Manufacturing optimisation of electrospun Eudragit® E PO using a factorial design

Hend Abdelhakim[*1], Catherine Tuleu[1], Alastair Coupe[2], Mohan Edirisinghe[3] and Duncan Craig[1]

[1]University College London (UCL), School of Pharmacy, 29-39 Brunswick Square, London, UK, [2]Pfizer Limited, Global R&D, Sandwich, Kent, UK and [3]UCL, Department of Mechanical Engineering, Torrington Place, London, UK. * hend.abdelhakim.16@ucl.ac.uk

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Introduction

Electrospinning is used to manufacture nanofibres for various applications, including drug delivery. The fibres produced are affected by a number of parameters, shown in Fig. 1:

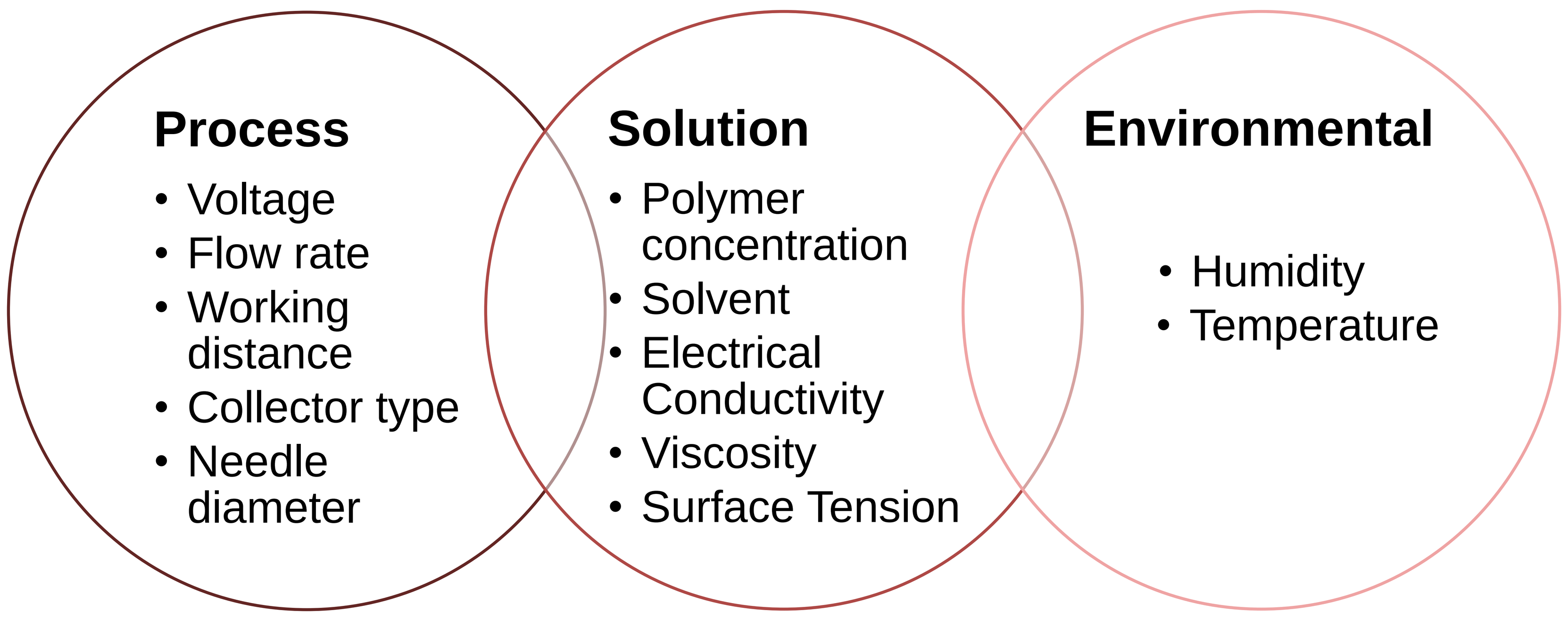

Fig. 1 - **Interdependent parameters that may influence electrospinning [1]**

The aim of this study is to optimise the manufacturing of Eudragit® E PO (E-EPO), Poly(butyl methacrylate-co-(2-dimethylaminoethyl) methacrylate-co-methyl methacrylate) 1:2:1 fibres by varying a number of parameters using a definitive screening, fractional factorial design. This is the first electrospinning study of E-EPO for the purpose of producing a taste-masked paediatric oral dosage form.

Two criteria were set as the desired outcomes:

1. Reduce fibre diameter to nano-range.
2. Minimise beading.

Materials & Methods

E-EPO was donated by Evonik (Darmstadt, Germany). All solutions were prepared to 100% using absolute ethanol. Spraybase® electrospinning apparatus was used to manufacture the fibres. A Scanning Electron Microscope (SEM) FEI Quanta 200FEG, was used to image the fibres. ImageJ 1.46R was used to measure diameters. JMP Pro 12.0.1 was used to create the fractional design and for data analysis. Parameters investigated and their different levels are shown in Table 1.

Table 1 - **A table displaying the factors and the three corresponding levels for each**

Factor	Low	Medium	High
Applied voltage (kV)	10.00	17.50	25.00
Flow rate (mL/h)	0.50	1.25	2.00
Gap distance (mm)	150.00	200.00	250.00
E-EPO concentration (%w/v)	25.00	35.00	45.00
Water in solvent (%v/v)	0.00	10.00	20.00

Results & Discussion

If a systematic approach was used to run experiments for all combinations of the five chosen factors at three levels for each, this would have resulted in 3^5, or 243 separate experiments. The factorial design allowed for optimisation with only 14. These were performed over two different days. The temperature ranged between 23.5 – 24°C and the relative humidity (RH) ranged between 27 – 28 %.

Minimising beading

Increasing polymer concentration was found to be the most significant factor (**p = 0.004**) in producing non-beaded fibres**.** The other parameters were not statistically significant; p values are shown in Table 2. Examples of fibres are shown in Fig. 2 and Fig. 3.

Table 2 - **Statistical significance of different parameters on reducing beading & diameter**

Effect on beading	p	Effect on diameter	p
Concentration	0.004	Concentration	0.008
Flow rate	0.180	Voltage	0.220
Distance	0.700	Water addition	0.260
Water	0.764	Distance	0.641
Voltage	0.778	Flow rate	0.820

As well as identifying key parameters, the factorial approach can also be used to predict optimum conditions. For bead-free fibres, these were predicted to be 45% E-EPO, 20% water, flow rate of 0.9 mL/h, voltage of ~21 kV, and distance of 150 mm, with an R^2 of 0.93. This was validated experimentally, thereby lending weight to the predictive approach.

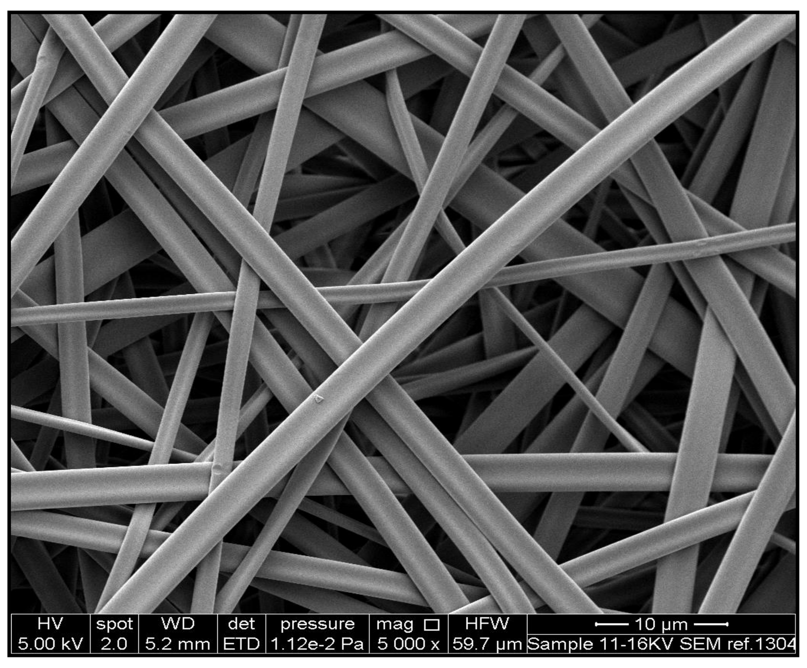

Fig. 2 - **SEM image of 45% E-EPO, in 20% Water, processed at 16 kV, gap distance of 150 mm and flow rate of 0.5mL/h, Mean diameter = 2789 nm**

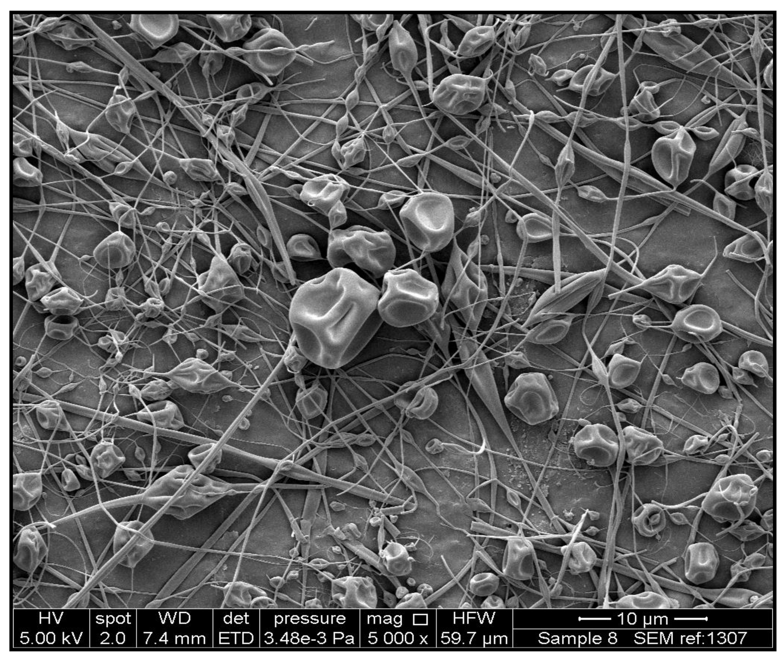

Fig. 3 - **SEM image of 25% E-EPO, in 0% Water, processed at 25 kV, gap distance of 250 mm and flow rate of 2mL/h,. Mean diameter = 416 nm , beading = 150/ 3 mm²**

Minimising diameter

Minimising fibre diameter was most affected by a decrease in polymer concentration (p = 0.008). The significance of the other parameters is shown in Table 2. The optimum parameters were predicted to be 28% E-EPO, 20% water, flow rate of 0.5 mL/h, voltage of 25kV, and distance of 150 mm to generate fibres with an average diameter of 155nm, R^2 = 0.92**.** Experimental validation produced non-beaded fibres with an average diameter of 930 nm (± 348).

Optimisation - When both outcomes were modelled together, the prediction profiler tool, shown in Fig. 4, predicted that at 25kV, 35% E-EPO, 0.5mL/h flow rate, distance of 150mm, and addition of 20% water, fibres with an average diameter of 621 nm will be formed. They will also contain 37 beads per 3 mm² (i.e. very low beading). When validated experimentally non-beaded fibres with an average diameter of 1508 nm (± 250) were formed .

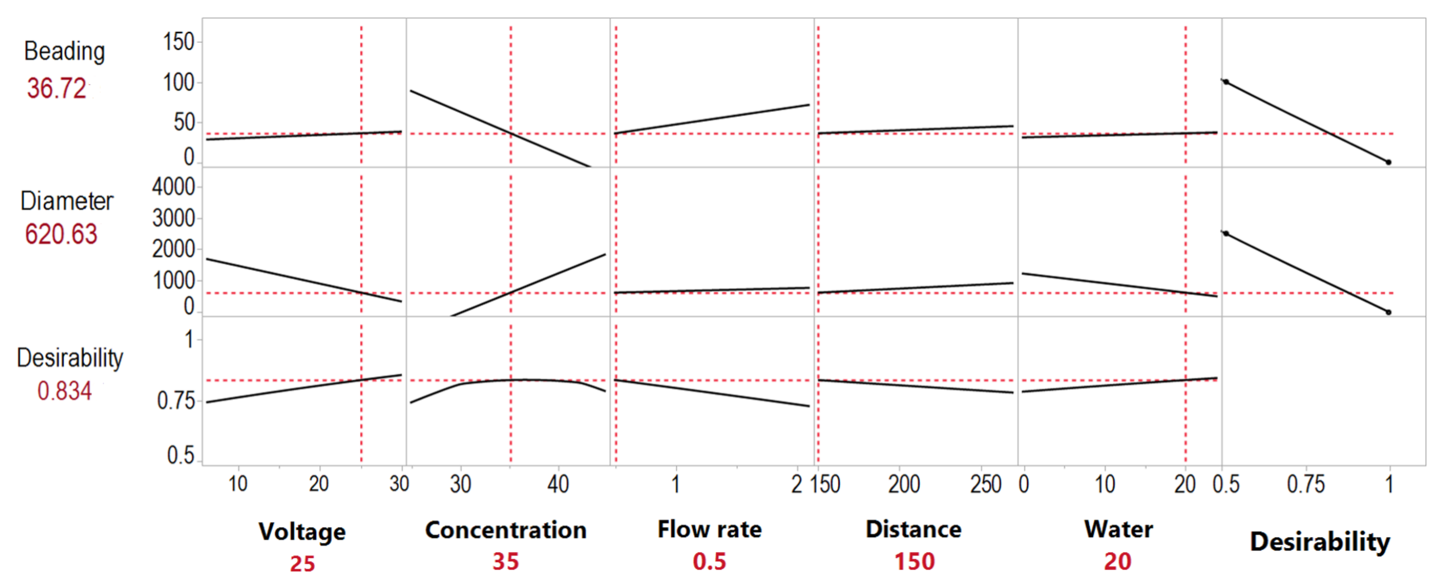

Fig. 4 - **Prediction tool showing the relationship between the parameters and outcomes.**

Conclusion

We describe a factorial approach that allows both the identification of the most influential manufacturing conditions for nano-diameter fibres and absence of beading as well as the prediction of optimal conditions for both outcomes. The study has therefore not only suggested parameters for producing E-EPO fibres but has also developed an approach for the rational choice of electrospinning conditions.

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Reference:

1. Hu, X. et al., 2014. Electrospinning of polymeric nanofibers for drug delivery applications. *Journal of Controlled Release*, 185(1), pp.12–21.