



Challenges, Approaches & Applications of Orotransmucosal Drug Delivery System

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Authors' contributions

This work was carried out in collaboration among all authors. The first author HM and the corresponding author ASH led the review work and wrote the draft of manuscript. Authors KN and MMHR performed literature search and input data. The last author SI and the third author MSR managed the analyses of the study. All authors read and approved the final manuscript.

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ABSTRACT

Orotransmucosal drug delivery is an alternative method used for a systemic drug delivery system. It is used as a favored route for non-parenteral administration of emergency drugs and agents. It can be used both for lipid-soluble and water-soluble drugs. It increases drug solubility and reduces permeability of the lipid bilayer membrane. Mucosal surfaces are often rich in blood supply, allowing for rapid drug transport into the systemic circulation and in most cases avoiding degradation by first-

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pass hepatic metabolism. These systems contact with absorbent surfaces improves absorption at the application site and increases dwell time. It involves several physiological features of the oral cavity. Technical difficulties and biological impediments can be used as broad categories to group oral administration issues. Orotransmucosal drug delivery system uses an absorption rate four times that of the skin. It is easily accessible and heals rapidly from trauma and injury. It has a smaller surface area than the skin and can only be exposed for brief periods of time. Thus, this delivery method is the best for medications with high therapeutic potency. Efficient orotransmucosal drug delivery can be achieved in the oral cavity's buccal, sublingual, palatal and gingival regions. Mastication or chewing food can improve or impair medication absorption in the oral cavity. Mucoadhesive drug delivery systems can be lost or damaged when used to fill chewing gum with drugs that are released when the chewing gum is chewed. This report also provides input for future orotransmucosal drug developments to treat oral mucosa diseases.

Keywords: *Orotansmucosal; transmucosal; mucosal; oral mucosa; mucosae; mucoadhesion; mucoadhesive; OTFC.*

1. INTRODUCTION

Orotansmucosal drug delivery is an alternative method of systemic drug delivery system. Oral administration of drugs through mucous membranes has several advantages and limitations. Mucosal surfaces often have a rich blood supply, allowing for rapid drug transport into the systemic circulation and in most cases avoiding degradation by hepatic first-pass metabolism, thus enhancing drug bioavailability. The system's contact with the receptive surface improves absorption at the site of application, increases residence time and allows for once or twice daily dosing (Madhav et al., 2009).

This method of delivery enabled the acquisition of clinically relevant plasma levels of cannabidiol. The absorption profile indicates that cannabidiol and other lipophilic molecules should be delivered through oral mucosa for systemic absorption from a device that conceals the drug and prevents its washout by the saliva flow and subsequent ingestion into gastrointestinal tract (Itin et al., 2020).

Orotansmucosal drug delivery uses an absorption rate four times that of the skin. Orotansmucosal drug delivery systems are limited to existing products and candidates until changes occur in the drug selection and development process (Madhav et al., 2009).

Orotansmucosal administration is the preferred route for non-parenteral administration of rescue drugs and drugs when rapid onset of action is required. Furthermore, advances in drug delivery technology have increased the potential for transmucosal systemic delivery of biological agents (Hearnden et al., 2012).

In recent years, orotansmucosal drug administration has emerged as an attractive route of administration for pediatric patients. In this route of administration, the drug is absorbed through the buccal mucosa, bypassing hepatic first-pass metabolism and avoiding drug elimination metabolism in the gastrointestinal tract (Lam et al., 2014).

The oral mucosa has a smaller surface area than the skin. It can only be exposed for brief periods of time. The oral route of drug delivery is probably the one that both patients and doctors favor out of all the available drug delivery methods. However, oral administration of some groups of medications is not permitted due to drawbacks. As a result, different absorptive mucosae are taken into consideration as prospective drug delivery sites (Madhav et al., 2009).

For systemic drug delivery, the mucosal linings of the nasal, rectal, vaginal, ocular and oral cavities offer several benefits over peroral administration. These benefits include the potential for avoiding the first pass effect, avoiding pre-systemic elimination within the GI tract and depending on the specific medication, a superior enzymatic flora for drug absorption (Shojaei, 1998).

The nasal cavity as a site for systemic drug delivery has been investigated by many research groups and the route has already reached commercial status with several drugs. However, the potential irritation and permanent harm to the ciliary action of the nasal cavity from repeated administration of nasal dosage forms, as well as the significant intra- and inter-subject variability in mucus secretion in the nasal mucosa could

significantly affect drug absorption from this site (Shojaei, 1998).

The mucosae of the rectal, vaginal and ophthalmic tracts all have advantages, but due to the low patient acceptance of these sites, they are more often used for local applications than for systemic drug delivery. The oral cavity is very well tolerated by patients, the mucosa is relatively permeable with a strong blood supply, it is resilient and recovers quickly from stress or damage and the absence of virtually all Langerhans cells makes the oral mucosa tolerant to potential allergens. Moreover, orotransmucosal drug administration avoids the GI tracts pre-systemic elimination and first passes impact. These elements render the oral mucosal cavity an extremely desirable and practical location for systemic medication administration (Shojaei, 1998).

Three types of drug distribution are distinguished inside the oral mucosa. Drug administration through the mucosal membranes lining the floor of the mouth is known as sublingual delivery. Drug administration through the mucosal membranes lining the cheeks is known as buccal delivery. Drug administration into the oral cavity is known as local delivery (Shojaei, 1998).

Drug bioavailability and controlled release rate are both boosted by oral mucoadhesive drug administration, which also improves pharmacokinetics. Also, it was demonstrated that employing this approach compared to commercial drug formulations (Golshani et al., 2022).

2. TYPES OF OROTRANSMUCOSAL DRUG DELIVERY ROUTE

2.1 Buccal Route

The buccal mucosa is a useful route for the treatment of either local or systemic therapies. It is overcoming the drawbacks of conventional administration routes. It is more tolerant to potential allergens and resilient compared to other mucosal tissues (Patel et al., 2011). When it is used as less of a tendency to cause irreversible irritation or injury. As a result, it is a prospective site for the regulated orotransmucosal drug delivery system in a variety of chronic systemic therapy (Giannola et al., 2007). However, certain medications may undergo chemical alteration due to salivary

synthesis and composition. Additionally, unintentional swallowing may cause drugs to be lost from the site of absorption (Madhav et al., 2009).

The small absorption area and the barrier property of the buccal mucosa contribute to the limitations of this route. Furthermore, due to the constant intake of saliva in the oral cavity, long-term storage of dosage forms to improve absorption at this point is a major challenge (Giannola et al., 2007). Easy access to the membrane sites makes it possible to apply, locate and remove the delivery system quickly. Additionally, there is a good chance that the transmucosal membrane in the oral cavity will allow for longer delivery (Madhav et al., 2009).

2.2 Sublingual Route

The sublingual mucosa is a rapid onset site is sought. It is more permeable and thinner than the buccal mucosa. It has a large surface area and has high blood flow (Chiappin et al., 2007). Although the sublingual route is not always effective for the administration of medications in the treatment of acute diseases. It is challenging to maintain the dose form in contact with the mucosa. Its surface is constantly cleansed by saliva and tongue action (Giannola et al., 2007). This method can avoid the first-pass effect and prevent the medications from encountering digestive juices. The membrane sites of this route make it possible to apply, locate and remove the delivery system quickly (Madhav et al., 2009).

2.3 Palatal Route

The only recognized route of administration that gets around all these issues with these medications ineffectiveness when taken orally is the parenteral route. However, these formulations are expensive, have the lowest patient compliance and call for recurrent administration (Shakya et al., 2011). The palatal mucosa is keratinized and of intermediate thickness, which reduces its permeability. These epithelia are all covered in a mucus coating. The soft-palatal mucosa was the most practical and accessible novel site (Madhav et al., 2009). It is used as a retention dosage form to introduce therapeutic agents for systemic administration. The soft palate must have a smooth surface and be flexible to prevent mechanical irritation and local pain (Shakya et al., 2011).

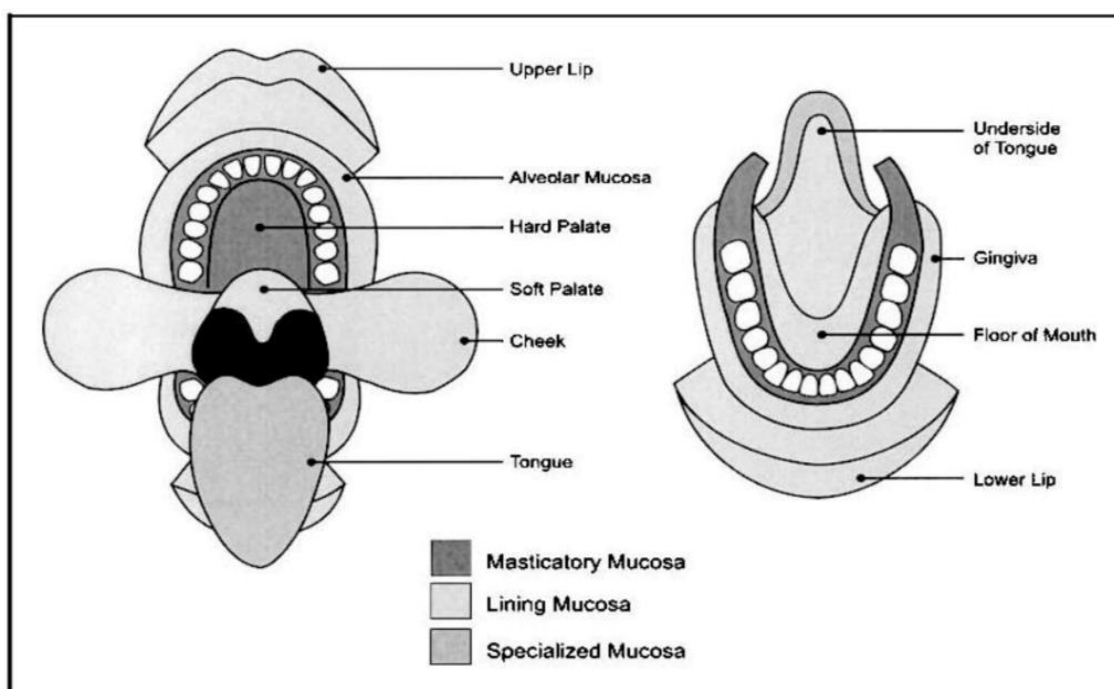


Fig. 1. Graphic representation of the various mucosa in the oral cavity

2.4 Gingival/ Mucoadhesive

Mucosal adhesions are conditions in which two substances, mucus or mucous membranes, stick together for a long period of time. The term mucoadhesion refers to the attachment of drug carriers to the mucus layer of specific biological areas for the purpose of drug delivery (Shaikh et al., 2011). A series of phenomena, whose roles depend on the characteristics of the mucoadhesive must occur for mucoadhesion to take place. Bone marrow transplantation and radiation therapy to the head and neck, especially bone marrow conditioning regimens for the treatment of oral cancer (Chowdary and Srinivas, 2000). It can cause mucositis is an inflammatory condition of the mouth mucosa. Dose-related mucosal damage causes painful ulcerations, issues with swallowing, speaking and eating, as well as an elevated risk of infections. Significant morbidity may result from this and anti-cancer treatment may possibly be postponed or stopped altogether (Shakya et al., 2011).

The oral cavity consists of various structures, which includes sublingual, buccal, labial, palatal and gingival tissues (Fig. 1) (Zhang et al., 2002).

3. GI TRACT BARRIERS IN OROTRANS-MUCOSAL DRUG DELIVERY SYSTEM

3.1 Physiochemical Barrier

Pharmaceuticals taken orally pass via both the upper and lower portions of the GI tract, with the latter segment having the most obstructions to oral delivery while also being the site of most of the drug absorption. Drug efficacy can be decreased if it is degraded before it reaches the small intestine for absorption due to the acidic environment and enhanced proteolytic activity in the upper GI tract (El-Kattan and Varma, 2012). The drug is exposed to the stomach's degradative environment and strong proteolytic gastric enzymes as it travels through the upper GI tract. These medicines must also be able to overcome mechanical stress that hinders the drugs development. Particularly, due to the rapid breakdown of proteins and other big biologics in the gut (Gavhane and Yadav, 2012). According to one study, when bovine milk immunoglobulin was incubated with pepsin at a pH of 2, it's in vitro rotavirus-neutralizing activity was reduced by 96%, illuminating the negative impacts of the GI environment on large biologics (Petschow and Talbott, 1994). Therefore, it is important that biologics must be specially modified to endure the natural characteristics of the gut (Le et al., 2022).

In order to withstand the natural properties of the gut, biologics must be properly adjusted. Also, due to the phenomenon known as first-pass metabolism, oral medications have lower systemic availability as compared to medications that are administered intravenously or intranasally. In their study, where cyclosporin was administered to the small bowel of two patients after liver transplantation, enzymatic degradation demonstrated this effect (Pond and Tozer, 1984). The first-pass effect is a term used to describe how the concentration of an oral drug is reduced before meeting systemic circulation due to decreased gastric residence time. After 60 minutes of administration, patient's portal blood contained between 25% and 51% of the total metabolites produced from cyclosporin, indicating cyclosporin was being metabolically degraded more quickly (Kolars et al., 1991). The prolonged response that the oral treatments were initially intended to produce is directly decreased by this decreased availability of the drug in the systemic circulation (Petschow and Talbott, 1994). The extreme physiochemical circumstances present in the GI tract are likely to blame for the decrease in medication availability in the systemic circulation. Oral medications are often supplied at a higher dose to counteract the first-pass effect; however, this alters the toxicity and effectiveness of numerous pharmaceuticals (Le et al., 2022).

3.2 Epithelial Barrier

Tight junctions in the GI tract's epithelial layer further control how chemicals flow across and within this surface, acting as the immune system's initial line of defense. For molecules to pass through this layer and enter the systemic circulation, they must consider the underlying mechanisms of active/passive transport (Keselowsk et al., 2020). These tight junctions act as a barrier that affects both paracellular and transcellular transport of molecules through epithelial tissue (Tscheik et al., 2013). As a result, overcoming these obstacles shortens pharmaceuticals stay in the stomach and increases the difficulty of giving oral medications a sustained impact. The same epithelium that serves as a defense mechanism can also be used to carry medications to the immune system. Furthermore, this study demonstrated that in vitro transcytosis via epithelium was possible with these nanoparticles attached to IgG Fc (Pridgen et al., 2013). Finally, this research revealed oral administration. This approach of using FcRn to target epithelium can be used to develop

tolerance in autoimmune illnesses as well as immunity against infectious infections (Le et al., 2022).

3.3 Intestinal Microbiota

Microbiota refers to the microorganisms that live in animal's guts and are essential for preserving immunological homeostasis (Rooks and Garret, 2016). The host and gut microbiota work together to boost the immune system through a series of microbiota-dependent cascades inside the epithelium and to support the growth of bacteria in the mucus. A compromised immune system, however, can still make such bacteria a hazard mucus (Cerf-Bensussan and Gaboriau-Routhiau, 2010). It is also crucial to remember that, while though the GI tract plays a crucial role in food digestion thanks to a variety of unique properties, a dynamic environment and intricate regulatory systems, it can also reduce the effectiveness of medications taken by mouth (Rooks and Garret, 2016). The same bacteria that stop drugs from passing through the gut can also be employed to treat immunotherapies by themselves (Cerf-Bensussan and Gaboriau-Routhiau, 2010). Strangely, this study coated EcN with yeast membrane to target the M cells by using the β -glucan imbedded on the membrane of the yeast (Lin et al., 2021). This study was significant in showing that oral distribution of yeast membrane coated EcN could localize to the Peyer's patches, where it might trigger an immunological response to stop the breakdown of the intestinal barrier (Le et al., 2022).

3.4 Mucosal Immune System of the Gut

The specialized mucosal layer that covers the surface of the epithelium is one of the first lines of immune defense in the GI tract. The intestines goblet cells, which form the mucosal layer, secrete a gel-like material are glycoproteins (Hansson, 2012). However, oral treatments are less readily available to their targets due to the GI tracts ongoing mucus production (James, 1993). In order to protect the body's native microbial flora, the mucosal system acts as a specialized immune defense system of the GI tract, recognizing luminal foreign substances and either removing them or neutralizing them (Johansson et al., 2013). The charged glycoproteins on the mucosal surfaces of the GI tract vary in thickness. Drugs must pass through the mucosal barrier before entering the systemic circulation (Ensign et al., 2012). Mucus is continuously secreted and excreted swiftly,

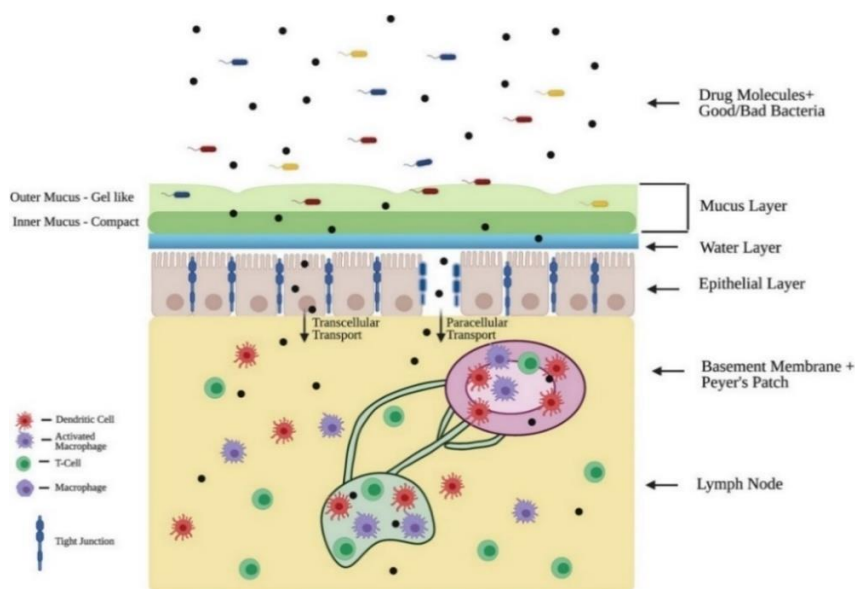


Fig. 2. Drug molecules bypassing various barriers in the intestinal tract to reach systemic circulation

trapping and eliminating foreign structures simultaneously and reducing the period. The gut mucosa presents a particularly difficult obstacle for immunotherapeutics (Bernkop-Schnurch and Fragner, 1996).

Especially, it was demonstrated that the steric mucosal barriers size-dependent barricade was evidenced by the fact that the diffusion coefficient reduced as protein molecular weight increased when evaluated in vitro in pig intestinal mucus (Olmsted et al., 2001). Moreover, it has been discovered that large proteins, particularly antibodies can bind to mucins via electrostatic interactions or strong hydrogen bonds, thereby trapping and preventing them from reaching systemic circulation (Sigurdsson et al., 2013). Hence, it is essential to create oral to systemic immunotherapeutics that can get past the mucosal barriers (Le et al., 2022).

Limitations on the amount of traffic in the GI tract and the amount of absorbable surface must also be overcome by immunotherapeutics (Fig. 2) (Le et al., 2022).

4. CHARACTERISTICS OF OROTRANS-MUCOSAL DRUG DELIVERY SYSTEM

4.1 Permeability of the Oral Mucosa

Permeability barriers prevent exogenous and endogenous substances from entering the body through the oral mucosa. It serves to prevent

fluid loss from underlying tissues to the environment (Shimono and Clementi, 1976). The lipid content of the upper layers of the epithelium makes up most of the permeability barrier (Kulkarni et al., 2009). Suprabasal cells have strong intercellular desmosome junctions and membrane-coated granules (MCG) on their apical surfaces. Strong intercellular desmosome junctions and membrane coating granules (MCGs) are produced on the apical surfaces of supra-basal cells as they develop (Shojaei, 1998). These MCGs deliver lipophilic substances to the intercellular gaps to maintain epithelial integrity. The ability of this lipophilic substance to slow the flow of hydrophilic substances across epithelium (Salamat-Miller et al., 2005). Epithelium is a major barrier to permeability, suggesting that high hydration of connective tissue acts as some resistance to lipophilic substances (Madhav et al., 2009).

Due to the varying epithelial thickness and levels of keratinization at various sites, the oral mucosa's permeability varies across distinct areas (Sankar et al., 2011). Compared to non-keratinized tissues, keratinized tissues exhibit decreased permeability. This is caused by the lipid composition of the membrane-coated granules of keratinized tissue (Ganem-Quintanarc et al., 1997). The buccal mucosa and hard palate have the lowest levels of permeability and the sublingual mucosa is most easily permeable (Squier and Hall, 1985).

There are three ways to move material past the permeability barrier of the oral mucosa: passive diffusion, including (i) trans-cellular and paracellular diffusion (Li et al., 2005), (ii) carrier-mediated transport and endocytosis/ exocytosis (Salamat-Miller et al., 2005), (iii) in which cells actively take up and excrete material through the endocytic pathway (Sudhakar et al., 2006). Lipid-soluble compounds, non-ionized species and molecules with small molecular weights are the materials that diffuse the easiest (Hoogstraate et al., 1994). Dextran with a molecular weight of less than 20,000 Da. Although diffusible, dextran's with molecular weights greater than 20,000 Da do not. A substance's path of passive diffusion is determined by its lipophilicity, its partition coefficient between lipophilic and hydrophilic areas and its intercellular space diffusion coefficient (Sood et al., 2005). Drugs with high Pka values diffuse more effectively through oral mucosa (Madhav et al., 2009).

4.2 Increased Permeability in Diseased Mucosa

The orotransmucosal drug diffuses more freely into the tissue of ulcerated or eroded areas due to the lack of a permeability barrier (Harsanyi et al., 1986). Orotansmucosal drug affected by lichen planus has significantly increased permeability compared to when not eroded or ulcerated. However, the diminished barrier function may also cause the medicine to be quickly lost from ulcer sites. This may lead to improved drug delivery into mucosal regions affected by disease as compared to adjacent normal tissue (Sankar et al., 2011).

Malignant and oral lesions can exhibit altered drug permeability in the mucosa. The permeability of the cigarette carcinogen nitrosornicotine in leukoplakic spots and the non-lesional regions around them was investigated. Only the non-lesioned portions directly around the leukoplakia had statistically significant higher permeability than the surrounding areas, which were both the leukoplakia and normal oral mucosa (Banoczy et al., 2003).

5. CHALLENGES IN OROTRANS-MUCOSAL DRUG DELIVERY SYSTEM

In the GI tract, oral medications are transported and absorbed. While most medications are distributed through the systemic circulation to function throughout the body, some of them have local effects on the stomach (Dimmitt et al., 2012). There are upper and lower segments of the GI tract. The mouth, pharynx, esophagus, stomach and duodenum, the first segment of the small intestine are all considered to be parts of the upper GI tract (Treuting et al., 2018). The remaining small intestine and the cecum, colon and rectum of the large intestine are all parts of the lower GI tract (Cheng, 1974). All segments of the GI tract have a similar structure. Mucus, submucosa and multiple muscle layers enclose the lumen and are encircled by smooth muscle cells (Dimmitt et al., 2012). Lamina propria, muscularis mucosae and other epithelial cells make up the mucosal layer that lines the inner portion of the GI tract. These cells are important for the transport of food and drug molecules as well as for gastrointestinal immunity (Treuting et al., 2018). One of the reasons why drug absorption takes place predominantly in the small intestine is that it has a wide absorption area and a lengthy residence duration, which provides additional opportunities for drug absorption (Lennernas, 1998). In addition, the jejunum and ileum of the small intestines three major sections have more absorption capacity than the duodenum (Rubin and Langer, 2016). The average segment length, pH, mucus thickness, drug residence time and bacterial diversity/population in various segments are some of the environmental parameters that affect medication integrity and absorption (Ensign et al., 2012). Technical difficulties and biological impediments can be used as broad categories to group oral administration issues (Dressman et al., 1990). Biological barriers are any biological elements that alter the properties of medications taken orally or prevent their effective absorption in the target (Rouge et al., 1996). The difficulty in making oral delivery devices is referred to as a technical challenge. Technical difficulties could arise when developing various properties to overcome biological barriers or when scaling up and commercializing a system (Homayun et al., 2019).

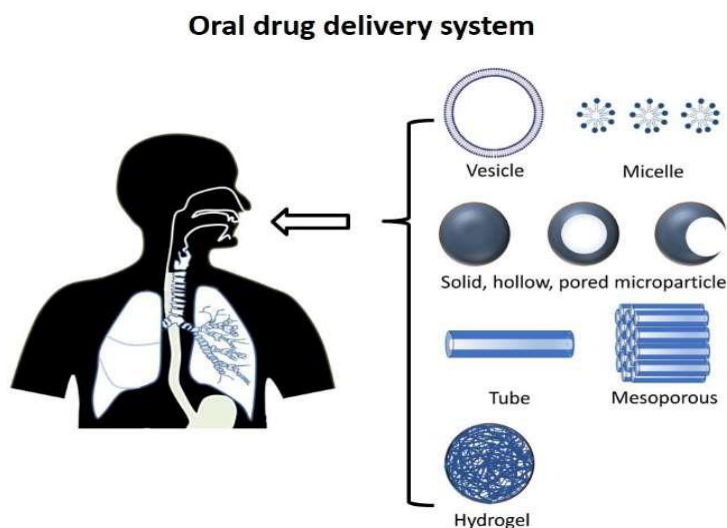


Fig. 3. Schematic illustration in the challenges of orotransmucosal drug delivery system

Orotansmucosal drug delivery systems can be categorized as intestinal patches, gastrointestinal microneedles and particulate carriers. Particulate carriers also include micelles, liposomes and micro/nanoparticles (Fig. 3) (Homayun et al., 2019).

6. MECHANISM OF ACTION IN OROTRANSMUCOSAL DRUG DELIVERY SYSTEM

The mechanism of orotransmucosal drug administration fentanyl citrate (OTFC) was examined. The following transport features were included in a created mathematical model: fentanyl citrate lozenge dissolving, equilibrium between neighboring layers, saliva and oral mucosal membrane diffusion. The governing equations and boundary conditions were discretized for using an orthogonal-collocation-based solution approach. The equations were integrated about time using the Mathematica built-in function NDSolve. A 200 g dosage was used for simulations (Kim and Simon, 2011).

The oral mucosa is accessibility, excellent blood supply, bypass of hepatic first-pass metabolism, quick healing and permeability profile for local and systemic drug delivery systems (Fig. 4) (Hearnden et al., 2012).

7. OROTRANSMUCOSAL DRUG DELIVERY SYSTEMS

Drug delivery is the process or technique of administering a pharmacological ingredient to

have a therapeutic impact in humans or animals. For peptide and protein therapies in particular, the importance of nasal and pulmonary therapy offers exciting alternatives to parenteral drug administration. A few drug delivery systems for pulmonary and nasal delivery have been developed and are being investigated. Examples of these include cyclodextrins, prodrugs gels, microspheres, proliposomes and liposomes. The ability to transfer into an aerosol, stability against forces generated during aerosolization, biocompatibility, specific bind target cell, in the lung, release of the drug in a predetermined manner and degradation within a reasonable amount of time are all requirements that must be met by nanoparticles made of biodegradable polymers (Tiwari et al., 2012).

Table 1 lists the orotransmucosal dosage forms available in the market (Madhav et al., 2012).

8. APPLICATIONS OF OROTRANSMUCOSAL DRUG DELIVERY SYSTEM

A pediatric formulation must be in a dosage form that the intended age group can handle and allow accurate dose administration. For this susceptible age group, it is especially crucial to consider the types and quantities of excipients employed in the formulation (Lam et al., 2014).

There are several barriers that need to be overcome in the development of orotransmucosal products (Fig. 5) (Lam et al., 2014).

Table 1. Lists of orotransmucosal dosage forms available in the market

Brand Name	Active Drugs	Applications	Manufacturer	Dosage Form
Onsolis	Fentanyl citrate	Opioid analgesic	Meda Pharmaceuticals	Buccal soluble film
BEMA	Buprenorphine	Opioid analgesic	Wolters Kluwer Health	Buccal soluble film
Gel-kam	Fluoride	Anticavities	CHATTEM Company	Oral gel
Actiq	Fentanyl citrate	Opioid analgesic	Wolters Kluwer Health	Lozenge on a stick
Fentora	Fentanyl citrate	Opioid analgesic	Wolters Kluwer Health	Buccal tablet
Sublimaze	Fentanyl Citrate	Opioid analgesic	Wolters Kluwer Health	Injection
ACT fluoride rins	Fluoride topical	Anticavity	CHATTEM Company	Oral solution
Amnatadine oral solution USP	Amnatadine hydrochloride	Antiviral	Qualitest Pharmaceuticals	Oral solution
Rapamune	Sirolimus	Hepatic impairment	Wyeth Pharmaceuticals	Oral solution
Saphri	Asenapine maleate	Schizophrenia, bipolar disorder	Catalent UK Swindon Zydys Ltd	Sublingual tablet
Gleclair	Glycyrrhetic acid/ povidone/ sodium hyaluronate	Relieve mouth pain and irritation	Wolters Kluwer Health	Oral gel

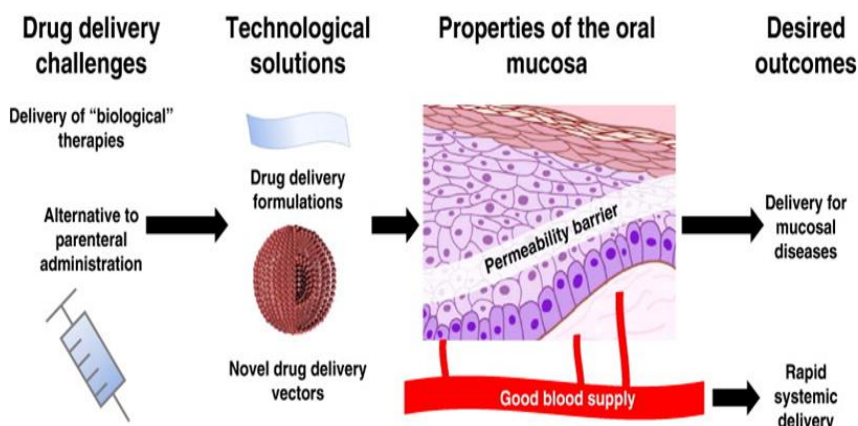


Fig. 4. Mechanism in the action of orotransmucosal drug delivery system

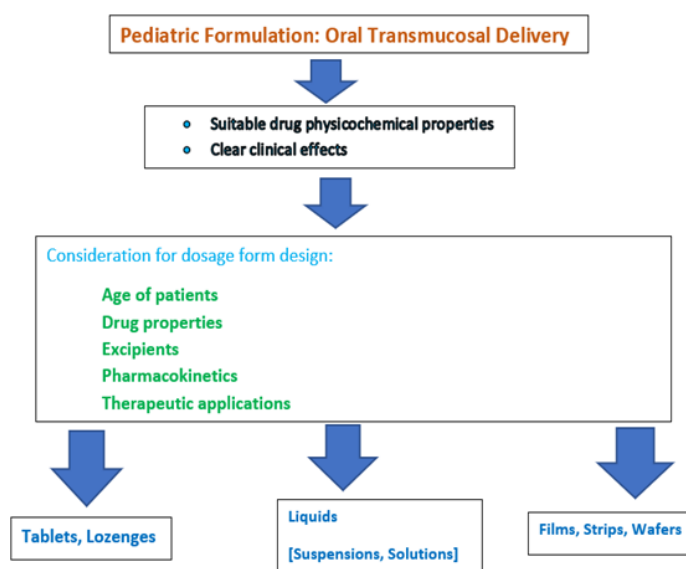


Fig. 5. Orotansmucosal drug delivery for pediatric use

- ✓ Angina-Organic and Nitrate Compounds
- ✓ Acute Seizures; Asthma & Allergy
- ✓ Chronic Severe Pain
- ✓ Migraine; Hypertension
- ✓ Smoking Cessation; Alcohol Abuse
- ✓ Hormonal Treatments
- ✓ Diabetes-Emerging Indication for Transmucosal Delivery
- ✓ Transmucosal Delivery of Traditional Drugs; Proteins, Peptides, Vaccines (Goyal et al., 2018).

9. OROTRANSMUCOSAL VACCINATION

The only vaccines that are given orally in the United States are the rotavirus, adenovirus, cholera vaccine and oral typhoid vaccines, even though there are more than 20 vaccines that are now delivered there (Rouphael et al., 2017). Many vaccines are currently administered via

intradermal or intramuscular injections, which come with risks and a high price tag for mass immunization (Ozawa et al., 2017). The mucosal location, where the majority (>90%) of pathogens enter the body, is unfortunately where vaccinations given intramuscularly or intradermally only partially or occasionally offer protection (Miquel-Clopes et al., 2019). As a

result, it can be very advantageous to target and induce mucosal immune responses against self- or pathogenic proteins for tolerance (Liu et al., 2013). An interesting target for developing vaccines that induce tolerance is the mucosal immune system, which is notable for tending to be immunosuppressive (D'Elia et al., 2019). However, due to a lack of delivery systems that can deliver proteins (antigen) and adjuvants to the mucosal immune system, there are surprisingly few oral or intranasal vaccines on the market (Acevedo et al., 2014).

Antigen-presenting cells are exposed to transcytosed antigens by specialized M-cells with the purpose of inducing immunological responses (Holmgren and Czerkinsky, 2005). The expression of immunologic memory via directly generating cytotoxic T cell activation has been shown to be effective in mice studies in producing a persistent immunological response with mucosal vaccination by targeting DCs (Mohamadzadeh et al., 2005).

In autoimmune disorders, where tolerance to numerous antigens is required, mucosa-targeted vaccinations can also have a significant impact (Toussirot, 2002). Autoimmune illnesses cause immune responses to be mounted against self-antigen (Park et al., 2009). Regarding oral antigen delivery specifically, clinical trials have yielded conflicting results and no cure has yet been approved (Trentham et al., 1993). By directly delivering target antigens to the mucosal immune systems cells, one possible method for eliciting a potent tolerance-inducing response (Akahata et al., 2010). Additionally, a formulation that can deliver molecules that promote tolerance in addition to an antigen can significantly enhance immune responses (Atwe et al., 2014).

The development of orotransmucosal vaccination administration methods has advanced significantly and pre-clinical testing of these systems has also taken place (Van der Lubben et al., 2001). For instance, M cells in the Peyer's patches can pick up chitosan and alginate microparticles, which can then be directly absorbed by the MALT to trigger a series of immunological responses (Choe et al., 2010). The connected systemic and mucosal responses required for persistent immunity have been successfully induced by polymeric nanoparticles

like poly (lactide-co-glycolide) (PLGA) (Acharya et al., 2016). The encapsulation of antigens or immunomodulatory agents using liposomes, biosomes, bacterial outer membrane vesicles (OMVs), virus-like particles (VLPs) and chemically processed pollen grains, which have found pre-clinical success against viral respiratory diseases or antibiotics entrapped in biosomes with success against the bacterium *Burkholderia pseudomallei* are additional candidates (Sarti et al., 2011). These biomaterials positive pre-clinical results intestinal immunity is contained inside gut-associated lymphoid tissue at inductive sites made up of T and B cells within the Peyer's patches and effector sites within the lamina propria. Antigen uptake is made possible by M-cells along the epithelia (Le et al., 2022).

Table 2 lists the current and new approaches for orotransmucosal vaccine delivery systems used in the oral route (Rhee, 2020).

10. OROTRANSMUCOSAL PRODUCTS AVAILABLE IN BANGLADESH

According to the examination of market data for the previous 20 years (2002-2021) collected from CortellisTM (Yun et al., 2010). The commercialized items from the beginning of 2012 to the end of 2021 will be presented in the parts that follow, along with their approval processes (Hua, 2019). Several sold-out pills helped to achieve this: Oravig®/ Loramyc® and FentoraTM both feature OraVescent® and Lauriad® technologies respectively (Pather et al., 2008). Several gels have undergone systemic and local testing. OralBalance® is a salivary substitute for the treatment of dry mouth (Vazquez et al., 2012). For the local delivery of antimicrobial agents for buccal infections, suspensions or solutions are typically marketed as mouthwashes or rinses (Darwish et al., 2010). Periogard® and Listerine® for the treatment of gingivitis and Amicar® for the treatment of acute oral or systemic bleeding syndromes. Spray formulations for solutions or suspensions are also possible (Malallah et al., 2018). One instance is a study using a lingual spray to deliver oxytocin that aims to improve reactions when compared to the nasal route, the traditional route for this use and minimize social dysfunction in illnesses (Bastos et al., 2022).

Table 2. Current and new approaches for orotransmucosal vaccine delivery

Sl. No.	Delivery System	Examples	Applications	Advantages	Disadvantages
1.	Solutions	Rotavirus Vaccine	Live attenuated, proteins, peptides	Inexpensive buffer, flexible, easily administration	Using of bicarbonate salts to neutralize gastric acid, dilution of formulation
2.	Emulsions	MF59, ASO3, ASO2	Whole cell killed, proteins, peptides	Easily flavored, rate of absorption is increased, oily sensation is easily removed	Efficacy by the oral route uncertain, no licensed oral vaccine yet
3.	Pills and capsules	Antisense oligonucleotides, mRNA vaccines, live-attenuated vaccines (Vivotif)	Live attenuated, whole cell killed, proteins, peptides	Highly adaptable, controlled release, easy administration	The formulation process may damage components
4.	Virus-like particles	Hepatitis A/B/E Virus, SARS-COV-2, Human immune deficiency Virus (HIV)	Plasmid DNA, proteins, peptides	Nonreplicating, highly uptake, self-assembling	Expensive, no licensed oral vaccine yet
5.	Virus Vector	Adenovirus, yellow fever virus, pox virus	Metabolic diseases, heart defects, neurodegenerative disorders	Capable of triggering powerful and long-lasting cellular responses	Pain at the injection site, fatigue and headache
6.	Immuno stimulating complexes	ISCOM, SCOMATRIX	Proteins, Peptides	Intrinsic adjuvant capabilities, efficient induction of CTLs	Difficulty of loading hydrophobic antigens
7.	Liposomes	Hepatitis B/C, RSV, Influenza	Proteins, DNA, Peptides	Ease of surface modification, controlled release	Poor antigen loading efficiency, low stability, nonspecific interactions
8.	Proteasomes	Neisseria meningitides, Shigella, Haemophilus influenza type b (Hib)	Cell, Tissue, Protein and Peptide synthesis	Boost immune function, promote cardiovascular health, prevent colon cancer	Diarrhea, nausea, vomiting and allergic reactions

11. RECENT RESEARCH CARRIED OUT ON OROTRANSMUCOSAL DRUG DELIVERY SYSTEM

➤ Transmucosal double-layer sequential dissolving MNs designed by using

hyaluronic acid methacryloyl (HAMA), hyaluronic acid (HA) and polyvinyl pyrrolidone (PVP). MNs have the advantages of small size, easy operation, good strength, rapid dissolution and one-time delivery of two drugs. Morphological test results showed that the HAMA-HA-

PVP MNs were small and intact in structure. The mechanical strength and mucosal insertion test results indicated the HAMA-HA-PVP MNs had appropriate strength and could penetrate the mucosal cuticle quickly to achieve orotransmucosal drug delivery. The in vitro and in vivo experiment results of the double-layer fluorescent dyes simulating drug release revealed that MNs had good solubility and achieved stratified release of the model drugs. The results of the in vivo and in vitro biosafety tests also indicated that the HAMA-HA-PVP MNs were biosafe materials. The therapeutic effect of drug-loaded HAMA-HA-PVP MNs in the rat oral mucosal ulcer model demonstrated that these novel HAMA-HA-PVP MNs quickly penetrated the mucosa, dissolved and effectively released the drug and achieved sequential drug delivery. Compared to monolayer MNs, these HAMA-HA-PVP MNs can be used as double-layer drug reservoirs for controlled release, effectively releasing the drug in the MN stratification by dissolution in the presence of moisture. They inferred that the need for secondary or multiple injections can be avoided, thus improving patient compliance. This drug delivery system can serve as an efficient, multi-permeable, mucosal and needle-free alternative for biomedical applications (Meng et al., 2023).

- The first study on the possibility of orotransmucosal drug delivery presented to the best of their knowledge. It was one of the safest triptans, namely eletriptan hydrobromide (EB) in migraine. Based on a comprehensive set of in vitro and ex vivo experiments, they highlighted the conditions required for orotransmucosal delivery, potentially giving rise to similar or even higher, drug plasma concentrations expected from conventional oral administration. With histology and tissue integrity studies, they concluded that EB neither induces morphological changes nor impairs the integrity of the mucosal barrier following 4 h of exposure. On a cellular level, EB is internalized in human oral keratinocytes within the first 5 min without inducing toxicity at the relevant concentrations for orotransmucosal delivery. Considering that the pKa of EB falls within the physiological range, they systematically investigated the effect of pH

on both solubility and transmucosal permeation. When the pH is increased from 6.8 to 10.4, the drug solubility decreases drastically from 14.7 to 0.07 mg/ml. At pH 6.8, EB gave rise to the highest drug flux and total permeated amount across mucosa, while at pH 10.4 EB showed greater permeability coefficient and thus a higher ratio of permeated drug versus applied drug. Permeation experiments with model membranes confirmed the pH dependent permeation profile of EB. The distribution of EB in different cellular compartments of keratinocytes is pH dependent. High drug ionization leads to higher association with the cell membrane, suggesting ionic interactions between EB and the phospholipid head groups. Moreover, they showed that the chemical permeation enhancer DMSO can be used to enhance the drug permeation significantly. This study presented important findings on the orotransmucosal drug delivery of eletriptan via the oral cavity and paves the way for clinical investigations for fast and safe migraine treatment (Valetti et al., 2022).

- The absorption routes on the impact of oral residence time investigated in the orotransmucosal drug delivery system. In this experiment, they used risperidone orodispersible film (ODF) and evaluated the prediction on the fraction of intraoral absorption of the orotransmucosal drug delivery in risperidone. Given that, AUC_{0-t} ($P=0.4327$), $AUC_{0-\infty}$ ($P=0.32780$), C_{max} ($P=0.0531$) and T_{max} ($P=0.27775$) values. These values were not shown in statistical differences. These values were among i.g., supralingual and sublingual administration of risperidone oral dosage form in Beagle dogs. The absorption percentage of oral mucosa is 7.0%, 11.4% and 19.5% and the oral residence time is 2 min, 5 min and 10 min. The PBPK absorption model for risperidone could be simplified to include the ACAT model (Chen et al., 2020).
- Various factors can be reported to obtain ranging from absorption and distribution. We administered the active ingredient caffeine to give mice and compared it with Quickstrip. It is a standard oral gavage delivery at an equivalent dose of 20 mg kg^{-1} . It has been also used in HPLC

assessment of serum concentrations of caffeine. It resulted in higher serum levels of caffeine at 1, 10 and 30 min. It also produced greater bioavailability compared to gavage, as demonstrated by the area under the curve analysis (Hines et al., 2019).

12. CURRENT STATUSES OF OROTRANSMUCOSAL DRUG DELIVERY SYSTEM

There have been many different dose forms created, including toothpastes, mouthwashes, lozenges, gels, chewing gum, lollipops, films, patches, pills and even specific devices (Hao and Heng, 2003). However, due to mechanical stresses and the washing effect of saliva, conventional dosage forms have some drawbacks. In terms of preventing and treating local diseases or boosting orotransmucosal medication dosage form administration, formulations that delay drug release in the mouth have many benefits (Madhav et al., 2009). When compared to more traditional administration methods for children, orotransmucosal drug delivery has a few significant advantages (Lam et al., 2014).

The ineffective and unpredictable oral absorption of many hydrophilic macromolecular medicines is the principal barrier to their utilization as possible therapeutic agents. Recombinant DNA research has just recently advanced and contemporary synthetic and biotechnological technologies enable biochemists and chemists to generate large amounts of a wide range of peptides and proteins with improved pharmacological efficacy. The medicinal potential of these substances depends on our capacity to develop reliable and efficient delivery mechanisms. In addition to developing effective non-parenteral delivery systems for complete proteins and peptides to the systemic circulation, polypeptide cloning and synthesis will continue to be a problem for pharmaceutical scientists. A variety of kinds of transmucosal and transdermal penetration enhancers can be used to increase buccal permeation (Puratchikody et al., 2011).

Researchers are currently searching for new drug transport mechanisms outside of conventional polymer networks. The preparation and use of responsive polymeric systems using copolymers with desirable hydrophilic/hydrophobic interaction, block or graft copolymers, complexation networks responding

via hydrogen or ionic bonding and new biodegradable polymers particularly from natural edible sources are the main areas of focus in the development of novel materials in controlled release buccal adhesive drug delivery (Sudhakar et al., 2006). Scientists are working to create buccal adhesive systems through a variety of methods to increase the bioavailability of orally ineffective or less effective medications by modifying the formulation strategies. Additionally gaining interest is a novel buccal adhesive delivery system that protects the local environment while directing drug delivery to the buccal mucosa. Commercially effective dose forms now include solids, liquids and gels administered to the oral cavity (Puratchikody et al., 2011).

Current treatments do not prevent patients from developing mucositis that still limits the use of chemotherapy and radiation therapy (Sankar et al., 2011). The development of orotransmucosal drug delivery systems for medicinal drugs, particularly proteins and peptides, has two key challenges. The first issue is the digesting enzymes in the gastrointestinal (GI) system, specifically in the stomach, inactivating sensitive peptides. This can be avoided by creating drug carriers that shield the medications from the harsh conditions of the stomach before releasing the drugs into more favorable parts of the GI tract, particularly the lower parts of the intestinal tract and the oral mucosa (Blanchette et al., 2004).

13. FUTURE PROSPECTS IN OROTRANSMUCOSAL DRUG DELIVERY SYSTEM

Numerous novel formulations have reached different stages of development and approval as well as varying degrees of manufacturing and marketing success. A completely new class of biological medications has been created as a result of developments in molecular biology. These innovative medications still have not realized their full potential. Since parenteral administration is currently the only method available for delivering biological medications directly into the bloodstream to treat chronic conditions, many of these medications are being developed for this purpose. They would be extremely helpful in the treatment of many diseases if they could be administered transmucosally. Future research should focus on developing a delivery system that can effectively transfer novel biological therapies into and/or

across the oral mucosa. If these new treatments are administered to the right locations in a self-administrable manner, they may significantly alter the way many systemic and oral disorders are treated. If research on gene therapy can translate positive outcomes from lab settings into clinically secure and efficient dosage forms (Hearnden et al., 2012).

Future developments in vaccine design and administration of tiny proteins/peptides will influence buccal adhesive medication delivery. Due to the protection offered to medicinal entities and the higher absorption that results from increased contact time provided by the bioadhesive component, microparticulate bioadhesive systems are particularly intriguing (Sudhakar et al., 2006). The capacity to affect how medications are absorbed across the buccal mucosa faces exciting difficulties. Before the delivery through the buccal mucosa is safe and productive, many problems still need to be solved. The successful development of these innovative formulations necessitates the integration of a substantial amount of newly available information regarding the chemical make-up and physical composition of these unique materials (Puratchikody et al., 2011).

Oral cell-targeted delivery has shown tremendous promise in the field of health over the past few decades and has greatly improved the precise delivery of nutraceuticals in the body. Highly biosafe cell-targeted delivery systems are made from a variety of edible materials. The following areas of CDSEM performance need improvement when compared to delivery systems made of synthetic materials: improving the mucosal barriers removal, bioavailability and gastrointestinal stability (Li et al., 2022).

In recent years, research, experimentation and several clinical trials have focused a lot of attention on the fascinating field of drug delivery and nanomedicine in modern science (Pandit and Zeugolis, 2016). The recent drug delivery system has great potential, despite the obstacles that have prevented it from being used clinically. To help achieve efficiency we need to take research findings from the bench to the bedside, collaboration across academic theory, laboratory experimentation, medical knowledge, pharmaceuticals and excellent research is needed (Haider, 2020). Cell therapies have the potential to significantly address the bio-acceptability problems that drug delivery systems encounter. These will result in an effective single

dosage that prevents a significant buildup of medications in the system (Vargason et al., 2021). Cell therapies break through innate biological barriers, produce responses that seem natural within the system and appear to be a seemingly sustained source of complex biologics. Molecular imprinting polymers, inorganic mesoporous nanoparticles and microfluids are a few strategies being used to address drug delivery issues (Adepu and Ramakrishna, 2021). Using priming agents that can modify the biological environment in which drugs are administered—particularly those that can alter tissue form and function to support the administered drug without endangering the patient—is one method to increase the efficacy of drug delivery (Khalid et al., 2017). In the field of biomaterials, cell-based drug systems should also be taken into consideration. This refers to the use of cells in conjunction with nanobiomaterials, as cells are a natural part of the human body. This is a novel approach that is still in theory but looks to be very creative, encouraging drug delivery methods to achieve the maximum pattern of drug delivery. The effectiveness of these contemporary drug delivery systems and the difficulties associated with their use still require a great deal of study and clinical testing (Ezike et al., 2023).

14. RESULTS AND DISCUSSIONS IN OROTRANSMUCOSAL DRUG DELIVERY SYSTEM

An orthogonal collocation on finite elements combined with the NDSolve function was used to numerically solve the orotransmucosal fentanyl citrate delivery model for a 200- μg dose. A new manufacturing method, aimed at maintaining a high flow in the long term, was considered based on the release rate and the amount of drug synthesis that enters the systemic circulation. A normal run is displayed. Six different time-varying fentanyl citrate concentrations across a mucosa membrane are shown in one-eighth of each spherical shell (Kim and Simon, 2011).

Fentanyl concentrations in oral mucosal delivery have been shown at three-minute intervals by using one-eighth of a sphere (Fig. 6) (Kim and Simon, 2011).

A relatively new method of drug delivery is orotransmucosal products. The soft palatal drug delivery system is distinct from other orotransmucosal drug delivery systems and could be regarded as a new class of drug

delivery systems. This strategy is justified by the non-keratinized tissues that make up the soft palate tissue, which postpones absorption and prolongs drug release. Furthermore, salivary secretion and tongue activity have no effect on the site, making it a prime candidate for drug delivery soon. Drugs can be strategically targeted to the brain using this approach as well (Madhav et al., 2012).

The soft palatal mucosa is used as a primary drug delivery site for various APIs by appropriately formulating mucoadhesive-loaded

plates. This is the main finding of the research done on the soft palatal drug delivery system.

The results are noteworthy and encouraging in terms of extending the duration of drug delivery. However, this platform has a limitation in that, in order to achieve a prolonged release dosage form, the dose of API should be reduced and the dosage form needs to have significant mucoadhesivity with soft palatal mucosa (Madhav et al., 2012).

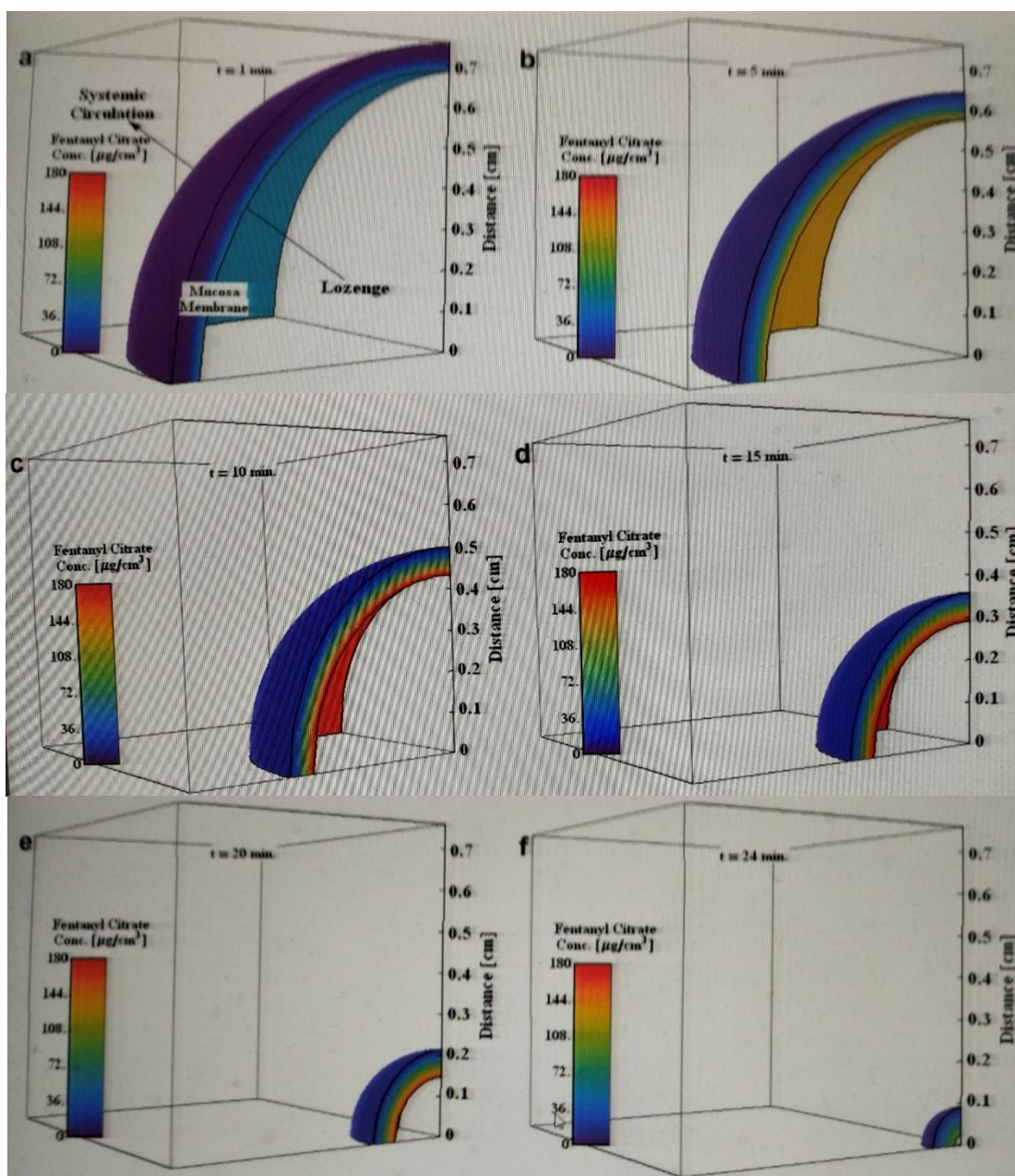


Fig. 6. Fentanyl concentrations in orotransmucosal drug delivery system

In vitro and *In vivo* study results have demonstrated that a substantial amount of drug reaches the brain via neural pathway for eliciting its pharmacological response. This innovative approach can also be used as a platform for brain targeting, which has been scientifically confirmed by suitably formulating insulin loaded bioadhesive films and same has been evaluated for its mucoadhesibility.

A novel discovery and inherent qualities of the soft palatal mucosa for systemic targeting of API delivery to the brain have been demonstrated by soft palatal drug delivery research. The ultimate objective in this field is to investigate the mucosal platform as an orotransmucosal drug delivery site for delivering API to the brain via systemic or site-specific targeting to minimize the dose of the drug and prolong its release (Madhav et al., 2012).

Researchers in this field should familiarize themselves with the anatomy, physiology, nerve supply, fundamentals of mucoadhesion and factors to be considered when choosing an appropriate excipient for the creation of mucoadhesive dosage forms. The largest obstacle to achieving good patient compliance is to have a soft palatal platform with distinct mucosal features from buccal and sublingual mucosae and a potential mucosal layer that can act as a targeting site for drug delivery. Though there are currently a few mucoadhesive formulations on the market, most APIs will soon be formulated as mucoadhesive formulations. This idea can be applied to maximize a drug's dosage and reduce any negative side effects. The orotransmucosal drug delivery system produces the drug's prolong ability and sustainability by delivering different APIs through soft palatal mucosa, lingual mucosa, nasal mucosa, oral aural mucosa, intestinal mucosa, lung mucosa, vaginal mucosa and sublingual platforms. This reduces the frequency of dosing and increases patient compliance (Madhav et al., 2012).

15. CONCLUSION

There are various methods being researched right now to efficiently transfer a variety of medicinal substances from the digestive tract into the bloodstream. Patient's preferences for oral dosage forms and some types of medicines better efficacy and toxicity are the driving forces behind these initiatives. Medicine has long been applied to the oral cavity to treat conditions that

originate in the mouth. The transmucosal route is becoming increasingly popular for systemic drug delivery due to its significant advantages compared to the oral route. Most devices only use chemical or physical release control to change the release rate. Orotansmucosal drug delivery has a few significant advantages. Drugs for the treatment of mucosal illnesses can be delivered topically, which can lessen adverse effects and enhance therapeutic results. Topical delivery technologies in oral medicine have more potential than has been yet completely realized. Further research targeting orotransmucosal drug applications is needed to improve treatment outcomes for diseases and disorders. The potential of local delivery methods for orotransmucosal drugs has not been yet fully realized. Current topical dermatological therapies are frequently inappropriate for use on oral mucosa since they were not intended for orotransmucosal drug administration. Using new formulations and techniques, researchers are investigating how to overcome permeability barriers, protect pharmaceuticals from enzymatic conditions and reliably reach their targets in therapeutic doses.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

As per international standards or university standards, Participants' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standards or university standards, written ethical approval has been collected and preserved by the author(s).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

- Acevedo R, Fernandez S, Zayas C, Acosta A, Sarmiento ME, Ferro VA, et al. (2014). Bacterial outer membrane vesicles and vaccine applications. *Frontiers in Immunology*, 5, 121.
- Acharya AP, Carstens MR, Lewis JS, Dolgova N, Xi CQ, Clare-Salzler MJ, et al. (2016). A cell-based microarray to investigate combinatorial effects of microparticle-encapsulated adjuvants on dendritic cell activation. *Journal of Materials Chemistry B*, 4(9), 1672-1685.
- Adepu S, Ramakrishna S. (2021). Controlled drug delivery systems: current status and future directions. *Molecules*, 26 (19), 5905.
- Akahata W, Yang ZY, Andersen H, Sun S, Holdaway HA, Kong WP, et al. (2010). A VLP vaccine for epidemic Chikungunya virus protects non-human primates against infection. *Nature Medicine*, 16(3), 334-338.
- Atwe SU, Ma Y, Gill HS. (2014). Pollen grains for oral vaccination. *Journal of Controlled Release*, 194(28), 45-52.
- Banoczy J, Squier CA, Kremer M, Wertz PW, Kovesi G, Szende B, et al. (2003). The permeability of oral leukoplakia. *European Journal of Oral Sciences*, 111(4), 312-315.
- Bastos F, Pinto AC, Nunes A, Simoes S. (2022). Oromucosal products-market landscape and innovative technologies: A review. *Journal of Controlled Release*, 348, 305-320.
- Bernkop-Schnurch A, Fragner R. (1996). Investigations into the diffusion behaviour of polypeptides in native intestinal mucus with regard to their peroral administration. *Pharmacy and Pharmacology Communications*, 2(8), 361-363.
- Blanchette J, Kavimandan N, Peppas NA. (2004). Principles of transmucosal delivery of therapeutic agents. *Biomedicine and Pharmacotherapy*, 58(3), 142-151.
- Cerf-Bensussan N, Gaboriau-Routhiau V. (2010). The immune system and the gut microbiota: Friends or foes? *Nature Reviews Immunology*, 10(10), 735-744.
- Chen F, Liu H, Wang B, Yang L, Cai W, Jiao Z, et al. (2020). Physiologically based pharmacokinetic modeling to understand the absorption of risperidone orodispersible film. *Frontiers in Pharmacology*, 10, 1692.
- Cheng H. (1974). Origin, differentiation and renewal of the four main epithelial cell types in the mouse small intestine. *American Journal of Anatomy*, 141(4), 481-502.
- Chiappin S, Antonelli G, Gatti R, De Palo EF. (2007). Saliva Specimen: A new laboratory tool for diagnostic and basic investigation. *Clinica Chimica Acta*, 383(1-2), 30-40.
- Choe SW, Acharya AP, Keselowsky BG, Sorg BS. (2010). Intravital microscopy imaging of macrophage localization to immunogenic particles and co-localized tissue oxygen saturation. *Acta Biomaterialia*, 6(9), 3491-3498.
- Chowdary KPR, Srinivas L. (2000). Mucoadhesive drug delivery systems: A review of current status. *Indian Drugs*, 37(9), 400-406.
- Darwish M, Hamed E, Messina J. (2010). Fentanyl buccal tablet for the treatment of breakthrough pain: Pharmacokinetics of buccal mucosa delivery and clinical efficacy. *Perspectives in Medicinal Chemistry*, 4(4), 11-21.
- D'Elia RV, Woods S, Butcher W, McGahon J, Khadke S, Perrie Y, et al. (2019). Exploitation of the bilosome platform technology to formulate antibiotics and enhance efficacy of melioidosis treatments. *Journal of Controlled Release*, 298(16), 202-212.
- Dimmitt RA, Sellers ZM, Sibley E. (2012). XIV-Gastrointestinal System-70 gastrointestinal tract development. In: Gleason CA, Juul SE. editors. *Avery's Diseases of the Newborn*. The Netherlands, Elsevier, 1032-1038.
- Dressman JB, Berardi RR, Dermentzoglou LC, Russell TL, Schmaltz SP, Barnett JL, et al. (1990). Upper gastrointestinal (GI) pH in young, healthy men and women. *Pharmaceutical Research*, 7(7), 756-761.
- El-Kattan A, Varma M. (2012). Oral absorption, intestinal metabolism and human oral bioavailability. In: Paxton, J. editor. *Topics on Drug Metabolism*. United States, IntechOpen Limited, 1-34.
- Ensign LM, Cone R, Hanes J. (2012). Oral drug delivery with polymeric nanoparticles: The gastrointestinal mucus barriers. *Advanced Drug Delivery Reviews*, 64(6), 557-570.
- Ezike TC, Okpala US, Onoja UL, Nwike CP, Ezeako EC, Okpara OJ, et al. (2023). Advances in drug delivery systems, challenges and future directions. *Heliyon*, 9(6), 17488.
- Ganem-Quintanar A, Falson-Rieg F, Buri P. (1997). Contribution of lipid components to

- the permeability barrier of oral mucosa. *European Journal of Pharmaceutics and Biopharmaceutics*, 44(2), 107-120.
- Gavhane YN, Yadav AV. (2012). Loss of orally administered drugs in GI tract. *Saudi Pharmaceutical Journal*, 20(4), 331-344.
- Giannola LI, De Caro V, Giandalia G, Siragusa MG, Campisi G, Florena AM, et al. (2007). Diffusion of naltrexone across reconstituted human oral epithelium and histomorphological features. *European Journal of Pharmaceutics and Biopharmaceutics*, 65(2), 238-246.
- Giannola LI, De Caro V, Giandalia G, Siragusa MG, Tripodo C, Florena AM, et al. (2007). Release of naltrexone on buccal mucosa: Permeation studies, histological aspects and matrix system design. *European Journal of Pharmaceutics and Biopharmaceutics*, 67(2), 425-433.
- Golshani S, Vatanara A, Amin M. (2022). Recent advances in oral mucoadhesive drug delivery. *Journal of Pharmacy and Pharmaceutical Sciences*, 25,201-217.
- Goyal AK, Singh R, Chauhan G, Rath G. (2018). Non-invasive systemic drug delivery through mucosal routes. *Artificial Cells, Nanomedicine, and Biotechnology*, 46(2), 539-551.
- Haider S. (2020). Nanoparticles: The future of drug delivery. *Journal of Young Investigators*, 38, 1–2.
- Hansson GC. (2012). Role of mucus layers in gut infection and inflammation. *Current Opinion in Microbiology*, 15(1),57-62.
- Hao J, Heng PWS. (2003). Buccal delivery systems. *Drug Development and Industrial Pharmacy*, 29(8), 821-832.
- Harsanyi BB, Hilchie JC, Mezei M. (1986). Liposomes as drug carriers for oral ulcers. *Journal of Dental Research*, 65(9), 1133-1141.
- Hearnden V, Sankar V, Hull K, Juras DV, Greenberg M, Kerr AR, et al. (2012). New developments and opportunities in oral mucosal drug delivery for local and systemic disease. *Advanced Drug Delivery Reviews*, 64(1), 16-28.
- Hines RM, Khumnrak M, Macphail B, Hines DJ. (2019). Administration of micronized caffeine using a novel oral delivery film results in rapid absorption and electroencephalogram suppression. *Frontiers in Pharmacology*, 10, 983.
- Holmgren J, Czerkinsky C. (2005). Mucosal immunity and vaccines. *Nature Medicine*, 11(4), S45-S53.
- Homayun B, Lin X, Choi HJ. (2019). Challenges and recent progress in oral drug delivery systems for biopharmaceuticals. *Pharmaceutics*, 11(3), 129.
- Hoogstraate AJ, Cullander C, Nagelkerke JF, Senel S, Verhoef JC, Junginger HE, et al. (1994). Diffusion rates and transport pathways of fluorescein isothiocyanate (FITC)-labeled model compounds through buccal epithelium. *Pharmaceutical Research*, 11(1), 83-89.
- Hua S. (2019). Advances in nanoparticulate drug delivery approaches for sublingual and buccal administration. *Frontiers in Pharmacology*, 10, 1328.
- Itin C, Barasch D, Domb AJ, Hoffman A. (2020). Prolonged oral transmucosal delivery of highly lipophilic drug cannabidiol. *International Journal of Pharmaceutics*, 581, 119276.
- James SP. (1993). The gastrointestinal mucosal immune system. *Digestive Diseases*, 11(3), 146-156.
- Johansson MEV, Sjoval H, Hansson GC. (2013). The gastrointestinal mucus system in health and disease. *Nature Reviews Gastroenterology and Hepatology*, 10(6), 352-361.
- Keselowsky BG, Acharya A, Lewis JS. (2020). Innate and adaptive immunity: The immune response to foreign materials. In: Wagner WR, Sakiyama-Elbert SE, Zhang G, Yaszemski MJ. editors. *Biomaterials Science (Fourth Edition)*. Amsterdam, Academic Press, 747-775.
- Khalid A, Persano S, Shen H, Zhao Y, Blanco E, Ferrari M, et al. (2017). Strategies for improving drug delivery: Nanocarriers and microenvironmental priming. *Expert Opinion on Drug Delivery*, 14(7), 865–877.
- Kim KS, Simon L. (2011). Transport mechanisms in oral transmucosal drug delivery: Implications for pain management. *Mathematical Biosciences*, 229(1), 93-100.
- Kolars JC, Awni WM, Merion RM, Watkins PB. (1991). First-pass metabolism of cyclosporin by the gut. *Lancet*, 338(8781), 1488-1490.
- Kulkarni U, Mahalingam R, Pather SI, Li X, Jasti B. (2009). Porcine buccal mucosa as an In vitro model: Relative contribution of epithelium and connective tissue as permeability barriers. *Journal of*

- Pharmaceutical Sciences*, 98(2), 471–483.
- Lam JKW, Xu Y, Worsley A, Wong ICK. (2014). Oral transmucosal drug delivery for pediatric use. *Advanced Drug Delivery Reviews*, 73, 50-62.
- Le T, Aguilar B, Mangal JL, Acharya AP. (2022). Oral drug delivery for immune engineering. *Bioengineering and Translational Medicine*, 7(1), 10243.
- Lennernas H. (1998). Human intestinal permeability. *Journal of Pharmaceutical Sciences*, 87(4), 403–410.
- Li N, Sood S, Wang S, Fang M, Wang P, Sun Z, et al. (2005). Overexpression of 5-lipoxygenase and cyclooxygenase 2 in hamster and human oral cancer and chemopreventive effects of zileuton and celecoxib. *Clinical Cancer Research*, 11(5), 2089–2096.
- Li X, Wei Z, Xue C. (2022). Oral cell-targeted delivery systems constructed of edible materials: Advantages and challenges. *Molecules*, 27(22), 7991.
- Lin S, Mukherjee S, Li J, Hou W, Pan C, Liu J. (2021). Mucosal immunity-mediated modulation of the gut microbiome by oral delivery of probiotics into Peyer's patches. *Science Advances*, 7(20), 677.
- Liu J, Wu J, Wang B, Zeng S, Qi F, Lu C, et al. (2013). Oral vaccination with a liposome-encapsulated influenza DNA vaccine protects mice against respiratory challenge infection. *Journal of Medical Virology*, 86(5), 886-894.
- Madhav NVS, Semwal R, Semwal DK, Semwal RB. (2012). Recent trends in oral transmucosal drug delivery systems: An emphasis on the soft palatal route. *Expert Opinion on Drug Delivery*, 9(6), 629-647.
- Madhav NVS, Shakya AK, Shakya P, Singh K. (2009). Orotransmucosal drug delivery systems: A review. *Journal of Control Release*, 140(1), 2-11.
- Malallah OS, Garcia CMA, Proctor GB, Forbes B, Royall PG. (2018). Buccal drug delivery technologies for patient-centred treatment of radiation-induced xerostomia (dry mouth). *International Journal of Pharmaceutics*, 541(1-2), 157-166.
- Meng Y, Li XJ, Li Y, Zhang TY, Liu D, Wu YQ, et al. (2023). Novel double-layer dissolving microneedles for transmucosal sequential delivery of multiple drugs in the treatment of oral mucosa diseases. *ACS Applied Materials and Interfaces*, 15(11), 13892-13906.
- Miquel-Clopes A, Bentley EG, Stewart JP, Carding SR. (2019). Mucosal vaccines and technology. *Clinical and Experimental Immunology*, 196(2), 205-214.
- Mohamadzadeh M, Olson S, Kalina WV, Ruthel G, Demmin GL, Warfield KL, et al. (2005). Lactobacilli activate human dendritic cells that skew T cells toward T helper 1 polarization. *Proceedings of the National Academy of Sciences of the United States of America*, 102(8), 2880-2885.
- Olmsted SS, Padgett JL, Yudin AI, Whaley KJ, Moench TR, Cone RA. (2001). Diffusion of macromolecules and virus-like particles in human cervical mucus. *Biophysical Journal*, 81(4), 1930-1937.
- Ozawa S, Clark S, Portnoy A, Grewal S, Stack ML, Sinha A, et al. (2017). Estimated economic impact of vaccinations in 73 low- and middle-income countries, 2001–2020. *Bulletin of the World Health Organization*, 95(9), 629-638.
- Pandit A, Zeugolis DI. (2016). Twenty-five years of nano-bio-materials: Have we revolutionized healthcare? *Nanomedicine*, 11(9), 985–987.
- Park KS, Park MJ, Cho ML, Kwok SK, Ju JH, Ko HJ, et al. (2009). Type II collagen oral tolerance; Mechanism and role in collagen-induced arthritis and rheumatoid arthritis. *Modern Rheumatology*, 19(6), 581-589.
- Patel M, Karigar A, Savaliya P, Ramana MV, Ashwini D. (2011). Buccal drug delivery system: The current interest. *International Research Journal of Pharmacy*, 2(12).
- Pather SI, Rathbone MJ, Senel S. (2008). Current status and the future of buccal drug delivery systems. *Expert Opinion on Drug Delivery*, 5(5), 531-542.
- Petschow BW, Talbott RD. (1994). Reduction in virus-neutralizing activity of a bovine colostrum immunoglobulin concentrate by gastric acid and digestive enzymes. *Journal of Pediatric Gastroenterology and Nutrition*, 19(2), 228-235.
- Pond SM, Tozer TN. (1984). First-pass elimination basic concepts and clinical consequences. *Clinical Pharmacokinetics*, 9(1), 1-25.
- Pridgen EM, Alexis F, Kuo TT, Levy-Nissenbaum E, Karnik R, Blumberg RS, et al. (2013). Transepithelial transport of Fc-targeted nanoparticles by the neonatal Fc receptor for oral delivery. *Science Translational Medicine*, 5(213), 167.
- Puratchikody A, Prasanth VV, Mathew S, Balaraman AK. (2011). Buccal drug

- delivery: Past, present and future -- A review. *International Journal of Drug Delivery*, 3(2), 171-184.
- Rhee JH. (2020). Current and new approaches for mucosal vaccine delivery. *Mucosal Vaccines*, 325-356.
- Rooks MG, Garrett WS. (2016). Gut microbiota, metabolites and host immunity. *Nature Reviews Immunology*, 16(6), 341-352.
- Rouge N, Buri P, Doelker E. (1996). Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. *International Journal of Pharmaceutics*, 136(1-2), 117-139.
- Rouphael NG, Paine M, Mosley R, Henry S, McAllister DV, Kalluri H, et al. (2017). The safety, immunogenicity, and acceptability of inactivated influenza vaccine delivered by microneedle patch (TIV-MNP 2015): A randomised, partly blinded, placebo-controlled, phase 1 trial. *Lancet*, 390(10095), 649-658.
- Rubin DC, Langer JC. (2016). Anatomy and development-small intestine: Anatomy and structural anomalies. In: Podolsky DK, Camilleri M, Shanahan F, Fitz JG, Wang TC, Kalloo AN. editors. *Yamada's Atlas of Gastroenterology*. United Kingdom, Wiley Blackwell Press, 19-24.
- Salamat-Miller N, Chittchang M, Johnston TP. (2005). The use of mucoadhesive polymers in buccal drug delivery. *Advanced Drug Delivery Reviews*, 57(11), 1666-1691.
- Sankar V, Hearnden V, Hull K, Juras DV, Greenberg MS, Kerr AR, et al. (2011). Local drug delivery for oral mucosal diseases: Challenges and opportunities. *Oral Diseases*, 17(1), 73-84.
- Sarti F, Perera G, Hintzen F, Kotti K, Karageorgiou V, Kammona O, et al. (2011). In vivo evidence of oral vaccination with PLGA nanoparticles containing the immunostimulant monophosphoryl lipid A. *Biomaterials*, 32(16), 4052-4057.
- Shaikh R, Singh TRR, Garland MJ, Woolfson AD, Donnelly RF. (2011). Mucoadhesive drug delivery systems. *Journal of Pharmacy and Bio Allied Sciences*, 3(1), 89-100.
- Shakya P, Madhav NVS, Shakya AK, Singh K. (2011). Palatal mucosa as a route for systemic drug delivery: A review. *Journal of Control Release*, 151(1), 2-9.
- Shimono M, Clementi F. (1976). Intracellular junctions of oral epithelium: I. Studies with freeze-fracture and tracing methods of normal rat keratinized oral epithelium. *Journal of Ultrastructure Research*, 56(1), 121-136.
- Shojaei AH. (1998). Buccal mucosa as a route for systemic drug delivery: A review. *Journal of Pharmacy and Pharmaceutical Sciences*, 1(1), 15-30.
- Sigurdsson HH, Kirch J, Lehr CM. (2013). Mucus as a barrier to lipophilic drugs. *International Journal of Pharmaceutics*, 453(1), 56-64.
- Sood S, Shiff SJ, Yang CS, Chen X. (2005). Selection of topically applied non-steroidal anti-inflammatory drugs for oral cancer chemoprevention. *Oral Oncology*, 41(6), 562-567.
- Squier CA, Hall BK. (1985). The permeability of skin and oral mucosa to water and horseradish peroxidase as related to the thickness of the permeability barrier. *Journal of Investigative Dermatology*, 84(3), 176-179.
- Sudhakar Y, Kuotsu K, Bandyopadhyay AK. (2006). Buccal bioadhesive drug delivery - a promising option for orally less efficient drugs. *Journal of Controlled Release*, 114(1), 15-40.
- Tiwari G, Tiwari R, Sriwastawa B, Bhati L, Pandey S, Pandey P, et al. (2012). Drug delivery systems: An updated review. *International Journal of Pharmaceutical Investigation*, 2(1), 2-11.
- Toussiroit EA. (2002). Oral tolerance in the treatment of rheumatoid arthritis. *Current Drug Targets, Inflammation and Allergy*, 1(1), 45-52.
- Trentham DE, Dynesius-Trentham RA, Orav EJ, Combitchi D, Lorenzo C, Sewell KL, et al. (1993). Effects of oral administration of type II collagen on rheumatoid arthritis. *Science*, 261(5129), 1727-1730.
- Treuting P, Dintzis S, Frevert C, Liggitt HD, Montine K. (2018). Upper Gastrointestinal Tract. In: Treuting PM, Dintzis SM, Montine K. editors. *Comparative Anatomy and Histology: A Mouse, Rat, and Human Atlas (Second Edition)*. London, Academic Press, 190-211.
- Tscheik C, Blasig IE, Winkler L. (2013). Trends in drug delivery through tissue barriers containing tight junctions. *Tissue Barriers*, 1(2), 24565.
- Valetti S, Riaz A, Doko A, Sultana K, Eskandari M, Prgomet Z, et al. (2022). Oral transmucosal delivery of eletriptan for neurological diseases. *International Journal of Pharmaceutics*, 627(4), 122222.

- Van der Lubben IM, Verhoef JC, Van Aelst AC, Borchard G, Junginger HE. (2001). Chitosan microparticles for oral vaccination: Preparation, characterization and preliminary In vivo uptake studies in murine Peyer's patches. *Biomaterials*, 22(7), 687-694.
- Vargason AM, Anselmo AC, Mitragotri S. (2021). The evolution of commercial drug delivery technologies. *Nature Biomedical Engineering*, 5(9), 951–967.
- Vazquez JA, Sobel JD. (2012). Miconazole mucoadhesive tablets: A novel delivery system. *Clinical Infectious Diseases*, 54(10), 1480-1484.
- Yun GA, Choi SU, Park KH, Rhee YS, Lee BJ, Lee JH. (2010). Pharmaceutical devices for oral cavity-based local and systemic drug delivery. *Journal of Pharmaceutical Investigation*, 40(spc), 113-118.
- Zhang H, Zhang J, Streisand JB. Oral mucosal drug delivery: Clinical pharmacokinetics and therapeutic applications. *Clinical Pharmacokinetics*, 41(9), 661-680.

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