Available online at *www.ujpronline.com*
Universal Journal of Pharmaceutical Research
An International Peer Reviewed Journal
ISSN: 2831-5235 (Print); 2456-8058 (Electronic)

REVIEW ARTICLE

BUCCAL DRUG DELIVERY SYSTEM: A TOOL FOR THE EFFECTIVE DELIVERY OF PHARMACEUTICALS

Bhartee Pathak, Kapil Kumar
Department of Pharmaceutics, Global Institute of Pharmaceutical Education and Research, Jaspur Road, Kashipur, US Nagar, Uttarakhand, India.

Article Info:

Article History:
Received: 9 April 2017
Reviewed: 11 May 2017
Accepted: 25 June 2017
Published: 15 July 2017

Cite this article:
Pathak B, Kumar K. Buccal drug delivery system: a tool for the effective delivery of pharmaceuticals. Universal Journal of Pharmaceutical Research 2017; 2(3): 19-24.
http://doi.org/10.22270/ujpr.v2i3.RW2

***Address for Correspondence:**
Bhartee Pathak, Department of Pharmaceutics, Global Institute of Pharmaceutical Education and Research, Jaspur Road, Kashipur, US Nagar, Uttarakhand, India.
E-mail: *pathakbhartee451@gmail.com*

Abstract

The Buccal drug delivery system includes drug administration through the buccal mucosa, mainly composed of the lining of the cheeks. Buccal drug delivery system provides a convenient route of administration for both systemic and local drug actions. Buccal films can improve the therapeutic effect of drug by increasing the absorption of drug through oral mucosa which increases the drug bioavailability by reducing the hepatic first pass effect. In recent years, many researchers are working on the delivery of drugs through the oral mucosa which have a high first pass metabolism or degrade in the gastrointestinal tract. Furthermore, buccal drug delivery has a high patient acceptability compared to other non-oral transmucosal routes of drug administration. It provide direct access to the systemic circulation through the internal jugular vein thus avoids acid hydrolysis in the gastrointestinal tract and bypasses drugs from the hepatic first pass metabolism leading to high bioavailability. This article deals with the development and evaluation parameters used at present and future role of the system for the treatment of diseases by incorporating different class of drugs.

Keywords: Buccal drug delivery system, buccal films, hepatic first pass effect.

INTRODUCTION

Amongst the various routes of drug delivery, oral route is considered better for patient. Based on our understandings on different aspects of absorption and metabolism, many drugs cannot be delivered successfully through the oral route, because after administration the drugs are subjected to extensive pre-systemic clearance, which often leads to a lack of significant correlation between membrane permeability, absorption[1]. Buccal drug delivery refers to the delivery of drugs within/through the buccal mucosa to affect local/systemic pharmacological actions. The buccal route is responsible for maintaining a delivery system at a particular position for an extended period of time therefore it has a great appeal for both local as well as systemic drug bioavailability[2]. The buccal mucosa is relatively permeable with a rich blood supply and absorption occurring from this place is efficient, and the route also provides rapid drug transport to the systemic circulation and avoids degradation by gastro-intestinal enzymes and first pass hepatic metabolism[3].

The delivery of drug requires some type of dosage form present in the oral cavity, which release drug and then diffuses from the mucosa into the blood flow and is then added to the blood circulation.

Advantages

1. Bypass of the gastrointestinal tract and hepatic portal system therefore increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first-pass metabolism. The drug is also protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.
2. Improved patient compliance because of the elimination of associated pain with injections;
3. A relatively rapid onset of action can be achieved relative to the oral route, and the formulation can be removed if therapy is required to be discontinued as the buccal patches are there.
4. Increased ease of drug administration
5. High blood supply and good blood flow rate cause rapid absorption.
6. Mucosal surfaces do not have stratum corneum. Thus, the major barrier layer to transdermal drug delivery is not a factor in transmucosal routes of administration.

Disadvantages

As compared to the sublingual membrane the buccal membrane has low permeability.

1. Limited surface area is available for absorption.
2. This route cannot administer drugs which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odour.
3. This route is unacceptable for those drugs which are unstable at pH of buccal environment.
4. The continuous secretion of the saliva (0.5-2 l/day) takes place which leads to subsequent dilution of the drug. Drugs with large dose are difficult to be administered[4].
5. Drugs which are unstable at buccal pH cannot be administered.

BUCCAL MUCOSA OVERVIEW

Oral mucosa is divided into two parts:

A. Epithelium:

The epithelium, act as a protective layer for the tissues and is divided into:

(a) Non-keratinized surface in the mucosal lining of the soft palate, the ventral surface of the tongue, the floor of the mouth, alveolar mucosa, vestibule, lips, and cheeks.

(b) Keratinized epithelium, found in the hard palate and non-flexible regions of the oral cavity. Basement membrane and connective tissue: Basement membrane is a boundary which is found in between the basal layer of epithelium and connective tissue. It consists of extracellular materials. The organisation which determines the mechanical stability, resistance to deformation, extendibility of tissue is made up of bulk of connective tissue. The cells of oral epithelia are surrounded by an intercellular grond substance called as mucus. The oral cavity is marked by the presence of saliva produced by the salivary glands.

Mucus is secreted by the major and minor glands as a part of saliva[5].

(B). Mucus

The mucus is composed of proteins and carbohydrates. Mucus plays an important role in the absorption of buccal dosage form. Cell-cell adhesion takes place. It is assumed that the permeability of buccalmucosa is 4 to 4000 times greater than that of skin.

Saliva

It is considered as an protective fluid for all tissues of the oral cavity. Saliva is composed of 99.5% water in addition to proteins, glycoproteins and electrolytes. Continuous mineralization of the tooth enamel takes place. To hydrate oral mucosal dosage forms.

MECHANISM OF BUCCAL ABSORPTION

Buccal drug absorption takes place by passive diffusion of the non-ionized species. Passive diffusion is a process which is mainly governed by a concentration gradient, through the intercellular spaces of the epithelium. The buccal mucosa is considered as a lipoidal barrier to the passage of drug

Factors affecting buccal absorption:

The oral cavity is a complex environment for drug delivery as there are many interdependent and independent factors which reduce the absorbable concentration at the site of absorption. The factors are as follows:

1. Factors related with membrane: This mainly involves degree of keratinization, surface area available for absorption, mucus layer of salivary pellicle, intercellular lipids of epithelium, basement membrane and lamina propria.

2. Factors related with environment:

i). **Saliva**: The thin film of saliva coats throughout the lining of buccal mucosa and is called salivary film. The thickness of salivary film is 0.07 to 0.10 mm. The thickness, composition and movement of this film affected by the rate of buccal absorption.

ii). **Salivary glands**: The minor salivary glands are located in epithelial or deep epithelial region of buccal mucosa. They constantly secrete mucus on surface of buccal mucosa.

iii). **Buccal tissues movement:** Buccal region of oral cavity shows less active movements. The mucoadhesive polymers are to be incorporated to keep dosage form at buccal region for long periods to withstand tissue movements during talking and if possible during eating food or swallowing[6].

BUCCAL PATCHES

A buccal patch is a non dissolving thin matrix modified- release dosage form. Buccal patch is mainly composed of one or more than one polymer films or layers containing the drug and/or other excipients. The patch may contain a mucoadhesive polymer layer which bonds to the oral mucosa, gingiva, or teeth for controlled release of the drug into the oral mucosa (unidirectional release), oral cavity (unidirectional release), or both (bidirectional release). The patch is then removed from the mouth and disposed of after a specified time[7].

TYPES OF BUCCAL PATCHES

Matrix type (Bi-directional)

The buccal patches designed in a matrix configuration including drug, adhesive, and additives mixed together. Bi- directional patches release drug in both the mucosa as well as mouth. **Reservoir type (Unidirectional)**

The buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. These types of buccal patches are used for drug delivery in the buccal cavity for local as well as systemic effect[8]. **Ideal characteristics**

An ideal buccal adhesive system should possess the following characteristics:

1). The drug should be released in a controlled fashion.
2). The patch should facilitate the rate and extent of drug absorption.
3). It should possess good patient compliance.
4). It should not create problem in normal functions such as talking, eating and drinking.
5). It should have good resistance to the flushing action of saliva.

Table 1: Mucoadhesive polymers used in buccal delivery system.

Polymers	Examples
Semi-natural/natural	Agarose, chitosan, gelatin, hyaluronic acid, various gums (guar, hakea, xanthan, gellan, carragenan, pectin, and sodium alginate)
Synthetic	Cellulose derivatives, CMC, sodium CMC, HEC, HPC, HPMC, Poly(acrylic acid)-based polymers, Poly(N-2-hydroxypropyl methacrylamide) (PHPMAm), PVA, PVP, thiolated polymers
Water-soluble	CP, HEC, HPC, HPMC (cold water)
Water-insoluble	Chitosan (soluble in dilute aqueous acids), EC, PC
Cationic	Aminodextran, chitosan, trimethylated chitosan
Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC
Non-ionic	Hydroxyethyl starch, HPC, poly(ethylene oxide), PVA, PVP

COMPOSITION

1. Drug- active pharmaceutical ingredient (API):
For buccal drug delivery, it is important to increase the contact between API and mucosa to obtain the desired therapeutic effect. The important drug properties that affect its diffusion through the patch as well as the buccal mucosa are molecular weight, chemical function and melting point. The selection of a suitable drug for design of buccal drug delivery system should be based on following characteristics:

1. The conventional single dose of the drug should be low.
2. The drugs having biological half-life between 2-8 hours are good candidates for controlled drug delivery.
3. The drug absorption should be passive when given orally.
4. It should not produce any irritancy, allergy and discoloration or erosion of teeth.

2. Mucoadhesive polymers: Mucoadhesives are synthetic or natural polymers which interact with the mucus layer covering the mucosal epithelial surface and main molecules constituting a major part of mucus (table 2). Polymers are also used in matrix where the drug is embedded in the polymer matrix, which controls the duration of release of drugs.

2.1. Properties of ideal mucoadhesive polymer.
An ideal polymer for mucoadhesive drug delivery system should have the following characteristics:-

1. The polymer and its products should be non-toxic and non-absorbable from the GIT.
2. It should not be irritant to the mucus membrane.
3. It should allow easy incorporation of the drug and offer no hindrance to its release.
4. 4.The polymer must not decompose on storage or during the shelf life of the dosage form.
5. The polymer should be easily available in the market and economical.

3. Backing membrane: Backing membrane plays a major role in the attachment of bioadhesive devices to the mucus membrane.

1. The materials used as backing membrane should be inert.
2. It should be impermeable to the drug and penetration enhancer.
3. The commonly used materials in backing membrane include carbopol, magnesium separate, HPMC, HPC, CMC, polycarbophil etc.

4. Penetration enhancers: Substances that facilitate the penetration through buccal mucosa are referred as penetration enhancers. Various compounds have been investigated for their use as buccal penetration and absorption enhancers which can increas the flux of drugs through the mucosa and act by reducing the viscosity of the mucus and saliva overcomes this barrier[9].

5. Plasticizers: These are the materials which are used to achieve softness and flexibility of thin films of polymer or blend of polymers. Examples of common plasticizers includes glycerol, propylene glycol, PEG 200, PEG 400, castor oil etc. The plasticizers helps in releasing of the drug substances from the polymer base as well as acting as penetration enhancers. The choice of the plasticizer depends upon the ability of plasticizer material to solvate the polymer and alters the polymer-polymer interactions. When used in correct proportion to the polymer, these materials impart flexibility by relieving the molecular rigidity.

METHODS OF PREPARATION

Mucoadhesivebuccal patches can be prepared by the following methods:

A. Solvent casting: In this method, all ingredients are firstly weighed accurately and mixed in pestle and mortal. Then the mixture is added to solvent system, which contains the plasticizer. The solution is then transferred to petri- dish. The petri-dish is covered with inverted funnels to allow evaporation of the solvents. These are kept at 20-25ºC temperature for 24 to 48 hours depending upon the solvent system used. After evaporation of the solvent a thin layer of the protective backing material is laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of the desired size and geometry

B. Direct milling: In this type of patches manufacturing there is not the use of solvents. Drug and excipients are mechanically mixed by direct milling without the presence of any liquids[11].

EVALUATION OF BUCCAL PATCHES

The following tests are used to evaluate the Buccal Patches:

1. Weight uniformity: A particular numbers of different patches from each batch are weighed and the weight variation is calculated.

2. Thickness uniformity: The thickness of each patch is measured by using digital vernier calipers at five different positions of the patch and the average is calculated.

Table 2: Commercially available buccal dosage forms.

Commercial name	Bioadhesive polymer	Company	Dosage form
Saliveze	Sodium CMC	Wyvern	Artificial saliva
Suscard	HPMC	Forest	Tablet
Orabase	Pectin, gelatin	ConvaTech	Oral paste
Luborant	Sodium CMC	Antigen	Artificial saliva
Zilactin	….	Zila	Buccal film
Corcodyl gel	HPMC	Glaxosmithkline	Oromucosal gel
Miconaczole Lauriad	Modified starch, CP-934	Bioalliance	Tablet
BEMA Fentanyl	….	BDSI's	Tablet
EmezineTM	CP 934 and PVP K-30	BDSI's	Tablet
Corlan pellets	Acacia	Celltech	Oromucosal pellets
Gaviscon liquid	Sodium alginate	Rickitt Benckiser	Oral liquid
Buccastem	PVP, Xanthum gum, Locust bean gum	Rickitt Benckiser	Tablet
Tibozole	Polycarbophil and CP 934P	Tibotec	Tablet

3. Folding Endurance: The folding endurance of each patch is determined by repeatedly folding the patch at the same place till it is broken or folded up to 300 times, which is considered satisfied to reveal good film properties.

4. Surface pH: The prepared buccal patches are swelled for 2 hrs on the surface of an agar plate, prepared by dissolving 2% (w/v) agar in warm phosphate buffer at pH 6.8 under stirring and then poured the solution into a petri dish till gelling at room temperature. The surface pH is determined by placing pH paper on the surface of the swollen patch. The mean of three readings is recorded.

5. Drug content uniformity: For drug content uniformity, 3 cm patch (without backing membrane) is separately dissolved in 100 ml of ethanol and simulated saliva solution (pH 6.2) mixture (20:80) for 12 h under occasional shaking[12].

6. Swelling Index: Buccal patches are weighed individually (W1) and placed separately in petri dishes containing phosphate buffer pH 6.8. The patches are removed from the petri dishes and excess surface water is removed using filter paper[13]. The patches are reweighed (W2) and swelling index (SI) is calculated as follows:

$$SI = \frac{W2 - W1}{W1}$$

7. Moisture content: The buccal patches are weighed accurately and kept in dessicator containing anhydrous calcium chloride. After 3 days, the patches are taken out and weighed. The moisture content (%) is determined by calculating moisture loss (%) using the formula[14]:

$$\text{Moisture content (\%)} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}}$$

8. *In-vitro* drug release: rotating paddle method is involved in studying the drug release from the bilayered and multilayered patches. The dissolution medium consisted of phosphate buffer pH 6.8. The release is performed at 37±0.5°C, with a rotation speed of 50 rpm. The backing layer of buccal patch is attached to the glass disk with instant material. The disk is allocated to the bottom of the dissolution vessel. Samples (5 ml) are withdrawn at predetermined time intervals and replaced with fresh medium. The samples are then filtered through Whattman filter paper and analyzed for drug content after appropriate dilution[15].

FACTORS AFFECTING BDDS

1. Molecular weight

In general, bioadhesive strength of a polymer increases with molecular weights above 100,000[16].

2. Flexibility

Bioadhesion starts due to the diffusion of the polymer chains in the interfacial region. Thus, it is important that the polymer chains contain a substantial degree of flexibility for desired entanglement with the mucus.

Mobility and flexibility of polymers can be related to their viscosities and diffusion coefficients, where higher flexibility of a polymer causes greater diffusion into the mucus network[17].

3.Hydrogen bonding capacity

Hydrogen bonding is another important factor in mucoadhesion of a polymer. For mucoadhesion to occur, desired polymers must have functional groups that are able to form hydrogen bonds. Flexibility of the polymer is important to improve this hydrogen bonding potential[18].

4. Cross-linking density

The average pore size, the number average molecular weight of the cross-linked polymers, and the density of crosslinking are three important and interrelated structural parameters of a polymer network. Therefore, it seems reasonable that with increasing density of cross-linking, diffusion of water into the polymer network occurs at a lower rate which, in turn, causes an insufficient swelling of the polymer and a decreased rate of interpenetration between polymer and mucin[19].

5. Charge

It is reported by many researchers that nonionic polymers appear to undergo a smaller degree of adhesion compared to anionic polymers. Chitosan is a cationic high-molecular-weight polymer, have shown to possess good adhesive properties[20].

6. Concentration

When the concentration of the polymer is too low, the number of penetrating polymer chains per unit volume of the mucus is small, and the interaction between polymer and mucus is unstable. In general, the more

concentrated polymer would result in a longer penetrating chain length and better adhesion[21].

CONCLUSIONS

The buccal drug delivery system is a promising mean for systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules. Mucoadhesive drug delivery systems may be useful for many pharmaceuticals and can be modified to adhere to any mucosal tissue, including those found in oral cavity, gastrointestinal tract, vagina, eye etc[22]. The liquid formulation of insulin plays a very important role in the treatment of Diabetes. Various forms of doses form. Recently due to the various research done the novel drug delivery system is introduced via liquid aerosol formulation has been developed[23]. Development of suitable delivery devices can take place, permeation enhancement improvement, and buccal delivery of drugs that undergo a first-pass effect, such as cardiovascular drugs, analgesics, and peptides. The further research on vaccines may leads to the formulation of many new buccal products[24]. In mucoadhesive placebo buccal patches we can use any potent drugs which fulfill the criteria for buccal patch as drug delivery system[25]. *In-vivo* studies for the prepared mucoadhesive buccal patches may be beneficial for future products. Stability studies can justify the feasibility of the mucoadhesive buccal patches[26]. Buccal nitroglycerin can be used for acute therapy for an anginal attack as well as for chronic prophylaxis. Nitroglycerine is an important treatment for heart attack symptoms[27].

AUTHOR'S CONTRIBUTION

Pathak B: writing original draft, conceptualization, methodology, investigation. **Kumar K:** Writing, review, and editing, supervision. Final version of manuscript is approved by all authors.

ACKNOWLEDGEMENTS

The authors extend their thanks and appreciation to the Global Institute of Pharmaceutical Education and Research, Kashipur, Uttarakhand, India to provide necessary facilities for this work.

DATA AVAILABILITY

The data supporting the findings of this study are not currently available in a public repository but can be made available upon request to the corresponding author.

CONFLICT OF INTEREST

None to declare.

REFERENCES

1. Gandhi RB, Robinson JR. Oral cavity as a site for bioadhesive drug delivery. Adv drug del Rev 1994; 13:43-74.*https://doi.org/10.1016/0169-409X(94)90026-4*
2. Rathod S, Surve GD, Phansekar M, Bhagwan A. review on mouth dissolving film technology. Int J Pharm Res Schol 2014; 3(1): 635-47. *https://doi.org/10.4103/2230-973X.114897*
3. Giradkar KP. Design development and *in vitro* evaluation of bioadhesive dosage form for buccal route. Int J Pharm Res Dev 2010; 2:28-34. *https://doi.org/10.1208/S12249-008-9125-X*
4. Khanna R, Agarwal SP, Ahuja A. Mucoadhesive buccal drug delivery: a potential alternative to conventional therapy. Int J Pharm Sci 1998; 60(1): 1-11. 15. *https://doi.org/10.1208/s12249-008-9083-3*
5. Rao S, Song Y, Peddie F, Evans AM. A novel tri-layered buccal mucoadhesive patch for drug delivery: assessment of nicotine delivery. J Pharm Pharmacol 2011; 63:794–99. *https://doi.org/10.1111/j.2042-7158.2011.01283.x*
6. Venkatalakshmi R, Sudhakar Y, Buccal drug delivery using adhesive polymeric patches. Int J Pharm Sci Res 2012; 3(1): 35-41. *https://doi.org/10.13040/IJPSR.0975-8232.3(1).35-41*
7. Sattar M, Sayed OM, Lane ME. Oral transmucosal drug delivery current status and future prospects. Int J Pharm 2014; 471: (1-2): 498–506. *https://doi.org/10.1016/j.ijpharm.2014.05.043*
8. Mujoriya R, Dhamande K, Wankhede UR, Angure S, A Review on study of buccal drug delivery system. Inn Sys Design Eng 2011; 2(3): 24-35. 27.PMID: 23008684
9. Desai KGH, Kumar TMP. Development and evaluation of noval buccal adhesive core-in-cup tablets of propranolol hydrochloride. Indian J Pharm Sci 2004; 66(4):438. *https://doi.org/10.1208/s12249-009-9304-4*
10. Aungst BJ, Rogers NJ. Site Dependence of Absorption-Promoting Actions of Laureth 9, Na Salicylate, Na2 EDTA, and Aprotinin on rectal, nasal, and buccal insulin delivery. Pharm Res 1988; 5 (5): 305–308. *https://doi.org/10.1023/a:1015930821648*
11. Salamat-Miller N, Chittchang M, Johnston TP. The use of muco adhesive polymers in buccal drug delivery. Adv drug deliv review 2005; 57(11): 1666-1691. *https://doi.org/10.1016/j.addr.2005.07.003*
12. Lalla JK. Gurnancy RA. Polymers for mucosal delivery-swelling and mucoadhesive evaluation. Indian drugs 2002; 39(5): 48-55.
13. Cilurzo F, Cupone IE, Minghetti P, Selmin F, Montanari L. Fast dissolving films made of maltodextrins. Eur J Pharm Biopharm 2008; 70: 895-900. *https://doi.org/10.1016/j.ejpb.2008.06.032*
14. Shin SC, Bum JP, Choi JS. Enhanced bioavailability by buccal administration of triamcinolone acetonide from the bioadhesive gels in rabbits. Int J Pharm 2000; 209:37–43. *https://doi.org/10.1016/S0378-5173(00)00542-1*
15. Shrutika M. Gawas, Asish Dev, Ganesh Deshmukh, S. Rathod. Current approaches in buccal drug delivery system pharmaceutical and biological evaluations 2016; 3 (2): 165-177.
16. Kraan H. Buccal and sublingual vaccine delivery. J Control Release 2014; 190: 580–92. *https://doi.org/10.1016/j.jconrel.2014.05.060*
17. Andrew GP, Laverty TP, Jones DS. Mucoadhesive polymeric for controlled drug delivery. Europ J Pharm Biopharm 2009; 71(3): 505-518. *https://doi.org/10.1016/j.ejpb.2008.09.028*
18. Wong CF, Yuen KH, Peh KK. Formulation and evaluation of controlled release Eudragit buccal patches. Int J Pharm 1999; 178: 11–22. *https://doi.org/10.1016/S0378-5173(98)00342-1*
19. Solomonidou D, Cremer K, Krumme M, Kreuter J. Effect of carbomer concentration and degree of neutralization on

the mucoadhesive properties of polymer films. J Biomater Sci Polym 2001; 1191–1205. *https://doi.org/10.1163/156856201753395743*
20. 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. *https://doi.org/10.1016/j.jconrel.2006.04.012*
21. Thimmasetty J, Pandey GS, Sathesh Babu PR Design and *in vivo* evaluation of carvedilol buccal mucoadhesive patches. Pak J Pharm Sci 2008; 21(3): 241-248.
22. Jafar A, Ali N, Djavad F, Massoud A, Mahammad RSS. Development and evaluation of buccoadhesive propranolol hydrochloride tablet formulation: effect of fillers. Il Farmaco 2004; 59:155-161. *https://doi.org/10.1016/j.farmac.2003.11.011*
23. McCarron PA, Donnelly RF, Zawislak A, Woolfson AD, Price JH, McClelland R. Evaluation of a water-soluble bioadhesive patch for photodynamic therapy of vulval lesions. Int J Pharm 2005; 293:11–23. *https://doi.org/10.1016/j.ijpharm.2004.11.035*
24. Hassan EE, Gallo JM. A simple rheological method for the *in vitro* assessment of mucin-polymer bioadhesive bond strength. Pharm Res 1990; 7:491–5. *https://doi.org/10.1023/A:1015812615635*
25. Rossi S, Ferrari F, Bonferoni MC, Caramella C. Characterization of chitosan hydrochloride--mucin rheological interaction: Influence of polymer concentration and polymer: Mucin weight ratio. Eur J Pharm Sci 2001; 12:479–85. *https://doi.org/10.1016/S0928-0987(00)00194-9*
26. Christian K, Karin A, Melanie G, Christian W, Paul D, Andreas BS. *In vivo* determination of the time and location of mucoadhesive drug delivery systems disintegration in the gastrointestinal tract. Magn Reson Imaging 2008; 26:638–643.*https://doi.org/10.1016/j.mri.2008.01.004*
27. Nakhat PD, Kondawar AA. Studies on buccoadhesive tablets of terbutaline sulphate. Indian J Pharm Sci 2007; 505-510.*https://doi.org/10.4103/0250-474X.36934*