Electrospinning

Investigating the controllability of the fabrication processes behind potential nano to microscale electrospun/VIPS composites with the aim to be applied to enhanced drug release applications.

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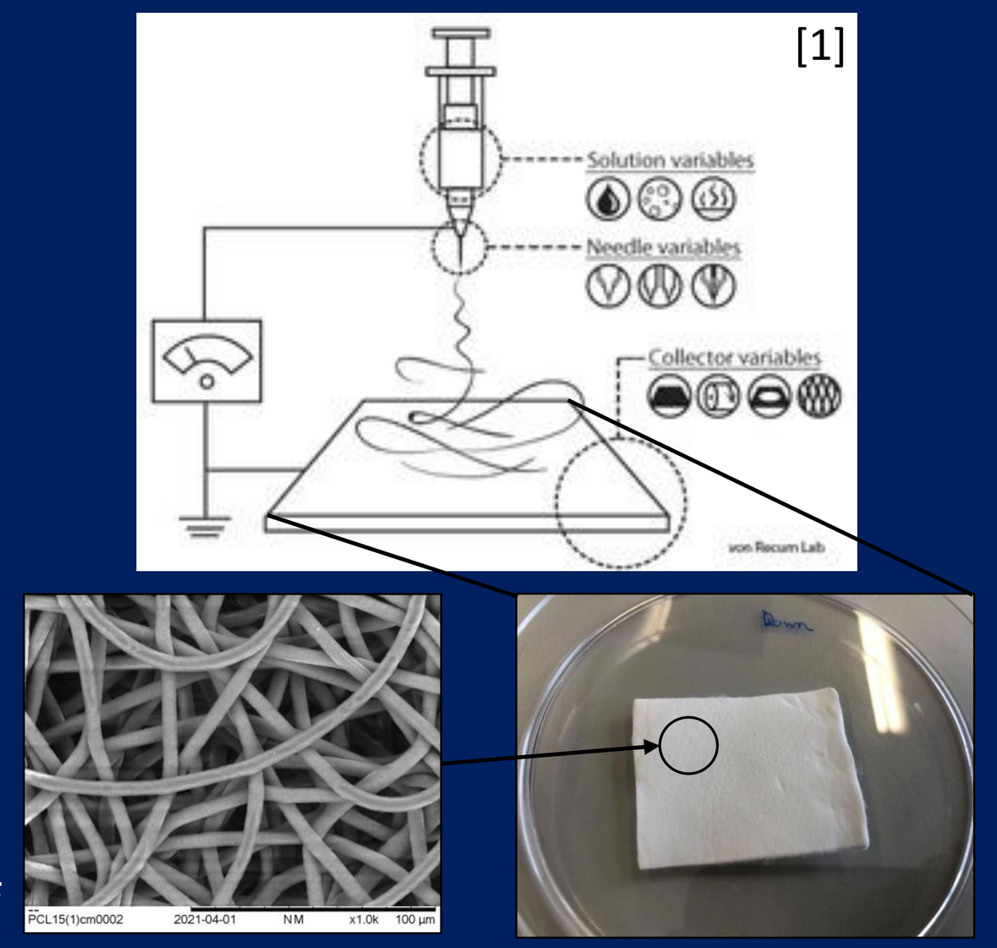
Introduction

Electrospinning

Electrospinning is a process whereby a polymer solution is loaded into a syringe and fed at a controlled flowrate through a nozzle. A potential difference (order kV) is applied between the nozzle and a collector drawing the solution into fibres which accumulate on a conductive collector. For these investigations poly(caprolactone) (PCL) fibres are produced using PCL/chloroform solution.

Applications

- Drug delivery
- Filtration
- Regenerative medicine



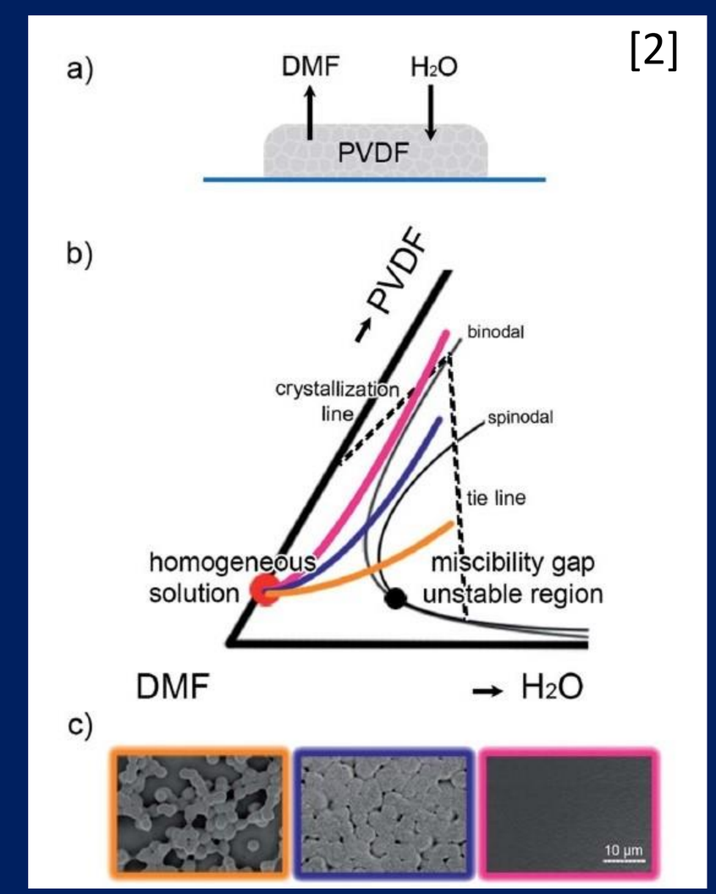
SEM micrograph of PCL electrospun fibres

Vapour-induced phase separation (VIPS)

Vapour-induced phase separation is a ternary phase process whereby a non-solvent phase penetrates a polymer solution(polymer and solvent phases). By altering processing conditions it is possible to change the reaction trajectory to create membranes of different morphologies. For this investigation the trajectory is chosen to pass into the 'unstable region' so forming microspheres (orange in diagram to right). This investigation studies the water/dimethylformamide(DMF)/poly(vinylidene fluoride) (PVDF) ternary system.

Applications

- Membrane distillation
- Membrane reactors
- Ultrafiltration



VIPS/electrospun composites

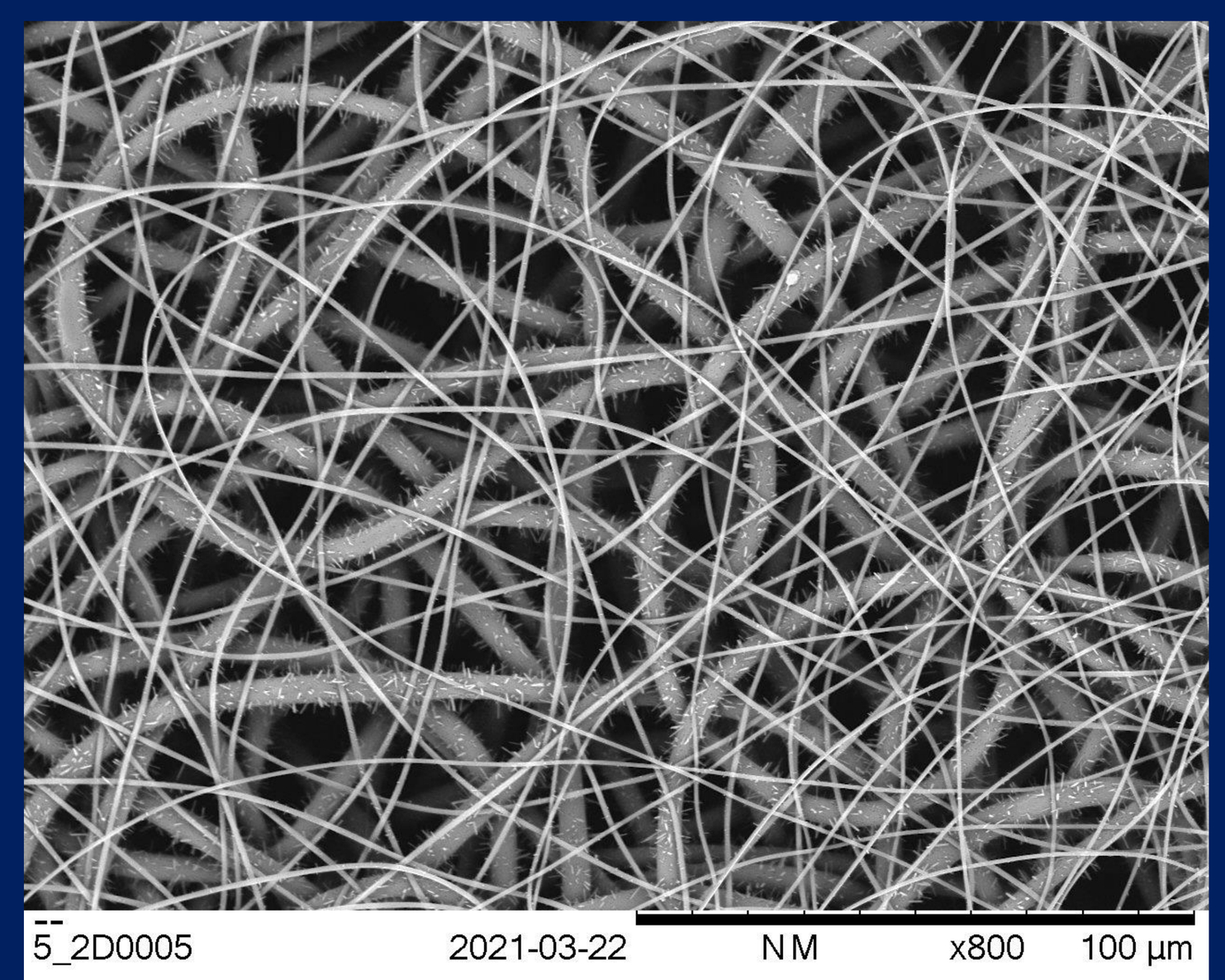
Combining these processes allows for polymer composites with enhanced mechanical properties and an even wider range of potential applications. This investigation first replicates the formation of such composites and then focusses on the modelling and controlling the formation with the view to applying these VIPS/electrospun composites for enhanced drug delivery applications.

Objectives

- Investigate the key parameters affecting electrospinning, validating an existing model by experimental means
- Validate an existing model for VIPS however applied to VIPS/electrospun composites, explored through the use of an open source training segmentation algorithm to measure the distribution of microspheres through the cross section of an electrospun mat.
- Show how a kinetic Monte Carlo algorithm can be used to model the nucleation of microspheres during VIPS.
- Investigate encapsulation a model drug (caffeine) into the VIPS/electrospun fibre composite and study the release profile to make a comparison to existing drug release techniques.

Conclusions

- Parameters considered important by Thompson *et al.* [4] found to be less significant than initially stated. Likely other parameters coupled to these that were not controlled have a greater affect than proposed.
- A kMC algorithm was used to predict microsphere nucleation on the fibre surface. Surface topography had no noticeable effect on the nucleation of microspheres due to the low roughness that the pores presented. It was found the model broke down for large numbers of iterations as layers of clusters prevented molecules further reaching the surface. Further changes to the algorithm could allow molecules to re-dissolve so reducing molecular build up.
- It was found caffeine could not be encapsulated within VIPS/electrospun fibre composites due to the hydrophobic nature of PVDF.
- Caffeine was successfully encapsulated in pure electrospun mats by dissolution in the electrospinning solution resulting in a novel caffeine@PCL structure.



- A very high rate of release was found perhaps indicating potential for fast acting applications such as pain relief given investigation into encapsulation alternative drugs.
- Further investigation could study the implementation of multi-layer composites for decreasing water penetration into the mat and so reducing drug release rate (example composite imaged above).

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References

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[4] C. J. Thompson, G. G. Chase, A. L. Yarin, and D. H. Reneker. Effects of parameters on nanofiber diameter determined from electrospinning model. Polymer, 48(23):6913-6922, 2007.

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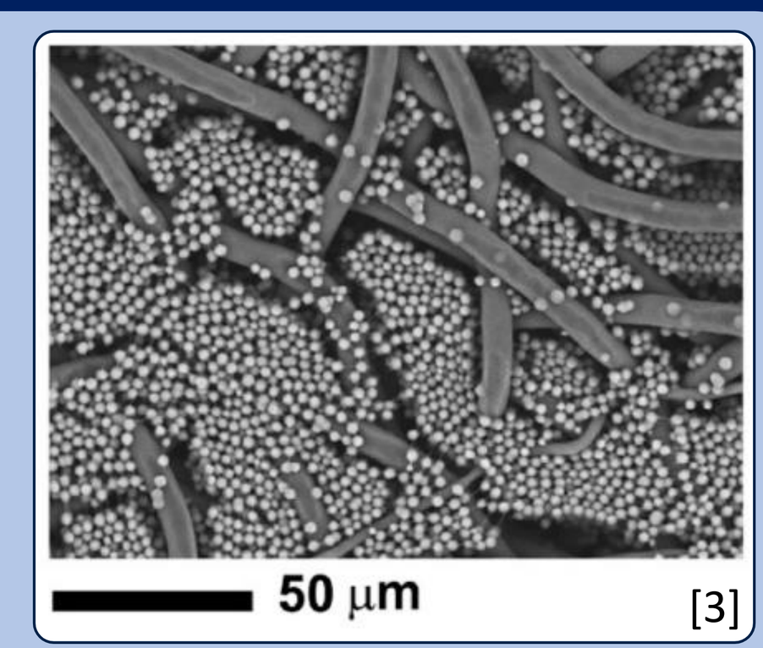
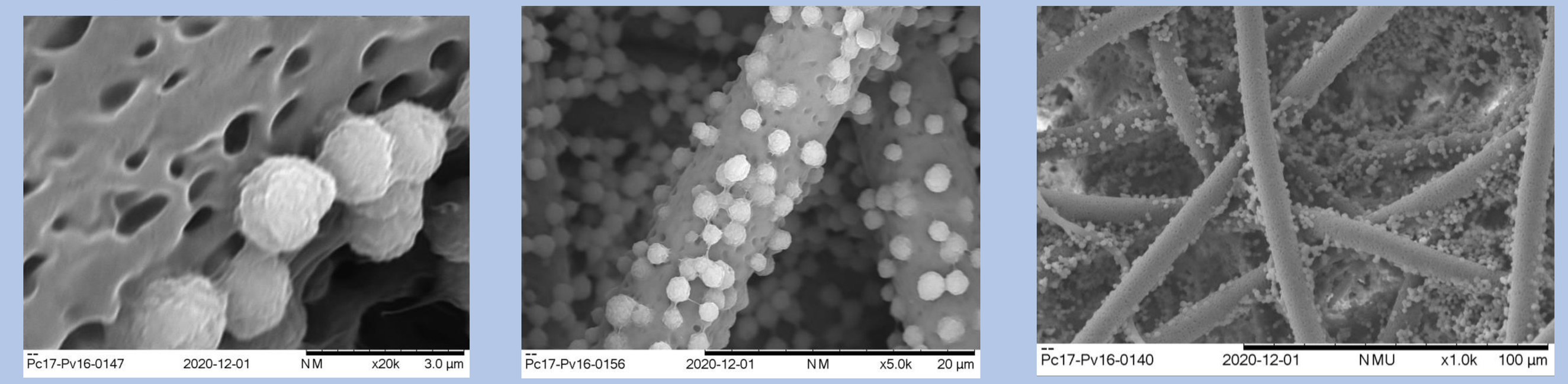
Investigations

Preliminary work

Successful formation of VIPS/electrospun composites

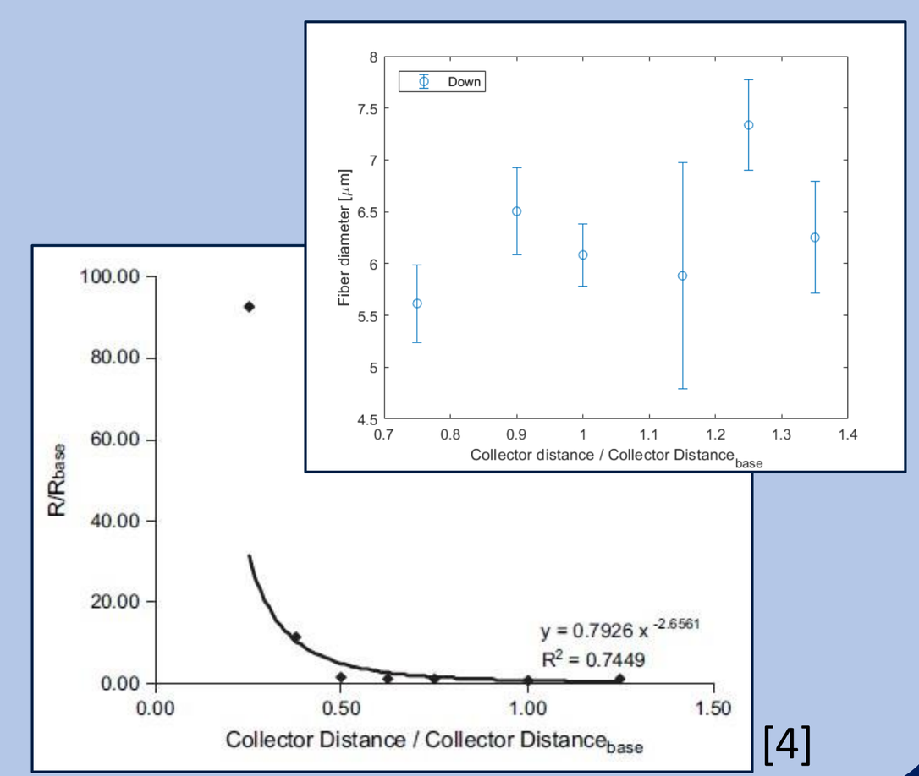
Building on a method reported in a study by Balzamo *et al.* [3] VIPS/electrospun fibre were fabricated which can be seen in the SEM images displayed. Comparison between literature (right) and the images captured (below) perhaps indicated a relationship between fiber surface texture and whether the microspheres nucleated between fibres or on the fibre surface itself. This is built on using kinetic Monte Carlo simulation.





Verification of electrospinning model

A study by Thompson *et al.* [4], built on a parametric model, suggested five parameters had the greatest affect on final fibre diameter: volumetric charge density, collector distance, initial jet radius, relaxation time and viscosity. An attempt was made to verify several of these relationships through experimental means. The result for collector distance (distance between needle and collector) are shown here (right). Practically it was only possible to study the area of little change between 0.7 and 1.4 normalised collector distance however the variance in the results indicates other parameters that were not predicted to be significant such as humidity may play a larger role.



Drug encapsulation

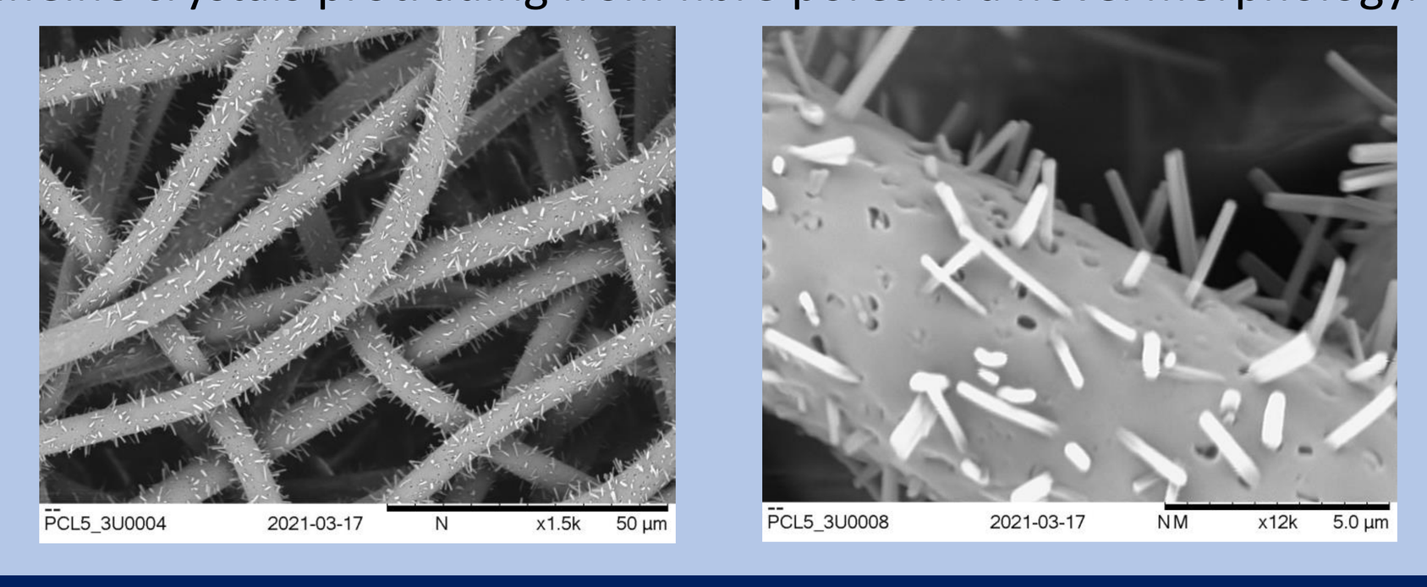
Methods

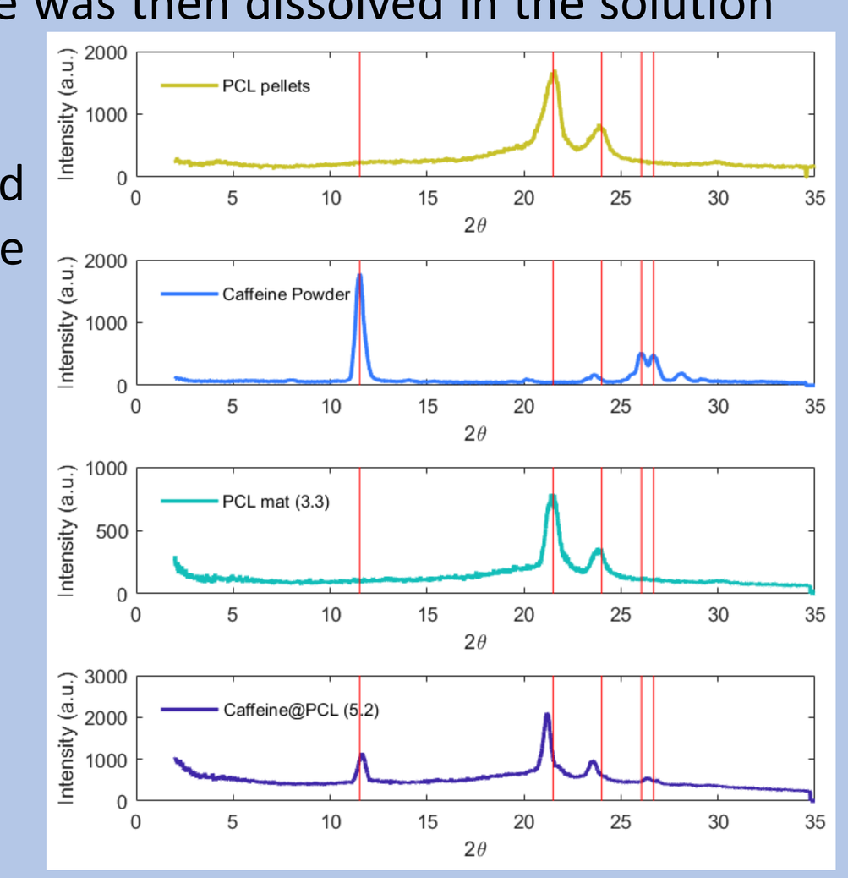
Several attempts were attempted to incorporate caffeine into prefabricated electrospun mats and mats containing microspheres. Unfortunately encapsulation in mats containing PVDF microspheres by immersion of the mat and addition of caffeine solution by pipette, were unsuccessful due to the hydrophobicity of PVDF.

Following this a method was devised to encapsulate caffeine in the PCL fibres during electrospinning. PCL was dissolved in chloroform at 15% w/v concentration. Caffeine was then dissolved in the solution at 20mg mL^{-1} and then electrospun under usual conditions.

Results

The encapsulation of caffeine in the electrospun mats was confirmed using SEM, ATR-FTIR and XRD (right). SEM showing needle-like caffeine crystals protruding from fibre pores in a novel morphology.



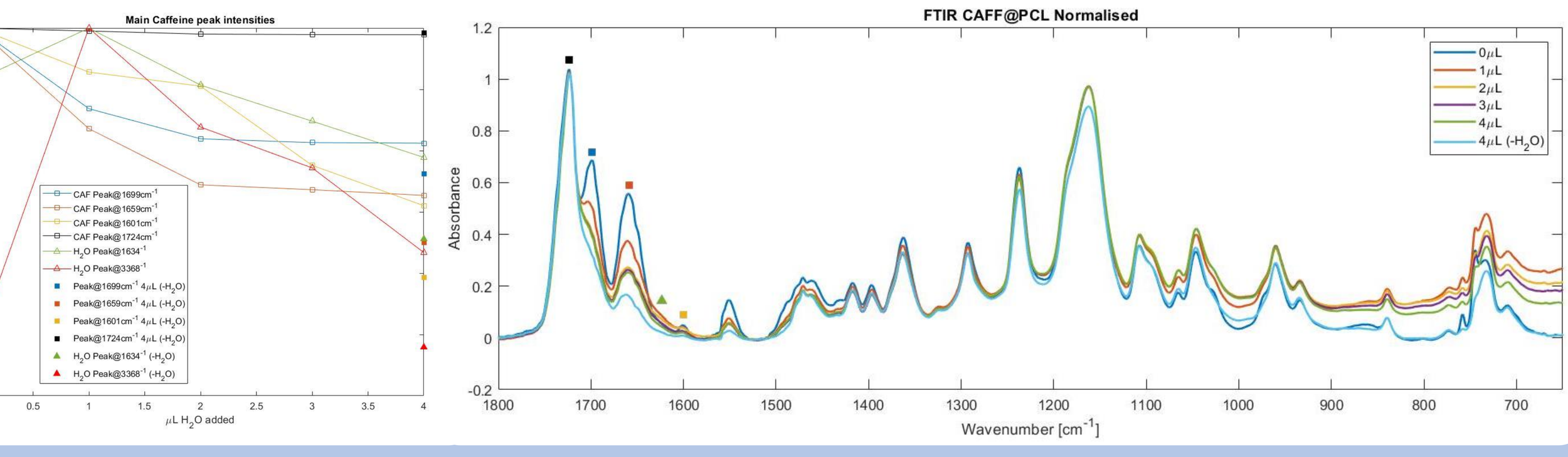


Drug release

FTIR vibrational modes that were not effected by the addition of water were chosen to be analysed. Within the region of 650 – 1800 cm^{-1} water contributes a broad libration band and a narrow band at 1639 cm^{-1} corresponding to H-O-H bending. Therefore the following bands chose were:

- C=O stretch (1724 cm^{-1}) due to PCL.
- Both C=O stretches (at 1694 cm^{-1} and 1645cm^{-1}) due to caffeine.

Both caffeine C=O stretching bands were observed to reduce exponentially likely due to caffeine dissolving into solution and saturating the water encapsulated locally within the mat so reducing the uptake of caffeine on subsequent additions. The peak of lower wavenumber analysed in the study at 1601cm^{-1} also reduced in intensity however appeared to show a more linear release likely due to distortion from H-O-H bending. Also shown are peaks corresponding to H-O-H bending (1725cm^{-1}) and −O−H stretching (3338cm^{-1}).

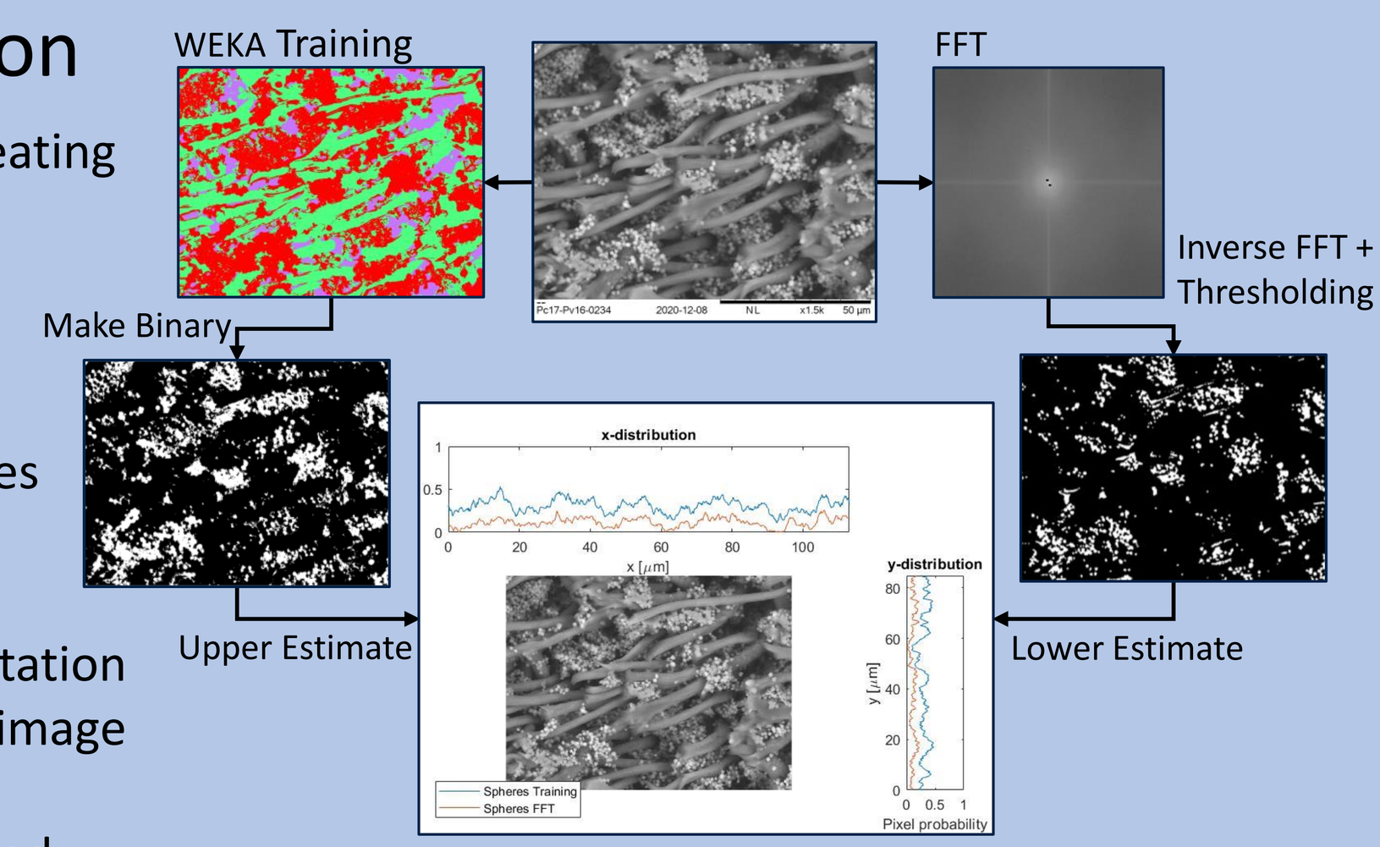


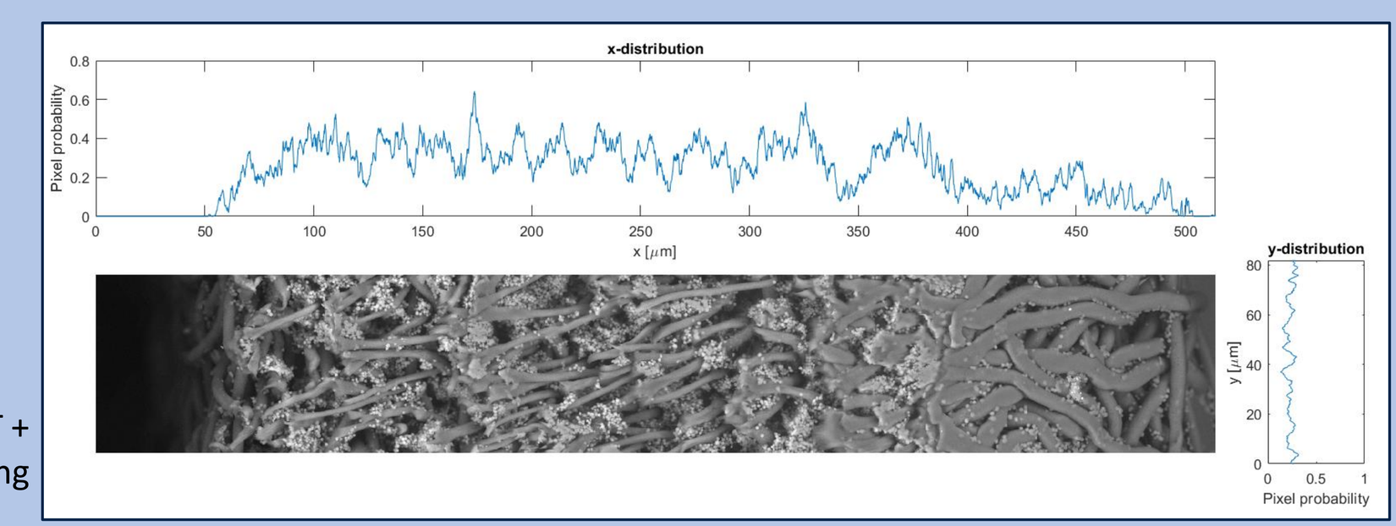
Vapour-induced phase separation (VIPS)

Model Verification

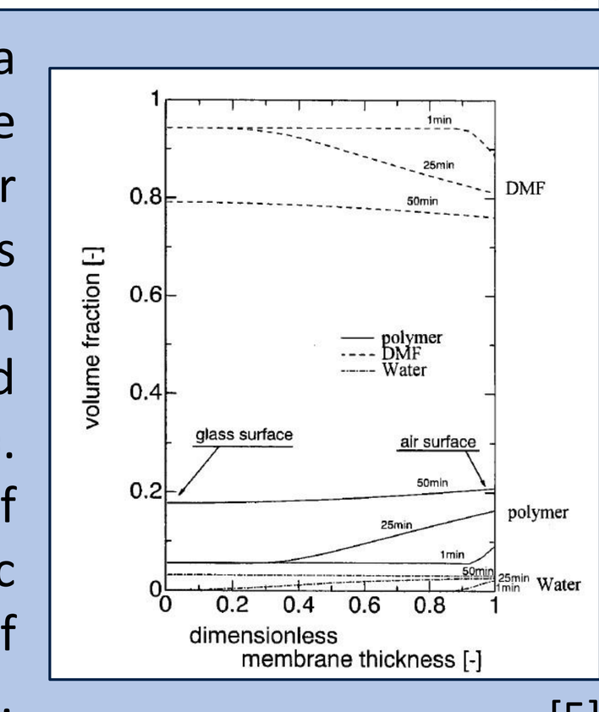
Two methods used for creating upper and lower bound estimates of microsphere density:

- FFT filtering – fibres attenuated then spheres isolated through thresholding.
- WEKA training segmentation in ImageJ - sections of image classified into sphere/fibre/background.





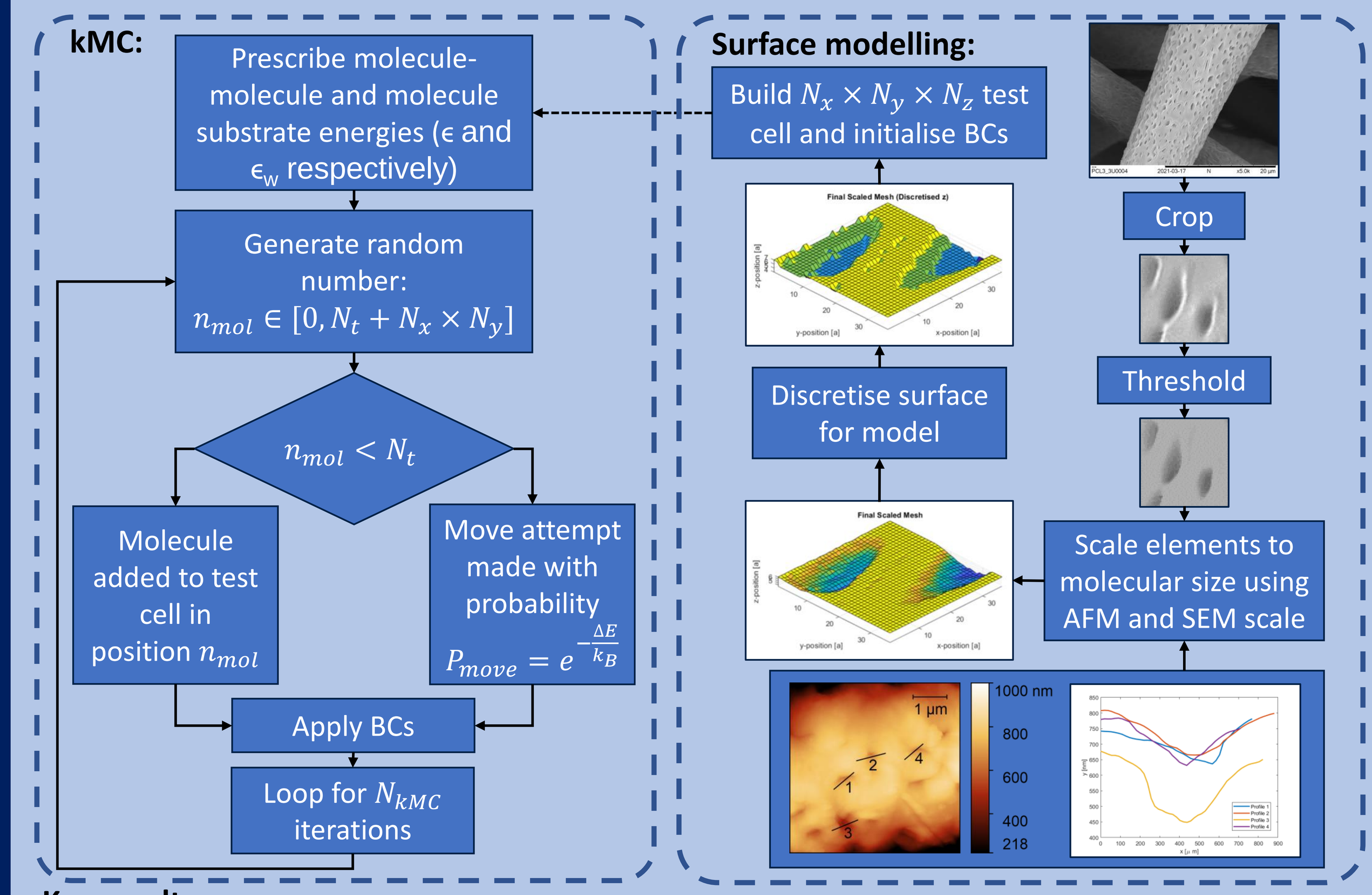
Through stitching of SEM images a profile was created through the thickness of the mat (above). For the undistorted section this was identified to be close to uniform which matches the model derived by Matsuyama *et al.* [5] (right). Note the distortion to the right of the stitched image due to plastic deformation during cutting of sample making this area unusable.



[5]

Kinetic Monte Carlo (kMC) simulation

kMC algorithm created in Matlab (adapted from Grosfils *et al*. [6]):



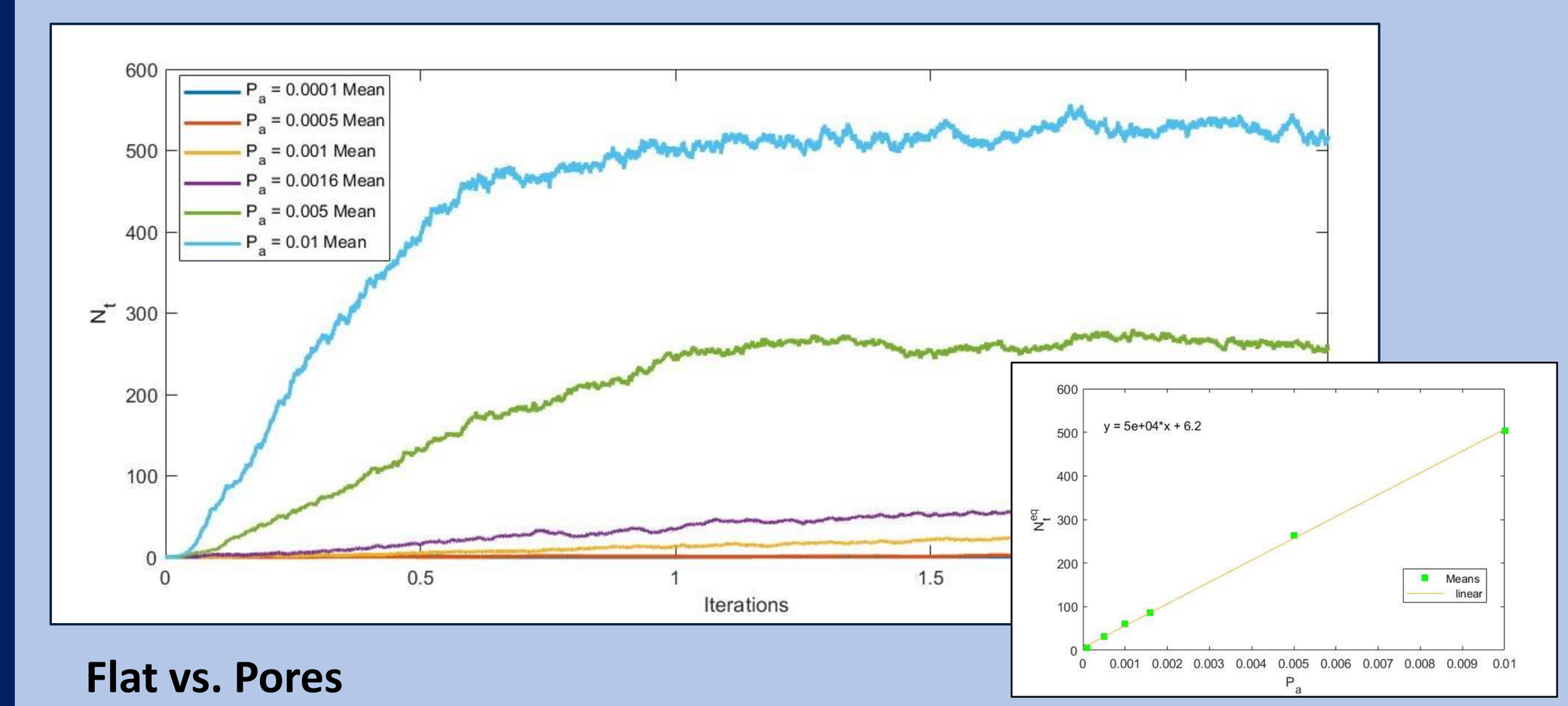
The kMC algorithm was adapted to include three physiologically based steps:

1. Molecules allowed to be added to the test cell at any z-position to simulate molecules coming out of solution.
2. To replicate nucleation around a PCL fibre, high magnification images of the fibre surface were taken using SEM and combined with AFM topography data on the fibre surface. Pixel intensity data was hence scaled using the topography data in z and by scaling each grid element to be the size of a molecule (as in the Grosfils *et al.* [6])
3. A potential function was added to simulate the interactions between molecules at longer distances by attenuating the interaction parameters according to a distance squared function.

Key results:

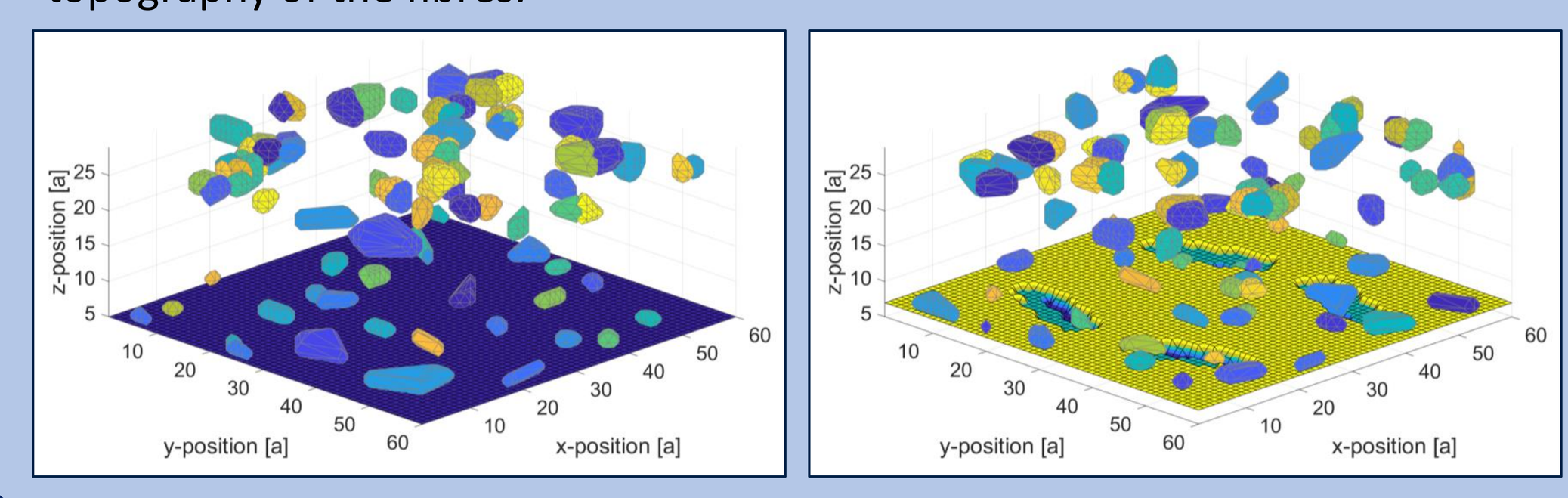
Variation in P_a

Through varying P_a, it was shown that increasing this parameter increased the number of molecules within the test cell when equilibrium was reached. This was to be expected as the parameter P_a is proportional to the density within the bulk solution above the test cell. Therefore if this is increased, the concentration gradient is also increased leading to an increase in molecules at a higher rate (according to Fick's first law of diffusion) and to a higher number at equilibrium. The precise relationship between number of molecules at equilibrium, N_t^{eq} and the parameter, P_a was shown to be linear.



Flat vs. Pores

It was found that by changing the simulation surface to flat, there was no significant increase in the number of molecules observed at the substrate surface. Therefore the simulation predicts microsphere nucleation location is not affected my the surface topography of the fibres.



Clustering (microsphere nucleation)

The simulation was run over 10^7 iterations with ϵ_w= 0, 0.1, 0.2 and 0.3. It was observed visually that as ϵ_w was increased, the number of molecules clustering on the substrate surface also increased. Within the pores, however, there appeared to be an optimal value of ϵ_w at 0.2, leading to a maximum number of clusters nucleating here. The figures shown below illustrate this effect. Clusters in images shown below were identified using a K-means algorithm.