Oral Mucosal Drug Delivery- An Adjunct to the Current Therapeutic Strategies in the Dental Management of Oral Diseases: Review

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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

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 [1] (*Figures 1 and 2*).

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 [2]. Development 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 (*Table 1*).

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 [4].

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

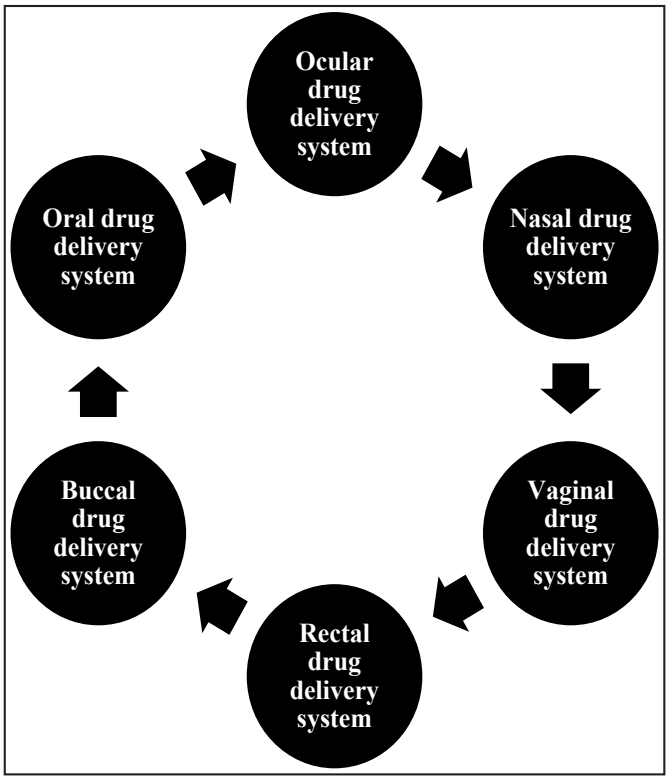

Figure 1: *Mucoadhesive drug delivery systems.*

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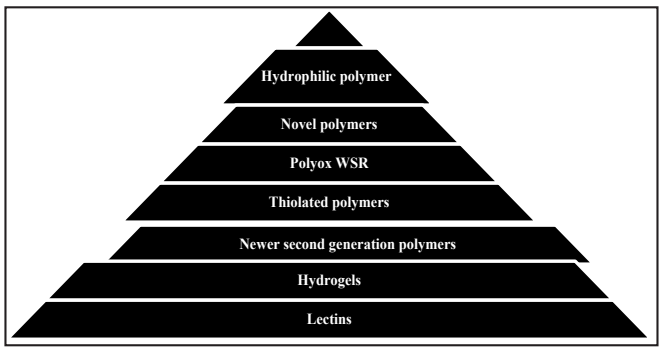

Figure 2. *Types of Mucoadhesive Polymers..*

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.

Role of Mucosal Drug Delivery in Oral Disorders [5].

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 formulations [9] which include intraepithelial delivery of Transforming growth factor β-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 skin [10]. 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-α biological agents or rituximab have benefit in application for oral mucosal pemphigus.
- Intralesional triamcinolone acetonide 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 aphthous 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 [13].

Table 1*. Theories of Bioadhesion.*

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.

Table 2. *Topical drugs for recurrent aphthous stomatitis.*

Topical corticosteroids	Hydrocortisone hemisuccinate (pellets) Triamcinolone acetonide (in adhesive poste) Fluocinonide (cream) Betamethasone valerate (mouthrinse) Betamethasone -17- valerate (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) Cyclosporin (mouthrinse) Topical 5-aminosalicylic acid, Prostaglandin

Topical drugs for recurrent aphthous stomatitis is shown in *Table 2*.

Oral cancer

Treatment [14]

- 13-Cis-retinoic acid (iso-tretinoin) inhibits 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 remedies [15] are provided in *Table 3*.

Infections

Antifungal drugs

Most common fungal infection which needs topical application of antifungal drugs is oral candidiasis. Antifungal drugs fall into 2 categories – azoles and polyenes. Topical drugs for fungal infections and antiviral drugs are shown in *Table 4 and 5*

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. Scometric 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 monostearate, lecithin are added

Table 3. *Xerostomia Remedies.*

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 • Xanthan gum	Moisturizing gel Moisturizing liquid Antibacterial paste Mouth wash Chewing gum	Salivix, Salivin Saliva sure	Trident chewing gum Extra chewing gum Biotene chewing gum

Table 4*. 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 Pastille, 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.

Table 5*. 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
Gancyclovir	Metabolizes to gancyclovir triphosphate, which inhibits viral DNA polymerase.	Cytomegalovirus	Renal insufficiency, fever, headache
Pencyclovir	Metabolizes to pencyclovir triphosphate, which inhibits viral DNA polymerase	Herpes simplex	None
Famcyclovir	Metabolizes to famcyclovir 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

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 caffeine 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 tablets [19]

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 prosthesis [20]

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 sublingually [22] 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 patches [23]

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 – Polycarbophil, 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 caps [24]

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 labelled 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 System [25]

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 folic acid 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 Glycosylphosphatidyinositol 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 [22]. Best 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 and deletions. Bleomycin which is highly toxic inside the cell which is normally nondiffusible through the plasma membrane [19,20]. Thus bleomycin is used as agent for drug delivery using sonoporation [23].

Epidermal 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 Bleomycin are often administrated in an intravenous or intratumoral injection along with electrochemotherapy.

Conclusions

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.

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