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Buccal Film: Insight for Treatment of Various Disease

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Abstract : Buccal drug delivery system is novel drug delivery system which localize the delivery of drug to tissues of the oral cavity for treatment of bacterial and fungal infection, periodontal disease. Buccal films have been identified as an alternative approach to conventional dosage forms. The thin film have been found to be convenient to swallow, self-administrable, and fast dissolving dosage form, consist of all of which make it as a versatile platform for drug delivery. The objective of this article is tocheck buccal drug delivery by discussing the structure and environment of the oral mucosa and highlighting the components of film and brief description of advantages of buccal drug delivery system, mucoadhesive polymers, and buccal formulation used for treatment of various disease.
Keywords : Buccal delivery, Buccal film, Permeation enhancer, Polymers, Disease.

Introduction

Buccal drug delivery system is very different type delivery system which is locally deliver drug to tissues of the oral cavity used for fungal infection and bacterial infection[1] its type of drug delivery is very safe for deliver the drug which also have an ability to remove the toxic and adverse effect. Buccal[2].Buccal mucosa has an ability for direct administration of drug through buccal route into the systemic circulation via avoiding the first pass metabolism [3]. Some of the potential sites for attachment of any mucoadhesive system which includes buccal cavity, , eyes, rectal area, nasal cavity sublingual route and gastrointestinal area [4].As the treatment through buccal films, patches are accomplished by applying it for systematic condition, and gives hydrophilic and unstable proteins, oligonucleotides and polysaccharides well as conventional drug molecules [5]. Buccal cavity consist of both keratinized epithelium and nonkeratinized. Keratinized part are composed of neutral lipids ceramide and nonkeratinized composed of polar lipids cholesterol sulphate and glaucocerinites. Nonkeratinized part of buccal is mostly explored to deliver drug especially protein/ peptides. Delivered drug reaches to systemic circulation through jugular duct via network of blood vessels [6]. The structure of buccal mucosa are found in figure no 1.

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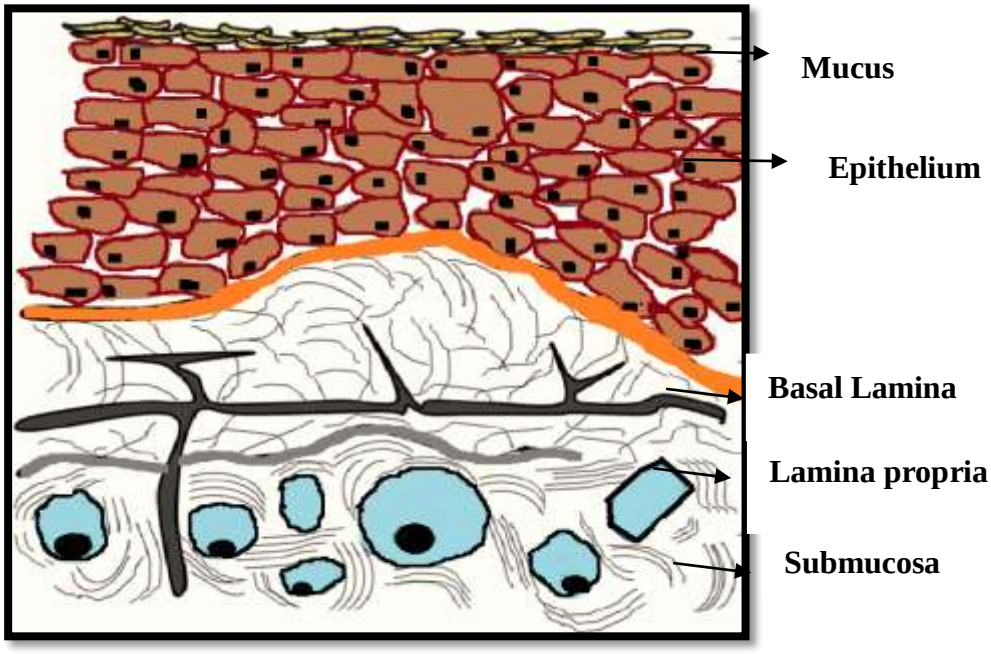

Figure 1: Structure of buccal mucosa

Oral mucosa:

100 cm^2 one third is the total area of the buccal cavity in buccal surface. thickness of this area is 0.5 mm which lined with epithelium. The oral mucosa is important for protecting tissues lipids based permeability barrier in epithelium. Epithelium layers are protect the tissue from the fluid loads and also protect from the harmful environmental attack of agent like antigens, microbial toxin, carcinogens days. Lips, cheeks, plate, soft plate all are part of oral cavity. The floor of oral mucosa comprise of two reasons, other real vestibule which is confined by cheeks, teeth, lips, gingival. The tongue is project from the oral cavity and the teeth ,gums which are back to the faucets with roof containing the hard and soft plate. The tongue projects from the floor of the cavity [7,8]. Structure of oral mucosa has been found in figure 2.

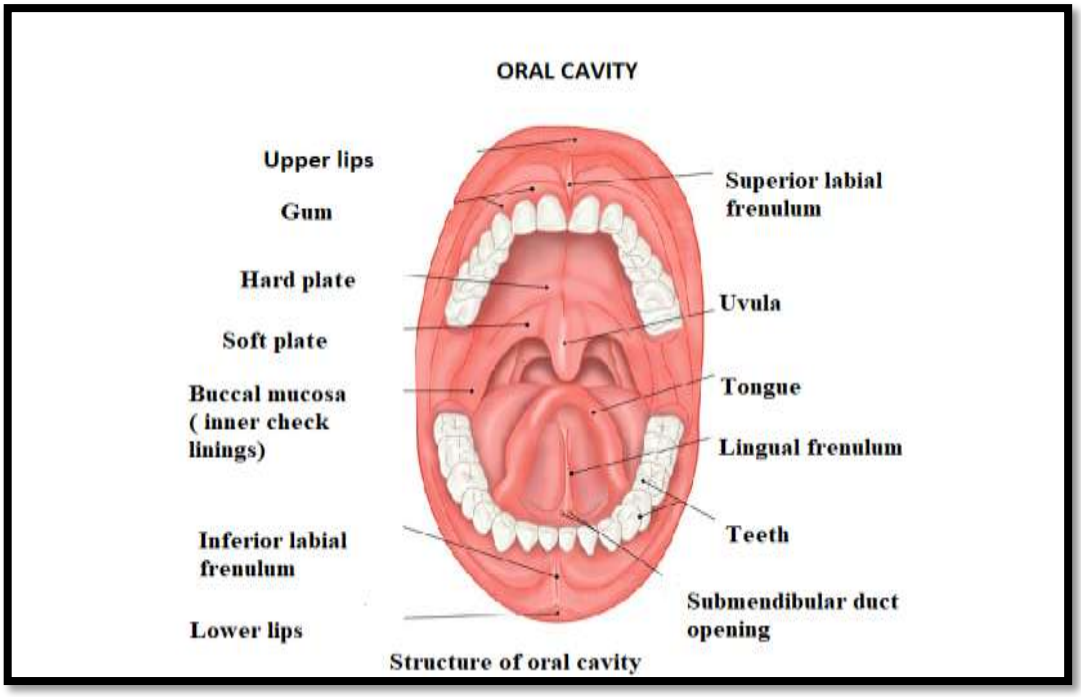

Figure 2: Structure of oral mucosa

Buccal film:

Buccal film dosage form are meant that for buccal administration. Which has improved the safety , efficacy and patient compliance. The buccal films are applied on the buccal mucosa. Buccal films are suited for oral as well as systemic drug delivery, and buccal films are effective dosage form with an enhanced bioavailability, when compared to others dosage form as it bypass the hepatic first pass metabolism. Buccal films are non-invasive dosage form suitable for both Geriatric and Paediatric disease. It does not swallowing of drug. Mucoadhesive buccalfilms have been widely used because they are nontoxic, biocompatible and inexpensive and also have an appropriate peel, tensile and shear strength [9]. For example, novel mucosal adhesive film called *"Zilactin"* consists of an alcoholic solution of hydroxy propyl cellulose and three organic acids. The film which is applied to the oral mucosal can be retained in place for at least 12 hours even when it is challenged with fluids [10].

Advantages of buccal film:[11,12,13]

- Prolonged release.
- Drug can be administered in unconscious and trauma patient's.
- Some drugs those are unstable in the acidic medium easily can be administered by buccal route.
- Flexible in shape, size and surface.
- A highly fast onset of action can be achieved.
- Buccal drug delivery system are Increased ease of drug administration.

even though much less permeable than the sublingual area, than the buccal mucosa has been properly vascularized, the drug may be rapidly absorbed in to the oral mucosa .

- Transmucosal delivery take place in less variables among patients, resulting in lower inter situation variability as compared to transdermal patch.

Disadvantages of buccal film:[14,15,16]

- Limited absorption area&total surface area of the membranes of the oral cavity available for drug absorption is 50cm^{2}whichrepresents non-keratinized tissues, including buccal membrane.
- The barriers such as saliva, mucus, membrane coating granules, basement membrane and drug absorption through the mucosa.
- The hazard of choking by involuntarily swallowing the delivery system is a concern.
- Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and ultimately the involuntary removal of the dosage form**.**
- Once placed at the absorption site, the dosage form should not be disturbed.
- When the buccalfilm are placed on to the buccal mucosa than Eating and drinking are restricted.

Basic components of buccal film

Polymer

wide variety of polymers are available for the formulation of fast dissolving buccal film. The polymers having the film forming property. The most important step of preparation of buccal film is that selection of polymers for successful development of film. polymer can be use alone and the in the combination with other polymers to provide desired film forming properties. Polymers having qualities such as polymers should be inexpensive, not toxic, non-irritant, polymers should have the good wetting and spread ability property, it should be a tasteless, it should have sufficient shelf life [17]. Some polymers are with their properties given below in table no 1

Table 1: Properties and key findings of polymers are used in buccal film

Polymers	Properties	Key findings	Ref
Hydroxypropyl methyl cellulose (HPMC)	HPMC is a non-ionic polymer Colour- white Odour – odourless Tasteless Solubility- soluble in water, insoluble in ethanol and chloroforms.	HPMC is film forming polymer having the film forming ability about 2-20% concentration which is used for the controlled and delayed release.	[18, 19 20]
Polyvinyl pyrrolidone	Polyvinyl pyrrolidone is a non-ionic. polymer having high solubility. very high swelling index	Complex of the PVA and HPMC improves the film forming ability . Combination of ethyl cellulose and PVP increased flexibility.	[18,19]
Pullulan	Appearance -white, odourless, tasteless powder Solubility- it is soluble in hot and cold water.	Pullulan are blinding with sodium alginate and CMC may enhance the film forming properties.	[19]
Polyethylene oxide	Non-ionic polymers. Polyethylene oxide having high mucoadhesion with high molecular weight.	Film are with good resistance to tearing minimal or no curling.	[18,19]
Poly vinyl alcohol	Colour- white to cream in granular powder. Mw 20,000–200,000. Solubility- water soluble.	Films are more flexibles. Film are used in ophthalmic at concentration range 3-5%.	[19]
Chitosan	Colour- white to creamy powder Odourless Chitosan are biodegradable and biocompatible . Solubility- soluble in water and insoluble in 95% ethanol.	Chitosan are enhancing the transport of polar drug which across the epithelial surface.	[18,19]
Carrageenan	Carrageenan is an anionic polysaccharides which are extracted from the red seaweed chondruscrispsus, soluble in hot as well as cold water.	Act as a protein and peptides stabilizer by stearic stabilization	[18,19]
Sodium alginate	White or Buff powder, odourless, colourless and tasteless. Insoluble in organic solvents and acid. Sodium alginate are extracted from the brown seaweed by use of dilute alkali.	Sodium alginate having the gel forming and film forming properties. Compatible with water soluble resins.	[18]
Gelatin	Colour- yellow powder. Solubility- soluble in glycerine, alkali, hot water).	Gelatine having the very good film forming property and it is used in the preparation of sterile film, ophthalmic film, and sterile sponge.	[17]
Hydroxypropyl cellulose (HPC)	Colour- white to yellow Odourless, tasteless powder Mw 50,000–1,250,000	HPC having the very good film forming property and 5% w/w soluble are used in	[18, 19]

	Solubility – soluble in hot polar organic solvents such	film coating.	
Agar	Agar having the poor stable swelling Properties .	Agar having the gelling and film forming properties.	[18]
Guar gum	It has swelling properties It has good mucoadhesive property	Guar gum are used in the preparation of the mucoadhesive film	[20]
Acacia	Very poor mucoadhesion	Acacia is gum and it used in the preparation of film but it may have some difficulties during the preparation of film	[20]

Mucoadhesive polymers

Mucoadhesive polymer should have quickly hydrate, and quickly adhesive on buccal mucosal membrane, they are non-toxic, and non-irritant and cost effective polymers. The mucoadhesive polymers is most important ingredients in the development of buccal film formulation having the concentration range 0-20% w/w of dry polymer weight, it should preferably adhere quickly to moist tissue for the better absorption of drug into the systemic circulation [21].

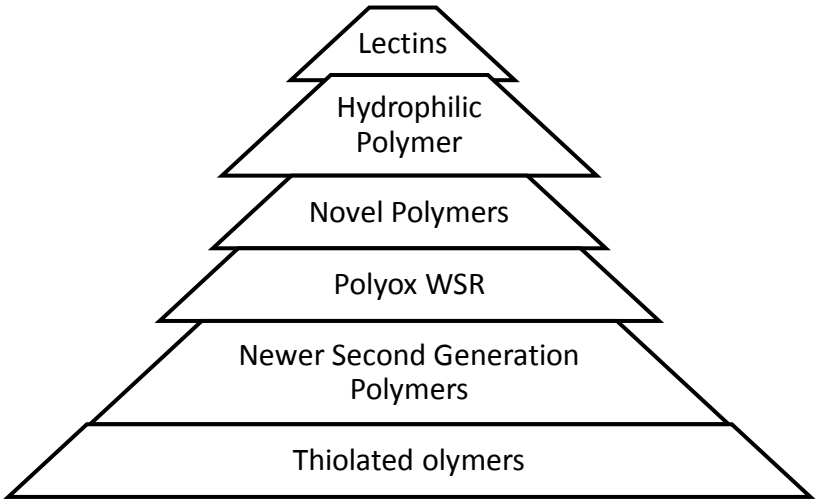

Figure 3: Mucoadhesive polymers

Permeation enhancers used in buccal film

The epithelium that lines the buccal mucosa is most effective barrier to the absorption of drug. Those substance are facilitated the permeation of drug through the buccal mucosa are referred as a absorption enhancer. The most common absorption enhances are bile salt, a zone, fatty acid and surfactant such as sodium dodecyl sulphate, chitosan [22]. Some permeation enanceare given in below table No 2.

Table 2: Name of the different permeation enhancer and there mechanism of action

Permeation enhancer	Mechanism	References
Aprotinin	A protein also called as bovine pancreatic trypsin inhibitor, the inhibitor used in the medication when drug are administered by the injection for reduce the bleeding during complex surgery such as liver, heart	[23]
Azone	It act as component at tight junctions, also increased the fluidity of lipids by layered membrane.	[24]
Cyclodextrin	Cyclodextrins are water soluble drug and enhance the solubility of hydrophilic drug and they also get complexed with lipophilic drugs.	[23]
Propylene Glycol	Propylene glycol increased the absorption of drug. propylene glycol with the combination with 5% oleic acid showed an increase in the flux by 10 times.	[24]
Lauric acid	Increasing the fluidity of lipid bilayer membrane	[25]
Polysorbate 80	Acting on the component at tight junctions Increasing the fluidity of lipid bilayer membrane;	[25]

Flavouring agents

Flavour are the sensory impression of food or other substances, that are used in the dosage form for the taste and smell . in the superior way up to 10%w/w of flavour are added in the buccal films formulation. Flavouring agents are obtained from natural plants and also from animals raw material essential oil, other water soluble extracts of menthol, mint such as peppermint, sweet mint, cinnamon, clove and fruit flavours like lemon and orange can be added as flavour in buccal film.

Plasticizers

Plasticizer are the common ingredients used in the preparation of buccal film because plasticizers having the capability for enhancement of mechanical properties like tensile strength and elongation of the film by embodies themselves between the chain of polymers and lowering the glass transmission temperature for making it softener and flexible. Plasticizer prevents cracks in and consequent peel off the film when we stored. [26]

Various Diseases Treated Via Buccal Film

Back through cancer pain and treatment

Back through pain consistently defined as any transitory pain and Patents who are suffering from cancer having back through cancer pain. Patient who is currently receiving the medication for controlling the pain levels.becomes in a superior way common as the patient progresses towards the more contemporary stages of the disease [27]. It has been known for onset of action and shot duration time , immediate release drugs are more effective than slower release treatments[28]. The back through cancer pain can be treated by the use of some opioids having short action and immediate release [29].USA and EU both are those country in which fentanyl buccal soluble film is indicated for the treatment of the back through pain mainly in adult, 18 adult [30]. Fentanyl buccal soluble film provides an additional opportunity for transmucosal propagation of fentanyl, delivery of fentanyl with half of the dose entering an initial, rapid absorption via the buccal mucosa because of high bioavailability. In clinical trials, the drug substance was associated by the whole of significant improvements in pain intensity scores and was commonly well tolerated in opioid-tolerant patients who having breakthrough cancer pain, some adverse effect opioid associated such as nausea and vomiting [31].

Oral ulcer also known as canker sores it is a common disorder which manly affects young and women. Ulcer occurs can occur anywhere in the mouth like on tongue, inside the tongue. It is painful or multiple lasting for 10 to 14 days with low possibility of scar formation. Oral ulcer can be treated via antiseptic, anti-inflammatory drug, anaesthetics, corticosteroids are the most common therapy of oral ulcer. Ornidazole and

dexamethasone films are used in the treatment of oral ulcer and they are protecting from wound surface and reducing pain. The therapeutic effects of ornidazole and dexamethasone films were investigated in the treatment of rabbit oral ulcer [32].

Oral cancer

Oral cancer arise is the fifth virtually common sign of the cancer in the world. Oral cancer can treated by the surgical excision radiotherapy chemotherapy[33, 34]. Buccal films are more effective non-invasive dosage form for the cancer patient and it is well tolerated by patients. It can be used repeatedly because it has not been any side effect. The use of mucoadhesive system for enhance the retention of drug tissue in the tissue for a heavy time. Moreover, 5-ALA is smoothly hydrophilic are not able to enter in cells easily also cause negative response to treatment. Polymeric films covered with large surface area of the mucosa playing the function of drug release protect as the physical level of site. The retention time will increase and frequency will be decreased [35].

Migraine

Migraine is also known as primary headache. In which patient having pulsate one sided headache.There are common symptoms of migraine such as vomiting, nausea and environmental sensitivity. Which often last 4-48 hrs [36]. First stage is prodrome, it means that early symptoms of disease and this phase of migraine can occur anywhere from hours or days before the actually attack Around 30% of people hurt the prodrome phase. Aura is the second stage of migraine. A megrim aura constantly precedes the migraine attack but also occur around the attack. aura can furthermore occur without an associated headache. The migraine attack itself can breathe little as four hours or as invent as several days. The attack is followed by a postdrome phase, to what place you might feel bushed or washed. Second stage is aura which means main headache in which migraine patients have head pain which can be unbearable and severe. In this stage pain occurs only on one side of the head. Third stage is postdrome or migraine section happens nearly right once headache. Some common symptoms of the postdrome section include: Inability to concentrate [37]. It can be treated by via rizatriptan benzoate because it having faster action than other drugs. After the orally administration of rizatriptan benzoate can absorbed and show bioavailability about 45% because of hepatic metabolism [38]. The dose of rizatriptan in oral dosage form can be recommended about 5–10 mg per use. Most of the patient having the experience when the suffering from nausea during the migraine buccal films are preferred are most applicable dosage form for the treatment of migraine patients [39].

Parkinson's disease

Parkinson's disease is a chronic progressive neurodegenerative disorder which is characterized by complications which can decrease the quality of life of the patient and also cause serious disorder. Around the world 10 million people are suffering from the Parkinson's disease much higher in over the age of sixty years.Wide variety of drugs from different classes are accessible for the treatment of Parkinson's disease [40]. Selegiline Buccal films are dosage for the early treatment of the Parkinson's disease which can adhere the buccal mucosa enhance absorption of drug through the buccal mucosa. It provide prolonged drug release and also enhance bioavailability. Physicochemical properties of selegiline indicate that this drug are molecular weight 187, pKa 7.5 and log p 2.8imply that this drug has favourable characters for extra permeation through the buccal mucosa, but few reports advocate that drug release can be controlled by means of loading the drug right into a carrier and impregnating into the film [41]. Selegiline is an irreversible and selective inhibitor of cerebral monoamine oxidase kind B it has established protection, efficacy and is considered as a primary-line therapy in early ranges of Parkinson's disease [42].

Orthopaedic patients

Patients ones sufferers affected by problems of the skeletal system and related muscle , joints, and ligaments needs regular and prolonged drug delivery for treatment of healing condition. Mucoadhesive drug delivery can avoid the destruction via gastrointestinal contents or hepatic first-pass inactivation of drug and ensure contact of the drug to the biological system for greater absorption of drug[43,44]. Tramadol hydrochloride buccal film are novel form of analgesic used in the treatment of those patient are suffering from orthopaedic injuries. Tramadol hydrochloride is a centrally-appearing artificial opioid analgesic binding to unique opioid receptors. it's much a non-selective, natural agonist at mu, delta and kappa opioid receptors with a better affinity for the mu receptor. Tramadol HCL is a centrally appearing analgesic used in the treatment of the persistent pain and tramadolHCL usually recommended as first line drug treatment of orthopaedic injury for

the treatment of adequate pain . the half-life of the tramadol HCL is about 5.5 h and the usual oral dosage routine is 50 hundred mg every 4-6 hrs with a most dosage of four hundred mg/day [45].

Dental pain

Toothache are most important reasons for increasing demand of medication, e. g. analgesics, local anaesthetics, vasoconstrictors and drug combinations. It's well known that persisted use of these drugs has drawbacks due to the excessive quantity of side effects complications, sickness, dizziness, sleepiness, gastrointestinal inflammation, tension, nervousness. some other alternative to analgesics are tricyclic antidepressants, such as doxepin hydrochloride [46]. The drug delivered through the oral cavity are interesting opportunity in toothache due to its analgesic local effect . It has also physical features due to high patient compliance like saliva, pH fluid volume, enzyme activity and the permeability of oral mucosa [47]. Mucoadhesive based buccal films are used in treatment of dental pain. For this purpose the three polymer are tested such as Chitosan, Sodium hydroxide, Propyl methylcellulose and Sodium carboxymethylcellulose [48].

Table 3 :List of some patent on buccal film

Patent no	Inventors	Year	Work	Ref
0303038	Pawar HK *et al.*	**2016**	Prepared oral film from a copolymer of polyvinyl alcohol and polyethylene glycol and at least one gum. The oral films may further contain a medicated active and non-medicated components.	[49]
065870	Martin L *et al*	**2014**	Prepared bioadhesive films for topical, local and systemic drug delivery. The filmcontained one or more polymeric layers. The drug may be	[50]
8475832	Myers *et al.*	2013	The present invention relates to self Supporting dosage forms which provide an active agent or treating narcotic dependence while providing sufficient buccal adhesion of the dosage forms.	[51]
8241661	Fuisz*et al.*	2012	Film was prepared by the method of depositing a fluid with the use of film forming polymers having the different density in to the single layer and drying .	[52]
8298583	Myers, Garry L.	2011	This invention relates to the pharmaceutical-based film system which includes various small-scale forms of pharmaceutically active agents in a film base such as Tetrahydrobiopterin.	[53]
7648712.	Bess *et al.*	2010	prepared a fast dissolving orally consumable films containing a taste masking agent such as dextromethorphan and water soluble film-forming polymer such as pullulan.	[54]
20090004254	Maibach, Todd.	2009	This is related to the manufacturing of the orally dissolvable edible film for the administration of the active drugs to the buccal cavity. The polymer used is pullulan.	[55]
20080260807	Sharp *et al.*	2008	Prepared a water soluble film of nicotine.	
20070172515	Fuisz, Richard C	2007	Prepared a film bandage for mucosal administration of active pharmaceutical ingredients in which first delivery vehicle may be mucoadhesive films which may adhere to mucosal tissue and the second may contain an active substance for delivery via mucosal membrane.	[56]

Table 4: List of commercially available buccal film table[57]

S. no	Name of drug	Marketed brand
1	Cool mint	Listerine
2	Diphenhydramine HCL	Benadryl
3	Phenylephrine HCL	Sudafed
4	Dextromethorphan HBr (7.5 mg)	Triaminic
5	Simethicone	Gas- x
6	Menthol/pectin	Orajel
7	Benzocaine menthol	Chloroseptic
8	Clonazepam	Klonopin wafers

Table 5: list of drug delivered via buccal route [58]

S.NO	DRUG	DOSE OF DRUG AS PER IP
1	Pantoprazole	40 mg
2	Morphine sulphate	50 mg
3	Omeprazole	20-40 mg
4	Nicotine	Prophylactic 15-30 mg
5	Piroxicam	10-20 mg
6	Oxytocin	Enhancement of labour intravenous infusion of a 15% dextrose solution count 1 unit.
7	Nifedipine	5-20 mg
8	Acyclovir	200-800 mg 4-5 time daily
9	Carbamazepine	200 mg
10	Metronidazole	200 mg
11	Ergotamine tartrate	1-2 mg by subcutaneous

Conclusion

Review concludes that the buccal films are the most acceptable dosage form which avoid the first pass metabolism and increased the bioavailability. Which can be used to all age groups, but sometime difficulties in swallowing in case of geriatric and paediatric patients. Buccal film can be manufactured at low cost and buccal film can be replaced with the conventional dosage form.

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Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

1. L. Martin, C.G. Wilson, F. Koosha, I.F. Uchegbu. Sustained buccal delivery of hydrophobic drug denbufylline using physically cross linked palmitoyl chitosan hydrogels. Eur J Pharm Biopharm., 2003,55:35-45.
2. G.N. Ganesh, M. Pallaprola, K. Gowthamaranjan, *et al*. Design and development of buccal drug delivery for labetalol using natural polymer. Int J Pharm Res& Dev., 2011,3:37-49.
3. N.S. Reddy, D.B, Kumar, N.K Kashyap. Formulation & evaluation of pantoprazole buccal patches. Int. j. Pharm& Ind. Res., 2012,2:37-40.

4. H. Amir. Buccal mucosa as a route for systemic drug delivery. J. Pharm Pharmaceutic Sci.,1998,1:15-30.
5. R. Bhati, N.K. Raja. A Detailed Review on oral mucosal drug delivery System. International journal of Pharmaceutical science and research., 2012,3: 659 -681.
6. F.LaFleur. Mucoadhesive polymers for Buccal drug delivery., Drug DevInd Pharm. 2014, 40:591-8.
7. R. Hooda, M. Tripathi. A Review an oral mucosal drug delivery system. The Pharma innovation,. 2012,1:14-21.
8. M.D.Siddiqui, G. Garg, P.K.Sharma. A short Review on A novel approach in oral fast dissolving drug delivery system and their patents. Advances in biological research., 2011,6:291-303.
9. R. Krampe, JC Visser, HW Frijlink, J Breitkreutz. Oral mucosal film preparations points to consider for patient centricity and manufacturing processes. Expert Open Drug Deliv., 2016,13:49-506.
10. N.Prasad, K. Satinder, R. Singh. A Review on buccal patches. Innoriginal International Journal of Sciences.,2016,51: 4-8.
11. B. Satyabrata, P. Ellaiah, B. Choudhury. Design and evaluation of methotrexate buccal mucoadhesive patches. Inter. J. Pharm. Biomed.,Sci 2010,1: 31-36.
12. J.K. Lalla, R.A. Gurnancy. Polymers for mucosal delivery swelling and mucoadhesive evaluation. Indian drugs., 2002, 39:48-55.
13. MS Wani, SRParakh, MH Dehghan, SAPolshettiwar, VVPande, VV Chopade. Current Status in buccal drug delivery., 2013, 3: 35-40.
14. D.S. Hsieh Ed. Barriers to transmucosal delivery of peptides and proteins. Drug Permeation Enhancement.,1994, 4: 323-343.
15. DM Brahmankar, SB Jaiswal. Biopharmaceutics and Pharmacokinetics A Treatise. Second edition, Vallabh Prakashan, New Delhi., 1995,3: 64-65.
16. A. Gupta, S. Garg, R.K.Khari. Measurement of bio adhesion strength of mucoadhesive buccal tablet design of invitro assembly. IndDrugs.,1992,30:152-155.
17. R.P. Dixit, S.P. Puthli. Oral strip technology: overview and future potential. J Contr Rel., 2009,139:94-107.
18. A.F. Borgas, C. Saliva, J.F. Coelho. oral films: current status and future perspectives: 1-Galenical development and quality attributes J. control release., 2015, 206: 1-19.
19. J.O. Morales, McCornville .Manufacture and characterization of mucoadhesive buccal films. Eur j pharm biopharma., 2011,77:187-199.
20. Y. Sudhakar, k. kuostu, A.k. Bandyopadhyay. Buccal bio adhesive drug delivery a promising option for orally less efficient drugs. J control release., 2006, 11415-40.
21. Clark MA, Hirst B, Jepson M. Lectin-mediated mucosal delivery of drugs and microparticles. Adv. Drug Deliv. Rev., 2000, 43:207-223.
22. M.R. Patel, R.B. Patel, *et al*. Effect of formulation components on the in vitro permeation of microemulsion drug delivery system of fluconazole. AAPS Pharm SciTech., 2009,10: 917-923.
23. C. Woertz, M. Preiss, J. Breitkreutz, P.kleinebudde. Assessment of test evaluating mucoadhesive polymers and dosage form an overview. Eur J Pharm., 2013,85:843-53.
24. L.R. Inman, J.R. Cantey. Specific adherence of Escherichia coli strain RDEC-1 to membranous M cells of the Peyer's patch in Escherichia coli diarrhoea in the rabbit. J Clin Invest., 1983, 71:1-8.
25. D. Shukla, S. Chakrabor, S. Singh, R. Mishra. Mouth dissolving tablet an overview journal of chemical and pharmaceutical research., 2009,1 :163-177
26. A. Bernkop,F.Gabor*et al*. An adhesive drug delivery system based on k 99- fimbriae. Eur J pharm sci. 1995; 3:239-9.
27. A. Chang, E.J. Roeland, R.S.Atayee. Transmucosal immediate-release fentanyl for breakthrough cancer pain opportunities and challenges for use in palliative care. J Pain Palliat Care Pharmacother., 2015, 29:247–60
28. G. Zeppetella, A. Davies, *et al*. A network metanalysis of the efficacy of opioid analgesics for the management of breakthrough cancer pain episodes. J Pain Symptom Manage., 2014, 47:772–85.
29. C.I. Ripamonti, D. Santini, E.Maranzano. Management of cancer pain: ESMO clinical practice guidelines. Ann Oncol. 2012.
30. S.T. Kumar. Onsoli fentanyl buccal soluble film.,Meda Pharmaceuticals US prescribing information.2011.
31. K.P. GarnockJones. Fentanyl Buccal Soluble Film A Review in Breakthrough Cancer Pain.Clin Drug Investig., 2016,36:413-9.

32. F. LaFleur. Mucoadhesive polymers for buccal drug delivery. Drug Dev Ind Pharm.,2014, 40:591-598.
33. H.MChen, C.H.Yu, *et al*. Topical 5- aminolaevulinic acid-mediated photodynamic therapy for oral verrucous hyperplasia, oral leucoplakia and oral erythroleukoplakia. Photodiagnosis Photodyn Ther. 2007;4: 44-52.
34. E.Natarajan, E. Eisenberg. Contemporary concepts in the diagnosis of oral cancer and precancer. Dent Clin North Am., 2011, 55:63-88.
35. W.E Grant, C. Hopper, A.J. MacRobert, P.M.Speight, S.G.Bown. Photodynamic therapy of oral cancer photosensitization with systemic aminolaevulinic acid. Lancet.,1993,342:14-147.
36. E.S. Kristoffersen,C.Lundqvist. Medication-overuse headache epidemiology diagnosis and treatment. Ther Adv Drug Saf., 2014, 5:87-99.
37. M.Lauritzen. Pathophysiology of the migraine aura the spreading depression theory. Brain.1994; 117:199-210.
38. B. Gilmore, M.Michael. Treatment of acute migraine headache. American family association. 2011; 83:271-80.
39. A.M. Avachat, K.N. Gujar, K.V.Wagh. Development and evaluation of tamarind seed xyloglucan-based mucoadhesivebuccal films of rizatriptan benzoate. CarbohydrPolym., 2013, 91:537-542.
40. K.M. Prakash, E. K. Tan. Development of Parkinson's disease biomarkers. Expert Rev Neurotherapy., 2010; 10:1811-25.
41. E. l. Mabrouk, G.M. Gazayerly, *et al*. Chitosan lactate wafer as a platform for the buccal delivery of tizanidineHCl: in vitro and in vivo performance. Int J Pharm .,2014,467: 100-12.
42. E. Needham, P.Worth. Parkinson's disease a guide to pharmacological management. Prescriber., 2012, 23:21-31.
43. S. Verma, *et al*. An overview on buccal drug delivery system. Ind J Pharm Sci Res. 2011; 2:1303 -21.
44. B.M. Boddupalli, *et al*. Mucoadhesive drug delivery system an overview. J Adv Pharm Tech Res., 2010, 1:381-7
45. G.N. Kalinkova. Studies of beneficial interactions between active medicaments and excipients in pharmaceutical formulations. Int J Pharm., 1999, 187:1-15.
46. R.I. Korzeniewska, A.Plaznik. Analgesic effect of antidepressant drugs. Pharmacol Biochem Behav., 1998, 59:331-8.
47. M.A. Casta, B. Ruiz,*et al*. Design development and characterization of buccal bio adhesive films of Doxepin for treatment of odontalgia. Drug Deliv., 2014,2: 1-8.
48. G. Shanker, K. C. Pawar,*et al*. Formulation and evaluation of bio adhesive buccal drug delivery of tizanidine hydrochloride tablets. AAPS Pharm SciTech., 2009, 10:1-5.
49. H. A. Pawar .An oral film comprising a medicinal or non-medicinal active copolymer of polyvinyl alcohol and polyethylene glycol and at least one gum. 2016. 0303038.
50. L. Martin, C.G. Wilson, *et al*. Sustained buccal delivery of hydrophobic drug Denbufylline using physically cross linked palmitoyl chitosan hydrogels. Eur J Pharm Biopharm, 55, 2003, 35-45.
51. L. Myers, H. Garry,*et al*. Sublingual and buccal film compositions.2013. US Patent 8475832.
52. C.Fuisz, *et al*. Biocompatible films with variable cross-sectional properties.2012. US Patent 8241661.
53. L. Myers, H. Garry,*et al*. Film delivery system for tetrahydrobiopterin. 2012. US Patent 8298583.
54. S.W. Bess,K. Neema,et al. 2010. Fast dissolving orally consumable films containing a taste masking agent, US Patent: 7648712.
55. MaybachTodd. Film comprising active drugs, US Patent application: 20090004254
56. C.R, Fuisz. Film bandage for mucosal administration of actives, US Patent application: 20070172515.
57. C.H. Sumitha, N. Karunasree, *et al.* Int. Chemical Research., 2009, 1: 24-27.
58. P. Kumar. Oral mucosal drug delivery system. Indian drug., 2004,41:63-70.

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