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Review article

An Insight Into Buccal Drug Delivery System

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Abstract

Oral drug delivery still remains the first choice as it offers wider range of advantages comparing to other route of administrations. Drug delivery systems are continuously advancing in the pharmaceutical discipline. The anatomy and physiological characteristics of oral cavity attracted the formulation scientist to work on newer buccal based system. Oral mucosal drug delivery system offers certain advantages; by passes first pass metabolism, rapid absorption, quick on set action. Barriers available in the oral epithelium shall be modified using the permeation enhancers using various approaches. Buccal drug delivery system has various formulation strategies including solid, semi-solid and liquid dosage forms. Oral buccal mucoadhesive system has well established *in vitro*, *ex vivo* and *in vivo* evaluations parameters. This review outlines the various concepts in buccal drug delivery system.

Introduction

Expenditures spent in the drug discovery is huge both in terms of money and time which enlightens the pharmaceutical industrialists to think to enhance the efficacy of drugs to deliver in alternate strategies to extend the market longevity and improve patient compliance. Though various novel strategies exist oral route remains the desired route for the administration of drugs. This is due to low cost, easy administration and patient compliance is high.

Past three decades various novel, newer and innovative formulation strategies are utilized and those products increasingly reach the market. Among these buccal mucosal route has received considerable attention in the last decade [1]. Drug delivery through oral cavity is convenient route due to various reasons, like administration of dosage form is easy, bypasses the first pass metabolism and eliminates the drug degradation through gastrointestinal tract. Regions available in the oral cavity shall be utilized for drug delivery those regions are buccal, sublingual, palatal, and gingival.

Buccal drug delivery especially noted to elicit local or systemic pharmacological actions through the buccal mucosa. Drugs used in these buccal delivery system are of treatment for the infections in the oral cavity and to elicit systemic therapeutic treatments [2]. The choice of region in oral cavity majorly depends on effect to be required local or systemic and permeability features of exists in the oral cavity regions.

Buccal drug delivery remains the choice of route to deliver the small molecules and macromolecules [3]. Macromolecules are majorly affected by significant barriers of biochemical and physiological parameters, such that it not suitable to deliver via oral conventional dosage forms. Macromolecules through oral route of administration encounters the first pass metabolism in major and are subjected to pre-systemic clearance in the liver [4]. This leads to affect the permeability, absorption and bioavailability.

Parenteral drug delivery too has various hindrances and poor oral bioavailability routed to explore the various alternate routes to deliver such drugs. Other major routes explored are mucosal route including, pulmonary, ocular, nasal, rectal, buccal, sublingual, vaginal, and transdermal. Among these buccal mucosal route has received considerable attention in the last decade [5].

Mucosal route of delivery without stimuli for enhancing the permeation and absorption of drug is less success. Formulations are incorporated with various stimuli factors like absorption enhancers, novel formulation strategies, and reversible chemical modifications to increase the bioavailability of the drugs [6].

Through understanding of permeability barriers, drug transport pathways across the buccal membranes and is mechanism is required for the optimized delivery of drugs though trans-buccal delivery systems. Buccal mucosa has excellent accessibility to smooth muscle region in the buccal cavity for the drugs supplied oral cavity and shall act as retentive dosage forms for longer duration. Buccal region has direct contact with the systemic circulation

through the internal jugular vein, there by drugs not affected by the hepatic metabolism. This process leads to increased bioavailability of drugs administered through buccal mucosa [7].

Advantages also includes painless administration, withdrawal of dosage forms is easy, less enzymatic activity, mild and reversible damage to the buccal mucosa, permeation can be modified by incorporation enzyme activity modifying agents, pH modifiers in the dosage forms. Buccal adhesive drug delivery systems release the drug in multi or unidirectional for local or systemic actions, remains attractive to researcher to continuously work in this type of drug delivery systems. However, inherent limitations, including short residence time, small absorption area, and barrier property of the buccal mucosa, are challenges to buccal drug delivery [8-9].

Dosage forms reportedly used for buccal route includes, as tablets, lozenges, chewing gums, films, patches, gels, paste, ointments, solutions, microspheres. Among all these film based products are promising and most successful method for the delivery through buccal systems [10-11]. Certain major limitations contributed by buccal mucosal delivery systems include the activity by salivary secretions, accidental swallowing of the dosage forms, buccal mucosal barrier for the permeation of drugs. This article outlines the concepts of buccal drug delivery, advantages and disadvantages, permeation enhancers, evaluation of various parameters of buccal drug delivery system, formulation strategies for buccal dosage forms.

Anatomy And Physiology of Oral Mucosa

Buccal regions has boundary within the lips, cheeks teeth and gums within the oral cavity [12]. Buccal mucosa has maxillary artery which supplies blood to these region. Blood supply is faster and higher compared to sublingual, gingival and palatal region, thus buccal mucosa assists passive diffusion of drug molecules across the mucosa. The thickness of buccal mucosa facilitates the retentive delivery systems [13]. The buccal epithelium rejuvenates every 5-6 days [14]. Buccal mucous layer be similar to other mucosal lining membrane like vagina, oesophagus. The oral mucosa surface area is about 200 cm^2, it has two layers, vascular and a vascular epithelium. The buccal epithelium serves as initial barrier and protecting the underlying tissues beneath this epithelium layer [15].

Oral mucosal cavity is lined by epithelium which is supported through connective tissue called lamina propria and differentiated from the epithelium by a basal membrane. Oral mucosal epithelium has variable structure and functions [16]. There are three types of oral mucosa namely, masticatory, lining, and specialized mucosa. The buccal masticatory mucosal epithelium were in keratinized in the region of gingival and hard palate regions, this is further subdivided into four layers, viz, keratinized, granular, prickle cell, and basal layers [17]. The remaining regions are of non-keratinized nature of epithelium; whereas the dorsal surface of the tongue and are made up of superficial, intermediate, prickle-cell, and basal layers. The tongue consists of both keratinized and non-keratinized mucosa. Blood flow in the oral mucosa is generally faster and richer than that in the skin [18].

Main permeation barrier exists in the outermost layer of epithelium, which is intercellular lipids discharged from membrane coating granules, a lipid organelles present in the prickle cell layer. This renders the epithelial cohesion and forms a barrier in the epithelium. Keratinized epithelium layer consists more neutral lipids which is associated with the barrier function. Non-keratinized epithelium layer consists more polar lipids. Permeability is more in the region of non-keratinized mucosa than the keratinized mucosa. The loosely packed intercellular lipids both in non-keratinized and in keratinized mucosa renders higher permeability in oral mucosa than of stratum corneum in the skin. Salivary secretions contribute more variations between the individuals, duration of adhesion, and regional variations in the oral cavity. Oral mucosal surface covered by the mucus layer acts a lubrication, protection and as wetting agent.

Absorption Pathways

Permeation of drug molecule on the oral epithelium has different permeation power which varies with the properties of drugs to be traversed and the natures of tissues to be traversed. In the oral mucosa have different regions with varying permeability potentials. There exists a decrease in permeability from the sublingual via buccal and palatal mucosa [19]. This is due to the varying thickness and degree of keratinization in these regions. Sublingual region is comparatively thin and non-keratinized, the buccal regions are thicker and non-keratinized, and the palatal region is intermediate while comparing thickness but it is keratinized [20].

Majority of the studies reported that the buccal absorption is taken place through passive diffusion [21]. There are two pathways in the passive diffusion namely transcellular or intracellular and paracellular or intercellular. Drug makes use of these both pathways simultaneously to permeate across buccal membranes according to the physicochemical properties of the drug to be permeated [22]. It is being noted that oral mucosa is both hydrophilic and lipophilic in nature. Thus the hydrophilic region of the intercellular spaces and cytoplasm acts as barrier to the lipophilic molecules. In the same manner lipophilic nature of the cell membrane and the intercellular lipids acts as barrier to the hydrophilic compounds.

Intercellular spaces were utilized by large molecules which is experimented by microscopical methods [23-24] using small proteins and dextran as visible tracers. There

is a barrier for the penetration of drug molecules exists due to modifications of intercellular substance in the superficial layers. Penetration property varies according to the physicochemical properties of the drug molecule and the type of tissue being traversed.

There are three route being available for a drug molecule to traverse the tissues, are Passive diffusion, Carrier mediated transport and endocytosis**.** Only very few situations uses endocytosis process, where molecules are taken up by the cells via phagocytosis or pinocytosis. There is very little chance for carrier mediated transport in the oral mucosa, still it is assumed that acidic stimulation of the salivary glands, along with the vasodilation facilitates absorption and enter into the circulatory system. The physicochemical properties of drug molecule, such as lipid solubility, molecular weight influences the absorption potential of the buccal mucosa [25]. Certain drugs absorption via buccal mucosa is increased when carrier pH is reduced and when increasing the pH absorption in decreased.

It is postulated that penetration potential is poor for ionized species through the oral mucosa when compared with non-ionized species. 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 decreased with an increase of pH [26]. However, the pH dependency that is evident in absorption of ionizable compounds reflects their partitioning into the epithelial cell membrane, so it is likely that such compounds will tend to penetrate transcellularly [27]. Increase in the permeability of the drug over the epithelial barrier shall be done by alternative the pH of the drug delivery system [28].

Barriers to Penetration Across Buccal Mucosa

Oral cavity poses certain significant challenges for the drugs to enter systemic circulation. First instances are to release the drug from the dosage forms to the site of absorption, buccal or sublingual region [29]. Followed by the drugs has to traverse the mucosal layers to reach the systemic circulation. The important barriers for the permeation is influenced by saliva, mucus, membrane coating granules, basement membrane, which retards the rate and extent of absorption of drug molecules through buccal mucosa. The major barrier is epithelium layer in the buccal mucosa membrane.

The oral mucosa's permeability is majorly due to the intercellular components which are exists in the intermediate cell layers of both keratinized and non-keratinized epithelia [30]. The actual barrier to the penetration of hydrophilic and lipophilic drugs is situated in the upper one-quarter of the buccal epithelium. Buccal epithelium is intermediate characteristics in terms of permeability with relate to intestinal mucosa and skin stratum corneum regions. Buccal mucosal lacks tight junctions which exists in the intestinal and nasal mucosa, thus buccal muosa is more permeable than other mucus membranes [31].

Formulation Design Perspectives

Physiological Perspective

Oral mucosal layer is highly vascularized has direct access to the systemic circulation, also by pass hepatic metabolism. This unique feature attracts the formulation scientists to develop buccal delivery route for the drugs with low dose and having high first pass metabolism.

Before conceptualizing a dosage form for buccal delivery system certain physiological considerations of oral buccal mucosa has to be taken care. This includes texture, thickness, turnover of mucus layer, salivary secretions and oral cavity environmental factors are to be taken care. Unidirectional release of drug from the dosage form with backing lining layer results in high drug penetration into the systemic circulation compared to bidirectional release buccal delivery systems.

The limited surface area in the oral cavity possesses the challenges to formulation scientists to focus on the size and dose of the drug load in the dosage forms. A general acceptable limit for the dosage forms is to be 1-3cm2 for the size and not exceeding 25 mg of daily dose of the active pharmaceutical ingredient. As well the duration of residence in the oral cavity is not to exceed 4-6 h approximately, which suggest a next cycle of intake of meal or liquid consumption, where the dosage form need to remove from the oral cavity [32-33].

The lipophilic drugs penetrate chooses transcellular route, hydrophilic drugs traverse through paracellular route. These two routes are used or coexist for all the drugs; the command over the route exists according to the physicochemical nature of drugs.

Passive diffusion of drug is characeterized pH partitioning theory, which is exhibited by ionizable drugs. Non-ionizable drug favored by increase in permeation through the transcellular route compared to ionizable drug. Thus pH of oral cavity is important parameter permeation across the buccal mucosa for ionizable drug.

Pathological Perspective

Though the oral cavity favors the absorption of drugs in comparable to gastro intestinal tract, it may be affected by the disease conditions. Disease condition modifies the thickness of the oral mucosal epithelium which is the primary barrier for the absorption of the drug across mucus membrane. This also affects adhesion duration of the dosage forms thus affects the retention time in the oral cavity [34-35]. Hence it is important to understand the disease conditions and pathological state of the oral cavity before designing effective buccal delivery system.

Pharmacological Perspective

Drug permeation across mucus membrane depends on the partition coefficient of the drug molecules. Lipophilic, non-ionized fractions of drug are better permeated compared to hydrophilic and ionized fraction of drugs. Modifying the lipophilicity through chemical modifications may increase the drug penetration power across the mucus membrane. Ionic fraction of weakly basic drugs is in increased state when there is decrease in pH which leads to decrease in permeation through buccal mucosal membrane. For local or systemic drug delivery via buccal route depends on the retentive time in the oral cavity, local concentration of drug, the fraction of drug transported across the mucosa to enter into the systemic circulation [36-37]

Successfulness of a delivery systems remains when it reaches the site of action for the intended application. Thus buccal delivery depends on whether the treatment is for local or systemic effects, which is also influenced by residence time and penetration of the drug. Irrespective of the treatment strategy foremost is the rug must be released from the dosage form and taken up by the oral mucosa. Physicochemical parameters of drug influence the delivery device for buccal delivery system [38]. Bad taste of drug and rough textured device will lead to poor patient compliance and non-acceptance of the delivery system.

Pharmaceutical Perspective

Therapeutic efficacy of delivery system influenced by drug release, permeation across the mucus membrane. Thus these factors to be carefully studied to formulate a successful device for the buccal delivery system. While considering developing a buccal delivery system organoleptic factors are needed to be characterized since the oral cavity has highly taste sensing organ. Additives are to be incorporated in the buccal delivery system for betterment of the dosage form for masking undesirable properties of drug and to improve better patient compliance. As additives are incorporated to modify the drug release pattern and absorption. Size, dose, frequency has to be considered while formulating a buccal delivery system. A delivery system with 1–3 cm2 size, daily intake of drug not exceeding 25 mg and 4-6 h duration of retention in the oral cavity is most preferable [39].

Penetration Enhancers

Penetration enhancers [40-41] facilitates decreasing the membrane barrier and enhancing the traverse of drug molecule across the buccal membrane. This is achieved by enhancing the cell membrane fluidity, solubilizing or extracting the structural intercellular and intracellular lipids, modifying the cellular proteins and altering the mucus structure and rheology. The buccal mucosa is lacking tight junctions and it is multilayered thus penetration enhancers may behave different here when compared to transdermal or intestinal drug delivery system. Permeation enhancing agent should be safe and non-toxic, pharmacologically and chemically inert, non-irritant, and non-allergenic.

Bile salts, fatty acids, and sodium lauryl sulfate are commonly experimented as penetration enhancers. Bile salts play a vital role as physiological surfactants in the absorption of lipophilic compounds and lipid soluble vitamins. Bile salts are extensively studied as permeation enhancing agents; its mechanism is by extracting protein or lipid and fluidization in the membrane. The effects caused by bilesalts in the buccal muosa is reversible in nature. Sodium lauryl sulfate has been studied by various formulation scientists to enhance the permeation, but it has exerts marked irritation to the buccal epithelium. This poses the concern for using Sodium lauryl sulfate as permeation enhancer.

Dosage Forms of Buccal Drug Delivery

Immediate release dosage forms namely buccal tablets, mouthwashes, chewable tablets, chewing gums reside short duration and poor absorption in gastro intestinal tract is the main concern [42]. Unidirectional release of drug from device of buccal systems, avoids loss of drug and avoids first pass hepatic metabolism, increased penetration through buccal mucosal membrane enhances the bioavailability of drugs.

Buccal mucosa is in the limelight during the last decade among formulation scientist as an alternative site of drug administration. This route offers an effective, safe and non-invasive route of administration of dosage forms. Oral mucosal delivery systems were classified into three approaches, sublingual, buccal and local delivery [43]. The choice of choosing any one of these approach over other approach influenced by the differences in anatomical and permeability characteristics among the various region in oral mucosal sites.

Buccal mucosal permeability is more in the sublingual region and it is easily achievable of rapid onset of action of drug where it is required. Thus sublingual region is most preferred route for the treatment of acute disorders. Buccal mucosal region is comparatively low permeable than the sublingual mucosa, followed by rapid onset is not achievable as it was done in sublingual route. This buccal mucosal route is a choice of route for treatment of chronic disorders, with sustained delivery. Thus these systems avoid fluctuating concentrations of drug in the systemic circulation where generally seen in conventional multiple dosage regimens.

Continuous interests in the oral buccal delivery systems are evidenced by various dosage form of conventional novel delivery systems. These systems are categorized as liquid, semi-solid, solid or spray formulations. The concept of all the dosage forms is to have rapid onset of action and longer retention time in the oral cavity for

extended release of drug from the dosage forms, these are also said to be potential advantages. Uncontrolled swallowing of released drug and unpredictable duration of retention in the oral cavity are certain limitations of the buccal delivery systems.

Solid Buccal Adhesive Dosage Forms

Tablets

Buccal adhesive tablets [44-45] were studied in the recent past either for local or systemic drug delivery. This type of adhesive tablets excellent bioadhesive properties which are directly placed and in contact with buccal mucosal layer. Being solid tablets size of the device is limitation due to limited surface contacts. Drug release from the tablets either unidirectionally targeting buccal mucosa or multidirectionally in to the saliva.

Hydrogel bioadhesive tablet adheres to the buccal mucosal layers upon contact with liquid hydration of the device leads to release the drug from the hydrogels. The swelling rate and bioadhesive polymer incorporation is key factor for extended duration of contact with buccal mucosa. Generally bioadhesive tablets are formulated and prepared by direct compression method. Chitosan was experimented in most bioadhesive buccal system as a carrier for drug, which offers numerous advantages for the buccal bioadhesive systems.

Bioadhesive tablets are explored to improve bioavailability of administered drug across oral buccal mucosa and it is of growing interest. Bioadhesive tablets exhibits intimate contact with mucosal surface in presence of saliva. After short residence time patient may not feel the presence of dosage form in the mucosa, and does all the routine activity including drinking and taking solid food contents without any discomfort. Tablets can be placed in the oral cavity in the region oral cavity including the palate, cheeks or between lip and gum.

The rigid physical nature of the tablet leads to patient discomfort and poor patient compliance is the main disadvantage of bioadhesive tablets. Care has to be taken not to move the position of the tablet which leads to possibility of swallowing the tablets. Drugs used for the chronic disorders shall be loaded in the adhesive tablets. Tablets are formulated by direct compression of power blend which can be attached to the oral mucosa and allowed to release the drug from the dosage form. Direction of release of the drug depends on the device fabricated either multidirectionally or unidirectionally. Being comparatively the tablet is large in size, patient feels discomfort on longer usage, also salivary secretions alters the position of the tablet in the oral cavity.

The composition generally consists of bioadhesive polymer such as polyacrylic acids or a cellulose derivative to which drug is mixed along with other excipients, there may be impermeable backing membrane to release the drug unidirectional. Solid dosage forms of buccal system were mostly studied for nitroglycerin sublingual tablet, fentanyl lozenge and prochlorperazine buccal tablets.

Wafers

Few literatures are available in the section of buccal wafers, this research focus on microbial infections with periodontitis. This device consists of composite wafer with adhesive property elicited by surface layers; the bulk layer comprises antimicrobial agents, biodegradable polymers and matrix polymers.

Lozenges

Lozenges for buccal delivery acts topically within the oral cavity. The drugs used as antimicrobials, corticosteroids, local anesthetics, antibiotics and antifungals were explored for the possibilities of buccal lozenges. Conventional lozenges release higher concentration of drug at an initial stage followed by the drug release declined this leads to sub-therapeutic levels drug concentration. The drug release from the lozenge depends on the patient as how they suck the lozenge. Thus bioadhesive lozenge release extended drug release with improved patient compliance.

Microparticulates

Multiparticle systems has benefical effect as it is small multiparticles easily accepted by the patients. These are delivered by suspending in a suitable vehicle to the oral cavity. Whereas, dose related problems is more compared to other type of dosage forms. Multiunit bioadhesive microparticle has advantages as that of tablets, also it offers additional benefits. They are having intimate contact with a lager mucosal surface area. They can also be delivered GI tract and upper nasal cavity which are less accessible. Being small size there is lower local irritation at the site of adhesion.

Semisolid Dosage Forms

Topical applications majorly used by semisolid dosage [46-48] forms such a gels, ointments and creams. The composition generally have polymer, excipient to dissolve or suspend the drug as fine powder in the base of aqueous or non-aqueous type. Semisolid formulations are more comfort than the solid buccal system, they shall be applied using finger to region of interest in oral cavity easily. Gels are applied through syringe into the periodontal pockets. Semisolid formulation delivery varying amount of drug compared to solid dosage forms. Poor retention capacity in the oral cavity is another drawback of semi-solid dosage forms. However, they may deliver variable amounts of active ingredients in comparison with a unit dosage form. By the use of bioadhesive polymer, Poloxamer 407 and Carbopol 974 this drawback can be minimized for certain extent.

Gels

Ploymer of crosslinked polyacrylic acid were studied for the Gel forming bioadhesive properties, which adhere to buccal mucosal surface for prolonged periods of time and releases the drug in controlled manner. Gels were explored for the possibility of buccal delivery of drugs. Gel formulation has certain advantages such as to form intimate contact with the mucosal membrane and rapid release of drug at the absorption site. The disadvantage includes inability to deliver accurate measured dose of drug at the site of absorption.

Hydrogels based semi-solid systems are also developed and it is found to be attractive dosage forms for the buccal drug delivery system. Buccal hydrogel systems referred as wet adhesive, is composed of polymers from hydrophilic nature, upon exposure to aqueous environment hydrated and swells to certain extent. Hydrogels are cross linked systems thus they do not dissolve in the aqueous medium, drug molecules are entrapped physically within it. Hydration leads to relaxation of cross linked system and drug molecules slowly release by diffusion from the hydrogel network or by degradation of polymer or combination of the both mechanism.

Adhesive polymer forms an integral part of this hydrogel based system to avoid poor retention of dosage form in the oral cavity. The polymer used provides an prolonged retention time, unidirectional drug release, good drug penetration, increased bioavailability and high bioadhesive efficacy and patient compliance.Natural gums, CMC, HPC, HPMC, polyacrilates, polyoxyethylenes are class of polymers used as hydrogels polymers. This hydrogel system used for the treatment of periodontitis with incorporation of antimicrobial agents. This system can be placed in periodontal cavity in smooth manner to provide long duration of action.

Patches/Films

Patches and films were formulated as buccal bioadhesive delivery systems. Patches and films offers advantages compared to ointments and creams. Films release the dose of drug at the absorption site in a measured manner. Buccal films are now commercially available shows the success of its formulation. Patches and flexible adhesive films are used as buccal mucosal delivery system. These device requires bioadhesive component to assist direct contact with the mucosa and prolong residence time, vehicle that releases the drug at an appropriate rate from the dosage forms and additives such as penetration enhancers and/or enzyme inhibitors.

These patches, films are generally manufactured by solvent casting methods using adhesive coating machines. This process involves the use of casting solution in which drug is dissolved, followed by casting film, drying finally it is laminated with backing layer. These concepts is similar approach of pressure sensitive adhesive based patch manufacturing. These dosage forms are thin, flexible, lest obtrusive and more acceptable to the patient. Thin nature is more susceptible to over hydration thus it may loss its bioadhesive properties [49].

Laminated patch and adhesive films is an another approach of buccal mucoadhesive system. The choice of polymer is important criteria for the development patch or film, which elicit the bioadhesive properties and has control over the rate of drug release. Laminated patch has impermeable backing layer which assist in unidirectional drug release, along with or without drug release and permeation modifiers. Patches adheres to the mucosal surface for longer duration with any discomfort to the patients.

Bioadhesive film gaining momentum in the research areas and newer innovations in the development of film based products. It is similar to that of patches with relate to manufacturing process, advantages and drawbacks. Films based buccal delivery system offers a physical flexibility, higher patient compliance and comfort, in comparison to adhesive tablets. Films offer a longer residence time while comparing to gels and ointments which shall be cleared off by salivary secretions easily. Film treating oral disease significantly since the polymeric adhesive film protects the underlying surface [50]. It has longer duration of manufacturing process, high cost are the certain disadvantages of film based buccal systems.

Oral cavity is used by patch formulations with an aim of systemic or local actions [51-52]. The literatures available shows there is more research inclined to develop various patches and film based buccal delivery system as it offers wider range of advantages over other dosage forms targeting oral cavity.

Liquid Dosage Forms

Highly viscous liquids may be used to lining the buccal mucosa. This behavior functions as protectants or as drug vehicles to the buccal mucosal surface. Polymers used in this liquid dosage forms aid the retention in the oral cavity by enhancing the viscosity of the products. Bioadhesive liquid dosage forms acts as artificial saliva used to treat dry mouth as, this solution consists of sodium CMC as bioadhesive polymers

Liquid dosage forms [53-55] expected to use for local action in the oral cavity, solutions, suspensions are classified into this liquid dosage forms. Commonly used antibacterial mouthwashes and mouth-freshener are commercially available. The liquid dosage forms are retained only for a brief period and release the drug uncontrolled manner into the oral cavity. By using iontophoretic techniques, controlled delivery of drug from the liquid dosage forms is possible; this technique is well adopted in transdermal drug delivery system.

Evaluation Of Buccal Bioadhesive Systems

Characetrization of any formulation gives an insight about the success of the dosage forms [56-64]. Carefully evaluating buccal delivery system by selecting appropriate model paves a way to deliver the drug candidate in buccal drug delivery system of choice. Several *in vitro*, *ex vivo* and *in vivo* methods have been employed for the evaluation of the buccal delivery system.

Drug Release From Dosage Forms

Conventional dosage forms have official pharmacopoeial methods for the determination of drug release from dosage forms. It needs high volume of dissolution medium and need to maintain sink conditions. Buccal drug delivery system release the drug exponentially at initial stage with cannot be determined with existing methods. Also buccal cavity environment needs to be simulated during the drug release studies. However, the initial fast release of some buccal dosage forms cannot be measured with the existing methods. These methods do not simulate the conditions prevailing for buccal administration where low liquid environment exists and a non-sink condition is more appropriate for a poorly permeable drug. Various modified methods are reported to study the release pattern of drug from buccal drug delivery system.

Bioadhesion Measurement

Bioadhesion is important for the buccal delivery system, factors such as salivary secretion, mastication; mucus turnover can significantly affect the performance of the delivery devices. The values obtained from different methods are having different results hence meaningful examination is required for the selected dosage forms for each technique. Bioadhesion were evaluated by direct staining method. The adhesion of polymer, quantified by measuring the staining intensity of control and treated cells by image analysis. This method well adopted for liquid dosage forms. Colorimetric detection system be carried out to study the binding of bioadhesive polymers to buccal epithelial cells. Surface topography changes can be examined using Atomic force microscopy and to determine the pattern of bioadhesion of polymer onto the buccal cell surfaces..

Duration of bioadhesion measured by gamma scintigraphy, electron paramagnetic resonance or transit studies with fluorescent-coupled dosage forms. The results are quantitative in nature and gives complete details of bioadhesive properties of the dosage forms. Mucoadhesion measurement also termed as macroscopic methods, these quantitative methods measures the force required to detach the adhesive bond between the membrane and surface of polymer adhesion. Peel, shear and tensile forces can be quantified according to the adhesive is being separated from the surface of substrate.

Tensile Test

The detachment of dosage form is measured, and it is depends on the type of polymer used in the formulation. This is indicative of bioadhesion strength of the dosage forms. To get reliable results the critical parameters should be monitored and fixed appropriately.

In Vitro Residence Time

It was determined using a modified disintegration apparatus, segment of mucosa was sticked to the surface of glass slide, and it is attached to the disintegration apparatus vertically. Hydrated dosage form under study is made contact with the mucosal surface for intimate contact. The glass slide allowed to move up and down such that tablet was out of the medium at the highest point and fully immersed into the medium when the glass slide is at the lowest point. The time taken to remove the tablet from the mucosal surface was observed.

Permeation Studies

This study helps in the feasibility of delivery system for the selected drug candidate, and helps in modifying the physicochemical properties for better permeation to happen along the mucosal membrane. Methods available to examine *in vitro*, *ex vivo* and *in vivo* buccal permeation profile were used. Diffusion cells were used to study the *in vitro* permeation characteristics of buccal delivery system; it is similar to the assembly of transdermal drug delivery system. Here in buccal system, buccal mucosa is dissected from the animal model kept as diffusion barriers. Maintaining the viability and integrity of the dissected mucosa during the study is tedious which ultimately affects the results.

In Vitro Methods

It uses diffusion cells, generally the apparatus consists a water jacket, internal compartment contains medium of interest where the drug to release. The dosage form is attached to the synthetic semipermeable membrane which is placed in the diffusion cell; the unidirectional release pattern is to be done by covering the rest of the surface. Drug release from the dosage form permeates through the membrane and enters into the receiving compartment. The concentration of drug available in the receiving compartment quantified periodically.

Ex Vivo Methods

Dissected animal buccal mucosal tissue used for examining the drug permeation. Preservation of the dissected tissue to be taken care this lies the success of this experiment. This method is useful ex-vivo method to evaluate buccal drug transport.

In Vivo Methods

Various animal models were used to conduct the *in vivo* studies for buccal delivery system. Rabbits are preferred over the dog, pig and monkey, since rabbit mucosa is similar to human buccal mucosa in terms of keratinization. Certain special attention is warranted while studying the buccal delivery system, keratinization of lining in the mucosal is the concern while selecting the animal model. This could affect the results of the buccal delivery system if not properly selected the animal model. Rabbit is chosen it has non-keratinized mucosal lining as like human tissue as well maintenance of rabbit is convenient when compared to pigs which also have non-keratinized buccal mucosa.

Toxicity And Irritation Studies

Being mucosal system is smooth, toxicity and irritation study is important parameter to be considered for the successful development of the buccal mucosal delivery system. Trained expert is required to conduct these studies. Histological examination gives more information about these studies. The rate of recovery is inversely proportional to the membrane damage. Buccal mucosa able recovers quickly than other mucosal membrane.

Other routine tests parameters shall be examined for the any buccal mucoadhesive system. These parameters include weight variation, hardness, friability, uniformity of content, *in vitro* drug release; tensile strength, film endurance, hygroscopicity for films; viscosity, effect of aging for gels and ointments.

Conclusion

Academicians and industrialists are in search of newer innovations for the existing drugs and off patent drug molecules instead of investing huge cost and time consuming process for the newer invention of drug molecules. The simple, convenient and non-invasive method of administration is key success for the buccal mucosal drug delivery system. The research interests towards buccal mucosal drug delivery system are growing year by year as it is evidenced from numerous literatures available in the various data bases. The future direction goes into developing a vaccine formulation using oral mucosal delivery system which has huge potential in the market. Success of buccal mucosal delivery system relies mainly on information through understanding of drug molecules and its behavior in the mucosal site. Various pharmaceutical industries are currently focused in development and commercializing buccal drug delivery technologies.

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