**Oral Mucosal Drug Delivery- an adjunct to the current therapeutic strategies in the dental management of oral diseases: Review.**

**Abstract:** Mucosal route of drug administration is one of the most effective routes of drug delivery in patients. This mucosal adhesive drug delivery possess many advantages which include bypassing first pass metabolism in liver and protects from enzymatic degradation of drug in gastrointestinal tract. This includes ocular, rectal, vaginal, nasal etc. oral mucosal drug delivery is one among them. Local drug delivery used to treat many oral mucosal diseases which include oral cancer, mucositis, candidiasis, lichen planus, vesiculobullous lesions, recurrent aphthous stomatitis, xerostomia etc. The current article focuses on the historical back ground of mucoadhesive mechanism and principles of mucosal drug delivery system based on adhesion to biological surfaces and invitro and invivo applications of this targeted mucosal drug delivery system in treating mucosal disorders.

**Key words:** First pass metabolism, Mucosal drug delivery, Mucoadhesive system, Mucosal

disorders.

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**Introduction:**

Drugs can be administered via many different routes to produce its pharmacological bio-effects. The intra oral route is most preferred route as it is convenient and produce rapid onset of action. However per-oral administration has many disadvantages like hepatic first pass metabolism and enzymatic degradation within the gastrointestinal tract. Transmucosal route of drug administration has distinct advantages over peroral administration for systemic drug delivery and action.

Mucoadhesive drug delivery systems are drug delivery system which utilizes property of certain bio-polymers which become adhesive on hydration to mucosa which deliver drug to local site on application with limited systemic perfusion or absorption. Mucosal layer covers a number of regions in the body which include urogenital system, ear, nose, throat, eye, gastrointestinal system, respiratory tract and oral cavity.

Mucoadhesive drug delivery systems include:1

**ORAL MUCOADHESIVE DRUG DELIVERY SYSTEM:**

Drug delivery via mucous membrane is divided into:

1. **Submucosal drug delivery system**
2. **Buccal drug delivery system**
3. **Local drug delivery system**

**Historical perspective:**

A new concept of bioadhesive drug delivery system into pharmaceutical sciences was introduced by research work by united states, japan and Europe in mid-1980’s.2 Later it was identified that some polymers alter permeability by loosening intercellular junction.2Development of mucoadhesive polymers introduced into science in 1947 after combination of tragacanth and dental adhesive powder to form a vehicle for application of penicillin into oral mucosa. Later improvement of this system resulted in combination of carboxymethylcellulose and petroleum and this advanced to introduction of oradhesives and trials of orabase in 1959.

**MUCOADHESIVE MECHANISM: 3**

Mucoadhesion involves wetting, adhesion, interpenetration of polymer chains. Mechanism of mucoadhesion includes

1. Intimate contact between bioadhesive and membrane (wetting phenomenon).
2. Penetration of bioadhesive into surface of mucous membrane (interpenetration).

Adhesion is prolonged due to formation of vanderwaal interactions, hydrogen bonds, electrostatic forces.

**THEORIES OF BIOADHESION: 4**

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| **THEORY** | **MECHANISM OF BIOADHESION** |
| **Electronic theory** | *Attractive electrostatic forces between glycoprotein mucin network and bioadhesive.* |
| **Wetting theory** | *Ability of bioadhesive polymer to spread and have intimate contact with mucous membrane.* |
| **Adsorption theory** | *Surface forces resulting in chemical bonding.* |
| **Diffusion theory** | *Physical entanglement of mucin strands and flexible polymer chains* |
| **Mechanical theory** | *Adhesion occurs as a result of interlocking of liquid adhesive into irregularities of rough surface.* |
| **Fracture theory** | *It is most accepted theory. It is the force required to separate two surfaces after bioadhesion is established.* |

Advantages:

1. Faster onset of action from the muosal surface
2. Drug is protected from degradation from acidic environment in gut.
3. Rapid absorption because of increased blood supply and increase in blood flow rates
4. Increase in bioavailability because of avoidance of first pass metabolism in liver.
5. Increased patient compliance –easy mode of administration.
6. Excellent accessibility.

Disadvantages:

1. Saliva washes away drugs.
2. Mastication may dislodge delivery device.
3. Taste factor consideration.
4. Relatively small surface area.

**TYPES OF MUCOADHESIVE POLYMERS5**

**Role of Mucosal Drug Delivery in Oral Disorders:**

**ORAL MUCOSITIS**

It is an inflammatory condition of oral mucosa which occurs as a result of cancer chemotherapy, particularly bone marrow transplant and head and neck radiotherapy in treatment of oral cancer. It is characterized by erythema, inflammation, pain and ulceration.

Treatment:

1. Benzydamine hydrochloride, non steroidal drug which can be used as topical application or can be used as 0.15% benzydamine mouth rinse as prophylactic treatment of radiation induced mucositis.6
2. Topical sucralfate during radiotherapy.7,8

* Novel formulations9 which include intraepithelial delivery of transformation growth factor beta-3(TGFB-3) to inhibit epithelial cell proliferation could help in prevention of oral mucositis and keratinocyte growth factor (KGF) for prevention and treatment of oral mucositis.
* Other treatment approaches include mucoadhesive covering agents include mouth washes and gels which provide protective covering for ulcerated mucosa ex. Gengigel, Gelclair and MuGard.
* Beneficial effects seen even on use of supersaturated calcium phosphate mouth rinse.

**ORAL LICHEN PLANUS**

Treatment:

* Tacrolimus, immunosuppressive drug which is produced by streptomyces tsukubaensis which belongs to macrolide family which has great penetration into oral mucosa.
* Triamcinolone acetonide, is one among most commonly used topical corticosteroids which is used at concentration between 0.05%-0.5% for 3-10 times a day applied for 3-5 minutes.
* Pimecrolimus, a derivative of macrolide ascomycin developed for inflammatory diseases of skin10. It represents new topical selective cytokine release inhibitor.
* Clobetasol propionate in the form of orabase or aqueous solution can be used at a concentration of 0.025-0.05% for 2-3 times a day applied for 3-5 minutes which induces vasoconstriction followed by reduction of inflammation due to alteration of histamine level and to the effects of catecholamine on the peripheral blood vessels.
* Flucinonide is corticosteroid used at concentration of 0.025-0.05% for 5-10 times a day for 3-5 minutes.
* Hydrocortisone hemisuccinate in aqueous form offer little benefit. Fluticasone propionate spray and betamethasone sodium phosphate mouth rinse used for management of symptomatic oral lichen planus.11

**PEMPHIGUS**

Treatment

* Topical corticosteroids play role in management of oral pemphigus vulgaris and it depends on severity of disease.
* Topical corticosteroids along with systemic immunosuppressants are used in treating severe mucocutaneous pemphigus
* Anti TNF-alpha biological agents or rituximab have benefit in application for oral mucosal pemphigus.
* Intralesional triamcinolone acetionide may lessen the signs and symptoms of oral pemphigus.

**MUCOUS MEMBRANE PEMPHIGOID**

Treatment

* In patients with lesions confined to oral mucosa, triamcinolone acetonide 0.1%, flucinolone acetonide 0.05%, clobetasol propionate 0.05% orabase for 3-4 times a day applied for 9-24 weeks to resolve the lesion.12

**RECURRENT APTHOUS STOMATITIS**

Treatment

* Main treatment involves use of topical agents for symptomatic relief which includes antibiotics, analgesics, nonsteroidal antiinflammmatory drugs and immunosuppressants. Of all the topical agents present to treat RAU 5% amlexanox appears to be one of the best. It is 2-amino-7-isopropyl-5-oxo-5H-(1) benzopyrano-(2,3-b)-pyridine-3-carboxylic acid ,topical anti-inflammatory and antiallergic drug.
* Topical drugs for recurrent aphthous stomatitis13

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| **TOPICAL CORTICOSTEROIDS** | Hydrocortisone hemisuccinote (pellets)  Triamcinolone acetonide (in odhesive poste)  Fluocinonide (cream)  Betamethasone valerate (mouthrinse)  Betomethosone-17-volerate (mouthrinse)  Flumethasone pivolate |spray)  Beclomethasone diproprionate (spray)  Clobetasol proprionate (cream)  Mometasone furoate (cream |
| **ANTIMICROBIALS** | Chlorhexidine gluconate (mouthrinse)  Triclosan (mouthrinse)  Topical tetracyclines (e.g.aureomycin, chlortetracycline, tetracycline) |
| **TOPICAL ANALGESICS** | Benzydamine hydrochloride (spray or mouthrinse)  Topical anaesthetics (gel) |
| **OTHER TOPICAL ANTIINFLAMMATORY DRUGS** | Amlexanox, Sodium cromoglycate (lozenges)  Carbenoxolone sodium mouthrinse, Azalestine  Human alpha-2-interferon (cream)  Ciclosporin (mouthrinse)  Topical 5-aminosalicylic acid, Prostaglandin |

**ORAL CANCER**

Treatment14

* 13-Cis-retinoic acid (iso-tretinoin) inhibit development of second primary tumors in patient with previous head and neck cancer. It induces remission of oral leukoplakia and prevents development of cancer in patient with oral leukoplakia.
* 5-aminolevulenic acid is only photosensitizer that can be applied topically.
* 1% bleomycin in dimethylsulfoxide used for treatment of dysplastic oral leukoplakia once daily for 14 consecutive days.

**OROFACIAL NEUROPATHIC PAIN**

In orofacial region, neuropathic pain can be caused by traumatic neuroma, trigeminal neuralgia, glossopharyngeal neuralgia, atypical odontalgia, burning mouth syndrome.

Treatment

* Burning mouth syndrome can be managed by topical application of clonazepam and then with other neuropathic drugs. Currently topical formulations of capsaicin (cream) and lidocaine (patch) can reduce neuralgic pain. These can be used along with systemic medications to reduce severity.14
* Preclinical studies provide evidence that peripheral application of opioids, anti-adrenergic drugs, antidepressants can be used to reduce neuropathic pain.

**XEROSTOMIA**

Xerostomia Remidies15

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| --- | --- | --- | --- |
| Biopolymer based (carboxymethylcellulose, hydroxyethylcellulose) | Salivary enzyme based(lactoperoxidase, lysozyme, glucose oxidase) | Acid based(malic, citric, ascorbic acid) | Petroleum based(petroleum derivative) |
| Plant mucilage products   * Alovera gel * Salinum   Animal mucilage products   * Bovine mucine * Porcine mucine * Xantham gum | Moisturizing gel  Moisturizing liquid  Antibacterial paste  Mouth wash  Chewing gum | Salivix,  Salivin  Saliva sure | Trident chewing gum  Extra chewing gum  Biotene chewing gum |

**INFECTIONS**

Antifungal Drugs

Most common fungal infection which need topical application of antifungal drugs is oral caandidiasis. Antifungal drugs fall into 2 categories – azoles and polyenes.

**TOPICAL DRUGS FOR FUNGAL INFECTIONS**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drugs** | **Dosage** | **Form** | **Recommended Treatment** | **Side Effects** |
| AMPHOTERICIN B | Lozenge 10mg oral suspension | Topical(systemic) | Slowly dissolved in mouth 3-4 times a day after meals  Place in mouth after food and retain near lesion 4 times a day. | gastrointestinal  disorders. |
| NYSTATIN | Cream  Pastelli, 100,000 units  Oral suspension 100,000 units | Topical only | Apply to affected area 3-4 times a day.  Apply after meals 4 times a day | Gastrointestinal disorders.  Hypersensitivity. |
| CLOTRIMAZOLE | Cream  Solution | Topical only | Apply to affected area 2-3 times daily  5 ml 3-4 times daily. | Gastrointestinal disorders |
| MICONAZOLE | Oral gel  Cream. | Topical(Systemic) | Apply to affected area 3-4 times daily.  Apply twice per day. | Gastrointestinal disorders.  Burning. |

**ANTIVIRAL DRUGS**

|  |  |  |  |
| --- | --- | --- | --- |
| **Antiviral drugs** | **Mechanism of action** | **Virus affected** | **Side effects** |
| Acyclovir | Metabolizes to acyclovir triphosphate, which inhibits viral DNA polymerase. | Herpes simplex, varicella- zoster,  cytomegalovirus | Gastrointestinal disturbances,  headache, rash |
| valacyclovir | Metabolizes to valacyclovir triphosphate, which inhibits viral DNA polymerase. | Herpes simplex, varicella- zoster,  cytomegalovirus | Gastrointestinal disturbances,  headache, rash |
| Ganciclovir | Metabolizes to gancyclovir triphosphate, which inhibits viral DNA polymerase. | Cytomegalovirus | Renal insufficiency,  fever, headache |
| Penciclovir | Metabolizes to pencyclovir triphosphate, which inhibits viral DNA polymerase | Herpes simplex | None |
| famcyclovir | Metabolized to famciclovir triphosphate, which inhibits  viral DNA polymerase | Herpes simplex, varicellazoster | Headache, nausea, diarrhea |
| Lamivudine | Inhibition of viral DNA polymerase  and reverse transcriptase. | Hepatitis B, human immune-deficiency  virus type 1 | Anemia, skin and eye irritation,  bronchospasm. |
| amantadine | Blockage of M2 protein ion channel and ability to modulate intracellular pH. | Influenza A | Nausea, anorexia, CNS dysfunction |

**Evaluation of Buccoadhesive Dosage Form 16,17**

**In Vitro/ Ex vivo methods**

1. Tensile strength
2. Shear strength

3) Adhesion weight method

4) Fluorescent probe method

5) Flow channel method

6) Mechanical spectroscopic method

7) Falling liquid film method

8) Colloidal gold staining method

9) Iscometric method

10) Thumb method

11) Adhesion number

12) Electrical conductance

**In vivo method**

1) Radioisotopes

2) Gamma scintigraphy

3) Pharmaco scintigraphy

4) Electron paramagnetic resonance

5) Isolated loop technique

6) X-ray

**DOSAGE FORMS**

A wide range of formulations have been developed which counteract the problems faced in drug delivery to sublingual and buccal mucosae to systemic circulation.

**Delivery against oral microflora:**

Dental caries is caused by indigenous microbiata and biofilm on tooth surface. Streptococcus mutans produce biofilm on tooth surface which cause dental caries. Dental drug delivery system (3 DS) using chlorhexidine 0.2% which consists of individual retainer with proper fit onto the arches which contain antibacterial drug mostly chlorhexidine which is widely accepted antibacterial agent which kills bacteria on tooth surface but not on oral mucosa. 3DS applied twice daily for 5 minutes and done along with 0.2% chlorhexidine mouthrinse for 1 minute every day after lunch for 9 days.18

**Chewing gums:**

A base which consists of elastomers, resins, waxes and fats. Emulsifiers such as glycerol monosterate, lecithin are added to facilitate uptake of saliva by gums. Resin esters and and poly vinyl acetate are added to reduce and prevent sticking of gums to teeth. Gum formulations containing caffine showed rapid release and absorption of agent compared to capsulated form. Various formulations such as vitaminC, Diphenhydramine, Methadone, Verapamil have developed. Recently sustained release of catechins developed. One of most successful application of chewing gum is nicotine replacement therapy.

**Lozenges**

Lozenges are alternative dosage form of capsules and tablets when patient is unable to swallow. Buccal lozenges are extensively used to deliver drug systemically and also bath the oral cavity which is kept between cheeks and gums. For example Zinc lozenges has been used in common cold. Oral mucosal administration of fentanyl citrate, a medication for breakthrough pain, resulted in a bioavailability substantially greater than oral administration and led to faster achievement of peak plasma concentration.

**Buccal and Sublingual Tablets19**: These tablets are placed between the cheek and gum or the lip and gum (buccal) or under the tongue (sublingual) until they dissolve. Nitroglycerin tablets have been used extensively in the form of buccal and sublingual tablets for quick onset and fast relief from angina. Similarly isosorbide dinitrate is available in the form of sublingual tablets to be placed under the tongue or chewable tablets where the tablet has to be chewed in the mouth for 2 min before swallowing, and the drug is adsorbed through the oral mucosa. Other formulations that have been used are nifedipine (sublingual capsules), sublingual misoprostol for labor induction, methyl testosterone (buccal and sublingual tablets), buprenorphine (sublingual and buccal), and selegiline for monoamine oxidase-B inhibition.

**Sublingual dispensary prosthesis20:**

Sublingual route of drug administration is one of the most effective methods of drug delivery in patients. The connective tissue beneath the sub lingual epithelium is profusely supplied by capillaries, hence facilitating direct diffusion of drugs into the blood stream, thus ensuring the fast onset of action. Many varieties of drugs for angina pectoris such as Isosorbide dinitrate, Anti-hypertensives,21 antidepressants, vitamins can be administered sublingually22 with highly predictable rapid clinical onset and efficacy. Some patients may experience considerable difficulty in retaining the sub lingual tablets in the mouth, due to various pathologic reasons like parkinsonism, myofacial dyskinesia, neuro-muscular disorders, stroke, psychological and psychiatric disorders. In such cases, sublingual drug dispensing prosthesis can help the patients, because it retains the tablet in the chamber and also protects them from the displacing action of the tongue.

**Films and Patches23:** Patches are flexible dosage forms that adhere to a specific region of the mucosa and depending on the type of delivery intended (local or systemic) it provide either a unidirectional flow or a bidirectional flow of drug. Different patches are designed to achieve objectives such as local and systemic drug delivery, varying duration of action and varying rates of release. In general, most patches contain either a ‘‘matrix system’’ in which the drug is dispersed along with excipients or the mucoadhesive, or a ‘‘reservoir system.’’ permeation of the drug into the membrane will depend on the surface area of the patch.

A novel buccal delivery system Striant1 approved by the Food and Drug Administration (FDA) in 2003 is a controlled and sustained release buccal mucoadhesive system, containing 30 mg of testosterone and bioadhesive excipients. The patch contains the bioadhesive polymer PCP, along with other inert ingredients including hydroxypropylcellulose, mono-hydrated lactose, and cornstarch. After the patch was placed on the gum above the right or left canine, testosterone was slowly released from the matrix. The film which is applied to the oral mucosa can be retained in place for at least 12 hours even when it is challenged with fluids.

**Fast Caps24:** A new type of fast dissolving drug delivery system based on gelatine capsules was developed. In contrast to conventional hard capsules, the fast caps consist of gelation of low bloom strength and various additives to improve the mechanical and dissolution properties of the capsule shell. The advantage of these fast disintegrating capsules are high drug loading, possible solid and liquid filling, no compression of coated taste-masked or extended release drug particles/pellets, simple manufacturing, good mechanical properties , mechanical stability and requirement of special packaging.

**Semisolid Preparations (Ointments and Gels)**

Bioadhesive gels or ointments have less patient acceptability than solid Bioadhesive dosage forms, and most of the dosage forms are used only for localized drug therapy within the oral cavity. One of the original oral mucoadhesive delivery systems –“orabase”– consists of finely ground pectin, gelatin and sodium carboxy methyl cellulose dispersed in a poly (ethylene) and a mineral oil gel base, which can be maintained at its site of application for 15- 150 minutes.24

**Powders**

Hydroxypropyl cellulose and beclomethasone in powder form when sprayed onto the oral mucosa of rats, a significant increase in the residence time relative to an oral solution is seen, and 2.5% of beclomethasone is retained on buccal mucosa for over 4 hours.

**Carrier-Associated Suspensions:**  newer approach to buccal administration of insulin involves using insulin associated with a carrier, namely erythrocyte ghosts (EG). The insulin was administered either free or attached to carrier systems (erythrocyte ghosts–insulin, EG–INS) to streptozotocin diabetic rats by instilling the dose in the oral cavity using a syringe. To prevent swallowing of the dose, the rats were anesthetized, and blood samples were collected from the tail over 5 h. The magnitude of blood glucose level decline was found to be at its maximum of 39.53 mg/dl (at 2 h) for free insulin and 26.23 mg/dl (at 4 h) for EG–INS insulin, showing that the carrier-associated system was significantly effective at decreasing the blood glucose levels.

**Nanoparticles:** In an effort to develop an effective bioadhesive system for buccal administration, insulin was encapsulated into polyacrylamide nanoparticles by the emulsion solvent evaporation method. Though nanoparticle formation ensures even distribution of the drug, pelleting of the nanoparticles was performed to obtain three-dimensional structural conformity. In addition, it was hypothesized that the pelletized particles will remain adhered to the mucosa, leading to good absorption. While studying bioadhesion and drug release profiles, it was found that the system showed a sustained drug release profile that was mainly governed by polymer concentration. A significant and non-fluctuating hypoglycemic response with this formulation was observed after 7 h in diabetic rats.

**Liposomes:** Liposomes have been used in the local delivery of drugs to the oral mucosa. Farshi *et al.*, studied the biodistribution of dexamethasone sodium phosphate (DSP) encapsulated in multilamellar vesicle (MLV) liposomes labeled with 99mTc in ulcerated and intact oral mucosae of rats. The liposomes were found to localize the drug in the ulcerated area and increase local drug concentration while decreasing systemic concentration.

**Microparticulate Delivery Systems:** Microparticulate delivery systems containing piroxicam in amorphous form were designed to improve the drug dissolution rate via the sublingual route. Two low-swellable mucoadhesive methacrylic copolymers, namely Eudragit1 L sodium salt (EuLNa) and Eudragit1 S sodium salt (EuSNa), were chosen as carriers for the preparation of the microparticles. Two series of microparticles containing piroxicam and EuLNa or EuSNa in ratios ranging from 15:85 to 85:15 (m =m) were prepared by spray drying.

**Target drug delivery system25:**

It is a method of delivering drug to patient so that it increases concentration of drug in specific region compared to other areas. Target drug delivery seeks to improve efficacy and reduce side effects.

**Approaches of target drug delivery system:**

**QUANTUM DOTS**

Quantum dot is a semiconductor nanostructure that confines motion of conduction band electrons, valency band holes, exitons in all three spatial directions. The confinement can be due to electrostatic potentials, the presence of semiconductor surface, presence of interface between different semiconductor materials. The ability to tune size of Quantum dots is advantageous for many applications.

**LIPOSOMES**

These are vesicular concentric structures, range in size from nanometers to several micrometers. It contains phospholipids bilayer. Properties include biocompatible, biodegradable, and non-immunogenic. They play a significant role in formulation of certain drugs to increase their therapeutic efficacy which include antimicrobials, antitumor agents, anti viral drugs, vaccines, gene therapeutics. These liposomes are used to reduce toxicity and side effects of drugs.26

**TRANS DERMAL APPROACH**

Trans dermal delivery system is topically administered medications in the form of patches that delivers drug for systemic effect at a controlled rate. A transdermal delivery device is used to deliver drug which may be passive or active and mostly in the form of patch. The drug is placed in relatively high dosage on inside of patch, and when this patch is worn for an extended period of time, drug diffuses directly into bloodstream across the skin.

**FOLATE TARGETING**

It is a method of drug delivery system used in biotechnology. It involves attachment of folicacid to a drug to form folate conjugate. It is based on principle that folate has high affinity for folate receptor protein, which is present on surface of human cancer cells. Folate conjugate also has high affinity for folate receptor protein which increases cellular uptake by endocytosis. Molecules ranging from small radiodiagnostic imaging agents to large DNA plasmid formulations have been successfully delivered inside folate receptor positive cells and tissues.folate receptor is a glycosylphosphotidylinositol linked protein that captures its ligands from extracellular milieu and transports into the interior of cell via non destructive recycling endosomal pathway.

**SONOPORATION**

Ultrasonication techniques are used to deliver proteins, DNA and other formulations into cells. ultrasound energy often amplified by use of microbubble activities, generates, transient, non-specific pores on membranes, a process called sonoporation. This transient pores allows permeation to extracellular molecules for a limited time window into the interior of cells which are otherwise non permeable.22Best example of sonoporation is bleomycin. Cytotoxicity of bleomycin is because of direct DNA damage caused by single or double strand breakage that causes DNA fragmentation, chromosomal gaps, deletions. Bleomycin which is highly toxic inside the cell which is normally nondiffusible through the plasma membrane.19,20Thus bleomycin is used as agent for drug delivery using sonoporation.23

Epidermoid growth factor receptor is usually over expressed inside tumor effected cells and such oveexpression marks poor prognosis. Anti-EGFR antibody is a specific drug delivery system used to treat squamous cell carcinoma.

A number of invitro studies have performed by the application of non-thermal ultrasound energy for controlling drug release, while antiproliferative agents, such as 5-fluorouracil, mitomycin C and BLM are often administrated in an intravenous or intratumoral injection along with electrochemotherapy.

**Conclusion:**

In conclusion, the oral mucosa's accessibility, high blood supply, by-pass of the hepatic first pass metabolism, quick recovery time after damage and permeability profile makes it an attractive and

interesting area for topical drug delivery research in the management of plethora of oral diseases. With the appropriate carrier mediated technologies, delivery techniques and the choice of the polymer the oral mucosa could, in the future, be utilised for the treatment of many diseases both mucosal and systemic. Further advances in mucobuccal adhesive technology and sustained local drug release and target specific delivery also have the potential for reducing the systemic side effects from ingested or injected therapies, where an oral mucosal disease is the target of therapy.

**References**

1. Akhter H, Gupta J, Mohiuddin Md, Md. Shah Faisal Md shah. A comprehensive review on buccal drug delivery system. *IJPRD.* 2011; 3(11): 59-77.
2. Roy SK and Prabhakar B. Bioadhesive polymeric platform for transmucosal drug delivery system. *Trop J Pharm Res.* 2010; 9(1): 91-104.
3. Prajapati V, Bansal M, SharmaPK. Mucoadhesive Buccal Patches and Use of Natural Polymer in Its Preparation – A Review. *International Journal of PharmTech Research.* 2012; 4(2): 582-589
4. Smart JD. The basics and underlying mechanisms of mucoadhesion. *Adv Drug Del Rev.* 2005; 57: 1556-68.
5. Sudhakar Y, Kuotsu K, Bandyopadhyay A.K. Buccal bioadhesive drug delivery - A promising option for orally less efficient drugs. *J. Contr. Rel.* 2006; 114: 15-40
6. Epstein JB, Silverman S Jr, Paggiarino DA, Crockett S, Schubert MM, Senzer NN, Lockhart PB, Gallagher MJ, Peterson DE, Leveque FG. Benzydamine HCl for prophylaxis of radiation induced oral mucositis: results from a multicenter, randomized, double-blind, placebocontrolled clinical trial. *Cancer* 2001:92(4):875-85.
7. Franzen L, Henriksson R, Littbrand B, Zackrisson B. Effects of sucralfate on mucositis during and following radiotherapy of malignancies in the head and neck region. A double-blind placebo-controlled study. *Acta Oncol* 1995; 34(2):219-23.
8. Allison RR, Vongtama V, Vaughan J, Shin KH. Symptomatic acute mucositis can be minimized or prophylaxed by the combination of sucralfate and fluconazole. *Cancer Invest.* 1995:13(l):16-22.
9. [Sankar V](http://www.ncbi.nlm.nih.gov/pubmed?term=Sankar%20V%5BAuthor%5D&cauthor=true&cauthor_uid=21382140), [Hearnden V](http://www.ncbi.nlm.nih.gov/pubmed?term=Hearnden%20V%5BAuthor%5D&cauthor=true&cauthor_uid=21382140), [Hull K](http://www.ncbi.nlm.nih.gov/pubmed?term=Hull%20K%5BAuthor%5D&cauthor=true&cauthor_uid=21382140), [Juras DV](http://www.ncbi.nlm.nih.gov/pubmed?term=Juras%20DV%5BAuthor%5D&cauthor=true&cauthor_uid=21382140), [Greenberg MS](http://www.ncbi.nlm.nih.gov/pubmed?term=Greenberg%20MS%5BAuthor%5D&cauthor=true&cauthor_uid=21382140), [Kerr AR](http://www.ncbi.nlm.nih.gov/pubmed?term=Kerr%20AR%5BAuthor%5D&cauthor=true&cauthor_uid=21382140) et al.  Local drug delivery for oral mucosal diseases: challenges and opportunities. [*Oral Dis.*](http://www.ncbi.nlm.nih.gov/pubmed/21382140) 2011; 17(1): 73-84.
10. Lopez-Jornet P, Camacho-Alonso F, Salazar-Sanchez N. Topical tacrolimus and pimecrolimus in the treatment of oral lichen planus: an update. *J Oral Pathol Med*. 2010; 39(3):201-5.
11. Thongparosam K, Dhanuthai K. Steroids in the treatment of lichen planus: a review. *J Oral Science.* 2008; 5(4):377-85.
12. Ata-Ali F, Ata-Ali J. Pemphigus vulgaris and mucous membrane pemphigoid: update on etiopathogenesis, oral manifestations and management. *J Clin Exp Dent*. 2011; 3(3):246-250.
13. Jurge S, Kuffer R, Scully C, Porter SR. Number VI. Recurrent aphthous stomatitis. *Oral Diseases.* 2006;12(l):l-21
14. Sheikh S, Gupta D, Pallagatti S, Singla I, Gupta R, Goel V. Role of Topical Drugs in Treatment of Oral Mucosal Diseases A Literature Review. *The New York State Dental Journal.* 2013; 58-64.
15. Gorovenko MR, Clark DC, Aleksejuniene J*.* Over thecounter xerostomia remedies currently available*in*Canada*.* *CJDH*. 2009*;* 43*(*2*):*71-77*.*
16. S.K. Gupta, I.J. Singhavi, M. Shirsat, G. Karwani, A. Agrawal, A. Agrawal, Buccal adhesive drug delivery system: a review. *Asian J. Biochemical and pharmaceutical research*. 2011; 2(1):105-114.
17. Verma N and Chattopadhay P. Polymeric platform for mucoadhesive buccal drug delivery system: a review. *IJCPR*. 2011; 3(3):3-8.
18. Takeuchi H, Senpuku H, Matin K, Kaneko N, Yusa N, Yoshikawa E ET AL. New Dental Drug Delivery System for Removing Mutans Streptococci from the Oral Cavity: Effect on Oral Microbial Flora. *Jpn. J. Infect. Dis* 2000; 53: 211-12.
19. Anders, R., et al. Buccal absorption of protirelin: An effective way to stimulate thyrotropin and prolactin. *J Pharm Sci.*1983; 58:1-10
20. Ganapthy D, Ariga P, Selvaraj A. Sublingual drug dispensing prosthesis. *Indian J Dent Res*. 2012; 23: 434-7.
21. Cummings DM, Amadio P Jr, Nelson L, Fitzgerald JM. The role of calcium channel blockers in the treatment of essential hypertension. *Arch Intern Med*.1991; 151(2): 250-9.
22. Schoenberger JA, Testa M, Ross AD, Brennan WK, Bannon JA. Efficacy, Safety, and Quality-of-Life Assessment of Captopril Antihypertensive Therapy in Clinical Practice. *Arch Intern Med.*1990;150(2):301-306
23. Bhati and madan. A detailed review on oral mucosal drug delivery system. *ijpsr*. 2012; vol. 3(1): 659 -681
24. Rakesh Hooda, Mohit Tripathi A Review on Oral Mucosal Drug Delivery System. *The Pharma Innovation*. 2012; 1(1): 14-21
25. Manish G and Vimukta S. Targeted drug delivery system: A Review. *Res. J.Chem.Sci.* 2011; 1 (2): 135-38.
26. Yadav A, Ghune M, Jain DK. Nano-medicine based drug delivery system. *Journal of Advanced Pharmacy Education & Research.* 2011; 1(4):201-13.