M1230-08-51

Spray Drying Processability of Methacrylic acid copolymers in Amorphous Dispersions: A QbD Approach

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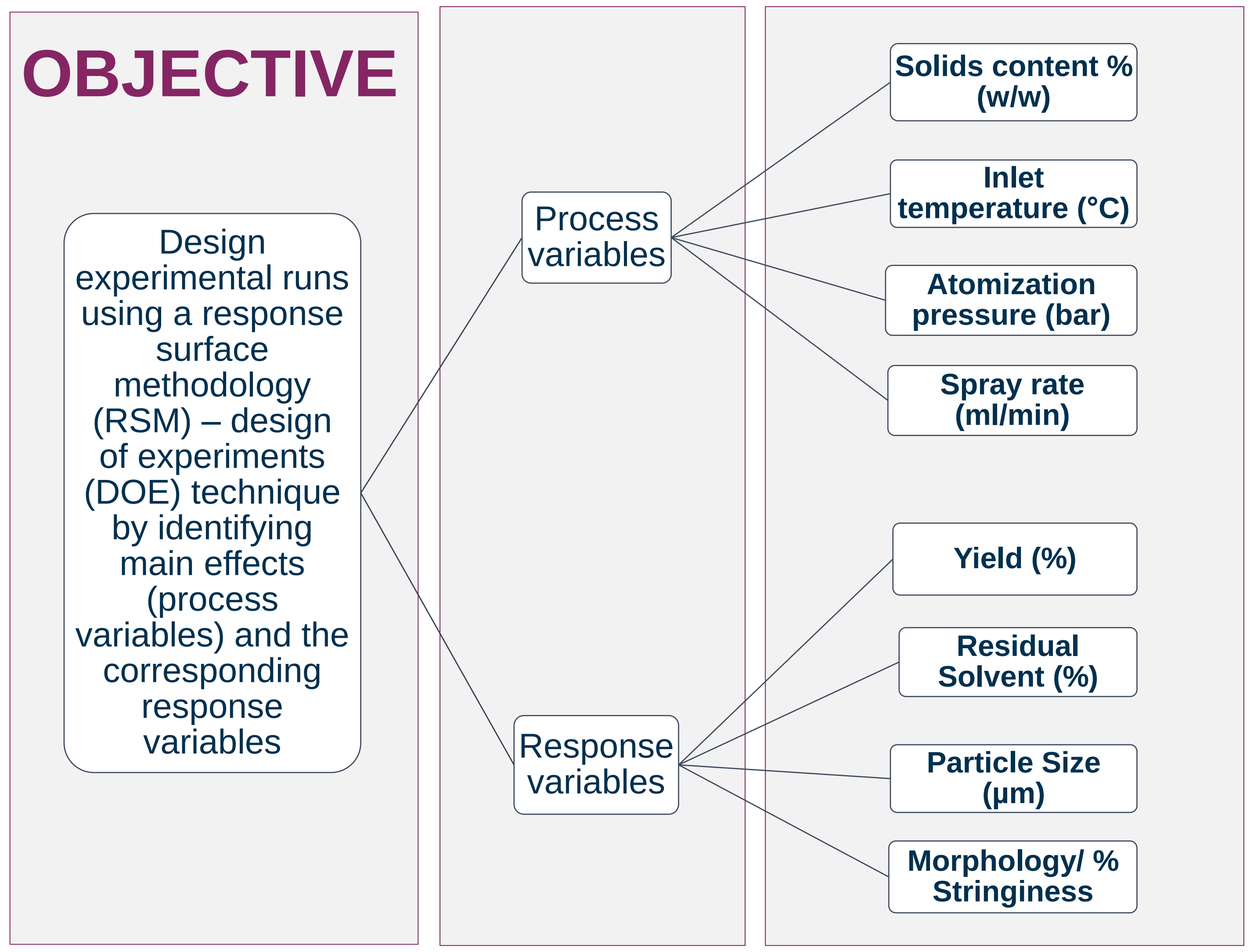
PURPOSE

- Methacrylic acid copolymers, e.g. **Eudragit® L 100, Eudragit® S 100 and Eudragit® L 100-55** are enteric polymers that demonstrate promise for formulating **amorphous solid dispersions (ASD**) of low solubility molecules, attributed to their high glass transition temperature (Tg) enabling **high drug loading** and **improved physical stability**.
- Using spray drying as a process to formulate ASD of methacrylic acid copolymers is challenging due to issues such as **string formation** resulting in **low yields** and **excessive chamber buildup.**
- In this work, a **QbD approach** was utilized to establish a spray drying process space using **Eudragit® L 100** as our model polymer. **Critical processing parameters** affecting the spray drying process were identified in order to determine optimal operating conditions.

OBJECTIVE



Design experimental runs using a response surface methodology (RSM) – design of experiments (DOE) technique by identifying main effects (process variables) and the corresponding response variables

Process variables

- **Solids content % (w/w)**
- **Inlet temperature (°C)**
- **Atomization pressure (bar)**
- **Spray rate (ml/min)**

Response variables

- **Yield (%)**
- **Residual Solvent (%)**
- **Particle Size (µm)**
- **Morphology/ % Stringiness**

METHODS

- A **22-run** custom design was generated within the limits depicted in Table 1 using statistical software **JMP®14 by SAS** with an **I-Optimality** criterion.
- A solvent system of **90:10 acetone: water** was used to prepare the spray solutions at the predetermined solids % (w/w)
- The solutions were sprayed on a **BÜCHI B-290** mini spray dryer at the stated spray conditions; each a batch size of about 300-350 g.
- The data (responses) generated from the experimental runs was modelled to a **stepwise regression** fit with a stopping rule of p-value threshold.

Table 1. The limits for independent variables (process factors) generating the 22-run design

Independent variables	Limits
Spray rate	10-30 ml/min
Atomization Pressure	1-3 bar
Inlet temperature	70-180°C
Solids %	3-7 % (w/w)

Dependent variables (responses)

Morphology (% Strings)

- Estimated from the unit area coverage of the strings to regular spray dried dispersion (SDD) using captured SEM images of the individual runs (n=3)
- **FEI Quanta 200 Scanning Electron Microscope**

Residual Solvent (% LOD)

- A small amount of the wet SDD was analyzed by the standard drying program
- **Sartorius MA37 Moisture Analyzer**

% Yield

- Collected SDD was weighed to calculate a wet yield
- SDD was dried in a **convection tray dryer** at 40°C for 24 hours and weighed to obtain % Yield

Particle size (µm)

- D90 (µm) of the dried samples was plotted as a function of the independent variables
- **Malvern Mastersizer 3000 using a Aero S dry powder disperser**

RESULTS

- Table 2 summarizes responses modeled to quadratic regression, ordered as a function of "goodness of fit"
- The particle size data demonstrated a good fit with R^2 value of 0.954; significantly affected by the spray rate, inlet temperature, % solids and the secondary interaction terms of % solids with spray rate, atomization pressure and inlet temperature as depicted in Table 3.

Table 2. Summary of response variables and goodness of fit

Fit group (Response)	Summary of Fit		Analysis of Variance
	R^2	R^2 Adjusted	
Particle size	0.954	0.917	< 0.0001
Presence of Strings	0.807	0.73	0.0001
Yield	0.685	0.633	< 0.0001
Loss on Drying	0.271	0.194	0.0496

- Terms significantly affecting % yield are the inlet temperature and % solids (w/w); at any inlet temperature, there is a linear decline in the % yield on increasing the total % solids (w/w) observed in Figure 2.

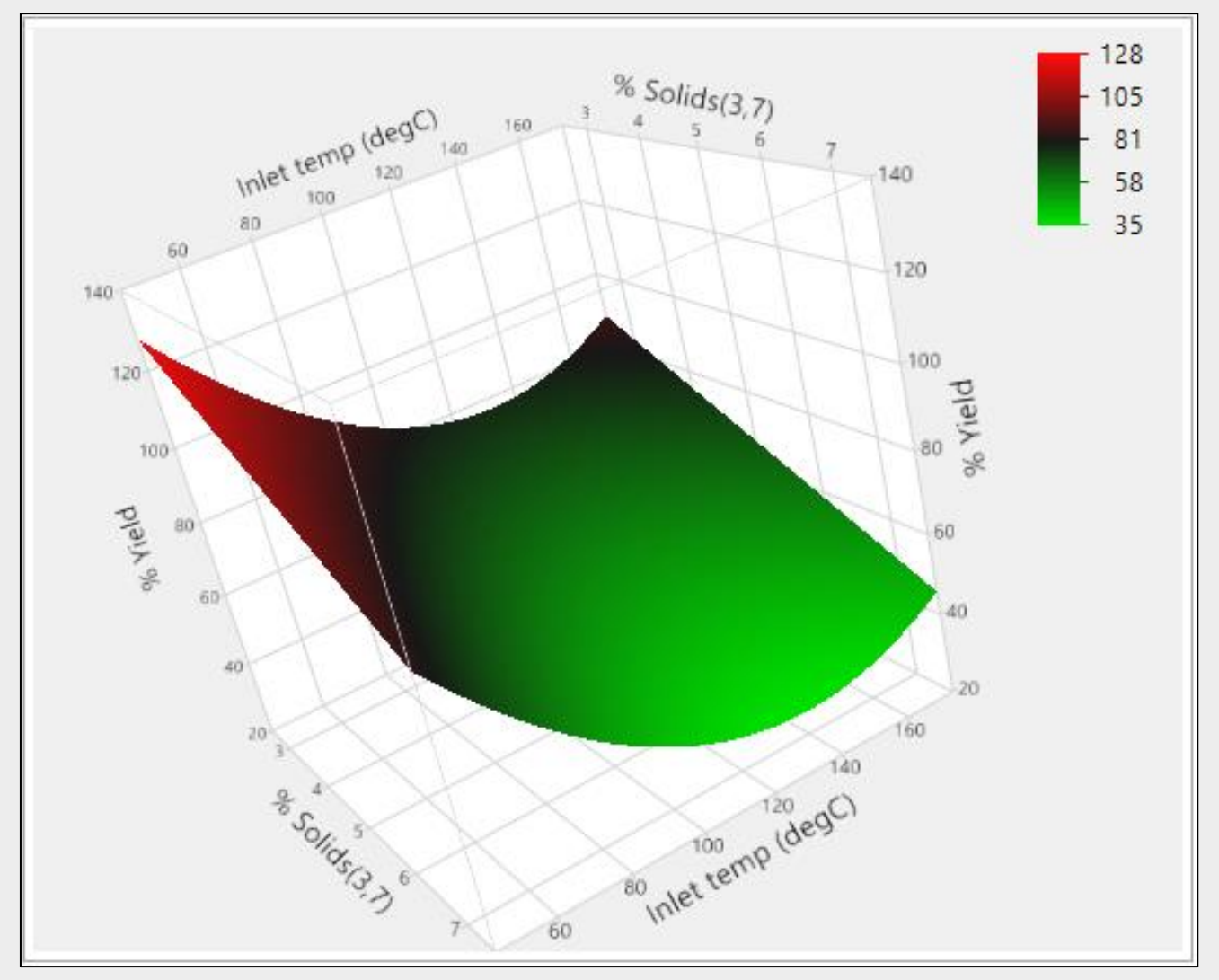


Figure 2. Effect of inlet temperature (°C) and % w/w solids on % Yield

- Increasing the inlet temperature demonstrated a significant decline in the residual solvent (% LOD) as can be observed in Figure 3.

- A significant increase in presence of strings was observed on increasing % solids.
- Figure 1 depicts the combined effect of flow rate and % solids; increasing the spray rate at a higher % solids demonstrated a marked decline in the strings generated

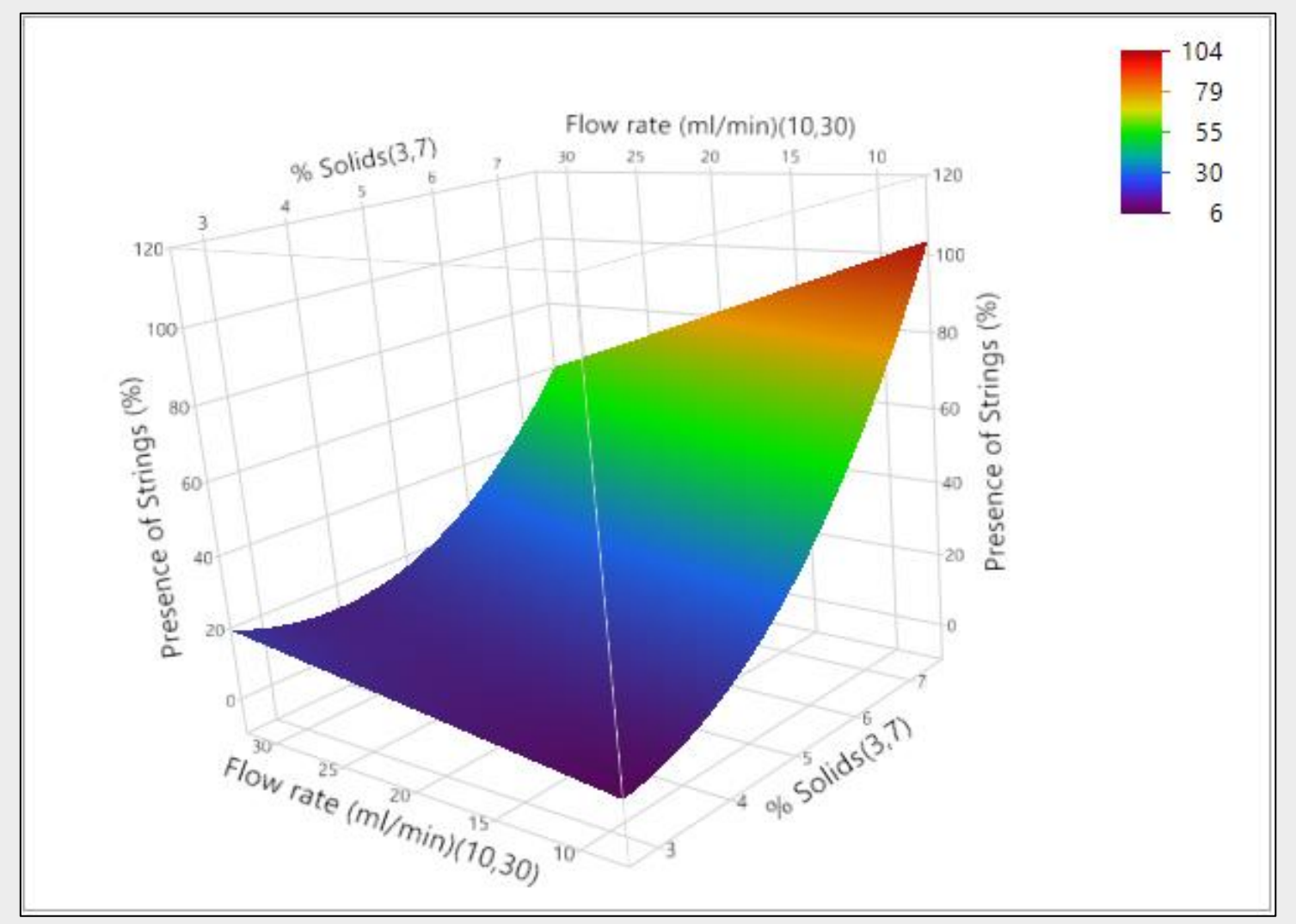


Figure 1. Effect of spray rate (ml/min) and solids content (% w/w) on the morphology of SDD

Table 3. Summary of individual independent variables and their interactions terms significantly affecting responses

Dependent variables	Independent variables	P-value
% Yield	Inlet temperature	0.0282
	% Solids	< 0.0001
%LOD	Inlet temperature	0.0155
Particle size	Spray rate	< 0.0001
	Inlet temperature	< 0.0001
	% Solids	0.0197
	% Solids* Spray rate	< 0.0001
	% Solids* Atomization pressure	0.0107
	% Solids* Inlet temperature	< 0.0001
% Strings	% Solids	< 0.0001

RESULTS

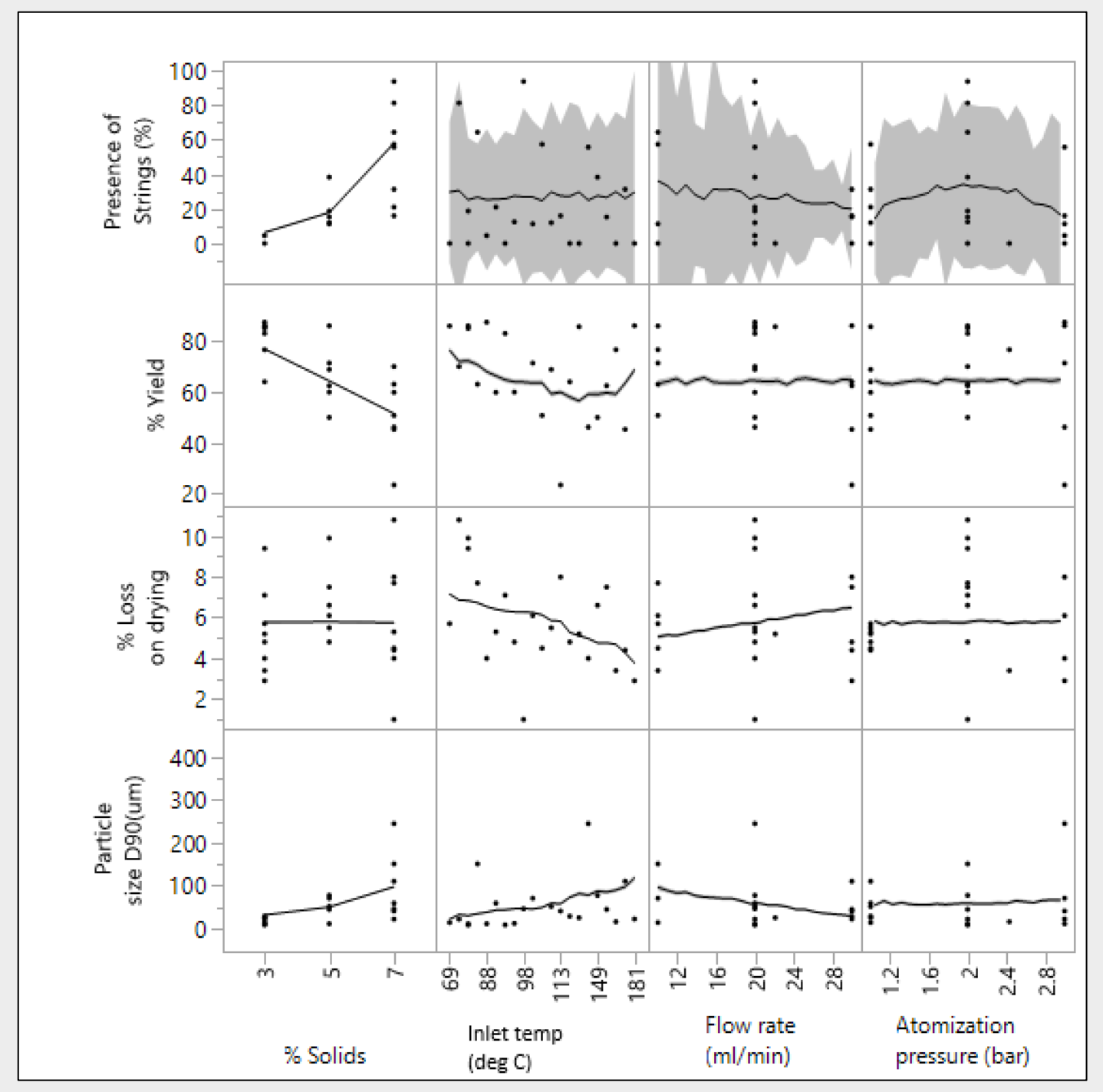


Figure 3. Marginal model plot depicting the marginal effects of independent variables spray rate (ml/min), atomization pressure (bar), inlet temperature (°C) and solids % (w/w) on responses, % yield, % loss on drying (LOD), particle size distribution (PSD), presence of strings (%)

- Figure 4 (A, B) shows SEM images of the SDD, depicting differences between the stringy and spherical/collapsed spherical morphology as a result of changing processing parameters

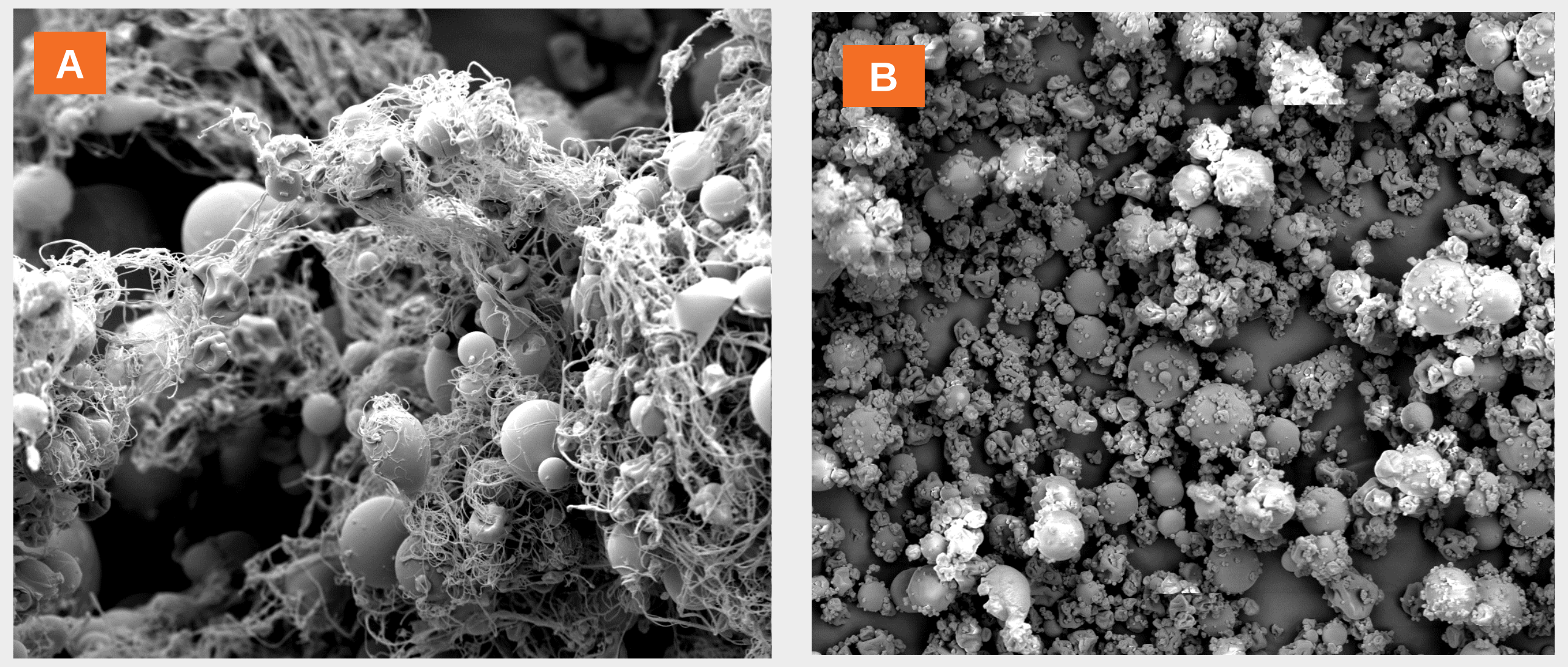


Figure 4. SEM images (1500 X magnification) of 100% EUDRAGIT® L 100 SDD, sprayed from 90:10 Acetone: Water at (A) 7% (w/w) total solids, inlet temperature of 102°C, atomization pressure 1 bar and spray rate 10 ml/min and (B) 3% (w/w) total solids, inlet temperature of 137°C, atomization pressure 1 bar, and spray rate 22.1 ml/min

CONCLUSIONS

- **This study enabled identification of the desired process space for spray drying methacrylic acid copolymers such as Eudragit® L 100.**
- **Critical processing parameters were identified and a parametric study was conducted.**
- **Findings indicate that maintaining a lower solids content and lower inlet/outlet temperatures minimizes stringiness.**
- **For achieving high solids content, it was determined that colder inlet/outlet temperatures and higher spray rates improve process efficiency.**
- **It was determined that atomization pressure did not demonstrate a significant effect on the processability.**