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Buccal Drug Delivery System

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Abstract

The utilization of medications to treat illness is entering a new phase in which an increasing variety of cutting-edge drug delivery techniques are being used. The oral mucosa has a number of characteristics that make it an appealing location for drug administration but also present a number of challenges for researchers in terms of effective and efficient therapeutic active agent delivery. Nevertheless, a number of obstacles were solved with the invention of novel distribution strategies.High blood flow, quick recovery, avoiding the hepatic first-pass impact, and pre-systemic elimination in the gastrointestinal tract are just a few benefits of oral mucosa delivery. However, the main drawbacks of buccal delivery include its relatively small surface area and considerable drug loss from swallowing and salivary flow. For distribution into and/or across the oral mucosa, a variety of formulations, including sprays, pills, mouthwashes, gels, pastes, and patches, are now employed. Numerous formulations for buccal drug delivery systems have been created over the past 20 years, but only a few number have proven successful enough to be approved as medicines.

The absence of standardized methodologies to assess the in vitro effectiveness of buccal dosage forms may be one of the primary causes of this poor outcome.The purpose of this study is to explain the advantages of buccal dosage forms and buccal drug delivery, as well as to examine current research and in vitro analysis techniques for buccal dosage forms.

Key-words: Buccal drug delivery system, mucoadhesive, buccoadhesive, bio-adhesive, polymers

Introduction

The buccal drug delivery system is the system in which the drugs are delivered through mucosal membrane into the systemic circulation by placing drug in between cheeks and gums.[1] The oral route is a desirable site for drug delivery among the several drug delivery methods. The most practical and accessible location for the local and systemic administration of medicinal medicines was discovered to be the buccal cavity. By extending the dosage form's time of residence at the application or absorption site and facilitating close contact between the dosage form and the absorption surface, the buccal adhesive drug delivery system helps to enhance the therapeutic effectiveness of the medicine.[2]

Due to the high total blood flow that provides systemic bioavailability, avoiding first pass hepatic metabolism and gastrointestinal drug degradation, the buccal route is superior than the oral route in a number of ways. Additionally, it is convenient for patient administration and appropriate for administering and removing dosage forms.[3] There are other applications for mucoadhesive polymers in buccal medication delivery.

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Recently, a variety of mucoadhesive products, such as tablets, films, patches, disks, strips, ointments, and gels, have been created. The buccal patch, however, provides more comfort and flexibility than the other devices. Additionally, since oral gels are rapidly removed by saliva, a patch can get around the issue of the relatively short residence period of oral gels on mucosa.[4]

Buccal route is more prevalent with patient compliance when transmucosal medication administration methods such rectal, vaginal, nasal, and buccal routes are compared.[5] In fact, several medications that have a high first pass metabolism due to liver breakdown and are sensitive to extremely acidic conditions of the stomach cannot be delivered via this route. Different mucoadhesive systems that are administered by routes other than the oral route, such as the buccal, nasal, and vaginal, have been developed to address these issues.[6]

Advantages:[7]

- In this system physical state, surface, shape, and sizes are all flexible.
- It is possible to make the drug simple to administer and to stop the therapy in an emergency.
- Buccal delivery can be used to distribute some medications that are unstable in the acidic environment of the stomach.
- The medication can be given to trauma patients who are unconscious.
- It starts working quickly.
- There is medication absorption through passive diffusion.
- Enables the localization or long-term retention of the medicine in the designated oral cavity area.
- It is possible to deliver medicines with limited bioavailability due to excessive first pass metabolism.
- Since the mechanism of absorption is passive, no energy is needed.
- Under the implemented planned system, there is a restriction of a diffusion limited mucous build up due to a lack of noticeable mucus secreting goblet cells. It is possible to deliver medicines with limited bioavailability due to excessive first pass metabolism.

Disadvantage:[8]

- This method is ineffective for delivering ionic medications.
- The number of medications that can be administered in this way is Constrained by the poor skin permeability.
- It is critical to distinctly define the clinical requirement.
- With age, the skin's barrier function varies from one spot to another and from one person to another.
- Compared to the sublingual membrane, the buccal membrane has a modest level of permeability.
- It is not safe to deliver medications that are unstable at buccal pH.
- Drugs that irritate the mucosa, have an unpleasant taste, have a bitter aftertaste, or have an offensive odor cannot be administered this way.
- Only deliver the little dose of medication that is necessary.
- Drugs with large doses are frequently challenging to give.
- possibility that the patient will forget to consume the medication.
- Until the medication release is complete, eating and drinking may be restricted.
- There is a small amount of absorbable surface area.

Ideal properties:

- The polymer needs to be inert, nontoxic, non-irritating, and incapable of being absorbed by the GI tract.
- It should ideally establish a powerful non-covalent connection with the mucin layer covering the surfaces of epithelial cells.
- It should have some site specificity and adhere to moist tissue fast.
- The price of the polymer shouldn't be too expensive to make it difficult to market the produced dosage form.[9]
- Should have a controlled release of the medicine.
- The polymer should not be toxic and should not include any leachable impurities.[10]

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- Good spreadability, wetting, swelling, solubility, and biodegradability qualities are required.
- pH must to be biocompatible and have good viscoelastic characteristics.
- Should be mechanically strong enough and adhere to buccal mucosa fast.
- Polymer needs to be readily available and reasonably priced.
- Should have bio-adhesion characteristics in both the liquid and dry states.
- It should possess properties that enhance penetration and prevent localised enzymes.
- The molecular weight needs to be ideal.
- It must not encourage the growth of secondary infections such dental caries.[11]

Dosage form:

- Solid dosage form:
  1) Buccal powder
  2) Buccal tablet
  3) Bio-adhesive microsphere
  4) Bio-adhesive wafers
  5) Bio-adhesive lozenges
- Semi-solid dosage form:
  1) Buccal patch
  2) Buccal film
  3) Buccal gel
  4) Buccal hydrogels
  5) Medicated chewing gum
- Liquid dosage form:

Solid dosage form:

Buccal Powder:

Nifedipine is administered as buccal tablet and buccal film dosage forms, which reduce diastolic blood pressure. Buccal bio-adhesive powder dosage forms are sprayed onto the buccal mucosa.[12]

When beclomethasone and hydroxypropyl cellulose powder are sprayed into the oral mucosa of rats, the residence period is significantly extended compared to an oral solution, and 2.5% of the drug is kept on the buccal mucosa for more than 4 hours.[13]

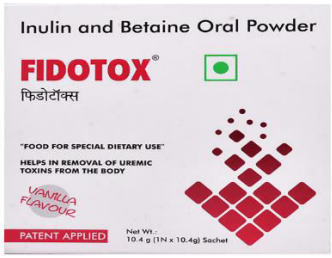

Figure.1

Buccal Tablet:

Different techniques, such as direct compression or wet granulation, can be used to make bio-adhesive tablets. The tablets for the buccal route must be prepared and compressed to a suitable degree only to produce a firm tablet because they will be put into the buccal pouch where they may melt or erode. In the presence of saliva, these tablets take on an adhesive quality and stick to the buccal mucosa for the duration of the drug release. Some tablets deliver the medication either unidirectionally to the buccal mucosa or bidirectionally into the saliva at the target region.Small, flat, slightly variable-diameter discs are the buccoadhesive tablets allow API delivery during extended contact with the buccal mucosa without significantly impairing speaking, eating, or drinking. The drug delivery rate from the polymeric matrix will be influenced by the balance between swelling, erosion, and diffusion mechanisms. Alginate, pectin, xanthan, chitosan, and cellulose derivatives are polysaccharides that are frequently utilized in tablet manufacturing. The results of this field's research have led to the creation of brands like Oravig®, Loramyc®, DFGNitrograd®, Suboxane, Buccastem®, and Striant®.[14]

Figure.2

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Bio-adhesive Microsphere:

A crucial component of a cutting-edge medication delivery system is the microsphere. The major function of this mucoadhesive microsphere is to target a particular bodily cavity. Due to their high surface-to-volume ratio, close interaction with the mucus layer, and accurate drug targeting to the absorption site, bio-adhesive microspheres provide advantages such as effective absorption and increased bioavailability of medications.[15]

Tablets have less advantages than microspheres. Microspheres' physical characteristics allow for close contact with a sizable mucosal surface. The success of these microspheres is constrained by their brief residence duration at the site of absorption, despite the fact that they can be administered to less accessible areas such the GI Tract and nasal cavities and produce less local irritation at the site of adhesion.[16]

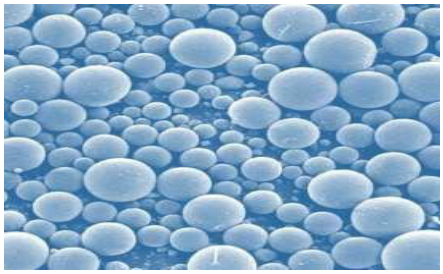

Figure.3

Bio-adhesive Wafers:

The periodontal medication delivery device is new. This is employed to treat bacterial infections. The delivery system is a composite wafer made of microbiological agents, biodegradable polymers, and matrix polymers in the bulk layer with adhesive surface layers in the surface layers.[17]

The main benefits of wafers as BDDS are low residual moisture and increased drug loading (for low solubility drugs), protection against mechanical removal, and their ability to maintain their swollen structure for a long time, thereby improving drug absorption. In general, the main features of wafers as BDDS are the same as those for buccal films/patches, hydrogels, or sponges: flexibility, elasticity, softness, muco-adhesivity. Alginate, pectin, xanthan, carrageenan, cellulose derivatives, chitosan, and thiolated polysaccharides are polysaccharides utilized in wafer compositions. There are commercial wafers on the market, such as WafermineTM and WafesilT. The above-mentioned dosage forms can also be made of hybrid substances that include micro- or nanoparticles, microspheres, nanofibers made of polysaccharides, or colloidal systems wrapped in a polysaccharide coating to shield the drug.[18]

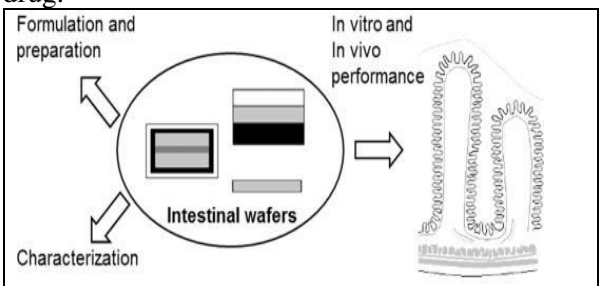

Figure.4

Bio-adhesive Lozenges:

Drugs that act topically in the mouth, such as antibiotics, corticosteroids, local anesthetics, and antifungals, can be delivered via bio-adhesive lozenges.[19]Because the medication release in the oral cavity is first high and then quickly declines to subtherapeutic levels, lozenges require numerous daily doses.[20]

Figure.5

Semi-solid dosage form:

Buccal Patch:

The formulations for buccal medication delivery that have attracted the most attention are patch systems. Due of their physical flexibility, which only slightly annoys the patient, they have higher patient compliance than tablets.[21]

Buccal patches are made using two techniques: direct milling and solvent casting. When using the solvent casting process, the drug and polymer solution is cast onto a backing layer sheet, and the patches are punched out of the intermediate sheet. In a process called direct milling, the

formulation's ingredients are properly mixed to the correct thickness, and the desired shapes are cut and punched out in the case of patches. Backing layer serves as a protective layer that is applied and is impermeable.[22]

To address some of the shortcomings of existing dosage forms, flexible adhesive patches have been created. Transmucosal delivery patches have special properties, such as relatively quick drug delivery onset, prolonged drug release, and quick drop in serum drug concentration after patch removal. Additionally, because a buccal patch is limited to the buccal area to which it is connected, there may be less inter- and intraindividual variability in the absorption profile. Generally speaking, there are three types of oral mucosal patches: those with a dissolvable matrix, those with a non-dissolvable backing, and those with a dissolvable backing. Drug release into the oral cavity is accomplished with the use of patches with a soluble matrix. They function similarly to the solid dos e form and share many of its drawbacks. Drug matrix stays in the oral cavity for a longer period of time when a mucoadhesive layer is present, either as part of the drug matrix or as an extra layer linked to it. These patches are therefore longer acting and may be able to deliver more medications than conventional open dose forms. Additionally, they utilise the entire mucosa of the oral cavity, as opposed to other closed systems, which often use smaller sections. These kinds of patches can be used to treat regional illnesses like candidiasis or mucositis. Typically, patches with non-dissolvable backing are made for systemic administration. The drug concentrations are controlled and the medicine is constantly supplied for 10 to 15 hours since they are closed systems and the formulations are shielded from saliva. These systems' drawbacks include the fact that they only utilise a tiny mucosal area and need the patient to remove the backings after drug administration. Dissolvable-backed patches are similar to those with non-dissolvable-backed backing in many ways, but they have the benefit of dissolving completely in the mouth. Patches with a soluble backing have a shorter action time than those without. In comparison to more invasive means of administration, oral mucosal dose forms could be inexpensive, simple to administer, and painless. Each delivery method offers highly unique delivery qualities that can be applied to a wide variety of therapies. The majority of patches offer a longer time frame for delivering drugs to and through the buccal mucosa that have been produced as either solvent cast mucoadhesive polymer discs or drugs.[23]

The mucoadhesive film is occasionally referred to as a "buccal patch" in scientific literature. In film/patch formulations, polysaccharides such as cellulose derivatives, alginate, pectin, xanthan, carrageenan, hyaluronan, chitosan, and thiolated polysaccharides are frequently employed. Commercial products including Onsolis®, Setofilm®, Triaminic®, and buccal patches such as OraMoist® and Dentipatch have been created as a result of this field's study.[24]

Figure.6

BuccalFilms:

Drugs can be delivered directly to a mucosal membrane using flexible films. The fact that they deliver a precise dose of medication to the spot makes them superior than creams and ointments. Commercially, buccal adhesive films are already in use.[25]

These are the newest dosage forms created, and they are intended for buccal administration. An excellent film should be soft, elastic, flexible, and strong enough to resist breaking from mouth motions' force. It should have strong bioadhesive properties and hold in the mouth to deliver the intended effect. In order to avoid discomfort, there shouldn't be much film swelling. The procedure of solvent casting is frequently employed to create buccal films. Drug and (possibly) polymer(s) are dissolved in solvent combination. After the solution was turned into a film and allowed to dry, lamination was completed using a backing or lining layer. The backing layer prevents salivary diffusion into the drug layer, which reduces drug

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loss and lengthens adhesion time in the oral cavity. The main drawbacks of the solvent casting method include its lengthy processing times and some environmental issues caused by the use of various solvents. To get around the issues, hot-melt extrusion is used. dosing formulations for liquid buccal adhesives liquids for coating the buccal.[26]

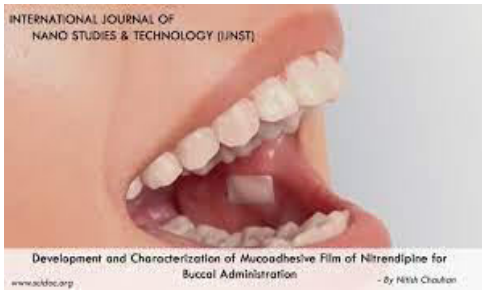

Figure.7

Buccal Gel:

Gels are typically transparent, clear semisolid BDDS that contain solubilized medications. They have a long history of usage in the oral cavity for medication delivery because the formulations are simple to spread across the mucosal membrane. Because they contain more water, they are less irritating and can release API more quickly at the absorption site. Mucoadhesive polysaccharides, such as sodium carboxymethylcellulose, hyaluronic acid, or xanthan gum, were added to increase the retention of these kinds of formulations by modifying viscosity and regulating drug release. On the market are commercial gels like Gengigel® and Aftex Forte Oral Gel.[27]

Viscous liquids have mostly been studied for their ability to coat the mucosa and serve as a barrier or a means of medication administration for the treatment of local illnesses, such as fungal infections and motility dysfunction. Researchers demonstrated that the esophagus surface can be coated to deliver therapeutic medicines to the injured mucosa and to protect against reflux using sodium alginate suspension as a new bio-adhesive liquid. On the esophageal surface, different bio-adhesive formulations' retention behavior was assessed in settings that simulated salivary flow. Carmellose salt and theromo-sensitive poloxamer (Lutrol 407) performed poorly in terms of retention, but polycarbophil and xanthum gum both had high bio-adhesive capability. a covalently joined poloxamer, polyacrylic acid, and carbopol hydrogel that is thermosensitive. Following oral delivery, this "esophageal bandage" showed notable esophageal retention.[28]

Figure.8

Buccal Hydrogels:

The hydrophilic nature of hydrogels allows them to absorb water, expand their form, and keep their structural integrity while doing so. Hydrogels are 3D structures that can have various pore sizes and forms. The composition, morphology (gels, micro-/nanoparticles, cross-linked matrices), and physicochemical characteristics of hydrogels will affect chain relaxation and interaction with other chemical compounds, allowing them to load various hydrophilic API, protect the drug from the action of some external factors, react to a stimulus to release the drug, and form adequate interchain bridges with elements of the biological medium. Alginate, pectin, hyaluronan, xanthan gum, carrageenan, and chitosan are the polysaccharides that are most frequently utilized to make hydrogels. The following industrial goods are a result of this field's research: Tantum verde® SOS after URGO Filmogel® Mouth Ulcers.[29]

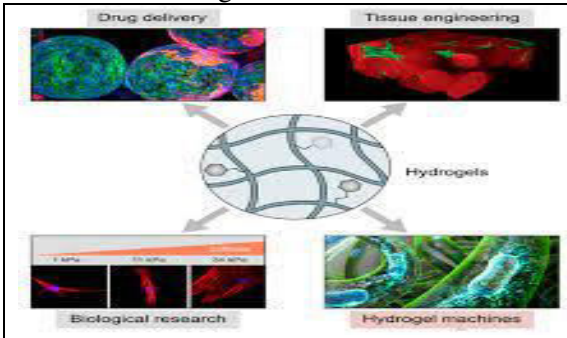

Figure.9

Medicated Chewing Gum:

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Chewing medicated gum releases a significant amount of the medicine after chewing, demonstrating local activity in the mouth. Additionally, it may demonstrate absorption via systemic circulation. It is possible to use medicated gum for nicotine replacement therapy. Similar caffeine-containing chewing gums are also offered.[30]

One of the contemporary methods for oral transmucosal medication administration is chewing gum. The ability to manage medication release over an extended period of time and the potential to increase variability in drug release and retention durations are two benefits of chewing gum over alternative oral mucosal drug delivery methods. Convenience is one benefit of chewing gum. Additionally, a person may be able to regulate their drug consumption by simply altering how quickly and vigorously they chew their gum or by throwing it out entirely. Chewing gum has many of the same restrictions as other solid formulations because it is an open system as well.[31]

Figure.10

Liquid Dosage Form:

These are offered as drug suspensions or solutions in acceptable vehicles. This kind of dose form, used for local action, is marketed as antibacterial mouthwashes and mouth fresheners. There are many other types of polymers used, but chitosan has the best capacity for binding. The buccal cavity is best coated with viscous liquid formulations, either as a vehicle or a protectant.[32]

The buccal surface may be coated with viscous liquids as either protective coatings or drug delivery vehicles for the mucosal surface. A newly created liquid aerosol formulation named Oralin from Generex Biotechnology is currently undergoing clinical phase II testing.This device enables the delivery of specific insulin doses into the mouth using a metered dose inhaler in the form of tiny aerosolized droplets.[33,34]

Formulation additives:

1. Drug substance
2. Bio-adhesive polymers
3. Backing membrane
4. Penetration enhancers
5. Plasticizers

Drug substance:

One must choose whether the intended action is for a local or systemic effect, and for a quick or delayed release before developing mucoadhesive drug delivery systems. When choosing a drug for the design of buccoadhesive drug delivery systems, pharmacokinetic characteristics are significant.[35]

Rational for selection of drug in BDDS:

- The medicine used for the buccal formulation depends on certain properties.
- A molecular mass of no more than 1000 Dalton.
- Strong non-covalent bonds have to be formed between it and the mucin/epithelial surface.
- High molecular weight and limited distribution are required.
- It has to be compatible with biological membranes.[36]
- A little dose of the medication should be administered once (less than or equal to 25 mg).
- Drugs that exhibit first pass metabolism can be administered orally to prevent this first pass metabolism.[37]
- When a drug is taken orally, its Tmax undergoes numerous modifications or increases in values.
- Drug absorption after oral administration needs to be passive.[38]
- should have hydrophilic and lipophilic characteristics.[39]
- biological properties should be low melting point.
- It has to be robust.
- T1/2 have to be decreased. (2-8 hours)
- The oral mucosa is not irritated.
- The following polymers are frequently utilized in pharmaceutical applications as bio-adhesives:

Natural polymers, such as sodium alginate and gelatin. Synthetic or semi-synthetic, such as PVA, PEG, HPMC, PVP, and carbomers, etc.[40]

Sr. No.	Active Ingredients	Sr. No.	Active Ingredients
1	Metronidazole	13	Chitosan
2	Nifedipine	14	Testosterone
3	Propranolol	15	Zinc sulphate
4	Danazol	16	Morphine sulphate
5	Nicotine	17	Acyclovir
6	Omeprazole	18	Metoprolol tartrate
7	Carbamazepine	19	Lignocaine
8	Arecoline	20	Oxytocin
9	Protirelin	21	Diclofenac sodium
10	Piroxicam	22	Pentazocine
11	Terbutaline sulphate	23	Ergotamine tartrate
12	Theophylline	24	Hydrocortisone acetate[41]

Bio-adhesive polymers:

The characterisation and selection of appropriate bio-adhesive polymers for the production of buccoadhesive dosage forms is the initial step in the process. In buccoadhesive delivery systems, bio-adhesive polymers are essential. Polymers are also utilized in matrix devices, which regulate the rate of drug delivery by enclosing the drug in a polymer matrix. Bio-adhesive polymers are among the most diverse materials and are widely employed in the treatment and care of patients. Through the use of the core layer or rate-controlling layer, the medicine is released into the mucous membrane. The oral drug delivery mechanism is significantly improved by the use of bio-adhesive polymers which attach to the mucin or epithelial surface.

The many parameters, including mucoadhesive strength, thickness, in vitro release, and the residence period of the drug delivery device, are determined by the application of bio adhesive polymer. High molecular weight polymers are typically used because they have efficient release rate control features. To get the best results, a polymer should have the characteristics listed below.

- It needs to be neutral.
- It must be suitable for the surroundings and the medicine.
- It must be attached to the mucous membrane rapidly and remain attached for the necessary amount of time.
- Both the polymer and the byproducts of its decomposition must be safe.
- The polymer must not break down while being stored or during the dosage form's shelf life.
- The polymer has to be reasonably priced and accessible on the market.
- It needs to make it simple to include the medicine into the formulation.[42]

	Categories	Examples
Source	Semi natural/ Natural	Agarose, chitosan, gelatin, Hyaluronic acid, Various gums (guar gum, xanthan, gellan, carrageenan, pectin and sodium alginate).
	Synthetic	Cellulose derivatives: [CMC, thiolated CMC, NaCMC, HEC, HPC, HPMC, MC.]

		Poly (acrylic acid)-based polymers: [CP, PC, PAA, polyacrylates, poly (methyl vinyl ether-co-methacrylic acid), poly (2- hydroxy ethyl methacrylate), poly (acrylic acidcoethyl hexyl acrylate), poly (methacrylate), poly (isobutylcyanoacrylate), copolymer of acrylic acid and PEG].
		Others: polyoxyethylene, PVA, PVP, thiolated Polymers.
Aqueous solubility	Water soluble	CP, HEC, HPC, HPMC (cold water), PAA, NaCMC, sodium alginate.
	Water insoluble	Chitosan (soluble in dilute aqueous acids), EC, PC.
Charge	Cationic	Aminodextran, Chitosan, (DEAE)- dextran, TMC
	Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, NaCMC, xanthan gum.
	Non-ionic	Hydroxy ethyl starch, HPC, poly (ethylene oxide), PVA,
Potential	Covalent	PVP, scleroglucan
	Hydrogen bond	Cyanoacrylate
Bioadhesive forces	Electrostatic interaction	Acrylates [hydroxylatedmethacrylate,poly(methacrylic acid)], CP, PC, PVA, Chitosan[43]

Backing membrane:

To avoid unwanted medicine loss from all sides of the device, the backing membrane used for the formulation must to be impermeable to both drug and mucus. The materials that are used for backing membrane preparation should be inert, insoluble, or have a low water solubility; examples include ethyl cellulose, carbopol, sodium alginate, HPMC, HPC, polycarbophil, magnesium stearate, and CMC.

In order to attach bio-adhesive devices to the mucous membrane, the backing membrane is important. Buccal bio-adhesive patches with such a membrane reduce drug loss and improve patient compliance.[44]

Permeation enhancer:[45]

Permeation enhancers are substances which help in permeation through buccal mucosa. The drug's physicochemical characteristics, administration site, vehicle, and other additives all affect the choice of enhancer and its efficacy.

Although medications taken by mouth avoid the stomach's first pass metabolism and degradation, their bioavailability is only modest. The co-administration of a permeation enhancer is important, especially for peptides. You can use the many methods to get improved absorption.

- By co-administering a permeation enhancer, drug absorption through tissue is improved. These substances may change the drug's characteristics (by forming complexes) or reduce the mucosal barrier (by simulating the fluidization of intracellular fluids by desmosomes).
- by using enzyme inhibitors to reduce drug breakdown while being transported through the tissue.

Class of permeation enhancers	Examples
Thiolated polymers	Chitosan-4-thiobutylamide, chitosan- 4thiobutylamide/GSH, chitosan-cysteine, Poly (acrylic acid)-homocysteine, polycarbophilcysteine,polycarbophil-cysteine/GSH, chitosan-4thioethylamide/GSH, chitosan-4-thioglycholic acid
Surfactants	Sodium lauryl sulphate, polyoxyethylene, Polyoxyethylene-9-lauryl ether, Polyoxythylene20-cetylether, Benzalkonium chloride, 23-lauryl ether, cetylpyridinium chloride, cetyltrimethyl ammonium bromide
Chelators	EDTA, citric acid, sodium salicylate, methoxy salicylates.
Non-surfactants	Unsaturated cyclic ureas.
Fatty acids .	Oleic acid, capric acid, lauric acid, lauric acid/ propylene glycol, methyloleate, lysophosphatidylcholine, phosphatidylcholine
Inclusion complexes	Cyclodextrins.
Bile salts .	Sodium glycocholate, sodium deoxycholate, sodium taurocholate, sodium glycodeoxycholate, sodium taurodeoxycholate
Others	Aprotinin, azone, cyclodextrin, dextran sulfate, menthol, polysorbate 80, sulfoxides and various alkyl glycosides.

Plasticizers:

The plasticizers are utilized to increase the delivery device's folding endurance. They give the dosing form considerable flexibility to increase patient compliance and acceptance. PEG-400, PEG-600, dibutyl phthalate, propylene glycol, glycerol, and castor oil are a few examples of frequently used plasticizers.

Marketed products:

Commercially Available Oral Mucoadhesive Drug Delivery Systems				
Drug	**Dosage form**	**Type of release**	**Product name**	**Manufacturer**
Chlorhexidine digluconate	Oromucosal gel	Controlled	Corsodyl gel	GalaxoSmithKline
Hydrocortisone sodium succinate	Oromucosal pallets	Controlled	Corlan pellets	Celltech
Buprenorphine HCl and Naloxone	Tablet	Quick	Sulbutex	Reckitt Benckiser
Proclorperazine	Tablet	Controlled	Buccastem	Reckitt Benckiser
Testosterone	Tablet	Controlled	Straint SR	Columbia Pharmaceuticals
Zolpidem	Spray	Quick	Zolpimist	NovaDel[46]

Sr. no.	Brand name	Active ingredient	Company
sssa1	Effentora	Fentanyl citrate	Cephalon (UK) Limited

2	TemestaExpidet	Lorazepam	Wyeth Pharmaceuticals
3	Suscard	Glyceryl Trinitrate	Pharmax Limited
4	Subutex	BuprenorphineHClTablets	Reckitt Benckiser
5	Stementil	Prochlorperazine maleate	Sanofi-Aventis or Sanofi
6.	Oravig	Miconazole	Bio Alliance pharma
7.	Nicorette	Nicotine	GlaxoSmithKline[47]

Evaluation:[48]

1. **Drug-excipients interaction studies:**
   Studies of the interactions between drugs and their excipients plays a vital role in formulation and development of solid dosage forms. To evaluate any research on drug excipient interactions Thin layer chromatography, Fourier Transform Infra-Red Spectrum (FTIR), X Ray Diffraction (XRD), differential scanning calorimeter (DSC), and DSC can all be employed. Due to its ability to display shifting melting endotherms and exotherms, changes in appearance, and fluctuation in the corresponding enthalpies of the reaction, the differential scanning calorimeter is used as a quick evaluation device to identify possible incompatibilities.
2. **Physical evaluation:**
   It comprises uniformity in the content, weight, and thickness. By comparing the average weight of 10 randomly chosen patches from each batch with each individual patch, weight variation evaluation was carried out. The film's thickness needs to be measured at five different points (the center and the four corners), after which the mean thickness should be determined. Air bubbles, samples with nicks or tears, and samples with a mean thickness variation of more than 5% are excluded from analysis. Each formulation's three 20 mm-diameter patches were placed separately in 100 ml volumetric flasks with 100 ml of pH 6.8 phosphate buffer solution, which was then continuously swirled for 24 hours. The solutions were filtered, appropriately diluted, and subjected to UV spectrophotometer analysis. Finalization was based on the average of three patches.
3. **Surface pH:**
   In order to check for potential side effects in vivo, the pH of the buccal patch's surface was measured. It is vital to maintain the surface pH as close to neutral as possible since an acidic or basic pH may irritate the buccal mucosa. For this, a composite glass electrode was employed.
   Buccal patches are placed on an agar plate surface and left there for two hours, allowing them to swell. A pH paper is placed on the surface of the swollen area to measure the surface pH.
4. **Swelling study:**
   In separate 2% agar gel plates, each patch is independently weighed (designed by W1), incubated at 37 $\pm 1^0$C, and checked for any physical changes. The patches are periodically taken from the gel plates at intervals of one hour up to three hours, and extra surface water is wiped away using filter paper. The swollen patches are reweighed (designed by W2), and the swelling index (SI) is computed as follows:
   SI= (W2 – W1)/W1 .100
5. **Folding endurance:**
   One patch was folded at the same location repeatedly until it broke, or it was folded manually up to 300 times, which was deemed sufficient to show good patch characteristics. The value of folding endurance is determined by how many times the patch could be folded in the same location without breaking. Five patches are used in this test.
6. **Thermal analysis study:**

Differential Scanning Colorimeter (DSC) is used in this thermal analysis studies.

7. **Morphological characterization:**
Scanning electron microscopy (SEM) is used to study morphological characteristics.
8. **Water absorption capacity test:**
Agar plates with circular patches on the surface (with a surface area of 2.3 cm2) were made in simulated saliva and incubated at 37 $\pm 0.5^0$ C. Samples are weighed (wet weight) at intervals of 0.25, 0.5, 1, 2, and 4 hours, then allowed to dry for a week in desiccators over anhydrous calcium chloride at room temperature. The final constant weights are recorded after a week.
9. **Palatability test:**
A palatability test is carried out based on the taste after the bitterness and the physical appears of the substance. According to the criteria, each batch is given an A, B, or C grade. The formulation is regarded as average if it receives at least one A grade. When a formulation receives two A grades, it is deemed to be good, and when it receives three A grades, it is said to be very good.
10. **Stability study in human saliva:**
Fast dissolving film stability studies are conducted for all batches in accordance with ICH requirements. The films were assessed for physical appearance, drug content, and disintegration time after a predefined amount of time. Up to three months, the stability research of the improved mucoadhesive patch formulation was carried out at 40°C, 37± 5^0 C, and 75 ± 5 % RH. All parameters maintained their values after three months, with the exception of the volume entrapment efficiency, % elongation, and % drug release after eight hours, which experienced significant alterations.
11. **In vitro drug release:**
The rotating paddle method described in United States Pharmacopoeia (USP) XXIII was used to examine the rate of drug release from bilayered and multilayered tablets. The phosphate buffer with a pH of 6.8 serves as the dissolving media. The experiment was conducted at a at 37 °C ± 0.5 °C temperature of and a rotational speed of 50 rpm. The glass disk was connected to the buccal tablet's backing layer membrane using an instant adhesive (cyanoacrylate glue). The disintegration vessel's bottom was given over to the disk. 5 ml of the sample were removed and replaced with new medium at predefined intervals of time. The samples were filtered using Whatman filter paper before being subjected to UV spectrophotometry analysis at the appropriate nm dilution.
12. **In vitro drug permeation:**
The in vitro buccal drug permeation investigation of Drugs through the buccal mucosa of sheep or rabbit is carried out at 37°C ± 0.2° using Keshary-Chien or Franz type glass diffusion cells. It contains the donor and receptor compartments, both of which were linked with brand-new buccal mucosa. The buccal tablet's core side was facing the mucosa, and the compartments were firmly fastened. 1 ml of phosphate buffer (pH 6.8) is put in the donor compartment, and seven ml are put in the receptor compartment. By agitating the receptor compartment at 50 rpm with a magnetic bead, the hydrodynamics condition was kept. A UV spectrophotometer can be used to evaluate a 1 ml sample for drug content at an appropriate nm at a predetermined interval of time.
13. **Ex-vivomucoadhesion time:**
The buccal patch is applied to newly sliced buccal mucosa of sheep and rabbit to identify the appropriate time. A mucoadhesive patch is moistened with a drop of phosphate buffer (kept at 6.8) and pasted to the fresh buccal mucosa by lightly pressing with a fingertip for 30 seconds. The fresh buccal mucosa is then tied on the glass slide. The glass slide is then placed in a beaker with 200 ml of pH 6.8 phosphate buffer at a constant temperature of 37 ± 1^0C. After two minutes, the environment is simulated for

the buccal cavity by stirring at a 50rpm pace, and patch adhesion is tracked for 12 hours. the moment when the patch's color and form change, the patch collapses, and the that time the content of drug are noted.

Conclusion

The systemic distribution of drugs that are ineffective when taken orally, as well as an effective and attractive substitute for the noninvasive delivery of powerful peptide and protein therapeutic molecules, are the goals of the promising area of continuous research on buccal drug delivery. Therefore, additional efforts should be made to employ this delivery system by using more buccal permeability enhancers for the benefit of this delivery system's future aspects. For medications that need to avoid the GI [gastrointestinal] tract due to intestinal enzyme degradation, gastric pH, or significant hepatic first pass action, the buccal mucosa is a promising delivery route. The oral mucosa has been used for the administration of tiny pharmacological molecules thus far because their adsorption happens faster and more continuously. Only a small number of medications currently provide the benefits that are clinically significant. However, future growth may be influenced by the development of innovative formulations such bioadhesive preparations.

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