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Review Article

A REVIEW ON BUCCO-ADHESIVE DRUG DELIVERY SYSTEMS FOR ORAL SUB-MUCOUS FIBROSIS: CHALLENGES, OPPORTUNITIES AND FUTURE PERSPECTIVES

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ABSTRACT

Oral sub-mucous fibrosis (OSF) is a chronic, insidious disease which might affect the oral cavity (oral mucosa) including pharynx and larynx. Numerous approaches and anticancer molecules have been explored in the literature to treat OSF with different modes of action. However, complete cure for OSF is limited due to the lack of an ideal carrier for safe and effective delivery of potent drug moieties. There are several challenges such as anatomical or histological barriers and appropriate animal model need to be explored and optimized to develop the efficient treatment for oral sub-mucous fibrosis. Constant progression in the development of new formulations has led to the effective management of the disease associated with the mucosa using mucosal or muco-adhesive drug delivery systems. Muco-adhesive drug delivery systems (such as gel and patches) have gained unique position as drug cargoes. Therefore, present review is an attempt to contemplate on OSF in terms of pathogenesis, currently available treatment shaving their mode of action, major challenges encountered during treatment, usefulness/feasibility of muco-adhesive dosage forms, opportunities/future scope of muco-adhesive drug delivery in OSF and recent developments in the delivery of various anti-cancer drugs in the treatment of OSF.

Key words: Oral sub-mucous fibrosis, oral cancer, anticancer molecules, muco-adhesive drug delivery system.

INTRODUCTION

Oral submucous fibrosis (OSF) is a progressive oral mucous disease that usually affects any area of the oral cavity which further moves to pharynx and larynx. It is possibly a malignant and precancerous state[1]. It is represented by blanching and rigidity of the oral mucosa, which later restricts the opening of the mouth, resulting in non-tolerance to hot and spicy foods[2]. Individuals with OSF are more vulnerable to oral cancer and are found mainly in South Asian individuals[3]. In this condition, excessive collagen synthesis or decrease during collagen degradation increases mucosal rigidity and contributes to the deposition of fibrous connective tissue on the surface layer of oral mucosa[4]. OSF patient has two major problems, inability to open the mouth and difficulties to function and feeling of burning. The disease symptoms can vary from person to person. Initially, patients suffer from burning rather than allergic reactions[5]. Multiple factors such as chewing areca nut, excessive consumption of chilies, nutritional deficiencies immunological and genetic factors are involved in the pathogenesis of OSF.[6,7] (Table 1)

Table 1: Factors associated with treatment of OSF

Factors	Mechanism	Activities	Major Outcomes	Reference
Aloe Vera (Polysaccharides, Sterols)	Promote wound healing Inhibiting prostaglandins (similar to Aspirin)	Anti-inflammatory, Anticancer, Immunomodulatory and Gastro protective	Improve pain and burning sensation	27, 30, 31
Turmeric (curcumin)	Inhibition of NF-κB, ERK, JNK, p38 activation. Stimulate DNA repair enzyme	Antioxidant, anti-proliferative, anti-inflammatory activity	Enhance wound healing	25, 32, 33
Carotenoids	Cell cycle arrest, induction of apoptosis, anti-metastasis, inhibition of angiogenesis	Antioxidant, anticancer, anti-inflammatory	Reducing burning sensation	28, 34
Borneol	Inhibit TIMP-1 production, fibroblast proliferation and collagen deposition	Anti-fibrosis activity	Enhance healing process	35
Spirulina	Oxidative free radical scavenges	Antioxidant property	Improved mouth opening and burning sensation	27
Enzymes a) Hyaluronidase b) Chymotrypsin	Depolymerization of hyaluronic acid	Decrease collagen formation	Improving pain and burning sensation	29, 36
Placental extract	Biogenic stimulation	Interfere with proliferation of fibroblast and collagen	Improved inflammation	29

		deposition, decrease collagen formation		
Immunized Cow`s milk	Modulate cytokine production	Suppress inflammatory reactions	Protect tissue from further inflammation	29, 36
Tea	By free radical scavenging	Reduce oxidative stress	Protection from tissue damage	37
Salvianolic acid B		Reduces inflammatory factors	Improved mouth opening and burning sensation	38, 39
Allicin	Inhibition of TNF-α and NF-κB expression	Anti-inflammatory and antioxidant activity	Improved mouth opening and burning sensation	40
Vitamins (A, B Complex, C, D, E), antioxidants & minerals (Fe, Cu, Mg)	Improve wound healing and tissue repair	Stabilize and deactivate the free radicals, vitamins and minerals improve the disease condition	Fulfill nutritional requirement	29, 36, 41
Steroids a) Dexamethasone b) Betamethasone c)Hydrocortisone d)Triamcinolone	Inhibition of inflammatory cytokines by sensitized lymphocytes	Decrease fibroblastic proliferation and deposition of collagen	Enhance healing process	29, 40, 42
Peripheral vasodilators a) Pentoxifylline b) Nylidrin hydrochloride	Suppress leucocyte function, inhibit TNF-α, and T and B cell activation Vasodilation of arterioles	Stimulates fibrinolysis Improvement of blood flow and transport of drug and nutrient to the site	Improved mouth opening and burning sensation	29, 36, 43

Among these, the most common factor responsible for OSF is chewing areca nut that affects the fibroblast which may affect the initiation of disease. Chemically Areca nut belongs to the flavonoids and alkaloid family (i.e., arecoline, are caidine, guvacine, guvacoline). Out of all alkaloids, arecoline is potentially active factor that is involved in OSF pathogenesis causing irregular collagen production. Tannins and catechins are the components of flavonoids, carry out the metabolism of collagen[6.]Chewing areca nut along with various components such as lime, tobacco and other betel quid collectively initiate the OSF[8].

In clinical stages, the extent of fibrosis varies from blanching of oral mucosa to cancerous lesion and problems with opening of t he mouth, trismus (spasm of the jaw muscles) is categorized und er functional stages that connect the disease with its functional p rogression[9]. Depending upon the epithelial morphological variations of oral mucosa, OSF can also be categorized as an advanced diseases condition. Collagen spreads initially in the diseases and the inflammation predominates with complete hyalinization as the diseases progresses.[10.] Diseases initiation, it's progression and mouth opening at different levels may be suggested by histological data[3]. (Table 2)

Table 2: Classification of OSF disease

	Stage 1	Stage 2	Stage 3	Stage 4	Reference
Morphological Changes	Dispersed collagen, predominant edema	Early hyalinization in juxtaepithelium, thick and separate bundle of collagen	Moderate hyalinization of juxtaepithelium, normal/constricted blood vessels	Complete hyalinization, narrow blood vessel	10
Clinical Changes	Stomatitis/blan ching of oral mucosa	Palpable fibrous band with/without stomatitis	Palpable fibrous band with/without stomatitis	Previous condition with malignant disorder	9
Disease progression	Limiting to lamina propria	Superficial region of muscle bundle	Deeper region of muscle bundle	Fibrosis replaces muscle bundle	3
Functional Changes (mouth opening in mm)	>35	>35-25	15-25	<15	9

There are many plants based herbal medicinal products (i.e., curcumin, aloe vera, carotenoids, vitamins and minerals) proved potent against OSF and are exclusively used in the treatment of the disease. Out of all herbal drugs, curcumin is most potent and effective natural agent having intense therapeutic as well as biological activity such as anti-inflammatory, antioxidant, analgesic and antiproliferative.[25]Aloe Vera is also used to treat OSF with other anti-inflammatory, anti-cancer and immunomodulatory practices.[26] Aloe Vera gel has antioxidant, anti-inflammatory, anti-angiogenic activity which is beneficial in the OSF treatment.[27] Carotenoids also exhibits antioxidant, anti-inflammatory, anti-proliferative and anti-metastatic activities and are also used in the treatment of OSF. Carotenoids induce apoptosis which inhibit the cell growth and progression of disease.[28]. The protective action is illustrated by vitamins and minerals in the treatment of OSF diseases which provide nutrition and protection around the area which is infected.

Placental extract has several amino acids which are effective against the collagen synthesis which interferes with fibroblast proliferation and its deposition. Treatment of OSF with steroids and peripheral vasodilators inhibit the inflammation and later on dilate the blood vessels which ensure the proper blood, nutrients and other supplements supply to the site of injury.[29]

Oral sub-mucous fibrosis (OSF)
Occurrence, Clinical Features, Pathogenesis

Initially patients suffer with problems like burning sensation or intolerance to hot and spicy foods which further leads to ulceration & dryness of mouth and finally fibrosis is detected in lateral stage which initiates the conditions such as rigidity of tongue, lips and palate.[1, 44].

During OSF pain generates at the site of disease on palpation which is its important characteristic and also patient may feel the pain in the ear and fibrosis may spread to the nasopharynx or esophagus. Blanched oral mucosa with palpable fibrous band is the most common clinical sign in OSF.[6, 46].Areca nut is the most important pathogenic factor in OSF. Genetic factors, immunological factors and the deficiency of essential vitamins and minerals may be responsible for the generation of OSF[47]. The diseases mechanism states that it occurs due to interruption in collagen synthesis and its metabolism.[1] Arecoline is the primary alkaloid contributing to OSF pathogenesis whereas synergistic effect is shown by tannins. Arecoline is primarily responsible for collagen synthesis and later for its metabolism. The difference between deposition and degradation process of collagen which often leads to enzyme (lysyl oxidase) up-regulation & down regulation[12,19].The mechanism involved in OSF pathogenesis is to induce chronic inflammation , increased collagen synthesis and to decrease collagen degradation.[6]The prominent mechanism involved in OSF diseases is the inhibition of collagen phagocytosis and stabilization of extracellular matrix..[12]Chewing Tobacco and smoking leads to oxidant or antioxidant imbalance which triggers oxidative stress which further results in lipid peroxidation damage to macro and micro molecule cell DNA damage which interrupts antioxidant defense mechanism. During tobacco chewing and smoking, heat is generated which further stabilizes the free radicals. The auto oxidation of areca nut polyphenols plays an important role in triggering and initiating oral cancer and demonstrated its function in oral cancer by reactive oxygen species (ROS).Continuous exposure of areca nut and generation of free radical causes oxidative damage of lipid, protein and DNA and plays a crucial role in OSF pathogenesis.[17, 31]Similar to betel quid, tobaccos shows carcinogenic activity and are at important risk factor for OSF.[20, 48]

Treatment available for OSF

(i) Natural origin

Curcumin

Curcumin possess pleotropic therapeutic properties such as antioxidant, anti-inflammatory, anti-proliferative, antibacterial activity, etc. Currently it is being tested for different diseases such as oral cancer, colon cancer, psoriasis, Alzheimer disease, pancreatic cancer, different pre-cancerous conditions.[49]In OSF, it has anti- inflammatory effect and acts by inhibiting various molecules that give their participation in inflammatory reaction and thereby causing fibrinolysis, cellular growth arrest by inhibiting lipid peroxidation which leads to reduction of collagen synthesis.[50]Curcumin proved it's role in OSF by inhibiting the cell proliferation and apoptosis induction which reduces expression of collagen I as well as collagen III[51].Turmeric oil (TO), turmeric oleoresin (TOR) and turmeric extract (TE) also have therapeutic efficacy in OSF. TO is effective *in vitro* and *in vivo* while TOR is more effective in DNA damage of oral mucosa as compared to TO. Both TO and TOR have good free radical scavenging activity. It is also reported that TOR reduces lipid peroxidation and enhances catalase activity in OSF patients[26].

Tulsi

Ayurveda has listed various formulations extracted from Tulsi which have specific immunomodulatory and metabolic functions along with various biological activities like anti-inflammatory, antioxidant, antitumor, etc. [52]The major constituent extracted from the leaves of tulsi is Ursolic acid (UA) which is useful in inhibiting NF-κB induced from various carcinogens, proliferation and induces apoptosis, arrest cell cycle in G1-G0 phase. Additionally, it participates in the inhibition of inflammatory enzymes and also in modulating inflammatory reactions.[32, 53]

Aloe Vera and Spirulina

Aloe Vera and spirulina are also called as wound healing hormone. These herbals function as emollient consisting of resins and mannoprotein containing different amino acids. It has been reported that polysaccharide (chemical constituent of aloe Vera leaves) has wound healing, anti-inflammatory, anticancer, immunomodulatory activities. This indicates the presence of cytotoxic, radioprotective and anti-angiogenic properties of anthraquinone[27].Aloe Vera exhibits anti- inflammatory property against various animal models.[30, 31]. Spirulina is defined as a microalgae protein consisting of carotenoids, and micro-nutrients and also contains phenolic acid, tocopherols and beta-carotene which have antioxidant activity. Spirulina has been proved more potent than aloe vera in treating OSF[27].

Carotenoids

These are the natural pigment isolated from plant and responsible for colors of various fruits and vegetables. It has antioxidant and anticancer activity which is beneficial in oral precancerous lesion such as leukoplakia and used in management of OSF. Lycopene is known to inhibit the abnormal fibroblast in OSF and also responsible for up-regulation of lymphocyte resistance to stress and suppresses inflammatory response.[34]Various mechanisms (like anti-angiogenic, anti-proliferative, cell cycle arrest, anti-metastatic and apoptotic activities) are involved for the management of cancerous as well as precancerous conditions such as OSF and oral leukoplakia.[28] Beta-carotene is reported for its antioxidant property and improvement of cellular immunity.[31]

Borneol

It is a terpene having analgesic, anti-inflammatory and antibacterial properties. Traditionally it is used in china for wound, burn and skin infections and acts as penetration enhancer.[54]It has antifibrotic activity *via* inhibition of fibroblast proliferation, collagen deposition and tissue inhibitor of metalloproteinase-I (TIMP-I). It can be used for healing as well as penetration enhancer in OSF.[35]

Enzymes and placental extract

The enzymes which are active in the treatment of OSF are hyaluronidase and chymotrypsin[29, 42] Hyaluronidase participates in hyaluronic acid depolymerization and thus decreases the formation of collagen whereas chymotrypsin acts as a proteolytic and anti-inflammatory agent..[55]It is recommended that traditional treatment of chymotrypsin with injection is risky however conservative treatment has been proved safe and effective.[56]Placental extracts consist of amino acids, vitamins, nucleotides and steroids. This extract is responsible for activating pituitary and adrenal gland which further regulate the metabolism of tissue through the mechanism termed as biogenic stimulation.[29, 42]

Tea and immunized cow milk

Tea is a natural pigment which has an antioxidant property. It is widely used as famous beverages. Tea in combination with vitamins shows improvement of OSF. Tea is a pigment used as famous beverages and also shows antioxidant activity. No side effect of tea pigment is reported till now.[57]Immunization of cow milk with human intestinal bacteria shows anti-inflammatory activity by modulating the production of cytokines and thereby improve the symptoms of OSF.[29, 36]

Allicin and Salvianolic acid- B

Allicin is the organophosphorous compound produced from the alliin (amino acid) by catalyzing enzyme alliinase. It shows anti-inflammatory as well as antioxidant activity and significantly reduced lipid peroxidation. Allicin tend to decrease TNF-α level and inhibit cytokine production in a dose-dependent manner and

thus to be used in OSF.[40, 58] Salvianolic acid-B is obtained from the root of Salvia plant which significantly decreases the level of different factors contributed to the inflammation such as nitric oxide, TNF-α, Interleukin-1β (IL-1 β), ROS etc. in a dose-responsive manner and increase the expression of anti-inflammatory cytokines IL-10 and transforming growth factor-β1(TGF- β1) in animal model.[39] It also causes dilation of artery and ensures the transport of nutrition and other vital materials to the site of action. It showed anti-inflammatory, angiogenesis properties and inhibit collagen synthesis when used together with triamcinolone acetonide.[38]

Vitamins and Minerals

Some vitamins exhibit antioxidant activities which are responsible for stabilization and deactivation of free radicals. Vitamins like A, B complex, C, D, E and minerals like Iron, Copper, Magnesium collectively with or without other drugs improve the condition of OSF.[41]They are helpful in tissue repair and wound healing. Tissues become prone to oxidative stress due to deficiency of vitamins and minerals. So, tissue protection from these pathogenic factors can contribute in the treatment of OSF.[29, 36]

Synthetic Drugs

Steroids

Corticosteroids are mainly involved in OSF treatment which serve as an immunosuppressive agent and acts by inhibiting inflammatory reactions. They are applied topically and as a submucosal injection. Hence, decrease fibroblastic proliferation and deposition of collagen.[29,36] It is reported that dexamethasone, betamethasone, hydrocortisone and triamcinolone are used clinically.

Steroids are more active at the initial stage of the disease, but lat er they are not effectivein reversing the normal condition. When injection of dexamethasone is used in combination with enzymes (chymotrypsin and hyaluronidase), it shows better result[29, 42] and with placental extract and hyaluronidase dexamethasone also showed result clinically for the management of OSF. Triamcinolone and Salvianolic acid- B collectively shows considerable improvement in the clinical features of disease.[38] This particular effect resulted due to their anti-inflammatory, anti-collagenesis and angiogenesis properties.

Peripheral vasodilators

These are cardiovascular drugs (Nylidrin hydrochloride) that dilate the capillaries and ensure that the target site is properly supplied with nutrients and other therapeutic agents. Pentoxifylline inhibiting the functions of leucocytes which in turn inhibits TNF and T and B cells. It also participates in alteration of fibroblast physiology and stimulation of fibrinolysis.[29, 36]

Mucosal drug delivery

The lack of poor systemic availability of oral route results the other alternative route for administration of most of the pharmaceutical products. Reasons for the use of alternative route for administration of pharmaceuticals are their unfavorable physico-chemical properties including size, charge, hydrophilicity, susceptibility to acid, enzymatic hydrolysis, and degradation *via* bacterial fermentation. Alternative routes are more convenient with improved compliance to the patients, controlled release rate and increase targeting to diseased tissues. Many alternative routes of administration have been followed with different degrees of success.[59]

In recent years, oral mucosal drug delivery system has gained much attention which is a non-invasive method for the administration of drug. Oral mucosa consists of an epithelium (40-50 cell layers thick), lamina propria, submucosal, and mucus (secreted by salivary glands) layer over the epithelium. This membrane is keratin deficient with underlying blood vessels. It has relatively very good permeability by both transcellular and para-cellular mechanism. Oral mucosa plays various functions from modulating drug release to absorption. It has a protective nature which favors the existence of pH labile drugs *i.e.* protein, peptides and enzymes. It works as barrier in the tissue absorption of drugs and other substrates, as it influences the bioavailability of drugs. Bio-adhesion to the mucus layer and to the epithelial cell surface favors increased residence time. Salivation offers sufficient lubrication to the formulation which helps in efficient dissolution of the incorporated drug. At physiological pH, the mucus network carries negative charge because of the presence of sialic acid and sulfate residues, which contributes to the bioadhesion of the formulation significantly.

When oral mucosal drug delivery administered orally, the avoidance of pre-systemic clearance and first-pass elimination of the drugs with lower bioavailability and higher first pass metabolism takes place which is considered as its major advantages.[60] Major challenge associated with the oral mucosal drug delivery is the drug residence time. It delivers drug locally and systemically and; therefore, it needs to stay in contact with the membrane for long time. However, mouth movement, flushes of saliva, food ingestion and uncontrolled swallowing can prevent such devices from adhering to the buccal mucosa which leads to reduced or no pharmaceutical efficacy. There will be acceptability problem with the drugs having unpleasant taste. An ideal buccal drug delivery system should adhere to the buccal mucosa quickly with sufficient stability to effect treatment [61] (Fig.1).

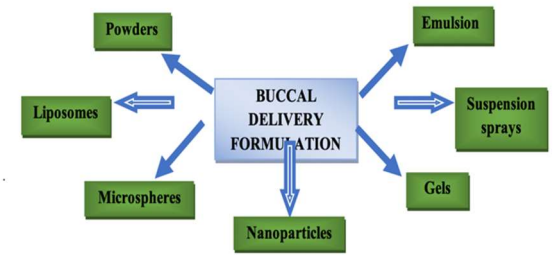

Fig. 1: Different types of buccal drug delivery formulations

These non-mucoadhesive formulations are administered in limited volume of 25-200 µL due to their mucociliary clearance exhibit short residence times. This is mainly because of the mucus layer which moves through the oral cavity results in particle clearance for every 2-5 min and limits the time available for drug absorption from the applied dosage form which results in poor bioavailability. There is a persistent need for the development of controlled release delivery system to prevent rapid mucociliary clearance and improve the bioavailability of drugs. Muco-adhesive buccal drug delivery systems have the ability to adhere to the buccal mucosa, enhance the residence time within the cavity, intensify the contact between the mucosa and the drug, increase the drug concentration at the site of deposition and facilitate drug absorption to enhance bioavailability.[62]

Fate of buccal route of administration in drug delivery

Delivery of therapeutic agents through various mucosal and transmucosal routes has gained significant attention. Among all the absorptive mucosa including nasal, buccal, sublingual, pulmonary, rectal, and vaginal; the mucosa of the oral cavity is viewed as a convenient and easily accessible site for the delivery of therapeutic agents. Buccal drug delivery system has many advantages over per-oral delivery and is emerging as an alternative for the local/parenteral route because of the administration of compounds *via* the mucosa of the oral cavity which offer local administration of the drugs and avoids presystemic metabolism in the gastrointestinal tract (GIT) and hepatic first-pass elimination. In addition, the buccal mucosa is a well vascularized tissue with a rich blood supply, relatively permeable and offers a passive system for drug absorption which does not require any activation. Unlike in the case of rectal and transdermal routes, the presence of higher amount of saliva in oral cavity ensures relatively large amount of water for drug dissolution. Mucoadhesive buccal drug delivery system includes permeation enhancer/ enzyme inhibitor or pH-modifier in the formulation and versatility in designing as multidirectional or unidirectional release systems for local or systemic action.[60] Buccal mucosa allows drug delivery for both local and systemic therapies. Local delivery to tissues of the oral cavity has a number of applications, including treatment of local conditions such as bacterial and fungal infections, periodontal disease, aphthous stomatitis and vesiculo bullous diseases.[63] When drugs are systemically administered through buccal mucosa, various drawbacks associated with the per-oral route are circumvented as drugs directly enter the systemic circulation which avoids the hepatic first pass metabolism and leads to high bioavailability. This route provides significant reduction of dose and its side effects. The buccal mucosa offers an easily accessible and well-accepted site for systemic drug delivery for the treatment of chronic diseases. Mucosal drug delivery route has become a novel route of drug administration due to its various advantages. This route prolongs the residence time of the dosage form at the site of application. Delivery system remains in close contact with the absorption tissue, the mucous membrane thus contributes to improved and better therapeutic performance of the drug for both local and systemic effects. [64] Following trans-mucosal route of administration may offer rapid onset of action of the drugs relative to the oral route. Muco-adhesive formulation can be removed, or therapy can be terminated easily whenever required. This might be the most suited route for drug administration to the patients who are less co-operative and unconscious. Muco-adhesive nature of these formulations prevents accidental swallowing of the drugs. Owing to the ease of the administration, the oral cavity is an attractive site for the delivery of drugs. Mucosal (local effect) and transmucosal (systemic effect) drug administration is possible through this route. In the first case, the aim is to achieve a site-specific release of the drug on the mucosa, whereas the second case involves drug absorption through the mucosal barrier to reach the systemic circulation.[65]

Fundamental consideration in drug delivery through mucosa

Fundamentals are considered during drug delivery through buccal mucosa which helps in developing efficient dosage form and offer better treatment option to the patient. Drugs having bitter or unpleasant taste or obnoxious odor, or which irritate the mucosa must be avoided for buccal delivery. Drugs that are unstable at buccal pH require special attention. Since this route favors smaller dose of the drug, swallowing saliva may offer loss of drug and advantages of buccal route. Drugs which follow passive diffusion for their transport are favored for administration by this route. At the time of administration, eating and drinking are restricted as the dosage forms can be swallowed by the patient. As the surface area of the buccal mucosa in less than that of small intestine, rectum this route offers lesser permeability per unit area. Sometime the structural integrity of the formulation gets disrupted by the swelling and over hydration of the bio-adhesive polymers.

The bucco-adhesive strength of the polymers is affected by the several factors for instances polymer related factors, environmental and physiological factors. Factors associated with polymer are hydrophilicity, molecular weight, concentration of active polymer, flexibility of polymer chains, hydrogen bonding capacity, swelling, cross-linking density and surface charge. Muco-adhesive polymers possess several hydrophilic functional groups, like hydroxyl and carboxyl which allow hydrogen bonding with the substrate and swell in aqueous media. Swell ability the friction between the mucous membrane and formulation. Low-molecular-weight polymers penetrate the mucus layer better. The optimum molecular weight is between 10^4 and 4×10^6 Daltons. Polymers with higher molecular weights will not get moistened quickly to expose free groups for interaction with the substrate, while polymers with low molecular weights will form loose gels or will dissolve quickly. For linear polymers, the muco-adhesion strength increases with increases in molecular weight. The importance of concentration of active polymer lies in the development of a strong adhesive bond with the mucus and can be explained by the polymer chain length available for penetration into the mucus layer. When the concentration of the polymer is too low, the number of penetrating polymer chains per unit volume of the mucus is less, and the interaction between polymer and mucus is unstable. In general, the more concentrated polymer would result in a longer penetrating chain length and better adhesion. Increased concentration of bio-adhesive polymer, usually from 1.0 –2.5%, in principle, increased the binding potential. However, at a critical concentration polymer produces an “unperturbed” state due to a significantly coiled structure, on account which accessibility and penetration to the polymer in the solvent drastically reduce. Chain flexibility is critical for interpretation and entanglement of muco-adhesive polymers. As water-soluble polymers become cross-linked, mobility of individual polymer chains decreases and thus the effective length of the chain that can penetrate into the mucous layer decreases, which reduces bio-adhesive strength. The increased chain interpretation was attributed to the increased structural flexibility of the polymer upon incorporation of PEG. For better muco-adhesion, desired polymers must have functional groups (COOH, OH, etc.) that are able to form hydrogen bonds. Polymers such as poly (vinyl alcohol), hydroxylated methacrylate, and poly (methacrylic acid), as well as all their copolymers, are polymers with good hydrogen bonding capacity. Hydration is required for a muco-adhesive polymer to expand and create a proper “macromolecular mesh” of sufficient size, and also to induce mobility in the polymer chains in order to enhance the interpenetration process between polymer and mucin. Polymer swelling permits a mechanical entanglement by exposing the bio-adhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and the mucous network. The average pore size, the average molecular weight of the cross-linked polymers, and the density of cross-linking are three important and interrelated structural parameters of a polymer network. Therefore, it seems reasonable that with increasing density of cross-linking, diffusion of water into the polymer network occurs at a lower rate which, in turn, causes an insufficient swelling of the polymer and a decreased rate of interpenetration between polymer and mucin. The charge sign of polymer is an important element for bio-adhesion. The strength of muco-adhesion of polymers with carboxyl groups was much stronger than that of those with

neutral groups. Some generalizations about the charge of bio-adhesive polymers have been made previously, where nonionic polymers appear to undergo a smaller degree of adhesion compared to anionic polymers. Strong anionic charge on the polymer is one of the required characteristics for muco-adhesion. It has been shown that some cationic polymers, such as chitosan, exhibit superior muco-adhesive properties, especially in a neutral or alkaline medium.

Environmental factors include pH, applied strength and initial contact time. The pH of the polymer–substrate interface and the pH of saliva as a dissolution medium affect the behavior of the polymer. Depending on the saliva flow rate and method of determination, the pH of this medium has been estimated to be between 6.5 and 7.5. The pH of the microenvironment surrounding the muco-adhesive polymer can alter the ionization state and, therefore, the adhesion properties of a polymer. Mucus has a different charge density depending on pH due to differences in dissociation of functional groups on the carbohydrate moiety and the amino acids of the polypeptide backbone. Poly-carbophil does not show a strong bio-adhesive property above pH 5 because of unionized carboxyl groups for reaction with mucin molecules however, at higher pH, the chains are fully expanded due to electrostatic repulsion of carboxylate anions. Application of the systems over mucosal layer with higher pressure may alter depth of diffusion of chains available for muco-adhesion. However, longer contact time between the bio-adhesive systems and mucus layer determines the extent of swelling and help in penetration of the bioadhesive polymer chains in mucosal layer deeply. Moreover, bio-adhesive strength increases as the initial contact time increases.

Physiological Factors like mucin turnover rate and disease state may also alter bucco-adhesive strength of the polymers. Mucin turnover varies widely, depending on location. Values range from hour today. However, residence times of bio-adhesives that are thought to attach to mucin are typically longer than the reported mucin turnover, suggesting that the alteration of bio-adhesive properties of the polymers by higher mucin turnover. The residence time of dosage forms is limited by the mucin turnover time, which has been calculated to range between 47-270 min in rats and between 12-24 h in humans. Concomitant diseases like increases in body temperature, ulcer disease, colitis, tissue fibrosis, allergic rhinitis, bacterial or fungal infection, and inflammation can alter the physicochemical properties of mucus or its quantity. On account of which bio-adhesive properties gets altered.[63]

Mode of transport through mucosa

Drug absorption through a mucosal surface is generally efficient because the stratum corneum, epidermidis, the major barrier to absorption across the skin, is absent. The primary mechanism of drug absorption through oral mucosa is the passive transport, where two main pathways are involved: the intracellular (or transcellular) and the intercellular (or para-cellular). Lipophilic compounds generally transported through transcellular diffusion, while hydrophilic compounds transported through para-cellular route. Most of the drugs may diffuse through both the routes simultaneously, although the route with the least penetration resistance is usually preferred over the other. Studies with microscopically visible tracers such as small proteins and dextrans suggest that the major pathway across stratified epithelium of large molecules is via the intercellular. It is generally recognized that the lipid matrix of the extracellular space plays an important role in the barrier function of the para-cellular pathway, especially when the compounds such as peptides are hydrophilic and have a high molecular weight. The absorption potential of the buccal mucosa is influenced by the lipid solubility and molecular weight of the diffusant. Absorption of some drugs via the buccal mucosa is found to increase when carrier pH is lowered and vice versa. In general, for peptide drugs, permeation across the buccal epithelium is thought to be through para-cellular route by passive diffusion. Since the mucosa could represent an effective permeability barrier, some strategies have been proposed to improve drug absorption. Recently, it was reported that the drugs having a monocarboxylic acid residue could be delivered into systemic circulation from the oral mucosa via its carrier. The permeability of oral mucosa and the efficacy of penetration enhancers have been investigated in numerous in vitro and in vivo models. Various kinds of diffusion cells, including continuous flow perfusion chambers, using chambers, Franz diffusion cells and Grass–Sweetana, have been used to determine the permeability of oral mucosa. Passive diffusion is the principal mechanism of buccal absorption. However, this assumption may be misleading as the oral mucosa contains active, carrier-mediated transport systems for few small molecules, such as monosaccharides and amino acids. On occasion, absorption occurs by endocytosis where molecules are engulfed by the cells.

General Considerations in Dosage Form Designing

Physiological Aspects

Constant saliva flow and tissue sensitivity are the main challenges in the delivery of drugs to / through the oral cavity. Usually, the residence time of drugs administered to the oral cavity is short; within less than 5 to 10 minutes. This problem is supposed to be solved by buccal muco-adhesive formulations. Bio-adhesive polymers provide a way of adding a delivery system to the buccal mucosa and thus provide significantly longer retention times at the absorption site. These also provide a means of confining and maintaining high local drug and/or excipient concentrations to a given, relatively small area of the mucosa in order to minimize losses to other regions and limit potential side effects. Some inherent drawbacks are also related to the buccal drug delivery mechanism for small areas of absorption and the barrier properties of buccal mucosa. The size of a buccal dosage type is limited by the very limited area of the delivery system available. In addition, this size limit limits the amount to the minimum. Generally speaking, 1–3 cm2 buccal delivery systems should be paid with 25 mg or less of the medication. For thickness restricted to a few millimeters, the ellipsoid form is most suitable.

Pathological Aspects

State of diseases will change the thickness of the epithelium and thus the barrier property of the mucosa is modified. The strength of the secretion and the properties of the mucus may be altered under such conditions or during treatment. Such modifications will affect a bioadhesive delivery device's application and retention. To develop an efficient buccal delivery system, therefore, it is necessary to understand the structure of the mucosa under appropriate disease conditions. Therefore, drugs with the potential to change the oral cavity's physiological conditions (dryness of the mouth) may not be sufficient for buccal delivery.

Pharmacological Aspects

Buccal dosage types are designed to deliver medication locally or systemically. Therefore, the selection of dosage forms is very important as they are designed to deliver at the site of action (systemic) and the location to be handled (periodontal pockets, gingival, teeth, and buccal mucosa).

Pharmaceutical Aspects

The drug must be extracted from the delivery system and eventually absorbed by the oral mucosa, regardless of the type of

dosage method. Poor saliva solubility of drugs may significantly delay the release of drugs from the dosage form. Solubility enhancement strategies increase the solubility of poorly water-soluble drugs and provide opportunities to establish their muco-adhesive form of semi-solid dosage.[66, 67]Factors to be considered during the production of buccal mucosa formulations are the release and penetration of drugs through buccal mucosa. In addition to physicochemical properties, the organoleptic properties of the drug or the delivery system should also be considered. Organoleptic excipients offer elegance and render dosage forms more appropriate. Another important consideration is the selection of ingredients, since acidic / basic compounds also induce saliva secretion that can enhance drug dissolution and drug loss through involuntary swallowing. When developing muco-adhesive dosage forms over one additive for one purpose, the use of multifunctional ingredients is preferred. This could help to keep the formulation smaller. Due to the rapid turnover of the buccal epithelium; the permeability of the buccal mucosa has changed intermittently and is considered less permeable, thus not providing rapid absorption and good bioavailability after sublingual administration. Incorporating enhancers of penetration (bile salts, fatty acids and sodium lauryl sulfate) may increase the permeability of the drug by altering the fluidity of the cell membrane, intercellular and/or intracellular structural lipids, cell proteins or mucus structure. Dosage forms may include enzyme inhibitors to enhance drug bioavailability. There is maximum permeation at the pH at which these drugs are mainly unionized .PH monitoring is crucial to the successful delivery of ionizable drugs to the buccal system. Including some pH modifiers in the formulation may be necessary in order to temporarily modulate the microenvironment at the application site for better drug absorption. It should be noted that pH can also affect the load on the surface of the mucus, as well as certain ionizable groups of polymers that may affect the strength of the muco-adhesive. Therefore, to maximize both drug permeation and muco-adhesion, pH needs to be carefully regulated.

Challenges in oral sub-mucous fibrosis treatment:

In OSF juxta-epithelial inflammatory reaction (fig.2) accompanied by a fibro-elastic shift in the lamina propria and epithelial atrophy leading to rigidity of the oral mucosa, resulting in trism and inability to eat. The pathogenesis is thought to involve inflammatory juxta-epithelial reaction and fibrosis in the oral mucosa, probably due to increased collagen cross-linking by up regulation of lysyl oxidase activity. Fibrosis or collagen accumulation results from the effects of areca nut, which increases the production of collagen (e.g., isoline induced, an alkaloid) and reduces the degradation of collagen. OSMF is now considered to be a metabolic disorder of collagen. The oral mucosal cavity has a fairly permeable mucosa with a rich supply of blood. Robust and covered with a stratified epithelium, it shows short recovery times after stress or injury, and it is resistant to possible allergens.

Oral mucosal drug delivery is divided into different delivery systems i.e. sublingual delivery (systemic delivery of drugs through the mucosal membranes lining the mouth floor), buccal delivery of drugs through the mucosal membranes lining the cheeks or buccal mucosa, gums and local delivery (delivery of drugs to the oral cavity).There is a different drug delivery type, Intra-periodontal pocket drug delivery where the drug is administered at a specific site, within the periodontal pocket that is usually used to treat periodontitis .[68]

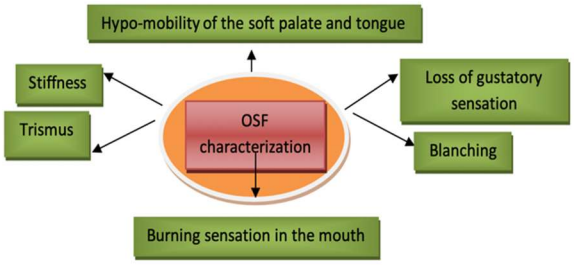

Fig.3: Characterization of OSF

Anatomical and physiological barriers

There are two obstacles to medication permeability in this mucosa. The intercellular spaces and cytoplasm are generally hydrophilic in nature and the cell membrane has a low partition coefficient. The intercellular spaces therefore serve as the main barrier to the permeation of lipophilic compounds and the cell membrane serves as the main transport barrier for hydrophilic compounds. The transport of the drug in the oral mucosa and many other mucosa's can therefore require a mixture of paracellular and transcellular routes. These two routes are used simultaneously by all compounds, except that depending on the physicochemical properties of the diffuser, one route is usually preferred over the other.[68]

Enzymatic degradation

Low permeability

The mucosa is keratinized in areas under mechanical stress (e.g., gingival and hard palate) close to the skin epidermis. Keratinized epithelium has a mitotically active basal layer composed of cells that advance to the surface through a variety of intermediate layers where cells are shed outside. These are generally waterproof and contain neutral lipids (e.g. ceramides and acylceramides) associated with the role of the barrier. Nevertheless, non-keratinized epithelia contain no acylceramides and only small quantities of ceramides. Such epithelia contain small amounts of neutral but polar lipids, cholesterol sulfate and glucosylceramides in particular.[69]

Sometimes the drug's intrinsic physicochemical properties such as molecular size, solubility, partitioning, crystallinity, thermodynamic activity, stability, pKa and half-life may be restricted to drug absorption. The poor solubility of the drug defines a wide site gradient, and the diffusion rate is low. The crystalline state and thermodynamic behavior of a substance are associated with the diffuser concentration. Small molecules, 100 Da, will quickly pass through the mucosa as this permeability decreases with increasing molecular size. Drugs with high molecular weights like peptides, oligonucleotides and hormones have low permeability, resulting in low bioavailability. [60] The drug's pKa indicates the degree of ionization of the molecule that affects permeability and maximum absorption occurs when molecules are not ionized but decreases as the degree of ionization increases. Most drugs are weak acids or bases, and as a compromise between the unionized and ionized forms, they remain in solution. Also unionized non-polar drugs enter the membrane, and unionized species concentrations on both sides of the membrane are similar. It is assumed that the unionized form is lipophilic enough to cross membranes. The ionized fraction is regulated by the environmental pH as well as the pKa drug.[63]

Dilution of drug by saliva

Saliva moist in the mouth protects the decay of the tooth as it forms protective membranes around the teeth, helps digestion and controls oral cavity bacterial floral. Due to the constant flow of saliva in the oral cavity, it is very difficult for the drugs to stay in the oral cavity for a significant time to facilitate absorption.[60]

Lack of efficient treatment

The diagnosis of oral submucosis has been varied and largely ineffective over the past decades. All available treatments such as iron and its supplements, multivitamins including lycopene, pentoxifylline, local steroid submucosal injections, hyaluronidase and chylomicrons, aqueous extract of healthy human placenta, and fibrous band surgery only provide the patient with a short-lived symptomatic relief. This is primarily due to the disease's unknown etiology and progressive nature. Actually, there is a wide range of oral submucous fibrosis therapies that do not provide a simple answer to how it should be treated. The purpose of the article is to classify the published literature on the role of different drugs in the treatment of oral submucous fibrosis.[70]

Lack of appropriate *in vitro*/*in vivo* model

OSMF's etiology is uncertain. For this situation, the various theories proposed indicate a multifactorial origin. Various studies have included many environmental factors, including capsaicin in chilies, deficits in micronutrients, immunological and genetic predisposition. However, the current scientific literature shows that areca nut is the major etiological factor. Areca chewing and OSMF are clearly associated, but a precise mechanism remains elusive and controversial.[71] Most of the specialist suggested that OSF had no single cause, but that it was multi-factorial. Several different factors are combined to cause illness, such as chewing betel nut or cigarettes, smoking, consuming chilies, obesity, vitamin deficiency, autoimmunity, and genetic predisposition. There is increasing evidence; however, that areca nut is the primary etiological factor. Recently, several clinical and experimental investigations have shown that the copper found in areca nut and its association with OSMF is casual. Chewing areca nut significantly increases the soluble concentration of copper in the saliva and then increases the activity of local lysyl oxidase in the oral mucosa, promoting fibrogenesis through the crosslinking of collagen fibers.[72]

Available dosage forms for mucosal drug delivery

Solid Dosage Forms:

In recent years, bio-adhesive tablets have been developed to enhance the bioavailability of administered drugs in the oral cavity. Such tablets are spread between the upper lip and gum at different sites in the oral cavity, i.e. the palate, the cheek's mucosa. Such tablets are hardened at the administration sites, adhered to the substrate and held until dissolution and/or release is complete. After a short time, the patient will no longer notice the existence of the tablet.

The tablet should not be shifted once in place in the mouth, as this results in faster release of drugs. The position of successive tablets on either side of the mouth can be changed. Patients with dentures can place the tablet between the lip and the gum in any comfortable position. The tablet's location in the mouth seems to have a major impact on tolerance and retention time. Depending on the location, the retention times ranged between 4–6 hours and 7–12 hours, respectively. Normally, it is critical that buccal tablet excipients do not induce or stimulate salivation because in this case a greater fraction of the drug can be swallowed instead of becoming bioavailable or absorbed. Several devices, such as Nicorette-1 (nicotine), Suscard-1 (glyceryl trinitrate), and Striant-1 (testosterone), have been produced and are already available on the market, while others are still in the development stage. Much effort is currently being made to address the problems of the absorption of high-molecular weight compounds such as peptides and proteins, primarily because their oral bioavailability is low. Some of the medicines provided by the buccal path are oxytocin, chymotrypsin, and insulin. Nevertheless, there is still a considerable amount of effort needed to improve the rate and degree of absorption of these molecules across the buccal mucosa. It is also important to examine the use and effect of permeability enhancers on the physiology of the oral cavity. It is important to highlight the possible problems that children and the elderly may have with the use of adhesive tablets. The probable irritation caused by the drug added to the mucosa and the risk of the medication type separating from the mucosa, being swallowed and then adhering to the esophagus wall are among the potential problems. Buccal adhesive tablets are usually prepared by direct compression but can also be used with wet granulation techniques. Multilayered tablets can also be prepared by adding and compressing layer by layer the ingredients. You may use some newer approaches to prepare tablets that melt at body temperature. Muco-adhesive tablets are mainly used in the oral cavity but can also be used in gynecology. Tablets are supplemented with carbomers [Striat], natural gums and resins Buccastem], hydroxypropylmethylcellulose (HPMC) (Suscard) and combinations of polymers such as Carbopol, Polycarbophil, HPMC and Na-carboxymethylcellulose (CMC) in diltiazem and metoclopramide-containing buccal tablets. With tablets, like other non-wetting solid Muco-adhesive Drug Delivery System, the muco-adhesion results from the dehydration of a mucosal region. Given the proven effectiveness of the local application of muco-adhesive buccal tablets, for example, in the treatment of oral cavity candidiasis, the key limitation on their large use stems from their size and shape, as the drug delivery system needs to be in close contact with the mucosal surface.

Bio-adhesive micro / nanoparticles provide the same advantages as tablets, but their physical properties allow them to touch a lager mucous surface intimately. These are usually administered as a watery suspension or mixed in a paste or ointment or used as aerosols. Particulates have the advantage that they are relatively small and that patients are more likely to accept them. Bioadhesive polymeric carbopol, polycarbophil, chitosan or gantrez microparticles must adhere to porcine esophageal mucosa, with particles prepared from polyacrylic acids exhibiting greater muco-adhesive strength during tensile tests. However, in elution studies, chitosan or Gantrez particles have been found to persist for longer periods of time on mucosal tissue. Nanoparticles were recorded for local delivery to the oral mucosa. In a proof-of-concept study, two types of nanoparticles, solid lipid nanoparticles incorporating either idarubicin or BODIPYFL C12 as fluorescent model samples and polystyrene nanoparticles (Fluo-Spheres) were investigated using monolayer human oral squamous cell carcinoma (OSCC) cell lines and normal human oral mucosal explants. The results showed the internalization of solid lipid nanoparticles by OSCC cells. The observed penetration of nanoparticles into the underlying connective tissue through the epithelium and basement membranes suggested the possibility of delivery of oral transmucosal nanoparticles for systemic therapy. Monti and his colleagues developed an atenolol-containing microsphere using Poloxamer 407 and tested in vivo formulations in rabbits as a guide against a marketed tablet formulation. The atenolol concentration remained higher than the reference tablet during the entire elimination process after administration of the

microsphere formulations, indicating a sustained release profile from the microsphere. However, in spite of a lower drug dosage, the absolute bioavailability of microsphere formulations was higher than that of reference tablets, suggesting a possible dose reduction by oral transmucosal administration of atenolol microparticles. Liposomes are one of the alternatives for poorly soluble drugs and are therefore not delivered efficiently from a solid dosage form. Silymarin liposomal buccal delivery, for example, showed steady permeation through a 6-hour chicken buccal pouch, higher than free drug powder. The small size of microparticles compared to tablets means that they are less likely to cause local inflammation at the adhesion site and that the unpleasant sensation of a foreign object within the oral cavity is minimized.

The bio-adhesive wafer delivery system is a composite wafer with adhesive surface layers, whereas the bulk layer consists of antimicrobials, biodegradable polymers and matrix polymers. A slow release of bio-adhesive lozenge provides the potential for extended release of drugs with improved patient compliance. Bio-adhesive lozenges may be used to distribute medications that work in the mouth, including antimicrobials, corticosteroids, local anesthetics, antibiotics, and antifungal medicines. A bio-adhesive lozenge was identified as a means of delivering antimicrobials to the oral cavity. The drawback of these bio-adhesive lozenges is the short residence period at the absorption site, which depends on the formulation size and type, and as they dissolve within 30 minutes, the total amount of the product that can be administered is reduced. The patient generally monitors the breakdown or disintegration of lozenges, i.e. how deep one sucks the unit. Increased production of sucking and saliva contributes to uncontrolled swallowing and substance loss in the GIT. Therefore, in general, solid dosage forms have much greater inter- and intra-individual differences in absorption and bioavailability. Those forms of system are also unable to provide drug release unidirectional. Another major obstacle to the efficiency of such dosage forms is the continual secretion of saliva.

Semisolid Dosage Forms

Bio-adhesive patches are systems that can range from simple erodible and non-erodible adhesive films to more sophisticated systems that can be designed to release the drug uni-directionally or multi-directionally. Like tablets, polymer films are versatile enough to take the shape of the underlying surface; they also have a number of advantages over creams and onions, as they can retain an effective dose of the muco-adhesive framework on the application site. An oral cavity's mucosa is an ideal surface for inserting retentive delivery systems such as patches, since it comprises a wide range of smooth and immobile tissue. Muco-adhesive patches for oral cavity mucosa administration may have several designs depending on different considerations, such as the clinical function and the physicochemical and pharmacokinetic properties of the active ingredient. Two specific rationales for the production of mucosal patches may be considered for the therapeutic purpose: patches may be intended to deliver a drug to the systemic circulation in a manner superior to other routes of administration, or local oral mucosal therapy may be used. There are more traditional dosage formulations available as alternatives for both patch groups. Oral gels, oral liquids and lozenges are the most frequently used alternatives today. There are a variety of dosage forms for systemic action, including oral dosage forms of continuous or controlled release, transdermal patches, and injectable depot formulations. It is important to have clear advantages over alternative products for a good mucosal patch. Oral mucosal patches can be applied directly to the infected mucosal area and have the ability to provide effective drug levels to the site of action and to retain them over a prolonged period of time. Conventional treatment, on the other hand, exposes the tissues affected to the dosage for a very short time. Today, buccal patches designed to routinely distribute drugs have obviously received more attention from the scientific community than the patches used to deliver drugs locally. Bio-adhesive patch formulations for drug delivery systems are definitely promising alternatives. Patches / films are laminates consisting of an impermeable back layer, a reservoir layer containing drugs from which the drug is released in a controlled manner, and a bio-adhesive surface for mucosal attachment. Patches are laminates consisting of an impermeable back layer, a reservoir layer containing drugs from which the drug is released in a controlled manner, and a bio-adhesive surface for mucosal attachment. Flexible films / patches were prepared to deliver drugs directly to a mucosal membrane using either solvent casting or hot melt extrusion techniques. These offer advantages in providing a controlled dosage of medication to the site compared to creams and ointments.

Hydrogel-based adhesive semi-solid systems are an appealing dosage type. They can be used to deliver the drug through buccal mucosa or intra-periodontal pocket with the possibility of extending the period of residence and improving bioavailability. The benefits of gels are the formation of close contact with the mucosal surface and the rapid release at the application site of the medicinal substance. Adding muco-adhesive polymers, typically carbomers, to gels improves effectiveness due to increased toughness on mucous membranes and long duration of action. Hydrogels formed from polymers and can be hydrated without dissolution in an aqueous environment, functioning as a drug delivery mechanism by physically trapping molecules that are then released gradually after gel hydration through diffusion or erosion. Semisolid systems have the benefit of being provided with a syringe, making it easy to put in periodontal pockets and easy to spread throughout the oral cavity mucosa. Gels increase the bioavailability of solutions. Ointments are less popular as a buccal formula. The main disadvantage is that the dosage of the muco-adhesive system cannot be managed. Consequently, gels have limited applications for the muco-adhesive system with narrow therapeutic indexes and for locations that are difficult to access but are an effective drug delivery system for ophthalmology, oral medicine and gynecology. Another downside is poor retention at the application site when the hydrogel polymer has no adhesive properties.

It provides a high level of active in the oral cavity for local impact. It releases active substances at carefully controlled levels, allowing for prolonged oral cavity exposure. Though medicated chewing gums present difficulties in controlling the dose given, they still have some advantages as drug delivery devices, particularly in the treatment of oral cavity diseases and nicotine replacement therapy. There are some consumer products on the market. Recently, caffeine chewing gum was developed to relieve sleepiness. It is absorbed at a significantly faster rate and has been equivalent to the formulation of capsules. Nicotine chewing gums is sold for prevention of smoking.

Liquid Dosage Forms

For appropriate aqueous cars, it can be treatments or drug suspensions. These types of dosage forms are typically used to exert local action in the oral cavity, and for this reason some antibacterial mouthwashes and mouth-freshener are available commercially. The drawback of these liquid dosage forms is that they are not readily maintained or aimed at buccal mucosa and can distribute fairly unregulated quantities of drugs throughout the oral cavity. From the wide range of polymer solutions,

chitosan is the most binding solution, followed by methylcellulose, gelatin, carbopol and polycarbophil. Viscous liquids can be used to cover the buccal surface as defensive or as vessels for the delivery of drugs to the mucous surface. Artificial saliva solutions are used to treat dry mouths that are retained on mucous surfaces to provide lubrication. These solutions include CMC sodium as a bioadhesive polymer.

Advances in buccal drug delivery for the treatment of OSF

Unsatisfactory clinical management of OSMF continues. Signs and symptoms persist and progress despite attempted treatments. Many types of medicines are used to treat crippling fibrosis. There is, however, no adequate impact. For many factors, not a single drug has successfully reversed the onset and progression of OSMF, such as the progressive nature of the disease, the complete lack of knowledge of the pathogenesis of the disease, the restricted routes of administration and the use of sufficient dosages of administration. Examining the proper route of administration and dosage for the treatment is very critical. The researchers have made several attempts and from these attempts it is known as the most suitable route of administration in OSMF care [75]. Buccal drug delivery system has become a major drug administration carrier as it is easily accessible for self-medication and safe as the systems can be quickly administered and removed from the application site. Nonetheless, the short residence time at the site of application is a common problem for the buccal drug delivery system, but this problem was solved by the use of bio-adhesive polymers that display adhesive interactions with biological membranes. Muco-adhesive buccal dosage types have recently been produced for OSMF, including adhesive tablets, capsules, gels and films, but buccal films are favored in terms of flexibility and comfort over adhesive tablets. For the treatment of OSMF, a localized buccal disease, Averineni et al. announced the developed muco-adhesive films of valdecoxib. Such films will bypass the relatively short period of residence of oral gels on the mucosa that are easily washed and dissolved by saliva. These are also ideal for the protection of wound surfaces, thereby minimizing discomfort and increasing the effectiveness of treatment. Compared to conventional oral administration, these buccal films have the benefit that they contain a lower dose of drugs that is appropriate for therapeutic effect because they are located directly at the inflammation site. [76]. In 2013, after topical administration over buccal mucosa, Alam et al. researched the effectiveness of aloe vera gel in OSMF care. The efficacy of aloe vera gel (as an adjuvant to medicinal treatment) was tested in 60 patients in a double-blind, placebo-controlled, parallel-group randomized controlled trial. They indicated that aloe vera gel is the beneficial complement in the treatment of OSMF to medicinal and surgical approaches. Nevertheless, the effectiveness of the well-known delivery systems in OSMF care has yet to be studied. There is no single report available to date on the targeted distribution of drugs to the OSMF site. But, in the area where people use Pan masala, this condition becomes more common.

Opportunities and future scopes of mucosal drug delivery for oral sub-mucous fibrosis

Drug delivery through the mucosal route has enormous usefulness in the treatment of oral submucosal fibrosis, it will be the leading choice in the near future as it opens patients ' doors to self-medication, ease of administration, no pain at the site of administration, etc. It is therefore highly desirable to extend the awareness to build muco-adhesive drug delivery systems (films, patches, gels) and to combine these drug delivery systems with nanotechnological approaches. A review of the literature shows the lack of available knowledge on drug delivery carriers, toxicity profile, safety pharmacology, clinical trials, preclinical and clinical pharmacokinetic studies for the distribution of drugs used for OSF treatment. There is no universally accepted protocol published for in vivo trials, toxicity profile evaluation, pharmacokinetic tests and safety pharmacology, so almost all medicines are not approved by the USFDA as the primary OSF treatment. Local and structural availability problems have not yet been identified which should be discussed in order to evaluate the therapeutic value or risk ratio. Oral mucosal site has several benefits, such as abundant aqueous setting, large absorption region, favorable pH, although researchers seem reluctant to position a useful anti-OSF muco-adhesive dosage type from the bench to the industrial scale. As a result, on the global market, very few formulations are available. Stability and scale-up are more issues. The interactions between drugs and the mucosal layer need to be properly investigated. It is stated that several phyto and synthetic molecules are effective against OSF. The quest for an effective delivery carrier continues to limit high molecular weight, oral toxicity, much less permeability and hydrophobicity. The formulation based on nanocarriers could therefore make these molecules more effective against the disease.

Delivery systems based on nanotechnology are often used today to solve problems such as low solubility, bioavailability, permeability, contact, high toxicity, instability, etc. In the delivery of steroidal drugs such as triamcinolone acetonide and dexamethasone, the role of muco-adhesive dosage forms should be explored. Many plant-based medications such as curcumin, ursolic acid, aloe vera, spirulina, carotenoids (lycopene), borneol, allicin and synthetic molecules such as corticosteroids have been used from time to time for symptomatic inflammation relief, lipid peroxidation inhibition, wound, oxidative stress, hyperproliferation, algesia such as conditions usually found in OSF however, comprehensive treatment of OSF is yet to be achieved. Such problems result in a lower rate of conversion into the commercial of proprietary technologies. It is obvious from the clinical trials in progress that there is a great future for OSF's mucosal drug delivery systems.

CONCLUSION

This analysis includes an up-to-date overview of the OSMF program and allows students, clinicians and researchers to better understand this disorder. There are many numerous therapies used to treat OSMF; however, OSF histopathology is still suggested as the diagnostic gold standard. Muco-adhesive buccal patches have recently received significant interest in the delivery of drugs and have become the most popular route of administration for OSMF treatment. Adherence of buccal patches to the mucosal membranes will increase the gradient of the drug concentration at the absorption site and improve drug bioavailability. Such formulations are used to reduce the side effects found in medications administered by the system. Research in this field is still in its infancy and it is inevitable that growing attention will be concentrated on this area to explore potential targets or lead molecules for OSMF treatment.

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