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REVIEW ARTICLE

BUCCAL DRUG DELIVERY SYSTEM: AN OVERVIEW ABOUT DOSAGE FORMS AND RECENT STUDIES

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ABSTRACT
Management of illness through medication is entering a new era in which growing number of novel drug delivery systems are being employed and are available for therapeutic use. Pharmaceutical research and development is currently focused on the development of drug delivery systems to target a drug to the desired organ or site with the aim of minimizing its overall distribution in the body. The oral mucosa has many properties which make it an attractive site for drug delivery but simultaneously provide several problems for researchers for effective and efficient delivery of therapeutic active agents. However, with the development of novel delivery techniques overcome several challenges. Oral mucosa delivery has many advantageslike high blood flow, rapid recovery, prevention of hepatic first-pass effect and pre-systemic elimation in gastrointestinal tract. On the other hand relatively small surface area and significant loss of drug due to swallowing and salivary flow are main limitations of buccal delivery. Different formulations including sprays, tablets, mouthwashes, gels, pastes and patches are presently used for delivery into and/or across the oral mucosa. Over the last 20 years, a wide range of formulations has been developed for buccal drug delivery systems but unfortunately few have been accomplished to be a medicine. One of the main reasons of this unsuccessful result could be the lack of the standardized methods which evaluate *in vitro* performance of buccal dosage forms. Thus aim of this review, to discuss the potential of buccal drug delivery and buccal dosage forms and also explore recent studies and *in vitro* analysesmethodology of buccal dosage forms.
Keywords: Buccaldosage forms, buccal mucosa, drug delivery, mucoadhesion.

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INTRODUCTION
Drug research and development has been progressing in improving the quality of life of patients as well as contributing to the treatment of diseases[1,2]. Development of new a drug molecule is expensive and time consuming. Because of this, the scientist and researchers in the drug development industries are focusing on alternative routes of administration to add to the potential of approved drugs or to overcome the drawbacks of the oral route. Buccal drug administration has remarkable advantages such as prevention and elimination of first-pass effect in the gastrointestinal tract, having a more favorable enzymatic environment for the absorption of certain drugs, having low cost, easy administration to pediatric and geriatric patients and also patients with intellectual disabilities[2,3,4]. The oral mucosa is highly vascularized, drugs absorbed through the mucosa and enter the systemic circulation directly. Furthermore, the high blood flow and permeability of the oral mucosa makes it an ideal site of administration for the rapid systemic delivery of a drug in the treatment of pain, seizures and angina pectoris[5,6]. When transmucosal drug administration routes such as rectal, vaginal, nasal and buccal routes are compared, buccal route is prominent with patient compliance. For example rectal and vaginal delivery systems are in part less acceptable ways for patients. In terms of drug administration, rectal and vaginal administration may sometimes lead to slow and sometimes incomplete drug absorption and may vary in the same person or between individuals[7]. For nasal application; the limited area of the nasal cavity, the rapid removal of the administered drug, and the variable physiological functions of the nasal cavity are among the disadvantages of this application[6]. With the development of mucoadhesive formulations, the local and systemic effects of drug delivery systems have increased. The likelihood of using biological

agents such as genes, peptides and antibodies that can be reduced by the administration of oral mucosa may increase[6,8]. Pharmaceutical researchers are conducting further research on the development of novel drug delivery systems to enhance the therapeutic effects of existing molecules relative to novel drug molecules. At this point, buccal drug systems are thought to have great potential, and this review summarizes general information about buccal drug delivery systems and provides information about recent studies.

Oral cavity

Anatomical structure of oral cavity

The oral cavity consists of the lips, cheeks, tongue, hard palate, soft palate and the base of the mouth, and its surface consists of oral mucosa. Oral mucosa; buccal, sublingual, gingival, palatal and labial mucosa, buccal mucosal tissues (buccal), the bottom of the mouth (sublingual) and the ventral surface of the tongue accounts for about 60% of the oral mucosal surface area. The buccal cavity has a very limited surface area of around 50 cm^2 but the accessibility of the site makes it a preferred location for delivering therapeutic agents. Buccal and sublingual tissues are suitable site for buccal administration and these are the regions with the highest permeability in the oral mucosa[9]. The sublingual mucosa is relatively more permeable than the buccal mucosa; hence, formulations for sublingual delivery are formulated to release the active agent immediately. The mucoadhesive formulation is of importance for the delivery of active agents to the buccal mucosa where the active agent has to be released in a controlled manner. Hence, the buccal cavity is more suitable for mucoadhesive drug delivery.The epithelium of the oral cavity resembles the skin epithelium, but exhibits distinct characteristics from the skin in terms of keratinization, protective and lubricating mucus. Mucus is a translucent and viscous secretion that forms a thin and continuous gel layer that adheres to the mucosal epithelial surface. Mean thickness of mucus varies from about 50-450 µm in humans,and it secreted by the globet cells lining the epithelia. Generally, mucus components; water (95%), glycoproteins and lipids (0.5-5%), mineral salts (1%) and free protein (0.5-1%). The saliva produced by the salivary glands in the oral cavity and as part of the saliva, mucus secreted from the major and minor salivary glands are present, allowing the adhesion of mucoadhesive drug delivery systems during drug administration[10,11]. The pH of saliva is 5.5 to 7.0 and viscosity value is 1.09±0.11 mPa.s. Saliva is composed of 99% water and is complex fluid containing organic and inorganic material. Secretion of saliva is highest during working hours. Continuous available volume of it 696±312 µl. Protective fluid for all tissues of the oral cavity, continuous mineralization/demineralization of the tooth enamel and moisten the oral cavity are main functions of saliva[12].

The Advantages and Disadvantages of Buccal Drug Administration

The buccal area has a highly vascularized tissue and a neutral environment. The route of drugs through the buccal mucosa is like a slow i.v. infusion. Thus higher bioavailability of some medicines may be achieved with fewer doses compared to conventional oral dosage forms. Absorption, the size of the drug molecule, its sensitivity to hydrophilicity, its enzymatic degradation, and its application to the oral cavity need to be taken into consideration to accomplish the above mentioned achievement[13,14,15].

BUCCAL DOSAGE FORMS

Numerous dosage forms are available for buccal administration, such as tablets, films, lozenges, sprays, gels, lollipops, gums and powders. In addition, new formulations such as sponges can be used for buccal drug administration[17,18,19]. Buccal dosage forms include dry dosage forms that need to be moistened before buccal tablets are administered[11]. In recent years, various mucoadhesive buccal tablet formulations have been prepared by direct compression for local or systemic effect. Buccal tablets can be developed to release the active ingredient into the saliva either unidirectionally or multidirectionally by targeting the buccal mucosa[18]. The buccal films/patches comprise an impermeable layer of the active substance/formulation, a reservoir layer containing the formulation in which the active substance is released in a controlled manner, and a mucoadhesive surface for attachment to the mucosa. Compared to creams and ointments, they are more advantageous in delivering a certain dose of the drug to the site[20]. Buccal films are more preferred than buccal tablets. Because buccal tablets are more flexible and can be applied more easily. In addition, they can reduce pain by protecting the wound surfaces and improve treatment efficacy[21]. Buccal films are particularly designed for pediatric patients[22].

Buccal gels and ointments are semi-solid dosage forms and have the advantage of easy administration to the buccal mucosa. The problem of low adhesion of the gels in the field of application was overcome by the preparation of mucoadhesive formulations[2]. Buccal gels or ointments are less preferred by patients than buccal tablets and films, but are generally administered for local effect[11]. Buccal dosage forms may be developed for systemic effect or for local treatment of the oral mucosa. When selecting the dosage form, the target site of action and the properties of the active substance should be considered[23]. For mucosal and transmucosal administration, conventional dosage forms cannot provide therapeutic drug levels in the mucosa and circulation due to the physiological nature of the oral cavity (the presence of saliva and the effect of mechanical stress). The constant flow of saliva and the mobility of tissues within the mouth makes it difficult to keep the dosage form in the oral cavity. The residence time of medications administered to the oral cavity is generally between 5 and 10 minutes. Since the dosage form remains in the absorption area for a very short time, an unpredictable distribution is observed. In order to achieve the desired therapeutic effect, it is important to increase the contact time between the formulation and the mucosa. For this purpose, mucoadhesive buccal formulations are developed using mucoadhesive polymers. To develop an ideal mucoadhesive buccal drug delivery system, it is important to identify and understand the forces

responsible for adhesive bond formation[24].There are three sites that are effective for the formation of adhesive bonds between the polymer and mucus:

- Surface of bioadhesive material
- First layer of mucosa
- Interface between mucosa and bioadhesive material

Mucoadhesion is a complex process and adhesion mechanisms of polymers to mucosal surfaces have not yet been fully understood. However, numerous theoriessuch as adsorption theory, wetting theory, electrical theory, diffusion theory and fracture theory have been proposed[10,25]. In particular, buccal systems are needed to treat local diseases of the mucosa[24,26]. In order to provide therapeutic requirements, buccal dosage forms include; penetration enhancers to increase the permeability of the active substance by transmucosal administration or mucosal administration; enzyme inhibitors to protect the active substance from degradation by mucosal enzymes. Due to the limited absorption area with respect to the site of administration of the buccal dosage form, they are generally preferred for a buccal delivery system of 1-3 cm^2 and for active ingredients with a daily dose of 25 mg or less. The ellipsoidal shape is most preferred in films/patches and the thickness of buccal drug delivery systems is generally limited to a few millimeters[27]. Many diseases can affect the thickness of the buccal epithelium and ultimately alter the barrier property of the mucosa. Some diseases or treatments may also affect mucus secretion and properties[10]. Due to these physiopathological conditions, changes in the mucosal surface may make it difficult to administer and retain a buccal delivery system. Therefore, it is necessary to evaluate the structure of the mucosa under the relevant disease conditions in order to develop an effective buccal release system. In addition, it should be noted that active substances that have the potential to alter the physiological conditions of the oral cavity may not be suitable for buccal administration[27].

***In vitro* evaluation of buccal dosage forms**

Several dosage forms have been developed and evaluated to suitability applying oral mucosa. Regardless of the properties of dosage forms different methods are required for quality control studies and evaluation of release, permeation and mucoadhesion properties[12]. Some test like uniformity of content, permeability study, buccal absorption test and residence time should be performed for all dosage forms. On the other hand, the test like weight variation, friability, tensile strength or viscosity are necessary for some dosage forms. *In vitro* disintegration tests are generally performed for solid dosage forms like films and tablets to determine the disintegration rate when thedosage form come in contact with the mucus and saliva. Disintegration of these dosage forms can also be examined visually while dissolution studies. Between all the buccal mucosal products listed in USP 35, the monograph of isosorbide dinitrate sublingual tablets has specific information aboutdissolution test. Hence, comparison of different products or evaluation of newly developed formulations is problematic because of the lack of standardized methods available in the pharmacopeia. In this monograph, the USP dissolution apparatus II is used at a paddle speed of 50 rpm with 900 ml water dissolution medium which does not correlate with *in vivo* conditions of buccal mucosa and the result couldn`t reflect *in vivo* dissolution. Several studies have been performed to dissolution studies in smaller volumes or with different devices for mimic *in vivo* conditions. Fabregas and Garcia used apparatus III for the dissolution of hydrocortisone hemisuccinate buccal mucoadhesive tablets[28].

Ikinci *et al.*, used a Franz diffusion cell method as an alternative for the release of nicotine from buccal tablets. The *in vitro* residence time test is specifically useful to evaluate the time to remain at the buccal mucosa for mucoadhesive drug delivery systems[29]. Nafee *et al.*, used modified disintegration test apparatus for determination of residence time[30]. The disintegration medium was 800 ml of pH 6.75 isotonic phosphate buffer and rabbit intestinal mucosa was used for the test. The hydrated mucoadhesive tablet was brought into contact with the membrane. The time necessary for erosion or detachment of the tablet was determined. Kockisch *et al.*, proposed a dynamic *in vitro* retention testing system[31]. The porcine esophageal mucosa was held flat by application of a moderate vacuum through small openings at the base plate of the cell. The tissue was kept 37°C; 90% RH and was allowed to equilibrate for a period of 1 h. To ensure that the tissue was sufficiently hydrated, artificial saliva was circulated over the tissue at a rate of 1 ml/min using a peristaltic pump. Polymer microparticles were placed onto the center of the mucosal surface with a small glass funnel. The time taken for the particles to travel along mucosa was used as a measure of particle retention[31]. Mucoadhesion tests have been performed in the literature based on different method such as modified Wilhelmy plate surface, modified dual tensiometry, texture analysis and rotating cylinder methods. Between all the methods the texture analyzer is generally usedliterature in the recent years because of the varied experimental setups, precision and reproducibility of results. Buccal permeation studies must be conducted to determine the feasibility of this route of a drug candidate and the type of enhancer during the pre-formulation studies. Thesestudies are usually enforced to determine the barrier properties of different mucosal tissues. Similar like transdermal drug delivery, different types of diffusion cells with modifications are suitable to performed permeation studies for buccal dosage forms. Human buccal tissues may be the most suitable to mimic *in vivo*conditions researchers usually use animal tissue because it is not easy to reach human tissues. Permeation studies involve methods that would examine *in vitro*, *ex vivo* and/or *in vivo* buccal permeation profile and kinetics of absorption of the drug[12,20].

Recent studies and on buccal drug delivery and future approaches

Pather *et al.*, summarized challenges for the development and approval of buccal dosage forms as; including low dose drugs, biology and permeability issues and the complexity of them, need a special

mechanismto enhance the absorption of the drug without causing undue side effects, the taste of the drug, patient acceptability, dose titration for *in vivo* studies may prove to be difficultanddifficulties related with regulations, authorities and economical circumstances[32]. Very few innovative dosage forms for buccal drug delivery have reached the clinical development phase. The main strategies have been the incorporation of permeation enhancers or mucoadhesive constituents to conventional dosage forms.For example, surfactants, bile salts, fatty acids, cyclodextrins and chelators have been shown to enhance mucosal permeability and absorption of various compounds[33] by changing mucus rheology, increasing the fluidity of the lipid bilayer membrane, acting on the components at tight junctions, inhibiting mucosal enzymes; and increasing the thermodynamic activity of drugs[20]. In addition, the incorporation of mucoadhesive constituents has been demonstrated to enhance formulation retention time with the sublingual or buccal mucosa[34]. The major obstacle to the use of many hydrophilic macromolecules is inadequate and irregular oral absorption. With the development of recombinant DNA technology, buccal administration is thought to be important in order to develop protein and peptide formulations in the future and deliver them to the systemic circulation by a non-parenteral administration[26]. In line with recent developments in buccal drug delivery systems such as lipophilic gel, buccal spray and phospholipid vesicles, numerous studies have been conducted on the buccal administration of peptides. In particular, some researchers have proposed the use of glyceryl monooleate phases of cubic and lamellar liquid crystals as buccal drug delivery systems for peptide-structured drugs[35]. Some researchers have developed liquid crystal systems for the buccal administration of KSL-W, an antimicrobial decapeptide to treat multispecific oral biofilms[36]. In addition, a new insulin liquid aerosol formulation has been developed. This formulation has been shown to allow metered dose insulin administration in the form of aerosolized droplets for buccal administration. Compared to conventional dosage forms, a significant increase in the level of the active ingredient has been shown in the buccal dosage form. Studies have shown that this oral aerosol formulation is rapidly absorbed from the buccal mucosa and provides the necessary postprandial plasma insulin levels in diabetic patients. This new, painless, oral insulin formulation; rapid absorption, an application technique with high patient compliance and full dosing have been reported to have many advantages[37]. Another interesting novel buccal formulation used gold nanoparticle technology to form a film soluble in buccal mucosa. Clinical trials have been reached in two approaches to insulin buccal administration: oromucose sprays of the peptide, a permeability enhancing film, and gold nanoparticles embedded in a soluble film[38,39]. In another study, soy lecithin and propanediol were used for insulin buccal spray formulation. Soy lecithin has a high affinity for biological membranes, but its solubility is low and the solubility of propandiol and soy lecithin could be increased. Insulin buccal spray was applied to diabetic rabbits and the hypoglycemic effect of the formulation was investigated. When the results were examined, it was shown that there was a significant decrease in blood glucose levels of rabbits treated with insulin buccal spray compared to the control group. To investigate insulin delivery from the buccal mucosa, the distribution of fluorescence probe in the epithelium using confocal laser scanning microscopy and fluorescence probe isothiocyanate-labeled insulin penetration were examined. The results demonstrated that the fluorescent probe isothiocyanate-labeled insulin can pass through the buccal mucosa, and that insulin passes through the epithelium, which includes both intracellular and paracellular pathways[40]. The world's first approved transbuccal release system for testosterone replacement therapy in men is a mono-convex, tablet-like mucoadhesive buccal system, with a recommended dose of 30 mg at a 12-hour interval. This transbuccal delivery system is presented as an alternative to patches, gels or injectable testosterone formulations[21,41]. Biodegradable mucoadhesive drug technology has been developed to provide both local and systemic effects of drugs in mucosal tissues, and includes a small disc with biodegradable layers that enable rapid release of the active ingredient over a period of time. This disc adheres to the buccal mucosa and transmits the active ingredient to the mucosa while eroding in the mouth[42]. Transmucosal administration is also thought to provide significant benefit in the application of new classes of biological drugs, such as nucleic acids, antibodies, and proteins[26]. A recent study was showed succeded results which wereaimed to design and evaluate zolpidem nanoparticle-impregnated buccal films for the treatment of insomnia with a prolong drug action. Zolpidem-loaded PLGA nanospheres were succeded *in vitro* and *in vivo* tests[43]. In another recent study it was shown that nabumetone, nonsteroidal anti-inflammatory drug, including buccal films were prepared using polymers like HPMC, Eudragit, sodium alginate, and sodium CMC in varying proportions were subjected to *in vitro* quality control parameters *ex-vivo* permeation and stability studies and the formulations showed optimum results and good control over dug release along with correlation between *in vitro* and *ex vivo* studies[44]. Somayaji *et al.*, used an ethylcellulose strip as delivery medium for tetracycline and metronidazole to reduce microorganisms in periodontalpockets[45]. Patients were given supragingival scalingand then divided into 5 groups, depending on thelength of time the medication was in place. Sites weremarked for tetracycline, metronidazole, and placebo. Results showed that tetracycline andmetronidazole could both be applied locally to periodontal sites using ethyl cellulose strips and markedly suppress the subgingival bacteria over a periodof several days[45]. A novel saliva activated bioadhesive drug delivery systemwas developedby Taware *et al.*, for lidocaine hydrochloride and compared its effect with topical gel preparation in dentistry. Aim of this study, was determining the feasibility of the system as a viable alternative to infiltration anesthesia in dentistry.It was found that

drug delivery system adhered to gingival withina minute and produced peak effect in 15 minutesand produced greater depth of anesthesia than the marketed topical gel[46].Although there are many formulation studies have been reported in the literature, particularly to improve retention and absorption in the buccal and sublingual regions, very few of them have translated to the clinical phase. This is because it needs to be a clear benefit of efficacy and/or safety with any new drug formulation compared to clinically available dosage forms[47]. In addition, comprehensive evaluations of the pharmacokinetics, stability, efficacy, and safety of the formulations are required in appropriate animal models as well as in clinical studies, based on regulatory standards and protocols[48]. Gilhotra *et al.*, has overviewed mucoadhesive buccal drug delivery systems in terms of a clinical perspective and studies have shown that buccal drug delivery will be increase for the treatment of cardiovascular diseases, migraine, epilepsy and antimicrobial, anti-inflammatory, hypoglycaemia, muscle relaxation, emesis concomitant chemotherapy, smoking deterrent therapies and also for protein and hormone delivery[49]. An ongoing clinical study of a buccal film has begun on April 13 2019 for the treatment of epilepsy as diazepam containing buccal film

Nanoparticulate systems have been incorporated into various dosage forms for buccal drug delivery, including gels, sprays, tablets, filmsand patches.

These nanoparticulate formulations have been shown to:

i. Improve drug permeability across the epithelium; (ii) modify drug release kinetics (e.g., controlled release or sustained release).
ii. Provide solubilization (i.e., to deliver compounds which have physicochemical properties that strongly limit their aqueous solubility); and/or
iii. Protect compounds that are sensitive to degradation (e.g., peptides).

These factors all aim to promote higher sublingual or buccal bioavailability of drugs for subsequent systemic absorption[39,47]. In the development process of buccal delivery systems, research and invention has been fairly active in this area, especially during the last. The ongoing research and development is expected to yield at least a few successes in the form of products approved for marketing in a short time. Especially the products contain peptides and protein based active substance seems to be a high potential to be in the drug market.Initial development successes by established companies with the collaboration of universities, mayencourage researchers by new entrants into the field andstimulate more vigorous development. Further successes are likely to lead to some opportunisticentrants into buccal dosage forms development.

CONCLUSION

The buccal mucosa provides many advantages for local and systemic drug administration. Buccal drug administration is an important field of research as it allows for systemic administration of drugs with low oral bioavailability. It is also a suitable alternative in the delivery of peptides and protein-structured drugs. Pediatric population still great need of developing flexible and appropriate drug dosage forms, it is expected to develop new and more buccal dosage forms especially designed for pediatric applications that can improve transepithelial drug permeability and improve existing therapies and allow new forms of treatment.

AUTHOR'S CONTRIBUTION

All authors have worked equally in this work.

REFERENCES

1. Chowdhury SR. Floating drug delivery system - a new era in novel drug delivery system.Int JPharma Chem Research; 2012;1(5): 55-64. *https://doi.org/10.1208/pt060347*
2. Verma S, Kaul M, Rawat A, Saini S. An overview on buccal drug delivery system. Int J Pharm Sci Res 2011; 2(6):1303-1321.
3. Lin L, Wong H. Predicting oral drug absorption: mini review on physiologically based pharmacokinetic models. Pharmaceutics; 2017; 9(4):41. *https://doi.org/10.3390/pharmaceutics9040041*
4. Madhavi BR. Buccal film drug delivery system-an innovative and emerging technology. J Mol Pharm Organic Proc Res 2013;1(3):1-6. *https://doi.org/10.4172/2329-9053.1000107*
5. De Caro V, Giandalia G, Siragusa MG, Sutera FM, Giannola LI. New prospective in treatment of Parkinson's disease: studies on permeation of ropinirole through buccal mucosa, Int J Pharm; 2012:429(1-2):78-83. *https://doi.org/10.1016/j.ijpharm.2012.03.022*
6. Hearnden V, Sankar V, Hull K, *et al*. New developments and opportunities in oral mucosal drug delivery for local and systemic disease.Adv Drug Deliv Rev; 2012: 64(1):16-28. *https://doi.org/10.1016/j.addr.2011.02.008*
7. Tukker, Joseph J, Garg S. Rectal and vaginal drug delivery. In: Aulton's Pharmaceutics; 2013:732-751.
8. Smart JD. Buccal drug delivery. ExpOpinDrug Deliv 2005;2(3):507-517.PMID: 23008684
9. Zhang H, Zhang J, Streisand JB. Oral mucosal drug delivery: clinical pharmacokinetics and therapeutic applications. Clin pharm; 2002:41(9):661-680. *https://doi.org/10.2165/00003088-200241090-00003*
10. Manohar SD, Sridhar DA, Mallikarjuna SC. Drug delivery from the oral cavity: A focus on mucoadhesive buccal drug delivery systems. PDA J Pharm Sci Techn 2012; 66(5):466-500. *https://doi.org/10.5731/pdajpst.2012.00877*
11. Reddy RJ, Maimuna A, Mohammed Asif H. A comprehensive review on buccal drug delivery system, Int J Res Dev Pharm Life Sci 2017; 6(3):2606-2618.
12. Patel VF, Liu F, Brown MB. Modeling the oral cavity: *In vitro* and *in vivo* evaluations of buccal drug delivery systems. J Cont Rel 2012; 10,161(3):746-56. *https://doi.org/10.1016/j.jconrel.2012.05.026*
13. Costa JSR, de Oliveira Cruvinel K, Oliveira-Nascimento L. A mini-review on drug delivery through wafer technology: Formulation and manufacturing of buccal and oral lyophilizates. J Ad Res2019:20:33-41. *https://doi.org/10.1016/j.jare.2019.04.010*
14. Çelik B. Risperidone mucoadhesive buccal tablets: formulation design, optimization and evaluation. Drug Design Deve Therap 2017; 11:3355-3365. *https://doi.org/10.2147/DDDT.S150774*
15. Campisi G, Paderni C, Saccone R, Fede O, Wolff A, Giannola L. Human buccal mucosa as an innovative site of drug delivery. Curr Pharm Design 2010; 16(6):641-652. *https://doi.org/10.2174/138161210790883778*
16. Patel M, Bharadia PD, Chhabria MT. A Systemic Review on buccal drug delivery systems. SciFed Mat Res Lett 2017; 1(3):1-7. PMID: 23008684

17. Çelik B, Özdemir S, Demirkoz AB, Üner M. Optimization of piribedil mucoadhesive tablets for efficient therapy of Parkinson' s disease : physical characterization and *ex vivo* drug permeation through buccal mucosa. Drug Dev Ind Pharm 2017: 43(11):1836-1845. *https://doi.org/10.1080/03639045.2017.1349785*
18. Hao J, Heng PWS. Buccal delivery systems. Drug Dev Ind Pharm; 2003:29(8):821-832. *https://doi.org/10.1081/ddc-120024178*
19. Barua S, Kim H, Jo K, *et al*. Drug delivery techniques for buccal route: formulation strategies and recent advances in dosage form design. J Pharm Inv 2016; 46(7):593–613. *https://doi.org/10.1007/s11095-014-1485-1*
20. Reddy PC, Chaitanya KSC, Rao YM. A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods, DARU J Pharm Sci 2011; 19(6):385-403.PMID: 23008684
21. Venkatalakshmi R, Sudhakar Y, Madhuchudana Chetty C, Sasikala C, Mohan VM. Buccal drug delivery using adhesive polymeric patches. Int J Pharm Sci 2012; 3(1):35-41.
22. Trofimiuk M, Wasilewska K, Winnicka K. How to modify drug release in paediatric dosage forms? Novel technologies and modern approaches with regard to children's population, Int J Mol Sci 2019; 20(13): 3200. *https://doi.org/10.3390/ijms20133200*
23. Khanvilkar K, Donovan MD, Flanagan DR. Drug transfer through mucus. Adv Drug Deliv Rev 2001; 48(2-3):173-193.*https://doi.org/10.1016/S0169-409X(01)00115-6*
24. Rençber S, Yaprak S, Ferda F, *et al*. Formulation and evaluation of fluconazole loaded oral strips for local treatment of oral candidiasis, J Drug Deliv Sci Tech 2019; 49:615-621.*https://doi.org/10.1016/j.jddst.2018.12.035*
25. Boddupalli BM, Mohammed ZNK, Nath A. R, Banji D. Mucoadhesive drug delivery system: An overview. J Adv Pharm Tech Res; 2010:1(4):381-387. *http://dx.doi.org/10.13040/IJPSR.0975-8232.4(3).970-82*
26. Puratchikody A, Prasanth VV, Mathew ST, Kumar AB. Buccal drug delivery: past, present and future - A review. Int J Drug Deliv 2011; 1(2):171-184.
27. Salamat-Miller N, Chittchang M, Johnston TP. The use of mucoadhesive polymers in buccal drug delivery. Adv Drug Deliv Rev 2005;57:1666-1691. *https://doi.org/10.1016/j.addr.2005.07.003*
28. Fábregas JL, García N. *In vitro* studies on buccoadhesive tablet formulations of hydrocortisone hemisuccinate. Drug Dev Ind Pharm 1995:21(14): 1689-1696. *https://doi.org/10.3109/03639049509069258*
29. İkinci G, Şenel S, Wilson CG, Şumnu M. Development of a buccal bioadhesive nicotine tablet formulation for smoking cessation. Int J Pharm 2004: 277(1-2):173-8 *https://doi.org/10.1016/j.ijpharm.2003.10.040*
30. Nafee NA, Ismail FA, Boraie NA, Mortada LM. Mucoadhesive delivery systems. Evaluation of mucoadhesive polymers for buccal tablet formulation. Drug Dev Indu Pharm 2004; 30(9):985-993. *https://doi.org/10.4103/0975-7406.76478*
31. Kockisch S, Rees GD, Young SA, Tsibouklis J, Smart JD. Polymeric microspheres for drug delivery to the oral cavity: An *in vitro* evaluation of mucoadhesive potential. J Pharm Sci 2003; 92(8):1614-23.*https://doi.org/10.1002/jps.10423*
32. Pather SI, Rathbone MJ, Şenel S. Current status and the future of buccal drug delivery systems. Exp Opin Drug Deliv 2008;5(5):531-542. *https://doi.org/10.1517/17425247.5.5.531*
33. Marxen E, Jin L, Jacobsen J, Janfelt C, Hyrup B, Nicolazzo JA. Effect of permeation enhancers on the buccal permeability of nicotine: *ex vivo* transport studies complemented by MALDI MS imaging. Pharm Res 2018; 35(3):70.*https://doi.org/10.1007/s11095-017-2332-y*
34. Sharma D, Sharma A, Garg R. Design, development and *in vitro/ex vivo* evaluation of mucoadhesive buccal film of benzydamine hydrochloride for the effective treatment of *Aphthous Stomatitis*. Recent Patents Drug Deliv Form 2019; 12(4):277-294. *https://doi.org/10.3389/fphar.2019.01328*
35. Lee J, Kellaway IW. Buccal permeation of [D-Ala2, D-Leu5]enkephalin from liquid crystalline phases of glyceryl monooleate. Int J Pharm2000:195:35-38. *https://doi.org/10.1016/S0378-5173(99)00357-9*
36. Bernegossi J, Calixto GMF, Da Silva Sanches PR, *et al*. Peptide KSL-W-loaded mucoadhesive liquid crystalline vehicle as an alternative treatment for multispecies oral biofilm. Molecules 2016; 21(1):1-14. *https://doi.org/10.3390/molecules21010037*
37. Modi P, Mihic M, Lewin A. The evolving role of oral insulin in the treatment of diabetes using a novel Rapid Mist TM system. Diabetes/Metabolism Res Rev 2002; 18(1): 38-42. *https://doi.org/10.1002/dmrr.208*
38. Easa N, Alany RG, Carew M, Vangala A. A review of non-invasive insulin delivery systems for diabetes therapy in clinical trials over the past decade. Drug Disc Today 2019; 24(2):440-451. *https://doi.org/10.1016/j.drudis.2018.11.010*
39. Morales JO, Brayden DJ. Buccal delivery of small molecules and biologics: of mucoadhesive polymers, films, and nanoparticles. Current Opin Pharmacol 2017:36:22-28. *https://doi.org/10.1016/j.coph.2017.07.011*
40. Bhati R, Nagrajan RK. A detailed review on oral mucosal drug delivery system. Int J Pha Sci Res 2012; 3(03):659-681.*http://dx.doi.org/10.13040/IJPSR.0975-8232.3(3).659-81*
41. Wang C, Swerdloff R, Kipnes M, *et al*. New Testosterone Buccal System (Striant). Delivers physiological testosterone levels : pharmacokinetics study in hypogonadal men. The J Clin Endo Met 2015; 89:3821-3829. *https://doi.org/10.1210/jc.2003-031866*
42. Batchelor H. Novel bioadhesive formulations in drug delivery. The Drug Delivery Companies Report Autumn/Winter, Pharma Ventures Ltd. 2004. *https://doi.org/10.2147/CEG.S31404*
43. Al-Dhubiab BE. *In vitro* and *in vivo* evaluation of nano-based films for buccal delivery of zolpidem. Brazilian Oral Res 2016;30(1):e126. *https://doi.org/10.1590/1807-3107BOR-2016.vol30.0126*
44. Tangri P, Jawla S, Mishra R. Chronicles of pharmaceutical science constitution and assessment of nabumetone loaded buccal films. Chronicles Pharm Sci; 2019:4(1):22-29.
45. Somayaji BV, Jariwala U, Jayachandran P, Vidyalakshmi K, Dudhani R V. Evaluation of antimicrobial efficacy and release pattern of tetracycline and metronidazole using a local delivery system. J Periodont 1998:69(4):409-413. *https://doi.org/10.1902/jop.1998.69.4.409*
46. Taware CP, Mazumdar S, Pendharkar M, Adani MH, Devarajan P V. A bioadhesive delivery system as an alternative to infiltration anesthesia. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology Endodontics; 1997:84(6):609-615.
47. Hua S, de Matos MBC, Metselaar JM, Storm G. Current trends and challenges in the clinical translation of nanoparticulate nanomedicines: Pathways for translational development and commercialization. Frontiers Pharmacol 2018; 9:790.*https://doi.org/10.3389/fphar.2018.00790*
48. Hua S. Advances in nanoparticulate drug delivery approaches for sublingual and buccal administration. Front Pharmacol 2019; 10:1-9. *https://doi.org/10.3389/fphar.2019.01328*
49. Gilhotra RM, Ikram M, Srivastava S, Gilhotra N. A clinical perspective on mucoadhesive buccal drug delivery systems. J Biomed Res 2014; 28(2):81-97 *https://doi.org/10.7555/JBR.27.20120136*