Nanotechnology Perceptions
ISSN 1660-6795
www.nano-ntp.com

Novel Mucosal Deliver of Selegiline: A Review

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The low bioavailable of pharmaco active drugs limits their pharmacological potential so different approaches to improve are employed to enhance their bioavailability. Selegiline active molecules with low absorption parameter convey a higher risk of failure for drug innovation and development. Pharmacokinetics, pharmacodynamics, and several other parameters, such as drug distribution, protein binding, are majorly affected. Formulation of mucoadhesive dosage form will help in bypass the problem faced by oral dosage form which is mainly first pass mechanism. The poorly absorbed drug restrains the therapeutic efficacy of drug and also create difficulties its pharmaceutical development. This review mainly describes several other mucoadhesive formulation for bioavailability enhancement.

Keywords: Selegiline, mucoadhesive, buccal drug delivery, oral cavity, mucoadhesive dosage.

1. Introduction

Deprenyl (phenylisopropyl-N-methylpropinylamine) was discovered in Hungary by Z. Ecseri and J. Knoll in 1961. E-250, formerly described as such, was identified as a new spectrum irreversible inhibitor of monoamine oxidase (MAO).(1) E-250 included a racemic mixture of the two enantiomers, (-) and (+)-deprenyl.E-250 had psychostimulant characteristics and was noted for its antidepressant efficacy in humans; however, the doses provided were somewhat high (50-100 mg daily).E-250 was seen to mitigate the hypertensive effects of tyramine, unlike other MAO inhibitors.(2) The two optical isomers of E-250 were later separated. The 1-form shown reduced toxicity; (+)-deprenyl elicited hyperthermia and agitation in rats, but the 1-form was about 500 times more potent as an MAO inhibitor. The l-form was later designated the official generic name, Selegiline.(3)Selegiline Monoamine Oxidase Inhibitor and Monoamine Oxidase Type B Inhibitor. Selegiline was investigated as a potential therapeutic agent for Parkinson disease, owing to its extensively studied neuroprotective properties. Many studies also confirmed the drug's favourable tolerability. Nevertheless, certain trials demonstrated only marginal, clinically insignificant enhancements in behavioural functions. There is research conclude that selegiline offer mild transient benefits these ids because of

drug's low bioavailability. The compound was synthesized by Zoltán Ecseri at Chinoin Pharmaceuticals in 1962, alongside a series of structurally related drug candidates, however, this compound exhibits very low oral bioavailability, posing a challenge for drug delivery. The buccal route allows drugs to enter systemic circulation directly, potentially leading to faster onset of action, which is crucial for managing symptoms of Parkinson. Which can be a good targeted route to deliver Selegiline. To deliver selegiline which offer promising alternatives that bypass the challenges associated with oral administration, providing faster absorption and potentially improving the pharmacokinetic profiles of drugs. (4) The existing drug delivery system involves formulations, such as mixing the drug with edible binders or preparing it as a solution. Although these methods are very common, they have some major flaws to deliver selegiline. Conventional DDS often has problems like dosage that isn't regulated, low bioavailability, release that isn't controlled, less therapeutic efficacy, and even poses toxicity.(5) For example, low bioavailability, toxicity etc. Therefore, there is a demand for new drug delivery systems (NDDS) that can get past the drawbacks of usual methods. NDDS for selegiline aim to increase the competence of the treatment of drugs while lowering the number of side effects, often by improving the delivery, targeting, or release of the drug. To boot, new drug delivery system can offer controlled and sustained release profiles, which ascertain that the drug remains at therapeutic levels for prolong periods. Oral route of drug delivery is extensively implemented for drug administration, particularly for chronic conditions that require prolong treatment. (6)The drug delivers sublingually or through buccal cavity is absorbed into the rich vascular network found in the oral mucosa, allowing for swift and efficient entry into systemic circulation. These routes are particularly useful for drugs that require rapid onset of action or that are poorly absorbed in the GI tract. Conventional oral drug delivery remains the most commonly used route, its limitations, such as pre-systemic metabolism and enzymatic degradation.(7) In this review we will explore the buccal drug delivery of selegiline including discussion on buccal and sublingual anatomy and pathways and how it is deploy as a novel approach to deliver selegiline through buccal route.

Selegiline

Selegiline, a monoamine oxidase (MAO) inhibitor, is sanctioned by the U.S. Food and Drug Administration (FDA) as an adjunctive therapy for individuals with Parkinson's disease and major depressive disorder in adults. The MAO enzymes are involved for the catabolism of neurotransmitters like norepinephrine, serotonin, and dopamine. Inhibiting these enzymes will obstruct the reuptake of neurotransmitters in the central nervous system, leading to increased concentrations of physiologically active monoamines in the synaptic cleft. Selegiline is furthermore used off-label for the management of early Parkinson's disease and the treatment of attention-deficit hyperactivity disorder. This activity offers a comprehensive summary of selegiline's indications, mechanism of action, routes of administration, notable side effects, contraindications, and monitoring protocols .(8)This knowledge also improves the proficiency of healthcare team members to successfully lead patient treatment and address specified conditions as part of an interprofessional team.(9)

The Mechanism of Action of Selegiline

Selegiline functions as an irreversible monoamine oxidase inhibitor (MAOI).The MAO enzymes are involved for the catabolism of neurotransmitters like norepinephrine, serotonin,

and dopamine.(10) Inhibiting these enzymes will obstruct the reuptake of neurotransmitters in the central nervous system (CNS), leading to increased concentrations of physiologically active monoamines at the synaptic cleft.(2)At reduced dosages, selegiline demonstrates selective inhibition of B-type monoamine oxidase (MAO-B). The aetiology of Parkinson's disease is the degeneration of dopamine-producing neurones in the substantia nigra of the midbrain, resulting in a reduction of dopamine in the striatum. Consequently, the treatment of Parkinson's disease focusses on specific MAO-B inhibition, given that MAO-B mostly metabolises dopamine.

The selective suppression of MAO-B is not the intended result of using selegiline for the treatment of major depressive disorder in adults. (11)The efficacy of selegiline in treating major depressive disorder (MDD) is due to its suppression of the isoenzymes MAO-A and MAO-B. The monoamine hypothesis of depression asserts that the pathophysiological foundation of depression is characterised by a reduction in serotonin, norepinephrine, and dopamine levels in the central nervous system. The objective of treating MDD is to elevate the levels of all three monoamine neurotransmitters, hence nonselective inhibition of both MAO subtypes is favoured. (12)

The whole mechanism of action of selegiline, like to other psychotropic medicines, remains incompletely elucidated. While the aforementioned pathways are well acknowledged, several hypothesised mechanisms may also enhance selegiline's therapeutic usefulness. A theory posits that selegiline's metabolites, such as amphetamine, may contribute to its mechanism of action by augmenting the release of monoamine neurotransmitters. (13)Moreover, selegiline may have neuroprotective benefits, possibly decelerating the advancement of Parkinson's disease, by enhancing the synthesis of neurotrophins, including brain-derived neurotrophic factor, nerve growth factor, and glial cell line-derived neurotrophic factor. These neurotrophins are essential for protecting neurones against inflammation. Selegiline may preserve healthy brain tissue by inducing and activating several antioxidative stress and anti-apoptotic mechanisms. (14)

Pharmacokinetics of Selegiline

The absorption of selegiline experiences significant first-pass metabolism in the liver and gastrointestinal system. The oral formulation has limited bioavailability (4%).The distribution of selegiline results in peak plasma levels of its metabolites being roughly 4 to 20 times greater than the highest plasma concentration of selegiline itself.(15) Nevertheless, the levels of amphetamine and methamphetamine do not elicit stimulatory effects. Selegiline has significant plasma protein binding, particularly with macroglobulin and albumin. The metabolism of Selegiline results in the formation of N-desmethyl selegiline, L-amphetamine, and L-methamphetamine. N-desmethylselegiline has MAO-B inhibiting action. The average elimination half-life of selegiline is 2 hours. Under steady-state concentration, the elimination half-life increases to 10 hours.(16)

The Oral Cavity

The oral cavity consists of specialised soft and hard tissues that have evolved to start and support oral processes, including mastication, prehension, deglutition, and phonation. Labia The exterior anatomy of the oral cavity. Teeth are the structures that chew food.(17) Gingiva

it is the tissue around the teeth is the hard palate, which is the bony front section of the oral cavity's roof, while the soft palate refers to the muscular posterior section of the roof of the mouth. Retromolar trigone it is the region posterior to the wisdom teeth. Gustatory receptors are present in the tongue facilitate taste. The oral cavity is lined by a mucous membrane (the oral mucosa) consisting of a stratified squamous epithelium which plays and important role in drug absorption when it is deliver through buccal route.(18)

Oral Epithelium

The inside of the mouth is lined with stratified squamous epithelium, a very well organized, bloodless, and partially permeable tissue. It depends on where it is and what it needs to do to change the thickness and degree of keratinization. There are rete pegs, which are projections from the deeper layers of the epithelium that connect with papillary projections from the lamina propria. (19) The basement membrane, a non-cellular structure that supports the epithelium and links it to the connective tissue, lies between these two layers. The oral mucosa is divided into three main types which are lining mucosa, masticatory mucosa and specialized mucosa, with each having its own histology, clinical features, and functions. (20)This mucosa covers the parts of the mouth that move whereas masticatory Mucosa is made up of the attached gingiva and the hard palate. It is covered by squamous epithelium that is either keratinized or para-keratinized. The mucosa is very close to the bone below and helps to support the stress from biting. Specialized mucosa is on the back of the tongue and has different kinds of lingual papillae and taste buds that help us taste things. In this case, the epithelium can be keratinized or not keratinized. (21)

Layers of the Oral Epithelium

The keratinized oral mucosa consists of four distinct layers. The cuboidal cells that are connected to the basement membrane are known as the stratum basale tissues, known for their mitotic capacity. Stratum granulosum is Cells contain keratohyalin granules, which stain darkly with hematoxylin.Stratum corneum is the outermost layer, consisting of flat, keratinized cells devoid of a nucleus, which stain pink with eosin.In the non-keratinized epithelium (lining mucosa), the stratum filamentosum and stratum distendum replace the granular and cornified layers. The non-keratinized epithelium has a thinner spinous layer and lacks the granular layer.(22)

Oral Epithelium Replenishment

The oral epithelium has a high turnover rate, with cells being replaced every 14 to 21 days. The process begins in the stratum basale, where mitotic cells proliferate, differentiate, and migrate to the surface. The turnover is faster in movable mucosa than in masticatory mucosa. Homeostasis is maintained by balancing cell division and desquamation (shedding of the superficial layer).(23)

Non-Keratinocyte Cells in the Oral Epithelium

In addition to keratinocytes, the oral epithelium contains several specialized non-keratinocyte cells, including. Melanocytes is Located in the basal layer; these cells produce melanin and contribute to skin and mucosal pigmentation. Langerhans Cells are found in the stratum spinosum; they play an important role in immune surveillance by acting as antigen-presenting cells. Merkel Cells are Sensory receptors located in the stratum basale, primarily in the

keratinized epithelium, contributing to mechanoreception.(24)

Lamina Propria

The lamina propria is a layer of connective tissue that is located underneath the epithelium. It is made up of blood vessels, nerves, fibroblasts, macrophages, mast cells, and inflammatory cells, all of which are embedded in a matrix of proteoglycans and glycoproteins. (25)

Buccal Mucosa as a Site for Drug Delivery

The buccal mucosa is thought to be a good place to deliver drugs because its surface is smooth and doesn't move around much. This makes it perfect for long-lasting formulations. However, its permeability is lower than that of the sublingual mucosa, making it more suited for sustained delivery applications rather than rapid drug absorption. While buccal drug delivery has certain advantages, including avoiding first-pass metabolism and presystemic elimination, it also has limitations, such as low drug bioavailability. Various penetration enhancers have been investigated to improve drug absorption, such as sodium glycocholate and bile salts, which increase permeability by opening intercellular and transcellular routes.(26) There are three ways that drugs can be delivered in the mouth, sublingually, buccalally, and locally. Which of these routes to use depends on how the different oral mucosal sites are built and how well they let substances through. (27)Because the sublingual mucosa is pretty permeable, it helps drugs absorb quickly and be bioavailable. This makes it convenient, easy to get to, and generally accepted. Most sublingual drug formulations are made up of tablets that break down quickly or soft gelatine capsules that are filled with liquid drug solutions. These quickly dissolve and provide a high local concentration of the drug for absorption across the sublingual mucosa.(28)

However, the buccal mucosa is less permeable than the sublingual area, leading to slower absorption and lower bioavailability. In spite of these drawbacks, the buccal cavity has distinct leverage for specific applications, such as sustained-release drug delivery systems and systemic transmucosal delivery sublingual delivery is supreme for drugs requiring rapid onset, buccal delivery is more suited for drugs needing sustained release, especially those with low permeability. The vascularised and smooth surface of the buccal mucosa enhances the retention of drug delivery systems, such as mucoadhesive formulations. Therefore, the buccal mucosa is increasingly studied for the delivery of large molecules, peptides, and proteins, which benefit from sustained release. However, a significant pitfall of buccal drug delivery is the low flux, which results in lowered drug bioavailability. To resolve this, researchers have explored various permeation enhancers to improve drug transport across the buccal epithelium layer.(29) Many compounds used in other mucosal tissues for boosting drug permeation have shown efficacy in enhancing buccal drug delivery. For instance, small molecules such as butyric acid and butanol, ionizable drugs like acyclovir and propranolol, large molecular weight hydrophilic polymers like dextran’s, and peptides including octreotide, insulin, and luteinizing hormone-releasing hormone (LHRH) have been explored. The use of di- and tri-hydroxy bile salts, such as sodium glycocholate (SGC), has shown promising results. (30)Studies demonstrated that SGC significantly increased the permeability of porcine buccal mucosa to fluorescein isothiocyanate (FITC)-labeled dextran, boosting permeability by 100-200 times. This effect was concentration-dependent, with lower concentrations enhancing intercellular transport and higher concentrations opening up a transcellular route.(31)

Also, the ways that penetration enhancers like sodium deoxycholate and sodium lauryl sulfate help get drugs into the mouth are explained. Their research showed that these enhancers make it much easier for drugs like salicylic acid to pass through the buccal mucosa of rabbits. This suggests that the top layers and protein regions of the epithelium are very important for keeping the barrier function of the buccal mucosa.(32)

Buccal Drug Absorption Pathways

There are two main pathways for passive drug transport across the oral mucosa, paracellular route and transcellular route in paracellular Route the Drugs diffuse between cells, primarily suitable for hydrophilic compounds and in transcellular Route the Drugs pass directly through the cells, ideal for lipophilic compounds. While both pathways may be used simultaneously, one generally predominates based on the drug's physicochemical properties.(33)

Factors Affecting Buccal Absorption

There are several factors can influence drug absorption through the buccal mucosa, including, membrane Factors like degree of keratinization, surface area, mucus layer, intercellular lipids, basement membrane, and lamina propria. Environmental Factors like the presence of saliva, mucus secretion from salivary glands, and the movement of oral tissues. These factors interact to reduce the concentration of drugs available for absorption, making the buccal mucosa a challenging but promising route for drug delivery. (34)The paracellular route (between cells) and the transcellular route (through cells) are the two passive transport pathways that drugs go through the oral mucosa. While drugs can use both pathways simultaneously, one typically dominates depending on the drug's physicochemical properties. Hydrophilic drugs struggle to pass through the lipophilic cell membrane, whereas lipophilic drugs face resistance within the hydrophilic intercellular spaces and cytoplasm. The primary barrier for hydrophilic drugs is the cell membrane, while the intercellular spaces create the main resistance for lipophilic drugs. Given that the oral epithelium is stratified, solute permeation may involve a combination of these routes, with the pathway offering the least resistance being favoured.(35) The buccal cavity presents a difficulties environment for drug absorption, with various factors manipulating the concentration of the drug at the site of absorption. These factors can be classified into membrane and environmental factors. Membrane factors like degree of keratinization, the extent of keratinization in the buccal mucosa affects drug permeability, with more keratinized tissues acting as a stronger barrier. Intercellular lipids present in the epithelium can create resistance to drug permeation, particularly for hydrophilic drugs. Also, area for absorption is also plays an important role, a larger surface area aids greater drug absorption. Mucosal lining which is the moist, inner lining of oral cavities impede drug absorption, as it acts as a physical barrier.(36) Intercellular lipids which are present in the epithelium, can create withstanding to drug permeation, particularly for hydrophilic drugs. Basement membrane and lamina propria are the structures contribute to the barrier function of the mucosa and affect drug transport to the systemic circulation. Thicker membranes impede drug absorption, as the drug must travel a greater distance to reach the systemic circulation. (46)Blood supply and lymphatic drainage also impact the absorption good blood supply aids drug absorption, while lymphatic drainage can lower drug availability by removing the drug from the absorption site. Cell renewal and enzyme content is the high turnover rate of cells and the presence of enzymes can lead to drug degradation before absorption occurs.(37)

Environmental Factors of oral cavity-like saliva, salivary glands, movement of oral tissues affect buccal absorption. A thin layer of saliva coats the buccal mucosa, which affect drug absorption. The thickness, of this salivary film influence drug permeation across the mucosa. The salivary glands in the buccal mucosa secrete mucus. While this mucus can help retain mucoadhesive drug formulations, it also serves as a potential hindrance to drug permeation. The Movement of oral tissues have an impact in oral absorption ,the buccal region exhibits lesser tissue movement compared to other areas of the oral cavity.(38) Regardless, movements such as talking, eating, and swallowing can displace drug formulations from the absorption site. To counter this, mucoadhesive polymers are often encompassed into buccal drug formulations to maintain the drug at the buccal region for extended periods, allowing for continuous absorption despite tissue movement.(39)

Factors Affecting Oral Mucoadhesion

Mucoadhesion is the ability of a substance to adhere to mucosal tissues, is a critical aspect in the structure and effectiveness of various drug delivery systems, particularly those targeting mucosal surfaces such as the oral cavity.(40) The numerous factors influence mucoadhesion, encompassing properties related to the polymers used, environmental conditions, and physiological variables. Understanding these factors is essential for optimizing the performance of mucoadhesive formulations.(41) Factors like molecular weight, Active Polymer Concentration, Polymer Chain Flexibility, Spatial Conformation, Cross-Linking Density, Hydrogen Bonding Capacity, Charge Sign of Polymer and Hydration are the polymer related factors effecting muccoadhesion. Molecular weight plays a remarkable role in determining the bioadhesiveness of polymers. For linear polymers,increase in molecular weight generally enhances mucoadhesion. (42)This is because high molecular weight polymers can provide more physical tangle with the mucosal surface. They can also generate an expanded surface area for interaction with mucin molecules. Nonetheless, molecular weight and the polymer type employed also influence mucoadhesion. Spatial Conformation is also plays an significant role,the spatial arrangement of a polymer molecule can also influence its adhesive properties. Polymers with different spatial conformations interact differently with mucosal surfaces.(43) For example, dextran, despite having a very high molecular weight (19,500,000), exhibits comparable adhesive strength to polyethylene glycol (molecular weight 200,000). This is due to dextran's helical structure, which can conceal many of its adhesive active groups. In contrast, linear polymers like PEG expose more of their functional groups, affecting their adhesive behaviour. Cross-linking density impacts the hydration and swelling of the polymer network.(44) More the cross-linking density generally leads to reduced water migration into the polymer matrix, decreasing swelling and the rate of interpenetration with mucin.so, excessive cross-linking can deter the polymer's ability to swell and interact with mucosal tissues, affecting muco-adhesion. (45)Hydrogen bonding is another important factor in muco-adhesion. (58)Polymers that can form hydrogen bonds with mucosal tissues are generally more adhesive. Functional groups which are capable of hydrogen bonding, such as hydroxyl or carboxyl groups, enhance the mucoadhesive potential of the polymers. Polymers such as hydroxylated methacrylate, polymethacrylic acid, and polyvinyl alcohol, along with their copolymers, are recognised for their high hydrogen bonding capacity, which contributes to their effective mucoadhesion.(46)

Advantages of Buccal Drug Delivery

Some of the main benefits of buccal drug delivery are listed below. The ability of buccal drug delivery to avoid first-pass metabolism—a process in which medications are absorbed through the gastrointestinal tract and subsequently metabolized by the liver before entering the systemic circulation—is one of its most important advantages. Buccal delivery can improve a drug's bioavailability by preventing first-pass metabolism, which means that a larger portion of the dose is absorbed into the bloodstream in an active form. This is particularly crucial for medications (such as nitro-glycerine and fentanyl) that have a high hepatic metabolism and low oral bioavailability. Avoiding Hepatic Metabolism as well Drugs administered by the buccal route enter the bloodstream through the buccal mucosa's extensive vascular network and are immediately absorbed. By doing this, the drug avoids being partially broken down by the liver's metabolic enzymes, which would otherwise occur before it enters the bloodstream.(47) One more benefit of buccal delivery is dose reduction. After buccal administration, a greater amount of the drug is available in its active form, so lower doses may be needed to achieve the desired therapeutic effect, lowering the risk of side effects and enhancing patient safety. Enhanced Patient Adherence, particularly in the Elderly and Paediatric Segments. For patients who may have trouble swallowing traditional oral dosage forms like tablets or capsules, such as the elderly and paediatric population, buccal drug delivery is especially helpful in enhancing patient compliance.(48) Lozenges, patches, and buccal films can be applied easily, doing away with the need for needles or other devices. They provide a practical, non-invasive drug delivery method that most patients tolerate well. Dysphagia, or difficulty swallowing, affects a large number of elderly patients and can make taking conventional oral medications difficult. By avoiding the need to swallow, buccal drug delivery lessens discomfort and increases adherence to prescribed dosage schedules. Youngsters frequently object to swallowing big or bitter pills. Buccal formulations are more palatable to younger patients and can mask unpleasant tastes, especially flavoured films or lozenges. They also lessen the chance of choking, which is an issue with regular tablets or capsules.(49)

A painless and non-invasive method of administration is buccal delivery, as contrasted to other methods of drug delivery, such as injections, which can be uncomfortable, painful, and anxiety-inducing, the buccal route is less intrusive. Because buccal drug delivery does not involve the use of needles, it is a more comfortable option for patients who are afraid of injections than parenteral routes (such as intravenous or intramuscular injections). Patients who need long-term medication for chronic conditions will particularly benefit from this because buccal delivery is non-invasive, using needles can increase the risk of infection. Those with chronic illnesses or those with compromised immune systems should pay special attention to this. Since the mucosal surface is not very sensitive, buccal formulations are applied there, guaranteeing a painless drug administration experience. It is therefore perfect for medications that need to be given often or over extended periods of time.(50) Drugs can be released from buccal drug delivery systems in a controlled or immediate manner, resulting in a prolonged duration of therapeutic effects. This improves patient compliance by lowering the frequency of dosing. Drugs can be engineered into buccal films and patches to release over several hours, resulting in consistent plasma levels and minimizing the need for multiple daily doses. (51)This makes them suitable for patients with chronic conditions.(52) Because buccal

delivery provides direct drug action at the site of application, it is useful for treating local conditions within the oral cavity, such as infections (like oral thrush) or inflammation (like mouth ulcers) because the medication enters the bloodstream through the mucosa, buccal delivery can have systemic effects in addition to local ones. Because of its adaptability, it can be used in a variety of therapeutic settings. Because buccal drug delivery bypasses the gastrointestinal tract, it's a great choice for medications (like NSAIDs) that could irritate or discomfort the stomach when taken orally.(53) Additionally, it prevents medications from being broken down by digestive enzymes or the stomach's acidic environment. Food does not affect drug absorption when administered buccally because it avoids the digestive system, which can change the absorption profile of some oral medications.(54)

Buccal Delivery of Selegiline

Dosage Forms to Deliver Selegiline Through Buccal Route

Muccoadhessive Selegiline Tablet

Mucoadhesive selegiline tablets is a good option for mucosal drug delivery. The diameter of them is roughly 5-8 millimetres, and they are tiny, flat, and oval in shape. Immobilized medication delivery devices are what bio adhesive tablets are at their core. It is possible for it to manifest as monolithic, partly covered, or multilayered matrixes. In order to facilitate local or systemic medication administration, they are positioned directly on the mucosal surface. This makes it easier for the patient to administer s selegiline that is administered. These become pliable, stick to the mucosa, and remain in place until the full disintegration or release of the substance. selegiline may be delivered to a variety of locations inside the oral cavity with the use of this delivery method. (55)

Buccal Patches of Selegiline

The buccal patches can be also use for buccal deliver of selegiline. They have more patient compliance mainly due to the ease of application, thinness and elasticity that make it less discomfort to the patient. It is a safe and convenient mode of administration because the drug absorption can be terminated if any undesirable effects occur. The selegiline can be delivered in a unidirectional or bidirectional way either into the sub mucosal layers, oral cavity. The use of an impermeable backing layer helps in maximize the drug concentration gradient and prolong the adhesion since this system is protected from saliva. (56)

Buccal Films of Selegiline

Mucoadhesive film offers the strong adhesion with mucosal membrane, which will help to get greater surface area, increase the total absorption and are intended for local and systemic therapy and it will be convenient approach to deliver selegiline. Formulation of selegiline mucoadhesive film will increase the bioavailability of drug. The l film should be flexible, elastic and soft but enough strong to withstand the breakage due to stress results from mouth movement.(57)

Mucoadhessive Microsphere of Selegiline

Mucoadhesive microspheres are microparticles and microcapsules ranging from 1 to 1000 μm in diameter, composed wholly of mucoadhesive polymer or including an exterior layer with adhesive properties selegiline microspheres has the capability for both controlled and spatial

medication delivery. The integration of mucoadhesiveness into microspheres results in improved absorption and increased bioavailability of selegiline. Mucoadhesive microspheres of salenium may be designed to stick to the mucosal linings of the buccal cavity, facilitating both localized and systemic medication absorption in a regulated way.(58)

Adhesive Buccal Gels Consisting Selegiline

Various adhesive gels may be used to deliver drugs via the buccal mucosa and allow sustained release. Gel forming bioadhesive polymers include cross- linked polyacrylic acid that has been used to adhere to the mucosal surfaces for extended periods of time and provide controlled release of drug at the site of absorption. Designed of a novel selegiline gel, hydrogel based, bioadhesive, intelligent response system for controlled drug release has been reported . This system combined several desirable facets into a single formulation; a poly (hydroxyethyl methacrylate) layer as barrier, poly (methacrylic acid-g-ethylene glycol) as a biosensor and poly (ethylene oxide) to promote mucoadhesion. The limitations for gel formulations are inability to deliver a measured dose of drug to the site and as a result have limited uses for drugs with narrow therapeutic window.(59)

Medicated Chewing Selegiline Gums

Although medicated chewing gums pose difficulties in regulation of the administered dose, they still have some advantages as drug delivery, particularly in the treatment of diseases of the oral cavity and in nicotine replacement therapy. Some commercial products are available in the market. A new approach to deliver Salenium can be applicable. Selenium will absorbed at a significantly faster rate and its bioavailability will increase.(60)

Bio Adhesive Selegiline Wafers

The delivery system is a composite wafer with surface layers possessing adhesive properties, while the bulk layer consists of antimicrobial agents, biodegradable polymers and matrix polymers. selegiline wafer can be also formulate and effective delivery to treat Alzheimer.

Bioadhesive Selegiline Lozenges

A slow release bioadhesive lozenge offers the potential for prolonged drug release with improved patient compliance. Bioadhesive lozenges may be used for the delivery of drugs that act within the mouth including antimicrobials, corticosteroids, local anaesthetics, antibiotics and antifungals. A Salenium bioadhesive lozenge has been reported as a means to deliver antifungal agents to the oral cavity. The limitation of these bioadhesive lozenzes is the short residence time at the site of absorption which depends to the size and type of formulation and since dissolve within 30min, the total amount of the drug that can be delivered is limited. The dissolution or disintegration of lozenges is usually controlled by the patient, i.e. how hard they suck the unit. Increased sucking and saliva production causes uncontrolled swallowing and loss of drug down the GI tract. Thus, solid dosage forms generally have a much higher inter- and intra-individual variations in absorption and bioavailability. Also, these types of system are not able to provide unidirectional release of drugs. Continuous secretion of saliva is another major hurdle to the performance of such dosage forms.(61)

Limitations of Buccal Drug Delivery of Selegiline

There are certain advantages to buccal drug delivery of selegiline, but there are drawbacks as

well. A few issues, such as the limited absorption surface area, the potential for food and drink to interfere, and the variability of mucosal absorption, can reduce the overall efficacy of this drug delivery technique. When designing and utilizing buccal drug delivery systems, these issues must be carefully considered in order to maximize their potential. Due to the small area of the buccal mucosa, medications can only interact with the tissue there and not enter the bloodstream. (62)Comparing surface areas, the buccal mucosa has a surface area of only 50 cm^2, whereas the gastrointestinal tract has an absorption surface area of approximately 200 m^2. Because of the small surface area, larger doses of drugs cannot be absorbed through the buccal route. Furthermore, only a small amount of selegiline can be absorbed at a time due to the small absorption surface. This is a significant issue for medications that require high dosages to be effective. These factors make the buccal route preferable for potent medications that should only be taken occasionally. Additionally, the small surface area alters the rate and amount of drug absorption—particularly for poorly absorbed drugs. Certain compounds may become less bioavailable and function more slowly as a result of this than if they are taken through alternative routes. (63) Food, drink, and saliva are all continuously present in the buccal cavity, which can hinder the absorption of selegiline and the efficiency of buccal delivery systems. These variables may shorten the duration of drug contact with the mucosa, change the environment's pH, or physically remove buccal films or patches. selegiline absorption may be decreased if buccal films, tablets, or patches are dislodged from their prescribed application site by eating, drinking, or speaking. Mucoadhesive buccal systems, which depend on regular contact with the mucosa for efficient drug delivery, frequently experience this problem. Changes in the pH of the surrounding environment can affect drug absorption because certain drugs have pH-dependent permeability and solubility. Acidic foods and beverages, for instance, can reduce the pH of the buccal cavity, which can impact the solubility of medications with weak bases. Eating and drinking may cause salivary flow to increase, which could dilute the medication's formulation and lower its concentration at the mucosal surface. Drug bioavailability and absorption may suffer as a result. Mucosal thickness, enzyme activity, and patient characteristics may significantly influence mucosal drug absorption. This may lead to complications with medication absorption and their therapeutic effectiveness.(64)

Strategies For Overcoming Challenges in Buccal Drug Delivery of Selegiline

To meet therapeutic needs, mucoadhesive buccal administration of selegiline must incorporate mucoadhesive agents to ensure sustained contact with the absorption site, penetration enhancers to facilitate drug permeation through the mucosa (transmucosal delivery) or into the deeper epithelial layers (mucosal delivery); enzyme inhibitors to safeguard the drug from degradation by mucosal enzymes and solubility modifiers to improve the solubility of poorly soluble drugs.(65) The primary benefits of bioadhesive systems are the prolonged retention of selegiline -containing formulation in the oral cavity and the targeted delivery of medicines to specific areas. Typically, essential structural attributes for bioadhesive polymers include robust hydrogen bonding groups, significant anionic or cationic charges, elevated molecular weight, chain flexibility, and surface energy features that promote spreading over the mucus layer. Adhesive polymer sources should generally be natural or synthetic, water-soluble or water-insoluble, and charged or uncharged polymers.

Fictional narrative Second-generation mucoadhesive polymers, including lectins, bacterial

adhesions, and thiolated polymers, are categorised as novel techniques to address the limitations of conventional mucoadhesive formulations. Lectins are naturally occurring proteins that are essential in biological recognition processes involving cells and proteins. These are proteins or glycoproteins that have a high specific affinity for carbohydrates. Following initial attachment to mucosal cells, lectins may either persist on the cell surface or, in instances of receptor-mediated adhesion, potentially undergo internalisation by endocytosis. Recent investigations have examined the sticky capabilities of bacterial cells. Bacterial adherence to various targets is derived from distinct cell-surface components or appendages, termed fimbriae, which enable attachment to other cells or inanimate surfaces. These are extracellular, elongated filamentous protein polymers produced by bacteria that significantly contribute to several illnesses. Bacterial fimbriae attach to the binding sites of particular receptors. (66) A significant link exists between the presence of fimbriae on bacterial surfaces and their pathogenicity. This technique is appealing due to its ability to enhance the drug's residence duration on the mucus and its receptor-specific interactions, akin to those of plant lectins. Escherichia coli (E. coli) has been shown to particularly attach to the lymphoid follicular epithelium of the ileal Peyer's patch in rabbits. Furthermore, many staphylococci have the capacity to cling to the surfaces of mucus gel layers rather than to mucus-free surfaces. Consequently, drug delivery using bacterial adhesion may serve as an effective approach to enhance the administration of certain medications or carrier systems. The K99-fimbriae antigen, an adhesion protein derived from E. coli, has been covalently bonded to polyacrylic acid networks. The developed polymer–fimbriae platform demonstrated a substantial enhancement in adhesion in vitro relative to the control (unmodified polymer). Thiolated polymers (thiomers) represent a second-generation mucoadhesive generated from hydrophilic polymers, like polyacrylates, chitosan, or deacetylated gellan gum. The presence of thiol groups facilitates the formation of covalent connections with cysteine-rich subdomains of the mucus gel layer, resulting in enhanced residence duration and improved bioavailability. Thiomers replicate the natural process of released mucus glycoproteins, which are covalently tethered in the mucus layer by the production of disulphide bonds. First-generation mucoadhesive polymers engage in non-covalent secondary contacts, but second-generation systems use covalent bonding processes that result in interactions less affected by variations in ionic strength and pH. Furthermore, the presence of disulphide bonds may substantially modify the drug release mechanism from the delivery system owing to enhanced stiffness and cross-linking. In these platforms, a diffusion-controlled drug release mechanism is predominant, while in first-generation polymers, anomalous transport of selegiline into the bulk solution is more prevalent.(67)

Future Prospective

The recent advances in mucoadhesive drug delivery systems for oral application present a promising avenue for pharmaceutical research and development. However, these innovations come with a set of challenges. Selecting the most suitable polymers for these systems is crucial, as they need to be biocompatible, safe, and possess effective mucoadhesive properties. Scientists are finding ways to develop buccal adhesive systems through various approaches to improve the bioavailability of orally less/inefficient drugs like selegiline by manipulating the formulation strategies. Polymeric science needs to be explored to find newer mucoadhesive polymers with the added attributes of being biodegradable, biocompatible, non-toxic,

mucoadhesive for specific cells or mucosa, and which could also function as enzyme inhibitors for the successful delivery of selegiline. However, the invention of new biomaterials, tailor-made copolymers, has excellent potential for mucoadhesive drug delivery system of selegiline, but the formulations based on them still have to go a long way to find their path in actual clinical practice.

2. Conclusion

The approach to deliver selegiline to treat AD through mucoadhesive drug delivery systems has experienced significant advancement, propelled by a detailed comprehension of the factors affecting adhesion, such as polymer properties, environmental conditions, and physiological variables. It will be a efficient approach to deliver selegiline. These advancements have facilitated the creation of more efficient and targeted therapies for diverse mucosal surfaces. Research in buccal drug delivery has revealed remarkable growth and advances in the past few decades. The buccal mucosa holds a great promise for systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules. This review areas of interest are the novel buccal adhesive delivery system of selegiline where the drug delivery is directed towards buccal mucosa by protecting the local environment. In spite of significant advances in the delivery of selegiline through mucoadhesion buccal route, there is no consensus between scientists in relation to the mechanisms of the interaction between materials and components of mucosal tissue. Many scientists have addressed the development of MBDDS and studied the efficacy of their use, though here too there remain significant gaps, as there is no generally accepted method for assessing mucoadhesive properties. The lack of standardized techniques often leads to discordant and unclear results. Efforts have to be made to develop standardized in vitro and ex vivo biological models that allow one to characterize and compare different materials and formulations in terms of their capability to promote drug absorption via the buccal route. Looking into the future, researchers find the fate of buccal adhesive drug delivery turning towards vaccine formulations and delivery of small proteins/peptides. selegiline bioadhesive systems are particularly interesting because they offer protection to therapeutic entities as well as the enhanced absorption that result from increased contact time provided by the bioadhesive component. Delivery of selegiline through bioadhessive system can clearly play a fundamental role as non-parenteral drug delivery systems.

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