Review Article **Novel drug delivery system**

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LOCAL DRUG DELIVERY IN THE TREATMENT OF ORAL LICHEN PLANUS: A SYSTEMATIC REVIEW

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ABSTRACT

Oral lichen planus (OLP) is a chronic, mucocutaneous, inflammatory disease characterized by cell-mediated immune dysfunction. The oral cavity has proven to be a potential topical delivery site for local delivery of therapeutic agents. This paper aims to analyze the existing literature on the local drug delivery in the treatment of oral lichen planus. Electronic search of scientific papers was carried out to identify relevant articles. Results revealed a review paper on the local drug delivery for treatment of oral lichen planus, a case report where two cases of erosive lichen planus were treated with Clobetasol propionate in custom-fitted tray, a randomized control trial where a new mucoadhesive prolonged release tablet containing Clobetasol propionate was used for the management of oral lichen planus. The potential for local delivery systems in oral lichen planus hasn't yet been fully realized and further research is needed in order to improve treatment outcomes.

KEYWORDS : Oral lichen planus, local drug delivery, topical formulations, therapeutics

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INTRODUCTION

Oral lichen planus is a rare chronic autoimmune mucocutaneous inflammatory disease that may cause bilateral white striations, papules or plaques with or without erythema and ulceration involving any part of the oral mucosa[1,2]. It is associated with cell mediated immune dysfunction. These lesions are chronic, rarely undergo spontaneous remission, potentially premalignant and often a source of morbidity particularly when erosive / ulcerative or erythematous lesions are present[3]. Atrophic and erosive OLP involving the gingiva are often referred to as desquamative gingivitis, a descriptive clinical term used for bright red edematous patches involving the full width of the attached gingiva[4]. Almost all the published reviews agree that only erosive/ulcerative or symptomatic OLP should be treated[5,6]. The main aim in treating these lesions is to control the symptoms and to improve the quality of life of the patients. Though topical steroids are the mainstay of palliative treatment, alternative therapeutic approaches are highly regarded given the lack of strong evidence on any available treatment modality[7]. As such the topical formulations have not been designed to be used in an aqueous environment constantly bathed in saliva, which may cause much of the drug to be washed off and lost[8]. Delivery systems that are designed specifically for the oral mucosa capable of sustained release would be beneficial in the treatment of oral lichen planus. Based upon the review by Thongprasom and Dhanuthai in 2008, the commonly used topical steroids were Betamethasone, Fluticasone, Fluocinolone, Dexamethasone and Clobetasol propionate in the form of mouthwash, spray, Cream / gel / adhesive paste, mouthwash and Cream / aqueous solution /ointment / adhesive paste respectively. Treatment of OLP as given in the review by Thongprasom in 2013 included Amitriptyline, Pimecrolimus, Hyaluronic acid, Tacrolimus and Aloe vera in the form of mouthwash, cream, mucoadhesive gel, mouthwash and gel respectively.

MATERIALS AND METHODS

A literature search was done to identify articles that mentioned about novel local drug delivery options in the treatment of oral lichen planus. Electronic search of scientific papers was carried out in Pubmed (MeSH), Science direct and Cochrane databases using specific keywords.

RESULTS

Results revealed a review paper on the local drug delivery for treatment of oral lichen planus[8].There was a case report where two cases of erosive lichen planus were treated with handling gel containing clobetasol propionate, *Calendula officinalis* L, pectin and nystatin used in bleaching – like custom-fitted ethylene vinyl acetate tray[9]. There was a double blinded placebo controlled randomized control trial where a new mucoadhesive prolonged release tablet containing 24 lg clobetasol- 17 propionate (CP) was used for the management of oral lichen planus[10]. Apart from these, a Cochrane library based systematic review on the interventions used for treating oral lichen planus was also referred to look into the latest treatment options[11].

Table 1
Treatment of OLP - Review by Thongprasom and Dhanuthai in 2008

Topical steroid	Form of drug delivery
Betamethasone	Mouthwash
Fluticasone	Spray
Fluocinolone	Cream / gel / adhesive paste
Dexamethasone	Mouthwash
Clobetasol propionate	Cream / aqueous solution /ointment / adhesive paste

Table 2
Treatment of OLP – review by Thongprasom in 2013

Sl.no.	Author / year	Therapeutic drug	Delivery form
1	Javadzadeh et al, 2008	Amitriptyline	Mouthwash
2	Voltz et al, 2008	Pimecrolimus	Cream
3	Nolan et al, 2009	Hyaluronic acid	Mucoadhesive gel
4	Rouxel et al, 2010	Tacrolimus	Mouthwash
5	Reddy et al, 2012	Aloe vera	Gel

Table 3
Novel drug delivery forms in the treatment of OLP

Sl.no.	Author / year	Therapeutic drug	Form of drug delivery
1	Cilurzo et al, 2010	Clobetasol propionate	Mucoadhesive prolonged release tablet
2	Machado et al, 2010	Clobetasol propionate and *Calendula officinalis* gel	Custom fitted ethylene vinyl acetate tray

DISCUSSION

Oral mucosa, comprising of a stratified squamous epithelium and a connective tissue component, acts as a barrier between all soft tissues and the external environment, thereby retaining the tissue fluids and excluding extrinsic materials. There are 3 different types of oral mucosa within the oral cavity: masticatory mucosa (i.e., gingiva and the hard palate), specialized mucosa (i.e., the dorsum of the tongue), and lining mucosa (e.g., buccal mucosa, the floor of mouth), representing 25%, 15%, and 60% of oral mucosa, respectively[12]. However, in mucosal disease like lichen planus, there is loss of this permeability barrier and drugs diffuse more freely into the tissue than intact mucosa. Oral mucosal delivery has the potential to treat many different conditions and diseases. Each therapy requires distinct penetration and drug retention profiles in order to optimize the treatment and minimize the side effects[8]. The loss of the permeability barrier in ulcerated or eroded areas of oral mucosa causes the drugs to diffuse more freely into the tissue than in intact areas of mucosa[8]. Thus, oral cavity has proven to be a potential topical delivery site for local delivery of therapeutic agents. Buccal delivery exposes the drugs to the enzymatic activity of saliva and epithelial cells. Attempts to protect biological drugs from the enzymatic environment (e.g. in nanocarriers) or reduce the enzymatic activity of the epithelium (e.g. with enzyme inhibitors) may overcome this problem and enable therapeutic proteins and biological drugs to be delivered topically to oral lesions[8]. Topical formulations have several drawbacks, including difficulties in applying the medication at various oral sites, taste alterations, limited contact time and possible swallowing of a formulation not designed for the buccal route. There is evidence that topical application of corticosteroids such as betamethasone mouthwash, fluticasone spray, fluocinolone cream, fluocinolone acetonide gel or in adhesive paste, dexamethasone mouthwash, clobetasol propionate (as cream, aqueous solution, ointment or in an oral adhesive paste) and mometasone furoate can each cause a lessening of the symptoms of OLP as reviewed by Thongprasom and Dhanuthai in 2008. In recent years, there have been several studies of the potential efficacy of topical calcineurin inhibitors, notably tacrolimus and pimecrolimus for the treatment of OLP, but as yet there remain no well-powered studies that truly demonstrate clinical efficacy[8]. Since oral lichen planus has been suggested to be a TNF- α driven disorder, topical thalidomide (1% in paste) may be as effective as topical 0.043% dexamethasone in paste for the short-term treatment of OLP as suggested by Sugerman in 1972. However, the use of thalidomide, even topically, is of concern because of its known adverse side effect profile. There are no open or randomized controlled studies of the efficacy of anti TNF –α agents like infliximab, adalimumab or etanercept for the treatment of OLP [8]. Delivery systems that facilitate topical

delivery of these to affected areas of mucosa could, however, revolutionize the treatment of OLP. Francesca Cilurzo et al, in their placebo controlled double blinded randomized controlled trial, evaluated the utility of a 24 lg clobetasol propionate (CP) mucoadhesive tablet based upon a poly(sodium methacrylate, methylmethacrylate) (PMM), a mucoadhesive non-swellable polymer[10]. The criteria of acceptance were based on mucoadhesive properties, lack of swelling and drug release over a 6-h period. It was compared to 125 lg CP in a conventional ointment in Orabase. The results of this study showed that the use of low concentration CP in mucoadhesive tablets offers an efficacious treatment of different clinical types of OLP. Previous studies of topical steroid for management of oral mucosal disease have assessed drug delivery in non-sustained release forms. This study revealed that such vehicles may have utility in the delivery of anti-inflammatory medications and other agents for treatment of oral conditions[10]. Machado et al in their case report, described two cases of DG that were treated with handling gel containing clobetasol propionate, *Calendula officinalis* L, pectin and nystatin used in bleaching – like custom-fitted ethylene vinyl acetate tray[9]. More than one-year follow up showed periodic recurrence, however with longer disease-free periods and less severe symptoms. A custom-fitted tray was made with a 1.5 mm thick ethylene vinyl acetate sheet, which covered the upper and lower dental arch. The patient was instructed to fill the tray with the gel and keep it in place for 15 min, three times a day and to refrain from eating and drinking for at least 30 min after application. Following completion of 2-weeks treatment, substantial improvement was observed in the gingival lesions. The patient reported reduction of pain. The application of corticosteroids by means of a tray in the treatment of severe atrophic-erosive gingival lesions has already been reported as an efficacious therapy[13]. The use of trays allows good control over the contact time between the medication and the lesion. Besides, without their use the clinician cannot be sure that the patient will place the medication on all the gingival lesions or that the desired contact time will be maintained. The application of this handling gel by means of a tray may be an efficacious treatment of desquamative gingivitis[9]. *Calendula officinalis* L is a medicinal plant that has bactericide, antiseptic and anti-inflammatory properties[14]. The herb and pharmaceutical preparations derived from it have been positively reviewed for the promotion of wound healing and as a topical antiinflammatory[14]. Evidence demonstrates that *Calendula* used in a variety of concentrations might be effective in shortening the duration of wound healing[15,16.]

CONCLUSION

Local drug delivery can provide a more targeted and efficient drug-delivery option than systemic delivery for diseases of the oral mucosa. The main advantages of local drug delivery include (i) reduced systemic side effects, (ii) more efficient delivery as a smaller amount of drug is wasted or lost elsewhere in the body, (iii) targeted delivery as drugs can be targeted to the diseased site more easily when delivered locally, thereby reducing side effects[8]. Problems with oral mucosal delivery include developing drugs or delivery systems that (i) overcome the permeability barrier; (ii) protecting biological drugs such as peptides and proteins from enzymatic degradation; (iii) having an acceptable taste to patients; and (iv) are easily administered and are not easily swallowed by accident[17.] The use of topical delivery systems could deliver these agents directly across the oral mucosa to the site of disease and could dramatically improve the treatment of these conditions whilst limiting the potential of systemic complications. The oral mucosa has a small surface area compared with skin and limited exposure times make this delivery route most appropriate for drugs exhibiting high therapeutic potency as relatively small quantities of drug can be delivered[18.] Local drug delivery of drugs for the treatment of oral lichen planus lesions is able to reduce side effects and improve treatment outcomes. Therapeutic anti-TNF-a antibodies and peptides and other similar biologicals have huge potential for improving the treatment of common oral mucosal diseases such as OLP[8]. Currently, this is precluded by the need for long-term parenteral administration and the risk of potentially serious systemic side

effects. Bioadhesive liquid systems (oral rinse and sprays) have been proposed for the treatment of several oral diseases, such as oral lichen planus and other immunologically mediated diseases, aphthous stomatitis, oral mucositis, hyposalivation and potentially malignant disorders, such as leukoplakia and erythroplakia[19]. However, the use of topical delivery systems that could deliver these agents directly across the oral mucosa to the site of disease could dramatically improve the treatment of OLP whilst limiting the potential of systemic complications[8].The potential for topical delivery systems in oral medicine has not yet been fully realized and further research targeted to oral medicine applications is needed in order to improve treatment outcomes.

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