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Review Article

Oral Transmucosal Delivery Systems: Exploring Innovative Dosage Forms, Current Industrial Applications and Regulatory View

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ABSTRACT

Oral transmucosal drug delivery systems represent an innovative approach for the administration of therapeutic agents through the mucosal membranes, such as sublingual and buccal membranes in the mouth, offering advantages of rapid onset of action, bypass the first pass metabolism, and enhanced patient compliance. Current review explores the various dosage forms of oral transmucosal delivery, highlighting their unique formulations and delivery mechanisms. This review also discusses the cutting-edge technologies driving the development of transmucosal systems, such as mucoadhesive polymers, permeation enhancers, which improve bioavailability and therapeutic efficacy. Furthermore, the industrial applications of transmucosal drug delivery systems are examined in light of current market trends, with an emphasis on their use in pain management, hormone therapy, and emergency care. The review article also covers the regulatory challenges and commercialization of oral transmucosal products, detailing the impact of agencies such as the US FDA, Europe EMA and Central Drugs Standard Control Organization (CDSCO) on product development, and safety assessments. In conclusion, while oral transmucosal drug delivery systems have demonstrated significant potential, continued research, innovation, and regulatory clarity are required to fully harness their benefits in diverse therapeutic areas.

Keywords: Buccal Delivery, Mucoadhesive Polymers, Regulatory view, Sublingual, Transmucosal Drug Delivery.

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INTRODUCTION

Oral Transmucosal Drug Delivery Systems (OTDDS) refers to the administration of pharmaceutically active substances through the mucous membranes within the oral cavity, enabling direct absorption into the systemic circulation. This method leverages the rich vascularization of the oral mucosa to facilitate rapid and efficient drug absorption. The oral transmucosal route can be divided into two primary delivery pathways: the buccal route and the sublingual route (Lam *et al*., 2014; Palem *et al*., 2011).

In the buccal route, the drug is absorbed through the buccal mucosa, which is located on the inner lining of the cheek and gum. This pathway allows for the drug to be absorbed directly into the bloodstream through the blood vessels beneath the mucosal surface (Squier and Brogden, 2011). Conversely, in the sublingual route, the drug is absorbed via the mucosa on the ventral surface of the tongue and the floor of the mouth, which also provides a direct path into systemic circulation (Gilhotra *et al*., 2014).

The oral transmucosal delivery route offers several advantages over conventional drug administration methods, such as oral ingestion. Notably, it allows for the bypassing of first-pass metabolism, a key challenge associated with oral drug administration, where the liver metabolizes a significant portion of the drug before it reaches systemic circulation. By circumventing this process, transmucosal delivery increases the bioavailability of the drug (Palem *et al*., 2011). Additionally, OTDDS avoids the harsh conditions of the gastrointestinal tract, such as acidic pH and digestive enzymes, which can degrade many drugs when taken orally. Furthermore, oral transmucosal systems provide a rapid onset of action, making them especially beneficial for conditions requiring quick therapeutic responses, such as pain relief or emergency treatments. These systems also offer improved patient compliance, as they eliminate the need for injections and are often more convenient,

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discreet, and comfortable for patients to use (Khanvilkar *et al.*, 2001). As a result, oral transmucosal drug delivery has emerged as a promising alternative to traditional drug delivery methods, with applications in a wide range of therapeutic areas, including pain management, hormone replacement therapy, and the treatment of acute medical conditions. The current review article covers the regulatory challenges and commercialization of oral transmucosal products, detailing the impact of agencies such as the US FDA and Europe EMA on product development, and safety assessments.

ORAL MUCOSA

Oral Mucosa - Anatomy and Physiology

The oral mucosa, which serves as the primary site for oral transmucosal drug delivery, has a total surface area of approximately 200 cm^2. It is composed of three distinct layers: the epithelial layer, the basement membrane, and the lamina propria (Figure 1), each of which plays a critical role in the absorption and barrier functions of the mucosa (Bagan *et al.*, 2012).

The epithelial layer, which is about 40-50 cell layers thick, forms the outermost protective barrier of the oral mucosa. It is composed of stratified squamous cells that function as a defence mechanism, protecting the underlying tissues from harmful substances, pathogens, and microorganisms present in the oral cavity (Palem *et al.*, 2011). Additionally, the epithelium helps to regulate the loss of fluids from the deeper tissues, maintaining the hydration and integrity of the oral mucosa. Its dense structure makes it a primary obstacle for drug penetration, requiring the formulation of drugs in specific forms that can overcome this barrier for effective transmucosal delivery (Palem *et al.*, 2012).

Beneath the epithelial layer lies the basement membrane, which is approximately 1-2 µ thick. This membrane serves as a selective barrier, limiting the diffusion of larger or more complex molecules and proteins. While it contributes to the overall protection of the mucosal tissues, it also presents a challenge for the absorption of certain drugs. To facilitate the efficient penetration of drugs, formulation strategies often aim to enhance permeability or temporarily disrupt the basement membrane's restrictive properties.

The lamina propria, the layer beneath the basement membrane, is composed of connective tissue rich in blood vessels, lymphatic vessels, and extracellular matrix components. This layer is responsible for providing structural support and maintaining the mechanical properties of the oral mucosa. The blood supply in the lamina propria is crucial for the systemic absorption of drugs. Through this vascular network, molecules that successfully penetrate the epithelial barrier are transported into the bloodstream, allowing for rapid entry into systemic circulation a key benefit of oral transmucosal delivery. The lamina propria thus plays an essential role in facilitating the passage of therapeutic agents from the oral cavity into the body, contributing to the efficiency and bioavailability of transmucosal drug delivery systems (Boddupalli *et al.*, 2010). Together, these three layers epithelium, basement membrane, and lamina propria form a complex, dynamic structure that acts as both a protective barrier and a conduit for drug absorption, making them pivotal in the design and optimization of oral transmucosal drug delivery systems.

Mechanism and Theories of Mucoadhesion

Mucoadhesion is the process by which two surfaces adhere to one another, with at least one of those surfaces being a mucous membrane.

The formation of a mucoadhesive bond typically occurs in three distinct steps (Figure 2). One of the three is wetting and swelling of the polymer - the mucoadhesive formulation begins to adhere to the mucous membrane due to surface tension and the attractive forces present at the adsorption site. Polymers in the formulation have an affinity for water, causing them to absorb moisture and swell upon contact with the mucus layer. This swelling enhances the intimate contact between the mucoadhesive material and the mucosal surface, facilitating the initial adhesion. Two of three step is interpenetration between polymer chains and the mucosal membrane - once the polymer swells, there is an interdiffusion or interpenetration of the polymer chains with the mucous gel network. This results in the formation of a contact area between the polymer and the mucosal surface. The extent of interpenetration how deeply the polymer chains infiltrate the mucus, determines the strength and stability of the adhesive bond. The more extensive the interpenetration, the stronger the adhesive interaction between the polymer and the mucous membrane. Three of three step is formation of chemical bonds between the entangled chains - in the final stage, the polymer chains become physically entangled with the mucin molecules present in the mucus. This entanglement is accompanied by the formation of various types of chemical bonds, such as covalent bonds, hydrogen bonds, and van der Waals interactions, between the polymer and the mucous membrane. These interactions further strengthen the mucoadhesive bond, ensuring that the mucoadhesive formulation remains in place for prolonged periods, which is crucial for effective drug delivery. Together, these three steps wetting, swelling, interpenetration, and chemical bond formation contribute to the overall mucoadhesion process, ensuring that the formulation can securely adhere to the mucosal surface for efficient drug delivery (Pooja *et al.*, 2014).

There are several theories includes wetting theory, adsorption theory, electrostatic theory, fracture theory, diffusion theory, and mechanical theory (Figure 3) that explain the phenomenon of mucoadhesion, each focusing on different aspects of the interaction between mucoadhesive materials and the mucosal surface (Palem *et al.*, 2010).

TRANSMUCOSAL DOSAGE FORMS

Various transmucosal dosage forms have been developed, each designed to optimize drug absorption and efficacy through specific mucosal sites, such as the oral cavity, and other mucosal membranes. Below are the different dosage forms classified into conventional and novel / advanced transmucosal dosage forms used in modern pharmaceutical applications.

Conventional transmucosal dosage forms

Tablets are small, flat and oval with a diameter of 5-8 mm and thickness of 2 mm. Tablet is the most common dosage form for oral transmucosal delivery, because of its low cost of production and ease of administration. Orally disintegrating formulations and mucoadhesive formulations are the two major types of formulations for oral transmucosal administration. Orally disintegrating tablets usually have a short residence time, fast disintegration and dissolution in saliva without water consumption. Mucoadhesive formulations are used for buccal administration, offering extended release. Usually, transmucosal tablets exhibit inter and intra-individual variation in absorption and bioavailability as it is difficult to control drug concentration, as the media is constantly diluted by saliva (Senel *et al.*, 2012).

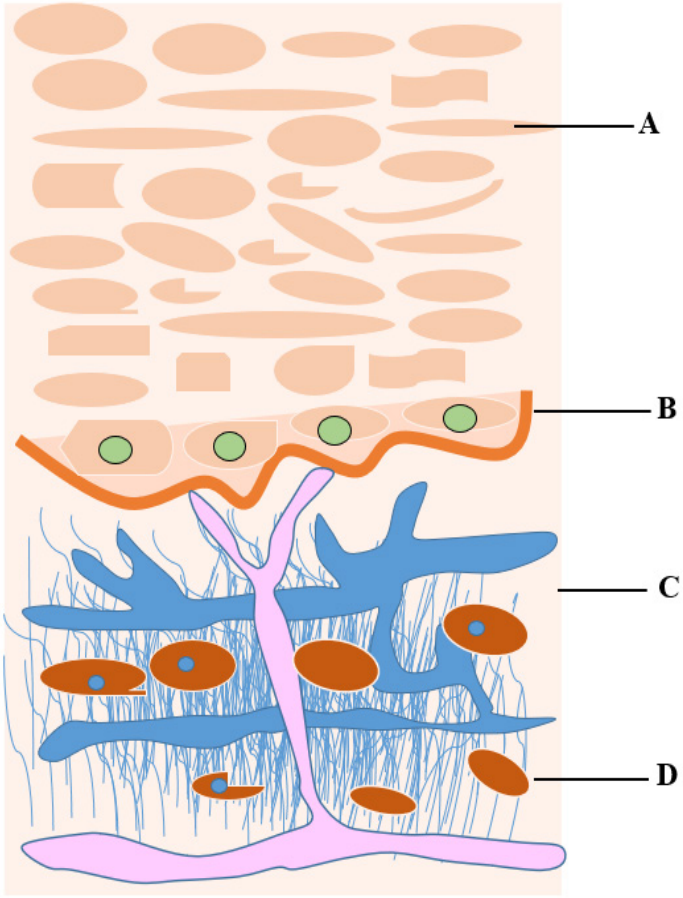

Figure 1: Cross-sectional representation of Oral mucosa: A. Oral epithelium, B. Basement membrane, C. *Lamina propria* and D. Sub mucosa.

Lozenges are solid preparations in a flavored, sweetened compressed base containing one or more medicaments. They gradually dissolve on the back surface of the tongue and provide local drug delivery to the mouth, tongue etc., Lozenges are used to maximize the local drug activity. Gels and ointments are semi-solid dosage forms and they have the advantage of ease of dispersion throughout the oral mucosa, rapidly release drug at the absorption site by forming an intimate contact with the mucosal membrane. These are of limited use for drugs with a narrow therapeutic window because the residence time of gels is small due to washing away by saliva (Needleman *et al.*, 1998).

Advanced transmucosal dosage forms

Sprays

An ideal spray system produces spray patterns of a suitable ovality and particle size and will deliver it in an appropriate unit dose volume. Sprays produce a very fine mist, which coat the entire oral mucosa, thereby increasing the total surface area through which drug molecules can be absorbed (Hiremath *et al.*, 2011). Spray delivers the drug as fine particles or droplets, hence the lag time for the drug at the site of absorption is reduced. Sprays have a fast onset of action and longer duration of action. Rapid and extensive drug absorption is observed due to large surface area of the mucosa. The formulation of spray generally consists of two essential components - product concentrate and propellant. The product concentrate consists of the active ingredient and other excipients such as penetration enhancers, solvents, antioxidants, flavoring agents, sweeteners, preservatives, acidifying agents, and co solvent. Propellant provides the driving force to expel the product concentrate from the container. It is also responsible for developing proper pressure in the container. Propellants can be either liquefied gases or compressed gases. When the propellant is a liquefied gas, it also functions as a solvent or vehicle for the product concentrate. The propellant used should be pure, non-toxic, non-reactive, chemically inert and should have good solvent action on various active ingredients (Parmar and Patel, 2017). Oral insulin spray is used as an alternative to the insulin injections. The insulin spray (Oralin), has rapid absorption and a comparable metabolic control in both type 1 and type 2 diabetic patients, when compared with subcutaneous insulin injection. Glytrin Spray is a sublingual spray that contains glyceryl trinitrate and produces relief from angina attacks (Palem *et al.*, 2016; Parmar *et al.*, 2022).

Microparticles and Nanoparticles

Microparticles and nanoparticles diffuse into the mucous gel layer by virtue of their small size. These formulations maintain an intimate contact between the drug and the buccal mucosa. Microparticles and nanoparticles are versatile carriers that can be tailored to offer enhanced permeability across the buccal epithelium. These particles can be embedded into films, patches or gels. Permeability enhancers and protease inhibitors are

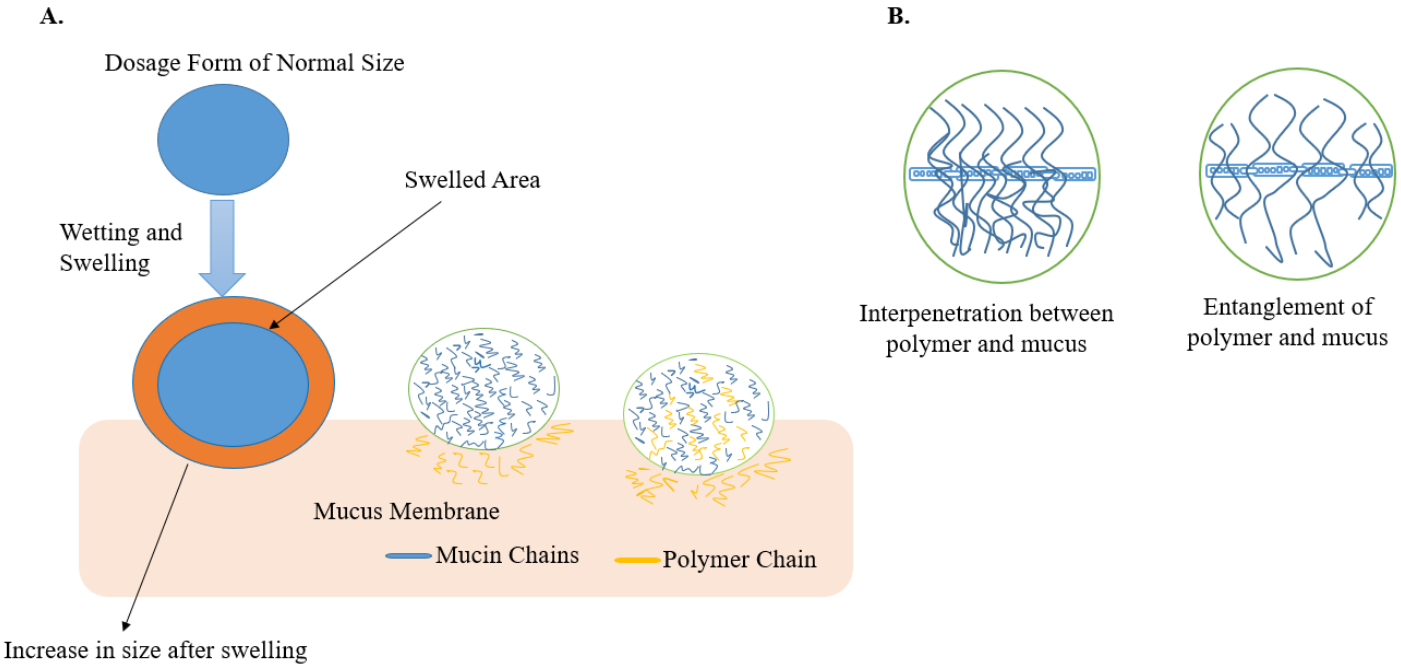

Figure 2: Mechanism of Mucoadhesion and different steps involved A). Wetting and swelling of polymers; B). Interpenetration between polymer chains and mucosal membrane; C). Formation of chemical bonds between the entangled chains.

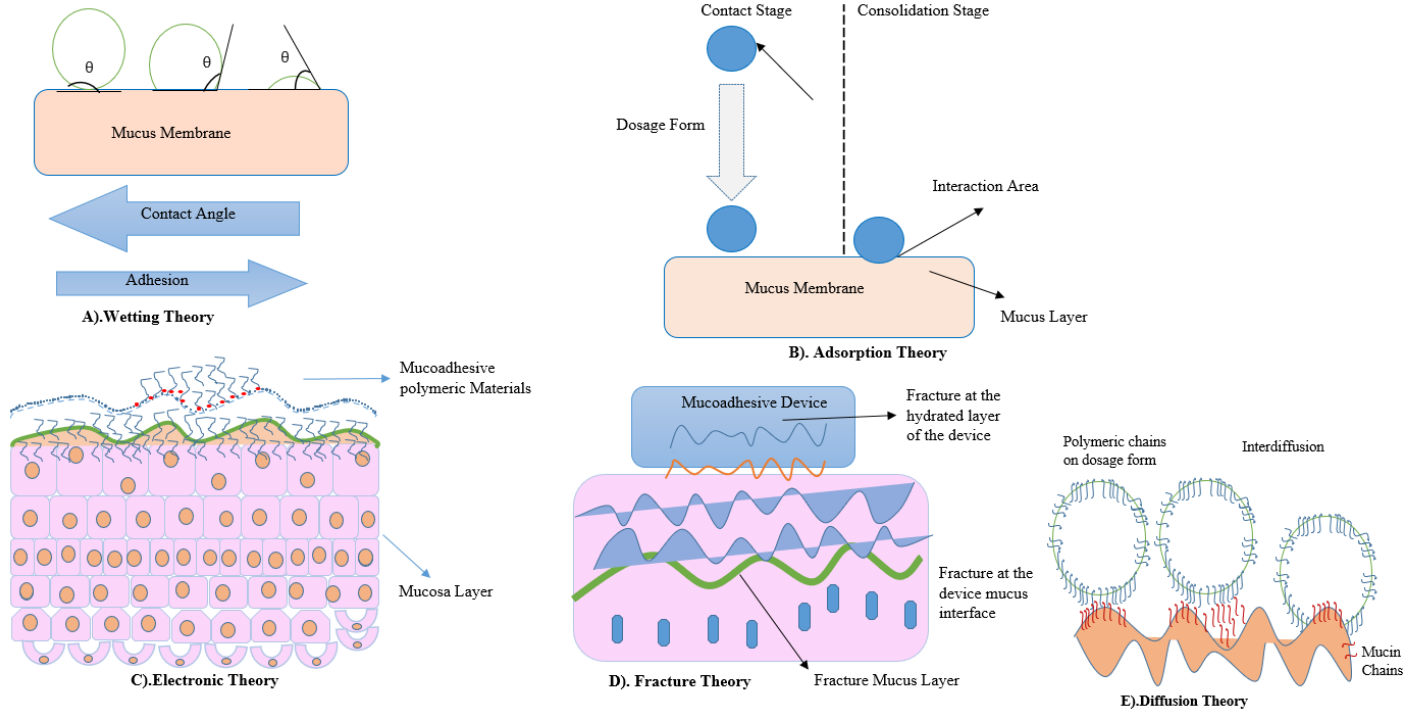

Figure 3: Theories of Mucoadhesion – A). Wetting theory; B). Adsorption theory; C). Electronic theory; D). Fracture theory E). Diffusion theory.

Table 1: Transmucosal dosage forms - basic components, examples and applications.

Component	Use of component in transmucosal delivery	Examples
Film-forming polymer (40-50%)	Polymers provide structural integrity to the films and facilitate disintegration. Hydrophilic polymers are used so that film can dissolve rapidly in the oral cavity and enter into systemic circulation. Polymers can be used alone or in combination to achieve the desired film properties.	Natural - pectin, pullulan, sodium alginate, gelatin, sodium starch glycolate, maltodextrin.
		Synthetic - hydroxy propyl cellulose, hydroxy propyl methylcellulose, sodium carboxymethyl cellulose, croscarmellose sodium, polyvinyl alcohol, polyethylene oxide, polyvinyl pyrrolidone, kollicoat, eudragit.
Plasticizer (0-20%)	Plasticizers increase the flexibility and tensile strength of the film. They lower the Tg of the polymer thus, reducing the friability of the film. Plasticizers must be compatible with the drug, solvent, and polymer used.	Glycerine, propylene glycol, polyethylene glycol, sorbitol, malic acid, diethyl phthalate, tributyl citrate, triethyl citrate, triacetin and castor oil.
Saliva stimulating agent (2-6%)	These agents increase the production of saliva and help to disintegrate and dissolve the film at a faster rate. The acids generally used in food production are utilized as saliva stimulating agents. Citric acid is the most preferred among them.	Ascorbic acid, malic acid, citric acid, tartaric acid, and lactic acid
Sweetening agent (3-6%)	These agents are used to improve the taste and patient compliance by masking the unpleasant taste of the API.	Natural - xylose, ribose, glucose, sucrose, maltose, dextrose, mannitol, sorbitol, fructose, liquid Glucose, isomaltose
		Synthetic - aspartame, saccharin, sucralose, cyclamates, Acesulfame k, neotame
Surfactant (q.s)	Surfactants act as wetting agents, helping the film to dissolve in a short time and release the API quickly.	Sodium lauryl sulfate poloxamer 407, polysorbate
Superdisintegrant (0-8%)	These agents cause rapid disintegration due to the combined effect of swelling and water absorption. Super Disintegrants absorb water and swell, thus improving disintegration and dissolution.	Sodium starch glycollate, cross povidone, polacrilin potassium.
Flavoring agent (q.s)	These agents impart flavor to the formulation. Flavoring agent should be compatible with the API and other excipients.	Peppermint, cinnamon, mint, raspberry, cherry, strawberry, maple, vanilla, berry
Coloring agent (q.s)	These agents impart color to the formulation. Coloring agents are selected according to the flavor used. FDandC approved coloring agents are incorporated in the oral film.	Titanium oxide, silicon oxide
Active pharmaceutical ingredient (5-30%)	It is the primary component that provides the therapeutic effect. Micronized API can improve the texture, dissolution and uniformity of the film.	Montelukast sodium, triclosan, metoclopramide hydrochloride, telmisartan, amlodipine, dicyclomine hydrochloride, ropinirole hydrochloride.

used to improve the bioavailability of drugs delivered through the oral transmucosal route. Microparticles and nanoparticles offer several advantages such as increase in the diffusion rate of the drug across the mucus layer, protection of the drug from degradation, prolonging the drug residence and contact time with the mucosa, controlled drug release profile resulting in a decreased number of administrations. These are used to improve the overall pharmacokinetics and pharmacodynamics of the drugs. Microparticles and nanoparticles with neutral charge or positive charge exhibit better mucoadhesion due to the negative charge of the mucus. The particles designed with hydrophilic polymers have a favorable permeation owing to the aqueous nature of saliva (Macedo *et al.*, 2020).

The uptake of drug-loaded microparticles and nanoparticles through the oral epithelium occurs by two major pathways: the transcellular route (directly through the epithelial cells) and the paracellular route (through the intercellular space between the epithelial cells). The delivery of therapeutic proteins and peptides by the buccal mucosa has gained popularity over the years. These drugs have high molecular weight that hinders their permeation through the intestinal epithelium and undergo enzymatic degradation in the gastrointestinal tract. Nanoparticles have

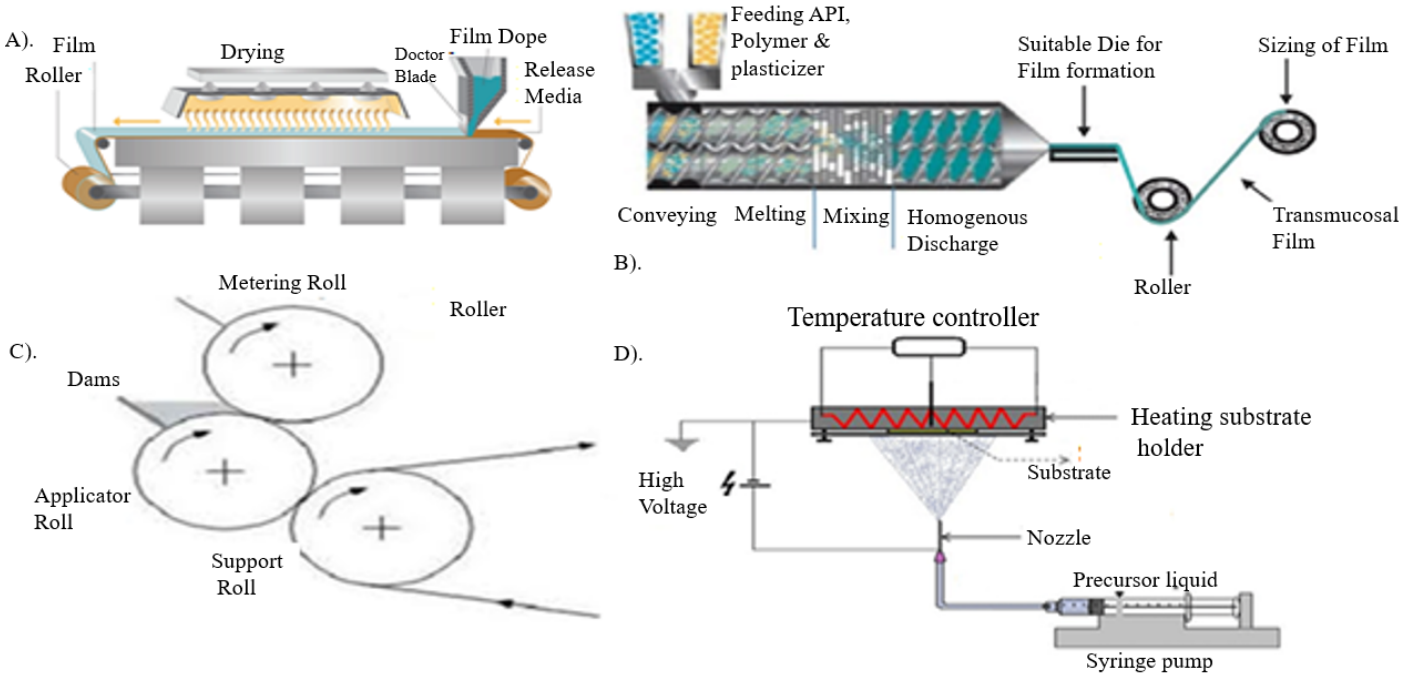

Figure 4: Manufacturing methods of Transmucosal films - A). Solvent based film casting system; B). Hot melt extrusion method; C). Rolling method; D). Electro spraying method.

taken the lead for the development of proteins delivery systems due to their ability to facilitate the buccal uptake and protect their bioactivity (Palem *et al*., 2012; Hua, 2019).

In situ gels

Conventional dosage forms have problems related to rapid drug loss at the application site. These limitations could be overcome by *in situ* gels that are administered as viscous fluids. These liquids undergo a transition to gels or solid depots after application, under the influence of various stimuli. The mucoadhesivity of polymers prolongs the retention time of the dosage form at the application site with sustained or controlled release of the drug (Simona *et al*., 2024). The administration of *in situ* gelling systems in the oral cavity has been principally studied for the local treatment of oral mucositis to control the pain, modulate the inflammatory response, enhance the wound healing process and prevent bacterial and fungal infections. It creates a protective layer on the ulcerative lesions that reduces the risk of microorganism infections. The design and composition of *in situ* gelling systems ensure prolonged residence time at the injury site and sustained drug release, to avoid repeated administrations (Vigani *et al*., 2020).

Transmucosal Films

Oral transmucosal films are flexible, ultra-thin films designed to rapidly disintegrate and dissolve, releasing the Active Pharmaceutical Ingredient (API) directly into the oral cavity. They consist of a mucoadhesive layer in which the drug is dissolved and a drug-free backing layer that acts as a shield for the drug from the oral cavity. This ensures that unidirectional drug release to the oral mucosa is achieved. Oral transmucosal films have several unique features, which include rapid onset of drug delivery, sustained drug release and less inter- and intra-individual variability (Vasisht *et al*., 2010). The selection of polymers, excipients, and manufacturing methods for transmucosal drug delivery plays a key role in developing stable, effective, and patient-friendly formulations. The primary role of polymers in transmucosal drug delivery systems is to serve as matrices for drug release and to maintain the integrity and stability of the dosage form during its residence in the mouth. These polymers should be non-toxic, biocompatible, and able to facilitate drug release through the mucosal membranes and classified the polymers used in transmucosal delivery based on source (natural, semi-synthetic and synthetic); based on solubility (water soluble and water insoluble); based on charge (anionic, cationic and non-inonic) and based on potential adhesive forces (covalent, hydrogen bond and electrostatic interaction) (Rewathi *et al*., 2014).

The choice and classification of excipients used in transmucosal delivery are presented in Table 1. Excipient selection is crucial in the formulation's stability, drug release, and bioavailability (Sevinc and Ozakar, 2021). Key excipients used in transmucosal delivery includes sweeteners, flavoring agents, disintegrates, plasticizers, stabilizers etc. Manufacturing methods like film casting, hot melt extrusion, rolling method and electro spraying provide a range of options for formulating transmucosal systems (Figure 4) are discussed in detail.

Solvent casting

It is the most preferred method to manufacture of films. Water-soluble components are prepared by mixing on a magnetic stirrer. API and other excipients are then added to the above mixture to obtain a viscous solution. The solution is then poured into a petri dish and the solvents are allowed to evaporate either at room temperature or in the oven for a short period of time.

Hot melt extrusion

Polymers that have low molecular weight and low viscosity are preferred in this method. API is mixed with polymer in solid form, the mixture is then melted in an extruder with heaters. Finally, the dies shape the melt into films.

Rolling method

In this method, water or water/alcohol mixtures are the most commonly used solvents. API and other components are dissolved or dispersed in a small amount of aqueous solvent through a high shear process. This viscous mixture is then transferred onto the carrier roller and rolled. The resulting films are prepared by cutting into desired sizes and then dried in a controlled manner. This method provides films with better content uniformity and the thickness of the films is controllable.

Electro spraying

It is a newly emerged method. It involves spraying a liquid under the influence of a heavy electric field. The bulk liquid jet is broken into fine liquid droplets of identical charge. The electrical forces overcome the surface tension of the liquid under the influence of an external electric field applied during electro spraying. The basic experimental set up of electro spraying consists of a high voltage power supply, a syringe pump, a plastic or glass syringe capped by a metallic needle with defined diameter and a grounded collector or substrate for collecting the particles. Viscosity and particle size are the two main parameters that influence the film characteristics in this method.

Semisolid casting

This method is preferred when acid insoluble polymers are used in the preparation of oral fast dissolving films. Water-soluble polymer solution is prepared which is then added to ammonium or sodium hydroxide solution of acid insoluble polymer such as cellulose acetate phthalate, cellulose acetate butyrate. Appropriate volume of plasticizer is then added to the solution for the formation of a gel mass. It is then casted into the films or ribbons by using heat-controlled drums.

The characterization of oral transmucosal dosage forms is essential to assess their quality, performance, and safety. Physicochemical, mechanical, *in vitro* characterization and *in vivo* evaluation methods of transmucosal films are described in detail in Table 2.

Current Industrial Applications of Transmucosal Delivery

Transmucosal drug delivery systems are becoming an increasingly important category in the pharmaceutical industry due to their ability to offer rapid absorption and avoid the first-pass metabolism in the liver, which is a limitation of traditional oral drug formulations. These systems allow drugs to be absorbed through the mucosal membranes of the oral cavity (buccal, sublingual), nasal passages, or other mucosal tissues.

However, transmucosal drug delivery also has several limitations, which can vary depending on the route used. One major challenge is limited permeability, as the mucosal epithelium serves as a barrier, particularly against large molecules such as peptides and proteins; hydrophilic and high molecular weight drugs often exhibit poor absorption. Additionally, enzymatic degradation at mucosal surfaces can compromise drug stability, especially for protein- and peptide-based drugs like insulin. Another drawback is the limited dose capacity, since only low to moderate doses can be delivered effectively due to the restricted surface area and volume available for absorption. Some drugs or formulations may also cause irritation or sensitivity at the site of administration, leading to discomfort or inflammation. Furthermore, uncontrolled drug loss can occur through saliva in buccal and sublingual routes or through mucus clearance in nasal, vaginal, or rectal routes, potentially reducing drug efficacy. Patient compliance can also be an issue, as unfamiliar or uncomfortable routes, such as rectal or vaginal administration, may be poorly accepted. Even buccal and sublingual delivery can be limited by unpleasant taste or mouthfeel. Lastly, formulation challenges remain significant, requiring specialized excipients and techniques to enhance drug penetration and retention. Stability concerns, including sensitivity to moisture and pH variations at mucosal sites, further complicate formulation development.

Industrial Applications

Patient Convenience and Compliance - One of the most significant advantages of transmucosal delivery systems is their ability to improve patient compliance, particularly for individuals who have difficulty swallowing tablets, such as pediatric, geriatric, or dysphagic patients. Transmucosal systems, especially oral films, sprays, or strips, offer greater convenience and ease of use compared to traditional oral tablets or injections. Their fast onset of action, minimal preparation, and straightforward administration make them particularly well-suited for managing acute conditions.

Faster Onset of Action

The rapid onset of action is a key factor driving the growing interest in transmucosal drug delivery. By bypassing the gastrointestinal tract and liver, thereby avoiding first-pass metabolism, transmucosal formulations can achieve quicker

Table 2: Physicochemical, mechanical, *in vitro* and *in vivo* evaluation methods of Transmucosal films.

Test		Description
Morphology		Scanning electron microscopy is used to study the morphology of films at a definite magnification. Presence of pores, surface uniformity and particle dispersion can be studied.
Mechanical properties	Thickness	Uniformity of thickness is directly related to accuracy of dose in the film. Thickness of a film is measured by using micrometer screw gauge or digital Vernier calipers. Film should be measured at five points (Centre and the four corners) and then mean thickness is calculated.
	Tensile strength	Tensile strength measures the mechanical strength and durability of the film. It is the maximum stress applied to a point of a film at which the film specimen breaks. It is calculated by the following equation: Tensile strength = Load at failure*100/ Film thickness* Film width
	Percent elongation	When stress is applied on the film, it stretches and this is referred as strain. As the amount of plasticizer increases, elongation of the film also increases. Percent elongation= $L*100/L_0$ L = Increase in length of film; L_0 = Initial length of film
	Folding endurance	Folding endurance assesses the film's ability to withstand repeated folding, indicating its flexibility and durability. It is determined by repeated folding of the film at the same place until it breaks. The number of times the film is folded without breaking is taken as the folding endurance value. High folding endurance indicates good flexibility.
Weight variation		This test ensures that each film contains uniform amount of the API. Weight variation is calculated by weighing 1x1cm^2 films from each formulation, individually on a sensitive scale. The weight variation limits for films is ±5% according to USP.
Swelling index		This test is important for measuring the water absorption capacities of films. Films are individually weighed and kept in simulated saliva solution in a petri dish. Then, the films are weighed at different time intervals until the increase in weight reaches a constant level. High swelling index ensures that film is dissolved rapidly. The degree of swelling is calculated using the below equation: $\alpha = w_t\text{-}w_o/w_o$ w_t = weight of film at time t w_o= weight of film at time zero
Surface pH		Surface pH of the film is determined by placing the film on the surface of 1.5% w/v agar gel followed by placing pH papers of range 1-11 on films. The change in the color of pH paper is observed and pH is determined. The ideal pH range is 5.5 to 6.5.
Contact angle		A goniometer is used to measure the contact angle. Take a dry film and place a drop of distilled water on the surface of the film. Images of water droplet are recorded with in 10 sec by means of digital camera. The contact angle is measured on both sides of drop and the average value is taken. Contact angle of 40°- 50° is considered ideal as it provides good wettability.
Transparency		Transparency of films is important in terms of patient compliance and preferability. UV spectrophotometer is used to determine the transparency of the films. Rectangular shaped film is taken and placed inside the spectrophotometer cell. Transparency of the film is determined at 600nm. It is calculated as follows: Transparency= $(\log T_{600})/b = -\epsilon C$ T_{600}= transmittance at 600nm b= film thickness (mm); C= concentration
Content Uniformity		Content uniformity is determined by a standard assay method described for a particular API in the pharmacopoeia. This test estimates the API content in individual film. Limit of content uniformity is 85-115% according to USP.
Disintegration test		Disintegration time is the time taken by a film to disperse when it comes in contact with saliva. Weight and thickness of the film play a significant role in disintegration. The disintegration test apparatus specified in the pharmacopoeias are used. Typical disintegration time is less than or equal to 30sec for sublingual films and 1 - 5 min for buccal films.

Test	Description
Dissolution	Dissolution test is carried out using USP Apparatus to determine the drug release. The apparatus is maintained at 37°C and stirred at a speed of 50 rpm. 500 mL phosphate buffer of pH 6.8 in used. Aliquots are withdrawn at predefined time intervals. Absorbance is then measured using a specific analytical tool to calculate the percentage drug released.
Stability	According to the ICH guidelines, stability of films is maintained under controlled conditions (25°C temperature/60% relative humidity and 40°C temperature/75% relative humidity) for 12 months. During this time, the films must be assessed for weight uniformity, morphological properties, film thickness, tensile properties, water content, and dissolution test.
Mouth dissolving time	Mouth-dissolving time evaluation for transmucosal films typically refers to determining how long it takes for a film, when placed in the mouth, to dissolve or disintegrate under normal conditions (e.g., salivation). The evaluation is an essential part of formulating these films, especially for oral drug delivery systems, as it impacts both the drug release and overall therapeutic efficacy. Mouth dissolving times typically evaluated by Visually, Modified USP Dissolution Apparatus method and Disintegration test etc.
Bioavailability (BA) and Bioequivalence (BE)	Bioavailability and bioequivalence testing are crucial for assessing the performance of transmucosal films, especially when transmucosal films are being developed for drug delivery. Since these transmucosal films are designed for systemic absorption through the mucosal membranes (like the buccal or sublingual mucosa), the testing ensures that the drug is delivered effectively and with consistent therapeutic effects.

systemic absorption and faster therapeutic effects. This is especially beneficial in treating acute conditions such as pain, nausea, and allergic reactions, where prompt intervention is crucial (Li *et al*., 1997).

Chronic Disease Management

Transmucosal delivery is increasingly utilized in the management of chronic diseases that require ongoing treatment (Reddy *et al*., 2024). For example, formulations such as buccal patches for testosterone replacement therapy and nicotine replacement are gaining widespread acceptance for daily use in the long-term management of conditions like hormone imbalances and smoking cessation (Palem *et al*., 2016; Palem *et al*., 2012).

Therapeutic Areas with Promising Growth

Pain Management

The demand for transmucosal products like buprenorphine, fentanyl, and sublingual morphine has risen significantly due to their effectiveness in managing breakthrough pain in cancer patients and addressing opioid dependence.

Central Nervous System (CNS) disorders

Diseases such as epilepsy and anxiety, which necessitate rapid therapeutic responses, have prompted the development of transmucosal products like lorazepam for seizure control and midazolam for fast sedation.

Nasal Spray Vaccines

Nasal drug delivery is also being explored for the administration of vaccines and biologics. For instance, intranasal flu vaccines are gaining traction as a less invasive alternative to traditional injections, making vaccine delivery easier and more comfortable for patients.

Current Regulatory View on Transmucosal Delivery

Transmucosal drug delivery systems, which include formulations designed to deliver drugs through the mucous membranes (buccal, sublingual, nasal, or other mucosal surfaces), are increasingly being recognized as an effective alternative to traditional oral and injectable dosage forms. However, like any drug delivery system, transmucosal formulations must adhere to stringent regulatory requirements to ensure their safety, efficacy, and quality.

Regulatory agencies, including the US Food and Drug Administration (FDA), European Medicines Agency (EMA), Central Drugs Standard Control Organization - India (CDSCO) and other global bodies, have established guidelines for the development, approval, and commercialization of transmucosal delivery systems.

FDA Guidelines

The FDA's Centre for Drug Evaluation and Research (CDER) oversees the approval of transmucosal products. The general principles for transmucosal drug delivery are similar to those for other oral drug delivery systems, with an emphasis on quality, bioavailability studies, safety, and efficacy. Guidance Documents: The FDA has issued several documents that guide the development of transmucosal products, including those for buccal tablets and sublingual formulations. These guidelines focus on ensuring that the drug release profile and the pharmacokinetic parameters meet the required standards.

Table 3: Comparative filing requirements between US, Europe and India regulatory authorities.

Aspect /filing requirement	U.S Food and Drugs Administration (FDA)	European Medicines Agency (EMA)	Central Drugs Standard Control Organization (CDSCO) - India
Approval process	New Drug Applications (NDA) for new drugs, Abbreviated New Drug Applications (ANDA) for generics, 505(b) (2) application for modifications of approved drugs.	Centralized procedure for marketing authorization.	New Drug Applications (NDA) for new drugs, Abbreviated New Drug Applications (ANDA) for generics.
Filing requirements	Preclinical data, clinical trials, bioavailability studies, manufacturing information, labelling.	Pharmaceutical development, clinical trials data, bioequivalence data, GMP compliance, stability studies.	Preclinical data, clinical trials, bioequivalence data, stability studies.
Bioequivalence	Bioequivalence studies are required for generics to demonstrate similar pharmacokinetic profiles to the reference product.	Bioequivalence studies are required for generics to demonstrate similar pharmacokinetic profiles to the reference product.	Bioequivalence studies are required for generics to demonstrate similar pharmacokinetic profiles to the reference product.
Clinical trials	Clinical trials are required for new drugs to demonstrate efficacy, safety and bioavailability.	Clinical trials are required for new drugs to demonstrate efficacy, safety and bioavailability.	Clinical trials are required for new drugs to demonstrate efficacy, safety and bioavailability.
Manufacturing requirements	Must comply with GMP, quality control and consistency are essential.	Compliance with GMP, adherence to European Pharmacopoeia standards.	Must comply with GMP and adherence to CDSCO guidelines.
Stability studies	It is required for NDA, ANDA filings.	Stability studies are required to ensure product quality.	Stability studies are mandatory to ensure product shelf life and quality.
Market authorization	Upon approval of NDA, ANDA submissions, nationwide market access is granted.	Centralized marketing authorization provides access to all EU countries.	Grants marketing authorization in India upon approval of NDA, ANDA submissions.

EMA Guidelines (EU)

The European Medicines Agency follows a similar approach to the FDA. The regulatory view for transmucosal formulations includes a thorough review of bioequivalence studies, clinical trial data, and stability studies. European Medicines Regulatory Network: For transmucosal delivery systems, special consideration is given to ensuring that they are manufactured according to the standards laid out by Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP).

Other Regulatory Agencies

Many countries, such as Canada, Japan, India and Australia, follow similar principles for approving transmucosal drug delivery systems. They often refer to the FDA or EMA guidelines for regulatory submission and approval. Comparative filing requirements for different regulatory agencies are tabulated in Table 3.

Current commercially available transmucosal delivery products tabulated in Table 4. These products are designed to take advantage of the mucous membranes' high permeability to quickly deliver active ingredients into the bloodstream, offering faster onset of action compared to traditional oral routes.

CONCLUSION

Oral transmucosal drug delivery systems represent a promising and innovative advancement in the pharmaceutical industry, with the potential to revolutionize the way treatments are administered and experienced by patients. The use of transmucosal delivery is rapidly expanding, with a growing range of products on the market and an exciting pipeline of new developments. As the field progresses, the regulatory environment is evolving to ensure these products meet strict standards for safety, efficacy, and stability. Regulatory agencies like the FDA and EMA have established clear guidelines that require demonstration of bioavailability, controlled drug release profiles, clinical safety, and long-term stability. With continued advancements in formulation technologies, manufacturing capabilities, and regulatory processes, transmucosal drug delivery systems are positioned to play an increasingly significant role in improving patient outcomes and enhancing the effectiveness of treatments across a wide range of therapeutic areas.

Table 4: Commercially Available Transmucosal Marketed Formulations.

Drug Name	Therapeutic class	Marketed product/ Brand Name	Dosage form	Manufacturer
Acyclovir	Antiviral	Sitavig	Buccal tablet	LNHC Inc
Miconazole	Antifungal	Oravig	Buccal tablet	Galt pharmaceuticals LLC
Diazepam	Benzodiazepines	Libervant	Buccal film	Aquestive therapeutics Inc
Buprenorphine HCl	Opioid addiction treatment	Belbuca	Buccal film	Biodelivery sciences international Inc
Buprenorphine HCl and naloxone HCl	Opioid addiction treatment	Suboxone	Buccal, sublingual film	Indivior Inc
Dexmedetomidine HCl	Sedative	Igalmi	Buccal, sublingual film	Bioxcel therapeutics Inc
Asenapine maleate	Antipsychotic	Saphris	Sublingual tablet	Allergan sales LLC
Buprenorphine HCl and naloxone HCl	Opioid addiction treatment	Zubsolv	Sublingual tablet	Orexo US Inc
Ergotamine tartrate	Antimigraine	Ergomar	Sublingual tablet	Pangea pharmaceuticals LLC
Nitroglycerine	Vasodilator	Nitrostat	Sublingual tablet	Viatris specialty LLC
Zolpidem tartrate	Sedative-hypnotic	Edluar	Sublingual tablet	Mylan specialty LP

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ABBREVIATIONS

OTDDS: Oral transmucosal drug delivery systems; **FDA:** Food and Drug Administration; **EMA:** European Medicines Agency; **API:** Active pharmaceutical ingredient; **Tg:** Glass transition temperature; **USP:** United States Pharmacopeia; **ICH:** International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; **CDSCO:** Central Drugs Standard Control Organization.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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