Review Article

Challenges, Approaches & Applications ofOrotransmucosalDrug Delivery System

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 in 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-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, palataland gingival regions. Masticationor chewing foodcan 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 futureorotransmucosaldrug developments to treat oral mucosa diseases.

Keywords: Orotransmucosal; Transmucosal;Oral Mucosa;LHRH; CT; Mucoadhesion; MCG.

1. Introduction

Orotransmucosal drug delivery is an alternative method of systemic drug delivery system. Oraladministrationofdrugsthroughmucousmembraneshas severaladvantagesandlimitations.Mucosalsurfacesoftenhavearichbloodsupply,allowing for rapiddrugtransportintothesystemiccirculationandinmostcasesavoidingdegradationbyhepaticfirst-passmetabolism,thusenhancingdrugbioavailability.
Thesystem'scontactwiththereceptivesurfaceimprovesabsorptionatthesiteofapplication,increasesresidencetimeandallowsforonceortwicedailydosing [1].

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 [2].

Orotransmucosaldrugdeliveryusesanabsorptionratefourtimesthatoftheskin.Orotransmucosal drug delivery systemsarelimitedtoexistingproductsandcandidatesuntilchangesoccurinthedrugselectionanddevelopmentprocess [1].

Orotransmucosaladministrationisthepreferredroutefornon-parenteraladministrationofrescuedrugsanddrugswhenrapidonsetofactionisrequired. Furthermore,advancesindrugdeliverytechnologyhaveincreasedthepotentialfortransmucosalsystemicdeliveryofbiologicalagents [3].

Inrecentyears,oraltransmucosaladministrationhasemergedasanattractiverouteofadministrationforpediatricpatients.Inthisrouteofadministration,thedrugisabsorbedthroughthebuccalmucosa,bypassinghepaticfirst-passmetabolismandavoidingdrugeliminationmetabolisminthegastrointestinaltract [4].

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 medicationsis not permitteddue to drawbacks. As a result, different absorptive mucosae are taken into consideration as prospective drug delivery sites[1].

For systemic drug delivery, the mucosal linings of the nasal, rectal, vaginal, ocularand 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 tractanddepending on the specific medication, a superior enzymatic flora for drug absorption[5].

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[5].

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 damageand the absence of virtually all Langerhans cells makes the oral mucosa tolerant to potential allergens. Moreover, orotransmucosal drug administration avoids the GI tractspre-systemic elimination and first passes impact. These elements render the oral mucosal cavity an extremely desirable and practical location for systemic medication administration [5].

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 [5].

Drug bioavailability and controlled release rate are both boosted by oral mucoadhesive drug administration, which also improves pharmacokinetics. Also, it was demonstrated thatemploying this approach compared to commercial drug formulations[6].

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. 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[7]. 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 [1].

The small absorption area and the barrier property of the buccal mucosa contribute to the limitations of this route. Furthermore,duetotheconstantintakeofsalivaintheoralcavity,long-termstorageofdosageformstoimproveabsorptionatthispointisamajorchallenge [7] .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 orotransmucosal cavity will allow for longer delivery [1].

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. 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 [8].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 [1].

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 complianceand call for recurrent administration. 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 [1]. It is usedasaretentiondosageformtointroducetherapeuticagentsforsystemicadministration.The soft

palate must have a smooth surface and be flexible to prevent mechanical irritation and local pain [9].

2.4 Gingival/ Mucoadhesive

Mucosaladhesionsareconditionsinwhichtwosubstances,mucusormucousmembranes,sticktogetherforalongperiodoftime.Thetermmucoadhesionreferstotheattachmentofdrugcarrierstothemucuslayerofspecificbiologicalareasforthepurposeofdrugdelivery[9]. A series of phenomena, whose roles depend on the characteristics of the mucoadhesivemust occur for mucoadhesion to take place.Bonemarrowtransplantationandradiationtherapytotheheadandneck,especiallybonemarrowconditioningregimensforthetreatmentoforalcancer.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 [9].

The oral cavity consists of various structures, which includes sublingual, buccal, labial, palatal and gingival tissues have been described in Figure 1 [10].

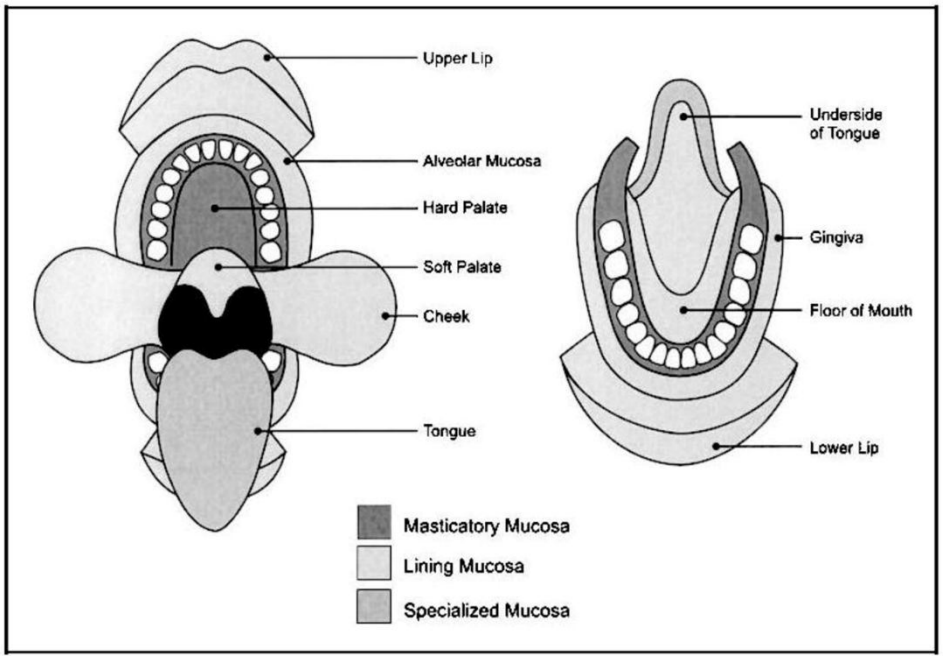

Figure 1: Geographic Representation of the Various Mucosa in the Oral Cavity

3. GI Tract Barriers in Orotransmucosal Drug Delivery System

3.1Physiochemical 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 [11]. The drug is exposed to the stomach's degradative environment and strong proteolytic gastric enzymes as it travels through the upper GI tract[12]. 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[12]. 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[13]. Therefore, it is important thatbiologics must be specially modified to endure the natural characteristicsof the gut[14].

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[15]. In their study, where cyclosporin was administered to the small bowel of two patients after liver transplantation, enzymatic degradation demonstrated this effect [15]. 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[16].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 [16].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 [13].The extreme physiochemical circumstances present in the GI tractare likely to blame for the decrease in medication availability in the systemic circulation.Oral medications are often supplied at a higher dose to counteract thefirst-pass effect; however, this alters the toxicity and effectiveness of numerous pharmaceuticals [14].

3.2Epithelial 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 [17]. These tight junctions act as a barrier that affects both paracellular and transcellular transport of molecules through epithelial tissue [18].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[19]. 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[14].

3.3Intestinal Microbiota

Microbiota refers to the microorganisms that live in animal'sguts and are essential for preserving immunological homeostasis [20]. 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 hazardmucus[21]. 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 environmentand intricate regulatory systems, it can also reduce the effectiveness of medications taken by mouth [20]. The same bacteria that stop drugs from passing through the gut can also be employed to treat immunotherapies by themselves [21]. Strangely, this study coated EcN with yeast membrane to target the M cells by using the -glucan imbedded on the membrane of the yeast [22]. 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 [14].

3.4Mucosal 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 [23]. However, oral treatments are less readily available to their targets due to the GI tracts ongoing mucus production [24]. 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 [25]. 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 [26]. Mucus is continuously secreted and excreted swiftly, trapping and eliminating foreign structures simultaneously and reducing the period. Because of its steric barriers and dynamic nature, the gut mucosa presents a particularly difficult obstacle for immunotherapeutics[27]. 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[28]. Moreover, it has been discovered that large proteins, particularly antibodiescan bind to mucins via electrostatic interactions or strong hydrogen bonds, thereby trapping them and preventing them from reaching systemic circulation [29]. Hence, it is essential to create oral to systemic immunotherapeutics that can get past the mucosal barriers [14].

Limitations on the amount of traffic in the GI tract and the amount of absorbable surface must also be overcome by immunotherapeuticsin Figure 2[14].

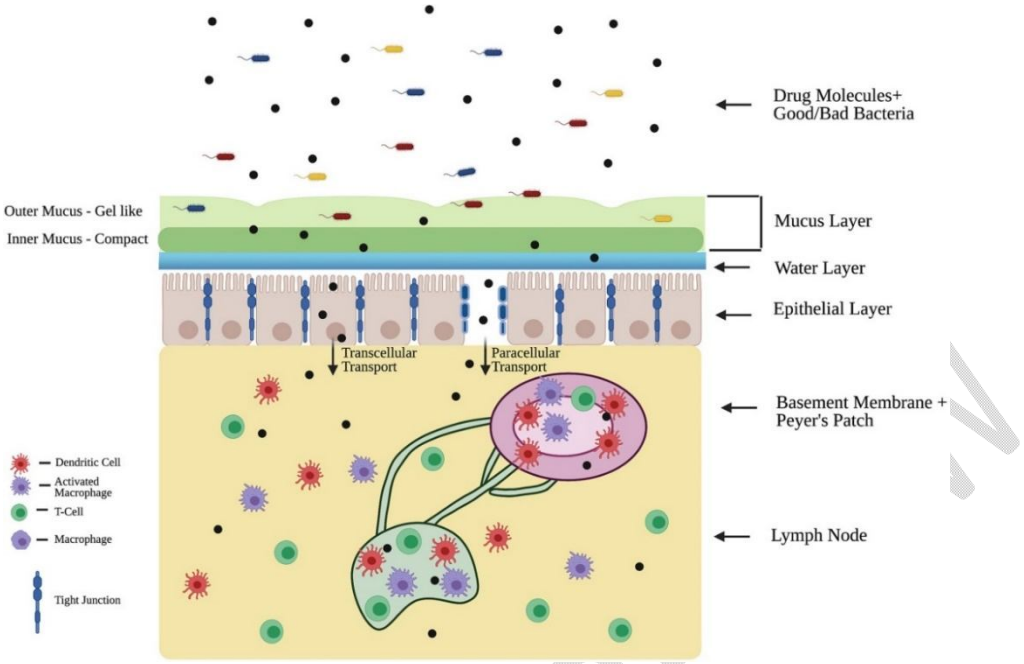

Figure 2: Drug Molecules Bypassing Various Barriers in the Intestinal Tract to reach Systemic Circulation

4. Characteristicsof Orotransmucosal Drug Delivery System

4.1 Permeability of the Oral Mucosa

Permeabilitybarrierspreventexogenousandendogenoussubstancesfromenteringthebodythroughthe orotransmucosa. It servestopreventfluidlossfromunderlyingtissuestotheenvironment [30]. The lipid content of the upper layers of the epithelium makes up most of the permeability barrier

[31]. Suprabasalcellshavestrongintercellulardesmosomejunctionsandmembrane-coatedgranules(MCG)ontheirapicalsurfaces. Strong intercellular desmosome junctions and membrane coating granules (MCGs) are produced on the apical surfaces of supra-basal cells as they develop [5]. TheseMCGsdeliverlipophilicsubstancestotheintercellulargapstomaintainepithelialintegrity.Theabilityofthislipophilicsubstancetoslowtheflowofhydrophilicsubstancesacrossepithelium [32].Epitheliumisamajorbarriertopermeability,suggestingthathighhydrationofconnectivetissueactsassomeresistancetolipophilicsubstances[1].

Due to the varying epithelial thickness and levels of keratinization at various sites, the oral mucosa's permeability varies across distinct areas.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 [33].The buccal mucosa and hard palate have the lowest levels of permeability and the sublingual mucosa is most easily permeable [34].

There are three ways to move material past the permeability barrier of the oral mucosa: passive diffusion, including (i) trans-cellular and para-cellular diffusion[35], (ii) carrier-mediated transport and endocytosis/exocytosis[32], (iii) in which cells actively take up and excrete material through the endocytic pathway [36]. Lipid-soluble compounds, non-ionized speciesand molecules with small molecular weights are the materials that diffuse the easiest [37]. Dextranwithamolecularweight of lessthan20,000Da.Althoughdiffusible,dextranswithmolecularweightsgreaterthan20,000Dadonot. A substances path of passive diffusion is determined by its lipophilicity, its partition coefficient between lipophilic and hydrophilic areas and its intercellular space diffusion coefficient [38]. DrugswithhighPkavaluesdiffusemoreeffectivelythroughorotransmucosa [1].

4.2Increased Permeability in Diseased Mucosa

Theorotransmucosadrugdiffusesmorefreelyintothetissueofulceratedorerodedareas due tothelackofapermeabilitybarrier [39].Orotransmucosaaffectedbylichenplanushassignificantlyincreasedpermeabilitycomparedtowhennoterodedorulcerated.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[40].

Malignantandorotransmucosallesionscanexhibitaltereddrugpermeabilityinthemucosa.The permeability of the cigarette carcinogen nitrosonornicotine 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 [41].

5. Challenges in Orotransmucosal Drug DeliverySystem

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[42]. There are upper and lower segments of the GI tract.The mouth, pharynx, esophagus, stomachand duodenum, the first segment of the small intestine are all considered to be parts of the upper GI tract[43]. The remaining small intestine and the cecum, colon and rectum of the large intestine are all parts of the lower GI tract [44]. All segments of the GI tract have a similar structure. Mucus, submucosaand multiple muscle layers enclose the lumen and are encircled by smooth muscle cells[42]. Lamina propria, muscularis mucosaeand 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 [43]. 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 [45]. In addition, the jejunum and ileum of the small intestines three major sections have more absorption capacity than the duodenum[46]. The average segment length, pH, mucus thickness, drug residence timeand bacterial diversity/population in various segments are some of the environmental parameters that affect medication integrity and absorption [26]. Technical difficulties and biological impediments can be used as broad categories to group oral administration issues [47]. Biological barriers are any biological elements that alter the properties of medications taken orally or prevent their effective absorption in the target [48]. 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 [49].

Schematic illustration in the Challenges ofOrotransmucosal Drug Delivery System has been shown in Figure 3[49].

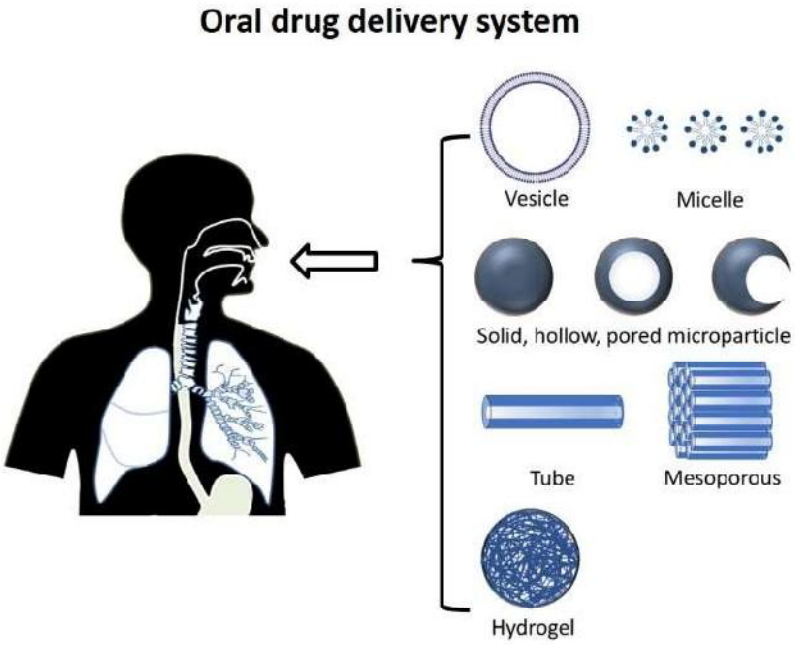

Figure 3: Schematic illustration in the Challenges of Orotransmucosal Drug Delivery System

6. Mechanism of Action in Orotransmucosal Drug Delivery System

The mechanism of fentanyl citrate oral transmucosal administration (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 [50].

The orotransmucosa is accessibility, excellent blood supply, bypass of hepatic first-pass metabolism, quick healing and permeability profile for local and systemic drug delivery systems in Figure 4 [3].

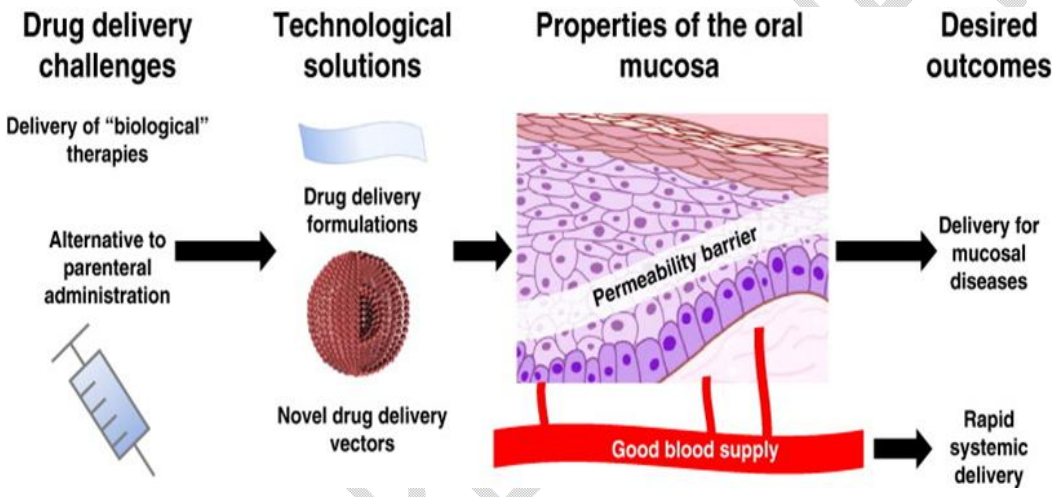

Figure 4: Mechanism in the Action of Orotransmucosal Drug Delivery System

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 [51].

Table 1 lists the orotransmucosal dosage forms available in the market [52].

Table 1: Lists of Orotransmucosal Dosage Forms available in the Market

Brand Name	Active Drugs	Applications	Manufacturer	Dosage Form
Onsolis	Fentanyl citrate	Opoid analgesic	Meda Pharmaceuticals	Buccal soluble film
BEMA	Buprenorphine	Opoid analgesic	Wolters Kluwer Health	Buccal soluble film
Gel-kam	Fluoride	Anticavities	CHATTEM Company	Oral gel

Table 1: Lists of Orotransmucosal Dosage Forms available in the Market (Contd.)

Brand Name	Active Drugs	Applications	Manufacturer	Dosage Form
Actiq	Fentanyl citrate	Opoid analgesic	Wolters Kluwer	Lozenge on a

			Health	stick
Fentora	Fentanyl citrate	Opoid analgesic	Wolters Kluwer Health	Buccal tablet
Sublimaze	Fentanyl Citrate	Opoid analgesic	Wolters Kluwer Health	Injection
ACT fluoride rins	Fluoride topical	Anticavity	CHATTEM Company	Oral solution
Amnatadine oral soluition 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 Zydis Ltd	Sublingual tablet
Gleclair	Glycyrrhetinic acid/ povidone/ sodium hyaluronate	Relieve mouth pain and irritation	Wolters Kluwer Health	Oral gel

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[4].

There are several barriers that need to be overcome in the development of orotransmucosal products in Figure 5[4].

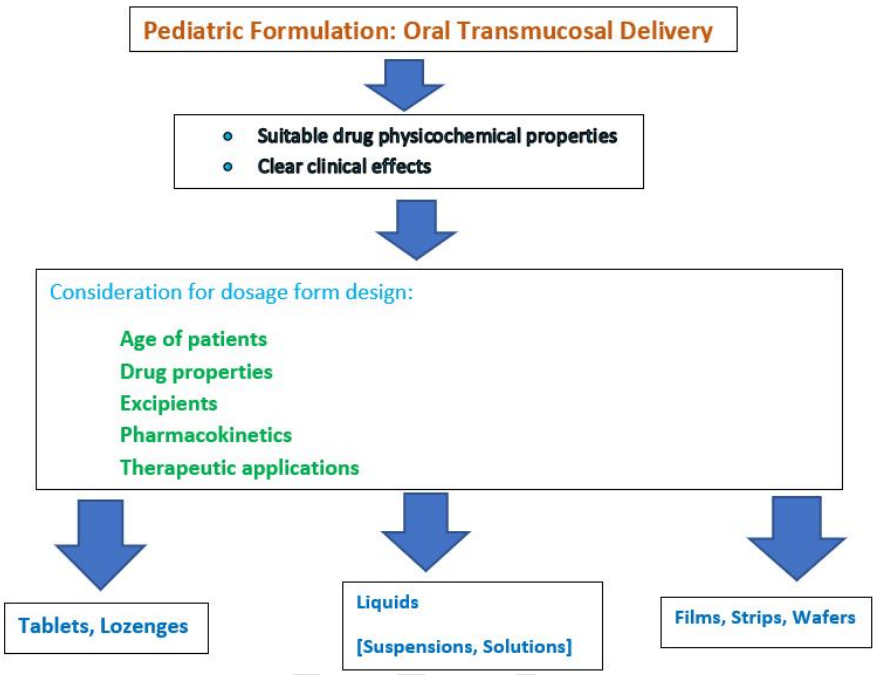

Figure 5: Orotransmucosal Drug Delivery for Pediatric Use

- ✓ 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 [53].

9.OrotransmucosalVaccination

The only vaccines that are given orally in the United States are the rotavirus, adenovirus, cholera vaccineand oral typhoid vaccines, even though there are more than 20 vaccines that are now delivered there [54]. Many vaccines are currently administered via intradermal or intramuscular injections, which come with risks and a high price tag for mass immunization[55]. 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 [56]. As a result, it can be very advantageous to target and induce mucosal immune responses against self- or pathogenic proteins for tolerance [57]. An interesting target for developing vaccines that induce tolerance is the mucosal immune system, which is notable for tending to be immunosuppressive [58]. 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[59].

Antigen-presenting cellsare exposed to transcytosed antigens by specialized M-cells with the purpose of inducing immunological responses [60]. 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[61].

In autoimmune disorders, where tolerance to numerous antigens is required, mucosa-targeted vaccinations can also have a significant impact [62]. Autoimmune illnesses cause immune responses to be mounted against self-antigen [63]. Regarding oral antigen delivery specifically, clinical trials have yielded conflicting resultsand no cure has yet been approved [64]. By directly delivering target antigens to the mucosal immune systems cells, one possible method for eliciting a potent tolerance-inducing response[65]. Additionally, a formulation that can deliver molecules that promote tolerance in addition to an antigen can significantly enhance immune responses[66].

The development of oral vaccination administration methods has advanced significantlyand pre-clinical testing of these systems has also taken place [67]. For instance, M cells in the Peyer's patches can pick up chitosan and alginate microparticles, whichcan then be directly absorbed by the MALT to trigger a series of immunological response[68]. The connected systemic and mucosal responses required for persistent immunity have been successfully induced by

polymeric nanoparticles like poly (lactide-co-glycolide) (PLGA) [69]. 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 diseasesor antibiotics entrapped in biosomes with success against the bacterium Burkholderiapseudomallei are additional candidates [70]. 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 [14].

Table 2 lists thecurrent and new approaches for orotransmucosal vaccine delivery systems used in the oral route [71].

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

Table 2: Current and New Approaches for Orotransmucosal Vaccine Delivery(Contd.)

Sl.	Delivery	Examples	Applications	Advantages	Disadvantages

No.	System				
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, Haemophillus 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

10. Orotransmucosal Products available in Bangladesh

According to the examination of market data for the previous 20 years (2002-2021) collected from CortellisTM [72]. 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 [73]. Severalsold-out pills helped to achieve this: Oravig®/ Loramyc® and FentoraTMboth feature OraVescent® and Lauriad® technologies respectively [74]. Several gels have undergone systemic and local testing. OralBalance® is a salivary substitute for the treatment of dry mouth[75]. For the local delivery of antimicrobial agents for buccal infections, suspensions or solutions are typically marketed as mouthwashes or rinses [76]. 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 [77]. 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 useand minimize social dysfunction in illnesses [78].

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 dissolutionand 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 orotransmucosal ulcer model demonstrated that these novel HAMA-HA-PVP MNs quickly penetrated the mucosa, dissolved and effectively released the drugand 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, multipermeable, mucosaland needle-free alternative for biomedical applications [79].

- 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 orotransmucosaldrug delivery of eletriptan via the oral cavity and paves the way for clinical investigations for fast and safe migraine treatment [80].

- 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 $_{0\text{-}t}$ (P=0.4327), $AUC_{0\text{-}\infty}$ (P=0.32780, Cmax (P=0.0531) and Tmax (P=0.27775) values. These values werenot 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 [81].
- 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 [82].

12. Current Statuses of OrotransmucosalDrug 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 [83]. 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 [1]. When compared to more traditional administration methods for children, orotransmucosaldrug delivery has a few significant advantages [4].

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[84].

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 [36]. 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, liquidsand gels administered to the oral cavity[84].

Currenttreatmentsdonotpreventpatientsfromdevelopingmucositisthatstilllimitstheuseofchemotherapyandradiationtherapy [40]. The development of oral 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 [85].

13. Future Prospects in OrotransmucosalDrug 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 medicationsstill 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 orotransmucosally. 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 [3].

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 [36]. 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 [84].

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, bioavailabilityand gastrointestinal stability [86].

In recent years, research, experimentationand several clinical trials have focused a lot of attention on the fascinating field of drug delivery and nanomedicine in modern science[87].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, pharmaceuticalsand excellent research is needed [88]. 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 [89]. Cell therapies break through innate biological barriers, produce responses that seem natural within the systemand appear to be a seemingly sustained source of complex biologics. Molecular imprinting polymers, inorganic mesoporous nanoparticlesand microfluids are a few strategies being used to address drug delivery issues[90].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 [91]. 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 [92].

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 (Appendix 1).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 [50].

Fentanyl concentrations in oral mucosal delivery has been shown at three-minute intervals by using one-eight of a sphere in Figure 6 [50].

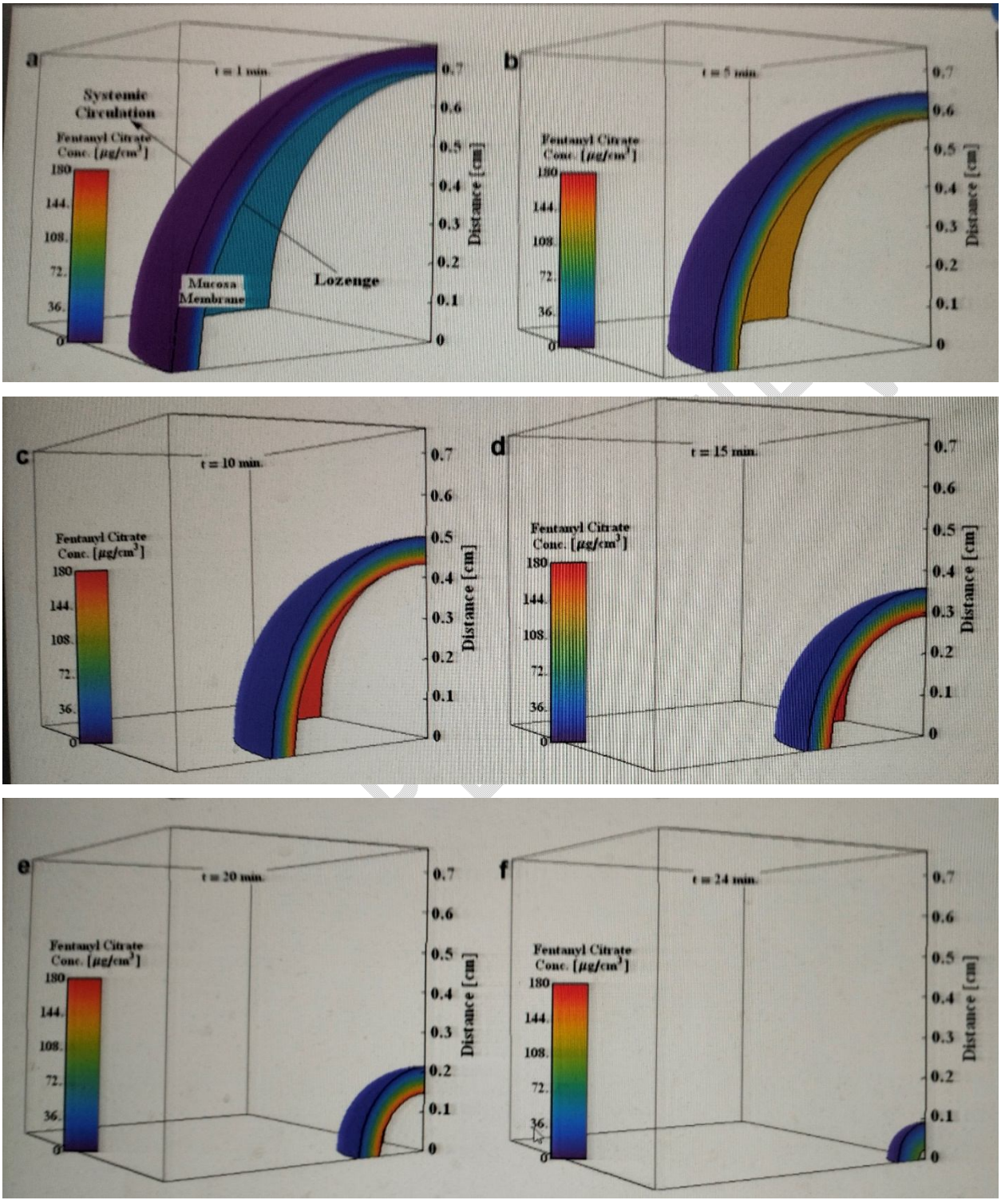

Figure 6: Fentanyl concentrations in oral mucosal delivery, shown at three-minute intervals, using one-eight of a sphere.

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 deliverysoon. Drugs can be strategically targeted to the brain using this approach as well[52].

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 [52].

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 loadedbioadhesive 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 anorotransmucosal 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[52].

Researchers in this field should familiarize themselves with the anatomy, physiology, nerve supply, fundamentals of mucoadhesionand 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 mucodhesive formulations on the market, most APIs will soon be formulated as mucoadhesive formulations. This idea can be

applied to maximize a drugs dosage and reduce any negative side effects. The orotransmucosal drug delivery system produces the drugs prolong ability and sustainability by delivering different APIs through soft palatal mucosa, lingual mucosa, nasal mucosa, oral aural mucosa, intestinal mucosa, lung mucosa, vaginal mucosaand sublingual platforms. This reduces the frequency of dosing and increases patient compliance [52].

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'spreferences 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. Theorotransmucosalrouteisbecomingincreasinglypopularforsystemicdrugdeliveryduetoitssignificantadvantagescomparedtotheoralroute.Most devices only use chemical or physical release control to change the release rate. Orotransmucosal 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. Furtherresearchtargetingoraldrugapplicationsisneededtoimprovetreatmentoutcomesforthediseases anddisorders. Thepotentialoflocaldeliverymethodsfororaldrugshasnotbeen yet fullyrealized.Current topical dermatological therapies are frequently inappropriate for use on oral mucosa since they were not intended for oral administration. Usingnewformulationsandtechniques,researchersareinvestigatinghowtoovercomepermeabilitybarriers,protectpharmaceuticalsfromenzymaticconditionsandreliablyreachtheirtargetsintherapeuticdoses.

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