IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A Comprehensive Review on Mucoadhesive Buccal Drug Delivery System

RATNAM HEMALATHA
M. Pharm
Hanamkonda – 506009

ABSTRACT

The use of mucoadhesive drug delivery systems is a promising innovation in the field of pharmaceuticals. Mucoadhesive drug delivery systems are particularly relevant for getting local and systemic drugs distribution in the Gastro Intestinal Tract (GIT) for a prolonged period of time at a predetermined rate. This is in contrast to oral controlled release drug delivery systems, which are often subject to extensive presystemic metabolism and degradation in the acidic environment of the stomach, resulting in insufficient absorption of the drugs. One of the advantages of mucoadhesive drug delivery systems is that they allow for direct passage of medication into the systemic circulation through the buccal mucosa, which is the lining of the mouth. This results in easy administration without pain, brief enzymatic activity, less hepatic metabolism, and higher bioavailability of the drug. Additionally, mucoadhesive drug delivery systems do not require extensive patient compliance or supervision, as is often the case with parental drug delivery systems.The mechanism of mucoadhesion involves the interaction between the mucoadhesive polymer and the mucus layer of the mucosal surface. Mucoadhesive polymers are designed to adhere to the mucosal surface and remain in place for an extended period of time, allowing for a sustained release of the drug. In-vitro and in-vivo mucoadhesion testing techniques are used to evaluate the efficacy of the mucoadhesive drug delivery system.In summary, mucoadhesive drug delivery systems offer several advantages over traditional oral controlled release and parental drug delivery systems, including higher bioavailability of the drug, ease of administration, and sustained release. Further research is needed to optimize the design of mucoadhesive drug delivery systems and to fully understand their potential in the field of pharmaceuticals.

Keywords: Buccal drug delivery system, Mucoadhesive drug delivery system, Mucoadhesion, mucoadhesive polymers, Permeation enhancers, Bioadhesive polymers.

INTRODUCTION

The development of the dosage form took place not by chance but by need. The developed dosage form should meet the needs of the patient and act efficiently, stable and economical and releases the drug to the desired location with least side effects [1]. Earlier there were conventional dosage forms that were prepared but recently they were replaced with NDDS, these generated positive outputs by increasing the life of the drug. Now NDDS is not just theory, extensive work is going on in all possible ways where it can be suitable and advantageous, one among them is buccaladhesive drug delivery system [2, 3 and 4].

There were many routes by which the NDDS can be administered but most preferred is oral route because of its high rate of acceptability and reproducibility. There were even some setbacks for oral route but these were not as much influenced during the phenomena of drug release.

Buccaladhesive delivery of drugs

The exceptional features of oral mucosa make it a feasible site for sustained release delivery systems, which could maintain a steady release of drug in the systemic circulation [5]. Various delivery approaches have been developed to deliver drugs into the oral cavity for either local or systemic action. These include mouthwashes, lozenges, gels, chewing gums, lollipops, films, patches, tablets and some specialized transmucosal devices [6].

The simplest and oldest dosage forms are lozenges and mouthwashes. The drug is constantly washed away by a considerable amount of saliva from these non-attached delivery systems resulting into initial burst effect followed by a rapid decrease in concentrations to below therapeutic levels [7]. Moreover, the dosage form must be palatable for a better patient compliance. Likewise, ordinary gels, pastes and even dosage forms for sustained release through buccal mucosa [8] such as medicated chewing gums, medicated lollipops and lozenges could not overcome the salivary scavenging effect. To overcome these limitations, delivery systems designed to remain in the buccal mucosa for prolonged periods based on the concept of bio/mucoadhesion have been developed [9].

BIOADHESION

It is the phenomenon in which a synthetic or natural macromolecule adheres to a biological tissue, which can be an epithelial surface or a mucus layer covering a tissue, and is held together for long periods of time by interfacial forces [10]. Several steps were involved in this phenomenon during bond formation [11]. The phenomena of polymer adherence to mucosal surfaces were not clearly described, and five theories for buccaladhesion were proposed [12]. Adsorption, diffusion, wetting, fracture, and electronic theories are all shared by all.

BUCCALADHESIVE POLYMERS

There are several advantages to using bioadhesive formulations over traditional drug delivery methods. They can prolong drug residence time at the site of application, resulting in more sustained and controlled drug release. They can also reduce dosing frequency, which improves patient compliance and lowers the risk of side effects. The choice of polymer is critical in the development of effective bioadhesive formulations. The polymer should be biocompatible, non-toxic, and capable of forming strong bonds with biological surfaces. Chitosan, hyaluronic acid, and polycarbophil are examples of polymers commonly used in bioadhesive formulations.

Bioadhesive formulations can be used in a variety of applications, such as drug delivery, wound healing, and tissue engineering. For example, bioadhesive patches can be used to deliver drugs through the skin or mucosal membranes, while bioadhesive gels can be used to promote wound healing or to coat surgical implants to prevent infection.

Overall, bioadhesive formulations have the potential to revolutionize drug delivery and other biomedical applications by providing more effective, targeted, and long-lasting treatments. The use of bioadhesive formulations has become increasingly popular in drug delivery and tissue engineering applications, as they can help to improve the efficacy and bioavailability of drugs, and can provide a scaffold for tissue regeneration. [13]. Bioadhesive polymers are designed to adhere to biological tissues, such as mucosal membranes, and deliver drugs or other therapeutic agents.

The key physicochemical features that make a polymer bioadhesive include:

Hydrophilicity: Bioadhesive polymers need to be hydrophilic, or water-loving, in order to interact with the moist surfaces of biological tissues. This helps to promote adhesion and improve the contact time of the drug or therapeutic agent with the tissue.

Hydrogen bond-forming groups: Many bioadhesive polymers contain functional groups that can form hydrogen bonds with the mucin glycoproteins in mucus, or with other biomolecules on the surface of the tissue. This helps to strengthen the adhesion and prolong the residence time of the drug or therapeutic agent.

Flexibility: Bioadhesive polymers need to be flexible and able to interpenetrate with the mucus or epithelial tissue in order to form a strong bond. This can help to increase the surface area of contact between the polymer and the tissue, leading to better adhesion.

Visco-elastic properties: Bioadhesive polymers should have visco-elastic properties, which means they can deform under stress and recover their shape when the stress is removed. This can help the polymer conform to the irregular surface of the tissue and maintain contact for a longer period of time. [14].

Basically, adhesive polymers can be classified as natural or synthetic, water-soluble or water insoluble, charged or uncharged polymers. A wide range of polymers were investigated as buccaladhesive in order to enhance buccal drug absorption by increasing the contact with the buccal mucosa for prolonged periods.

Drug delivery through the membranes of the oral cavity may be sub classified as follows [5]:

- Sublingual drug delivery system delivered the drug through mucosal membrane lining the floor of mouth into blood circulation.
- Buccal drug delivery system delivered the drug through mucosal membrane into blood circulation by putting a drug in between cheeks and gums.
- Local drug delivery system delivered the drug into the oral cavity.

MEASUREMENT OF BUCCALADHESIVE STRENGTH

Various tests were performed to ensure compatibility, physical and mechanical stability, surface analysis, and bioadhesive bond strength, including swelling, viscosity, temperature effect on viscosity, shear stress strength, buccal adhesive strength, falling sphere method, and detaching force measurement. All of these will provide information about the polymers used in the formulation.

Contact stage:

An intimate contact (wetting) takes place among the mucoadhesive and mucus membrane both from a decent wetting of the bioadhesive and a membrane or from the swelling of bioadhesive.

Consolidation stage:

Various physicochemical interactions such as hydrogen bonding, hydrophobic interactions and dispersion forces, takes place to consolidate and give a boost to the adhesive joint, leading to prolonged adhesion [6].

Structure and Design of Buccal Dosage Form:

Buccal Dosage form may be of [7]:

a. Matrix type: The design of buccal patch is a matrix configuration incorporates drug, adhesive, and components mixed together.

b. Reservoir type: In a reservoir system the design of buccal patch include a cavity for a drug and components separate from the adhesive. To prevent the loss of drug, to reduce deformation of patch and disintegration while in the mouth; and to control the direction of drug delivery an impermeable backing is applied.

IDEAL CHARACTERISTICS OF BUCCAL ADHASIVE DRUG DELIVERY SYSTEM [8]:

- Should facilitate the rate of drug absorption
- Should not cause any inconvenience or irritation to the patient
- Should stick to the site of attachment for a few hours
- Should discharge the medication in a controlled manner and
- Should allow the release of medication in an unidirectional way toward the mucosa

Classification of Buccal Bioadhesive Dosage Forms: [9, 10]

Buccal Bioadhesive Tablets:

Buccal bioadhesive tablets are dry dosage forms that must be moistened before being applied to the buccal mucosa. Bioadhesive polymers and additives are already used to make double and multilayered tablets. These tablets are solid dosage forms formed by direct compression of powder that can be placed in contact with the oral mucosa and allowed to dissolve or adhere depending on the type of additives included in the dosage form. This dosage form can deliver drugs to the mucosal surface or the oral cavity in multiple directions.

Buccal Bioadhesivc Semisolid Dosage Forms:

This dosage forms contain natural or synthetic polymers in powdered form which is dispersed in a polyethylene or in aqueous solution.

For example: Arabase.

Buccal Bioadhesive Patches and Films:

This films or patches include multilayered thin film or two poly laminates that are oval or round in shape, containing of basically of bioadhesive polymeric layer and impermeable backing layer to allow unidirectional flow of drug across buccal mucosa. These films are prepared by incorporating the medicament in alcohol solution of bioadhesive polymers.

Buccal Bioadhesive Powder Dosage Forms:

This dosage forms are a mixture of the drug and bioadhesive polymers and are sprayed onto the buccal mucosa the reduction in diastolic blood pressure after the administration of buccal film and buccal tablet of Nifedipine.

Advantages of buccal drug delivery system [11]:

- Drug is effortlessly administered and extinction of therapy in emergency may be facilitated.
- Drug release for prolonged duration of time.
- In unconscious and trauma patient's drug can be administered.
- Drug has high bioavailability because it bypass first pass metabolism.
- Some drugs are unstable in acidic environment of stomach can be administered by buccal delivery.
- Drug absorption occurs by passive diffusion.
- Due to close contact with the absorbing membrane surface, rate of absorption is high.
- Fast onset of action.

Limitations of buccoadhesive drug delivery [12]:

- Drugs which are unstable at buccal pH cannot be administered.
- Drug having unpleasant and bitter taste or an nauseating odor or causes irritation cannot be given by this route
- Drug having small quantity or dose can only be given by this route.
- Drugs which are required to be absorbed by passive diffusion only can be given by this route.
- Drinking and eating may be avoided.

Factors affecting mucoadhesion [13]:

- Polymer related factors: Several properties or characteristics of the active polymer play a vital role in mucoadhesion. Among them, concentration, swelling, polymer molecular weight, particular confirmation and polymer chains flexibility that may affect the mucoadhesion.

- Environment associated factors: pH of the polymer-substrate interface, functional strength and first contact time is able to influence the mucoadhesion.

- Physiological factors: Disease state and mucin turn over are the important physiological factors, which can also affect mucoadhesion.

Basic components of buccal drug delivery system are:

a. DRUG SUBSTANCE:

Before developing mucoadhesive drug delivery systems, it is necessary to determine whether the intended action is for local or systemic effect, as well as for rapid or prolonged release. Pharmacokinetic properties are critical in the selection of appropriate drugs for the design of buccoadhesive drug delivery systems.The drug should have following characteristics [14].

- The conventional single dose of the drug should be very less.
- The drugs having biological half-life between 2-8 hrs are suitable candidates for controlled drug delivery.
- Tmax of the drug shows many changes or higher values when administered orally.
- Through oral route drug may exhibit first pass effect or presystemic drug elimination.
- When administered orally the drug absorption should be passive.

b. BIOADHESIVE POLYMER:

The characterization and selection of suitable bioadhesive polymers in the formulation is the first step in the formulation of buccoadhesive dosage forms. Bioadhesive polymers are crucial in buccoadhesive drug delivery systems. Polymers are also used in matrix devices, which enclose the drug in a polymer matrix and control the duration of drug release. [15]. Bioadhesive polymers are the most diverse class of polymers, and they have a wide range of applications in patient health care and treatment. The drug enters the mucous membrane via the core layer or rate controlling layer. Bioadhesive polymers that adhere to the epithelial or mucin surface are effective and improve the oral drug delivery system significantly. [16].

c. BACKING MEMBRANE:

The backing membrane is critical in the attachment of bioadhesive devices to the mucus membrane. The backing membrane materials should be inert to the penetration enhancer and drug. This impermeable membrane on buccal bioadhesive patches prevents drug loss and ensures patient compliance. Magnesium stearate, HPC, polycarbophil, HPMC, CMC, carbopol, and other materials are used in backing membranes. [17].

d. PERMEATION ENHANCERS:

Permeation enhancers are agents that allow permeation through the buccal mucosa. The choice of permeation enhancer and its efficacy are determined by the drug's physicochemical properties, the nature of the vehicle, the site of administration, and other additives. [18].

EVALUATION OF BUCCAL DRUG DELIVERY SYSTEMS:

Drug-excipients interaction studies

Drug-excipient interaction studies are important during the formulation and development of solid dosage forms. To evaluate potential drug excipient interaction studies Differential scanning calorimeters (DSCs), X-ray diffraction (XRDs), Fourier Transform Infrared Spectrum (FTIRs), and thin layer chromatography are all options. Differential scanning calorimeters are used for quick evaluation of potential incompatibilities because they show shifts in melting endotherms and exotherms, changes in appearance, and variations in the corresponding reaction enthalpies. [19].

Physical evaluation

It consists of three components: content uniformity, weight uniformity, and thickness uniformity. Weight variation was assessed by comparing the average weight of ten randomly selected patches from each batch to the weight of an individual patch. The thickness of the film should be measured in five places (the centre and four corners) and the mean thickness calculated. Samples with nicks or tears, air bubbles, or a mean thickness variation of more than 5% are excluded from analysis. Three patches having diameters 20 mm of each formulation were taken separately in 100 ml volumetric flasks, 100 ml phosphate buffer solution having pH 6.8 were added and stirred continuously for 24 hours. The solutions were filtered, diluted suitably and analyse by using UV spectrophotometer. The average of three patches was taken as final reading [20].

Surface pH

The surface pH of the buccal patch was determined to investigate the possibility of any in-vivo side effects. Because a basic or acidic pH can irritate the buccal mucosa, it is critical to keep the surface pH as close to neutral as possible. [21]. A combined glass electrode was used for this purpose. The buccal patches were kept in contact with 1 ml of distilled water (pH 6.5 ± 0.05) and allowed to swell for two hours at room temperature and pH was noted down by bringing the electrode in contact with the surface of the patch and allowing it to equilibrate for 1 minute [22]. **Swelling studies**

Swelling increases the weight of patch:

A drug-loaded patch of 1x1 cm^2 was kept and weighed on a pre weighed cover slip, and then 50 ml of phosphate buffer (pH 6.6) was added. The cover slip was removed after every five minutes and weighed upto 30 minutes. The difference in the weights gives the weight increase due to absorption of water and swelling of patch [23].

Ex vivo mucoadhesive strength

For determining ex vivo mucoadhesive strength a modified balance method is used. Fresh buccal mucosa of rabbit or sheep obtained and used within 2 hours of slaughter. The mucosal membrane separated by separating underlying fat and loose tissues. The mucosal membrane were washed with distilled water and then with phosphate buffer (pH 6.8) at 370 °C. The buccal mucosa cut into small pieces and again washed with phosphate buffer (pH 6.8). A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer. The two side of the modified balance was made equal before the study, by putting a 5 g weight on the right-hand side of pan. A weight of 5 g was removed from the right-hand side of pan, which lowered the pan along with the

tablet over the mucosa. The balance was kept for 5 minutes contact time in this position. Equivalent to weight, the water was added at a slow rate with an infusion set of 100 drops per minute to the right-hand side of pan until the tablet detached from the mucosal surface. This detachment force gave the knowledge of mucoadhesive strength of the buccal tablet in grams. The glass vial was tightly fitted into a glass beaker filled with phosphate buffer (pH 6.8) at 37 °C ± 1 °C due to which it only touch the mucosal surface. The buccal tablet was stuck to the lower side of a rubber stopper with cyanoacrylate adhesive [26].

Ex- vivo mucoadhesive time

The ex vivo mucoadhesion time performed after application of the buccal patch on freshly cut buccal mucosa of sheep or rabbit. The fresh buccal mucosa was tied on the glass slide, and a mucoadhesive core side of each tablet was wetted with 1 drop of phosphate buffer (pH 6.8) and pasted to the sheep buccal mucosa by applying a light force with a finger tip for 30 seconds. The glass slide was then put in the beaker, which was filled with 200 ml of the phosphate buffer having pH 6.8, and kept at 37 °C ± 1 °C. A 50 rpm stirring rate was applied after two minute to simulate the buccal cavity environment, and tablet adhesion was monitored for 12 hours. The time taken for the tablet to detach from the buccal mucosa was noted as the mucoadhesion time [27].

In vitro drug release

United States Pharmacopoeia (USP) XXIII rotating paddle method used to study the drug release rate from the bilayered and multilayered tablets. The dissolution medium consist of phosphate buffer pH 6.8. The study was performed at 37 °C ± 0.5 °C, with a rotation speed of 50 rpm. The backing layer membrane of buccal tablet attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The disc was assigned to the dissolution vessel's bottom. At predetermined intervals, 5 ml samples were removed and replaced with fresh medium. The samples were filtered through Whatman filter paper and analysed by UV spectrophotometry at appropriate nm after appropriate dilution. [28].

In vitro drug permeation

Using Keshary-Chien or Franz type glass diffusion cell, the in vitro buccal drug permeation study of Drugs through the buccal mucosa of sheep or rabbit is performed at 37°C ± 0.2°C. It includes the donor and receptor compartments in which a fresh buccal mucosa was tied. The core side of the buccal tablet was facing the mucosa and the compartments clamped together. One ml phosphate buffer (pH 6.8) is placed in donor compartment and phosphate buffer (pH 7.4) is placed receptor compartment. The hydrodynamics condition was maintained in receptor compartment by stirring with a magnetic bead at 50 rpm. At a predetermined interval of time one ml sample can be withdrawn and test for drug content at suitable nm using a UV spectrophotometer [29].

Stability study in Human saliva

All batches are subjected to a stability study of fast dissolving films in accordance with ICH guidelines. The films were evaluated for disintegration time, drug content, and physical appearance after a predetermined time interval. The stability study of optimized mucoadhesive patch formulation was performed at 40 °C, 37 ± 5 °C & 75 ± 5 % RH upto three months. After three months, the values of all parameters remained the same, with minor changes occurring in the values of volume entrapment efficiency,% elongation, and% drug release after eight hours, which were significant. [30]**.**

Measurement of mechanical properties

The mechanical properties of the patches were evaluated using a microprocessor-based advanced force gauze and a motorised test stand (Ultra Test, Mecmesin, West Sussex, UK) with a 25kg load cell. A film strip with dimensions of 60 x 10 mm and no visible flaws was cut and positioned between two clamps separated by 3 cm. Clamps were designed to secure the patch without crushing it during testing; the strips were pulled apart by

the upper clamp moving at a rate of 2 mm/sec until the strip broke, while the lower clamp remained stationary. The film's force and elongation at the point where the strip broke were recorded. The tensile strength and elongation at break values was calculated using the formula [31].

$$\text{Tensile strength (kg. mm}^{-2}) = \frac{\text{Force at break (kg)}}{\text{Initial cross sectional area of the sample (mm}^2)}$$

$$\text{Elongation at break (\%. mm}^{-2}) = \frac{\text{Increase in length (mm)}}{\text{Original length Cross sectional area (mm}^2)} \times 100$$

Folding endurance

Folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times manually, which was considered satisfactory to reveal good patch properties. The number of times the patch could be folded at the same place without breaking gives the value of the folding endurance. This test is done on five patches [32].

Viscosity

Aqueous solutions containing both plasticizer and polymer prepared in the same concentration as that of the patches. A model LVDV-II Brookfield viscometer attached to a helipath spindle number four is used. The viscosity was measured at 20 rpm at room temperature. The recorded values the mean of three determinations [33].

Ageing

Bioadhesive patches were packed in petri dish lined with aluminum foil and placed in an incubator maintained at 37 ± 0.5 °C and 75 ± 5 % RH for six months. Changes in the release behavior, residence time, appearance, and drug content of the stored patches tested after 1, 2, 3, 4, 5 and 6 months. The data presented the mean of three determinations. Fresh and aged medicated patches, after 6 months storage, investigated using scanning electron microscope [34].

CONCLUSION:

Mucoadhesive buccal drug delivery system could be useful for designing newer or novel mucoadhesive dosage forms. The article could provide valuable information on the different mucoadhesive polymers, their characteristics, and their potential applications in drug delivery systems. Additionally, the article may provide insights on the formulation and evaluation of mucoadhesive dosage forms, as well as the factors affecting their mucoadhesive properties and drug release kinetics. All of these pieces of information could be beneficial for developing more effective and efficient mucoadhesive drug delivery systems that could improve patient compliance and therapeutic outcomes. Mucoadhesive dosage form has applications from various edges, including advancement of novel mucoadhesives, layout of the device, permeation enhancement and mechanisms of mucoadhesion. With the introduction of an enormous number of latest drug molecules because of medication revelation, mucoadhesive drug delivery will play a much progressively significant function in delivering these molecules.

REFERENCES:

1. Bhatt DA, Pethe AM. Mucoadhesive drug delivery systems: an overview. J Pharm Res 2010;3:1743-47.

2. Sayani AP, Chien YW. Systemic delivery of peptides and proteins across absorptive mucosae. Critical reviews in therapeutic drug carrier systems. 1996;13(1-2):85-184.

3. Alur HH, Johnston TP, Mitra AK. Encyclopedia of Pharmaceutical Technology, in: J. Superbrick, J.C. Boylan (Eds.), Peptides and Proteins: Buccal Absorption, Marcel Dekker Inc., New York. 2001;20: 193–218.

4. Senel S, Kremer M, Katalin N, Squier C. Delivery of bioactive peptides and proteins across oral (buccal) mucosa. Current Pharmaceutical Biotechnology. 2001 Jun 1;2(2):175-86.

5. Gandhi PA, Patel MR, Patel KR, Patel NM. A review article on mucoadhesive buccal drug delivery system. International Journal of Pharmaceutical Research and Development. 2011, Jul;3(5):159-73.

1. 6. Phanindra B, Moorthy BK, Muthukumaran M. Recent advances in mucoadhesive/bioadhesive drug delivery system: A review. International Journal of Pharma Medicine and Biological Sciences. 2013;2(1):68-84.

6. Rao NR, Shravani B, Reddy MS. Overview on buccal drug delivery systems. Journal of Pharmaceutical Sciences and Research. 2013 Apr 1;5(4):80.

7. Ducheˇne D, Touchard F, Peppas NA. Pharmaceutical and medical aspects of bioadhesive systems for drug administration. Drug development and industrial pharmacy. 1988 Jan, 1;14(2-3):283-318.

8. Mujorruya R, Dhamande K, Wankhede UR, Dhamande K. A review on study of buccal drug delivery system: Innovative System Design and Engineering.

9. Patel VF, Liu F, Brown MB. Advances in oral transmucosal drug delivery. Journal of controlled release. 2011 Jul 30;153(2):106-16.

10. Satyabrata B, Ellaiah P, Choudhury R, Murthy KV, Bibhutibhusan P, Kumar MS. Design and evaluation of methotrexate buccal mucoadhesive patches. Int J Pharm Biomed Sci. 2010;1(2):31-6.

11. Patil BS, Tate SS, Kulkarni U, RC H WG. Development and in-vitro evaluation of mucoadhesive buccal tablets of Tizanidine hydrochloride using natural polymer xanthan gum. Int J Pharm Sci. 2011;8(2):140-6.

12. Gandhi RB, Robinson JR. Bioadhesion in drug delivery. Indian Journal of Pharmaceutical Sciences. 1988 May 1;50(3):145.

13. Edsman K, Hägerström H. Pharmaceutical applications of mucoadhesion for the non oral routes. Journal of pharmacy and pharmacology. 2005 Jan;57(1):3-22.

14. Steward A, Bayley DL, Howes C. The effect of enhancers on the buccal absorption of hybrid (BDBB) α-interferon. International journal of pharmaceutics. 1994 Apr 11;104(2):145-9.

15. Vaughan DF. Pharmacokinetics of albuterol and butorphanol administered intravenously and via a buccal patch (Doctoral dissertation, Texas A&M University).

16. Wise DL. Handbook of pharmaceutical controlled release technology. CRC Press; 2000 Aug 24.

17. Indian Journal of Pharmaceutical Science, July-Aug. 2004; 66 (4): 371-536:556-562.

18. Repka MA, Repka SL, McGinity JW, inventors; Mcginity James W., assignee. Bioadhesive hot-melt extruded film for topical and mucosal adhesion applications and drug delivery and process for preparation thereof. United States patent US 6,375,963. 2002 Apr 23.

19. Anujkumar V, Naveen P, KumudPadhee M, Neeta S. Formulation development & evaluation of carvedilol bioerodible buccal mucoadhesive patches. Pharmacie Globale. Int J Comprehensive Pharm. 2011;3(7):1-5.

20. Miller NS, Johnston TP. The use of mucoadhesive polymers in buccal drug delivery, Advanced Drug Delivery Reviews 2005;57:1666–91.

21. Vishnu MP, Bhupendra GP, Madhabhai MP. Design and in vitro characterization of eudragit containing mucoadhesive buccal patches. Int J PharmTech Res2009; 1(3):783-9.

22. Ching HS. Bioadhesive polymers as platforms for oral controlled drug delivery II: Synthesis and evaluation of some swelling, water- insoluble bioadhesive polymers. J Pharm Sci 1985; 74(4):399–405.

23. Coutel EA, Maitani Y, Veillard M, Machida Y, Nagai T. Combined effects of pH, cosolvent and penetration enhancers on the in vitro buccal absorption of propranolol through excised hamster cheek pouch. Int J Pharm, 1992; 84:117-28.

24. Patel R, Shardul N, Patel J, Baria A. overview on buccal mucoadhesive films. Arch Pharm Sci & Res 2009; 1(2):212-7.

25. Khairnar A, Jain P, Baviskar D, Jain D. Development of mucoadhesive buccal patch containing aceclofenac: in vitro evaluations. Int J PharmTech Res. 2009 Oct;1(4):978-81.

26. Apoorva M, Neha C, Geeta A. Formulation and characterization of fast dissolving buccal films: A review. Der Pharmacia Lettre 2011; 3(1):152-65.

27. Siegel IA, Gordon HP. Surfactant-induced increase of permeability of rat oral mucosa to non electolytes in vivo. Arch Oral Biol.1985;30:43-7.

28. Leung SS, Robinson JR. Polymer structure features contributing to mucoadhesion: II. J ContrRel 1990; 12:187–94.

29. Bottenberg P, Cleymaet R, Muynek CD, Remon JP, Coomans D, Slop D. Development and testing of bioadhesive, floride- containing slow-release tablets for oral use. J PharmPharmacol 1991; 43:457-64.

30. Chandra SK, Ramesh G, Vamshi VY, KishanV, Madhsudanrao Y. Development of mucoadhesive patches for buccal administration of prochlorperazine: Evaluation of in vitro release and mechanical properties: Int J Pharma Sci and Nanotech ;1(1): 64-70.

31. Peppas NA, Buri PA. Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues. J ContrRel 1985; 2:257–75.

32. Harshad GP, Janak JJ, Tarun KP,Vishnu MP. Buccal patch: A technical note. Int J PhamSci, Rev Res 2010 Sep-Oct; 4(3):178-82.

33. Sudhakar Y, Knotsu K, Bandopadhyay AK. Bio adhesive drug delivery – A promising option for orally less efficient drugs. J Control Rel 2006; 114:15-40.