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Electrospun Fiber Based Mucoadhesive Patches In Oral Lesions – A Review

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ABSTRACT
Oral disease greatly affects quality of life, as the oral cavity plays an essential role in our day-to-day life including speech, mastication, food and liquid consumption. Treatment of oral disease is greatly limited by the dose forms that are currently available, which suffer from short contact times, poor site specificity, and sensitivity to mechanical stimulation. Mucoadhesive patches prepared using electrospinning offer the potential to address these challenges by allowing unidirectional site-specific drug delivery through intimate contact with the mucosa and with high surface areas to facilitate drug release. This review will discuss the range of electrospun mucoadhesive devices that have recently been reported to address oral inflammatory diseases, pain relief, and infections.
KEY WORDS: *Electrospinning, nanofibers, mucoadhesive patch, drug delivery, inflammatory diseases, infections, pain relief*

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I. INTRODUCTION:

The oral cavity plays an essential role in day-to-day life, including speech, mastication, eating, drinking etc.. These functions are all supported by healthy oral tissues—the impairment of which due to diseases can reduce quality of life[1,2]. Lesions of the oral cavity are surprisingly common and can range from ulcers, wounds, and abrasions[3]. Treatment of oral diseases can be difficult, where frequent high topical doses applied across the whole of the oral cavity, or drugs delivered systemically, are the main treatment options for often, small affected areas of the oral mucosa. Some localised topical treatment methods using gels or creams are currently on the market; however, many of these only have a short term therapeutic effect due to limited drug retention on the mucosa.

The field of oral medicine encounter several challenges in finding an appropriate drug delivery system that offers sustained drug release to directly target the lesion, because the moist environment in the mouth and flexibility of the mucosal tissue surfaces makes adhesion difficult. This represents a major unmet clinical need as there are currently no effective commercially available drug delivery systems that fully address these problems[4]

More recently, electrospun oromucosal drug delivery systems are being developed for local treatment of oral diseases. This review discusses the requirements, manufacture, and characterisation of electrospun mucoadhesive systems suitable for application to the oral mucosa and discusses materials currently in development for use in oral medicine.

II. ORAL MUCOSA:

The Oral cavity is lined by the mucous membrane which is known as Oral mucosa. It has four layers namely stratified squamous epithelium, basement membrane, lamina propria and submucosa. The epithelium consists of five layers (Stratum corneum, Stratum granulosum, Stratum spinosum and Stratum basale) depending on level of keratinisation. The hard palate, dorsum of the tongue and the gingiva are keratinised stratified squamous epithelium whereas the inner lips (labial mucosa), cheek (buccal) mucosa, soft palate and floor of the mouth are non-keratinised stratified squamous epithelium. The surface of the epithelium is bathed in mucins and inorganic salts are primarily secreted by sublingual salivary glands. These cause the gelation of the outer layer into a protective and lubricating layer of mucous with a thickness of 40–300 μm, followed by an additional 70 μm coating of saliva[5].

Diseased oral tissue usually originates in the epithelium. Auto-inflammatory diseases such as oral lichen planus occur as a result of immune cell-mediated damage of the stratum basale, while Candidiasis or denture stomatitis caused by Candida albicans can infect the upper epithelial layers. Therefore, the epithelium is the main drug delivery target for the treatment of most oromucosal diseases [6].

III. CURRENT OROMUCOSAL DRUG DELIVERY SYSTEMS:

The Oromucosal drug delivery systems currently in use are ;

1. Mouthwashes for local delivery of antimicrobials[7]
2. Mucoadhesive gels and pastes as protective layer over wounds[8]
3. Gels for systemic delivery for analgesics and antihypertensives[9]
4. Buccal tablets and lozenges are used for both topical and systemic delivery and may include mucoadhesives[10]

Here, drugs are released as the tablet dissolves, offering exposure time of up to 30 min . Several drugs have been used in the form of buccal tablets which includes opioid painkillers[11], nitroglycerin, steroid hormones for hormone replacement therapy[12] and as antifungals to treat oral candidiasis[13].

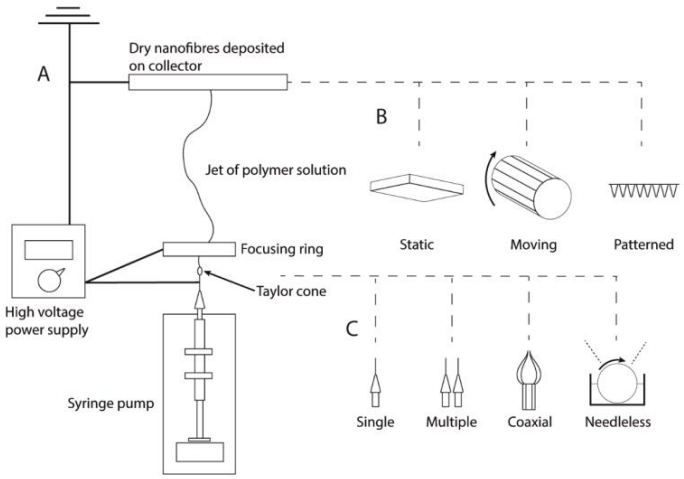
Due to constant salivary flow and mechanical forces, Oral mucosa is a highly challenging site for the development of a mucoadhesive dose form. There is a clear need for new formulations that allow specific delivery of a well-defined drug dose to the oral mucosa. Electrospun materials are an emerging technology for this application, due to their flexibility and thinness in comparison to tablets, which is expected to result in long term retention. Their high surface area and porosity allows for an increased number of mucoadhesive interactions with the mucosa and controlled drug release.

IV. ELECTROSPUN MUCOADHESIVE MATERIALS:

ELECTROSPINNING:

In 1600, William Gilbert reported electrospinning technology by the movement of liquid and electrostatic attraction of liquid droplets using electric forces[14]. A typical electrospinning set-up consists of a injection/syringe pump, spinneret needle loaded with polymer solution, a high voltage power supply, and a grounded collector plate (Figure 1). The polymer solution is pumped out at a controlled flow rate via spinneret to the needle which is connected to the high voltage power supply and then fibers draw from the needle tip (Taylor cone) under the electrostatic forces. The solvent evaporates rapidly during the flight, leaving a mat of polymer nanofibres on the collector plate[15].

Figure 1: Schematic diagram of typical electrospinning apparatus



There are several types of electrospinning methods for incorporation of drug delivery applications including solution electrospinning, emulsion electrospinning, surface modification electrospinning, side by side electrospinning, multi jet electrospinning, multiaxial electrospinning, coaxial electrospinning, and blending electrospinning[14]. There are 3 different types of collector which includes static, rotating and pattern; most commonly a static plate or a rotating drum can be used[16].

BIOCOMPATIBLE POLYMERS:

Polymers should be non-irritant and non-toxic both in the oral cavity and in the gastrointestinal tract, in case it is accidentally swallowed. Both natural and synthetic polymers can be electrospun into biocompatible drug delivery membranes.

Most commonly used synthetic polymers are biodegradable polyesters such as polylactic acid (PLA), polyglycolic acid (PGA), polylactic-co-glycolic acid (PLGA), and polycaprolactone (PCL)[17]. Most commonly

used water-soluble polymers are Polyethylene glycol (PEG), polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP)[16].

BIOADHESIVE POLYMERS:

Depending on the nature of the polymer, several different mechanisms may be involved in mucoadhesion which includes the effects of surface tension, dehydration, diffusion, electrostatic interactions, and chemical adsorption. Water-soluble polymers such as PVP swell rapidly, causing the dehydration of the mucus layer. The swelling results in intimate contact between the mucus glycoproteins and polymer and hydrates the polymers, further increasing the rate of diffusion into the substrate.

LAYERS OF MUCOADHESIVE PATCH:

An oral adhesion film consists of two layers (backing layer and adhesion layer) or a single layer (adhesion layer). It allows for two types of drug delivery;

1)unidirectional drug release - To the oral mucosa

2)Bidirectional drug release - To the mucosa and the oral cavity

V. THERAPEUTIC APPLICATIONS CURRENTLY IN DEVELOPMENT:

ANTI-INFLAMMATORY:

Certain factors such as pathogens, foreign bodies or ionising radiation are responsible for chronic inflammatory diseases in the oral cavity which are often mediated by dysregulated immune responses. Common chronic inflammatory diseases include oral lichen planus (OLP) affecting 1–3% of the world's population, and recurrent aphthous stomatitis (RAS), also known as aphthous ulcers or canker sores[18,19]. Its aetiology is poorly understood and no prophylactic treatments are available. These lesions are usually managed by corticosteroids or other anti-inflammatory agents. Systemic corticosteroid often results in unacceptable side effects, whereas topical agents, such as rinses, lozenges, and ointments also associated with some serious adverse effects, including adrenal suppression and secondary candidiasis and it must be reapplied several times per day and result in inconsistent dosing. Therefore, mucoadhesives, once carefully applied, may also prevent pain by providing a protective barrier against mechanical stimulation [20].

INDICATION	POLYMER	DRUG	SOLVENT	PROCESSING
ORAL LICHEN PLANUS[21]	Adhesive/drug release:PVP, Eudragit® RS100 Backing layer: PCL	Clobetasol-17-propionate	97:3 ethanol/water 9:1 DCM/DMF	Sequential electrospinning, heat treatment
RECURRENT APHTHOUS STOMATITIS[22]	Lower layer: PEO Upperlayer: PLLA	Diclofenac sodium Curcumin	Water HFP	Double-ring slit needleless spinneret

A pre-clinical study done by Colley et al (2018) [21] on electrospun patches loaded with the corticosteroid clobetasol-17-propionate for the treatment of chronic oral inflammatory diseases. The patches composed of a drug-loaded (up to 20 µg per patch) layer of mucoadhesive fibres consisting of PVP and Eudragit® RS100 with polyethylene oxide (PEO) particles electrospun from 97% ethanol. To promote unidirectional delivery and improve mechanical properties, a hydrophobic backing layer was introduced by electrospinning a second layer of polycaprolactone from 9:1 DCM/DMF and melting in an oven to produce a continuous film. Drug-loaded patches released 80% of the drug over a 6 h period. This expression is now a commercial technology of AFYX pharmaceuticals with the brand name Rivelin® and recently successfully met the primary end point in phase 2b clinical trials (ClinicalTrials.gov identifier: NCT03592342) for the treatment of OLP, showing a notable reduction in ulcer area, and is on track to become the first such electrospun mucoadhesive on the market.

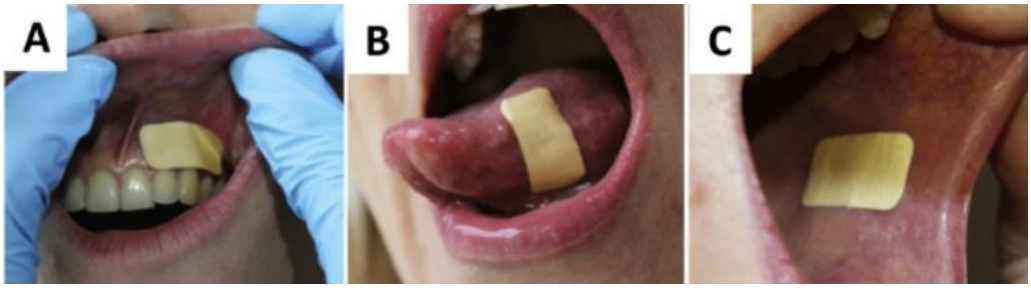


Figure 2: Mucoadhesive Rivelin® patches placed on the (A) gingiva, (B) lateral tongue, (C) buccal mucosa of a healthy human volunteer[21] (Courtesy: Colley et al, 2018)

Wei et al. (2019) [22] used needleless electrospinning with a double ring-shaped spinneret for the rapid production of 3-layer composite meshes consisting of a layer of mucoadhesive PEO nanofibres electrospun from water containing 30% w/w diclofenac sodium, and a layer of hydrophobic poly L-lactic acid (PLLA) nanofibres electrospun from 1,1,1,3,3,3-hexafluoro-2-propanol (HFP) containing curcumin at over 4% w/w. The release of curcumin from the fibres was sustained over a period of two weeks. The multiple layers of fibres make the system suitable for the co-administration of water-soluble and insoluble drugs, which is useful for inflammatory diseases, where a combination of different therapeutic agents may be beneficial.

LOCAL ANESTHETICS AND ANALGESICS:

Chronic oral mucosal pain is a common complaint that can have a wide variety of causes including infections, inflammation, chemotherapy, or surgery[23]. Over-the-counter oral non-steroidal anti-inflammatory agents (NSAIDs) and paracetamol are used to manage the oral pain, but with some side effects associated with long-term use. Topical anaesthetics such as lidocaine in the form of gels or lozenges , are also highly effective for local pain relief [24]

INDICATION	POLYMER	DRUG	SOLVENT	PROCESSING
Pain relief	Adhesive/drug release: PVP, Eudragit® RS100 Backing layer: PCL	Lidocaine	97:3 ethanol/water 9:1 DCM/DMF	Multiple-layer electrospinning, heat treatment

For the delivery of lidocaine HCl to the oral mucosa for the management of prolonged pain and as a local anaesthetic, Clitherow et al.[25] investigated the Rivelin® formulation, consisting of drug-loaded fibres of blended PVP and Eudragit® RS100 with a PCL backing film. Lidocaine HCl was loaded into the fibres at 2.5% w/w. The patches released approximately 80% of the loaded lidocaine within 1 h and permeation experiments showed a permeability of 136 μg cm^{-2} min^{-1} in ex vivo porcine buccal tissue.

Multiple studies have reported release of lidocaine HCl from biocompatible mucoadhesive materials and some early results show effective targeted delivery. Further in vitro and in vivo investigation is expected in the near future[26].

ANTIMICROBIALS:

Oral candidiasis is an opportunistic infection caused by overgrowth of Candida and most commonly by candida albicans in the oral cavity. It is most commonly occurs in predisposed conditions, such as people with diabetes, dentures, immunocompromised patients and those on long term antibiotic or steroidal therapy[27]. Topical antifungal steroid rinses containing nystatin or miconazole are the first line treatment for candidiasis. Although rinses are effective when applied 4 times per day, there is potential to minimise side effects using a specific delivery method. Sustained release through mucoadhesive patches may allow the minimum inhibitory concentration to be maintained without requiring such a high dose, thus reducing the side effects.

INDICATION	POLYMER	DRUG	SOLVENT	PROCESSING
Oral candidiasis	PVP	Clotrimazole Excipient: hydroxypropyl-β-cyclodextrin	7:2:1 ethanol/water/ benzyl alcohol	Conventional electrospinning
	PVP Backing layer: PVA/thiolated chitosan	Clotrimazole Excipient: hydroxypropyl-β-cyclodextrin	7:2:1 ethanol/water/ benzyl alcohol	Sequential electrospinning
	PVA/chitosan	Terbinafine hydrochloride	Water	Conventional electrospinning
	Gelatin	Nystatin	HFP	Electrospinning, UV cross-linking
	Adhesive/drug release: PVP, Eudragit® RS100 Backing layer: PCL	Dodecanoic acid	97:3 ethanol/water 9:1 DCM/DMF	Sequential electrospinning, heat treatment
Antibacterial	Adhesive/drug release: PVP, Eudragit® RS100 Backing layer: PCL	Lysozyme	97:3 ethanol/water 9:1 DCM/DMF	Sequential electrospinning, heat treatment

To improve the solubility and rapid release of clotrimazole, Tonglairoum et al. (2015)[28] developed electrospun PVP fibres with hydroxypropyl-β-cyclodextrin for the treatment of OC. PVP was used as a polymer and the cyclodextrin as an excipient to form inclusion complexes to enhance drug solubility. Clotrimazole was

loaded at over 20% by dry mass and the fibre mats electrospun from mixtures of ethanol, water, and benzyl alcohol. The fibres rapidly dissolved in artificial saliva, releasing all of the drug within 2 hr. To prolong the effect, the material was further developed into a sandwich patch by electrospinning a second mucoadhesive layer from water consisting of 5:1 PVA/thiolated chitosan. The resulting sandwich patches released Clotrimazole approximately 70% within 4 h[29].

Similarly, Szabó et al. (2016)[30] incorporated terbinafine HCl at approximately 7% w/w into 1:5 chitosan/PVA fibres from an aqueous solution. The fibres dissolved rapidly in artificial saliva, releasing all of the drug within 4 minutes.

Aduba et al. (2013)[31] also developed an electrospun material against oral candida. The 1:1 gelatin/nystatin fibres were electrospun from 1,1,1,3,3,3-hexafluoro-2-propanol and subsequently immersed in PEG diacrylate and 2,2-dimethoxy-2-phenylacetophenone as a photoinitiator dissolved in ethanol. Removing and curing using ultraviolet light exposure produced cross-linked fibres with improved structural stability in aqueous solutions. The release rate was relatively slow, with approximately 20–70% released within 24 h.

Clitherow et al. (2020)[32] incorporated various unsaturated fatty acids as alternative antifungal agents into both PCL and PVP/Eudragit® RS100 of the Rivelin® patch formulation at loadings of up to 22% and 12% w/w, respectively. Unlike in previous studies, disk diffusion inhibition and biofilm viability assays were used to demonstrate the potential of the patches at inhibiting both wild-type and azole-resistant C. albicans when applied directly to biofilms, thus clearly showing the effectiveness of mucoadhesive electrospun patches at treating Oral candidiasis. Dodecanoic acid was found to be the most effective of the fatty acids tested against pre-existing C. albicans biofilms.

Edmans et al. (2020)[33] incorporated lysozyme, into the Rivelin® formulation at a loading of 1% w/w by mixing the aqueous lysozyme-containing proportion of the electrospinning solvent into the polymer solution shortly before electrospinning. The patches released the enzyme at a suitable rate, with 90% of the enzyme released within 2 hr.

It is expected that further in vitro and in vivo research will be performed to translate these materials for clinical use.

VI. CONCLUSION:

Electrospun mucoadhesives make use of a scalable and industrially proven manufacturing process and are highly versatile in the range of drugs they can incorporate. They are attractive for drug delivery to the oral mucosa in that they are flexible and have a high surface area for drug release and, unlike existing dose forms, allow targeted delivery and prolonged retention times. It is envisioned that electrospun drug delivery devices will expand the range of treatments that can be applied to the oral mucosa and will have wide-ranging implications for the treatment of oral diseases.

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