Development of bioadhesive electrospun membranes for oral mucosal drug delivery

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Introduction

A major problem in the treatment of oral mucosal diseases such as oral lichen planus is the delivery of appropriate amounts of drug to the affected region. Frequently, drugs are applied in the form of mouthwashes or ointments, resulting in variable dosage and potential undesired side effects. Additionally, mouth movements and the production of saliva will tend to remove the drug and impair treatment efficiency. Thus, there is a need to develop systems capable of delivering controlled amounts of drug locally, and which can stay on a specific site for prolonged periods of time. The aim of this study was to develop bioadhesive membranes for oral mucosal drug delivery using water-soluble polymers and the solution-electrospinning technique.

Materials and methods

1) The electrospinning equipment was composed of a KDS200 syringe pump and an Alpha IV Brandenburg power source. Plastic syringes (1 ml) were used to drive the polymeric solutions into metallic 15-gauge blunt needles.

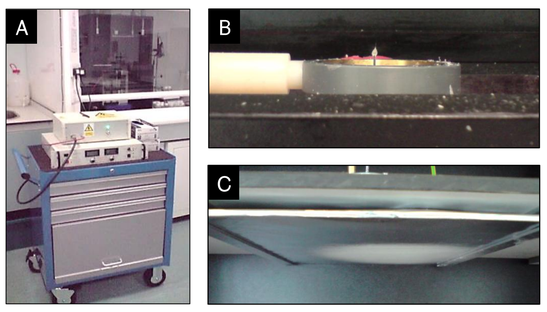

Figure 1. (A) Electrospinning equipment at the School of Clinical Dentistry of the University of Sheffield. (B) Formation of the Taylor cone on drop of polymer at the tip of a metallic needle after the application of a high voltage electrical current. (C) Mat formed on a collector plate by the deposition of electrospun fibres.

2) Solutions of polyvinylpyrrolidone (PVP, Mw 2 x 10^6 g mol^{-1}) and ammonio methacrylate copolymer Type B (AMC, Mw 32 x 10^3 g mol^{-1}) were prepared in 97% ethanol in order to fabricate the drug-delivering layer. Particles of dextrans (Dex, Mw 2 x 10^6 g mol^{-1}) and poly(ethylene oxide) (PEO, 2 x 10^6 g mol^{-1}) were added to the solutions in order to enhance the bioadhesive properties of the electrospun membranes.

Table 1. Polymeric compositions studied, and electrospinning conditions applied.

Compositions	PVP (Wt%)	AMC (Wt%)	Dex (Wt%)	PEO (Wt%)	Voltage (kV)	Flow rate (ml h^{-1})	Distance (cm)
PVP	(2.5 – 25)	-	-	-	15	(1 – 5)	(19 – 23)
PVP/AMC	10	(2.5 – 15)	-	-	(15 – 17)	2.5	19
PVP/AMC/Dex	10	10	(5 – 50)	-	17	2.5	19
PVP/AMC/PEO	10	10	-	(5 – 50)	17	2.5	19

3) A hydrophobic backing layer was prepared by electrospinning 10 wt% polycaprolactone (PCL, Mw 8 x 10^4 g mol^{-1}) on top of the drug delivery membrane. PCL was dissolved in dichloromethane and dimethylformamide (90%/10% vol/vol) and was processed using a current of 17 kV, a flow rate of 2.5 ml h^{-1}, and a distance of 21 cm. A thermal treatment (70°C, 15 min) was applied to the samples in order to improve attachment between the layers.

4) The morphology of the electrospun fibres was studied using scanning electron microscopy (SEM). Wetting properties were investigated *in vitro* using optical tensiometry, and by exposing samples of the membranes to distilled water (0.1 ml) in order to measure dissolution time and shrinkage.

Results and discussion

Electrospinning of PVP membranes

Electrospun PVP membranes were successfully produced using solutions with concentrations between 5 wt% and 15 wt%, as shown in Table 2.

Table 2. Compositions of PVP solutions used and outcomes obtained after electrospinning.

PVP (Wt%)	Flow rate (ml h^{-1})	Distance (cm)	Outcomes
2.5	(1 – 5)	19	No
5	5	19	Yes
7.5	5	19	Yes
10	5	19	Yes
12.5	5	19	Yes
15	5	19	Yes
20	2.5	23	Partially
25	1	23	Partially

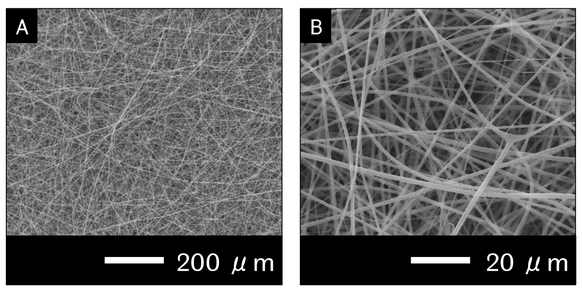

Figure 2. (A and B) SEM micrographs of electrospun PVP, showing fibres of cylindrical morphology and a significant degree of porosity.

Electrospinning of PVP/AMC membranes

Electrospun PVP/AMC membranes were successfully produced, with clear effects on material properties as the proportion of AMC increased.

Table 3. Compositions of PVP and AMC solutions used and outcomes obtained after electropinning.

PVP (Wt%)	AMC (Wt%)	Voltage (kV)	Outcomes
10	2.5	15	All compositions were processed successfully. Electrospun fibres became more rigid with greater proportion of AMC in the composition, increasing fibre compactness and decreasing porosity.
	5	15	
	10	17	
	15	17	

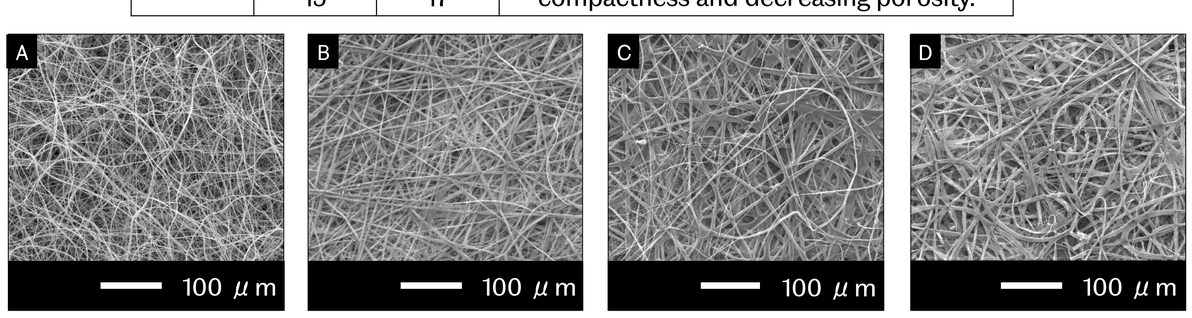

Figure 3. SEM micrographs of electrospun 10 wt% PVP and (A) 2.5 wt% AMC, (B) 5 wt% AMC, (C) 10 wt % AMC, and (D) 15 wt% AMC.

Addition of bioadhesive substances to the fibres

Table 4. Solutions containing bioadhesive substances and outcomes obtained after electrospinning.

	Content of bioadhesive substance in solution (Wt%)					
	5	10	20	30	40	50
Dex	Yes	Yes	Yes	Yes	Partially	No
PEO	Yes	Yes	Yes	Partially	No	No

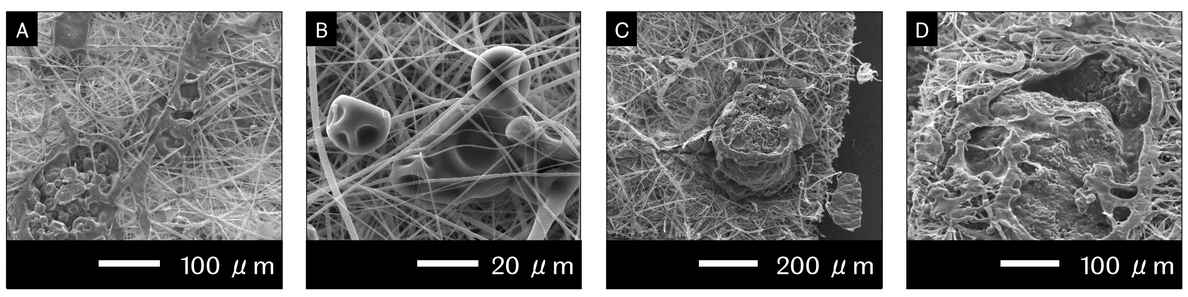

Figure 4. SEM micrographs of (A) and (B) electrospun PVP/AMC with dextran particles, and (C) and (D) electrospun PVP/AMC with poly(ethylene oxide) particles.

Hydrophobic PCL backing layer

Electrospun PCL was produced on top of the drug-delivery layer, creating a dual-layer system. The thermal treatment resulted in a significant reduction of porosity of the backing layer and an enhanced attachment between layers due to the melting of PCL.

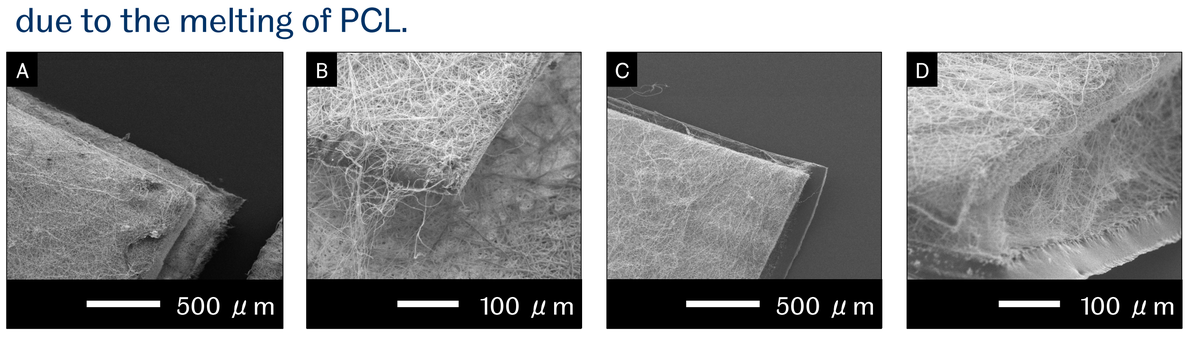

Figure 5. SEM micrographs of electrospun PVP/AMC and PCL layers (A and B) before the thermal treatment, and (C and D) after the thermal treatment.

Wetting properties

Exposure of PVP/AMC membranes to water showed that the increase of AMC in the composition resulted in decreased material solubility.

Table 5. Shrinkage and dissolution of samples exposed to distilled water .

PVP (Wt%)	AMC (Wt%)	Shrinkage (%)	Dissolution
10	0	-	Complete (<5 s)
	2.5	73.69	Partial (~30 s)
	5	66.64	Not complete (>30 s)
	10	0.44	Not complete (>30 s)
	15	1.01	Not complete (>30 s)

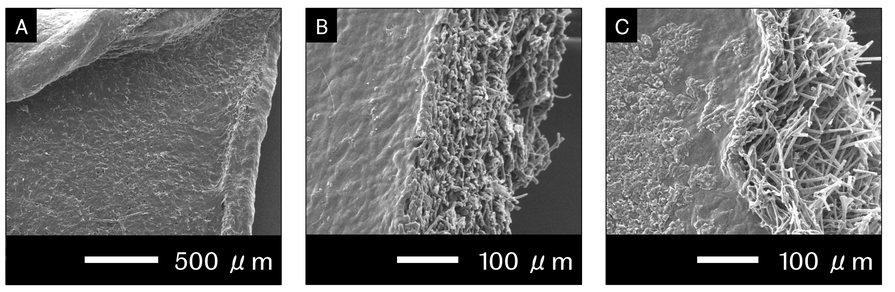

Figure 6. SEM micrographs of PVP with (A) 5 wt% AMC, (B) 10 wt% AMC, and (C) 15 wt% AMC after exposure to distilled water.

Optical tensiometry

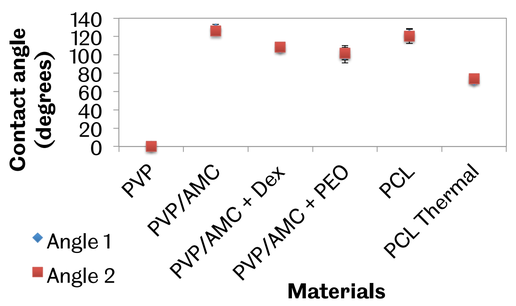

Figure 7. Optical tensiometry analysis of electrospun materials used in this study.

Results showed that the addition of AMC to PVP resulted in a significant increase of materials hydrophobicity. Further addition of Dex/PEO slightly increased hydrophilicity. Interestingly, PCL that has been thermally treated was more hydrophilic than untreated PCL, which may be due to the loss of micro- and nano-topography.

In conclusion, we successfully produced electrospun membranes made with bioadhesive materials with great potential for mucosal drug delivery applications. The dissolution rate of the membranes, as well as the drug release profiles, may be tailored by selecting appropriate compositions.