factors of drug-related impurities, residual acetone, particle size distribution and process yield.

METHODS

For each of the 16 experiments in the two-level design, *Compound G* and a pharmaceutically acceptable polymer were dissolved in acetone and spray dried using a *Procept 4M8Trix* Spray Drier operating in a closed-loop configuration. Resultant material was analysed for drug-related impurities (*Agilent* HPLC), residual acetone (*Agilent* GC-HS with FID) and particle size distribution via Laser Light Scattering (*Sympatech HELOS)*. The software *Design Expert* was employed to process the results of the response factors, establish the interaction coefficients and calculate the optimal process parameters that would yield the most desirable attributes of the spray dried ASD of *Compound G*.

RESULTS

On collation of the data for the response factors the interactions and their significances were computed via the software and the results are reported in Table 1. Strong interactions were detected for Drug-Related Impurities, however, their impact was low (Δ ± 0.02 % a/a), therefore this response factor was not prioritized in the subsequent process optimization computation. Similarly, the impact of the process parameters on experimental yield was shown to be either insignificant or of questionable benefit. For this reason, the response factors of residual acetone and particle size distribution were selected for progression to the optimization calculations. Multiple optimization computations were performed. However, on consideration of the option of a secondary drying step to remove residual acetone (if required) it was decided to prioritize particle size distribution. The relative weighting of these response factors and the desired outcome (minimize, maximize) are shown in Table 2. The results of the process optimization computation are reported in Figure 1, reporting recommended process parameters, predicted outcomes for the response factors investigated and the desirability coefficient. An intermediate process temperature was computed to yield optimal results with respect to the desired outcomes. All other process parameters were at the extremes of the design space, indicating the potential for further optimization.

Response	Air Temp.	Nozzle Size	Nozzle Pressure	Feed Rate	N. Size-N. Pressure	N. Size-Feed Rate	N. Pressure-Feed Rate	N. Size-N. Press.-Feed Rate
Drug-related Impurities, % a/a (p-value)		0.0225 (0.0011)	-0.02375 (0.0008)	-0.01625 (0.0069)	0.01375 (0.0158)	-0.02125 (0.0015)	-0.0025 (0.5943)	-0.015 (0.0104)
Residual Acetone, % w/w (p-value)	-0.0925 (0.0036)			0.0825 (0.0075)				
Process Yield, % (p-value)	-4.1875 (0.0148)		-4.0625 (0.0173)	-1.4375 (0.3432)			-3.3125 (0.0433)	
Dv90, µm (p-value)		-3.32687 (0.0730)	-4.62187 (0.0183)	3.27938 (0.0767)				
Dv50, µm (p-value)	-1.16563 (0.0150)	-0.996875 (0.0320)	-1.99438 (0.0004)					

Table 1: Interaction Coefficients (strong, intermediate, weak, insignificant)

Response Factor	Goal	Lower Limit	Upper Limit	Importance
Dv90 (µm)	Maximize	6.41	35.39	High
Dv50 (µm)	Maximize	2.28	12.77	
Dv10 (µm)	Maximize	0.58	1.83	
Residual Acetone (% w/w)	Minimize	0.05	0.57	Intermediate

Table 2: Response Factor Conditions For Optimization Computation

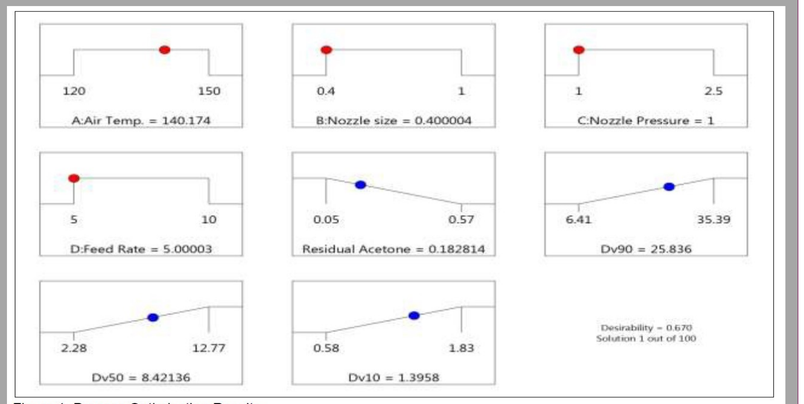

Figure 1: Process Optimization Results

CONCLUSION

In support of process scale-up activities, the criticality of the equipment parameters for a spray drying process was explored via experimental design. Conditions were identified to fine-tune material attributes of the ASD with respect to particle size distribution and residual acetone. Furthermore, the computation highlights scope to expand the design space for further optimization.

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