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Review Article

Bioadhesive polymers, permeation enhancers and types of dosage forms for buccal drug delivery

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Abstract

The buccal delivery is defined as the drug administration through the mucosal membranes lining the cheeks (buccal mucosa). The main impediment to the use of many hydrophilic macromolecular drugs as potential therapeutic agents is their inadequate and erratic oral absorption. Based on our current understanding of biochemical and physiological aspects of absorption and metabolism of many biotechnologically produced drugs, they cannot be delivered effectively through the conventional oral route. Because after oral administration many drugs are subjected to pre-systemic clearance extensive in the liver, which often leads to a lack of significant correlation between membrane permeability, absorption and bioavailability. Difficulties associated with the parenteral delivery and poor oral bioavailability provided the impetus for exploring alternative routes for the delivery of such drugs. This review covers the advantages, disadvantages of buccal delivery, drug and excipient selection especially bioadhesive polymers and permeation enhancers, and further a list of drugs developed as various dosage forms for buccal route of administration.

Keywords: Buccal delivery, bioadhesive/mucoadhesive, permeation enhancer, dosage forms.

Introduction

Conventional oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes[1, 2]. It remains the preferred route of administration in the discovery and development of new drug candidates and formulation. The popularity of the oral route is attributed to patient acceptance, ease of administration accurate dosing, cost effective manufacturing methods, and generally improve the shelf-life of the product[3-5]. In recent years, the interest in novel routes of drug administration occurs from their ability to enhance the bioavailability of drugs[6-9].

The concept of mucosal-adhesive or mucoadhesive was introduced into the controlled drug delivery in the early 1980's. Bioadhesive polyacrylic acid nanoparticles are an example of a novel drug delivery system designed for mucosal and topical drug delivery[10,11]. Mucoadhesive polymers are synthetic or natural polymers, which interact with the mucus layer covering the mucosal epithelial surface and mucin molecules constituting a major part of mucus[12]. They render the treatment more effective and safe, not only for topical disorders but also for systemic problems[13,14]. These dosage forms are self-administrable, cheap and have superior patient compliance. With the right dosage form design, the local environment of the mucosa can be controlled and manipulated in order to optimize the rate of drug dissolution and permeation[15].

Drugs can be absorbed from the oral cavity through the oral mucosa either sublingually or buccal. Buccal drug delivery was introduced by Orabase in 1947, when gum tragacanth was mixed with dental adhesive powder to supply penicillin to the oral mucosa[16]. In recent years, delivery of therapeutic agents through various transmucosal routes has gained significant attention. Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of dosing[17]. Extensive first-pass metabolism and drug degradation in the harsh gastro intestinal environment can be circumvented by administering the drug via buccal route and also other lipid carrier systems[18, 19].

The buccal delivery is defined as the drug administration through the mucosal membranes lining the cheeks (buccal mucosa). The main impediment to the use of many hydrophilic macromolecular drugs as potential therapeutic agents is their inadequate and erratic oral absorption[20]. Based on our current understanding of biochemical and physiological aspects of absorption and metabolism of many biotechnologically- produced drugs, they cannot be delivered effectively through the conventional oral route. Because after oral administration many drugs are subjected

to pre-systemic clearance extensive in liver, which often leads to a lack of significant correlation between membrane permeability, absorption and bioavailability[21-23]. Difficulties associated with the parenteral delivery and poor oral bioavailability provided the impetus for exploring alternative routes for the delivery of such drugs[24] (Rathbone et al., 1996).

Advantages

- Among the various trans mucosal routes, buccal mucosa has the excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa, hence suitable for administration of retentive dosage forms.
- Direct access to the systemic circulation through the internal jugular vein bypasses drugs from hepatic first pass metabolism leading to high bioavailability.
- Low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damages or irritates the mucosa, painless administration, easy drug withdrawal, facility to include permeation.
- Harsh environmental factors that exist in oral delivery of a drug are circumvented by buccal delivery.
- Enhancer/enzyme inhibitor or pH modifier in the formulation and versatility in designing as multidirectional or unidirectional release systems for local or systemic actions of buccal adhesive drug delivery systems as promising option for continued research.

Disadvantages

- The low permeability of the buccal membrane, specifically when compared to the sublingual membrane and a smaller surface area.
- The total surface area of the membranes of the oral cavity available for drug absorption is 170 cm^2, of which ~50 cm^2 represents non-keratinized tissues, including the buccal membrane.
- The continuous secretion of saliva (0.5–2 L/day) leads to subsequent dilution of the drug.
- Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and, ultimately, the involuntary removal of the dosage form.
- In addition to the swallowing, there is another inconvenience of such dosage form during drinking and eating by the patient.

Mucoadhesive drug delivery systems:

The oral cavity is an attractive site for drug delivery due to ease of administration, avoidance of possible drug degradation in the gastrointestinal tract, and first-pass metabolism. Within the oral mucosal cavity, delivery of drugs is classified into three categories:

I. Sublingual delivery, which is administration of the drugs via mucosal membranes lining the floor of the mouth i.e., sublingual mucosal to the systemic circulation.

II. Buccal delivery, which is administration of the drug via mucosal membranes lining the cheeks i.e., buccal mucosa to the systemic circulation.

III. Local delivery, for the treatment of conditions of the oral cavity, principally Aphthous Ulcers, fungal conditions and Periodontal diseases by the application of the bioadhesive system either to the palate, the gingiva or the cheek.

Buccal mucoadhesive dosage forms

Buccal mucoadhesive dosage forms can be categorized into 3 types based on their geometry.

- Type I is a single layer device with multidirectional drug release. This type of dosage form suffers from significant drug loss, due to swallowing.
- In type II devices, an impermeable backing layer is superimposed on top of the drug loaded bioadhesive layer, creating a double layered device and preventing drug loss from the top surface of the dosage form into the oral cavity.
- Type III is a unidirectional release device, from which drug loss in minimal, since the drug is released only from the side adjacent to the buccal mucosa. This can be achieved by coating every face of the dosage form, except the one that is in contact with the buccal mucosa.

Buccal dosage forms can also be classified as either a reservoir or matrix type. In the reservoir type, an excessive amount of the drug is present in the reservoir surrounded by a polymeric membrane, which controls the drug's release rate[25]. In the matrix type systems, the drug is uniformly dispersed in the polymer matrix, and drug release is controlled by diffusion through the polymer network. In general, dosage forms designed for buccal drug delivery should be small and flexible enough to be acceptable for patients, and should not cause irritation. Other desired characteristics of a buccal mucoadhesive dosage form include high drug loading capacity, controlled drug release (preferably unidirectional release), good bioadhesive properties, smooth surface, tastelessness, and convenient application. Erodible formulations can be beneficial because they do not require system retrieval at the end of desired dosing interval. A number of relevant buccal mucoadhesive dosage forms have been developed for a variety of drugs. Several peptides, including thyrotropin-releasing hormone, insulin, octreotide, leuprolide, and oxytocin, have been delivered via the buccal route. Buccal dosage forms can be used to treat both local and systemic conditions. Mainly the following types of buccal dosage forms are available in the market.

- Buccal tablets
- Buccal patches
- Buccal films
- Buccal hydrogels
- Buccal gels & ointments
- Buccal pellets

General criteria for candidate's drug:

One of the drug properties required for the practical buccal formulation will be high pharmacological activity or a low dose requirement. There is a limit to the size of a dosage form. The size of the dosage form should not exceed 12 cm^2 for buccal application or 3cm^2 for sublingual or gingival application. In general, any drug with a daily requirement of 25 mg or less would make a good candidate.

Other than dose considerations, the following properties will make the drug suitable candidate for buccal delivery:

- Relatively short biological half-life - Drugs with biological half-life 2-8 hr will in general be good candidates for sustained release dosage forms
- The maximal duration of buccal delivery is approximately 4–8 hr.

- Drug must undergo first pass effect or it should have local effect in oral cavity.
- Drugs susceptible to degradation:-Drug degradation either by stomach/intestinal enzymes or by first pass hepatic metabolism will be assured protection in buccal dosage form.
- Drug must undergo first pass effect or it should have local effect in oral cavity.

Formulation design

An ideal buccal adhesive system must have the following properties:

- Should adhere to the site of attachment for a few hours,
- Should release the drug in a controlled fashion,
- Should provide drug release in a unidirectional way towards the mucosa,
- Should facilitate the rate and extent of drug absorption,
- Should not cause any irritation or inconvenience to the patient and
- Should not interfere with the normal functions such as talking, drinking etc.

Bioadhesive polymers

The concept of biomucoadhesive polymers has been introduced into the pharmaceutical literature more than 40 years ago and nowadays it has been accepted as a promising strategy to prolong the residence time and to improve the specific localization of drug delivery systems on various membranes. Polymer is a generic term used to describe a very long molecule consisting of structural units and repeating units connected by covalent chemical bonds. The term is derived from the Greek words: polys meaning many, and meros meaning parts[26]. Bioadhesive polymers that adhere to the mucin/epithelial surface are effective and lead to significant improvement in the oral drug delivery (Table 1). The first step in the development of mucoadhesive dosage forms is the selection and characterization of appropriate bioadhesive polymers in the formulation[27,28].

Bioadhesive polymers should possess certain physicochemical features including hydrophilicity, numerous hydrogen bond-forming groups, flexibility for interpenetration with mucus and epithelial tissue, and viscoelastic properties[29]. Bioadhesive polymers also used for development of other delivery systems such as microspheres[30] (Vasir et al., 2003), peptide delivery[31] (Harris and Robinson, 1994), floating and floating-mucoadhesive[32-34], transfersomes system[35-37].

Ideal characteristics

- Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.
- Should have good spreadability, wetting, swelling and solubility and biodegradability properties.
- pH should be biocompatible and should possess good viscoelastic properties.
- Should adhere quickly to buccal mucosa and should possess sufficient mechanical strength.
- Should possess peel, tensile and shear strengths at the bioadhesive range.
- Polymer must be easily available and its cost should not be high.
- Should show bioadhesive properties in both dry and liquid state.
- Should demonstrate local enzyme inhibition and penetration enhancement properties.
- Should demonstrate acceptable shelf life.
- Should have optimum molecular weight.
- Should possess adhesively active groups.
- Should have required spatial conformation.
- Should be sufficiently cross-linked but not to the degree of suppression of bond forming groups.
- Should not aid in development of secondary infections such as dental caries.

Table 1: Mucoadhesive Polymers used in Buccal drug delivery

Criteria	Categories	Examples
Source	Semi-natural /natural	Agarose, chitosan, gelatin, Hyaluronic acid Various gums (guar, hakea, xanthan, gellan, carragenan, pectin, and sodium alginate)
	Synthetic	**Cellulose derivatives** [CMC, sodium CMC, HEC, HPC, HPMC, MC, hydroxyl ethyl cellulose]
		Poly(acrylic acid)-based polymers [CP, PC, PAA, polyacrylates, poly (methylvinylether-co-methacrylic acid), poly (2-hydroxyethyl methacrylate), poly (alkylcyanoacrylate), copolymer of acrylic acid and PEG]
		Others Poly(N-2-hydroxypropyl methacrylamide) (PHPMAm) PVA, PVP, thiolated polymers
Aqueous Solubility	Water-soluble	CP, HEC, HPC, HPMC (cold water)
	Water-insoluble	Chitosan (soluble in dilute aqueous acids), EC, PC
Charge	Cationic	Aminodextran, chitosan, trimethylated chitosan
	Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC
	Non-ionic	Hydroxyethyl starch, HPC, poly(ethylene oxide), PVA, PVP
Potential bioadhesive forces	Covalent	Cyanoacrylate
	Hydrogen bond	Acrylates [hydroxylatedmethacrylate, poly (methacrylic acid)], CP, PC, PVA
	Electrostatic force	Chitosan

Permeation enhancers

Membrane permeation is the limiting factor for many drugs in the development of buccal adhesive delivery devices. The epithelium that lines the buccal mucosa is a very effective barrier to the absorption of drugs. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin. Substances that facilitate the permeation through buccal mucosa are referred to as permeation enhancer[38]. Permeation enhancers are substances added to pharmaceutical formulation in order to increases the membrane permeation rate or absorption rate of a co-administered drug. They are used to improve bioavailability of drugs with normally poor membrane permeation properties without damaging the membrane and causing toxicity[39-42].

The goal of designing penetration enhancers, with improved efficacy and reduced toxicity profile is possible by understanding the relationship between enhancer structure and the effect induced in the membrane and of course, the mechanism of action. However, the selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other excipients[43,44]. In some cases, usage of enhancers in combination has shown synergistic effect than the individual enhancers. The efficacy of enhancer in one site is not same in the other site because of differences in cellular morphology, membrane thickness, enzymatic activity, lipid composition and potential protein interactions are structural and functional properties[45-49].

Penetration enhancement to the buccal membrane is drug specific. Penetration enhancement to the buccal membrane is drug specific[50,51]. Effective penetration enhancers for transdermal or intestinal drug delivery may not have similar effects on buccal drug delivery because of structural differences; however, enhancers used to improve drug permeation in other absorptive mucosa improve drug penetration through buccal mucosa. These permeation enhancers should be safe and non-toxic, pharmacologically and chemically inert, non-irritant, and non-allergenic[50].

However, an examination of the penetration route for transbuccal delivery is important because it is fundamental to select the proper penetration enhancer to improve the drug permeability[52] (Table 2).

Table 2: Mucosal penetration enhancers and mechanisms of action

Classification	Examples	Mechanism
Surfactants	**Anionic:** Sodium lauryl sulphate **Cationic:**Cetylpyridinium Chloride, cetyltrimethyl ammonium bromide **Nonionic:**Poloxamer, Brij, Span, Myrj, Tween **Bile salts:** Sodium glycodeoxycholate, Sodiumglycocholate, Sodium taurodeoxycholate, Sodium taurocholate, Azone	Perturbation of intercellular lipids, protein domain integrity
Fatty acids	Oleic acid, Caprylic acid,Lauric acid, Propylene glycol, Methyloleate, Phosphatidylcholine	Increase fluidity of phospholipid domain
Cyclodetrin	α, β, γ, Cyclodextrin, methylated β-cyclodextrins	Inlusion of membrane compounds
Chelators	EDTA, Citric acid, Sodium salicylate, Methoxy salicylates.	Interfere with Ca^{2+} Polyacrylates
Positively charged polymers	Chitosan, Trimethyl chitosan	Ionic interaction with negative charge on the mucosal surface
Cationic compounds	Poly-L-arginine, L-lysine	Ionic interaction with negative charge on the mucosal surface

Research on buccal adhesive drug delivery systems:

Several buccal adhesive delivery devices were developed at the laboratory scale by many researchers either for local or systemic actions. They are broadly classified in to

- Solid buccal adhesive dosage forms
- Semi-solid buccal adhesive dosage forms
- Liquid buccal adhesive dosage forms

Solid buccal adhesive formulations

Dry formulations achieve bio adhesion via dehydration of the local mucosal surface.

Buccal tablets

Tablets have been the most commonly investigated dosage form for buccal drug delivery to date. Buccal tablets are small, flat, and oval, with a diameter of approximately 5–8 mm[53]. Unlike conventional tablets, buccal mucoadhesive tablets allow for drinking and speaking without major discomfort. They soften, adhere to the mucosa, and are retained in position until dissolution and/or release is complete. These tablets can be applied to different sites in the oral cavity, including the palate, the mucosa lining the cheek, as well as between the lip and the gum. Successive tablets can be applied to alternate sides of the mouth. The major drawback of buccal bioadhesive tablets is their lack of physical flexibility, leading to poor patient compliance for long-term and repeated use[54,55].

Bioadhesive tablets are usually prepared by direct compression, wet granulation techniques can also be used. Tablets intended for buccal administration by insertion into the buccal pouch may dissolve or erode slowly; therefore, they are formulated and compressed with sufficient pressure only to give a hard tablet. To achieve unidirectional release, every face of the tablet, except the one that is in contact with the buccal mucosa, can be coated with water impermeable materials, such as ethyl cellulose, hydrogenated castor oil, etc., using either compression or spray coating. Multilayered tablets may be prepared by sequentially adding and compressing the ingredients layer by layer. Monolithic and two-layered matrix tablets are designed for buccal delivery of drugs. Monolithic tablets consist of a mixture of drugs with a swelling bioadhesive or sustained release polymer with a bi-directional release. They can be coated on the outer or on all sides but one face with water impermeable hydrophobic substances to allow the unidirectional drug release for systemic delivery[56].

Two layered tablets consist of an inner layer based on a bioadhesive polymer and an outer non-bioadhesive layer containing the drug for a bi-directional release but mainly a local action. Examples of drugs that loaded with matrix tablets are Propranolol, Timolol, Metronidazole, Metoclopramide, Nitroglycerin and Calcitonin (Table 3).

Table 3: List of investigated mucoadhesive buccal tablets

Active ingredient	Polymers used	Ref
Propranolol HCl	HPMC and PC	57
Promethazine	Sodium CMC and Carbopol 934P	58
Theophylline	CP 974P	59
Curcumin	*Anacardium occidentale*	60
Nifedipine	CMC and CP	61
Duloxetine Hydrochloride	HPMC K4M, Carbopol 934P and PEO WSR 303	62
Miconazole nitrate	Mixtures of HPMC, sodium CMC, CP 934P, and sodium alginate	63
Metronidazole	HEC, HPC, HPMC, or NaCMC combined with CP 940,	64

Semi-solid dosage forms

Buccal Patches

Patches are laminates consisting of an impermeable backing layer, a drug-containing reservoir layer from which the drug is released in a controlled manner, and a bioadhesive surface for mucosal attachment. Buccal patch systems are similar to those used in transdermal drug delivery. Two methods used to prepare adhesive patches include solvent casting and direct milling[65] (GUO, 1994).

In the solvent casting method, the intermediate sheet from which patches are punched is prepared by casting the solution of the drug and polymer(s) onto a backing layer sheet, and subsequently allowing the solvent(s) to evaporate. In the direct milling method, formulation constituents are homogeneously mixed and compressed to the desired thickness, and patches of predetermined size and shape are then cut or punched out. An impermeable backing layer may also be applied to control the direction of drug release, prevent drug loss, and minimize deformation and disintegration of the device during the application period[66] (Shirvan et al., 2019). The drugs and polymers that have been used to develop buccal mucoadhesive patches are listed in Table 4.

Table 4: List of investigated buccal mucoadhesive patches

Active ingredient	Polymers used	Ref
Domperidone	hydroxy propyl methyl cellulose, PVPK30, Eudragit RLPO, PEO	67
miconazole nitrate	Sodium CMC, chitosan, PVA, HEC, HPMC	68
Sumatriptan succinate	Gelatin, PVP	69
Carvedilol	HPMC E 15	70
Pioglitazone and felodipine	PEON80, HMCK$_4$M	15
Zolmitriptan	PVA and HPMC E-15	71

Buccal films:

Buccal films are preferred over tablets because of their flexibility and comfort. The films protect the wound surface, which reduces the pain and treats the disease more effectively. Flexible films may be used to deliver drugs directly to a mucosal membrane. They also offer advantages over creams and ointments in that they provide a measured dose of drug to the site. In addition, they can circumvent the relatively short residence time of oral gels on the mucosa, which are easily washed away and removed by saliva. An ideal film should be flexible, elastic and soft and adequately

strong to withstand breakage due to stress from mouth movements. Swelling of film, if occurs, should not be too extensive to prevent discomfort[72].

Bioadhesive films are similar to laminated patches in terms of their flexibility and manufacturing process. They are usually manufactured by a solvent casting method. The drug and polymer(s) are first dissolved in a casting solvent or solvent mixture. The solution is then cast into films, dried, and finally laminated with a backing layer or a release liner. The backing layer helps retard the diffusion of saliva into the drug layer, thus enhancing the adhesion time and reducing drug loss into the oral cavity. The solvent casting method is simple, but suffers from some disadvantages, including long processing time, high cost, and environmental concerns due to the solvents used[73]. Some of developed buccal films reported in Table 5.

Table 5: List of investigated buccal mucoadhesive films

Active ingredient	Polymers used	Ref
Domperidone	PEO N750 (X_1) and HPMC E5 LV	74
Insulin	Gelatin and CP 934P	75
Fluconazole	HPMC, HEC, chitosan, Eudragit and sodium alginate	76
Prednisolone	HPMC, Carbopol 940 and/or Eudragit® NE 40 D.	77

Buccal Gels and Ointments:

Semisolid dosage forms, such as gels and ointments, have the advantage of easy dispersion throughout the oral mucosa. However, drug dosing from semisolid dosage forms may not be as accurate as from tablets, patches, or films. Poor retention of the gels at the site of application has been overcome by using bioadhesive formulations[78] (Hua, 2019). A major application of adhesive gels is the local delivery of medicinal agents for the treatment of periodontitis, which is an inflammatory and infectious disease that causes formation of pockets between the gum and the tooth, and can eventually cause loss of teeth (Table 6).

Bioadhesive ointments have not been described in the literature as extensively as other dosage forms, especially when compared to tablets and patches. HPMC has been used as an adhesive ointment ingredient[79] (Smart, 2005).

Table 6: List of investigated buccal mucoadhesive gels

Active ingredient	Polymers used	Ref
Ibuprofen	Carbopol® 980 and polycarbophil	80
Ergotamine tartrate	PVA	81
Diclofenac sodium	Hydroxyethyl methacrylate	82
triamcinolone acetonide	HEC, PVP, and PC	83
Lidocaine	PEG, CP 934P,	84
Celecoxib	Chitosan	85

Buccal hydrogels:

They are formed from polymers that are hydrated in an aqueous environment and entrap drug molecules for slow release by diffusion or erosion. The advantages of these buccal hydrogels include extended retention time in the oral cavity, adequate drug penetration, high efficacy and patient acceptability[86,87]. Major application is a medicinal agent for the treatment of periodontitis, which is an inflammatory and infectious disease that causes formation of pockets between the gum and the tooth and leads to loss of teeth[88].

Conclusion:

Buccal drug delivery specifically refers to the delivery of drugs within/through buccal mucosa to affect local/systemic pharmacological actions. This review briefly describes advantages and limitations of buccal drug delivery, selection criteria of drugs and mucoadhesive and bioadhesive polymers, mechanism of permeation enhancers and various types of buccal delivery formulations.

References:

1. Sastry SV, Nyshadham JR, Fix JA. Recent technological advances in oral drug delivery–a review. Pharmaceutical science & technology today. 2000 Apr 1; 3(4):138-45.
2. Dudhipala N, Veerabrahma K. Candesartan cilexetil loaded nanodelivery systems for improved oral bioavailability. Therapeutic delivery. 2017 Feb; 8(2):79-88.
3. Dudhipala N. Enhancement of Solubility and Dissolution Rate of Trandolapril Sustained Release Matrix Tablets by Liquisolid Compact Approach. Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian J Pharm. 2015 Nov 24; 9(4).
4. Doodipala NR, Sunil R, Rao M. Development of floating matrix tablets of Ofloxacin and Ornidazole in combined dosage form: in vitro and in vivo evaluation in healthy human volunteers. International Journal of Drug Delivery. 2012 Oct 1; 4(4):462.
5. Thirupathi G, Swetha E, Narendar D. Role of isradipine loaded solid lipid nanoparticles on the pharmacodynamic effect in rats. Drug research. 2017 Mar; 67(03):163-9.
6. Doodipala N, Palem C, Reddy S, Rao Y. Pharmaceutical development and clinical pharmacokinetic evaluation of gastroretentive floating matrix tablets of levofloxacin. Int J Pharm Sci Nanotech. 2011; 4(3):1461-7.

7. Janga KY, Tatke A, Dudhipala N, Balguri SP, Ibrahim MM, Maria DN, Jablonski MM, Majumdar S. Gellan gum based sol-to-gel transforming system of natamycin transfersomes improves topical ocular delivery. Journal of Pharmacology and Experimental Therapeutics. 2019 Sep 1; 370(3):814-22.
8. Mahipalreddy D, Narendar D, Devendhar K, Dinesh S, Kiran S, Nagaraj B. Preparation and evaluation of ketoprofen enteric coated mini tablets for prevention of chronic inflammatory disease. J Pharm Drug Deliv Res. 2015; 4(2).
9. Dudhipala N. A review of novel formulation strategies to enhance oral delivery of zaleplon. J Bioequiv Availab. 2016; 8:211-3.
10. Ahuja A, Khar RK, Ali J. Mucoadhesive drug delivery systems. *Drug DevInd Pharm*. 1997; 23(5):489–517.
11. Dudhipala N, Youssef AA, Banala N. Colloidal lipid nanodispersion enriched hydrogel of antifungal agent for management of fungal infections: Comparative in-vitro, ex-vivo and in-vivo evaluation for oral and topical application. Chemistry and Physics of Lipids. 2020 Nov 1; 233:104981.
12. Bremecker K.D., Strempel H., Klein G., 1984. Novel concept for a mucosal adhesive ointment. J.Pharm.Sci, 73, 548-552.
13. Dudhipala N, Phasha Mohammed R, Adel Ali Youssef A, Banala N. Effect of lipid and edge activator concentration on development of aceclofenac-loaded transfersomes gel for transdermal application: in vitro and ex vivo skin permeation. Drug Development and Industrial Pharmacy. 2020 Aug 2; 46(8):1334-44.
14. Ch'ng HS, Park H, Kelly P, Robinson JR. Bioadhesivepolymers as platforms for oral controlled drug delivery: II.Synthesis and evaluation of some swelling, water-insoluble bioadhesive polymers. *J Pharm Sci*. 1985; 74:399– 405.
15. Palem CR, Dudhipala N, Battu SK, Goda S, Repka MA, Yamsani MR. Combined dosage form of pioglitazone and felodipine as mucoadhesive pellets via hot melt extrusion for improved buccal delivery with application of quality by design approach. Journal of Drug Delivery Science and Technology. 2015 Dec 1; 30:209-19.
16. Shojaei AH. Buccal mucosa as a route for systemic drug delivery: a review. *J Pharm Pharmaceut Sci*. 1998; 1(1):15–30.
17. Dudhipala N, Narala A, Bomma R. Recent updates in the formulation strategies to enhance the bioavailability of drugs administered via intranasal route. JBB, An Open Access Journal. 2016; 8(5):204-7.
18. Schenkels L, Gururaja TL, Levine MJ, in: Rathbone MJ (Ed.), Oral Mucosal Drug Delivery, Marcel Dekker, New York, 1996; 191–220.
19. Dudhipala N. A Comprehensive Review on Solid Lipid Nanoparticles as Delivery Vehicle for Enhanced Pharmacokinetic and Pharmacodynamic Activity of Poorly Soluble Drugs. Int. J. Pharm. Sci. Nanotechnol. 2019; 12:4421-40.
20. Swamy SK, Reddy LN, Goud BA. Development and in vitro evaluation of bioadhesive buccal tablets of hydralazine hydrochloride. Int. J. Pharm. Educ. Res.. 2014; 1:8-16.
21. Save T, Shah MU, Ghamande AR, Venkitachalam P. Comparative study of buccoadhesive formulations and sublingual capsules of nifedipine. *J Pharm Pharmacol*. 1994; 46:192– 195.
22. Goud BA, Swamy K, Kumar P. Formulation and evaluation of bioadhesive buccal tablets of simvastatin. Journal of Advanced Pharmaceutical Sciences. 2011; 1(1):29-38.
23. Dudhipala N, Veerabrahma K. Candesartan cilexetil loaded solid lipid nanoparticles for oral delivery: characterization, pharmacokinetic and pharmacodynamic evaluation. Drug delivery. 2016 Feb 12; 23(2):395-404.
24. Rathbone MJ, Ponchel G, Ghazali FA. Systemic and oral mucosaldrug delivery and delivery systems, in: M.J. Rathbone (Ed.), OralMucosal Drug Delivery, Marcel Dekker Inc., New York, 1996; 74:241–284.
25. Hao J, Heng PW. Buccal delivery systems. Drug development and industrial pharmacy. 2003 Jan 1; 29(8):821-32.
26. Park K, Robinson JR. Bioadhesive polymers as platforms for oral-controlled drug delivery: method to study bioadhesion. International journal of pharmaceutics. 1984 Apr 1; 19(2):107-27.
27. Lueßen HL, Lehr CM, Rentel CO, Noach AB, De Boer AG, Verhoef JC, Junginger HE. Bioadhesive polymers for the peroral delivery of peptide drugs. Journal of Controlled Release. 1994 Mar 1; 29(3):329-38.
28. Dudhipala N, Gorre T. Neuroprotective Effect of Ropinirole Lipid Nanoparticles Enriched Hydrogel for Parkinson's Disease: In Vitro, Ex Vivo, Pharmacokinetic and Pharmacodynamic Evaluation. Pharmaceutics. 2020 May; 12(5):448.
29. Kumar K, Dhawan N, Sharma H, Vaidya S, Vaidya B. Bioadhesive polymers: novel tool for drug delivery. Artificial cells, nanomedicine, and biotechnology. 2014 Aug 1; 42(4):274-83.
30. Vasir JK, Tambwekar K, Garg S. Bioadhesive microspheres as a controlled drug delivery system. International journal of pharmaceutics. 2003 Apr 14; 255(1-2):13-32.
31. Harris D, Robinson JR. Bioadhesive polymers in peptide drug delivery. Biomaterials. 1990 Nov 1; 11(9):652-8.
32. Dudhipala N, Narala A, Janga KY, Bomma R. Amoxycillin trihydrate floating-bioadhesive drug delivery system for eradication of helicobacter pylori: preparation, in vitro and ex vivo evaluation. J Bioequiv Availab. 2016; 8(3):118-24.
33. Narendar D, Arjun N, Someshwar K, Rao YM. Quality by design approach for development and optimization of Quetiapine Fumarate effervescent floating matrix tablets for improved oral bioavailability. Journal of Pharmaceutical Investigation. 2016 Jun 1; 46(3):253-63.
34. Donthi MR, Dudipala N, Komalla DR, Suram D, Banala N. Design and Evaluation of Floating Multi Unit Mini Tablets (MUMTS) Muco Adhesive Drug Delivery System of Famotidine to Treat Upper Gastro Intestinal Ulcers. Journal of Pharmacovigilance. 2015 Oct 12.
35. Pitta SK, Dudhipala N, Narala A, Veerabrahma K. Development of zolmitriptan transfersomes by Box–Behnken design for nasal delivery: in vitro and in vivo evaluation. Drug development and industrial pharmacy. 2018 Mar 4; 44(3):484-92.
36. Shruthi K, Narendar D, Arjun N, Kishan V. Development and Antimicrobial Evaluation of Binary Ethosomal Topical Gel of Terbinafine Hydrochloride for the Treatment of Onychomycosis. Int. J. Pharm. Sci. Nanotechnol. 2018; 11:3998-4005.
37. Nagaraj B, Anusha K, Narendar D, Sushma P. Formulation and evaluation of microemulsion-based transdermal delivery of duloxetine hydrochloride. International Journal of Pharmaceutical Sciences and Nanotechnology. 2020 Jan 31; 13(1):4773-82.
38. Hassan N, Ahad A, Ali M, Ali J. Chemical permeation enhancers for transbuccal drug delivery. Expert opinion on drug delivery. 2010 Jan 1; 7(1):97-112.
39. Padula C, Pescina S, Nicoli S, Santi P. New insights on the mechanism of fatty acids as buccal permeation enhancers. Pharmaceutics. 2018 Dec; 10(4):201.
40. Arjun N, Narendar D, Sunitha K, Harika K, Nagaraj B. Development, evaluation, and influence of formulation and process variables on in vitro performance of oral elementary osmotic device of atenolol. International journal of pharmaceutical investigation. 2016 Oct; 6(4):238.
41. Samanthula KS, Satla SR, Bairi AG. Development, In-Vitro and Ex-Vivo Evaluation of Muco-adhesive Buccal patches of Candesartan cilexetil. Research Journal of Pharmacy and Technology. 2019; 12(6):3038-44.
42. Nagaraj B. Development of Osmotically Controlled Oral Drug Delivery Systems of Tramadol Hydrochloride: Effect of Formulation Variables on In Vitro Release Kinetics. Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian J Pharm. 2016 Sep 10; 10(03).
43. Junginger HE, Hoogstraate JA, Verhoef JC. Recent advances in buccal drug delivery and absorption—in vitro and in vivo studies. Journal of controlled release. 1999 Nov 1; 62(1-2):149-59.
44. Dudhipala N, Veerabrahma K. Pharmacokinetic and pharmacodynamic studies of nisoldipine-loaded solid lipid nanoparticles developed by central composite design. Drug development and industrial pharmacy. 2015 Dec 2; 41(12):1968-77.
45. Aungst BJ. Absorption enhancers: applications and advances. The AAPS journal. 2012 Mar 1; 14(1):10-8.
46. Dudhipala N, Janga KY, Gorre T. Comparative study of nisoldipine-loaded nanostructured lipid carriers and solid lipid nanoparticles for oral delivery: preparation, characterization, permeation and pharmacokinetic evaluation. Artificial cells, nanomedicine, and biotechnology. 2018 Nov 5; 46(sup2):616-25.
47. Nagai T, Machida Y. Buccal delivery systems using hydrogels. Advanced drug delivery reviews. 1993 Jul 1; 11(1-2):179-91.

48. Şenel S, Hıncal AA. Drug permeation enhancement via buccal route: possibilities and limitations. Journal of Controlled Release. 2001 May 14; 72(1-3):133-44.
49. Krishna VM, Kumar VB, Dudhipala N. In-situ intestinal absorption and pharmacokinetic investigations of carvedilol loaded supersaturated self-emulsifying drug system. Pharmaceutical nanotechnology. 2020 Jun 1; 8(3):207-24.
50. Nicolazzo JA, Reed BL, Finnin BC. Buccal penetration enhancers—how do they really work?. Journal of controlled release. 2005 Jun 20; 105(1-2):1-5.
51. Nagaraj K, Narendar D, Kishan V. Development of olmesartan medoxomil optimized nanosuspension using the Box–Behnken design to improve oral bioavailability. Drug Development and Industrial Pharmacy. 2017 Jul 3; 43(7):1186-96.
52. Rossi S, Sandri G, Caramella CM. Buccal drug delivery: a challenge already won?. Drug Discovery Today: Technologies. 2005 Mar 1; 2(1):59-65.
53. Esim O, Savaser A, Ozkan CK, Bayrak Z, Tas C, Ozkan Y. Effect of polymer type on characteristics of buccal tablets using factorial design. Saudi Pharmaceutical Journal. 2018 Jan 1; 26(1):53-63.
54. Le ND, Tran PH, Lee BJ, Tran TT. Solid lipid particle-based tablets for buccal delivery: the role of solid lipid particles in drug release. Journal of Drug Delivery Science and Technology. 2019 Aug 1; 52:96-102.
55. Dudhipala N, Veerabrahma K. Improved anti-hyperlipidemic activity of Rosuvastatin Calcium via lipid nanoparticles: Pharmacokinetic and pharmacodynamic evaluation. European Journal of Pharmaceutics and Biopharmaceutics. 2017 Jan 1; 110:47-57.
56. Ventouras K, inventor; Novartis Consumer Health SA, assignee. Buccal delivery system. United States patent US 6,183,775. 2001 Feb 6.
57. Akbari J, Nokhodchi A, Farid D, Adrangui M, Siahi-Shadbad MR, Saeedi M. Development and evaluation of buccoadhesivepropranolol hydrochloride tablet formulations: Effect of fillers, *IL Farmaco*. 2004; 59:155– 161.
58. Chopparapu C, Palem CR, Yamsani MR. Development of Promethazine mucoadhesive tablets for buccal delivery: in-vitro, ex-vivo and in-vivo characterization. American Jr PharmTech Res. 2012; 2(1):1697-705.
59. Boyapally H, Nukala RK, Bhujbal P, Douroumis D. Controlled release from directly compressible theophylline buccal tablets. Colloids and Surfaces B: Biointerfaces. 2010 Jun 1; 77(2):227-33.
60. Gowthamarajan K, Jawahar N, Wake P, Jain K, Sood S. Development of buccal tablets for curcumin using Anacardium occidentale gum. Carbohydrate Polymers. 2012 May 16; 88(4):1177-83.
61. Varshosaz J, Dehghan Z. Development and characterizationof buccoadhesive nifedipine tablets. *Eur J Pharm Biopharm*. 2002; 54:135– 141.
62. Banala N, Peddapalli H, Dudhipala N, Chinnala KM. Transmucosal Delivery of Duloxetine Hydrochloride for Prolonged Release: Preparation, in vitro, ex vivo Characterization and in vitro-ex vivo Correlation. International Journal of Pharmaceutical Sciences and Nanotechnology. 2018 Sep 30; 11(5):4249-58.
63. Mohammed FA, Khedr H. Preparation and in vitro/in vivoevaluation of the buccal bioadhesive properties of slow release tablets containing miconazole nitrate. *Drug DevInd Pharm*. 2003; 29:321–337.
64. Luana periolia, Valeria Ambrogia, Fausta Angelicia, Maurizio Riccia, Stefano Giovanolia, Marinella Giovanolia, Marinella Capuccellab, Carlo Rossia. Development of mucoadhesive patches for buccal administration of ibuprofen. *J Contro Release*. 2004; 99:73-82.
65. Guo JH. Investigating the surface properties and bioadhesion of buccal patches. Journal of pharmacy and pharmacology. 1994 Aug; 46(8):647-50.
66. Shirvan AR, Bashari A, Hemmatinejad N. New insight into the fabrication of smart mucoadhesive buccal patches as a novel controlled-drug delivery system. European Polymer Journal. 2019 Oct 1; 119:541-50.
67. Palem CR, Gannu R, Doodipala N, Yamsani VV, Yamsani MR. Transmucosal delivery of domperidone from bilayered buccal patches: in vitro, ex vivo and in vivo characterization. Archives of pharmacal research. 2011 Oct 1; 34(10):1701-10.
68. Nafee NA, Ismail FA, Boraie NA, Mortada LM. Mucoadhesive buccal patches of miconazole nitrate: in vitro/in vivo performance and effect of ageing. International Journal of Pharmaceutics. 2003 Oct 2; 264(1-2):1-4.
69. Shidhaye SS, Saindane NS, Sutar S, Kadam V. Mucoadhesive bilayered patches for administration of sumatriptan succinate. Aaps Pharmscitech. 2008 Sep 1; 9(3):909-16.
70. Vamshi Vishnu Y, Chandrasekhar K, Ramesh G, Madhusudan Rao Y. Development of mucoadhesive patches for buccal administration of carvedilol. Current drug delivery. 2007 Jan 1; 4(1):27-39.
71. Shiledar RR, Tagalpallewar AA, Kokare CR. Formulation and in vitro evaluation of xanthan gum-based bilayered mucoadhesive buccal patches of zolmitriptan. Carbohydrate polymers. 2014 Jan 30; 101:1234-42.
72. Morales JO, McConville JT. Manufacture and characterization of mucoadhesive buccal films. European Journal of Pharmaceutics and Biopharmaceutics. 2011 Feb 1; 77(2):187-99.
73. Montenegro-Nicolini M, Morales JO. Overview and future potential of buccal mucoadhesive films as drug delivery systems for biologics. AAPS PharmSciTech. 2017 Jan 1; 18(1):3-14.
74. Palem CR, Dudhipala NR, Battu SK, Repka MA, Rao Yamsani M. Development, optimization and in vivo characterization of domperidone-controlled release hot-melt-extruded films for buccal delivery. Drug development and industrial pharmacy. 2016 Mar 3; 42(3):473-84.
75. Ritschel WA, Ritschel GB, Forusz H, Kraeling M. Buccal absorption of insulin in the dog. *Res Commun Chem Pathol Pharmacol*. 1989; 63:53– 67.
76. Yehia SA, El-Gazayerly ON, Basalious EB. Fluconazole mucoadhesive buccal films: in vitro/in vivo performance. Current drug delivery. 2009 Jan 1; 6(1):17-27.
77. Kumria R, Nair AB, Goomber G, Gupta S. Buccal films of prednisolone with enhanced bioavailability. Drug delivery. 2016 Feb 12; 23(2):471-8.
78. Hua S. Advances in nanoparticulate drug delivery approaches for sublingual and buccal administration. Frontiers in Pharmacology. 2019; 10.
79. Smart JD. Buccal drug delivery. Expert opinion on drug delivery. 2005 May 1; 2(3):507-17.
80. Marques AC, Rocha AI, Leal P, Estanqueiro M, Lobo JM. Development and characterization of mucoadhesive buccal gels containing lipid nanoparticles of ibuprofen. International Journal of Pharmaceutics. 2017 Nov 30; 533(2):455-62.
81. Tsutsumi K, Obata Y, Nagai T, Loftsson T, Takayama K. Buccal absorption of ergotamine tartrate using the bioadhesivetablet system in guinea-pigs. *Int J Pharm*. 2002; 238:161–170.
82. Cassidy J, Berner B, Chan K, John V, Toon S, Holt B, Rowland M. Human transbuccal absorption of diclofenacsodium from a prototype hydrogel delivery device. *Pharm Res*. 1993; 10:126–129.
83. Shin SC, Bum JP, Choi JS. Enhanced bioavailability by buccal administration of triamcinolone acetonide from the bioadhesive gels in rabbits. International journal of pharmaceutics. 2000 Nov 19; 209(1-2):37-43.
84. Tan YTF, Peh KK, Al-Hanbali O. Effect of Carbopol andpolyvinylpyrrolidone on the mechanical, rheological, andrelease properties of bioadhesive polyethylene glycol gels. *AAPS PharmSciTech*. 2000; 1:E24.
85. Cid YP, Pedrazzi V, de Sousa VP, Pierre MB. In vitro characterization of chitosan gels for buccal delivery of celecoxib: influence of a penetration enhancer. AAPS PharmSciTech. 2012 Mar 1; 13(1):101-11.
86. De Vries ME, Bodde HE, Busscher HJ, Junginger HE. Hydrogels for buccal drug delivery: Properties relevant for muco-adhesion. Journal of biomedical materials research. 1988 Nov; 22(11):1023-32.
87. Butreddy A, Narala A, Dudhipala N. Formulation and characterization of Liquid Crystalline Hydrogel of Agomelatin: In vitro and Ex vivo evaluation. Journal of Applied Pharmaceutical Science. 2015 Sep; 5(09):110-4.
88. Xu J, Strandman S, Zhu JX, Barralet J, Cerruti M. Genipin-crosslinked catechol-chitosan mucoadhesive hydrogels for buccal drug delivery. Biomaterials. 2015 Jan 1; 37:395-404.