Review Article

Technologies for the Improvement of Buccal Drug Delivery System

Sagar*
M.Pharm, Lloyd Institute of Management & Technology (Pharm) 11, Knowledge Park-II, Gr. Noida- 201306, India.
***Corresponding author's E-mail:** mauryasagar213@gmail.com

Received: 12-07-2019; **Revised:** 24-08-2019; **Accepted:** 03-09-2019.

ABSTRACT

Delivery of drug via oral cavity is an attractive region. Through this route, it is quite possible to exert local and systemic effects of drug after administration. Firstly, the main aim is to deliver the drug at the site of action to release the drug in the mucosa and secondly, it transports the drug through the mucosal membrane via crossing certain barriers and reaches into the systemic circulation. Problems such as high first pass metabolism, degradation of drug by certain enzymes present in the gastrointestinal tract arises when taken orally. To overcome this problem, delivery of drug through buccal region is adaptable. Buccal patches can improve the efficacy of drug and also increases the efficacy of drug. It can be removed if therapy is needed to be discontinued. The objective of this article is to development of formulation through different technologies.

Keywords: Oral cavity, Systemic circulation, Buccal patches, Technologies.

INTRODUCTION

For the intrinsic pharmacological effects, there are various types of routes available to produce the effects after the administration of drug. Amongst all the routes, the oral route is the most usual, common and preferable route for the administration of drug. The drug can be swallowed through this route and it enters into the systemic circulation primarily through the membrane of small intestine. Administration of drug is much easier as compared to the parental route due to ease of administration of the drug, it is the most routinely method.[1] Oral mucosal drug delivery system can be categorize into two parts one is buccal and other one is sublingual in both parts wide area is applicable for the administration of the drug through mucosal membrane which is present in the buccal cavity. In case of angina pectoris, it provides the fastest onset of action to produce the effect of drug. So, sublingual route is mostly preferred for the administration of drug.[2] Major advantage of buccal and sublingual route of administration is to bypass the first pass metabolism. So, drug can be utilized more efficiently. Within the oral mucosal cavity, especially the buccal region provides an effective route of administration of drug for systemic drug delivery.[3]

MUCOADHESIVES

Mucoadhesion is the process in which the non-covalent bonds are formed between the mucus gel layer and polymers such as hydrogen bonds and ionic interactions or physical entanglements.[4] If the polymer serves as mucoadhesives polymers, then it should possess some general physiochemical properties like: -

- It should possess anionic hydrophilicity containing numbers of hydrogen bond forming group.
- It should possess some surface property for wetting the mucosal tissue surface.
- To penetrate into the mucosal network tissue, it should possess some sufficient flexibility.[5]

Proteins and peptides based drugs are more sensitive drugs to the g.i.t. environment. These polymers offer protection to these types of sensitive drugs and it has also potential to increase bioavailability and decrease potential side effects. To reduce the toxic side effects, low concentration of drug can be used to absorb directly onto the target site. Both types of polymers (natural and synthetic) have potential to serve as mucoadhesive polymers.[6]

VARIOUS MUCOADHESIVES DRUG DELIVERY ROUTES

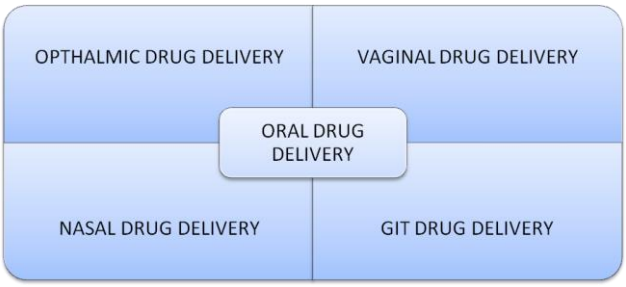

Figure 1: Diagrammatic representation of various mucoadhesives drug delivery system

Oral Drug Delivery System

For the administration of therapeutic agents, oral route still remains the perfect route for the administration because it has low cost of therapy and administration is easy, these two factors leads to the patient compliances.[7] It is the most preferable route for the drug administration, drug is swallowed and it enters into the systemic circulation. At least 90% drugs administered via oral route

to produce their systemic effect and it is cheap and best method for the self administration of medicaments.[8] In oral drug delivery system, the most common problem is associated with like:-

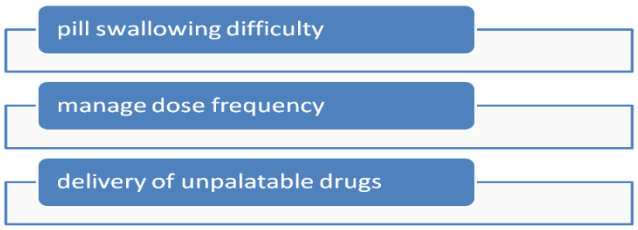

Figure 2: Diagrammatic representation of common problems associated with oral drug delivery system

Dysphasia, geriatric and pediatric type of patients are affected by pill swallowing difficulty. To overcome this problem, a new kind of dosage form has been developed {fast dissolving tablet (FDT)}, to eliminate the problem associated with swallowing difficulties. Oral disintegrating tablets (ODT) is also a new kind of dosage form, it has optimal strength and it disintegrate very rapidly in the oral cavity, and it takes upto 60 seconds to disintegrate. Now these days, over the conventional tablets, ODT gaining popularity because of their convenient and easy administration of drug and it is well suitable for the patients having dysphagia.[9] FDT and ODT type of dosage forms are modified release oral dosage forms these forms have brought new life into the drug. Because of the frequent dosing, toxicity related to the drug and its effect and G.I. disturbances, they lost their market values and potential. The term 'modified-release' drug is used to describe the product based on the principle of alter the rate of release the drug substances and timing of the drug or product. Several types of modified-release drug products are[10]**:-**

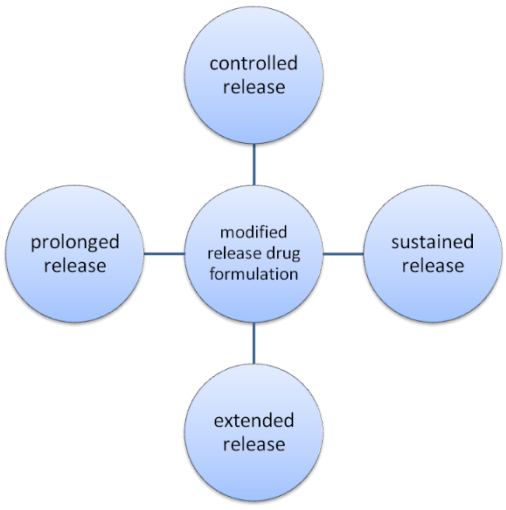

Figure 3: Diagrammatic representation of various types of modified release drug products

Controlled release dosage forms are those type of dosage form in which the release of drug (one or more) is continuously for a fixed period of time at predetermined pattern, either systemically or locally to specified target organ. The development of oral controlled-release drug delivery system grabs an attention towards it due to their flexible designing in dosage form. It provides effective and better level of drug and maintains the optimum drug concentration in plasma for prolonged duration of time with low dosing frequency and minimum side effects.[11] These formulations have some swelling properties because of the polymers or waxes or both and they control the release rate of drug. Reservoir system is also used for controlling the release rate of drug.[12]In many cases, it is still challenging problem to maintain a desired plasma level of drug after ingestion of drug product but at clinical level a stable drug plasma level is achieved after the oral administration of controlled release dosage form.[13]

Opthalmic Drug Delivery

For the treatment of numbers of eye disorders, application of the drug topically is well accepted and most popular method to administer the drug. The bioavailability is very poor of ophthalmic drugs due to the protective mechanism of the eye.[14] Newer, more sensitive diagnostic techniques and novel therapeutic agents provide high therapeutic efficacy associated with ocular drug delivery system. Solutions, suspension, and ointments these are the conventional ophthalmic formulations and they have many disadvantages one of them is major like poor bioavailability of drug. The main aim of designing a system for the achievement of an optimal concentration of drug at the active site of ocular system for the appropriate duration of time.[15]

New ocular drug delivery forms are:-

- *In-situ* gelling systems
- Liposome
- Nanoparticles
- Niosome
- Nanoemulsions
- Microemulsions

All these delivery forms are well suitable for hydrophilic or lipophilic drugs and they have the capacity to target at specific site and can be administered through different routes. In in-situ gelling system with appropriate excipients these systems became capable of increasing the precorneal residence time and also decrease the loss of the drug due to tears. For stable, effective and non-irritating formulations, nanoparticles are used to make product with different polymers, methods of preparation and composition for mucoadhesion, topical, periocular or intraocular administration.[16]

Table 1: List of commercially available ocular products

Brand Name	Chemical Salt	Manufacturer or Marketing Company	Use
Refresh tears eye drop	Carboxymethylcellulose	Allergen India Pvt. Ltd.	In dryness of eye and as eye lubricant
Restasis eye drop	Cyclosporine	Allergen	In dry eye
Acivir eye ointment	Acyclovir	Cipla	For eye infection

Vaginal Drug Delivery System

The vaginal site is traditionally used for the delivery of long acting drug because of the large surface area and great blood supply, it has a great potential for the systemic delivery of drug. The major advantage of the vaginal drug delivery system is to avoid the first pass metabolism that means the drug is directly enters into the systemic circulation. New controlled-release products currently being researched generally target the mucus-covered cervix, which can serve as a reservoir for such systems.[17] Vagina serves as a route for the administration of contraceptives, anti-fungal, and antimicrobials. It is also used for the achievement of local or systemic absorption. The vaginal wall is very well suited for the absorption of drugs for systemic use as it contains a vast network of blood vessels.[18]

The greatest advantage of such dosage forms is the possibility of maintaining them in the vagina for an extended period of time including day hours and night, thereby enabling lower dosing frequencies. A formulation given by this route as pessaries, vaginal tablets, inserts, cream, powders, douches, gel, etc.[19] Ideal vaginal drug delivery systems should be easy to use, discreet, of reversible application, painless to the patient, cost effective, widely available, and safe for continuous administration. It should also allow self-administration, with minimal interference with body functioning and daily life, and obtain high bioavailability with other medications.[20]The currently available vaginal dosage forms have certain limitations such as messiness, leakage and low residence time, leading to poor patient compliance and loss of therapeutic efficacy. Therefore, novel concepts and dosage forms are needed. Extensive research is ongoing to develop better vaginal drug delivery systems that can fulfill the user's requirements.[21]

Table 2: List of marketed products

Brand Name	Chemical Salt	Manufacturer Or Marketing Company	Use
Betadine vaginal pessaries	Povidone Iodine	Win-Medicare Pvt Ltd	Infection
Fenza vaginal capsule	Fenticonazole	Glenmark Pharmaceuticals Ltd	Fungal infections of vagina
Clingen vaginal suppository	Clindamycin + clotrimazole	Aristo pharmaceuticals pvt ltd	Syndromic treatment of vaginal discharge

Nasal Drug Delivery System

For the achieving of higher and faster absorption of drug, researchers have been selected the nasal mucosa as an alternate route of drug administration.[22] However olfaction is the primary function of nose, it humidifies and heats the inspired air and also filter the inspired air form airborne particulate. Apparently it has protective system against the foreign matter.[23] In the advancement of biotechnology field, proteins and peptide types of drugs are largely available for the treatment of variety of diseases but these types of drug are unsuitable in the gastrointestinal environment because it undergoes into the hepatic first pass metabolism and also degraded by the certain enzyme (digestive). Even, though the parentral route is not convenient for the long term therapy.[24] Nasal mucosa has a large surface area, it contains porous endothelial membrane which has high bold flow and the major advantage is avoidance of first pass metabolism and readily accessibility.[25]

In addition, this drug delivery system reduces the dose frequency, rapid achievement of therapeutic concentration of drug into the blood, rapid onset of action associated with fewer side effects.[26] It is a painless and non-invasive, it is not mandatory to sterile the preparation and also readily and easily administered by the patient: e.g. in an emergency cases, it also improves the delivery of non-lipinski drug.[27] In the Ayurvedic systems of medicine, it has been a recognized form of treatment it is also called "NASAYA KARMA".[28] Certain drugs are delivered to the nasal cavity because their intended site of action. These are administrated as nasal drops or sprays for a local effect. Such drugs in clinical use include decongestants, antibiotics and mucolytics.[29]

Table 3: List of nasal products available in market

Brand Name	Chemical Salt	Manufacturer or Marketing Company	Uses
Duonase nasal spray	Fluticasone propionate + azelastine	Cipla ltd	Sneezing and runny nose due to allergies
Avamys nasal spray	Glaxo smithkline pharmaceuticals ltd	Fluticasone furoate	Sneezing and runny nose due to allergies
Xyloflo nasal drops	Xylometazoline	Lupin	Relive stuffy nose

G.I.T. Drug Delivery System

The most famous route of administration for intrinsic action is an oral route. It is probable that at least 90% of all the drugs given by oral route in which the solid dosage form referred as the class of product.[30] Despite the enormous development in the drug delivery system for therapeutic agents, oral administration is still remains the most preferred route in the contrast of excellent accessibility, better patient compliances, painless and non-invasive route for the administration of drugs.[31] Because of the short gastric retention time (GRT), the absorption of drugs orally is often limited. GRT is the time required for the content enters into the small intestine from the stomach. Short half life of the drugs indicates that the drugs is easily absorbed from the GIT and also eliminate very quickly (blood circulation), this is the reason of frequent dosing.[32]

To overcome this problem, development of sustained-controlled release formulation to deliver the drug very slowly into the blood circulation and maintain effective concentration into the blood. Because it continuously supplied the drug at site of absorption and retained in the stomach for a long time.[33] But the satisfaction are yet to be blocked by the bash of short gastric retention time (GRT) and the uncertain hasty gastric rate may be permitted to induce partial drug release at the absorption site of the patient's body so, hindering the efficiency of the dosage.[34] Some factors play an important role in the absorption of drug like pH dependent solubility and stability because most of drugs are absorbed by passive diffusion in the unionized from. Ionization varies with pH; it can lead to the non uniform absorption. Due to presence of enzymes in GIT may lead to the alteration of absorption of drug.[35] GRDDs is one of the novel approach in this area in which dosage form can be retained on the stomach it is also a site specific drug delivery system for helping the absorption of drug for the longer period of time because it retained in the stomach.[36]. GRDDS are beneficial for such drugs by improving their[37]

- Bioavailability
- Therapeutics efficiency and
- Possible reduction of the dose.
- Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in the therapeutic levels
- Reduce drug wastage
- Improves solubility of drugs that are less soluble at high pH environment (e.g. weakly basic drug like domperidone, papaverine).
- The gastric motility pattern is systematized in cycles of activity as well as quiescence. The duration of each cycle is 90–120 min and it contains four phases, as mentioned in Table 4.[38]

Table 4: Four phases of migrating motor complex (MMC).

Phase	Description	Duration (min)
Phase I (basal phase)	Idle state without any contraction	30 to 60
Phase II (pre-burst phase)	Intermittent contraction	20 to 40
Phase III (burst phase)	The regular contraction at the maximal frequency causes the good material to migrate distally.	10 to 20
Phase IV	Transition period between phase III and phase I	0 to 5

Penetration Enhancer

These are the chemical compounds which are used to elevate the therapeutic effect of the drug at higher level via increase the permeability of stratum coneum.[39]

Ideal properties of chemical which are used as penetration enhancers should be[40]

- ➢ Safe
- ➢ Non-toxic
- ➢ Pharmacologically and chemically inert
- ➢ Non-irritant
- ➢ Non-allergenic

To improved efficiency and reduced toxicity profile is the main goal of penetration enhancer designing which is possibly done by understanding and correlate the enhancer structure, effect induced in the membrane and mechanism of action.

Physicochemical properties of drug, site of administration, nature of vehicle and excipients are the factors on this selection of enhancer and its efficacy depends.[41]

Associated with buccal drug delivery system the major disadvantage is the low bioavailability of drug because of the low flux of drugs across the mucosal epithelium. To increase the flux of drugs across the mucosal membrane various compounds have been used as penetration enhancer and absorption enhancers.[40]

Mechanism of penetration enhancer to improve the mucosal absorption.

- **Changing mucus rheology: -** thickness of viscoelastic layer which is formed by mucus affects drug absorption. Thickness of this layer is varying. Also Saliva alters the absorption by covering the mucus layer. To overcome this barrier, some penetration enhancers are capable of reducing the viscosity of mucus and saliva to improve the absorption.[42]
- **Increase the fluidity of lipid bilayer membrane: -** intracellular lipid packing disturbed by interaction with protein compounds or lipids.[43]
- **Acting of the component at tight junction: -** to overcome the enzymatic barrier problem, inhibiting the various peptidases and proteases which is present within the mucosal membrane.[44]
- **By enhancing the thermodynamic action of drugs: -** to enhanced the thermodynamic activity of the drug used some penetration enhancer to increase the solubility of the drug for better absorption by alter the partition coefficient.[45]

Enzyme Inhibitors

The environment of oral cavity and oral epithelium is highly enzymatic. This can cause degradation of drugs before they are delivered, therefore reducing bioavailability. In order to overcome this problem research has begun into the use of enzyme inhibitors. For example, use of enzyme inhibitors and permeability enhancer gluthaione to improve the delivery of pituitary adenylate cyclase activating polypeptide via a buccal delivery system for type 2 diabetes.[46]

Drug Delivery Vector

It may define as the drug molecule or an imaging payload may reach to the specific site of action to show their efficient action (therapeutic or diagnostic) and also to prevent their adverse effects. There are numbers of bio barriers present which is mainly composed of cells from different origin. So, the delivery of an active agent must cross these barriers to exert their action on target organs or locally.[47]The lipid bilayerd (plasma membrane) form boundary between the cell. So, the molecules firstly cross the oligosaccharides layer, it is made up of dense glycocalyx as thick as 2 µm for capillary endothelial cells. A sophisticated considerable role of the GAGs in uptake will be instrumental in the analytical development of delivery vectors with higher potency and also an option for certain cell types. Also a clear consideration of the dependence of GAG binding and proteins elaborate in delivery may enable a prediction of the tissue tropism of delivery vectors.[48]

Numbers of potent drugs are available in the market for the treatment of brain diseases. Therefore, they must be reached to site of action in order to cross the blood brain barrier (BBB). Only those drugs can cross the blood brain barrier which has small lipophilic molecules and they are able to permeate the BBB passively. Peptide based drug delivery vectors is an developing tool for the transport of substances to and fro across the BBB and one may analyze receptor-mediated transcytosis, adsorptive-mediated transcytosis, and the paracellular route. The latter, after all, being controversial due to the risk of co-delivery of blood-borne likely harmful substance.[49] Normally, an ideal delivery vector should possess several special properties, such as good biocompatibility, proper hydrophilicity, targeting specificity, low toxicity, high uptake efficiency, and so on However, all existing delivery systems have some inherent shortcomings more or less. For example, liposomes, which have been approved by US Food and Drug Administration (FDA) and widely used in clinics are easily degraded *in vivo* and their large size (>100 nm) will hinder the penetration and diffusion.[50]

Liposomes

In the view of their discovery more than 50 years ago, liposomes are achieving more and more popularity as a drug delivery tool for sophisticated therapeutic results. By definition, liposome is ‘‘a lipid vesicle or bubble in which aqueous compartments lie in the core or between the lipid bilayers and non-aqueous compartments also exist only in the lipid bilayers.[51] The discovery of phospholipids automatically forming spherical, self-closed bubbles known as liposomes, upon dispersion in water, guided a new age in drug delivery technology.[52] The role of bilayerd vesicles as competent carriers for drugs, vaccines, diagnostic agents and other bioactive agents have led to a rapid improvement in the liposomal drug delivery system.

Moreover, the site avoidance and site-specific drug targeting therapy could be achieved by formulating a liposomal product, so as to reduce the cytotoxicity of many potent therapeutic agent.[53]The therapeutic potency of the drug molecule is governed by the stability of the liposomes involving manufacturing steps, storage and delivery. A stable dosage form maintains the physical stability and chemical integrity of the active molecule during its developmental procedure and storage.[54] By coating the liposome shell with inert hydrophilic polymers such as polyethylene glycol (PEG), longer-circulating liposomes were produced that were shown to reduce adsorption of

various blood proteins and hence extend their circulation time. These were called stealth liposomes. Long circulating liposomes demonstrate dose-independent, non saturable, log-linear kinetics and increased bioavailability.[55]The first successful milestone in liposome-based products was the introduction of Doxil® to the U.S. market in 1995 for the treatment of patients with ovarian cancer and AIDS-related Kaposi's sarcoma after the failure of prior systemic chemotherapy or intolerance to such therapy. Gabizon and Barenholz commenced the development of Doxil® in Israel and the USA. It was the first nano-sized liposomal product to obtain regulatory approval.[56] Two important advantages of liposomes, in drug delivery of living organisms, are biocompatibility and biodegradability, which are due to lipid characteristics.[57] There are mainly two proposed pathways for enhancement of oral drug delivery by liposomes. The first is via drug release in the gastrointestinal lumen or via transformation of vesicles into mixed micelles, and subsequent permeation of drug molecules across the intestinal epithelia.[58]

Polymersomes

Amphiphiles are the substances that are used by controlling the weight of polymers, its polydispersity by controlling the polymer's molecular weight, polydispersity and relative hydrophilic to hydrophobic block ratio. The use of such amphiphilic block copolymers for generation of polymer vesicles, referred to as "polymersomes", has now become an attractive strategy to create stable and biocompatible structures for drug delivery applications.[59] As a new generation of the polymer-based colloidal carriers, polymersomes (Ps) have attracted rapidly growing interest . Ps are artificial vesicles that contain an aqueous solution in the core surrounded by a bi-layer membrane. The membrane can integrate hydrophobic drugs within its hydrophobic core. The possibility to load drugs into Ps has been highlighted for a number of applications in medicine, pharmacy, and biotechnology. It is well known that Ps is rather stable and that they may have rather long blood circulation times.[60]

On the other hand, compared with liposomes, polymersomes have many distinct properties, such as enhanced stability, lower permeability, membrane thickness, surface functionality and degradation kinetics.[61] Several methods have been used to prepare polymersomes, including the solvent-exchange method, film rehydration, electro formation, and the double-emulsion strategy. Electro formation has been used to construct giant polymersomes. Double emulsions (which have been prepared using capillary micro fluidics) are a reliable method for preparing polymersomes with acceptable monodispersity in size and uniformity in the bilayer membrane. Among these methods, the solvent-exchange method is widely used for its ease, reproducibility, and control over the size of nanoparticles. Although filter extrusion has been used to decrease the polydipersity index of liposomes, this method seems to be a very time consuming and difficult approach for polymersomes, even at elevated temperatures due to the polymersome membrane's robustness.[62]

Targeted Therapies

In a patient, drug biological effects are totally depends upon its own pharmacological properties. These effects are shown by the interaction between the drug and action site of the receptor at which the drug act. Although the efficacy of interaction between the drug and receptor depends upon the delivery of drug at the site of action on a such concentration at which it shown minimum side effects and maximum therapeutic effects because side effect and therapeutic efficacy are the major problem.[63] To overcome this problem, an effective approach is to development of targeted drug delivery systems through this system drug releases at the specific site of action. This could be leads to increase the patient compliance and improves the therapeutic efficacy of drugs or biological agents through improved pharmacokinetics and biodistribution.[64] Targeted drug delivery is an effective or smart drug delivery system for delivering the drug to the patient. Absorption of drug in this system through the biological membrane whereas the targeted release system release the drug in a dosage form.[65]

NPs are often used as a drug carrier, as they can deliver the chemotherapeutic agents to the targeted site of the tumor tissue without any damage of normal or healthy organs.

The ideal characteristics of NP carriers should be[66]

- biodegradable,
- stable,
- nonimmunogenic,
- easy to fabricate,
- cost-effective, and
- able to release their payloads only at the target site (

Drug targeting strategies divided into categories of "passive" and "active."

"**Passive targeting**" is based on accumulation that means the drug is accumulated at the site of tumor with leaky vasculature and covers the area around the tumor; this effect is commonly termed as enhanced permeation and retention (EPR) effect.

"**Active targeting"** is based on the interaction that means the interaction between the drug and drug carrier and target cells used to describe specific interactions usually through specific ligand–receptor interactions. The interaction between the ligand and receptor are possible only when the two components are having close proximity.[67]

Another targeted site for the delivery of drug into the systemic circulation is COLON at this site both local and systemic delivery of drug can take place. For the treatment of inflammatory bowel disease local delivery of drug allows topical application to treat that type of disease. Although,

for an effective treatment, it can be made if the drugs directly targeted into the colon thereby reducing the systemic side effects.[68] This site is also used for the systemic absorption of proteins and peptides due to the less proteolytic activity in colon mucosa than small intestine.[69]

CONCLUSION

In the past few decades, the growth and advancement in the research of buccal drug delivery has been remarkably noticed. The mucosa of buccal cavity provides several advantages over the other conventional method to deliver the drug in controlled manner for a prolong period of time. It is also bypass the first pass metabolism in the liver and it supplied very well lymphatic and vascular drainage both. It is safe for the patient because it can remove easily if adverse effects appear. The area is well favorable for retentive devices. This review focuses on the preparation of novel drug delivery system by using different technologies to provide the effective therapeutic results and reduce the chances of adverse effects.

REFERENCES

1. Kumar D, Rathi L, Tripathi A, Maddeshiya YP, A review on oral mucosal drug delivery system, International Journal of Pharmaceutical Science and Research, 1(5), 2010.
2. Bhati R, Nagrajan RK, A detailed review on oral mucosal drug delivery system, International Journal Of Pharmaceutical Science And Research, 3(3), 2012, 659-681.
3. Hooda R, Tripathi M, Kapoor Prof K, A review on oral mucosal drug delivery system, The Pharma Innovation, 1(1), 2012.
4. Andreas Bernkop-Schnurch, Mucoadhesive systems in oral drug delivery, Drug Discovery Today: Technologies I Drug Delivery formulation and Nanotechnology, 2(1), 2005, 83-87.
5. Vidyasagar N, Rao KM, Gnanaprakash K, Divya A, Sowjanya A, Gobinath M, A review on buccal drug delivery system, Journal of Pharmaceutical Research and Development, 1(2), 2012, 29-35.
6. Duggan S, Cummins W, Donovan OO, Hughes H, Owens E, Thiolated polymers as mucoadhesive drug delivery systems, European Journal of Pharmaceutical Sciences, doi: 10.1016/j.ejps.2017.01.008
7. Patil PC, Shrivastava SK, Vaidehi S, Ashwini P, Oral fast dissolving drug delivery system: a modern approach for patient compliance, International Journal of Drug Regulatory Affairs, 2(2), 2014, 49-60.
8. Yadav A, Singh T, Jain DK, Site specific oral drug delivery system, International Journal of Pharmaceutical Research Scholars, 2(4), 2013, 228-237.
9. Gupta H, Bhandari D, Sharma A, Recent trends in oral drug delivery: a review, Recent Patents on Drug Delivery & Formulation, 3(2), 2009, 162-173.
10. Rao N, Rao AA, Devi AS, Anil K, Naik VV, Rajesh A, Oral controlled release drug delivery system: an overview, International Journal of Pharma and Chemical Research, 1(1), 2015, 6-15.
11. Gahlyan M, Jain S, Oral controlled release drug delivery system- a review, Pharma Tutor Magazine, 2(8), 2014, 170-178.
12. Modi K, Modi M, Mishra D, Panchal M, Sorathiya U, Shelat P, Oral controlled release drug delivery system: an overview, Int. Res. J. Pharm., 4(3), 2013, 70-76.
13. Garbacz DH, Garbacz G, Eisenacher F, Klein S, Weitschies W, An oral controlled release drug delivery system for liquid and semisolid drug formulations, American Association of Pharmaceutical Scientists, 12(4), 2011, 1183-1185.
14. Ludwig A, The use of mucoadhesive polymers in ocular drug delivery, Advanced Drug Delivery Reviews, 57, 2005, 1595-1639.
15. Dhanpal R, Ratna JV, Occular drug delivery system- a review, International Journal of Innovative Drug Discovery, 2(1), 2012, 4-15.
16. Fessi H, Dubald M, Bourgeois S, Andrieu V, Ophthalmic drug delivery system for antibiotherapy- a review, Molecular Diversity Preservation International, 10(10), 2018, 1-31.
17. Sassi AB, Lisa CR, Vaginal drug delivery systems for HIV prevention, American Association of Pharmaceutical Scientists, 2(1), 2009, 78-87.
18. Sahoo CK, Nayak PK, Sarangi DK, Sahoo TK, Intra vaginal drug delivery system: an overview, American Journal of Advanced Drug Delivery, 1(1), 2013, 043-055.
19. Chatterjee A, Krishna SV, Ashok V, A review on vaginal drug delivery systems, International Journal of Biology, Pharmacy and Allied Sciences, 1(2), 2012, 152-167.
20. Neves JD, Bahia MF, Gels as vaginal drug delivery systems, International Journal of Phamaceutics, 318, 2006, 1-14.
21. Dobaria N, Mashru R, Vadia NH, Vaginal drug delivery systems: a reviews of current status, East and Central African Journal of Pharmaceutical Sciences, 10, 2007, 3-13.
22. Dey S, Mahanti B, Mazumder B, Malgope A, Dasgupta S, Nasal drug delivery: an approach of drug delivery through nasal route, Der Pharmacia Sinica, 2(3), 2011, 94-106.
23. Parmar H, Bhandari A, Shah D, Recent techniques in nasal drug delivery: a review, Int. Drug Dev. & Res., 2(3), 2010, 565-572.
24. Chhajed S, Sangle S, Barhate SD, Advantageous nasal drug delivery system: a review, International Journal of Pharmaceutical Sciences and Research, 2(6), 2011, 1322-1336.
25. Jadhav KR, Gambhire MN, Shaikh IM, Kadam VJ, Pisal SS, Nasal drug delivery system-factors affecting and applications, Current Drug Therapy, 2(1), 2007, 27-38.
26. Appasaheb PS, Manohar SD, Bhanudas SR, A review on intranasal drug delivery system, J. Adv. Pharm. Edu. & Res., 3(4), 2013, 333-346.
27. Upadhyay UM, Upadhyay S, Parikh A, Joshi P, Chotai NP, Intranasal drug delivery system- a glimpse to become maestro, Journal of Applied Pharmaceutical Science, 1(3), 2011, 34-44.
28. Alagusundaram M, Chengaiah B, Gnanaprakash K, Ramkanth S, Chetty CM, Dhachinamoorthi D, Nasal drug delivery system- an overview, Int. J. Res. Pharm. Sci., 1(4), 2010, 454-465.
29. Kumar SK, Varma MG, Vudaykiran A, Kumar RA, Sudhakar B, Nasal drug delivery system- an overview, International Journal of Pharmaceutical and Chemical Sciences, 1(3), 2012, 1358-1368.
30. Shaikh S, Molvi KI, Sayyed N, Various perspectives of gastroretentive drug delivery system: a review, American Journal of Advanced Drug Delivery, 1(4), 2013, 443-451.
31. Javadzadeh Y, Hamedeyazdan S, Novel drug delivery systems for modulation of gastrointestinal transit time, Research Gate, doi.org/10.57772/50250, 2014.
32. Shallusandhan, Satinderkakar, Singh R, Gastroretentive drug delivery systems: a review, Afr. J. Pharm. Pharmacol., 9(12), 2015, 405-417.
33. Nayak AK, Maji R, Das B, Gastroretentive drug delivery systems: a review, Asian Journal of Pharmaceutical and Clinical Research, 3(1), 2010, 2-10.
34. Sharma AR, Khan A, Gastroretentive drug delivery system: an approach to enhance gastric retention for prolonged drug release, International Journal of Pharmaceutical Sciences and Research, 5(4), 2014, 1095-1106.
35. Misra SK, Gastrointestinal targeting drug delivery system: a review, Journal of Pharmacy Research, 4(8), 2011, 2751-2754.

36. Kothiyal P, Badoni A, Ojha A, Gnanarajan G, Review on gastroretentive drug delivery system, The Pharma Innovation, 1(8), 2012, 32-42.
37. Nautiyal U, Jassal M, Kundlas J, Singh D, A review: gastroretentive drug delivery system(grdds), Indian Journal of Pharmaceutical and Biological Research, 3(1), 2015, 82-92.
38. Mandal UK, Chatterjee B, Senjoti FG, Gastro-retentive drug delivery systems and there *in vivo* success: a recent update, Asian Journal of Pharmaceutical Sciences, 11, 2016, 575-584.
39. Singh A, Sharma UK, Prajapati SK, A review on mucoadhesive buccal patches, International Journal of Research and Development in Pharmacy & Life Sciences, 6(4), 2017, 2654-2660.
40. Sharma S, Yogananda R, Buccal patches: boon to oral drug delivery system, Am. J. Pharm Tech Res., 2(6), 2012, 40-53.
41. Patel M, Karigar A, Savaliya P, Ramana MV, Dubal A, Buccal drug delivery system: the current interest, International Research Journal of Pharmacy, 2(12), 2011, 4-11.
42. Khan S, Parvez N, Sharma PK, Alam A, Warsi MH, Novel approaches-mucoadhesive buccal drug delivery system, Int. J. Res. Dev. Pharm. L. Sci., 5(4), 2016, 2201-2208.
43. Rao NGR, Sharvani B, Reddy MS, Overview on buccal drug delivery systems, J. Pharm. Sci. & Res., 5(4), 2013, 80-88.
44. Rao NGR, Neelgiri R, Reddy MS, Buccal patch as drug delivery system: an overview, 5(2), 2013, 40-47.
45. Javaid MU, Shahid S, Buccal patches: an advanced route of drug dosage delivery- a review, International Journal of Pharmacy & Pharmaceutical Research, 10(3), 2017, 206-216.
46. Thornhill MH, Hearnden V, Sankar V, Hull K, Juras DV, Greenberg M, Kerr AR, Lockhart PB, Patton LL, Porter S, New developments and opportunities in oral mucosal drug delivery for local and systemic disease, Advanced Drug Delivery Reviews, 64, 2012, 16-28.
47. Summers HD, Ware MJ, Majithia R, Meissner KE, Godin B, Rees P, Multiscale benchmarking of drug delivery vectors, Nanomedicine: Nanotechnology, Biology, and Medicine, 2016.
48. Favretto ME, Wallbrecher R, Schmidt S, Putte RVD, Brock R, Glycosaminoglycans in the cellular uptake of drug delivery vectors – by – standers or active players ?, Journal of Controlled Release, doi: 10.1016/j.jconrel.2014.02.011.
49. Brodin B, Kristensen M, Routes for drug translocation across the blood-brain barrier: exploiting peptides as delivery vectors, Journal of Pharmaceutical Sciences, doi: 10.1016/j.xphs.2017.04.080.
50. Zhigang J, Wei S, Drug delivery vectors based on filamentous bacteriophages and phage-mimetic nanoparticles, Drug Delivery, 24(1), 2017, 1898-1908.
51. Kim JS, Liposomal drug delivery system, Journal of Pharmaceutical Investigation, doi: 10.1007/s40005-016-0260-1, 2016.
52. Banerjee K, Banerjee S, Mandal M, Liposomes as a drug delivery system, Research Gate, doi: 10.1201/b18654-5, 2015.
53. Kalepu S, Kumar SKT, Betha S, Mohanvarma M, Liposomal drug delivery system- a comprehensive review, Int. J. Drug Dev. & Res., 5(4), 2013, 62-75.
54. Dutta RK, Yadav D, Kumar S, Pandey D, Liposomes for drug delivery, J Biotechnol Biomater, 7(4), 2017, 1-8.
55. Zylberberg C, Matosevic S, Pharmaceutical liposomal drug delivery: a review of new delivery systems and a look at the regulatory landscape, Drug Delivery, 23(9), 2016, 3319-3329.
56. Khan W, Bulbake U, Doppalapudi S, Kommineni N, Liposomal formulations in clinical use: an updated review, Molecular Diversity Preservation International, 9(12), 2017, 1-33.
57. Alavi M, Karimi N, Safaei M, Application of various types of liposomes in drug delivery systems, Advanced Pharmaceutical Bulletin, 7(1), 2017, 3-9.
58. Wei W, Haisheng H, Yi L, Jianping Q, Quangang Z, Zhongjian C, Adapting liposomes for drug delivery, Acta Pharmaceutica Sinica B, 9(1), 2019, 36-48.
59. Kumar N, Jain JP, Ayen WY, Self assembling polymers as polymersomes for drug delivery, Current Pharmaceutical Design, 17(0), 2011, 1-15.
60. Feijan J, Lee JS, Polymersomes for drug delivery: Design, formation and characterization, Journal of Controlled Release, 161, 2012, 473-483.
61. Qian, ZY, Liao JF, Wang C, Wang YJ, Luo F, Recent advances in formation, properties, and applications of polymersomes, Current Pharmaceutical Design, 18, 2012, 3432-3441.
62. Mallik S, Anajafi T, Polymersome-based drug-delivery strategies for cancer therapeutics, HHS Public Access, 6(4), 2015, 521-534.
63. Mishra N, Pant P, Porwal A, Jaiswal J, Samad A, Tiwari S, Targeted drug delivery: a review, Am. J. Pharm Tech Res.,. 6(1), 2016, 1-24.
64. Patel MP, Patel RR, Patel K, Chitosan mediated targeted drug delivery systems: a review, J. Pharm Pharmaceut Sci, 13(3), 2010, 536-557.
65. Rani K, Paliwal S, A review on targeted drug delivery: its entire focus on advanced therapeutics and diagnostics, Scholars Journal of Applied Medical Sciences, 2(1C), 2014, 328-331.
66. Yu X, Trase I, Ren M, Duval K, Guo X, Chen Z, Design of nanoparticle-based carriers for targeted drug delivery, Jounal of Nanomaterials, 16(1D), 2016, 1-16.
67. Park K, Bae YH, Targeted drug delivery to tumors: myths, reality and possibility, NIH Public Access, 153(3), 2011, 198-205.
68. Philip AK, Philip B, Colon targeted drug delivery systems: a review on primary and novel approaches, 25, 2010, 70-78.
69. Sharma N, Harikumar SL, Polymers for colon targeted drug delivery: a review, International Journal of Drug Development & Research, 5(1), 2013, 21-31.

Source of Support: Nil, **Conflict of Interest:** None.