

A Smart Oro-Soft Palate Mucosal Drug Delivery: Credentials and Future Trends

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ABSTRACT

Over the last few decades pharmaceutical scientists throughout the world are trying to explore transdermal and transmucosal routes as an alternative to injections. The main impediment for the oral delivery of the drugs as potential therapeutic agents is their extensive pre-systemic metabolism, instability in acidic environment associated with inadequate and erratic oral absorption. The parenteral route is the only established route that overcomes all the drawbacks related with the orally inefficient drugs. However the parenteral formulations are expensive, need frequent administration, with less patient compliance and other harmful effects. Since ancient times oral transmucosal drug delivery has received intensive interest for the systemic delivery of drugs proved to have better systemic bioavailability achieved by oromucosal route. Oral mucosal drug delivery provides an alternative method of systemic drug delivery which offers many advantages for both parenterals and oral methods. The oral mucosa is highly vascularised, hence

drugs which are absorbed through the oral mucosa directly enter into the systemic circulation, bypassing the enzymes present in the gastrointestinal tract and first-pass metabolism in the liver. The various transmucosal sites available are sublingual and buccal, but also the soft-palatal mucosa was found to be the most convenient and easily accessible novel site for the delivery of therapeutic agents for systemic delivery as retentive dosage forms. It has adequate blood supply, rapid cellular recovery time after exposure to stress, flexible, smooth surface, devoid of mechanical irritation, local discomfort and non-invasive route. Recently soft palate route explore more attention towards the scientist as an alternative to buccal route for administering drugs using mucoadhesive drug delivery dosage forms. This review focuses the more recent advances in novel soft palate route and formulation strategies to design dosage forms to administer drug through this novel soft palate route.

Keywords: Transmucosal delivery, soft palate, permeability and novelistic platform

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1. INTRODUCTION

The oral route of drug delivery is highly acceptable amongst the various routes of drug delivery and the most preferred by the patient and the clinician. The lack of efficacy of certain drugs especially peptides and proteins due to decreased bioavailability, unpredictable and erratic absorption, GI intolerance, or pre-systemic elimination as well as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs which has prompted the search for other potential route for administration. A recent investigation of mucosal delivery of drugs for a large number of drugs had proved to be more promising. The mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity offer transmucosal routes of drug delivery with distinct advantages over peroral

administration for systemic drug delivery. These routes possibly bypass first-pass metabolism of drugs, avoidance of pre-systemic elimination within the GI tract and, depending on the particular drug, a better enzymatic flora for drug absorption.

The oral cavity, on the other hand, is easily accessible by patients, the mucosa is relatively permeable with a rich blood supply, it is robust and shows short recovery times after stress or damage [1-30], and the virtual lack of Langerhans cells [4] makes the oral mucosa tolerant to potential allergens. Furthermore, oral transmucosal drug delivery bypasses first pass effect and avoids pre-systemic elimination in the GI tract. These factors make the oral mucosal cavity a very attractive and feasible site for systemic drug delivery. The oral mucosa can be categorized into sublingual, gingival, buccal and soft-palatal mucosa through which systemic transmucosal drug delivery can be achieved.

Conventional buccal and sublingual dosage forms are typically short acting because of limited contact time between the dosage form and the oral mucosa. Since administration of drugs through these routes interferes with eating, drinking and talking therefore, these routes are generally considered unsuitable for prolonged administration, whereas soft-palatal medication delivers steady infusion of drugs over an extended period of time, because of the function of the soft palate to cover the glottis while swallowing, it is more fitted for sustained and controlled drug delivery also due to the presence of immobile mucosa and lack of permeability in comparison with sublingual mucosa. Even though the sublingual mucosa is relatively more permeable than the buccal mucosa but it is not suitable for an oral transmucosal delivery system because it lacks an expanse of smooth muscle and is constantly washed by a considerable amount of saliva making it difficult for device placement. Because of high permeability and rich blood supply, the sublingual route is capable of producing a rapid onset of action making it appropriate for drugs with short delivery period requirements with infrequent dosing regimen. While buccal drug delivery has low flux due to less permeability which results in low drug bioavailability, other drawbacks include salivary dilution of the drug and inability to localize the drug within a specific site of the oral cavity. A novel Velar or soft palate as a route for drug delivery proved to be a smart site with its anatomical position, surface area, existence of mucus layer, optimal thickness, non-keratinization, optimal permeability offers a favorable alternative to the other oromucosal routes for systemic drug delivery [5]. Therefore soft-palatal drug delivery is a feasible approach for correcting salivary dilution and achieving absorption site localization to retain the drug on the mucosa using a bio-adhesive system.

2. ORAL MUCOSAL SITE FOR DRUG DELIVERY

2.1. Anatomy, physiology and properties of the oral mucosa

The oral mucosa is composed of an outermost layer of stratified squamous epithelium, intermediate layer, lamina propria followed by the submucosa as the innermost layer [6]. The epithelium is similar to stratified squamous epithelia found in rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium. The structure and biochemistry of the oral epithelium are illustrated by Squier et al. [7, 8, and 9] and its biochemistry by Gerson et al. [10]. Oral mucosa can be categorized into sublingual, gingival, buccal and palatal mucosa. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 μ m, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue and the gingiva measure at about 100-200 μ m. The mucosae of the gingivae and hard plate are keratinized and the mucosae of the soft palate, the sublingual and the buccal regions, are not keratinized. The non-keratinized epithelia are more permeable to water than the keratinized epithelia through which oral transmucosal drug delivery can be achieved.

Mucus is a viscoelastic gel-like secretion which contains mostly water-insoluble glycoprotein bound to the apical cell surface of the entire oral cavity and acts as a protective layer to the cells below [11]. It is chemically consisting of 95–99% water, proteins, enzymes, electrolytes and nucleic acids with a large peptide backbone with pendant oligosaccharide side chains whose terminally ends with either sialic or sulfonic acid or L-fructose. The oligosaccharide chains are covalently linked to serine and threonine along the polypeptide backbone. About 25% of the polypeptide backbone is without sugars, the so-called 'naked' protein region, which undergo enzymatic cleavage. The remaining 75% of the backbone is heavily glycosylated. The terminal sialic groups have a pKa value of 2.6 so that the mucin molecule should be viewed as a polyelectrolyte under neutral or acid condition. At physiological pH the mucin network may carry a significant negative charge because of the presence of sialic acid and sulfate, residues and this high charge density plays an important role in mucoadhesion [12, 13].

2.2. Permeability

The oral mucosa is composed of somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa and there are considerable differences in permeability

between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosa. The permeability coefficient of a drug is a measure of the ease with which the drug can permeate a membrane. The permeability coefficient is a function of the membrane thickness (i.e., inverse to its thickness) degree of keratinization of the tissues, and the physicochemical properties of the drug like its molecular weight, size, and lipophilicity. This suggested rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being comparatively thin and non-keratinized, the soft palatal mucosa is non-keratinized and thin than buccal, the buccal is thicker and non-keratinized, and the hard palate is intermediate in thickness but keratinized. Drug permeability appears to be highest in the sublingual area and lowest at the gingival site [14]. It is recently believed that the permeability barrier in the oral mucosa is a result of intercellular material derived from the so-called membrane coating granules (MCG) [15, 16]. This barrier exists in the outermost 200 μm of the superficial layer. In both keratinized and non-keratinized epithelia, the limit of penetration corresponds with the level where the MCGs could be seen adjacent to the superficial plasma membranes of the epithelial cells. Due to the identical results were obtained in both keratinized and non-keratinized epithelia, keratinization is not a factor to play a significant role in the barrier function.

2.3. Conventional route versus transmucosal route for drug delivery

Drugs are preferred to administer traditionally and routinely by oral and by parenteral routes. Although generally convenient, both routes have a number of disadvantages, especially for the delivery of peptides and proteins, a class of drug that has been rapidly emerging over the last decades [17]. Orally administered drugs are exposed to harsh environment of the gastrointestinal tract, potential chemical and enzymatic degradation [18]. After gastrointestinal absorption the drug has to pass the liver, where, dependent on the nature of the drug, extensive first-pass metabolism can take place with subsequent rapid clearance from the blood stream [19]. Low permeability across the gastrointestinal mucosa is also often encountered for macromolecular drugs [20, 21]. Parenteral administration avoids drug degradation in the gastrointestinal tract and hepatic first-pass clearance but due to pain or discomfort during injection, patient compliance is poor, particularly if multiple daily injections are required as e.g. in the insulin therapy [22]. Injection related side effects like tissue necrosis and thrombophlebitis also

lead to low patient acceptability. In addition, administration by injection requires trained personnel which add to the relatively high costs of parenteral medication. Consequently, other absorptive mucosae are being considered as potential sites for drug administration including the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity. These transmucosal routes of drug delivery offer distinct advantages over peroral administration for systemic drug delivery such as possible bypass of the first pass effect and avoidance of presystemic elimination within the GIT.

2.4. Theories of mucoadhesion

The most widely investigated group of mucoadhesives for transmucosal drug delivery systems are hydrophilic macromolecules containing numerous hydrogen bond-forming groups [23]. The presence of hydroxyl, carboxyl or amine groups on the molecules favours adhesion. They are called "wet" adhesives they are activated by moistening and get adhere non-specifically to various surfaces. They may get over hydrated to form slippery mucilage unless water intake is restricted. There are two basic steps in mucoadhesion for dry or partially hydrated dosage forms [24]. First step is the "contact stage" where intimate contact is formed between the mucoadhesive and mucous membrane. Within the oral cavity the formulation can usually be readily placed into contact with the mucosal site and held in place to allow adhesion to occur. Second step is the "consolidation stage where various physicochemical interactions occur to consolidate and strengthen the adhesive bond which leads to prolonged adhesion.

Mucoadhesion is a complex process and numerous theories have been postulated to the mechanisms of mucoadhesion. These theories include mechanical interaction, electrostatic, diffusion-interpenetration, adsorption and fracture processes [25], at the same time as undoubtedly the most widely accepted theories are founded upon surface energy thermodynamics and interpenetration/diffusion [26]. The wettability theory is mainly applicable to liquid or low viscosity mucoadhesive systems and is essentially a measure of the spreadability of the drug delivery system across the biological substrate [27]. The electronic theory describes adhesion occurs by means of electron transfer between the mucus and the mucoadhesive system due to differences in their electronic configuration. The electron transport between the mucus and the mucoadhesive results in the formation of a double layer of electrical charges at the mucus and mucoadhesive border, this results in the formation of attractive forces within this double layer [28]. According

to fracture theory, the adhesive bond between systems is related to the force required to separate both surfaces from one another. This “fracture theory” relates the force for polymer detachment from the mucus to the strength of their adhesive bond. The bond fracture has been found to be greater when the polymer network strands are longer or if the degree of cross-linking within such a system is reduced [29]. According to adhesion theory, adhesion is defined as being the result of various surface interactions (primary and secondary bonding) between the adhesive polymer and mucus substrate. Due to chemisorption a primary bond results in adhesion due to ionic, covalent and metallic bonding, this is often undesirable due to their permanency nature [30]. The diffusion-interlocking theory proposes the time-dependent diffusion of mucoadhesive polymer chains into the glycoprotein chain network of the mucus layer. This is a two-way diffusion mechanism with penetration rate mainly depends upon the diffusion coefficient of both interacting polymers [31].



Fig 1. Interdiffusion of polymer chain of mucoadhesive device through mucus

2.5. Selected polymers for oro-soft palate mucoadhesive systems

The polymer with a high rate of retention at the applied and targeted sites is through the mucoadhesive bonds which include hydrophilicity, negative charge potential and the presence of hydrogen bond forming groups. Furthermore, the surface free energy of the polymer should be adequate so that “wetting” with the mucosal surface can be achieved. The polymer should also possess sufficient flexibility to penetrate the mucus network, biocompatible, non-toxic and economic [32]. According to the literature survey mucoadhesive polymers are divided into first generation mucoadhesive polymers and second generation mucoadhesive polymers. The first generation polymers are divided into three major groups based on their surface charges which include anionic,

cationic and non-ionic polymers. The anionic and cationic polymers exhibit stronger mucoadhesion [33]. Anionic polymers are the most widely used mucoadhesive polymers for various mucoadhesive formulations due to their high mucoadhesive strength and low toxicity. These polymers possess the major functional groups like carboxyl and sulphate groups which give rise to an overall net negative charge at pH values exceeding the pKa of the polymer. The classic examples include polyacrylic acid (PAA) and its derivatives and sodium carboxymethyl cellulose (Na CMC). PAA and Na CMC possess excellent mucoadhesive characteristics due to the formation of strong hydrogen bonding interactions with mucin [34]. Among the cationic polymer systems, chitosan is the most extensively investigated within the current scientific literature [35]. Chitosan is a cationic polysaccharide, produced by the deacetylation of chitin, the most abundant polysaccharide other than cellulose. Chitosan is a biopolymer due to its biocompatibility and biodegradability properties. Chitosan is reported to bind via ionic interactions between primary amino functional groups and the sialic acid and sulphonic acid substructures of mucus. The chemical derivatation can be done particular at the C-2 position forming a novel polymer with additional mucoadhesivity character. Using such modifications, the properties of chitosan may be tailored to suit the requirements of specific pharmaceutical technology challenges [36-38].

The term “cytoadhesives” belonging to second-generation polymer are less susceptible to mucus turnover rates, with directly binding to mucosal surfaces; more accurately. Surface carbohydrate and protein composition at potential target sites vary regionally with more accurate drug delivery can be achieved. Lectins are naturally occurring proteins that play a fundamental role in biological recognition phenomena involving cells and proteins. Soon after the establishment of early mucosal cell-binding, lectins seem to remain on the cell surface or in the case of receptor-mediated adhesion probably become internalised via endocytosis [39]. Although lectins offer significant advantages towards targeting site, some are poisonous or immunogenic, and the effects of repeated lectin exposure are still unidentified. Thiolated polymers are a type of second-generation hydrophilic mucoadhesive polymers like chitosan, deacetylated gellan gum or polyacrylates. The presence of thiol groups allows the formation of covalent bonds with cysteine rich sub domains of the mucus gel layer which leads to augmented residence time along with enhanced bioavailability [40-42]. Whilst first-generation mucoadhesive platforms are facilitated via non-covalent secondary interactions, the covalent bonding mechanisms involved in second-generation systems undergo interactions

that are less susceptible to changes in ionic strength and/or the pH. A novelistic approach on various natural sources for polymer extraction was done from various following sources like coca nucifera, arachis hypogea seed, guava, tamarind, banana, lallimantia royalena, mango, lotus corniculatus, lusora etc. These have been proved to possess mucoadhesive characters and had been tried for its mucoadhesion on the soft palate site and also for drug release characters[43].

3. ORO-SOFT PALATE

3.1. Histomorphology and positional environment of the soft palate

The soft palate is a mobile flap hanging posteriorly the hard palate being anteriorly in the oral cavity, sloping down the back between the oral and nasal parts of the pharynx. The soft palate or velum is a muscular palate made of the soft tissue constituting the back of the roof of the mouth [44]. Velum route prevents mechanical irritation and local discomfort due to its smooth surface and good flexibility. The soft palate is a thick fold of mucosa enclosing an aponeurosis, muscular tissue, nerves, lymphoid tissue, mucous glands and two small pits, the fovea palatine, one on each side of the midline is present. The anterior (oral) concave surface of the soft palate makes it suitable for self administration of drug delivery system with the help of thumb [45,46].

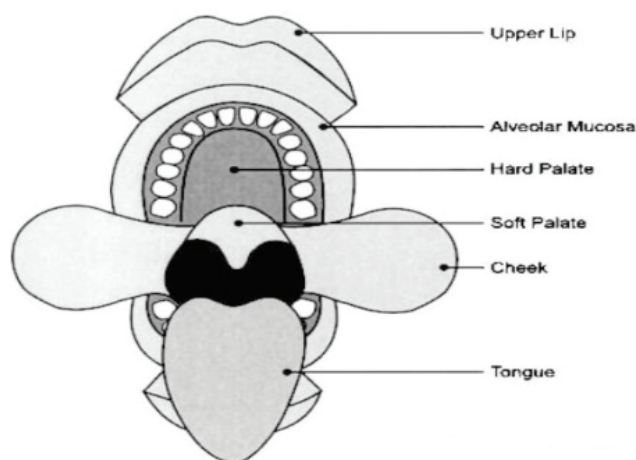


Fig.2. Position of the soft palate

The mucous membrane on the oral surface of the soft palate is highly vascularized. The papillae of the connective tissue are few and short, the stratified squamous epithelium is nonkeratinized, and the lamina propria shows distinctive layer of elastic fibers separating it from the submucous [47–49]. Typical oral mucosa is continuous around the free border

of the soft palate for a variable distance and is then replaced by nasal mucosa with its pseudo-stratified, ciliated columnar epithelium [50,51]. Oral side epithelium of the soft palate is covered consistently and uniformly with nonkeratinized stratified squamous epithelium of about 20–30 cell layers thick and which apparently withstand abrasive forces. The cell turnover time for the soft palate epithelium is about 5-6 days. The oral aspects of the palate, chiefly the anterior half are well gifted with seromucous glands, and small amounts of fatty tissues. The salivary glands secrete saliva around 750 ml which aid in moisturizing the palatal cavity to facilitate the dosage form adhesion [52]. These glandular secretions may serve as a glandular lubricant to reduce frictional forces. The ascending palatine branch of the facial artery and the greater palatine branch of the maxillary artery supply arterial blood to the soft palate. The blood supply by the facial artery to the palatal region is 0.89 ml/min/100 cm². The veins of the soft palate usually drain to the pterygoid venous plexus. The secretomotor supply to the majority of the mucosa of the soft palate moves via the lesser palatine nerve [53]. The soft palate region, floor of the mouth, sublingual, labial and buccal mucosa are the major absorption sites in the oral cavity; secondly the hard palate and gingival.

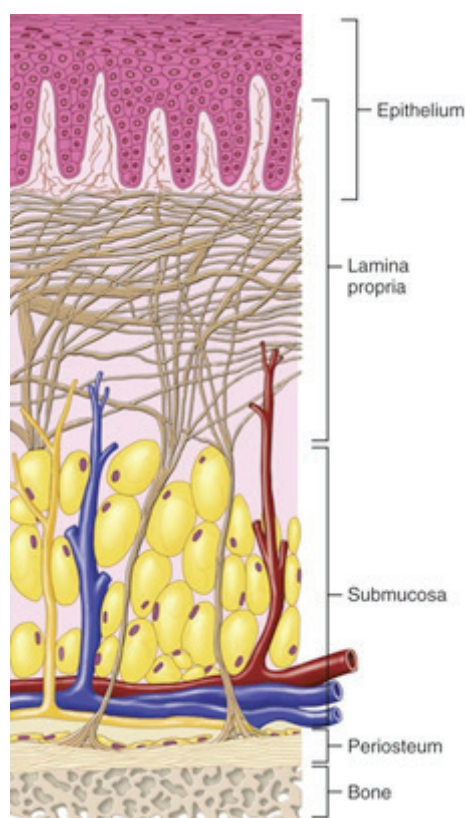


Fig.3. Histological overview of soft palate

3.2. Mucus physiology and its suitability

The oral epithelium is surrounded by a thin layer of mucus, the principle constituents made up of proteins and carbohydrates actually play a role in mucoadhesion and act as a lubricant, allowing cells to move relative to one another and helps in bioadhesion of mucoadhesive drug delivery systems [54]. The soft-palatal mucosa composed of stratum squamous epithelial cells, with thickness of about 100–200 μm consists of a nonkeratinized epithelial tissue with the absence of acrylamides with small amounts of lipids like cholesterol and glycosyl ceramides. The oral soft-palate mucosal permeability is about 4–4000 times more than the skin and the thickness of the palatal mucosa (158–224 μm) is intermediate between sublingual (111 μm) and buccal (594 μm) [55]. The mucosal pH of all oromucosal sites was ranged from 6.24 ± 0.05 to 7.36 ± 0.06 and mean pH values in the palate, buccal mucosa and the lingual were 6.8 ± 0.26 , 7.34 ± 0.38 , and 6.28 ± 0.36 , respectively. The mucosal pH aid in exploring as an optimal site for specific drug delivery since the palatal pH value (7.34 ± 0.38) is much more nearer to the pH value of blood as compared to the other oromucosal (buccal and sublingual) site and it also have the lowest salivary secretion measured by the Periotron method [56] emphasizing a major role in maintenance of suitable microenvironment because the salivary system is a powerful buffering system [57,58] usually capable of possessing a stable intraoral pH. The residual amounts of saliva on the oral mucosal tissues in the morning and afternoon were almost identical. The residual salivary thickness ranges from low of 0.16 ± 0.03 to high of 0.58 ± 0.05 in the lingual site; corresponding values for buccal ranged between 0.44 ± 0.06 to 1.13 ± 0.05 and 0.03 ± 0.003 mm on the soft palate [59]. Fortunately the enzyme activity is relatively low in the palatal mucosa comparatively with other mucosal area of the oral cavity [48, 55]. Due to this more promising characteristic, the soft palate route proves to be fitted for oromucosal controlled and sustained release of drugs.

3.2. Soft-palate mucosal suitability for drug diffusion

The oral mucosa is believed to be 4-4000 times more permeable than that of skin [60]. Squier and co-workers [61] revealed that the permeability of water through the buccal mucosa was approximately 10 times more, whilst in floor of the mouth the permeability was approximately 20 times more than skin. Though oral mucosa elicits various physiological challenges, its unique structural and physiological properties present numerous opportunities for systemic drug delivery. The thickness of the mucus is dependent on its location [62]. The thickness of the mucus blanket depends on the balance between the rate of secretion and the rate of shedding. Toxins and irritants can stimulate mucus secretion to a greater extent, increasing the thickness of the mucus blanket while efficiently and rapidly moving the irritants away from the epithelium

[63–65]. Secreting new mucus is markedly more efficient than simply washing the surface, because rinsing the surface fails to refresh the unstirred layer adhering to the epithelium. In contrast, by continuously secreting new mucus, the unstirred layer is continuously and rapidly replaced. Convection is also inhibited by formation of a lipid-rich mucin layer at the surface of the gel [66] which helps in holding the drug-delivery systems in position at this site. Due to a little fluid movement within the gel, solutes are assumed to permeate only by diffusion. The size and arrangement of mucin fibers contributes drastically to the kinetics of the diffusion process [67–69].

3.3. Factors affecting drug delivery through soft palate [70-76]

The lipid solubility of drugs is a prime factor for soft palate drug delivery. However with better lipid solubility, drugs chosen for oro-soft palatal drug delivery must have physiochemical properties, drug size and pKa value possible for drug movement through the mucosa at a rate capable of producing required therapeutic blood concentrations. The rate of absorption of hydrophilic compounds is a function of the molecular size. Smaller molecules (75-100 Da) normally exhibit rapid transport across the mucosa, with permeability decreases as molecular size increases. A weakly acidic and weakly basic drug exhibit appreciable lipid solubility and thus has ability to cross lipoidal biomembrane. Greater the lipid soluble a compound, higher is its absorption. The ionization of a drug is directly related to both its pKa and pH at the mucosal surface. The drug must resist, or be protected by salivary and tissue enzymes that could cause inactivation. The drug and bioadhesive polymers should not damage the oral cavity and the surrounding tissues by keratinolysis, discoloration or irritation etc.

3.4. Mechanism of drug transport via oro-soft palate

Drug can be transported across oro-soft palate by passive diffusion, carrier-mediated, active transport or other specialized mechanisms. Most predominant absorption mechanism is passive diffusion across lipid membranes via either the paracellular or transcellular pathways (Figure 3) [77]. The hydrophilic nature of the paracellular spaces and cytoplasm provides a permeability barrier to lipophilic drugs but can be favourable for hydrophilic drugs. In contrast, the transcellular pathway involves drugs penetrating through one cell and the next until entering the systemic circulation. The lipophilic cell membrane offers a preferable route for lipophilic drugs compared to hydrophilic compounds. Drugs can transverse both pathways simultaneously although one route could be predominant depending on the physicochemical properties of the drug [78].

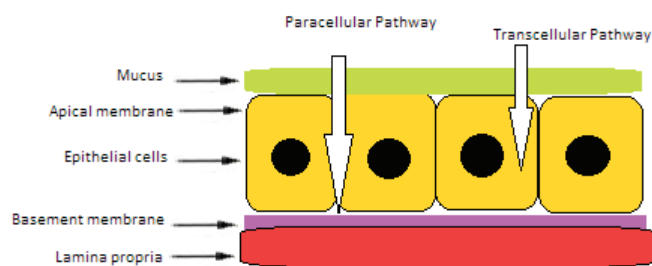


Fig 4. Mechanism of drug transport through soft palate mucosa

4. SOFT PALATE DRUG DELIVERY TECHNOLOGY

In the development of the soft palate drug delivery systems, mucoadhesion of the device is an important factor. Transmucosal drug-delivery system should rapidly attach to the mucosal surface and maintain a strong interaction without dislodgement. The term 'mucoadhesive' is usually meant for materials that bind to the mucin layer of a biological membrane. Mucoadhesive polymers can be utilized in efforts to achieve systemic delivery of drugs through the soft palate mucosae. Contact time should also be sufficiently long at the target site for complete drug release. As hydrophilic mucoadhesive polymers tend to lose adhesiveness upon hydration, restricted hydration and formation of a rigid gel network would be desirable for prolonged adhesion [79-87]. A short retention time, in relation to the drug release rate, will compromise bioavailability. The dosage form must provide reproducible effects at the retention site are also an important factor to be considered. An effective orotransmucosal drug-delivery system is that the mucoadhesion should not be impacted by surrounding pH of the site. Studies have shown that the bio-adhesiveness of polymers with ionizable groups is affected by the environment pH, it is noted that palatal pH is much more nearer to the pH of blood as compared to the other oromucosal (buccal and sublingual) site which makes it a suitable site for mucoadhesive drug-delivery systems. The fact that these mucoadhesive polymers are stable in the acidic environment of the stomach and at $\text{pH} \leq 7.4$ makes them ideal for targeted delivery to the palate, stomach and small intestine [88-96]. Mucoadhesive polymers should possess some general physiochemical features such as anionic hydrophilicity with hydrogen bond-forming groups, suitable surface wetting property with mucus/mucosal tissue surfaces and sufficient flexibility to penetrate the mucus network or tissue crevices for prolonged retention.

An ideal palatal drug-delivery system must meet several pre-requisites to be successful which is mainly depends on the mucoadhesive dosage forms, the potential impact of formulation excipients on the adhesive behavior of mucoadhesive drug-delivery systems and mucosal

surfaces also should be carefully taken into account. For example, excipients containing hydroxyl groups could form hydrogen bonds with the hydrophilic functional group of mucoadhesive polymers and, as a result, prevent their interaction with the mucosal surface [97]. In addition, hydrophobic lubricants (e.g., magnesium stearate and talc) tend to hinder the formation of strong bio-adhesive bonds and thus reduce the mucoadhesive strength significantly [98]. Therefore, in developing a mucoadhesive transmucosal dosage form, palatal mucosa serves as an excellent platform for delivery of variety of APIs by the help of a mucoadhesion concept. Continuous research into the improvement of the oral transmucosal delivery of drugs has resulted in the development of several conventional and novel dosage forms like solutions, tablets/lozenges, chewing gums, sprays, patches and films, hydrogels, hollow fibres and microspheres. The more recent dosage forms include pillar implants (ref) and bioplates [99]. These Oral transmucosal systems for systemic drug delivery are usually designed to deliver the drug for either i) rapid drug release for immediate and quick action, ii) pulsatile release with rapid appearance of drug into systemic circulation and subsequent maintenance of drug concentration within therapeutic profile or iii) controlled release for extended period of time. The more appropriate factors for delivery systems are shown below Table 1.

Table 1: Ideal factors for soft palatal drug delivery system design.

Factors	Explanation
Size of the dosage form	Dosage form should be of small size both by height and width due to limited area for mucoadhesion
Low dose of the drug molecule	High dose may be problematic due to the small surface area of soft palate
Mucosal adhesion	Involuntary swallowing of the system may possible if the mucoadhesion fails
Transport of drug across the soft palate mucosa	Drugs not absorbed by passive diffusion cannot be administered
pH of the absorption site	pH of the palatal mucosa 7.34 ± 0.38 (close to blood pH)
Venous drainage of the mucosal tissues	Venous drainage is not subjected to hepatic first-pass metabolism
Excipients for drug delivery	Excipients with unpleasant taste, odour may require suitable processing agents
Mucoadhesive agents Natural/synthetic	It should maintain an intimate and prolonged contact of the formulation over the site
Permeation enhancers	Required to improve drug permeation across mucosa
Enzyme inhibitors	To protect the drug from the degradation by some oral mucosal enzymes
Drug release	It should be unidirectional drug release to avoid wastage of drugs in the oral cavity

5. PERMEATION ENHANCERS SUITABLE FOR ORO-SOFT PALATE DELIVERY

The permeability barrier is probably the greatest challenge to overcome in order to be able to fully utilize the oral mucosa as a site for drug delivery. Attempts to reduce this barrier have been researched in the form of permeability enhancers [100-102]. Permeation enhancers are also required when an API has to reach the systemic circulation through the transmucosal route to exert its action. They must be non-irritant and have a reversible effect. The most common classes of permeation enhancers used for the orotransmucosal route listed in the table. (Table 2).

Table 2: List of permeation enhancer and its mechanism of action [103]

Classification	Examples	Mode of transport	Mechanism of action
Surfactants	Anionic Sodium lauryl sulfate Sodium laurate Laureth-9 Sodium dodecyl sulfate(SDS) Dioctyl Sodium sulfosuccinate	Paracellular	Perturbation of intercellular lipids, Protein domain integrity
	Nonionic Polyoxyethylene 9lauryl ethe(PLE) Tween80 Nonylp-henoxypolyoxyethylene(NPPOE) Polysorbates Sodium glycocholate	Paracellular	Perturbation of intercellular lipids, Protein domain integrity
	Cationic Cetylpyridinium chloride Chitosan, trimethyl chitosan, Poly L arginine, L	Paracellular	Ionic interaction with negative charge on the mucosal surface
Fatty acids and derivatives	Oleic acid Caprylic acid Mono(di)glycerides Lauric acid Linoleic acid Acylcholines, Acylcarnitine	Paracellular	Increase fluidity of phospholipids domains
Bile salts and derivatives	Sodium deoxycholate Sodium taurocholate Sodium taurodihydrofusidate(STDHF) Sodium glycodihydrofusidate Sodium glycocholate Sodium deoxycholate	Paracellular	Perturbation of intercellular lipids, Protein domain integrity
Sulfoxides	Dimethyl sulfoxide(DMSO) Decylmethyl sulfoxide	Paracellular	Perturbation of intercellular lipids Protein domain integrity
Chelating agents	EDTA Citric acid Salicylates	Paracellular	Interfere with Ca ²⁺
Monohydric alcohols	Ethanol Isopropanol	Paracellular	Disrupt arrangement of intercellular lipids
Polyols	Propylene glycol Polyethylene glycol Glycerol Propanediol	Paracellular	
Others (nonsurfactants)	Urea and derivative Unsaturated cyclic urea Azone(1dodecylazacycloheptan2 one) (laurocapram) Cyclodextrin	Paracellular	Perturbation of intercellular lipids, Protein domain integrity

5.1. Ideal characteristics of Permeation Enhancers [104,105]

- It should enhance the permeation of the poorly diffusible drugs
- It should be pharmacologically inert
- It should be chemically stable
- It should be compatible with other excipients and drugs
- It should be non toxic, non irritant and non allergic
- It should be biocompatible and biodegradable

Though, soft palate drug delivery penetration route assessment is significant because it has smooth and flexible surface which is more appropriate for a better permeability of the drug with the use of a suitable permeation enhancer.

5.2. Mechanisms of action of permeation enhancers [106,107]

The effect of penetration enhancers for mucosal absorption revealed by various literature sources revealed that the altered rheological behavior with a varying thickness of viscoelastic layer of the mucus often due to the changing environment of the oral cavity eventually affects drug absorption. Additionally, saliva covering the mucus layers also hinders the absorption. Permeation enhancers act by diminishing the viscosity of the mucus and saliva thereby overcoming the barrier for drug absorption however, the most favored mechanism of mucosal drug absorption is intracellular route. Some permeation enhancers disturb the intracellular lipid layers, increasing the fluidity of lipid bilayer membrane by interaction with lipid or protein components so that the drug delivery is facilitated. Permeation enhancers act on desmosomes, a chief component at the tight junctions of the cells causing enhanced absorption of poorly absorbed drugs. Permeation enhancers also act by overcoming the enzymatic barrier by blocking the action of various peptidases and proteases present in the mucosa. In addition with change in membrane fluidity also modify the enzymatic activity indirectly. Some permeation enhancers increase the solubility of the drugs by changing the partition coefficient of the drug. This leads to improved thermodynamic activity resulting in improved drug absorption.

6. ORAL SOFT PALATE MUCOSAL DOSAGE FORM STRATEGIES

The development of “non-attached” or “mobile” drug-delivery system is that would be physically maintained within the oral cavity in contact with a mucosal surface by a conscious

effort by the patient. Three types of non-attached drug-delivery systems are can be indentified are fast dissolving tablets, medicated chewing gum, drug loaded microporous hollow fibers [110–118]. However these delivery systems proved to be feasible for administration through the oral mucosa, there are some limitations. Research in this area has focused on the development of retentive oral mucosal drug delivery systems. A tremendous research has done by developing novel dosage forms for prolonging the duration of the absorption process. This impose that the dosage form should be remain sufficiently for a certain period of time and should release the drug in a controlled manner with a sufficient drug concentration delivered via the oral mucosa. To achieve this, a suitable drug delivery strategy is the design of “bioadhesive/immobilized” drug delivery system which can be retained on the mucosal surface by the use of suitable adhesive system [108,109].

6.1. Bioadhesive drug-delivery system

In recent years several bioadhesive dosage forms for oral mucosal drug administration have developed and some are available commercially. The subject of intensive research in this newest area is the one which offer advantage over non-attached systems for oral delivery. These include: (i) the immobilisation permit an intimate contact to be developed between the drug dosage form and the mucosa; (ii) a high drug concentration maintenance at the absorptive surface for a prolonged period of time; (iii) the dosage form can be immobilised specifically at major parts of the mucosa like buccal, labial, sublingual, palatal or gingival mucosa; and (iv) the system itself can protect the drug from environmental degradation.

The design of bioadhesive oral mucosal drug-delivery systems is relatively difficult because it is necessary to have two definite properties to the delivery system (i) Immobilisation (ii) Controlled drug release. Such dual properties within a single system can be attained by the use of smart polymers. By the concept of bioadhesion or mucoadhesion by using adhesive smart polymers it is possible to achieve the both immobilisation and controlled or sustained release of the drug. Development of mucoadhesive drug delivery systems intended for oral administration has been more growing area recent research. A pioneering approach was made by formulating mucoadhesive bioplate for soft palatal delivery of gentamicin and amikacin using natural mucaodehsive material extracted from various fruits and kernels/seeds [45,46,51,52]. Various immobilized drug delivery systems are shown below (Table 3).

Table 3: Different types of immobilized drug delivery systems.

Immobilized system	References
Powders	[91]
Microspheres	[92]
Tablets	[94–108]
Hydrogels	[109–115]
Film	[16–117]
Patches	[118–122]
Bioplate	[45,46,52]

7. EXPERIMENTAL MODEL FOR THE SOFT PALATAL DRUG PERMEATION STUDY [46, 51, 52]

Selection of an appropriate formulation for the delivery of drug through orosoft palatal mucosa depends mainly on the absorption criteria of the API. Due to which an *in vitro* palatal mucosal absorption study should also be performed. Palatal mucosal tissue of the animal which closely resembles the histology of the human soft palate mucosa can be selected for the study. As soon as the animal is slaughtered soft palate is dissected and removed carefully by clearing off all the tissues debris. The isolated soft palate tissue is stored in a refrigerator at about 4-5°C in Kreb's buffer or Ringer lactate solution until used. The isolated and preserved soft palate tissue is mounted on a diffusion study apparatus to study for the drug permeation using appropriate buffer solution. The tissue viability and integrity can be assessed by the permeation study that if the drug permeability does not change throughout the study time under a specified experimental pH and temperature, then the tissue is considered to be viable since it a great concern during the *in vitro* diffusion study. Similarly *in vivo* study can also be performed for the drug permeation study through the palatal mucosa.

8. ADVANTAGES OF THE SOFT PALATE DRUG DELIVERY

Soft palate is highly vascularized site with low enzyme activity as compared to other oral mucosal regions.

Rapid cellular recovery of the mucosa is an advantage for drug delivery.

Devoid of mechanical irritation and local discomfort due to its smooth surface and good flexibility.

It avoids the acid hydrolysis of drug in the GIT.

It can reduce hepatic side effects of drugs and avoid first pass metabolism.

Soft palatal medication can delivers steady infusion of drugs over an extended period.

Adverse effects and therapeutic failures frequently associated with intermittent dosing can be avoided.

Daily low dose of the drug can be elicited with equivalent therapeutics effect as compared with orally administered drug.

Drug showing poor and erratic absorption from the stomach or intestine can be administered via this route.

Therapeutic serum concentration can be achieved rapidly with greater bioavailability

Permeability coefficient is consistently higher in comparison to normal and hydrated skin.

Permeation enhancers or Peptide stabilizers can be used to modify the drug release from the dosage forms.

It can overcome the inconvenience caused by pain, tissue damage, and probable inflection by parenteral route.

Self medication is possible with proper patient counseling and termination of the drug delivery is achieved by removal of the dosage form from the site.

It provides a high patient acceptability as comparatively over other non-oral routes of drug administration.

9. LIMITATIONS OF SOFT PALATAL DELIVERY

Muco-irritable APIs and drugs are not suitable for delivery. Drugs which are unstable at oral pH cannot be administered via this route.

Drugs not absorbed by passive diffusion cannot be administered.

Drug having unpleasant taste and odor cannot be administered.

Inconvenience of dosage forms while eating or drinking.

Accidental swallowing of the dosage system, if mucoadhesion fails.

Dislodgement of bioadhesive device due to overhydration and swelling.

Loss of drug in the saliva, if the dosage form is not protected by impermeable backing membrane.

Surgical repair of soft palate tissue impose problem placing the dosage form.

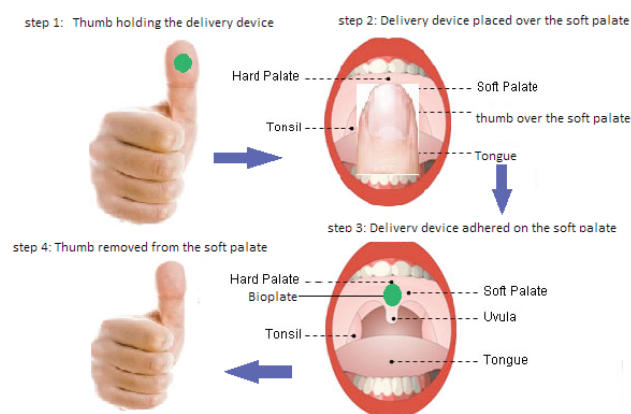
10. COUNSELING STEPS FOR PLACING THE DOSAGE FORM

Place the dosage form over the thumb

Locate the soft palate in the upper roof of the mouth

Attach the dosage form over the soft palate surface with minimal pressure

Remove the thumb gently leaving the adhered dosage form over the soft palate



11. FUTURE PERSPECTIVES

The oral route has undergone considerable research for the drug delivery. The other delivery routes chasing behind through research using novel formulations. Soft palatal site is a promising area for continued research with the aim of systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of protein and peptides. Although mobilized drug delivery systems are available in the market with few beneficial effects towards the drug delivery in the oral cavity they impose some limitations. Immobilized drug delivery systems are still to achieve their persona through oral transmucosal delivery. There is a need and challenge of needle-free vaccine delivery to obtain enhanced immunity. Research focuses on overcoming the hurdles of vaccine delivery towards an alternative delivery systems, tailored adjuvant technologies and novel route of administrations. Presently, invasive mode of vaccines administered via the parenteral route can trigger the systemic immune response analogous as that of parenterally-delivered vaccine. The effective mucosal vaccines will not provide adequate mucosal immune protection. At this juncture it is important to examine the development of mucosal vaccination strategies that can effectively trigger systemic as well as mucosal immunity. The potential of the soft palate site can be extended for the delivery of vaccines using nanocarrier systems such as multiple emulsions, liposomes, nanoparticles, and dendrimers etc. However a need for safe and effective permeation/absorption enhancers is essential for permeability through transsoft palatal mucosa. Rational design of formulations for soft palate drug delivery needs further attention towards vehicle property, polymeric nature that optimizes the retention, controlled release and noninvasive delivery of drugs. The use of lipids, nanostructured materials and amorphous form of

API and solid dispersions on a micro or nanoscale may be the technology of the future for orosoft palatal delivery.

12. CONCLUSION

The oral cavity for long has been a site of medicinal application in order to treat diseases in the mouth itself. The soft palatal site offers promising scope for controlled drug delivery. The mucosa possesses both vascular and lymphatic drainage. The soft palate delivery avoids first pass metabolism and presystemic elimination of the drug. This novel site is well suited for bioadhesive drug delivery devices and proves to be accepted by the patient. With the tailor-made device loaded with appropriate dose of the drug systemic delivery can be achieved in a controlled manner adapting with mucosal surface

permeability and environment. A pioneering approach was made by formulating mucoadhesive bioplate for soft palatal delivery of gentamicin and amikacin and evaluated for its mucoadhesiveness and drug permeability which revealed more promising results. The soft palatal offers a choice of noninvasive route for protein and peptides delivery. In near future this novel platform certainly gains more significance and motivate researchers both from academia and industry.

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Oral-yumuşak damak mukozasına uygulanan akıllı ilaç taşıyıcılar: Veriler ve geleceğin trendleri

ÖZET

Son yıllarda, dünyanın her yerinde eczacılık alanında çalışan bilim adamları, enjeksiyonlara alternatif olarak transdermal ve transmukozal yolları araştırmaya çalışıyorlar. İlaçların potansiyel terapötik ajan olarak oral uygulanmalarındaki esas engel, bunların yüksek oranda presistemik olarak metabolize olmaları, yetersiz ve değişken oral absorpsiyonla birlikte asidik ortamda da stabil olmamalarıdır. Parenteral yol, oral olarak etkisiz ilaçlarla ilgili bütün çekincelerin üstesinden gelen tek yoldur. Bununla birlikte, parenteral formülasyonlar pahalıdır, daha az hasta uyuncu ve diğer zararlı etkilerle birlikte sık uygulama da gerektirir. Oral transmukozal ilaç taşınması eski çağlardan beri ilaçların sistemik uygulanmasında yoğun ilgi görmüş, oromukozal yolla daha iyi sistemik biyoyararlanım sağlandığı kanıtlanmıştır. Oral mukozal ilaç taşınması, sistemik ilaç taşınması için hem parenteral hem de oral yöntemlere göre birçok avantaj sunan alternatif bir yol sağlar. Oral mukozal yüksek oranda vaskülarizedir, dolayısıyla ilaçlar gastrointestinal

bölgedeki enzimleri ve karaciğerdeki ilk geçiş etkisini atlayarak, oral mukozadan absorblanır ve doğrudan sistemik dolaşıma geçer. Dilaltı ve bukkal bölge absorpsiyon için uygun transmukozal alanlardır, bundan başka terapötik ajanların sistemik uygulanması için çok uygun ve kolaylıkla erişilebilir yeni bir alan olarak yumuşak damak mukozası da bulunmuştur. Bu alan yeterli kan akımına sahip, strese maruziyet sonrası hızlı selüler düzelmeye gösteren, mekanik iritasyonun olmadığı esnek ve düz yüzeye sahip olmasıyla birlikte, lokal rahatsızlık oluşturabilecek ve girişimsel olmayan bir yoldur. Son zamanlarda yumuşak damak yolu, mukoadeziv ilaç taşıyıcı dozaj şekillerini kullanarak ilaç uygulanması için bukkal yola alternatif olarak bilim adamlarının daha çok dikkatini çekmektedir. Bu derleme yeni yumuşak damak yolundaki ve ilaçları bu yeni yumuşak damak yoluyla uygulamaya yönelik dozaj formları tasarlamak için kullanılan formülasyon stratejilerindeki daha güncel gelişmelere odaklanmıştır.

Anahtar kelimeler: Transmukozal ilaç taşıma, yumuşak damak, permeabilite ve yenilikçi platform

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