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REVIEW ARTICLE

OROTRANSMUCOSAL DRUG DELIVERY SYSTEM: A FORGOTTEN HERO

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ABSTRACT:
Good oral health is of important for general health and well-being of the individual. Several innovative drug delivery systems have been developed for the local treatment and prevention of various diseases in the oral cavity. However, currently there are only few optimal systems and many of them are plagued with therapeutic challenges, like low drug efficacy and retention at targeted site of action. Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods. Because the oral mucosa is highly vascularised, drugs that are absorbed through the oral mucosa directly enter the systemic circulation, bypassing the gastrointestinal tract and first-pass metabolism in the liver resulting in rapid onset of action via more comfortable and convenient delivery route than the intravenous route. The purpose of this paper is to provide an insight into the latest drug delivery strategies for the local treatment and prevention of the oral pathologies and new potential bioadhesive local delivery systems. Furthermore, the most promising mucoadhesive systems proposed to locally treat oral diseases have been discussed.

Key words: Transmucosal drug, topical drug delivery, oral mucosal drug.

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INTRODUCTION:

The oral cavity is the first section of the digestive system and consists of different anatomical structures, like teeth, gingiva, hard and soft palate, tongue, lips and a mucosal membrane lining the inner surface of the cheek. Common oral diseases found commonly in the population include trauma, dental caries, periodontal diseases, oral malignancies and various oral infections.[1] These diseases can be effectively treated by topical therapeutic approaches, due to easy accessibility of the oral cavity.

Systemic drug delivery through transmucosal route offers distinct advantages over peroral route of administration such as possible bypassing of the first pass metabolism and avoidance of pre-systemic elimination within the GI tract.[2]

Until recently, only a few topical formulations were considered specific for the treatment of oral mucosal diseases, and most of these were borrowed from dermatology and were encumbered by all the inherent limitations associated with these formulations.[3] As such, they 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. Repeated dosing is also required to obtain a therapeutic dose. Hence, delivery systems designed specifically for the oral mucosa capable of sustained release would be beneficial in the treatment of various oral diseases.[4]

This review will examine the characteristics of oral mucosa which facilitate and impede the drug delivery through transmucosal route. Similarly, a discussion on various mucosal diseases that could benefit from the transmucosal delivery has been discussed. A summary of current therapies will be provided, highlighting their limitations and exploring how existing and new topical therapies might benefit from improvements in drug delivery and facilitate improvements in treatment outcomes.

ORAL MUCOSA: STRUCTURE AND CHARACTERISTICS

The oral mucosa is structurally consists of outermost layer of stratified squamous epithelium followed by basement membrane, a lamina propria and innermost layer of submucosa. The epithelium is similar to stratified squamous epithelia found in the rest of the body; it has a mitotically active basal cell layer which advances through intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium. [5] The epithelium of the buccal mucosa is about 40–50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer layers of cells. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers.

The oral mucosa in general a leaky epithelia, intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4–4000 times greater than that of the skin.[6]

There are 2 types of epithelium found; keratinized epithelium (gingiva & soft palate) and non-keratinized epithelium. The keratinized epithelium consists of keratinized layer at the most superficial layer of the epithelium. Non keratinized layer lacks keratinized zone at the superficial layer of epithelium. Both of these epithelium consist of keratinocytes which connected to each other with the help of desmosomal attachment.

In keratinized mucosa, membrane coated granules (keratohyaline granule) is produced by keratinocyte in the granulosum layer (fig 1). As the cell differentiation continues, this membrane coated granule moves apically and fuses with plasma membrane and releases its lipophilic content intracellularly. This lipophilic material slows the passage of hydrophilic material across epithelium.[7]

In non-keratinized mucosa, keratohyline granules are absent but they do produce two similar secretory organelles; a) a cored granules and b) lamellate granules which secrete their content into intercellular space (2/3rd from the basal layer to surface layer) and provide the permeability barrier. Its barrier function is less effective as compared to that of keratinized mucosa.[8-11]

MECHANISM OF ORAL LOCAL DRUG ABSORPTION

Drug absorption through a mucosal surface is generally efficient as compared to skin because of its high vascularity and absence of stratum corneum epidermis layer in oral mucosa. It depends on number of factors like, concentration of the drug, vehicle of drug delivery, mucosal contact time, venous drainage of the mucosal tissues, degree of the drug's ionization and the pH of the absorption site, size of the drug molecule, and relative lipid solubility.

There are 2 routes potentially involved in drug permeation across the epithelium membrane.

1. Transcellular route – via this route, small molecule diffuses from one side of the barrier through the cell and reaches to the other side (fig2a). Molecules which are hydrophobic, too small and neutral in charge can pass through this route. Absorption enhancer (table 1) are used to facilitate the drug absorption. They act by following mechanism to improve drug absorption through oral mucosa

a. Decreases viscosity of mucus and saliva
b. Increasing fluidity of lipid bilayer membrane
c. By overcoming enzymatic barrier

2. Paracellular route- In this the transport of molecules around or between cells. Tight junctions or similar interconnections exist between cells (fig2b). The intercellular tight junction is one of the major barriers to paracellular transport of macromolecules and polar compounds. Tight junction structure and permeability can be regulated by many potential physicochemical factors, including the concentration of cAMP and intracellular calcium concentrations. The absorbtion enhancers (table 2) like Poly-(acrylic acid) derivatives such as Carbomer 934® and Chitosans have been extensively studied for their possible uses as absorption enhancers that cause the loosening of tight junctions.[13,14,15,16]

A single drug can permeate through oral mucosa, using both routes simultaneously, but the route offering the least resistance to penetration is usually preferred, depending on the physicochemical properties of the drugs (e.g., size, lipophilia, hydrogen bond potential, charge, and conformation).[17]

WHERE TO DELIVER TO?

Oral mucosal delivery has potential to treat various disorders. To be successful, each therapy requires favorable drug penetration and retention to optimize treatment and minimize possible side effects. Superficial infections like candidiasis affects only superficial epithelial cells and drug used to treat these infections need not cross the permeability barrier

Diseases such as oral dysplasia like leukoplakia affect epithelial cells and drug need to penetrate and retained within epithelium with as little loss as possible. Diseases which affect basement membrane &adjacent connective tissue like oral lichen planus require drugs which should reach the basal cell by crossing the permeability barrier and should retain within epithelium and underlying connective tissue rather than being lost systemically into the circulation or through lymphatics.[18] (fig 3)

Advantages and disadvantages of the oral cavity as a site for drug delivery

There are certain advantages of oral cavity which makes it a reliable of site for transmucosal drug delivery such as easily accessibility, ease of administration, patient acceptability, well vascularized tissue, avoidance of gastrointestinal tract environment. The cellular turnover time of the oral mucosa is estimated to be 4–14 days. This is intermediate between the slow turnover rate of the skin and the fast turnover rate of gastrointestinal mucosa.

Transmucosal delivery route presents certain challenges like continuous saliva secretion, taste receptors that may present difficulties to patients and decreased compliance with drugs that are bitter, small surface area, involuntary swallowing of the delivery system could lead to choking and tissue irritation (table 3).[19]

Local drug delivery for specific oral diseases (table 4)

1. Oral leukoplakia-

It is a potentially malignant oral disease in which cancer is more likely to occur than in normal tissue. Topical retinoids have shown variable efficacy in management of oral premalignant lesion when used as a short term course.[20]

a. Acitretin- Two randomized controlled trials have been conducted to assess the effect of acitretin, used in various forms; as a mucoadhesive disc to provide an extended release of acitretin into oral cavity; and as a isotretin gel; both of which showed positive results.[21]

b. Bleomycin- Study demonstrated that bleomycin gel demonstrated variable efficacy of topical bleomycin gel in management of leukoplakia.[22]

c. Attenuated adenovirus- one novel study explored the efficacy of topical rinse containing an attenuated adenovirus engineered to destroy p53 mutant cell in cohorts of patient with oral epithelial dysplastic lesion. There were some positive responses although most were transient.[23]

d. Black raspberry anthocyanins- in one study the delivery of black raspberry anthocyanins in a bioadhesive gel showed limited efficacy in reversing or downgrading oral dysplastic lesion.[24]

e. Topical photosensitizing agent (5- aminolevulinic acid)- a study done using topical application on premalignant lesion followed by photodynamic therapy using a red light (630nm) have reported a high response rate upto 6 months.[25]

Table 1: Absorption enhancers used in transcellular route:

Examples	Mechanism
Surfactant- Sodium dodecyl sulphate	Perturbation of intercellular Lipids and protein domain integrity
Bile salt- Sodium deoxy-cholate	Perturbation of intercellular Lipids and protein domain integrity
Fatty acid- Capric acid, lauric acid	Increase fluidity of phospholipid domains

Table 2: Absorption enhancers used in paracellular route

Example	Mechanism
Methylated cyclodextrins	Opens the desmosomal junctions
Sodium EDTA	Interfere with Ca^{+} → no desmosomal contraction → loose junction
Carbomer 934 & chistosans	Loosens desmosomal junction

Table 3 (a): Advantages of the oral cavity as a site for drug delivery

Features	Advantages	Significance
Administration	The ease of accessibility referred to above means oral mucosal drug delivery systems are easy to administer	this property increases patient acceptability for oral mucosal drug delivery systems
Accessibility	The different sites in the oral cavity are easily accessible	This property increases patient convenience. Furthermore, the precise placement of the delivery system at any site in the oral cavity allows the targeting of a specific membrane, thus differentiating the different oral cavity routes
Patient acceptability	Highly acceptable site for drug delivery by the patient	This site for drug delivery is well accepted by the patient, increasing patient compliance
First-pass effect	The oral mucosa is a well vascularized tissue and the blood vessels drain directly into the jugular vein	Drugs penetrating the epithelium are delivered directly into the systemic circulation, thus avoiding the hepatic first-pass effect
Enzymatic barriers	The buccal mucosa provides an environment with reduced peptidase and protease activity	Significantly less drug metabolism is seen in the oral cavity
Cellular turnover time	The cellular turnover time of the oral mucosa is estimated to be 4–14 days. This is intermediate between the slow turnover rate of the skin and the fast gastrointestinal rate	A mucoadhesive device may be worn for many hours or even days without disturbing its adhesion due to rapid cell division. In addition, fairly rapid recovery is possible if slight tissue damage occurs due to wearing a dosage form
Avoidance of gastrointestinal Tract environment	Drugs absorbed across oral mucosa directly into the systemic circulation	Direct absorption of drugs into the systemic circulation avoids hydrolysis in the gastrointestinal tract. Swallowing of dissolved drug should be avoided

Table 3(b): Disadvantages of the oral cavity as a site for drug delivery

Features	Disadvantages	Significance
Saliva	Saliva is continually secreted into the oral cavity from major and minor salivary glands	The continuous secretion of saliva (0.5–2 L/day) can lead to dilution of the drug or excessively fast erosion of a dosage form. For patients secreting too little saliva (dry mouth syndrome), there may be insufficient saliva to allow dissolution of the drug
Taste receptors	The tongue contains taste receptors that may present difficulties to patients and decrease compliance with drugs that are bitter	This problem may be greater with certain patient populations such as the young and the elderly
Membrane Flexibility	Some of the oral mucosa (e.g. sublingual and buccal mucosa) is flexible and flexes as a consequence of normal functions of the mouth (e.g. speaking, chewing or swallowing).	This may adversely affect the dosage form If the oral mucosal drug delivery system contains a mucoadhesive, movements of the mouth or tongue may dislodge the dosage form from the site of administration.
Tissue irritation	tissue irritation may arise for some drug following the use of an oral mucosal drug delivery system	Irritation may lead to faster absorption and/or pain at the site of application
Surface area	The surface area of the oral cavity is small; it is approximately 214 cm^2.	The oral cavity has a smaller absorptive surface area compared to the small intestines
Choking hazard	Involuntarily swallowing of the delivery system could lead to choking	This potential hazard should be considered during the design of the delivery system and evaluated during the research or development phase
Membrane permeability	In general, oral cavity mucosa shows low permeability to drugs	Membrane thickness varies from a few hundred micrometres for the sublingual region to 500 μm for the buccal mucosa

Table 4: Local drug delivery for specific oral diseases

S.no.	Oral diseases	Drug	Dosage form	Result	Reference
1.	Potentially malignant disorders and oral cancer	5-FU	Matrix tablets	Matrix tablets containing 5% of 5-FU could be a useful means in topical treatment of OSCC	43
		Acitretin	Mucoadhesive 2-layer tablets	Efficacy in the treatment of oral leukoplakia without side effects	21
		Ketorolac	Oral rinse	Local delivery of a COX-containing oral rinse was well tolerated but produced no significant reduction in the extent of leukoplakia	44
		Tretinoin	Patch	The tretinoin patch is safe and effective for such chemoprevention in the hamster model	45
		Black raspberry anthocyanins	Bioadhesive gel	Reversing or down-grading oral dysplastic lesions	24
		Photosensitizing agents (5-aminolevulinic acid)	Gel	Followed by photodynamic therapy, a complete responsewas obtained in 10 of 12 treated patients	25
		Idarubicin	Solid lipid nanoparticles	Data confirm nanoparticle internalization by OSCC cells and support the premise that nanoparticle-based delivery provides higher final intracellular levels relative to bolus administration	46
		Engineered adenovirus	Oral rinse	Some complete response, most transient	23
2.	Oral mucositis	TGF- beta 3	Oral rinse	TGF–beta 3 penetrate the epithelium and is detected in thebasal cell layer at therapeutically effective concentrations	26
		TGF-beta3	Chitosan gel	Improved drug retention, protection against Candida infection; bioadhesive gel could act as protective barrier to reduce discomfort	27
		Keratinocyte growth factor	Adhesive gel	Tropical prevention and treatment of mucositis. Actually drug is administered systemically	28
		Gengigel; Gelclair; MuGard	Mucoadhesive covering agents	Physical coating and protection for thinned or ulcerated oralmucosa	29
3.	Oral lichen planus	Clobetasol	Mucoadhesive gel	The application of mucoadhesive tablet containing 24 gclobetasol 3 times a day appeared to be effective,avoiding the side effects of the generally used treatment	30
		Tacrolimus	Oral rinse	There is need for larger placebo-controlled, randomized studies with carefully selected and standardized outcome measures	47
4.	Oral infections	Metronidazole	Mucoadhesive tablets	Tablets performed 12-h drug sustained release for treatmentof periodontal disease	48
		Miconazole	Mucoadhesive buccal slow release tablet	Has shown more efficacy than conventional topical antifungal agents	37
5.	Salivary hypofunction and xerostomia	Physostigmine	Long-lasting gel	Locally applied gel relief in the feeling of dryness	39
		Interferon alfa	Tablets	Enhance salivary secretion in patients with primary Sjögren syndrome	40.41
6.	Recurrent aphthous stomatitis	Amlexanox	Mucoadhesive tablets	Efficacy and safety in reducing aphthous ulcer pain andlesion size	49
		Amlexanox	Adhesive patches (OraDisc)	Efficacy in the prevention and treatment of oral ulcerations	34

2. **Oral mucositis**-

It is an inflammatory condition of the oral mucosa which results from chemotherapy and radiotherapy of head and neck region.

a. Intraepithelial delivery of transforming growth factor beta 3 (TGFβ3) have shown significant potential for inhibiting epithelial cell proliferation and preventing mucositis.[26]

b. TGFβ3 in chitosan gel (bioadhesive) demonstrated improved drug retention at the application site with increased permeability (Six to seven) fold.[27]

c. Keratinolytic growth factor (KGF) – studies are going on to formulate topical preparation of KGF for the prevention and treatment of mucositis. Currently this drug administered systemically only.[28]

d. Other treatment- includes the use of mucoadhesive covering agents in the form of viscous mouth washes and

gel that provides physical coating and protection for thinned or ulcerated oral mucosa. Eg. Gengigel, Gelclair, MuGaurd.[29]

3. **Immunologically mediated diseases-**

These diseases constitute one of the most common groups of disorders to affect the oral mucosa. These disorders usually center upon T cell (eg. Oral Lichen planus) and B cell (eg. Pemphigus). The vast majority of studies of local therapeutic approaches to immunologically mediated oral mucosal disease have centered upon use of commercially available preparation that have been designed for cutaneous application. These preparations show suboptimal effects on oral mucosa because of different environment of oral cavity as compared to skin.

In one of the studies clobetasol containing mucoadhesive was more effective as compared to clobetasol ointment for treatment of OLP.[30] Kenacort gel was also found to be effective in OLP cases.[31] Topical thalidomide (1% in paste) is found to be as effective as topical dexamethasone (0.043%) in treatment of OLP.[32,33] A new mucoadhesive prolonged release tablet containing 24 µg clobetasol-17 propionate (CP). This formulation was selected to modify the tablet erosion rate in order to obtain a release of CP over a 6-h period and shown good results.[34]

4. **Recurrent apthous stomatitis** –

Amlexanox- In the form of cream and oradisk amlexanon is suggested to be an effective therapy for management of both prevention and management of recurrent apthous stomatitis. A study conducted by Murray et al in 2006 to determine the efficacy of OraDisc (active component 2 mg amlexanox) on the prevention of aphthous ulcers at the prodromal stage, has shown good results with nearly 50% of the study group showing improvement in erythema score, ulcer size and pain scores.[34]

5. Infections-

Infectious agents targeting the oral mucosa includes bacterial viral and fungal species.

a. Topical gelatian violet mouthrinse and nystatin mouth rinse – An in-vitro study conducted by Traboulsi et on the use of inexpensive topical alternatives, e.g. oil of melaleuca (tea tree oil (TTO)), chlorhexidine (CHX), povidone iodine (PI) and gentian violet (GV), to treat oral candidiasis in human immunodeficiency virus (HIV)-infected patients has been proposed in resource-poor countries, in which they found that GV, unlike the other topical agents tested, was fungicidal (minimum fungicidal concentration = 1 µg/mL) against Candida albicans isolates. In addition, GV showed activity against FLZ-resistant C. albicans[35].

b. Probiotic lozenges / chewing gums are found to be effective in bacterial induced dental diseases like dental caries and periodontitis. A randomized clinical study was designed to evaluate the effect of probiotic intervention using lactobacilli on the periodontal condition in which Freeze-dried Lactobacillus salivarius WB21 (WB21)-containing tablets or a placebo were given in the form xylitol tablet. The results indicates that probiotics could be useful in the improvement/maintenance of oral health in subjects at a high risk of periodontal disease[36].

c. Mucoadhesive buccal slow release tablet- this formulation contains 50mg miconazole applied once daily to treat pseudomembraneous candidiasis had shown efficacy and reduces the need to repeated application associated with conventional topical antifungal agents[37].

6. **Neuropathic pain**-

It defined as a condition that is initiated or caused by a primary lesion or dysfunction in the nervous system. In orofacial region, this can caused by deafferenation pain, traumatic neuroma, trigeminal or glossopharyngeal neuralgia.

Preclinical studies provide evidence that peripheral application of opiods, alpha adrenergic agent and antidepressant may be beneficial in neuropathic pain. In one of the open label trial conducted on 21 subjects to evaluate efficacy of topical amitriptyline and ketamine in neuropathic pain syndromes, in which 89% of subjects reported with reduced pain score and 10 % of subjects were painfree.[38]

7. **Salivary hypofunction and xerostomia-**

Salivary hypofunction is associated with a reduction in salivary fluid volume and/ or a change in salivary composition.

a. Epithelial sodium channel blocker (P552) – it is a unique therapeutic agent developed to maintain and stimulate hydration on body's mucosal surfaces. Can be used topically in the form of oral rinse and oral spray. But studies are still under observation.[18]

b. Topical physostigmine gel- when applied locally (1.8mg) produces long lasting relief in the feeling of dryness among subjects suffering from dry mouth and hyposalivation.[39]

c. Interferon alpha lozenges- there is some suggestion that 15 IU of interferon alpha lozenges 3 times a day enhances salivary secretion in patient with primary sjogrens syndrome.[40 41]

d. Anhydrous crystalline maltose, a food stabilizer and desiccant for use in foods, cosmetics, and pharmaceuticals, when delivered orally as a 200-mg lozenge three times daily for 24 weeks in patients with primary Sjogren's syndrome, resulted in improved salivary output and decreased complaints of dry mouth.[42]

FUTURE PRESPECTIVE[18]

In the future probably even more products will be approved for marketing based on advanced drug delivery platforms, such as macromolecular biological drug like rituximab and infliximab in the form of muco-adhesive gel and patches. In addition, attempts should be made to protect these biologivaldtug from enzymatic activity of epithelium for which nanocarrier and enzyme inhibitor can be added to the topical preparation.

Due to the size and other physical property of many protein and antibody based biological mucosal penetration is extremely poor and permeability enhancer or drug carrier system are necessary to improve penetration. Therapeutic anti TNF α antibodies and peptides and other similar biologicals have huge potential for improving treatment of OLP & RAS. So, topical preparation should be developed that could improve treatment of these conditions.

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