Available online **www.ijpras.com**

International Journal of Pharmaceutical Research & Allied Sciences, 2018, 7(1):33-40

Research Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Comparative Buccal Delivery of Cyclobenzaprine Hcl And Cyclobenzaprine (Base) Using Mucoadhesive Buccal Film

Amina Ahmady *

Department of pharmaceutics, Faculty of pharmacy, Kabul University, Kabul, Afghanistan

---

ABSTRACT

Since delivery of drug through buccal mucosa offer many advantages, buccal route has attracted great attention in recent years. Avoiding first pass metabolism, rapid absorption and ease of access of buccal mucosa are the major advantage of this route of delivery. Cyclobenzaprine HCl (CBZ HCl) is most commonly used muscle relaxant in case of muscle pain. New indication of CBZ HCl for improving sleep quality in patient with fibromyalgia and post-traumatic stress syndrome (PTSS) recently was approved by the FDA. CBZ HCl has low oral bioavailability (35-55%) due to extensive pre-systemic metabolism in the gut wall and liver. The aim of this research work was to compare the permeability of cyclobenzaprine (base) and cyclobenzaprine HCl (salt) via buccal mucosa and evaluate the effect of lecithin soya on their permeability. In addition, feasibility of formulating them as mucoadhesive buccal film was assessed. The film formulation made from POLYOX WSR N750 and HPMC was evaluated in term of film thickness, content uniformity, swelling index and adhesion time and drug release rate. Result obtained from ex-vivo permeability studies showed that the transferred mass during 2 hours was 0.36 ± 0.03 (mg/cm^2) and 0.27 ± 0.04 (mg/cm^2) for MF1 (contain CBZ HCl) and MF3 (contain CBZ base) respectively which shows buccal mucosa was more permeable to CBZ HCl than CBZ base. Soya lecithin was found to increase permeability of CBZ HCl (0.61 ± 0.07 (mg/cm^2)) but it did not enhance that of CBZ base (0.24 ± 0.04 (mg/cm^2)). The result demonstrated that CBZ in salt form is more suitable form, for delivery via buccal mucosa than basic form.

Keywords: *Cyclobenzaprine HCl, Buccal delivery, Permeation enhancer, Mucoadhesion, Buccal film*

INTRODUCTION

Cyclobenzaprine is most often used muscle relaxant for nonspasticity-related muscle pain [1]. Cyclobenzaprine hydrochloride is freely water soluble drug, having low oral bioavailability (33-55%) due to its extensive metabolism in both the gut wall and liver [2]. Some works have been done for improving bioavailability of cyclobenzaprine HCl by its administration via other routes. For instance, formulating the drug as buccal polar and non-polar spray or capsule, [3] its administration via nasal cavity [4] and pulmonary route, [5,6] but still IR and ER tablet and capsules are the only marketed product. Sublingual tablet of this drug is in phase two clinical trial for treatment of fibromyalgia and post-traumatic stress syndrome (PTSS).

Considering another route of drug administration is a solution for improving bioavailability of those drug substances that are poorly bioavailable due to high first pass metabolism [7]. Recently buccal route has attracted attention for achieving both local and systemic effect [8-11] Buccal route offers many advantages, due to the direct drainage of blood from the buccal epithelium into the internal jugular vein, avoiding first pass metabolism is possible. Since buccal mucosa is 4-4000 times more permeable than the skin and also because of high total blood flow, more rapid onset of drug action is expected. Accessibility of buccal mucosa and ease of application are other advantages of this route of

delivery [12-14].

Lipid composition of buccal mucosa which is non-keratinized is different from keratinized area such as palate and gingiva mucosa. The keratinized area mostly has neutral lipid such as ceramide and cholesterol, but the non-keratinized epithelium has polar lipid such as cholesterol sulfate, phospholipid and glucosylceramide. These properties make buccal mucosa a suitable route for delivery of hydrophilic macromolecules such as peptides and proteins [15].

Physicochemical properties of the drug molecule such as molecular size, partition co-efficient, will determine the absorption of drug across buccal mucosa. Sometimes for achieving therapeutic concentration, we have to increase the rate and extent of drug absorption. In such situation co-administration of chemical permeation enhancers is an option for enhancing the rate and extent of drug absorption. A wide range of chemicals are investigated and used as permeation enhancers such as: fatty acids, chelators, cyclodextrins, bile salts, surfactants, vehicle and adjuvant, enzyme inhibitors. At the same time, action of penetration enhancer is specific for different drugs as well as different types of biological barrier. Hoogstraate et al, studied the penetration enhancing effect of bile salt on the transport of hydrophilic macromolecule compound across the porcine mucosa. The result of this study showed that co-administration of trihydroxy bile salts such increased the in-vitro transport of fluorescein isothiocyanate (FITC) by a factor of a hundred or more [16]. Whereas another study by Caro et al., showed that sodium dehydrocholate did not increase the penetration of Galantamine through the buccal mucosa [17]. In research that were conducted by Artusi et al, sodium taurodeoxycholate did not has and increasing effect in permeability of through porcine buccal mucosa [11].

Mucoadhesion may be defined as a state in which two materials, one of which mucus or a mucous membrane, is held together for an extended period of time. Over the last two decade mucoadhesive dosage forms become of interest for their potential for both localized and systemic drug delivery [7]. Different mucoadhesive drug delivery systems have been developed for buccal administration. Among them, buccal films are more acceptable for the patient because of their flexibility and comfort. In contrast to mucoadhesive gels, buccal films provide more residence time and are more resistant to saliva outflow. In addition, buccal films provide wound surface protection and hence, are more effective in reducing pain and treatment of oral diseases [7].

The aim of the present study was to compare the permeability of salt and base form of cyclobenzaprine via buccal mucosa and to evaluate the effect of lecithin soya on their permeability. In addition, feasibility of formulating them as mucoadhesive buccal film was assessed and reported in this paper.

MATERIAL AND METHODS

1.1. Reagent/chemicals

Cyclobenzaprine HCl was kindly supplied by FLEMING LABORATORY (Hyderabad, India) and POLYOX WSR-N750 gifted by COLORCON ASIA PRIVATE LIMITED (Delhi, India). Other chemicals were supplied by Pharmaceutics Laboratory of Lovely Professional University, Punjab, India.

1.2. Drug assay

UV-Spectrophotometer (UV-1800, Shimadzu Co. Ltd. Japan) was used for assay of cyclobenzaprine HCl during dissolution test and ex-vivo permeation studies.

1.3. Preparation of buccal film

0.14g of CBZ HCl was accurately weighed and dissolved in 2ml distilled water. Plasticizer was dissolved in to the above mentioned mixture, followed by addition required amount of concentrate aqueous polymeric solution. After mixing properly, the formulation was poured into mold (glass petri plate with diameter 9 cm) and then was kept under vacuum for removing of air bubble. Then it was transferred to oven and dried at 40 ^{o}C overnight (15 - 16 h). For converting CBZ HCl to CBZ (base), amount of NaOH was added to MF3 and MF4 to neutralize the HCl of CBZ HCl and produce some extra amount of OH^- for maintaining basic pH of microenvironment and thus keeping CBZ in basic form [18]. Lecithin as a permeation enhancer was added into both formulation MF2 and MF4 and its effect on permeability of CBZ HCl (MF2) and CBZ (base) (MF4) was evaluated. Compositions of drug loaded films are shown in Table 1. Individual film was made by cutting the film to 1.5 × 1.5 cm pieces. Each individual film enveloped in aluminum foil and then they put in poly bag and stored at room temperature.

Table 1. Composition of drug loaded films

Formula	MF1	MF2	MF3	MF4
CBZ HCl (g)	0.14	0.14	0.14	0.14

HPMC E50 (g)	0.2	0.2	0.2	0.2
PEO (g)	0.5	0.5	0.5	0.5
Glycerin (ml)	0.14	0.14	0.14	0.14
Soya lecithin (g)	_	0.007	_	0.007
NaOH (g)	_	_	0.02	0.02
Drying time (h)	15	15	15	15

1.4. Characterization of buccal film

1.4.1. Thickness: Thickness of the three films was determined by using screw gauge. In each film, thickness of four corners and center was measured.

1.4.2. Weight Uniformity: Six patches were weighed individually and the average weights are calculated. Results are expressed as mean ± SD.

1.4.3. Drug Content and Content Uniformity: Three films were dissolved in 100 ml simulated saliva pH 6.8 separately. After complete dissolution, the drug content was determined by UV spectrophotometer at the wavelength of 290nm. The result is shown as mean ± SD.

1.4.4. Swelling Properties: Swelling properties were measured by placing the pre-weighed film (W_1) on the surface of agar gel 2% (W/V) for one minute. Increase in film weight was measured by weighing it again (W_2). Swelling index was calculated by the following formula.

$$SI = \frac{W2 - W1}{W1} * 100$$

1.4.5. Surface pH: The film was placed at the end of a test tube and 5ml distilled water was added to each test tube and kept for 1hr. PH was determined by bringing the electrode of pH meter in contact with the film surface [19].

1.4.6. In-vitro Release Studies: For in-vitro evaluation of drug release, films were attached to wall of 15 ml glass bottle to provide unidirectional release of drug. 10 ml simulated saliva pH 6.8 was added to the bottle and temperature was kept at 37 ^oC using water bath. At appropriate time point (15, 30, 45 and 60 min) 0.5 ml sample was taken from the dissolution media and again replaced with 0.5 ml fresh simulated saliva pH 6.8. Drug content was determined by using UV-Visible spectrophotometer at wavelength 290nm.

1.4.7. Adhesion time: Modified disintegration tester was used for measuring residence time and porcine intestine mucosa was used to simulate adhesive surface. Glass slide was covered with porcine intestine mucosa by use of adhesive glue and fixed on disintegration tester. Then film was wetted and attached on the surface of mucosa by applying gentle pressure for 30 sec. After running apparatus, it was allowed to move up and down in 500 ml simulated saliva pH 6.8 at 37 ^oc. The times taken for the film to detach from the surface or to be dissolved completely were recorded.

1.5. Ex-vivo permeation studies

Fresh Porcine buccal mucosa was provided from a local slaughterhouse and its epithelial was used as a biological barrier. Muscle and fat tissue were removed using surgical blade. Epithelial layer) was separated using heat treatment in normal saline solution at 70 ^oC for 1 min [20]. The tissue prepared so, was deepened in 20% glycerin solution and then was kept in the freezer at -20 ^oC [21] until being further used. Vertical Franz diffusion cell (29 ml capacities and surface area 2.54 cm^2) was used. Receptor compartment was filled with phosphate buffer pH 7.4; buccal film placed on the surface of mucosa and 1ml simulated saliva pH 6.8 was added to the donor compartment. 3 ml sample was taken in appropriate time interval (30, 60, 90 and 120 min) and fresh media was added for maintaining sink condition. Samples were analyzed by UV-spectrophotometer at 290 nm. All of the experiment was performed in triplicate and the results were recorded as mean ± SD.

RESULT AND DISCUSSION

Buccal route is an alternative route for improving bioavailability of the drug molecule that undergoes high first pass metabolism. In this research work permeability of CBZ HCl and CBZ base across buccal mucosa was assessed. More over suitability of buccal film formulation were considered. Our result revealed that CBZ HCl is more suitable for delivery through buccal mucosa by considering both permeability and films characteristics.

All results regarding weight, thickness, drug content, surface pH, swelling index, release percentage, adhesion time and permeability are summarized in table 2.

1.6. Morphology, Weight, Thickness and Drug Content Variation

MF1 and MF2 were translucent and had coarse surface. MF3 and MF4 were completely opaque, because of separation of CBZ base which there was as dispersed form in the film. Weight and thickness of films were in the range of 0.035–0.04g and 125–148μm respectively. Drug content of the films varied from 4.2 –5.5mg. Content variation was mostly due to variation in drying surface (Petri dish and oven shelf surface). Results are summarized in table 2.

Table 2. Data showing the characterization results of MF1-MF8

Formula	Weight (g)	Thickness (μm)	Drug content (mg/unit of film)	Loaded CBZ HCl (mg/unit of film)	Efficacy of drug loading in films (%)
MF1	0.037 ± 0.004	138.00 ± 14	4.84 ± 0.24	5	96.8
MF2	0.039 ± 0.004	148.67 ± 29	5.83 ± 0.97	5	116.6
MF3	0.035 ± 0.004	125.33 ± 26	5.13 ± 0.04	5	102.6
MF4	0.04 ± 0.008	140.67 ± 33	5.50 ± 0.14	5	110
Formula	**Surface pH**	**Swelling index**	**Release % in 1 h**	**Adhesion time (min)**	**Permeability (mg/cm^2) in 2 h**
MF1	6.9 ± 0.2	73 ± 3.5	63.04% ± 4.3	173.3 ± 8	0.36 ± 0.03
MF2	6.9 ± 0.1	71.62 ± 7.3	62.24 ± 5.1	180.0 ± 3	0.61 ± 0.07
MF3	9.3 ± 0.2	107.76 ± 11	48.02 ± 2.2	134.7 ± 4	0.27 ± 0.04
MF4	9.5 ± 0.1	92.44 ± 2.7	46.3 ± 2.1	147.7 ± 6	0.24 ± 0.04
All of the results are recorded as Mean ± SD of triplicate experiment					

1.7. Surface pH

The surface pH of films was in the range of 6.9–9.5. The surface pH of the mucoadhesive formulation has an important role in patient comfort. While physiologic pH of saliva is in the range of 6.2 – 7.4, [22] pH of MF3 and MF4 was 9.3 and 9.5 respectively which are out of this range and may cause mucosa damage and patient discomfort.

1.8. Swelling Index

Mechanism of drug release from hydrophilic polymeric matrix is solvent penetration, hydration and swelling of the polymeric matrix and the diffusion of dissolved drug to biological media. Swelling of polymeric film is necessary for both adhesion of the film to biological surface and release of drug. Formulated buccal films showed very interesting swelling value in one minute (71.62-107.6%) that can be an indicator of rapid adhesion to biological surface and rapid release of the drug. Film with added NaOH showed the highest swelling index as showed in table 2 and figure 1. Same result was obtained by Goyal et al., regarding pH dependent swelling properties of PEO [23].

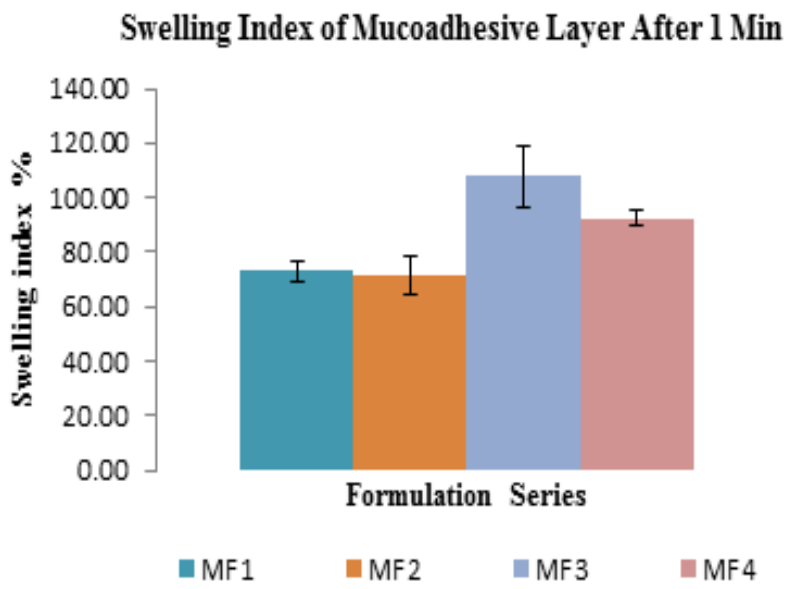

Figure 1. Swelling behavior of different formulation

1.9. In-Vitro Release Studies

Percentage of drug release from MF1, MF2, MF3 and MF4 were 63.04% ± 4.3, 62.24 ± 5.1, 48.02 ± 2.2, 46.3 ± 2.1 at the end of 120 min respectively. There was no significant difference between the release profile of MF1 and MF2. Although MF3 and MF4 exhibited the highest swelling index but they had the lowest drug release, may be due to less solubility of CBZ base than CBZ HCl salt. This showed the salt or basic state of CBZ, had more effect in drug release than swelling properties of the polymeric matrix. In addition, lecithin soya did not have any effect on the release rate of CBZ HCl and CBZ base.

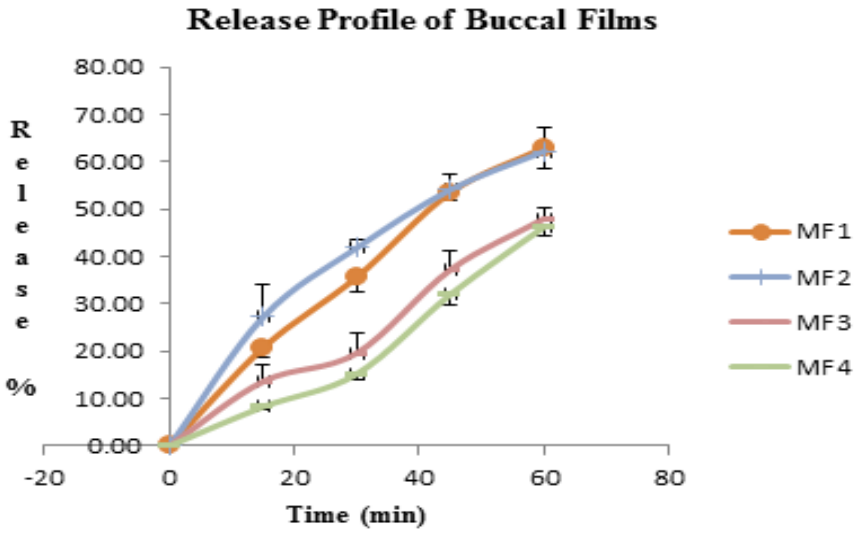

Figure 2. Release profile of buccal film in simulated saliva pH 6.8

1.10. Adhesion Time

The time it took for MF1, MF2, MF3 and MF4 to separate from buccal mucosa was 173.3, 180, 134.7 and 147.7 respectively. This result is regardless of separation of films edge and is related to complete separation or dissolution of films. From this data we can conclude that the addition of NaOH to formulation decreased adhesion time of films.

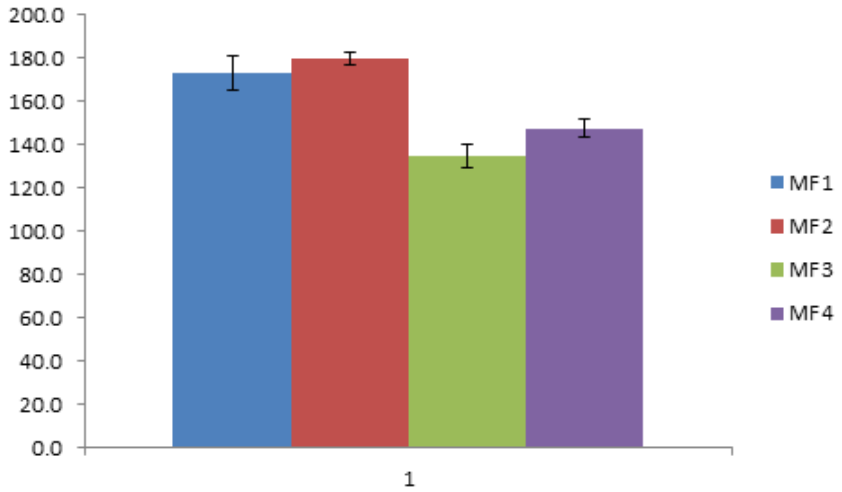

Figure 3. Adhesion time of film formulations

1.11. Ex-Vivo Permeation Studies

No work was found regarding determination of permeability of CBZ base or CBZ HCl through buccal mucosa, but some works have been done for evaluation of permeability of CBZ through skin. Lv et al., examined transdermal delivery of CBZ base and CBZ HCl from adhesive patch across isolated rabbit abdominal skin (with and without stratum corneum). They found that permeation of CBZ base was significantly higher than that of CBZ HCl (respectively 8.69 ± 2.48 µg/cm2 and 39.3 ± 4.73 µg/cm2 during 12 hr.). Permeability of CBZ base was higher in skin without stratum corneum (85.41±4.28 µg/cm2 during 12 hr.) [24].

Hartwing et al., conducted one study on permeability of CBZ base in adhesive transdermal delivery system through human cadaver skin. Their results showed permeability of CBZ from formulation 1 (without permeation enhancer) and formulation 2 (contain fatty alcohol as a permeation enhancer) was respectively 265 and 285 µg/cm2 during 24 hr. [25].

Comparing this result with our result shows that permeability of CBZ base and CBZ HCl through buccal mucosa is higher than skin (with and without stratum corneum). Second and more important point is that permeability of CBZ HCl through buccal mucosa is higher than permeability of CBZ base that is quite opposite of result which obtained by Lv et al., in which permeability of CBZ base is higher than permeability of CBZ HCl through skin. In the same way, base form of CBZ was selected by Hartwing et al., for delivery through skin. Of course this phenomenon can be justified by different characteristics of skin and buccal mucosa. It is obvious that physicochemical properties of drug molecules such as molecule size and partition coefficient as well as characteristics of biological membrane will determine the rate and amount of drug absorption across buccal mucosa. Non-keratinized buccal mucosa contains more hydrophilic lipid in the intracellular space, so it can be considered as a barrier against permeation of more lipophilic CBZ base [26]. Whereas, because of more lipophilic nature of biological membrane in skin, it is more permeable for CBZ base than CBZ HCl. Slower release of drug from MF3 and MF4, can be considered as another factor for lower flux of CBZ base. As in vitro dissolution studies showed, rate and amount of drug release from MF1 and MF2 were more than MF3 and MF4. As already mentioned, justification for this phenomenon is higher solubility of CBZ HCl as CBZ base.

Permeation enhancers were widely used to improve the permeation of drugs, because of easy to use, relatively stable and low cost. Lecithin soya which generally was considered to be safe was evaluated as a permeation enhancer. Lecithin increased permeability of CBZ HCl but did not show any increasing effect on permeability of CBZ base. Action of permeation enhancer is specifically for different drug molecules as well as different types of biological barrier. For example, in research that was conducted by Hartwing et al., fatty alcohol did not show any increasing effect in permeability of CBZ base through human cadaver skin, while Lv et al., examined the effect of nine mostly used permeation enhancer (Azone, menthol, Span 20, Tween 80, Propylene glycol, Oleic acid, 2-(2-ethoxyethoxy) ethanol, N-methyl – 2- Pyrrolidone) on permeability of CBZ base across rabbit abdomen skin and they found that only Span 20 can increase the permeability of CBZ base. Tian et al., showed that the permeation rate of insulin can be increased by co-administration of soybean-lecithin. They reported that soybean-lecithin is safer for buccal mucosa than deoxycholic acid and Azone [27]. Valen et al., showed that soybean-lecithin improves the partition of ketoprofen

in the n-octanol and is promising candidate for drug delivery system in dermatology and cosmetology [28].

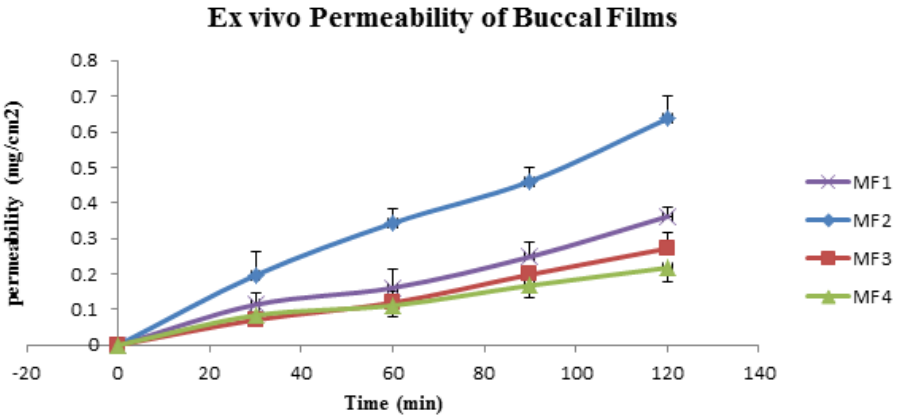

Figure 4. Ex-vivo permeation of CBZ HCl from MF6, MF7 and MF8 through porcine buccal mucosa

CONCLUSION

During this study, buccal permeation of both CBZ (base) and CBZ (salt) from mucoadhesive formulation was compared. Besides that, suitability of mucoadhesive buccal films was evaluated. Mucoadhesive film, loaded with 5 mg of CBZ, was prepared by casting solvent method. PEO was used as mucoadhesive polymer and HPMC as structural polymer. All films showed good physical properties. PH of the MF3 and MF4 containing additional amount of NaOH was higher than saliva pH, which may be irritant to buccal mucosa. During evaluation of adhesion time, MF1 and MF2 had remained on buccal mucosa until complete dissolution but in case of MF3 and MF4, they separated before complete dissolution. There was no significant difference between the release rate of MF1 and MF2 and also between MF3 and MF4. But release rate of MF1 and MF2 was higher than release rate of MF3 and MF4. This shows buccal films contain salt form of CBZ releasing the drug faster. Ex-vivo permeation studies showed that conversion of CBZ HCl to CBZ base not only did not increase permeability of CBZ, but also decreased it. Reason for this decrease can be slower release of drug from the MF3 and MF4 or presence of more hydrophilic lipids in intercellular space of non-keratinized buccal mucosa which can be considered as a barrier against permeation of more lipophilic CBZ. Lecithin increased permeability of CBZ HCl but did not show any increasing effect on permeability of CBZ base (unionized form). So, CBZ in salt form is more suitable form for delivery via buccal mucosa.

REFERENCES

1. Meleger, A.L. Muscle relaxants and antispasticity agent, Phys Med Rehabil Clin N Am., 2006, 17, 401-413
2. Brioschi, T.M.L.S., Schramm S.G., Kazue Kano E., Mori Koono E.E., Ching T.H., Reis Serra, C.H.D., Porta, V., Pharmacokinetics and Bioequivalence Evaluation of Cyclobenzaprine Tablets, BioMed Res Int, 2013, 1-6.
3. Dugger Iii, H.A., Buccal, polar and non-polar spray or capsule containing drugs for treating muscular and skeletal disorders, WO2004019905 A1 PCT/US, 2004.
4. Borsa, M., Pharmaceutical composition containing cyclobenzaprine suitable to intranasal administration**,** WO2012137054 A1 US/PCT, 2012.
5. Blondino, F.E., Poklis, J., Baker, M., Aerosol formulations and aerosol delivery of buprenorphine, US7501113 B2 US/EP, 2009
6. Patel, D., Naik, S., Chttani, K., Mathur, R., Mishra, A.K., Misra, A., Intranasal delivery of cyclobenzaprine hydrochloride-loaded thiolated chitosan nanoparticles for pain relief, J Drug Target., 2013, 21(8):759-769.
7. Shojaei, A.H., Buccal Mucosa As A Route For Systemic Drug Delivery: A Review, J Pharm Pharmaceut Sci., 1998, 1(1):15-30.
8. Abruzzo, A., Biqucci, F., Cerchiara, T., Cruciani, F., Vitali, B., Luppi, B., Mucoadhesive chitosan/gelatin films for buccal delivery of propranolol hydrochloride, carbohydrate polymers., 2012, 87(1):581-588.
9. Juliano, C., Cossu, M., Pigozzi, P., Rassu, G., Giunchedi, p., Preparation, In vitro characterization and preliminary in vivo evaluation of buccal polymeric films containing chlorhexidine, AAPS PharmSciTech., 2008, 9(4):1153-8.
10. Singh, S., Jain, S., Muthu, M.S., Tiwari, S., Tilak, R., Preparation and evaluation of buccal bioadhesive films containing clotrimazole, AAPS PharmSciTech., 2008, 9(2):660-7.

11. Artusi, M., Santi, P., Colombo, P., Junginger, H.E., Buccal delivery of thiocolchicoside: in vitro and in vivo permeation studies, Int J Pharm., 2003, 250(1):203-13.
12. Lamey, P.J., Lewis, M.A.O., Buccal and sublingual delivery of drugs. In: Salole, A.T., Florence EG. Routes of drug administration . Norfolk: Butterwotth and Co, 1990. P. 30-47.
13. McElnay, J.C., Buccal absorption of drugs. In: Boylan, J., Swarbrick JC. Encyclopedia of pharmaceutical technology. New York: Marcel Dekker, 1990. P. 189-211.
14. Nicolazzo, J.A., Reed, B.L., Finnin, B.C., Buccal penetration enhancers - How do they really work?, J Control Release., 2005, 105(1-2):1 - 15.
15. Satheesh Madhav, N.V., Semwal, R., Semwal, D.K., Semwal, R.B., Recent trends in oral transmucosal drug delivery system: an emphasis on the soft palatal route, Expert Opin. Drug Deliv., 2012, 9(6):629-47.
16. Hoogstraate, A.J., Senel, S.b., Cullander, C., Verhoef, J., Junginger, H.E., Effect of bile salts on transport rates and routes of FITC-labelled compounds across porcine buccal epithelium in vitro, J Control Release., 1996, 40(3):211-21.
17. De Caro, V., Giandalia, G., Siragusa, M.G., Campisi, G., Giannola, L.I., Galantamine Delivery on Buccal Mucosa: Permeation Enhancement and Design of Matrix Tablets, J Bioequivalence and Bioavailability., 2009, 1(4):127-134.
18. Hsu, T. M., Macy, R., Luo, E. G., Transdermal Administration of pharmacologically active amines using hydroxide-releasing agents as permeation enhancers. US 6,719,997 B2 US, 2004.
19. Bahri-Najafi, R., Tavakoli, N., Senemar, M., Peikanpour, M., Preparation and pharmaceutical evaluation of glibenclamide slow release mucoadhesive buccal film, Res Pharm Sci., 2014, 9(3):213-23.
20. Ganem-Quintanar, A., Quintanar-Guerrero, D., Buri, P., Jacques, Y., Permeability to fentanyl solutions and lipid composition of buccal epithelium surgically isolated versus heat separated, Int'l. Symp. Control. Rel. Bioact. Mater., 2000, 27.
21. Amores, S., Domenech, J., Colom, H., Calpena, A.C., Clares, B., Gimeno, Á., Lauroba, J., An improved cryopreservation method for porcine buccal mucosa in ex-vivo drug permeation studies using franz diffusion cells, Eur J Pharm Sci., 2014, 60:49-54.
22. Washington, N., Washington, C., Wilson, C.G., physiological pharmaceutics: Barriers to drug absorption. 2. s.l. : Taylor and Francis Inc, 2001.
23. Goyal, A., Shukla, P., Srivastava, A.K., Factors influencing drug release characteristic from hydrophilic polymer matrix tablet, Asian J Pharm Clin Res., 2009, 2: 93-98.
24. Lv, S., Quan, P., Wang, W., Fang, L., Two steps modification for improvement of cyclobenzaprine transdermal delivery: releasing from patch and penetrating through skin, Drug Dev Ind Pharm., 2016, 42(12):2070-77.
25. Hartwig, R., Mantelle, J., Houze, D., Li, C., Moncada, K., Permeation of cyclobenzaprine from transdermal delivery devices through human cadaver skin, Noven Pharmaceuticals, Inc., 2000, pp. 1-3.
26. Squier, C.A., Cox, P., Wertz, P.W., Lipid content and water permeability of skin and oral mucosa, J. Invest. Dermatol., 1991, 96(1):123-6.
27. Tian, W., Hu, Q., Xu, Y., Xu, Yi., Effect of soybean-lecithin as an enhancer of buccal mucosa absorption of insulin, Biomed Mater Eng., 2012, 22(1-3):171-8. doi: 10.3233/BME-2012-0704
28. Valenta, C., Wanka, M., Heidlas, J., Evaluation of novel soya-lecithin formulations for dermal use containing ketoprofen as model drug, J control Release., 2000, 63(1-2):165-73. doi: 10.1016/S0168-3659(99)00199-6