REVIEW ARTICLE

Topical drug delivery: An essential aid in the management of oral diseases

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Abstract

Topical medications play an important role in the management of oral lesions. Various topical medications ranging from topical anesthetics to topical antineoplastics have been widely used in dentistry. Topical medications have been extensively used as the first line of therapy in many conditions such as vesiculobullous diseases, oral infections like candidiasis, herpes simplex, potentially malignant disorders, neuropathic pain, and oral mucositis. Topical drug therapy provides targeted and more efficient drug delivery options for the local oral lesions as compared to systemic therapy. While accessibility, lower systemic side effects, and many other advantages are associated with the usage of topical oral medications, several challenges are also faced such as taste alterations, poor penetration, and limited surface area. The objective of this review is to provide insight into the mechanism of topical drug delivery, summary of various topical medications used in oral lesions, advantages and disadvantages, characteristic of oral mucosa and various challenges faced in delivering topical medications.

Keywords

Local drug delivery, oral diseases, oral lesions, oral mucosa, topical drugs

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Introduction

Oral mucosa is a stratified squamous epithelium, acts as a barrier and protects deeper tissues from trauma, prevents the entry of bacteria and toxic substances entering into the body. Oral mucosa can be the site for both local and systemic drug delivery. Topical application of medication allows the direct action of the drug onto the oro-mucosal lesion, thus increasing its therapeutic effectiveness. Topical drug administration is one among the various routes of drug administration.[1] Numerous oral mucosal lesions can be effectively treated by various topical therapeutic agents. Topical medications have been extensively used as the first line of therapy in many conditions such as vesiculobullous diseases, oral infections like candidiasis, herpes simplex, potentially malignant disorders, neuropathic pain, and oral mucositis. Many different formulations such as mucoadhesive tablets, mucoadhesive films, patches, gels, ointments, sprays, and oral rinsed are used for local oral drug delivery.[2] Drug delivery system can be formulated to bring about systemic effects after topical applications (for example, use of glyceryl trinitrate for angina relief, rapid pain relief, and seizures) or for local delivery for oral lesions (example include use of topical corticosteroids of oral lichen planus).[3] The objectives of this review is to provide insight into the mechanism of topical drug delivery, summary of various topical medications used in oral lesions, advantages and disadvantages, characteristic of oral mucosa and various challenges faced in delivering topical medications.

Mechanism of Topical Drug Delivery and Characteristic of Oral Mucosa

Oral mucosa can be divided into three types of mucosa namely masticatory mucosa (gingiva and the hard palate), specialized mucosa (dorsum of the tongue), and lining mucosa (buccal mucosa and the floor of the mouth).[4] Oral mucosa comprises of stratified squamous epithelium with vascular layer of mesoderm. Absorption of topical drugs across oral mucosa intended for systemic therapy or for the treatment of local diseases depends on several aspects such as characteristic of the mucosa, type and thickness and degree of keratinization, and lipid composition. Apart from these aspects, acceptability to the patient, drug release profile, and the practicality of using them also play an important role.[4] Type of mucosa, thickness of mucosa and keratinization: The permeability drug across the mucosa may vary depending on the thickness of the oral mucosa at different sites. Keratinized mucosa is less permeable to the drugs as compared to the non-
keratized mucosa. Gingiva and palate are least permeable sites, whereas buccal mucosa easily permeable mucosa while the maximum absorption occurs in the floor of the mouth. This could be due to lipid composition of membrane coating granules of the keratinized mucosa rather than the presence of keratin itself.\[7\] The connective tissue of sublingual area is rich in capillary blood supply, facilitating direct diffusion of drugs into the blood stream, with rapid onset of action.\[8\]

**Lipid composition**

Lipid content of the upper layers of the epithelium is mainly responsible for the permeability barrier function of the oral mucosa. Membrane coated granules released from suprabasal cells of epithelium, in turn, release lipophilic materials into the intercellular spaces, increasing epithelial cohesion.\[9\]

**Patient acceptability**

Topical drugs cause taste disturbances, may interfere in speech and eating. The drug should be easy for self-administration.

**Drug release profile**

Lipid soluble, non-ionized, and low molecular weight drugs and drugs with high pKa are easily diffusible across the mucosa. The passive diffusion of the drugs depends on its lipophilicity, partition coefficient between lipophilic and hydrophilic regions, and the diffusion coefficient of the substance in the intercellular space. The drug can be sustained release or repeated administration, depending on the condition that is to be treated.\[10\]

There are three modes of transport of topical drugs across oral mucosa: Passive diffusion, carrier mediated transport, and endocytosis/exocytosis.\[11-13\] Currently used formulation to deliver the topical medications to oral mucosa includes tablets, sprays, mouth washes, wafer/film, patches, gels, and pastes. Examples of each have been summarized in Table 1.\[5\]

**Table 1: Different formulations of oral drug delivery**

<table>
<thead>
<tr>
<th>Form</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet/lozenge/ troches</td>
<td>Micanazole, nicotine replacement therapy, lorazepam, fentanyl buccal tablet</td>
</tr>
<tr>
<td>Wafer/film</td>
<td>Fentanyl buccal tablet, buprenorphine/naloxone sublingual tablet</td>
</tr>
<tr>
<td>Spray</td>
<td>Insulin mouth spray, glyceryl trinitrate spray, flurbiprofen throat spray, nicotine inhalation system</td>
</tr>
<tr>
<td>Mouth wash</td>
<td>Chlorhexidine mouth wash, dexamethasone elixir, aminocaproic acid syrup</td>
</tr>
<tr>
<td>Gel</td>
<td>Bioadherent oral gel</td>
</tr>
<tr>
<td>Paste</td>
<td>Aml xenous, triamcinolone acetonide</td>
</tr>
</tbody>
</table>


tendency toward spontaneous resolution, such as non-complex recurrent aphthous stomatitis (RAS) helps in reducing symptoms and duration of disease.

2. A prolonged course of topical corticosteroids of an unpredictable duration: Indicated in cases of chronic or recurrent erosive lesions, such as oral lichen planus, mucous membrane pemphigoid, complex form of the recurrent aphthous ulcer.


4. Diseases that are not susceptible to topical corticosteroids: Presence of multiple mucosal involvements and presence of circulating antibodies require systemic treatment discourage the use of topical corticosteroids.\[14,15\]

Most common adverse effects after topical application of corticosteroids are oral candidiasis in 25-55% of patients. Other adverse effects include epithelial atrophy, hypopigmentation, contact dermatitis, burning mouth, hypoguesia, subcutaneous fat wasting, and cushingoid effect from systemic absorption.\[16\]

Topical corticosteroids are contraindicated in the treatment of primary bacterial infections and in patients with hypersensitivity to corticosteroids.\[1\]

**Topical immunomodulators**

**Tacrolimus**

Tacrolimus is a macrolide molecule, belonging to the group of calcineurin inhibitors, with an immunosuppressive property, mainly used after allogeneic organ transplant to reduce the risk of organ rejection. Topical preparation of tacrolimus is approved for the treatment of atopic dermatitis in adults and children. Studies have shown the efficacy of topical tacrolimus in curing the erosive form of lichen planus which is otherwise resistant to conventional forms of treatment. Tacrolimus binds to FK506, and the complex further binds to calcineurin to inhibit T-lymphocyte activation by inhibiting the phosphatase activity of calcineurin. Tacrolimus is available as 0.03% formulation for children and 0.1% formulation for adults. The posology varies from 1 to 4 times a day according to different studies. The most common side effects with the use of topical tacrolimus are a burning sensation, irritation, tingling sensation, and less
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High potency
0.05% and 0.5%, apply the medicine 3-10 times/day,

Moderate to
0.5 mg in 5 ml of water, given as rinse 2-3 min

Lidocaine
Topical anesthetics/analgesics/anti-inflammatory agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potency</th>
<th>Dose</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone</td>
<td>High</td>
<td>50-100 ug sprayed bid into the lesion</td>
<td>Severe recurrent aphthous stomatitis, Behcet’s syndrome, pemphigus vulgaris, pemphigoid</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>High</td>
<td>0.5 mg in 5 ml of water, given as rinse 2-3 min</td>
<td>Severe recurrent aphthous stomatitis, Behcet’s syndrome, pemphigus vulgaris, pemphigoid</td>
</tr>
<tr>
<td>Clobetasol propionate</td>
<td>High</td>
<td>0.025% and 0.05%, 2-3 times per day, and for a period of 3-5 min each application</td>
<td>Severe ulcerative-vesiculobullous lesions, multiple or extensive lesions, lesions that causes intense pain, impeding swallowing or speech</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>Mild</td>
<td>0.05% and 0.5%, apply the medicine 3-10 times/day, for a period of 3-5 min each time</td>
<td>Mild erosive lesions, with few symptoms and small in size</td>
</tr>
<tr>
<td>Fluocinolone</td>
<td>Moderate to high</td>
<td>0.025% and 0.05%, it being necessary to apply the medication 5-10 times/day and for 3-5 min</td>
<td>Severe recurrent aphthous stomatitis, Behcet’s syndrome, pemphigus, pemphigoid</td>
</tr>
</tbody>
</table>

commonly taste changes and flu like symptoms have been reported.\[17,18\]

Cyclosporine

Cyclosporine is a calcineurin inhibitor isolated from the fungus *Tolypocladium inflatum* gams. It inhibits T-cell activation that may be involved in inflammatory and immune diseases. Topical cyclosporine has been shown to be effective in a variety of oral mucosal disorders including oral lichen planus, RAS, pemphigoid, and pemphigus.\[19\] The effectiveness of cyclosporine in oral lesions is differ in different study. Harpenau et al. compared topical cyclosporine (500 mg, rinsed 5 min) with placebo in patients with oral lichen planus and showed statistically significant improvement in erythema, ulceration, and decreased pain scores with the use of cyclosporine.\[20\]

Azathioprine

Azathioprine is an immunomodulating agents used in organ and tissue transplantation, for treating autoimmune disorders and used as steroid-sparing agent. Azathioprine reduces T-cells, B-cells, and natural killer cells and inhibits cellular immunity, suppresses autoantibody formation, and prostaglandin synthesis. Topical azathioprine has been suggested for the management of graft versus host disease, pemphigus vulgaris, RAS and mucous membrane pemphigoid. For the treatment of graft-versus-host disease, matrix metalloprotease, and pemphigus, rinse was prepared by dissolving AZA in a 1% methylcellulose vehicle with cherry flavoring (5 mg/ml) and patients were instructed to rinse 5 ml of solution for over 1 min and to expectorate, 3-4 times/day. There was an improvement in the severity of erythema and ulceration and pain reduction. However, one randomized crossover study showed that usage of azathioprine was of no value in the treatment of RAS. No significant differences were observed in 18 patients who were administered with azathioprine (2 mg/day, pellets dissolved in the mouth, for 2 weeks) and placebo.\[21-23\]

Topical counterirritants

Capsaicin

Capsaicin causes local desensitization to thermal, chemical and mechanical stimuli after a period of initial irritation. Capsaicin induces selective and reversible desensitization of afferent sensory C fiber endings. Topical capsaicin is available in the concentrations of 0.025-0.075% in burning mouth syndrome, it is used as mouth rinse of 1:2 dilution with water. Studies have reported local adverse skin reactions to capsaicin in early treatment, but these side effects reduced after 1-2 weeks of treatment.\[24,25\] Topically, applied capsaicin may be a safe and effective treatment for post-therapeutic neuralgia. Watson et al. used 0.025% capsaicin to treat 33 patients with post-herpetic
neuralgia. 39% of patients achieved at least a good result and 55% were improved or better.\[30\]

**Topical chemopreventive agents**

Potentially malignant oral diseases consist of morphologically altered tissue in which cancer is more likely to occur than in normal tissue (examples include leukoplakia or erythroplakia). Topical agents are tried for premalignant oral lesions are topical retinoids and bleomycin.

**Topical retenoids**

Retenoids are derivative compounds of natural vitamin A. Topical retenoids have shown variable efficacy in oral potentially malignant diseases. Gorsky and Epstein reviewed use of vitamin A and its derivatives in the treatment of potentially malignant diseases. Epstein and Gorsky used 0.05% tretinoin gel that was applied topically 4 times/day in 26 patients with premalignant lesions. Complete clinical remission was reported in 27% of patients, a partial response was noted in 54% of patients, and clinical recurrence was experienced in about 50% of patients after the topical treatment was discontinued. 19% of the patients experienced localized soreness as the side effect.\[31,32\]

**Topical bleomycin**

Bleomycin, a cytotoxic antibiotic, has also been employed for squamous cell carcinoma of the head and neck region, esophagus, and skin. The use of topical 1% bleomycin was evaluated for the treatment of dysplastic oral leukoplakia in 19 patients. 75% of patients showed resolution of dysplasia and 94% of patients showed partial clinical resolution.\[33,34\]

**Topical neuropathic medications**

Neuropathic pain is a condition that is initiated or caused by a primary lesion or dysfunction in the nervous system. Currently, topical formulations of capsaicin, lidocaine, clonazepam and chlorzidepeoxide are available for treating neuropathic pain. Topical clonazepam and chlorzidepeoxide are benzodiazepines used for burning mouth syndrome. Chlorzidepeoxide works by slowing down the movement of chemicals in the brain. This results in a reduction in the anxiety, muscle spasm, and causes sedation. Clonazepam acts by locally disrupting the neuropathologic mechanism that underlies stomatodynia. It is used as 0.5-1 mg or as wafer 0.25 mg, applied 2-3 times daily.\[35,36\]

**Topical antibiotics**

**Metronidazole**

It is a nitroimidazole antibiotic, which is highly active against Gram-negative anaerobic organisms. It inhibits DNA synthesis and causes DNA degradation by oxidation, leading to single-strand and double-strand breaks and cell death.\[37\] In dentistry, 25% of metronidazole gel has been tried in the treatment of periodontal diseases, dry socket, and peri-implant diseases. In periodontitis, the most common found bacteria are Gram-negative anaerobic rods, such as *Porphyromonas gingivalis* and *Prevotella intermedia*. The local delivery of metronidazole gel is advantageous because of the ability of releasing antimicrobial agents in concentrations high enough to affect pathogens, even in subgingival biofilms.\[38\] Stellini et al. verified efficacy of metronidazole dental gel 25%, used as a topical antibiotic for the treatment of peri-implantitis and found that peri-implant diseases can be positively resolved with 60-70% decrease of Gram-negative and 40-50% increase in Gram-positive organisms and a good peri-implant soft tissue recovery.\[39,40\]

**Tetracyclines**

Use of tetracyclines in periodontitis and RAS is extensively focused area. Tetracyclines and their derivatives (doxycycline and minocycline), in gel or rinse format have been found to be effective in pain reduction in RAS. The mechanism is probably because of inhibition of bacterial protein synthesis and its impact on cytokine production, cellular degradation, and collagenase activity.\[41\] The collagenases and metalloproteinases form part of the inflammatory response and contribute to tissue destruction and ulcer formation. Tetracyclines inhibit collagenases and metalloproteinases and exert an immune modulating effect. Recommended dose of tetracycline is 100 mg in 10 ml of water, performing rinses for 2-3 min, 4 times a day during 3 days.\[42\] In regards to pain reduction, a minocycline 0.2% mouthwash showed superior pain control, by reducing the severity and duration of pain as compared to tetracycline 0.25% mouthwash.\[43\]

Various studies demonstrated use of topical tetracycline showed greater short-term clinical improvements following mechanical therapy in association with systemic or local tetracycline administration. Tetracycline, inhibits metalloproteinase activity and collagenases expressed by immune cells of the host and by microorganisms and thus help to diminish the periodontal infections.\[44,45\] Doxycycline has an additional property of stimulating the maturation and differentiation of osteoblast cell, increasing the activity of alkaline phosphatase, thus expounding an important effect on the periodontal regeneration.\[46\]

The topical administration of tetracycline for periodontal disease treatment can be administered in the pharmaceutical formulation of fibers, gels, strips, biodegradable, and non-biodegradable films. High concentrations of antibiotic in the ginvial crevicular fluid for 10 days were observed after the application of subgingival fibers of tetracycline.\[47\]

**Topical antifungal agents**

Topical agents that are the first line of therapy for the treatment of superficial oral fungal infections. They exhibit fungicidal or fungistatic actions with fewer side effects when applied topically and avoids drug to drug interactions which are more common in the case of oral applications. Topical antifungal agents are available as rinses, tablets, vaginal tablets, and creams.\[48,49\] Clotrimazole is an imidazole derivative used as the topical antifungal agent. It is a most potent topical agent, used as
10 mg troche, 5 times a day or applied as cream to the affected area for 3–4 times a day. Mild irritation, burning sensation and stinging sensation have been reported after local application of clotrimazole. Nystatin is a polyene antifungal agent available in rinse form, oral and vaginal tablets or creams. Acute oral candida infections respond well to topical nystatin when used for 7 to 21 days, applied 3–4 times daily. Nystatin cream can be applied to the dentures or angular chelitis. Nystatin is available as oral suspension (100,000 U/mL), troche (200,000 U/mL), and cream (100,000 U/g).[50]

Topical antiviral medications

Topical antiviral medications reduce the duration of viral shedding and shorten the healing time. Although topical treatment is much less effective compared to oral or intravenous therapies, it can be used to improve the length of time before all lesions becomecrusted, especially when applied during prodrome. Commonly used topical antiviral agent is acyclovir, which is a synthetic purine nucleoside analog with inhibitory activity against herpes simplex virus types 1 (HSV-1), HSV-2, and varicella-zoster virus and inhibits the replication of herpes virus. 5% topical acyclovir is used in the management of recurrent herpetic labialis and non-life threatening mucocutaneous herpes simplex in immunocompromised patients. Adverse effects include stinging and burning sensation after topical application.[51,52] Penciclovir, an acyclic nucleoside analog, inhibits viral DNA polymerase. 1% penciclovir cream is effective in reducing time to loss of crust, duration of lesions, and duration of pain of recurrent herpetic labialis. N-docosanol is 22-carbon primary alcohol that interferes with epithelial cell surface receptors and viral envelope proteins, thus blocks the virus from attaching to cell. 10% docosanol is effective in reducing the pain and healing time of herpetic lesions.[53] Foscarinet sodium is another antiviral agent which complexes with viral DNA polymerase and blocks viral DNA extension. 3% foscarinet cream can be recommended if lesions are known to be acyclovir-resistant and it reduces HSV shedding, resulting in more aborted lesions, reduction in lesion size and duration.[54,55]

Advantages and Disadvantages/Challenges Faced

There may be rapid loss of drug from the site of absorption because of salivary flushing and mechanical stress. The applied drug may cause unpleasant taste sensations. The drug may be inadequately distributed in the oral cavity leading to decreases therapeutic efficacy. Moreover, the barrier function of oral mucosa prevents may hinder the absorption of the drug completely.[2,56]

Conclusion

Oral local drug delivery is the most efficient drug delivery approaches that allow increased concentration of medication for management of local oral disease. Rich blood supply, rapid absorption and lower systemic side effects, easy accessibility makes it an attractive mode of drug delivery system. In cases where oral manifestations of systemic diseases still persists, despite the systemic treatment, administration of local therapies may boost the local concentration of the drug leading to the improvement in the condition. Unfortunately, most of currently used topical medications for oral diseases include those preparations that are intended to be used for skin. More oral preparation, specifically used for oral cavity keeping in mind of local challenges that are faced must be manufactured. We as dentist must be aware of different formulations and dosages of drugs that are available for the treatment of the oral diseases and emergency medicines that can be used for systemic therapeutic effects.

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