Sudarshan Publications

Available online at https://s-epub.in/index.php/trp/index

Pharma Research

An International Peer Reviewed, Indexed Journal

10.62655/s-epub.2025.v17.i01.pp67-74

MUCOADHESIVE BUCCAL TABLETS OF PROPRANOLOL: FORMULATION AND EX VIVO RESIDENCE TIME

MATTEO PELLEGRINI[1]*, JOHANNA KRANZBUEHLER[2], VALENTINA ZANETTI[1]

Affiliation [1]Department of Pharmaceutical Technology, Cilento Institute of Pharmaceutical Sciences, Salerno, Italy
[2]Department of Pharmaceutics, Fichtelgebirge Centre for Drug Research, Hof, Germany

*Corresponding author: Matteo Pellegrini, m.pellegrini2@cips-sa.it
ORCID iD: Matteo Pellegrini 0000-0001-0179-9692; Johanna Kranzbuehler 0000-0001-3805-6585; Valentina Zanetti 0000-0001-3764-4393

Article info

Received date:10-08-2024
Accepted date:15-12-2024
Published date:05-04-2025
ISSN;0975-8216

Keywords:

Propranolol, Buccal tablets, Mucoadhesion, Residence time, Controlled release

Abstract

Propranolol hydrochloride is a classic beta-blocker whose oral bioavailability is limited by extensive first-pass metabolism, which has made it a recurring candidate for delivery through the buccal mucosa. This narrative review summarises published work on mucoadhesive buccal tablets, with attention to the buccal route, the chemistry of mucoadhesion, polymer and excipient choices, and the tests used to judge a tablet, including ex vivo residence time on excised mucosa. It reports no new experimental data. Published studies agree that polymer type and proportion govern adhesion, swelling and release, and that propranolol permeates the mucosa readily. Tissue models differ between laboratories, and human residence-time and bioavailability data remain limited.

1. INTRODUCTION

Propranolol was the first clinically successful beta-adrenoceptor antagonist and remains in wide use for hypertension, angina, arrhythmias, migraine prophylaxis and essential tremor. It is well absorbed from the gut, yet only a fraction of an oral dose reaches the systemic circulation unchanged, because the liver removes much of the drug on its first pass [1, 2]. The result is a drug with large differences in plasma level between patients and a dose that has to be titrated carefully. For a molecule with these features, any route that avoids the portal circulation is worth examining.

The buccal mucosa, the lining of the cheek, is one such route. Drug absorbed there enters the jugular venous system and reaches the heart before it reaches the liver, so hepatic first-pass loss is avoided in principle [3, 4, 5].

The tissue is accessible, relatively robust and tolerant of a dosage form that remains in place for hours, provided the form can stay attached while the patient talks, swallows and drinks. A mucoadhesive tablet is one of the simplest ways of achieving that, and it can be made with the same equipment used for ordinary tablets [6, 7, 8].

This review brings together what has been published on mucoadhesive buccal tablets of propranolol and on the closely related literature that shapes their design. It reports no new experimental data. The sections that follow describe the buccal route and the properties of propranolol, the principles of mucoadhesion and the excipients used, the tests applied to such tablets with particular attention to ex vivo residence time, and the findings reported in the literature. The final section discusses the gaps that limit interpretation, among them the gap between tissue tests in a beaker and conditions in the mouth [9, 10, 11].

Interest in buccal delivery has grown steadily since the 1980s, partly because peptides and other drugs that cannot survive the gut need an alternative and partly because patient acceptance of a small tablet on the gum or cheek has proved higher than many expected. Propranolol sits at the easier end of that spectrum. It is a small, moderately lipophilic molecule that permeates the mucosa without help, so the technical work concentrates on holding the tablet in place and controlling the rate at which the drug leaves it, not on forcing a difficult molecule across the epithelium [7, 11, 12].

2. BUCCAL ROUTE AND PROPRANOLOL

The buccal mucosa is a non-keratinised stratified squamous epithelium several hundred micrometres thick, resting on a connective tissue layer with a rich blood supply. Its surface area is modest, but it is easy to reach and, unlike the skin, lacks a thick keratin barrier [4, 13]. The main barrier to permeation lies in the upper third of the epithelium, where lipids extruded from membrane-coating granules fill the intercellular spaces, and it is less formidable than in keratinised regions such as the palate or gingiva [13, 14]. Hydrophilic and large molecules still cross slowly, whereas small lipophilic drugs pass much more readily [3, 5].

Propranolol hydrochloride suits the route reasonably well. The base is lipophilic, with a log P of about 3 for the unionised base, while the hydrochloride salt dissolves freely in water and in saliva [1, 11]. After oral dosing, bioavailability is commonly cited as around a quarter of the dose because of extensive hepatic extraction, and the plasma half-life is only a few hours, which is why conventional tablets need dosing several times a day or a switch to a long-acting capsule [1, 2]. A buccal tablet offers the possibility of bypassing hepatic extraction and of releasing drug over a longer period at a controlled rate.

The buccal route is often set beside the sublingual one, and the comparison explains some design choices. The floor of the mouth is thinner and more permeable, so drugs are absorbed faster there, but saliva washes the area constantly and the tissue is poorly suited to a dosage form that must stay in place for hours. The cheek is less permeable, but it is a more stable site for retentive systems and tolerates a sustained-release product better [3, 5, 12]. Tablets, films and patches have all been used, and films are preferred for comfort and flexibility, whereas tablets can carry a higher drug load and are made on standard equipment [8, 15].

Permeation work on cultured and excised tissue supports that expectation. In studies of the TR146 human buccal epithelial cell model, and of porcine, monkey and human buccal mucosa, beta-blockers of higher lipophilicity such as propranolol crossed far more rapidly than hydrophilic ones such as atenolol, and the ranking followed lipophilicity closely [11]. Porcine buccal tissue has a lipid composition and morphology close to those of human tissue and has become the usual ex vivo substrate [16]. The data justify the choice of propranolol as a model drug, though they do not show what happens in a patient wearing a tablet [11, 16].

The oral cavity also imposes constraints that skin and gut do not. Saliva flows continuously, dilutes the dissolved drug and

carries some of it to the stomach, so a portion of the dose is swallowed whatever the intention [3, 5]. Eating, drinking and speaking disturb a tablet and shorten residence. Taste matters as well: propranolol is bitter and has local anaesthetic activity, so a tablet that dissolves at its surface may leave an unpleasant taste or a numb patch, which argues for a unidirectional design in which only the face against the mucosa is exposed [5, 7, 8].

Dose is a practical limit. Oral propranolol doses run from tens of milligrams to a few hundred milligrams a day, whereas the buccal surface can hold only a small tablet, and the fraction that permeates is not the full amount released. Simple arithmetic suggests that a tablet of around 100 to 200 mg total mass can carry a useful dose of a potent drug only if absorption is reasonably efficient [1, 4, 12]. Because bioavailability by the buccal route is higher than by mouth, an equivalent systemic exposure needs a lower dose, which helps, but the dose and the release rate need to be balanced with care.

3. MUCOADHESION AND FORMULATION

Mucoadhesion is the attachment of a material to the mucus layer or mucosal surface, and it is generally described as happening in two stages. In the contact stage the dosage form wets and spreads over the surface; in the consolidation stage, polymer chains interpenetrate with mucin and form secondary bonds, which may be hydrogen bonds, van der Waals forces or electrostatic interactions [17, 18]. Several theories describe the process, among them the wetting, adsorption, diffusion, electronic and fracture theories, and no single one explains every case [17, 19]. Practical formulation draws on all of them.

Many variables influence how well a polymer adheres. Molecular weight matters, because longer chains interpenetrate more deeply until a plateau is reached, and polymer concentration matters in a similar way, with an optimum above which the tablet over-hydrates and forms a slippery layer that detaches easily [17, 19]. Chain flexibility, the density of hydrogen-bonding groups and the degree of cross-linking also play parts. Environmental pH changes the ionisation of carboxyl groups in carbomer and so the degree of swelling, and turnover of mucus limits adhesion in time, since the layer itself is shed in hours [17, 20, 21].

The polymers most often used in buccal tablets are carbomers, hydroxypropyl methylcellulose (HPMC), sodium carboxymethylcellulose and chitosan. Carbomers carry many carboxyl groups and bond strongly to mucin through hydrogen bonding, but they swell vigorously and can irritate if used alone [20, 22]. HPMC grades of different viscosity provide gel-forming matrices that slow release and give moderate adhesion. Chitosan is cationic and adheres through electrostatic attraction to negatively charged sialic acid residues, with some effect on epithelial tight junctions as well [21]. Thiolated polymers form disulphide bonds with cysteine-rich mucins and show stronger adhesion in tests [23].

Combinations are the norm. Carbomer provides adhesion, HPMC controls swelling and drug release, and the ratio between the two is adjusted until the tablet adheres for the target period without eroding too early or turning into a hard, uncomfortable mass [6, 20, 24]. Increasing polymer content generally raises adhesive strength up to a point and slows release, after which excess polymer may over-swell and reduce contact. The same pattern has been reported for carvedilol, a related beta-blocker, and for nicotine and chlorhexidine tablets, which indicates that the principle is general and not specific to propranolol [24, 25, 26].

The nature of the drug is easy to overlook in formulation planning. Propranolol hydrochloride is a cationic drug in the mouth, whereas carbomer is an anionic polymer, and an ionic interaction between the two can slow release or hold part of the dose in the swollen matrix, an effect described for other basic drugs in carbomer systems [6, 22]. The salt is also freely soluble, so a hydrophilic matrix may release it quickly in the early minutes unless the gel layer forms promptly. These interactions are a reason to test several polymer ratios, and not just to copy a formula from a paper on a neutral model drug [10, 24].

The rest of the formula is conventional but not trivial. Direct compression is preferred where the powder flows well, with mannitol, lactose or microcrystalline cellulose as diluents and a low level of magnesium stearate as lubricant, since this hydrophobic salt can reduce wetting and adhesion if overused [8, 22]. A sweetener and flavour may be added, and a backing layer of ethylcellulose or a similar film may be applied to one face so that drug moves only towards the mucosa. Moisture content, particle size and compression force all affect hardness and hydration, and each can be tuned during development [6, 8, 22].

4. EVALUATION OF TABLETS

Evaluation starts with standard pharmaceutical tests: weight variation, thickness, hardness, friability and drug content, assessed against pharmacopoeial limits [27]. Friability below 1 percent is the usual target, although tablets with high polymer content may be harder to characterise by this test. Because the tablet is held against living tissue, surface pH is also measured, typically by letting the tablet swell in simulated saliva and placing a pH electrode against the surface, and the aim is a pH close to neutral to avoid irritation [8, 9]. Swelling index, the percentage weight gain on hydration, is recorded at intervals and reveals how quickly the matrix takes up water [6, 9].

Mucoadhesive strength is measured by detachment tests. In the classic arrangement a modified two-pan balance holds the tablet against a piece of mucosa, and the weight needed to separate them is recorded; modern versions use a texture analyser that records the peak force and the work of adhesion during controlled separation [9, 28]. Results depend on contact time, applied force, hydration and tissue source, and values from different laboratories cannot be compared directly [9, 29]. They are useful mainly for ranking formulations within one study, a limitation that is easy to forget when numbers appear in a table.

Ex vivo residence time is the test of most interest here. Freshly excised porcine buccal mucosa, usually obtained from an abattoir within hours of slaughter, is fixed to a glass slide or to the inside wall of a vessel with the mucosal side exposed. The tablet is pressed against the tissue for a short period, and the assembly is immersed in phosphate buffer at pH 6.8 and 37 °C while a moving rack, often the arm of a disintegration apparatus, repeatedly raises and lowers the tissue. The time to detachment or complete erosion of the tablet is taken as the residence time [9, 16, 29].

Residence time is useful but easily over-read. The method simulates hydration and movement, yet it lacks salivary flow, shear from the tongue and the changes in mucus turnover that occur in a living mouth. Tissue handling affects the result as well: freezing, long storage and the removal of the underlying connective tissue all change the surface, and the species and site of the tissue matter [9, 16]. A tablet that remains attached for eight hours in a beaker may last for a fraction of that time in a person, which is why the findings should be reported as a comparison between formulations rather than as a prediction of clinical behaviour [9, 29].

Drug release is generally measured in a paddle apparatus at 50 rpm with phosphate buffer at pH 6.8, often with one face of the tablet masked so that release is unidirectional. Release profiles are fitted to kinetic models, including zero-order, first-order, Higuchi and Korsmeyer-Peppas equations, and the diffusional exponent n is used to distinguish Fickian diffusion from anomalous transport and from relaxation-controlled release [30, 31, 32]. Model fitting is descriptive, not proof of mechanism, and comparisons are better made using model-independent measures such as similarity factors [33]. Stability studies follow ICH conditions and normally check appearance, drug content and adhesion over time, since ageing can alter the adhesive behaviour of buccal products, as reported for miconazole patches [34, 35].

Experimental design deserves more care than it often receives. Tissue from a single animal can differ from that of the next in thickness and surface condition, so tablets should be tested on tissue from several animals, with replicates and a reference formulation on every occasion [9, 29]. Contact force and time before immersion should be fixed and

reported, and the buffer volume and temperature kept constant. Without these controls, differences in residence time between formulations may be as likely to reflect handling as formulation. Reporting the median and range, or all individual values, serves readers better than a mean from three tablets [9, 16].

Permeation studies complete the picture. Tablets can be placed on excised mucosa mounted in Franz-type or flow-through diffusion cells, and drug appearing in the receptor medium is measured by HPLC or UV spectrophotometry. The experiment distinguishes release from the dosage form from passage across the tissue, which matters because a tablet may release drug quickly and still deliver it slowly if the tissue is the rate-limiting step. Using the epithelium alone, separated from connective tissue, gives a more realistic barrier than whole mucosa, since the tissue beneath the epithelium would be perfused in life [11, 16].

5. REPORTED FINDINGS

The evidence on buccal propranolol is dominated by laboratory studies of formulations and by permeation work, and the main findings are summarised in table 1. The entries are grouped under four headings, namely polymers, tablet design, propranolol-specific studies and test methods, and their distribution is shown in fig. 1. The table is selective, and entries on related drugs such as carvedilol, nicotine and chlorhexidine are included where they illustrate a principle that carries over to propranolol. Studies of propranolol tablets themselves are fewer than studies of patches and gels [10, 24, 25].

A few themes recur. Polymer choice and proportion consistently control adhesion, swelling and release, and the best-performing formulations combine a strongly adhesive polymer with a matrix-forming one [6, 20, 24]. Propranolol permeates buccal tissue well in every model that has been tested, and its flux is far higher than that of hydrophilic beta-blockers [11]. Release is usually described as diffusion-controlled or anomalous, with the proportion of HPMC determining how long the tablet lasts [24, 31, 32]. Residence time on porcine mucosa is reported in hours, although the details of the test differ between papers [9, 16].

Comparing dosage forms, patches and films are generally better tolerated and more flexible, while tablets deliver a higher drug load and are simpler to manufacture. The chitosan-containing propranolol patches show that the drug can be incorporated into a thin polymer film with controlled release, but the dose that a patch of cheek-sized area can carry is limited [10, 15]. Studies on miconazole patches report that ageing affected both adhesion and release, a reminder that stability testing should include mucoadhesive performance and not only drug content [34, 35]. Tablets sit between these options and have the advantage that conventional tablet machinery can make them at scale [8, 34].

Systemic evidence in people is thin. Pharmacokinetic work on buccal beta-blockers is far less common than formulation work, and where it exists it often involves small groups and limited sampling [1, 2, 12]. Nobody can say from the published tablets how closely ex vivo residence time tracks the time a tablet stays in the mouth of a patient, nor how much of the released propranolol is swallowed. These are the questions that decide whether a buccal tablet competes with a conventional one, and they have mostly been left unanswered while formulation papers multiply [4, 11, 12].

Table 1: Selected published findings relevant to mucoadhesive buccal tablets of propranolol

System or method	Reported finding	Ref.
Carbomer Mucoadhesive polymer	Strong adhesion through hydrogen bonding; swells rapidly and is usually blended with a matrix-forming polymer	[20, 22]
Chitosan Cationic polymer	Adheres by electrostatic attraction to mucin; also acts on epithelial tight junctions	[21]
HPMC Matrix polymer	Forms a gel layer that slows release and moderates swelling; viscosity grade matters	[6, 22]
Thiolated polymers Thiomers	Disulphide bonds with mucus cysteine groups gave stronger and longer adhesion	[23]

System or method	Reported finding	Ref.
Nicotine buccal tablet Direct compression	Adhesive tablet developed with mucoadhesive polymers for sustained local-to-systemic delivery	[25]
Chlorhexidine tablets Chitosan microspheres	Drug-loaded microspheres in tablets prolonged release and retention in volunteers	[26]
Carvedilol buccoadhesive tablets Beta-blocker	Polymer ratio controlled adhesion and release; acceptable properties achieved with blends	[24]
Propranolol patches Chitosan-containing	Mucoadhesive patches with controlled release were prepared and characterised	[10]
Propranolol permeability TR146, porcine, human tissue	Rapid permeation compared with hydrophilic beta-blockers; rank order followed lipophilicity	[11]
Porcine buccal mucosa Ex vivo substrate	Lipid composition and structure close to human buccal tissue; accepted as the standard model	[16]
Tensile and balance methods Adhesion testing	Detachment force depends on contact time, hydration and tissue; useful for ranking only	[9, 28]

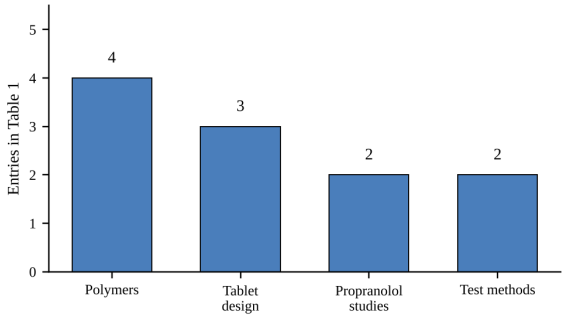


Fig. 1: Number of entries in table 1 by theme

Release kinetics in the carvedilol and propranolol work illustrate the trade-offs. A higher proportion of HPMC slows the early burst and prolongs release, but too much produces a gel that releases little drug in the first hours, whereas a high carbomer fraction increases adhesion yet can retard release of a basic drug [10, 24]. Fits to the Korsmeyer-Peppas model commonly give an exponent between 0.45 and 0.89 for cylindrical tablets, which is read as anomalous transport combining diffusion and polymer relaxation [31, 32]. The interpretation is reasonable, but it describes the curve and does not establish the mechanism.

6. LIMITATIONS AND FUTURE DIRECTIONS

The most serious limitation is the distance between bench and patient. Ex vivo tests omit saliva, mechanical stress and living blood flow, and most laboratories use different tissue sources, buffers, contact forces and end points [9, 16, 29]. Kinetic modelling gives a tidy description but reveals little about mechanism, and many papers report adhesion in arbitrary units that cannot be compared between studies [30, 33]. Stability data, taste assessment and irritation testing are reported far less often than release and adhesion, although they bear directly on whether a tablet could be marketed [6, 27, 35].

Progress would come from standardising the ex vivo method, reporting force, contact time and tissue handling in full, and including a reference tablet in every study so that results can be placed in context. Small human studies of residence time, using imaging or a tablet with a visible marker, would test how far the beaker model predicts the mouth. Pharmacokinetic studies comparing buccal and oral propranolol, with sampling that captures both early absorption and the swallowed fraction, are needed before the clinical value of the route can be judged [1, 2, 11, 12].

Quality and regulatory aspects need attention if a buccal product is to progress beyond the laboratory. Mucoadhesion is not a compendial test, so a specification for adhesion has to be justified from the development data, and the dissolution method must discriminate between batches with different polymer levels or compression force [8, 27]. Stability under ICH conditions, with attention to moisture uptake by hygroscopic polymers, is needed to support a shelf life, and excipient grades should be specified closely because viscosity differences between batches of HPMC or carbomer alter performance [22, 35]. These practical steps are less glamorous than permeation work but decide whether a product can be made reliably.

7. CONCLUSION

The published literature supports the view that propranolol is a sensible candidate for buccal delivery, since it is lipophilic enough to cross the mucosa without enhancers and suffers extensive first-pass loss when taken orally [1, 2, 11]. Mucoadhesive tablets built on carbomer, HPMC or chitosan can be made by direct compression and tuned to give adhesion and release over several hours, and the principles are well documented for several drugs [6, 24, 25].

What is still missing is evidence that ex vivo residence time predicts behaviour in people. Methods vary, tissue handling is seldom described in detail, and pharmacokinetic data for buccal beta-blockers are scarce [9, 16, 29]. Standardised tests, reference formulations and small human studies would turn a collection of formulation papers into a body of evidence that could support a decision about clinical use [12, 27, 35].

8. ABBREVIATIONS

HPMC-Hydroxypropyl methylcellulose, HPLC-High-performance liquid chromatography, ICH-International Council for Harmonisation, TR146-Human buccal epithelial cell line, UV-Ultraviolet

9. FUNDING

Nil

10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

12. REFERENCES

1. Johnsson G, Regårdh CG. Clinical pharmacokinetics of beta-adrenoreceptor blocking drugs. Clin Pharmacokinet 1976;1:233–63.
2. Shand DG, Rangno RE. The disposition of propranolol. I. Elimination during oral absorption in man. Pharmacology 1972;7:159–68.
3. Smart JD. Buccal drug delivery. Expert Opin Drug Deliv 2005;2:507–17.
4. Shojaei AH. Buccal mucosa as a route for systemic drug delivery: a review. J Pharm Pharm Sci 1998;1:15–30.
5. Rathbone MJ, Drummond BK, Tucker IG. The oral cavity as a site for systemic drug delivery. Adv Drug Deliv Rev 1994;13:1–22.
6. Salamat-Miller N, Chittchang M, Johnston TP. The use of mucoadhesive polymers in buccal drug delivery. Adv Drug Deliv Rev 2005;57:1666–91.
7. Sudhakar Y, Kuotsu K, Bandyopadhyay AK. Buccal bioadhesive drug delivery: a promising option for orally less efficient drugs. J Control Release 2006;114:15–40.
8. Hao J, Heng PWS. Buccal delivery systems. Drug Dev Ind Pharm 2003;29:821–32.
9. Nair AB, Kumria R, Harsha S, Attimarad M, Al-Dhubiab BE, Alhaider IA. In vitro techniques to evaluate buccal films. J Control Release 2013;166:10–21.
10. Patel VM, Prajapati BG, Patel MM. Design and characterization of chitosan-containing mucoadhesive buccal patches of propranolol hydrochloride. Acta Pharm 2007;57:61–72.
11. Nielsen HM, Rassing MR. TR146 cells grown on filters as a model of human buccal epithelium: IV. Permeability of water, mannitol, testosterone and beta-adrenoceptor antagonists. Comparison to human, monkey and porcine buccal mucosa. Int J Pharm 2000;194:155–67.
12. Patel VF, Liu F, Brown MB. Advances in oral transmucosal drug delivery. J Control Release 2011;153:106–16.
13. Squier CA, Wertz PW. Structure and function of the oral mucosa and implications for drug delivery. In: Rathbone MJ, editor. Oral mucosal drug delivery. New York: Marcel Dekker; 1996. p. 1–26.
14. Wertz PW, Squier CA. Cellular and molecular basis of barrier function in oral epithelium. Crit Rev Ther Drug Carrier Syst 1991;8:237–69.
15. Morales JO, McConville JT. Manufacture and characterization of mucoadhesive buccal films. Eur J Pharm Biopharm 2011;77:187–99.
16. Diaz del Consuelo I, Jacques Y, Pizzolato GP, Guy RH, Falson F. Comparison of the lipid composition of porcine buccal and esophageal permeability barriers. Arch Oral Biol 2005;50:981–7.
17. Smart JD. The basics and underlying mechanisms of mucoadhesion. Adv Drug Deliv Rev 2005;57:1556–68.
18. Peppas NA, Buri PA. Surface, interfacial and molecular aspects of polymer bioadhesion on

soft tissues. J Control Release 1985;2:257–75.

19. Ahuja A, Khar RK, Ali J. Mucoadhesive drug delivery systems. Drug Dev Ind Pharm 1997;23:489–515.
20. Peppas NA, Sahlin JJ. Hydrogels as mucoadhesive and bioadhesive materials: a review. Biomaterials 1996;17:1553–61.
21. Lehr CM, Bouwstra JA, Schacht EH, Junginger HE. In vitro evaluation of mucoadhesive properties of chitosan and some other natural polymers. Int J Pharm 1992;78:43–8.
22. Kibbe AH, editor. Handbook of pharmaceutical excipients. 3rd ed. Washington: American Pharmaceutical Association; 2000.
23. Leitner VM, Walker GF, Bernkop-Schnürch A. Thiolated polymers: evidence for the formation of disulphide bonds with mucus glycoproteins. Eur J Pharm Biopharm 2003;56:207–214.
24. Yamsani VV, Gannu R, Kolli C, Rao ME, Yamsani MR. Development and in vitro evaluation of buccoadhesive carvedilol tablets. Acta Pharm 2007;57:185–97.
25. Ikinci G, Senel S, Wilson CG, Sumnu M. Development of a buccal bioadhesive nicotine tablet formulation for smoking cessation. Int J Pharm 2004;277:173–8.
26. Giunchedi P, Juliano C, Gavini E, Cossu M, Sorrenti M. Formulation and in vivo evaluation of chlorhexidine buccal tablets prepared using drug-loaded chitosan microspheres. Eur J Pharm Biopharm 2002;53:233–9.
27. Council of Europe. European Pharmacopoeia. 9th ed. Strasbourg: European Directorate for the Quality of Medicines; 2016.
28. Park K, Robinson JR. Bioadhesive polymers as platforms for oral-controlled drug delivery: method to study bioadhesion. Int J Pharm 1984;19:107–27.
29. Gandhi RB, Robinson JR. Oral cavity as a site for bioadhesive drug delivery. Adv Drug Deliv Rev 1994;13:43–74.
30. Baker RW, Lonsdale HK. Controlled release: mechanisms and rates. In: Tanquary AC, Lacey RE, editors. Controlled release of biologically active agents. New York: Plenum Press; 1974. p. 15–71.
31. Harland RS, Gazzaniga A, Sangalli ME, Colombo P, Peppas NA. Drug/polymer matrix swelling and dissolution. Pharm Res 1988;5:488–494.
32. Bruschi ML. Strategies to modify the drug release from pharmaceutical systems. Cambridge: Woodhead Publishing; 2015.
33. O'Hara T, Dunne A, Butler J, Devane J. A review of methods used to compare dissolution profile data. Pharm Sci Technol Today 1998;1:214–23.
34. Nafee NA, Ismail FA, Boraie NA, Mortada LM. Mucoadhesive buccal patches of miconazole nitrate: in vitro/in vivo performance and effect of ageing. Int J Pharm 2003;264:1–14.
35. Carstensen JT. Drug stability: principles and practices. 2nd ed. New York: Marcel Dekker; 1995.