Taste-masked fibres for paediatric drug delivery

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Introduction

Electrospinning is being explored as an approach for oral drug delivery, particularly as historical issues of large scale production are now being better understood. Here we explore the manufacture of taste-masked fibres loaded with the bitter antihistamine drug chlorpheniramine maleate (CPM). We use a Design Of Experiment (DoE) definitive screening approach to optimise the manufacturing conditions for fibres composed of Eudragit E PO (E-EPO) loaded with CPM. A biosensor (E-tongue) approach was then used to asses the bitterness of the fibres produced compared to the drug alone.

Aims & Objectives

The aim of this study was to explore the potential of using electrospinning as a technique for generating taste-masked dosage forms.

The objectives were to reliably manufacture CPM-loaded E-EPO fibres, assess their morphology and their ability to mask the bitter taste of CPM, assessed by an electronic tasting system.

Methodology

Solutions of 25% to 45% E-EPO were prepared in either ethanol or ethanol and 10-20% water. A DoE approach was used to screen the most influential factors in producing smooth E-EPO fibres and the findings used to optimise the manufacturing process. JMP Pro 12.0.1 was used to create the screening design. Process parameters controlled were applied voltage (10-25 kV), flow rate (0.5-2.0 mL/h), and working distance (150-250 mm). CPM was added in a range of amounts as a ratio to E-EPO (1:2 to 1:8). Spraybase® electrospinning apparatus was used to manufacture the fibres. A Scanning Electron Microscope (SEM) FEI Quanta 200FEG, was used to image the fibre morphology. ImageJ 1.46R was used to measure diameters. Characterisation of solid state was undertaken using a Rigaku MiniFlex 600 X-Ray Diffractometer. Patterns were recorded over the 2θ range 3º - 90º at a scan rate of 3º/min, with an interval of 0.02 º. The data was viewed on X'Pert Data Viewer 1.2F. TS-5000Z E-tongue was used for taste assessment. OriginPro 2017 was used to complete a multivariate principal component analysis (PCA) and Euclidean distances were calculated from cluster centres.

Results & Discussion

Electrospinning

Using the DoE definitive screening design, E-EPO concentration was found to be the most statistically significant factor affecting the production of smooth nanofibres with a p-value of **0.004** for reduction of beading, and a p-value of **0.008** for reduction of diameter. Using this knowledge, drug loaded fibres were electrospun at concentrations ranging from 30-40% E-EPO in ethanol. Process parameters used were appled voltages of 10-15 kV, gap distances of 150-175 mm, and flow rates of 0.5-1.0 mL/h. At drug-to-polymer ratios between 1:2 and 1:4, particles were observed due to a change in conductivity and viscosity. At ratios of 1:6 onwards smooth fibres form.

The XRD patterns shown in Figure 1 shows the diffraction peaks for the crystalline CPM alone and the amorphous halo for E-EPO, as expected, while the drug loaded fibres showed no drug peaks, suggesting a molecular dispersion of the drug in the polymer matrix.

XRD

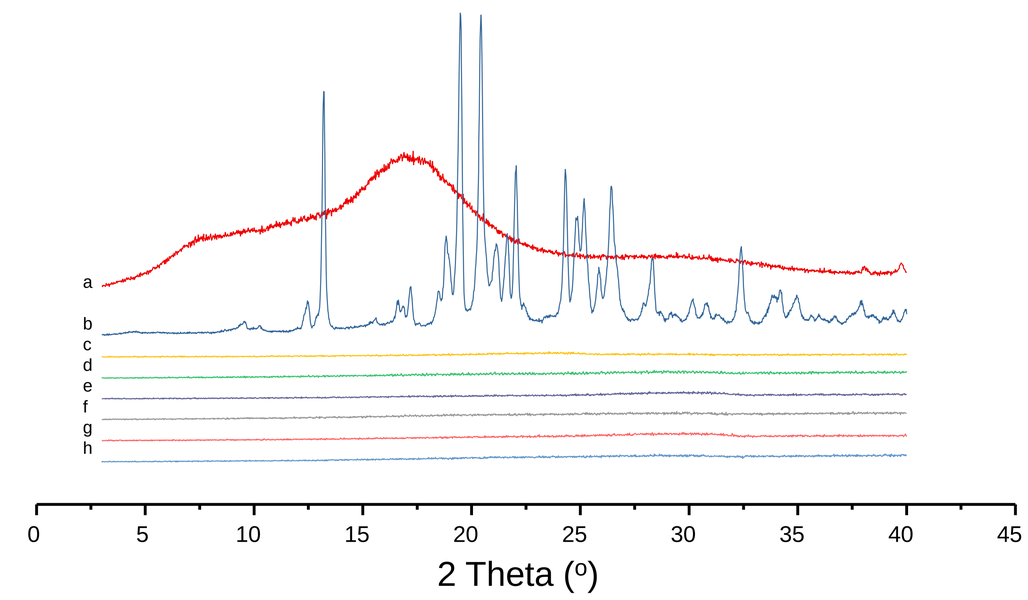

Figure 1: An XRD diffraction pattern of **(a)** Pure E-EPO **(b)** Pure CPM **(c)** Placebo 30% E-EPO fibre; Active fibres **(d)** 30% E-EPO , 1:6 CPM **(e)** 40% E-EPO, 1:6 CPM **(f)** 35% E-EPO, 1:6 CPM **(g)** 35% E-EPO, 1:8 CPM **(h)** 35% E-EPO, 1:7 CPM

SEM

Placebo and drug-loaded smooth non-beaded fibres were produced under the conditions shown in Figure 2.

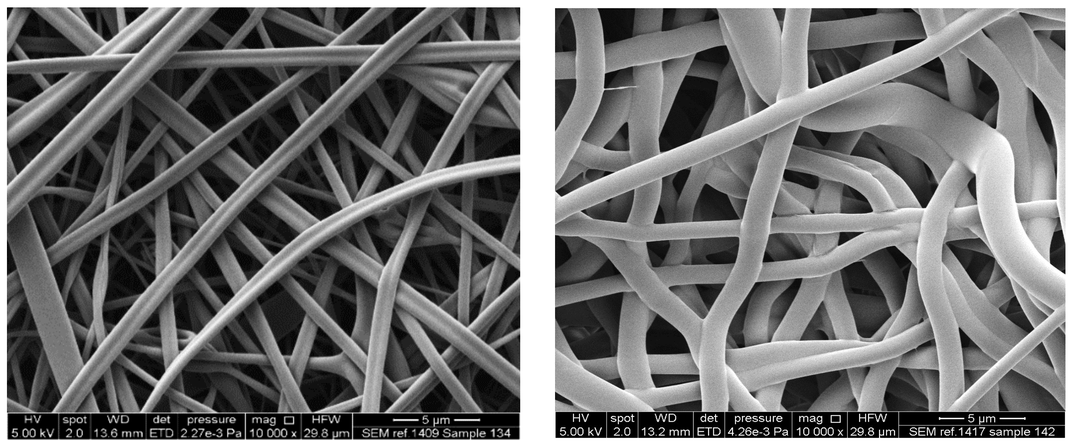

Figure 2. SEM images of electrospun fibres; **Left**: 35% E-EPO, processed at 15kV, gap distance of 175 mm, and flow rate of 1.0 mL/h. Mean diameter 893 ± 341 nm. T:26ºC. RH: 32%. **Right**: 35% E-EPO, 1:8 CPM to E-EPO, processed at 15kV, gap distance of 175 mm, and flow rate of 1.0 mL/h. Mean diameter 1507 ± 392 nm. T:23ºC, RH: 49%.

E-tongue

The larger the Euclidean distance between CPM and a formulation, the better the taste masking. Figure 3 shows a PCA biplot illustrating the distances from pure CPM.

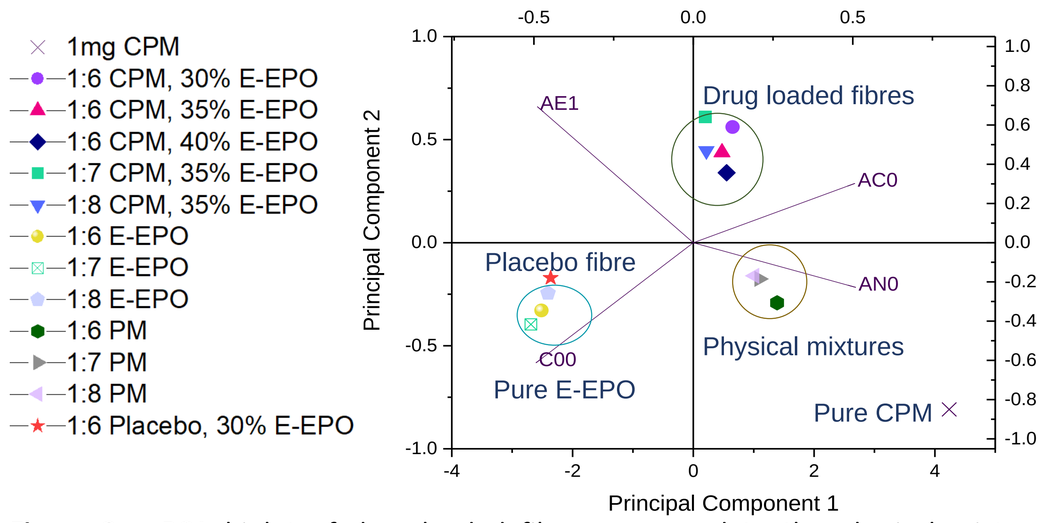

Figure 3 – PCA biplot of drug loaded fibres compared to the physical mixture, placebo fibre, pure E-EPO and pure CPM.

Conclusion

The DoE approach was used to identify and optimise the most influential factors for electrospinning smooth, non-beaded E-EPO fibres. 35% E-EPO is the optimum percentage of drug that allows for the transfer of process conditions from placebo to drug loaded fibres. 35% E-EPO fibres that have drug loads of 1:6, 1:7 and 1:8 yielded reproducible smooth, non-beaded fibres. XRD indicated that CPM was incorporated as a molecular dispersion, while SEM showed the fibres to be of satisfactory morphology and diameter. The E-tongue indicated good taste masking of CPM when incorporated into the fibres, compared to the physical mixture. The study has demonstrated it is possible to manufacture taste-masked nanofibers of CPM embedded in E-EPO.

Acknowledgments

This study is funded by MRC iCASE award No. 170156, and Pfizer Ltd. award No. 173803.