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Buccal Cavity Patches

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ABSTRACT: - Buccal Patches are the type of drug formulation that has normally a different course of administration through the buccal mucosa for drug delivery. The product is placed between upper gingiva (gums) and cheek to treat local and systemic conditions. Buccal bio adhesive films, releasing topical drugs in the oral cavity at a slow and predetermined rate, provide distinct advantages over traditional dosage forms for treatment of many diseases. Buccal patch has good accessibility to the membranes that line the oral cavity.Smart materials such as stimuli-responsive hydrogels, liposome-based patches, polymeric micelles, etc. play a vital role in the development of these drug delivery systems by their efficient carrier capacity, prolonging the residence time of the drug at the site of absorption, improved drug bioavailability, reduced dosing frequency and improved patience compliance. There are different designs and manufacturing methods such as electrospinning, electro spraying and 3D printing techniques which are considered as novel and efficient methods for preparation of buccal patches with some unique characteristics than traditional approaches such as solvent casting. These patches tend to help drug enter directly into the systemic circulation escaping hepatic first pass metabolism. This type of drug delivery method is considered useful for elevating the bioavailability of drugs. This review is a thorough study to apprehend the procedures involved in assessment of buccal patches and the modern approach towards this type of drug delivery. This article intends to analyze the overall profile of Buccal Patches and scope of future advances.

Keywords: Buccal patches, Electrospinning, Electrospraying, 3D printing, Bioavailability.

I. INTRODUCTION

1.1 Buccal drug delivery:

Bioadhesive drug delivery formulations were introduced in1947 when gum tragacanth was mixed with dental adhesivepowder to apply penicillin to the oral mucosa.In recentyears delivery of therapeutic agents via Mucoadhesive drugdelivery system has become highly interesting. Certaindrugs have lack of efficacy due to decreasedbioavailability, GI intolerance, unpredictable and erraticabsorption, or pre-systemic elimination of other potentialroute for administration. The recent development in thedrug delivery has intensified the investigation of mucosaldrug delivery. Such route includes oral, buccal, ocular,nasal and pulmonary routes etc[52][53].The pharmaceutical industry has engendered considerable interest making it a major participant in the healthcare industry. The advances and progress made by pharmaceutical industry have greatly contributed in terms of treatment of disease, thereby enhancing the quality of life Transmucosal routes of drug delivery which comprise of the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity offer excellent opportunities and potential advantages over peroral administration for systemic drug delivery[1]

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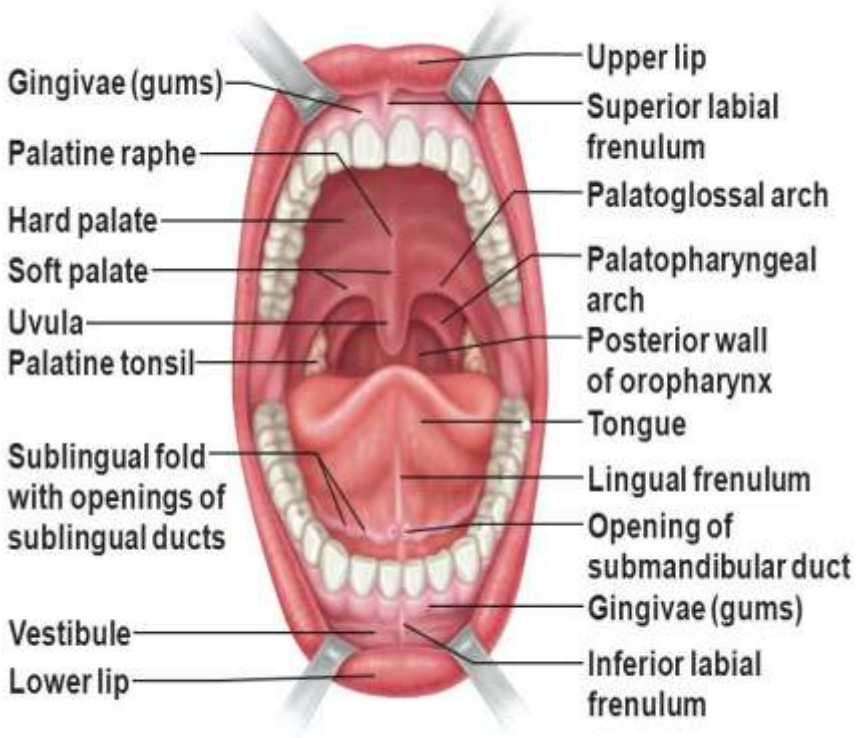

Fig:1 oral cavity

1.2 Mucoadhesive drug delivery system

Mucoadhesive drug delivery systems offer benefits over conventional delivery methods in terms of extended residence time of the drug at the site of application, a relatively large permeabilityof the mucus membranes that allow rapid uptake of a drug into the systemic circulation, and enhanced bioavailability of therapeutic agents resulting from the avoidance of some of the body's natural defence mechanisms.[2] Mucoadhesion, defined as the ability to adhere to the mucus gel layer, is a key element in the design of these drug delivery systems. Buccal mucosa is an attractive route for systemicdelivery of drugs since it is relatively permeable, with rich blood supply The problems such as high first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via the buccal route and, buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage form from the buccal cavity.

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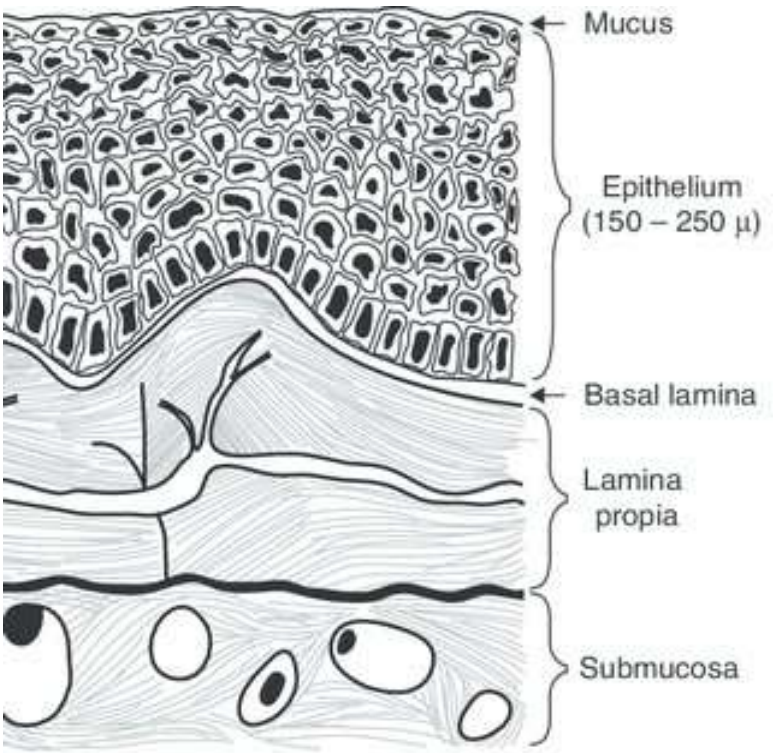

Fig:2 Oral mucosa

1.2.1 Structure of Oral Mucosa:

The oral mucosa is comprised of squamous stratified (layered) epithelium, basement membrane, the lamina propria and submucosa. It also contains many sensory receptors including the taste receptors of the tongue.[3]

Table 1: Thickness and surface area of oral cavity

Oral cavity membrane	Thickness (mm)	Surface area (cm^2)
Buccal mucosa	500-600	5.2
Sublingual mucosa	100-200	26.5
Gingival mucosa	200	--
Palatal	250	20.1

1.2.2 The mucoadhesive drug delivery system in the mucus membrane of oral cavity can be categorized into three delivery systems:[11]

• Sublingual delivery
• Buccal delivery
• Local delivery

These oral sites provide the high blood supply for the greater absorption of drug with sufficient permeability. From these three sites of oral mucoadhesive drug delivery system, the buccal delivery is the most convenient site.

1.2.3ADVANTAGES OF MUCOADHESIVE BUCCAL DRUG DELIVERY SYSTEM [10]

Mucoadhesive via buccal route offers following advantages: -

- Ease of drug administration and termination of drug action can be easily accomplished.
- Permits or retention of the drug to the specified area of oral cavity for extended period of time.
- Bypass hepatic first pass metabolism.
- Drugs with poor bioavailability owing to the high first pass metabolism can be administered conveniently.
- Ease of drug administration to unconscious patients.

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- Water content of saliva is being capable to ensure drug dissolution.

1.3 Structure and Design of Buccal Dosage Form: [3]

Buccal Dosage form can be of:

1.Matrix type: The buccal patch designed in a matrix configuration contains drug, adhesive, and additives mixed together.

2. Reservoir type: The buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. An impermeable backing is applied to control the direction of drug delivery; to reduce patch deformation and disintegration while in the mouth; and to prevent drug loss.

Fig. 3: Buccalpatch designed for bidirectional drug

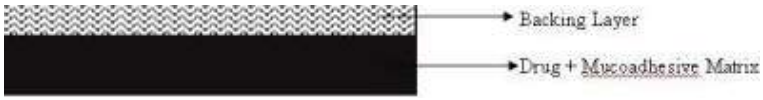

Fig. 4: Buccal patch designed for unidirectional drug

1.3.1Types of Buccal dosage form:

1. BUCCAL BIOADHESIVE TABLETS --

Buccal bio adhesive tablets are dry dosage forms that are to be moistened prior to placing in contact with buccal mucosa. Double and multi-layered tablets are already formulated using bio adhesive polymers and excipients. The two buccal bio adhesive tablets commercially available Bucco adhesive tablets in UK are Bucastem (Nitroglycerine) and Suscard buccaP (Prochloroperazine).[10]

2. BUCCAL BIOADHESIVE PATCHES AND FILMS --

Buccal bio adhesive patches consists of two poly laminates or multi-layered thin film round or oval as consisting of basically of bio adhesive polymeric layer and impermeable backing layer to provide unidirectional flow of drug across buccal mucosa. Buccal bio adhesive films arc formulated by incorporating the drug in alcohol solution of bio adhesive polymer.[10]

3. SEMISOLID PREPARATIONS(OINTMENTS and GELS)

Bioadhesive gels or ointments have less patientacceptability than solid bio adhesive dosage forms, andmost of the dosage forms are used only for localized drugtherapy within the oral cavity. One of the original oralmucoadhesive delivery systems -"orabase"- consists offinely ground pectin, gelatin and NaCMC dispersed in apoly (ethylene) and a mineral oil gel base, which can bemaintained at its site of application for 15-150 mins.[54].

4. POWDERS

HPC and beclomethasone in powder form when sprayed on to the oral mucosa of rats, a significantincrease in the residence time relative to an oral solution is seen, and 2.5% of beclomethasone is retained on buccal mucosa for over 4 hrs[54].

Table 2: List of permeation enhancers [8]

Permeation Enhancers	
Chelators	EDTA, Citric acid, Sodium salicylate, Methoxy salicylates.
Surfactants	Sodium lauryl sulphate, Polyoxymethylene,

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	Polyoxyethylene-9-laurylether, Polyoxythylene-20-cetylether, Benzalkonium chloride, 23-lauryl ether, Cetylpyridinium chloride, Cetyltrimethyl ammonium bro-mide.
Bile salts	Sodium glycocholate, Sodium deoxycholate, Sodium taurocholate, Sodium glycodeoxycholate, Sodium taurodeoxycholate.

1.3.2An ideal polymer for Bucco adhesive drug delivery systems should have following Characteristics.[4]

It should be inert and compatible with the environment.

• The polymer and its degradation products should be non-toxic absorbable from the mucous layer.

• It should adhere quickly to moist tissue surface and should possess some site specificity.

• The polymer must not decompose on storage or during the shelf life of the dosage form

The polymer should be easily available in the market and economical.

• It should allow easy incorporation of drug in to the formulation.

1.3.3Advantages of Buccal Patches: [4]

1. The oral mucosa has a rich blood supply. Drugs are absorbed from the oral cavity through the oral mucosa, and transported through the deep lingual or facial vein, internal jugular vein and brachiocephalic vein into the systemic circulation 5.

2. Buccal administration, the drug gains direct entry into the systemic circulation thereby bypassing the first pass effect. Contact with the digestive fluids of gastrointestinal tract is avoided which might be unsuitable for stability of many drugs like insulin or other proteins, peptides and steroids. In addition, the rate of drug absorption is not influenced by food or gastric emptying rate 6.

3. The area of buccal membrane is sufficiently large to allow a delivery system to be placed at different occasions, additionally; there are two areas of buccal membranes per mouth, which would allow buccal drug delivery systems to be placed, alternatively on the left and right buccal membranes.

4. Buccal patch has been well known for its good accessibility to the membranes that line the oral cavity, which makes application the oral cavity,
which makes application painless and with comfort.

5. Patients can control the period of administration or terminate delivery in case of emergencies. The buccal drug delivery systems easily administered into the buccal cavity. The novel buccal dosage forms exhibit better patient compliance.

1.3.4Limitation of buccal drug administration [10]

There is certain limitation via drug administered through buccal route: -

- Drugs with ample dose are often difficult to be administered.
- Possibility of the patients to swallow the tablets being forgotten.
- Eating and drinking may be restricted till the end of drug release.
- This route is unacceptable for those drugs, which are unstable at pH of buccal environment.
- This route cannot administer drugs, which irritate the mucosa or have a bitter or unpleasant taste.
- Limited surface area is available for absorption

1.4Mechanism of bio adhesion

Bio adhesion is an interfacial phenomenon in which two materials, at least one of which is biological, are held together by means of interfacial forces. The attachment could be between an artificial material and biological substrate, such as adhesion between polymer and/or copolymer and a biological membrane. In case of polymer attached to the mucin layer of the mucosal tissue, the term

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"mucoadhesion" is employed. "Bioadhesive" is defined as a substance that is capable of interacting with biological material and being retained on them or holding them together for extended period of t time.[21]

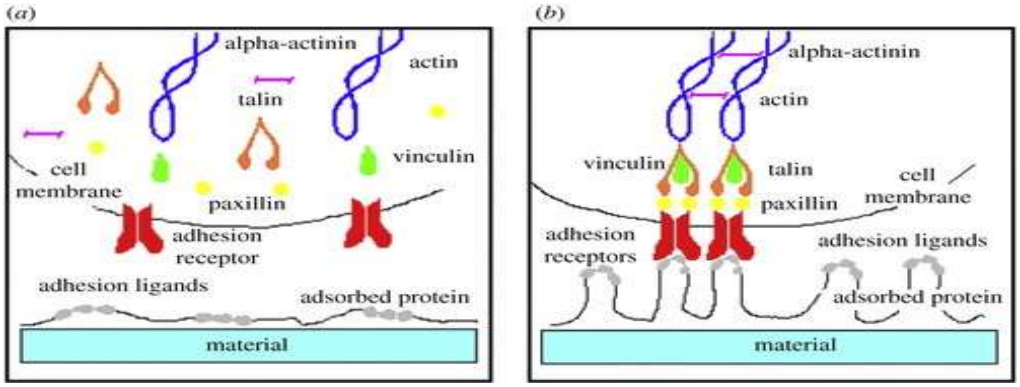

Fig. 5: Bio adhesive mechanism

1.4.1Characteristics of an Ideal Bucco adhesive System:[10]

An ideal buccal adhesive system should possess the following characteristics:

1. Quick adherence to the buccal mucosa and sufficient mechanical strength.
2. Drug release in a controlled fashion.
3. Facilitates the rate and extent of drug absorption.
4. Should have good patient compliance.
5. Should not hinder normal functions such as talking, eating and drinking.
6. Should accomplish unidirectional release of drug towards the mucosa.
7. Should not aid in development of secondary infections such as dental caries.
8. Possess a wide margin of safety both locally and systemically.
9. Should have good resistance to the flushing action of saliva.

1.4.2Basic Components of Buccal Bioadhesive Drug Delivery System:[4]

The basic components of buccal bio adhesive drug delivery system are:

1. Drug Substance
2. Bioadhesive polymers
3. Backing membrane
4. Penetration enhancer
5. Adhesive

1.5Advantages of Buccal Drug Delivery System:[3]

Drug administration via buccal mucosa offers several distinct advantages:

1. The buccal mucosa is relatively permeable with a rich blood supply, robust in comparison to the other mucosal tissues.
2. Bypass the first-pass effect and non-exposure of the drugs to the gastrointestinal fluids.
3. Easy access to the membrane sites so that the delivery system can be applied, localized and removed easily.
4. Improve the performance of many drugs, as they are having prolonged contact time with the mucosa.
5. High patient acceptance compared to other non-oral routes of drug administration.
6. Tolerance (in comparison with the nasal mucosa and skin) to potential sensitizers.
7. Increased residence time combined with controlled API release may lead to lower administration frequency.
8. Additionally significant cost reductions may be achieved and dose-related side effects may be reduced due to API localization at the disease site.
9. As a result of adhesion and intimate contact, the formulation stays longer at the delivery site improving API bioavailability using lower API concentrations for disease treatment.
10. Harsh environmental factors that exist in oral delivery of a drug are circumvented by buccal drug delivery.
11. It offers a passive system of drug absorption and does not require any activation.
12. The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal or transdermal routes.

1.6Disadvantages of Buccal Drug Delivery System:[7]

The main challenges of buccal administration are:

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1. Limited absorption area- the total surface area of the membranes of the oral cavity available for drug absorption is 170 cm2 of which ~50 cm2 represents non-keratinized tissues, including buccal membrane.
2. Barrier properties of the mucosa.
3. The continuous secretion of the saliva (0.5-2 l/day) leads to subsequent dilution of the drug.
4. The hazard of choking by involuntarily swallowing the delivery system is a concern.
5. Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and ultimately the involuntary removal of the dosage form.

II. LITERATURE REVIEW

Table 3 :Literature review

Sl no.	Author name	Title	Year	Description	Reference number
1.	Anroop B Nair	Mucoadhesive buccal film of almotriptan improve therapeutic delivery in rabbit model	2020	Administration of almotriptan as an oral therapy is largelylimited because of poor aqueous solubility and low bioavailability. Buccal films consist of mucoadhesive as well as film forming polymers.	1
2.	Felipe pereiraes	Manufacture and characterization of mucoadhesive buccal film based on pectin and gellan gum cotaining triamannolone acetonide	2018	Buccal films consist of mucoadhesive as well as film. forming polymers the interaction between hydrophilic polymers is sufficient to obtain films with adequate characteristics for use as drug release devices.	2
3.	Banbar e al-dubai	Formulation and evalution of nano base drug delivery system for the buccal delivery of acyclovir	2015	Oral bioavailability of acyclovir is limited, primarily because of low permeability across the gastrointesti-nal membrane. Acyclovirpolymeric nanospheres were prepared by double emulsion solvent evaporation technique. Nanospherewere embedded into buccoadhesive films comprising of different concentrations of polymers. Films were characterized for physico-mechanical prop-erties, mucoadhesive strength, hydration, drug release and ex vivo	3

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				permeation.	
4.	Waleed m khattab	Buccoadhesive delivery system for an anti-migraine drug: in vitro/ex vivo evalution	2013	Different dosage forms were developed based on this principle. Bucco-adhesive tablets of zolmitriptan represent an alternative delivery system to avoid hepatic first pass metabolism and provide prolonged and uniform drug release.	4
5.	Amanpreet kaur and gurpreet kaur	Mucoadhesive buccal patches based on interpolimar complexes of chitosan-pectin for delivery of carvedilol	2012	The study was designed to develop bio adhesive patches of carvedilol hydrochloride using chitosan (CH) and pectin (PE) interpolymer complexes and to systematically evaluate they're in vitroand in vivoperformancesinterpoly mer complexes bio adhesive patches of carvedilol hydrochloride was formulated. The bio adhesive patches were displaying sufficient bio adhesive strength and in vitro drug release.	5
6.	Mohammed jafar and sadath ali	Development and evalution of meloxicam solid dispersion loaded buccal patches	2011	Meloxicam, a non-steroidal anti-inflammatory drug is widely used in the treatment of rheumatoid arthritis, ankylosing spondulytis and osteoarthritis. A good in-vitro in-vivo correlation was observed in MSP1 patch. All solid dispersion loaded buccal patches showed excellent stability under tested conditions.	6
7.	Dennis douroumis	Controlled released from directly compressible thothylline buccal tablet	2012	Buccal adhesive formulations were developed using a water soluble resin with various combinations of mucoadhesive polymers. The prepared theophylline tablets were evaluated for tensile strength, swelling capacity and ex vivo	7

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				mucoadhesion performance	
8.	Maria immalolata la rotunda	Cyclodextrin-containing poly(ethyleneoxide) tablet for the delivery of poorly soluble drugs: potentional buccal delivery system	2006	Cyclodextrins are responsible for an increase in the erosion rate of the tablet and an improved dissolution of the drug inside the polymeric matrix.	8
9.	Noha a nafee, fatama a ismail	Mucoadhesive buccal patches of miconazole nitrate: in vitro / in vivo performance and effect of ageing	2003	Mucoadhesive patches containing miconazole nitrate using anionic (SCMC), cationic (chitosan) and non-ionic (PVA, HEC, HPMC) polymers showed satisfactory mucoadhesive characteristics.	9
10.	Noha adel nafee,Fatma Ahmed Ismail	Design and characteriza of mucoadhesve buccal patches containing cetylpyridinium chloride	2003	The non-ionic polymer, PVA, showed good mucoadhesive and swelling characteristics. Medicated PVA patches maintained a satisfactory residence time in the buccal cavity and ensured zero-order release of the drug over relatively long periods (7 h), which made them good candidates for stability studies.	10
11.	M juj m, M. Beirevi-Laan , S. Bengez	Novel cyclodextrin based film formulation intend for buccal delivery of atenolol	2009	Iincorporation of atenolol in the form of an inclusion complex into hydrophilic films may be an appropriate strategy to prepare a suitable formulation for buccal drug delivery. Atenolol formed a stabile inclusion complex with RAMEB in solution and in solid state.	11
12.	Nina langoth,Andreas Bernkop-Schnürch	Development of buccal drug delivery system based on thiolated polymer	2003	Thiolated PCP increased the stability of the synthetic substrate for aminopeptidase N-leu-pnitroanilide and the model drug leucin-enkephalin against enzymatic degradation on buccal mucosa.	12

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13.	K Chandra sekhar ,K. V. S. Naidu(et al 2008)	Transbuccal delivery of chlorpheniramine maleate from mucoadhesive buccal patches	2008	Buccal patches were prepared using solvent casting technique with HEC as polymer and propylene glycol as plasticizer. Polymer was added to 20 ml of distilled water and allowed to stand for 6 hr to swell. Propylene glycol and CPM were dissolved in 5 ml of distilled water and added to the polymer solution.	13
14.	Madgalin tarai, dr. H . lalhlenmawia	Novel , buco-compatible simvastatin buccal film: an integrative study of the effect of formulation variables	2013	The developed films were found to be bucco-compatible and formulation variables were observed to influence physico-mechanical as well as drug permeation characteristics of film.	14
15.	R. venkatalakshmi , Yajaman Sudhakar , Madhuchudana Chetty C., Sasikala C and Mohan Varma M	Buccal drug using adhesive polymeric patches	2012	The polymers which are insoluble in saliva or water can be used as efficient matrix systems through which rate of release of drug can be controlled as desired.	15
16.	Pradeep kumar koyi and Arshad bashir khan	Buccal patch: a review	2013	Buccal drug absorption occurs by passive diffusion of the nonionized species, a process governed primarily by a concentration gradient, through the intercellular spaces of the epithelium.	16
17.	Shalini Mishra,G. kumar and P. kothiyal	A review article: recent approaches in buccal patch	2012	The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic elimination in thegastrointestinal tract are avoided. The area is wellsuited for a retentive device and appears to be acceptable to the patient.	17
18.	Mohammad umar javaid and safwan shahid	Buccal patches: an advanced route of drug	2017	buccal patches have numerous advantages above the conventional drug	18

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		dosage delivery-a review		delivery system. The mucosa is well supplied with both vascular and lymphatic drainage and evading first-pass metabolism. Buccal drug delivery is an encouraging area for continued research with the purpose of systemic delivery of orally inefficient drugs.	
19.	Punitha s and girish y	Polymers in mucoadhesive buccal drug delivery system-a review	2010	Buccal adhesive systems offer innumerable advantages in terms of accessibility, administration and withdraw-al, retentivity, low enzymatic activity, economy and high patient compliance.	19
20.	a. puratchikody, Prasanth V.V, Sam T. Mathew, Ashok Kumar B	Buccal drug delivery: past,present and future- a review	2011	methods of drug release through trans-mucosal and transdermal methods would be of great significance, as by such routes, the pain factor associated with parenteral routes of drug administration can be totally eliminated.	20
21.	Shrivastava namita and monga munish garg	Current status of buccal drug delivery system-a review	2015	Buccal drug delivery is a promising area for continued research with the aim of 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.	21
22.	Singh r sharma d, garg r	Review on mucoadhesive drug delivery system special emphasis on buccal route	2017	Oral mucosal delivery offers a convenient way of dosing medication, not only to special populations with swallowing difficulties, but also to the general population. Mucoadhesive dosage forms provide prolonged contact time at the site of attachment, having high patient compliance and are economic as compare to other dosage forms.	22

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23.	Osamah s malauah	Buccal drug delivery technologies for patient central treatment of radiation-indused xerostomia(dry mouth)	2018	Local application to the buccal mucosa would have the advantages of ease of administration, good bioavailability and fast onset of action. Therefore, reformulation of pilocarpine, or other salivary stimulants, as a buccal formulation would be a significant step in improved pharmacotherapy of radiation-induced xerostomia.	23
24.	Surender Verma, Mahima Kaul	an overview of buccal drug delivery system	2011	The transmucosal route is becoming more and more popular because it does have significant advantages like avoidance of first pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract.	24
25.	Flavio Hernández-Castro	Randomized double-blind placebo-controlled trial of buccal misoprostolto reduce the need for additional uterotonic drugs during cesarean delivery	2016	Misoprostol is a synthetic prostaglandin E1 analog that has beendemonstrated to be an effective uterotonic agent in the third stage of labor and the immediate postpartum period. It can be administered by various routes including the poorly studied buccal-space pathway, where the dosage form is placed between gums and the inner lining of the cheek.	25
26.	Pragati Shakya, N. V. Satheesh Madhav	Evaluation of data polysaccharide (DPP)as a biomucoadhesen t and its comparison with various mucoadhesive polymer	2010	evaluate DPP as a Mucoadhesive polymer This biomaterial can serve as promising mucoadhesent for formulating the various transmucosal drug delivery systems	26
27.	Mamatha. Y, Prasanth V.V, Selvi Arunkumar, Sipai Altaf Bhai. M, Vandana Yadav	Buccal drug deliverya technical approach	2012	The buccal mucosa offers several advantages for controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the	27

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				liver and pre-systemic elimination in the gastrointestinal tract are avoided.	
28.	Pedro M. Castro,Patrícia Baptista	Combination of PLGA nanoparticles with mucoadhesive guar-gum films for buccal delivery of antihypertensive peptide	2018	Peptide-loaded nanoparticles, prepared in the scope of a factorial design, were tested in triplicate. A buccal delivery system based on the combination of previously optimized guar-gum films and PLGA nanoparticles was developed for the first time for the antihypertensive peptide	28
29.	Siok Yee Chan, Choon Fu Goh	Rice starch thin films as a potential buccal delivery system: Effect of plasticiser and drug loading on drug release profile	2019	The impact of the type of plasticiser on the properties of rice films is indicated by the water content, swelling index and drug release profile.	29
30.	Juliana Souza Ribeiro Costa, Karen de Oliveira Cruvinel a, Laura Oliveira-Nascimento	A mini-review on drug delivery through wafer technology: Formulation and manufacturing of buccal and oral lyophilizates	2019	Freeze-dried wafers can provide immediate or sustained delivery of APIs for local or systemic action. These wafers allow for ease of administration, protection against mechanical removal, and high drug loading	30
31.	Susmit Sneha	CURCUMIN - A NOVEL AYURVEDIC TREATMENT FOR ORAL LICHEN PLANUS	2017	The Curcumin was found to be safe at the prescribed dose and efficacious in controlling the signs and symptoms of OLP. It can be used as an alternative to the standard corticosteroid therapy in the management of OLP and thus alleviate the need for drugs with more serious adversities including corticosteroids.	31
32.	Jinsong Hao and Paul W. S. Heng	Buccal Delivery Systems	2003	The oral cavity is an attractive site for drug delivery due to ease of administration and avoidance of possible drug degradation in	32

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				gastrointestinal tract and first-pass Metabolism.	
33.	Alaadin Alayoubi, Lindsay Haynes, Hemlata Patil	Development of a fast dissolving film of Epinephrine hydrochloride as a potentialanaphyl actic treatment for pediatrics	2016	Four films with different polymer contents were evaluated in thisstudy. The formulation with the highest concentration of the polymer Lycoat formed smooth and clear film. The optimized formulation showed good mechanical properties attaining high level of flexibility, thickness uniformity and rapid disintegration and dissolution time.	33
34.	Ana Camila Marques, Ana Isabel Rocha, Paula Leal	Development and characterization of mucoadhesive buccal gels containing lipid nanoparticles of ibuprofen	2017	buccal administration of lipid nanoparticles. It was also possible to demonstrate the ability of NLC to promote a sustained release of drug, when incorporated in hydrogels. This fact evidences the importance of develop a mucoadhesive system for buccal administration of lipid nanoparticles.	34
35.	Georgios K. Eleftheriadis	Unidirectional drug release from 3D printed mucoadhesive buccal films using FDM technology: In vitro and ex vivo evaluation	2019	The presence of chitosan affected theex vivo performance of formulated films, demonstrating enhanced mucoadhesion and permeation properties. The overall study confirmed the hypothesis of 3D printing exploitation toward fabrication of oromucosal buccal dosage forms.	35
36.	Peeush Singhal, Gajendra Singh Jadoun	Formulation and Evaluation of Buccal Patches of Terbutaline Sulphate	2010	mucoadhesive buccal patch containing 280mg HPMC and 70mg Eudragit RL-100 produced buccal patches having good mucoadhesive strength and 96.89% drug release in 12 hr .	36
37.	Paolo Giunchedi, Claudia Juliano	Formulation and in vivo evaluation of chlorhexidine buccal tabletsprepared using drug-	2002	Buccal tablets were prepared by mixing and tabletting drug-loaded microspheres belonging to batch A with mannitol and saccharine or with mannitol, saccharine and	37

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		loaded chitosan microspheres		sodium alginate .	
38.	S.Velmurugan,B. Deepika, K.Nagaraju, Sundar Vinushitha	Formulation and in-vitro Evaluation of Buccal Tablets of Piroxicam	2010	Development of bioadhesive buccal drug delivery of piroxicam is one of the alternative routes of administration to avoid high gastric irritation and sustain release.	38
39.	Anne Mette Handler, Eva Marxen, Jette Jacobsen, Christian Janfelt	Visualization of the penetration modifying mechanism of laurocapram by Mass Spectrometry Imaging in buccal drug delivery	2019	the penetration of codeine through the buccal mucosa was not affected by the pre-treatment of laurocapram observed in MALDI images of the codeine-treated buccal mucosa.	39
40.	Isaac Ayensu, John C. Mitchel	Development and physico-mechanical characterisation of lyophilised chitosan wafers as potential protein drug delivery systems via the buccal mucosa	201	On the basis of characteristic performance and structural integrity after lyophilisation, the nondrug-loaded wafer 'formulation B' containing 6.5 mg each of plasticizer and cryoprotectant was the formulation of choice for drug loading and drug dissolution	40
41.	A. Jaipal, M.M. Pandey, S.Y. Charde, P.P. Raut, K.V. Prasanth, R.G. Prasad	Effect of HPMC and Mannitol on Drug Release and Bioadhesion Behavior on Buccal Discs of Buspirone Hydrochloride: In-vitro and In-vivo Pharmacokinetic Studies	2011	Effect of mannitol and HPMC on drug release and bioadhesive behavior from the designed buccal discs was studied successfully using a 32 factorial design. It can be concluded that the drug release pattern can be changed by selection of appropriate levels of two factors viz HPMC and mannitol.	41
42.	Javier O Morales	Buccal delivery of small molecules and biologics: of mucoadhesive polymers, films, and nanoparticles	2017	Buccal delivery of macromolecules including peptides and proteins is one of the delivery routes less investigated compared to the oral or pulmonary routes. Successful approaches to formulating small molecules in biocompat- ible films involve solvent casting and so far to a lesser extent, hot melt extrusion and ink-jet	42

				printing.	
43.	V. De Caroa, G. Giandaliaa, M.G. Siragusaa	New prospective in treatment of Parkinson's disease: Studies on permeation of ropinirole through buccal mucosa	2012	The drug passively crosses the membrane and allows the achievement of therapeutic drug levels in plasma. Nevertheless, an initial lag time is observed but the input rate can be modulated by permeation enhancement using limonene or by application of electric fields.	43
44.	Viralkumar F. Patel	Modeling the oral cavity: In vitro and in vivo evaluations of buccal drug delivery systems	2012	Several dosage forms have been developed and explored to enable drug delivery through the oral mucosa and include liquids , semi-solids and sprays	44
45.	Muhammad Hanif, Muhammad Zaman & Vesh Chaurasiya	Polymers used in buccal film: a review	2014	Mucosal membrane of oral cavity allows high permeation to certain drugs having high blood perfusion. Drugs with poor bioavailability as well as with shorter half-life can be administered easily. Buccal films can release the topical drugs with sustained and controlled effects and advantageous over the traditional drug delivery systems that are used in the curement of various disease.	45
46.	Bazigha K. Abdul Rasool	In Vitro Release Study of Nystatin from Chitosan Buccal Gel	2010	chitosan polymer is a candidate gelling agent for development of nystatin gel which can be used successfully for eradication of fungal infections in oral cavity.	46
47.	Miguel Montenegro-Nicolini	Overview and Future Potential of Buccal Mucoadhesive Films as Drug Delivery Systems for Biologics	2016	developments in buccal mucoadhesive drug delivery systems for biologics could be directed to vaccines, peptides, or proteins. Novel formulations need to consider the chemical nature and physical structure of these materials to provide adequate alternatives for	47

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				drug delivery.	
48.	Nazila Salamat-Miller, Montakarn Chittchang	The use of mucoadhesive polymers in buccal drug delivery	2005	Application of lectin and blectinomimeticsQ appears to be the most promising area of current research efforts aimed at the safe and effective delivery of drugs via the buccal mucosa	48
49.	Heleen Kraan, Hilde Vrieling , Cecil Czerkinsky ,Wim Jiskoot , Gideon Kersten , Jean-Pierre Amorij	Buccal and sublingual vaccine delivery	2014	Mucosal vaccine delivery in the mouth can be subdivided into sublingual and buccal delivery. Sublingual delivery occurs via the mucosa of the ventral surface of the tongue and the floor of the mouth under the tongue, whereas buccal delivery occurs via the buccal mucosa, which is located in the cheeks, the gums and the upper and lower inner lips.	49
50.	Hitoshi Shibuya, Masamune Takeda	Brachytherapy for Non-Metastatic Squamous CellCarcinoma of the Buccal Mucosa: An Analysis offorty-five cases treated with permanent implants	2009	There are several reports on treatment results in buccal cancer after surgery, radiotherapy, chemotherapy or a combination of these modalities	50

III. FORMULATION AND METHOD OF PREPARATION

3.1Method of Preparation:[4]

Two methods are used to prepare adhesive patches.

1. Solvent casting:

In this method, all patch excipients including the drug co-dispersed in an organic solvent and coated onto a sheet of release liner. After solvent evaporation a thin layer of the protective backing material is laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of the desired size and geometry

Table 4. Examples of mucoadhesive buccal patches and their characteristics.

Type	Polymer Constituents	Drugs Used	Manufacturing Method	Highlights
Controlled release	Carbopol, hydroxypropyl methylcellulose (HPMC), poloxamer and compritol 888	Lidocaine	Solvent casting	Free lidocaine and/or microspheres loaded patch fabricated using HPMC/carbopo

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	ATO			l and poloxamer Lidocaine microspheres prepared from Compritol 888 ATO employing spray congealing technique Change in formulation composition demonstrated to change the drug release mechanisms and able to provide either rapid, delayed or prolonged local anesthetic activity. [55]
Sustained release	Sodium alginate, HPMC, sodium carboxymethyl cellulose (NaCMC) and carbopol	Atenolol	Solvent casting	Patch prepared from sodium alginate Ex vivo permeation studies across goat buccal mucosa revealed 70.17 _ 2.28% release over a period of 24 h with maximum permeation flux (30.83 _ 1.23 _g/cm2/h) and minimum lag time (0.95 _ 0.22 h) Polymers used could provide sustained release of atenolol across porcine buccal mucosa for 24 h. [56]
Modified release	Xanthan gum, polyvinyl alcohol (PVA) and HPMC E-15	Zolmitriptan	Solvent casting	Bilayer patch prepared from xanthan gum In vitro drug release studies showed rapid

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				drug release; 43.15% within 15 min, followed by sustained release rate over 5 h Incorporation of 4% dimethyl sulfoxide demonstrated 3.29-fold drug permeation, transported 29.10% of drug after 5 h. [57]
Immediate release	HPMC,PVA, polyvinylpyrrolidone and ethyl cellulose	Carbamazepine	Solvent casting	Water impermeable polypropylene backing layer provided unidirectional drug release Due to high water uptake, PEG 400 containing batches showed maximum in vitro release and increased mucoadhesion Drug release was controlled by either diffusion or non-Fickian diffusion. [58]
Peptide delivery	Chitosan, choline and geranic acid	Insulin	Solvent casting	Viscous gel made of choline and geranic acid sandwiched between two layers of chitosan Significant increase (7-fold) in the cumulative insulin transport across the ex vivo porcine buccal tissue

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				was demonstrated (~26% of loaded insulin) In vivo studies in rat buccal pouch lowered blood glucose levels up to 50% in a dose dependent manner Serum insulin plateaued after 3 h for the duration of the study. [59]

2. Direct milling:

In this, patches are manufactured without the use of solvents. Drug and excipients are mechanically mixed by direct milling or by kneading, usually without the presence of any liquids. After the mixing process, the resultant material is rolled on a release liner until the desired thickness is achieved. The backing material is then laminated as previously described. While there are only minor or even no differences in patch performance between patches fabricated by the two processes, the solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent-related health issues.

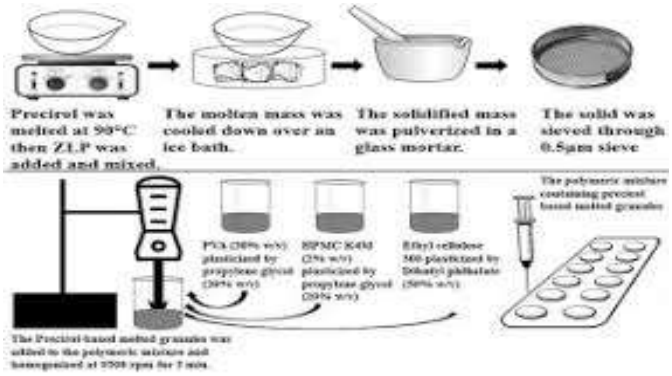

Fig:6 preparation of buccal patch

3.2 Composition of Buccal Patches:[15]

A. **Active ingredient.**

B. **Polymers (adhesive layer):** Hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, Carbopol and other mucoadhesive polymers.

C. **Diluents:** Lactose DC is selected as diluent for its high aqueous solubility, its flavouring characteristics, and its physico-mechanical properties, which make it suitable for direct compression. Other example: microcrystalline starch and starch.

D. **Sweetening agents:** Sucralose, aspartame, mannitol, etc.

E. **Flavouring agents:** Menthol, vanillin, clove oil, etc.

F. **Backing layer:** Ethyl cellulose, Poly vinyl alcohol etc.

G. **Penetration enhancer:** Cyano acrylate, etc.

H. **Plasticizers:** PEG-100, 400, propylene glycol, etc.

IV. EVALUATION PARAMETERS

4.1Evaluation of Buccal Patch

The following tests are used to evaluate the Buccal Patches:[1]

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Drug Content Uniformity, Ex-Vivo Residence Time, Thickness Testing, In-vitro drug permeation studies, In-vitro release studies, Moisture absorption studies, Surface pH study, In-vitro bio adhesion measurement, In-vitro permeation through porcine buccal membrane, Stability in human saliva, FTIR studies etc water (15:85, v/v). The flow rate was 2.0 ml/min and the run time15 min. The retention time of TPL was 3.1 min. The TPL calibration curve, at concentrations varying from 5_g/ml to 100_g/ml,

1. Surface pH:
Buccal patches are left to swell for 2 hr on the surface of an agar plate. The surface pH is measured by means of a pH paper placed on the surface of the swollen patch.[24]

2. **Thickness measurements:**
The thickness of each film is measured at five different locations (centre and four corners) using an electronic digital micrometre.[24]

3. **Swelling study:**
Buccal patches are weighed individually (designated as W1), and placed separately in 2% agar gel plates, incubated at 37°C ± 1°C, and examined for any physical changes. At regular 1-hour time intervals until 3 hours, patches are removed from the gel plates and excess surface water is removed carefully using the filter paper.

$$SI = \frac{(W2-W1)}{W1} \times 100$$

4. **Water absorption capacity test:**
Circular Patches, with a surface area of 2.3 cm2 are allowed to swell on the surface of agar plates prepared in simulated saliva (2.38 g Na2HPO4, 0.19 gKH2PO4, and 8 g NaCl per litter of distilled water adjusted with phosphoric acid to pH 6.7), and kept in an incubator maintained at 37°C ± 0.5°C. At various time intervals (0.25, 0.5, 1, 2, 3 and 4 hours), samples are weighed (wet weight) and then left to dry for 7 days in a desiccator over anhydrous calcium chloride at room temperature then the final constant weights are recorded. Water uptake (%) is calculated using the following equation

$$\text{Water uptake (\%)} = \frac{(W_w - W_f)}{W_f} \times 100$$

Where, Ww is the wet weight and Wf is the final weight. The swelling of each film is measured [27]

5. **Ex-vivo bioadhesion test:**
The fresh sheep mouth separated and washed with phosphate buffer (pH 6.8). A piece of gingival mucosa is tied in the open mouth of a glass vial, filled with phosphate buffer (pH 6.8). This glass vial is tightly fitted into a glass beaker filled with phosphate buffer (pH 6.8, 37°C ± 1°C) so it just touched the mucosal surface. The patch is stuck to the lower side of a rubber stopper with cyano acrylate adhesive. Two pans of the balance are balanced with a 5-g weight. The 5-g weight is removed from the left-hand side pan, which loaded the pan attached with the patch over the mucosa. The balance is kept in this position for 5 minutes of contact time. [30]

The water is added slowly at 100 drops/min to the right-hand side pan until the patch detached from the mucosal surface. The weight, in grams, required to detach the patch from the mucosal surface provided the measure of mucoadhesive strength.[30]

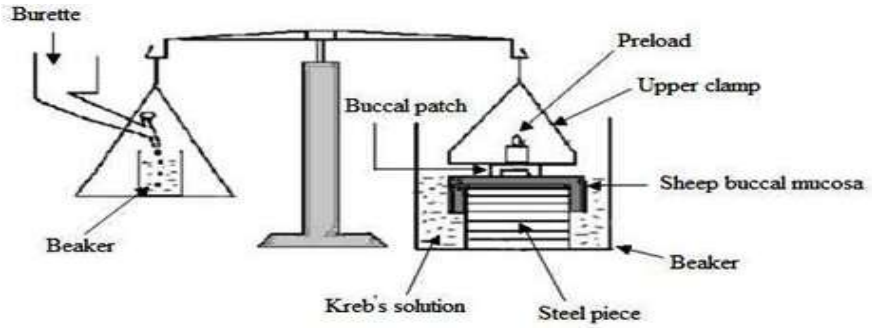

FIG.7: Measurement of mucoadhesive[7]

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6. **In vitro Drug Release:**

The United States Pharmacopeia (USP) XXIII-B rotating paddle method is used to study the drug release from the bilayered and multilayered patches. The dissolution medium consisted of phosphate buffer pH 6.8. The release is performed at 37°C ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of buccal patch is attached to the glass disk with instant adhesive material. The disk is allocated to the bottom of the dissolution vessel. Samples (5 ml) are withdrawn at predetermined time intervals and replaced with fresh medium. The samples filtered through Whatman filter paper and analyzed for drug content after appropriate dilution.[15]

The in- vitro buccal permeation through the buccal mucosa (sheep and rabbit) is performed using Keshary-Chien/Franz type glass diffusion cell at 37°C±0.2°C. Fresh buccal mucosa is mounted between the donor and receptor compartments. The buccal patch is placed with the core facing the mucosa and the compartments clamped together. The donor compartment is filled with buffer [24]

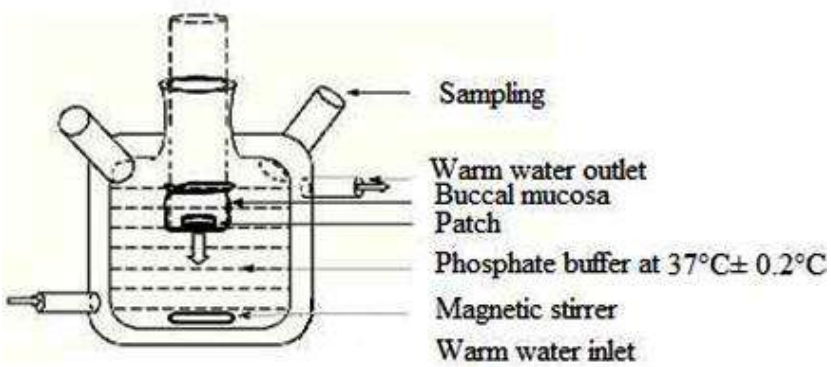

Fig.8: Schematic chematic diagram of franz diffusion cell for buccal patch[7]

7. **Permeation study of buccal patch:**[15]

The receptor compartment is filled with phosphate buffer pH 6.8, and the hydrodynamics in the receptor compartment is maintained by stirring with a magnetic bead at 50 rpm. Samples are withdrawn at predetermined time intervals and analyzed for drug content.

8. **Ex-vivo Mucoadhesion Time:**

The ex-vivo mucoadhesion time performed after application of the buccal patch on freshly cut buccal mucosa (sheep and rabbit). The fresh buccal mucosa is tied on the glass slide, and a mucoadhesive patch is wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide is then put in the beaker, which is filled with 200 ml of the phosphate buffer pH 6.8, is kept at 37°C ± 1°C. After 2 minutes, a 50-rpm stirring rate is applied to simulate the buccal cavity environment, and patch adhesion is monitored for 12 hours. The time for changes in colour, shape, collapsing of the patch and drug content is noted.[15]

9. **Measurement of mechanical properties:**

Mechanical properties of the films (patches) include tensile strength and elongation at break is evaluated using a tensile tester. Film strip with the dimensions of 60 x 10 mm and without any visual defects cut and positioned between two clamps separated by a distance of 3 cm. Clamps designed to secure the patch without crushing it during the test, the lower clamp held stationary and the strips are pulled apart by the upper clamp moving at a rate of 2 mm/sec until the strip break, the force and elongation of the film at the point when the trip break is recorded. [15]

V. SUMMARY

5.1Summary

Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Buccal patches are the type of drug formulation that has normally a different course of administration through the buccal mucosa for drug delivery.

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Table:5 summary of all chapters.

Chapters	Summary
1.	Aim and objectives of buccal drug delivery system and their dosages forms.
2.	Provides introduction to Buccal drug delivery system, Mucoadhesive, Bioadhesive, polymers uses, differents types of dosages form, advantages , disadvantages, limitation, applications.
3.	Discusses past work on buccal drug delivery system, buccal patches, tablets, polymers, drugs in a review of the literature.
4.	Discusses in detail methods of preparation of buccal patechs .
5.	Brief discussion of evaluation parameters of drug loaded buccal patches.
6.	Explains summary, conclusion .
7.	Provides detailed references.

VI. CONCLUSION

6.1Conclusion

The buccal mucosa offers several advantages for controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract are avoided. The area is well suited for a retentive device and appears to be acceptable to the patient. With the right dosage form design and formulation, the permeability and the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation. Buccal drug delivery is a promising area for continued research with the aim of 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. However, the need for safe and effective buccal permeation/absorption enhancers is a crucial component for a prospective future in the area of buccal drug delivery. Mucoadhesive buccal patches have been recently gained importance in drug delivery. The use of natural polymers is increasing in buccal patches formulation. A lot of work is still going on all around the world on mucoadhesive buccal patches using various natural polymer. This review is an effort to summarize the work done till date and to show the future pathway of mucoadhesive buccal patches preparation using natural polymer. The buccal mucosa offers several advantages over controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract are avoided. The area is well suited for a retentive device and appears to be acceptable to the patient. With the right dosage form design and formulation, the permeability and the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation.

6.2Future aspects: -

- In mucoadhesive placebo buccal patches we can use any potent drugs which fulfil the criteria for buccal patch as drug delivery system.
- We can perform the dissolution of medicated mucoadhesive buccal patch for drug release profile studies.
- We can further perform the in-vivo studies for the prepared mucoadhesive buccal patches.
- We can perform the stability test for the prepared mucoadhesive buccal patches.

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