



<https://ijrps.com>

ISSN: 0975-7538

Research Article

Design and evaluation of buccal mucoadhesive patches containing an anti hypertensive prodrug Trandolapril

P. Subhash Chandra Bose*¹, D.Saritha², R. Nagaraju³

¹Department of Pharmaceutics, MNR College of Pharmacy, Sagareddy, Telangana, India

²Department of Pharmaceutics, Sultan-ul-uloom College of Pharmacy, Hyderabad, Telangana, India

³Department of Pharmaceutics, Sri Padmavathi Visva Vidyalayam, Tirupati, Andhra Pradesh, India

ABSTRACT

The buccal region offers an attractive route for systemic drug delivery. Trandolapril is an ACE inhibitor widely used as an antihypertensive agent shows less oral bioavailability as it undergoes first pass metabolism. Trandolapril patches were prepared using HPMCK4M, Chitosan, HPMCP, PVP and PVA. FTIR and DSC studies revealed that there was no interaction between trandolapril and polymers. Gas phase chromatography was carried to estimate the residual Methanol, acetic acid and dichloromethane. The patches were evaluated for their thickness, folding endurance, weight uniformity, content uniformity, swelling behaviour, tensile strength, and surface pH. The tensile strength was higher for formulations containing HPMCP and HPMCK4M. *In vitro* release studies were conducted for trandolapril loaded patches in 6.6 pH phosphate buffer solution. Patches containing chitosan and HPMCK4M exhibited greater release than other formulations containing HPMCP, PVP, PVA and HPMCK4M. Patches exhibited drug release in the range of 63.8 to 99.9% in 8 hrs. Data of *in vitro* release from patches were fit to different equations and kinetic models to explain release profiles. Many of the buccoadhesive systems followed zero-order release kinetics. Buccoadhesive patches of trandolapril can be developed as potential controlled release formulations for the treatment of hypertension.

Keywords: Trandolapril; Buccal patches; Mucoadhesion; First pass metabolism; Residual solvents

INTRODUCTION

Conventional routes of drug administration have several disadvantages. The rate and extent of absorption can vary greatly depending on the drug, its formulation, the presence of food, drug interactions, first-pass metabolism and gastrointestinal pH. So various other routes for drug delivery are being developed which minimize these problems.

Buccal mucosa offers a convenient route for local and systemic drug delivery. In recent years, buccoadhesive drug delivery systems have gained considerable interest with regard to systemic delivery of drugs undergoing hepatic first-pass metabolism and premature drug degradation within the gastrointestinal tract. Lower enzymatic activity of saliva, facile removal of formulation, better patient acceptance and compliance are some other prominent meritorious visages of buccoadhesive systems. These factors make the oral mucosa a very attractive and feasible site for systemic drug delivery. A few drugs, such as Fluconazole (Yehia

et al., 2007) Carvedilol (Vamshi Vishnu *et al.*, 2007), Cetylpyridinium Chloride (Nafee *et al.*, 2003), Oxytocin (Cheng *et al.*, 1996), Miconazole Nitrate (Nafee *et al.*, 2003), Nystatin (Llabot *et al.*, 2007), have been successfully administered via the buccal route.

Trandolapril is an ACE inhibitor widely used as an anti-hypertensive agent. It is rationale to formulate the buccoadhesive dosage forms of trandolapril as it is known to have low oral bioavailability (Guay, 2003) due to an extensive first-pass effect. Further, its short half-life (less than 1 hr) and low molecular weight (430.54) make it an appropriate candidate for formulating it into a buccoadhesive dosage form.

MATERIALS AND METHODS

Materials

Trandolapril was a gift sample (Hetero Drugs, Hyderabad, India), HPMCP (Hydroxy propyl methyl cellulose pthalate), HPMCK4M were obtained from Dr. Reddy's lab, Hyderabad and Chitosan was obtained from Marine chemicals, Cochin. All the chemicals, solvents and reagents were of analytical grade and used further purification.

Preparation of mucoadhesive patches

In the present investigation, buccoadhesive patches of trandolapril were prepared by the solvent casting

* Corresponding Author

Email: penjurisubhash@gmail.com

Contact: +91-9848033974

Received on: 22-09-2011

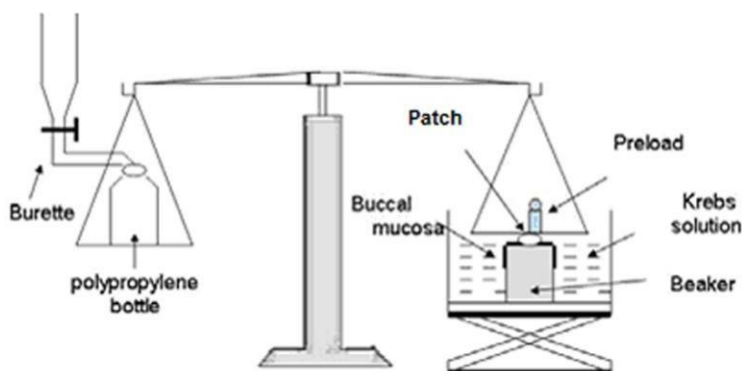
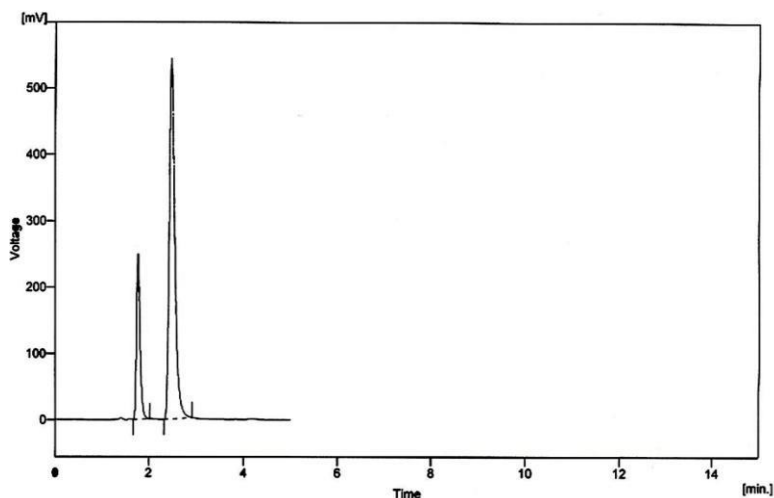
Revised on: 05-10-2011

Accepted on: 06-10-2011

Table 1: Composition of mucoadhesive buccal patches

Trandolapril (10mg/cm ²)								
Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
HPMCK4M (%)	1	1	1	1	1	1	1	1
Chitosan (%)	0.5	1	--	--	--	--	--	--
HPMCP (%)	--	--	0.5	1	--	--	--	--
PVA (%)	--	--	--	--	0.5	1	--	--
PVP (%)	--	--	--	--	--	--	0.5	1
Glycerine (mg)	60	80	60	80	60	80	60	80
Dichloro Methane (ml)	--	--	5	5	--	--	--	--
Methanol (ml)	--	--	5	5	--	--	--	--
Water (ml)	20	20	--	--	20	20	20	20

Abbreviation used: HPMC- Hydroxy Propyl Methyl Cellulose, HPMCP- Hydroxy Propyl Methyl Cellulose Pthalate, PVP – Poly vinyl Pyrrolidone, PVA-Poly Vinyl Alcohol.

**Figure 1: Diagram of the assembly used for the bioadhesive strength measurement****Figure 2: HPLC chromatogram of Trandolapril**

method. HPMCK4M was dissolved in sufficient quantity of water and used as basic polymer solution. Various polymeric solutions were prepared in suitable solvents as - Chitosan is soaked in 1% glacial acetic acid for 24 hours to get a clear solution, HPMCP is dissolved in a mixture of equal volumes of methanol, dichloromethane, PVA and PVP were dissolved in water. The polymer solutions are blended in combinations as shown in the Table 1 and checked for air entrapment. Drug was dissolved in little amount of water and further was added to polymer solution. Glycerine was used as plasticizers in the concentration of 20% w/w of

the polymer. This solution was poured on to a glass mould and left over night for air drying at room temperature; the dried polymeric patches were packed in aluminium foil and kept in desiccator till further use.

Drug-polymer compatibility studies

FT-IR spectroscopy

The test samples were dispersed in KBr powder and analyzed. FT-IR spectra were obtained by diffuse reflectance on FT-IR spectrometer type Shimadzu model 8033, USA. Compatibility between the drugs and polymers were compared by FT-IR spectra. The positions of

FT-IR bands of important functional groups of drugs were identified and cross checked in FT-IR spectra of formulation.

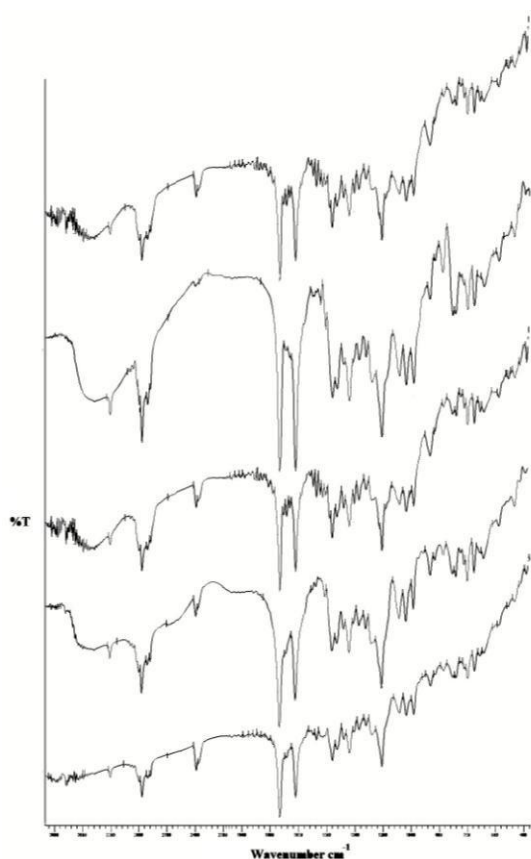


Figure 3: FT-IR spectra of Trandolapril and its formulations

Differential scanning calorimetry (DSC)

To study the compatibility between drug and polymers DSC studies were carried. DSC studies were carried out on Du Pont thermal analyzer with 2010 DSC module. Calorimetric measurements were made with empty cell (high purity gold discs of Du Pont Company) as the reference. The instrument was calibrated using high purity indium metal as standard.

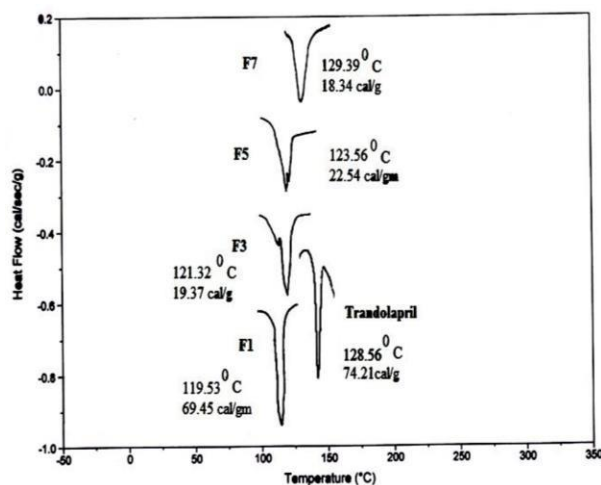


Figure 4: DSC thermograms of Trandolapril and its formulations

Evaluation of the patches

Thickness of the patches

The thickness of the patch was measured by screw gauge at five different positions of the patch and the average was calculated.

Uniformity of weight of the patches

Twenty patches (Each 1cm²) were weighed individually. Average weight of the patches was calculated.

Drug content uniformity of the patches

Calibration curve of trandolapril in phosphate buffer (pH 6.6) solution was obtained at λ_{\max} 216 nm with a UV-VIS spectrometer (UV-1601PC, Shimadzu Corporation, Tokyo, Japan). The calibration curve was constructed in the concentration range of 5-25 $\mu\text{g/ml}$ which obeys beer's law. Ten, 1 cm² (contains 10 mg of trandolapril) patches were placed in a beaker; 20 ml of pH 6.6 buffer was added and stirred to dissolve. The contents were transferred to a 100 ml volumetric flask and volume was made up with pH 6.6 buffer, filtered and analysed after suitable dilutions at 216 nm.

Folding endurance

Folding endurance of the patches was determined by repeatedly folding one patch (Khanna, 1997) at the same place till it broke or folded upto 200 times manually, which was considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance.

Determination of surface pH

The surface pH of the patch was determined in order to predict the possible irritative effects of the formulation on the buccal mucosa. The patches were allowed to swell at $37 \pm 1^\circ\text{C}$ for 2 hrs in 40 ml phosphate buffer pH 6.6. The surface pH was measured by means of pH paper placed on the surface of the swollen patch (Noha *et al.*, 2003).

Stability in buffer solution

Patches were placed in different phosphate buffer solutions of pH 6.0, pH 6.6 and pH 7.0 and stirred at 50 rpm maintained at $37 \pm 2^\circ\text{C}$. The solution was withdrawn at 1, 12 and 24 hr. and analyzed for the drug content spectrophotometrically. (Kim, 2000).

Swelling studies

Each patch which was individually weighed (W1) were placed in Petri dishes containing 4ml of phosphate buffer pH 6.6 and incubated at 37°C . (Semalty *et al.*, 2005) At time intervals of 0.5, 1, 2, 3, 4, 5, 6 hrs one Petri dish was removed from the incubator and swollen patches were weighed out (W2). Swelling index (SI) was calculated using following formula. $SI = (W2 - W1)/W1$.

Table 2: Evaluation Parameters of mucoadhesive patches

Formulation code	Thickness (μm)	Uniformity of weight (mg)	Drug content	Folding endurance	Surface pH
F1	166 \pm 4.24	17.97 \pm 1.26	9.85 \pm 2.62	>200	6-7
F2	188 \pm 3.15	18.9 \pm 2.16	9.62 \pm 1.70	>200	6-7
F3	221 \pm 2.42	18.37 \pm 1.26	9.88 \pm 1.42	>200	6-7
F4	202 \pm 2.24	17.19 \pm 1.11	9.46 \pm 1.24	>200	6-7
F5	198 \pm 3.25	18.13 \pm 0.25	9.07 \pm 0.16	>200	6-7
F6	202 \pm 5.57	17.80 \pm 0.38	8.93 \pm 0.79	>200	6-7
F7	206 \pm 2.86	18.07 \pm 0.26	9.67 \pm 1.09	>200	6-7
F8	210 \pm 3.84	18.89 \pm 0.16	9.01 \pm 0.91	>200	6-7

Table 3: Data of Stability studies of patches in different phosphate buffer solutions

Sl No.	Time (Hr.)	% drug content in buffers of different pH		
		pH 6.0	pH 6.6	pH 7.0
1	0	99.82 \pm 1.7	99.12 \pm 2.4	99.32 \pm 4.4
2	1	99.10 \pm 2.4	98.94 \pm 1.3	98.88 \pm 2.1
3	6	98.94 \pm 0.92	98.82 \pm 1.2	98.78 \pm 0.8
4	24	98.86 \pm 1.42	98.24 \pm 0.98	98.29 \pm 1.2

Tensile strength of the patches

The tensile strength of the Patches was carried out using Instron UTM (Hounsfield, UK) equipment at a speed of 50 mm/min. The method used a constant rate of straining method. A specimen patch sample of 10 \times 5 sq.cm was placed in the grips of the testing machine. The grips were tightened evenly and firmly to prevent slippage and the maximum load and extension were recorded (Khan, 2000).

In vitro bioadhesion test

The mucoadhesive strength of buccoadhesive systems was measured by a modified two-arm balance using porcine buccal mucosa (Smart, 1991). Porcine buccal mucosa was fixed to steel piece with adhesive. This was kept in a beaker and pH 6.6 buffer was added into the beaker upto upper surface of the mucosa to maintain mucosal viability. The patch was attached to the upper clamp with adhesive. The beaker was then slowly raised until the substrate comes in contact with the patch. A preload of was placed on the clamp for 5 minutes (preload time) so that the adhesion could be established. After this time, the preload was removed and water was added into the beaker by the burette at a constant rate. The addition of water was stopped when buccoadhesive system was detached from buccal mucosa. Weight required to detach the system from buccal mucosa was noted. Experiment was repeated with fresh mucosa in an identical manner.

Water vapor transmission rate studies for patch (Murthy et al., 2007)

One gram of calcium chloride was accurately weighed and placed in previously dried empty vials of equal diameter. The polymer patches were pasted over the brim with the help of an adhesive, and then the vials were weighed and placed over a mesh in dessicators,

containing 200 ml of saturated sodium bromide and saturated potassium chloride solutions. The dessicators were tightly closed and maintained at the 75% RH. Initial weight of the vial with patch was noted. The vials were removed from the dessicators after 24 hours and checked for weight loss, which was equal to the amount of water vapor transmitted. The average of triplicate readings was taken.

In vitro residence time

In vitro residence time was determined according to the method described by Nafee et al., 2004 Briefly, the apparatus consists of disintegration apparatus (Electrolab, EF-2, Mumbai, India) with 800 ml of phosphate buffer pH 6.6 maintained at 37 \pm 1 $^{\circ}$ C. Porcine buccal mucosa was glued to the glass slide and held vertically in the apparatus. The buccoadhesive patch was hydrated with 0.5 ml of phosphate buffer pH 6.6 and the hydrated surface was brought in contact with the buccal mucosa. The glass slide was allowed to move up and down so that the patch was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time required for the complete erosion or detachment of the patch from the mucosal surface was recorded (mean of triplicate).

Determination of residual solvents concentration (Di Martino et al., 2000).

Gas chromatography (Shimadzu GC-14B chromatograph, Japan) was used to estimate residual Methanol, acetic acid and dichloromethane in patches.

In vitro release studies

100 ml dissolution medium, phosphate buffer pH 6.6 maintained at 37 \pm 2 $^{\circ}$ C in 150 ml beaker was kept on a magnetic stirrer and stirred at 50 rpm. The backing layer of the patch was stuck to a glass disk of 2 cm.

Table 4: Evaluation Parameters of mucoadhesive patches

Formulation	Swelling Index	Tensile Strength (MPa) mean \pm SD *	Bio adhesive strength (Gm)	WVTR (g/m ² /day) mean \pm SD *	<i>In vitro</i> residence time (h)
F1	3.9 \pm 1.44	18.6 \pm 1.24	9.5 \pm 1.48	29.16 \pm 1.33	>6
F2	4.3 \pm 2.15	16.96 \pm 1.76	8.65 \pm 0.5	24.6 \pm 3.24	>6
F3	4.71 \pm 0.93	19.73 \pm 2.11	9.24 \pm 2.6	18.6 \pm 2.4	>6
F4	4.94 \pm 2.75	21.71 \pm 2.17	10.14 \pm 1.8	19.14 \pm 0.36	>6
F5	5.12 \pm 3.04	17.98 \pm 2.11	8.68 \pm 0.34	29.21 \pm 2.21	>6
F6	5.86 \pm 2.84	19.6 \pm 1.38	9.24 \pm 0.48	18.96 \pm 2.22	>6
F7	5.9 \pm 0.75	18.33 \pm 2.11	8.64 \pm 1.26	20.11 \pm 3.21	>6
F8	6.12 \pm 0.784	19.56 \pm 2.17	9.14 \pm 2.4	19.76 \pm 2.06	>6

Table 5: Residual solvent contents in patches

Residual Solvent ^a	Concentration Limit(ppm) (According to ICH guide lines)	Concentration in Patches (PPM)			
		F1	F2	F3	F4
Acetic acid (Class III)	5000	13.9636 \pm 2.74	11.2653 \pm 1.37	--	--
Dichloromethane (Class II)	600	--	--	8.4523 \pm 1.34	9.39521 \pm 1.73
Methanol (Class II)	3000	--	--	7.5431 \pm 0.931	8.5437 \pm 1.285

^a Estimated by Gas Chromatography

diameter using glue (Nafee *et al.*, 2004). This glass disk was attached to an L-shaped glass rod, which is fitted to a stand. Samples were withdrawn at regular intervals and the same volume of prewarmed (37 \pm 2^o C) phosphate buffer pH 6.6 was introduced into the beaker after each withdrawal to maintain sink condition. The samples were analyzed for drug content.

***In vitro* permeation studies**

Porcine buccal tissue from domestic pigs was obtained from local slaughterhouse and used in within two hours of slaughter. The tissue was stored in Krebs buffer at 4^oC after collection. The epithelium was separated from the underlying connective tissue by surgical method and the delipidized membrane was allowed to equilibrate for approximately for one hour in receptor buffer to gain the lost elasticity.

The buccal epithelium was carefully mounted in between the two compartments of a Franz diffusion cell (Semalty *et al.*, 2005). A, 1 cm² patch under study was placed in intimate contact with the excised porcine buccal mucosa and the topside was covered with aluminum foil as a backing membrane. Teflon bead was placed in the receptor compartment filled with 50 ml of pH 6.6 phosphate buffer. The cell contents were stirred with a magnetic stirrer and temperature of 37 \pm 1^oC was maintained throughout the experiment. The samples were withdrawn at every hour. Sink conditions were maintained. The samples were filtered, di-

luted suitably and analyzed using HPLC method (Laha *et al.*, 2008).

RESULTS AND DISCUSSION

Trandolapril and its formulations were subjected to FT-IR analysis. The obtained spectra are given in Figure 3. The characteristic peaks of pure drugs were compared with the peaks obtained for its respective formulations. From the FT-IR peaks it can be concluded that the peaks of pure trandolapril and formulations were found to be similar indicating that there was no significant interaction between trandolapril and polymers used.

In order to study any possible interactions between the drug and polymers, differential scanning calorimetric studies were carried out. The DSC thermograms obtained are reported in Figure 4. Trandolapril displayed a single sharp endothermic peak at 128.56^oC corresponding to its melting point of the drug and a peak at same temperature range was also observed in the formulation, confirming the stability of the drug in the prepared formulation. Slight change in the melting point of formulations may be due to presence of residual solvents.

The results of thickness and weight variation studies are given in Table 2. It was observed that the thickness of buccoadhesive patches containing chitosan and HPMCK4M was less compared to the other formulations. The weight of the patch was uniform irrespective

of the composition. The results of the drug content studies are given in Table 2. It was observed from the results that the prepared patches are uniform in drug content. Patches did not crack even after folding for more than 200 times. Hence it was taken as the standard limit. Folding endurance values of the patches were found to be optimum so they exhibit good physical and mechanical properties. Considering high alkaline or high acidic pH may cause irritation to the buccal mucosa and influence the degree of hydration of polymers (Chang, 1985 and Park, 1985), so the surface pH of patches was determined to optimize release and adhesion. The surface pH of all formulations was in the range 6-7 pH, i.e; close to buccal pH.

At the end of 24hrs trandolapril patches were stable in phosphate buffer solutions pH 6.0, 6.6 and 7.0. And found that drug loss was within the permissible limits (Table 3) indicates that there is degradation of drug in buffers.

Swelling studies were carried out in phosphate buffer pH 6.6 and is reported as swelling index in Table 4. Swelling index for the formulations is gradually increased. Formulation containing chitosan and HPMCK4M (F1& F2) showed faster swelling compared to other formulations. Maximum swelling was attained in 3hr, after which polymer started eroding slowly in the medium. The high initial uptake of water may be due to the faster hydration rate of HPMCK4M. Formulations containing HPMCP and HPMCK4M showed less swelling rate which may be attributed to low water solubility of HPMCP. The formulations containing PVP, PVA showed good swelling due to hydrophilic nature. The results of the tensile strength for the patches are given in Table 4. Highest tensile strength was observed formulation F4 and F2 showed least value. In formulations F1 and F2 the tensile strength decreased with increase in chitosan concentration. The tensile strength of patches F3 and F4 was more due to the presence of HPMCP which is hydrophobic in nature. The tensile strength of other formulations F5 to F8 showed less tensile strength due to hydrophilic nature of polymers (PVA & PVP). *In vitro* bioadhesive strength of the patches was measured using porcine buccal mucosa as biological membrane. The results are given in Table 4. The highest bioadhesive strength was observed in the formulation F4. Previous studies have demonstrated that the bioadhesive strength depends on the rate of swelling, pH, applied strength, initial contact time, and selection of the model substrate surface. As the concentration of chitosan was increased, the bioadhesive strength of the film decreased further, because chitosan has less solubility and swelling in pH 6.6.

The *in vitro* residence of patches showed that none of the polymer combination patches became detached from the porcine buccal mucosa during the experiments (Table 4). All the formulations exhibited more than 6 hours residence time. Water vapor transmission rate studies were carried out for all the formulations.

F3 and F4 showed less WVTR compared to all other formulations. This may be due to the hydrophobic nature of HPMCP, which is less permeable to water vapor. Residual solvent concentration of Methanol, acetic acid and dichloromethane are largely below the tolerated limits (Table 5)

In vitro release of trandolapril from buccal patches showed decrease in percent release with an increase in the amount of polymer (Figure 5 and 6) and time required for 50% of release was found to be maximum for F8 (7 hours) followed by other formulations. The least t50% 2 hours was observed for F1 formulation. The release of trandolapril from the formulations F1-F8 was found to be in the range 63.78 to 99.95%. As the swelling index decreased rate of release increased. Formulations F7 and F8 showed relatively retarded release with the least release observed for F8 63.78% in 8 hours due to higher swelling index of the formulation. The best fit model for F1 formulation was Higuchi matrix type of release. For other formulations 'n' is determined by Korsmeyer-Peppas's equation. For F2 formulation 'n' value is 0.8873, which suggest that more than one type of release phenomenon could be involved. For other formulations the n value is more than one indicates the zero order release.

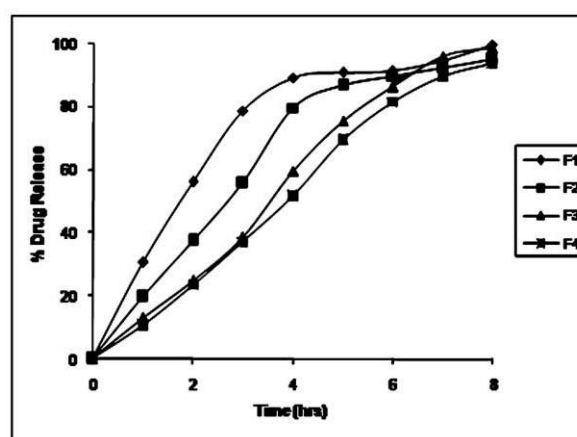


Figure 5: Cumulative % drug release from formulations F1to F4

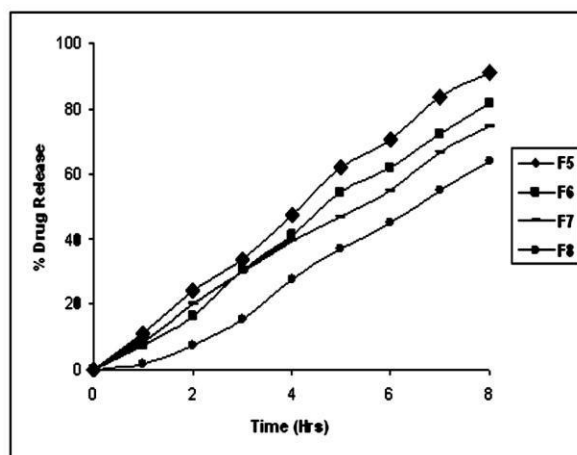


Figure 6: Cumulative % drug release from formulations F5to F8

Formulations which showed good *in vitro* release were selected for permeation study. In permeation study, the drug permeation from the formulations F1, F3 and F5 was found to be 58.92%, 48.55% and 46.82% respectively after 12 h (Figure 7).

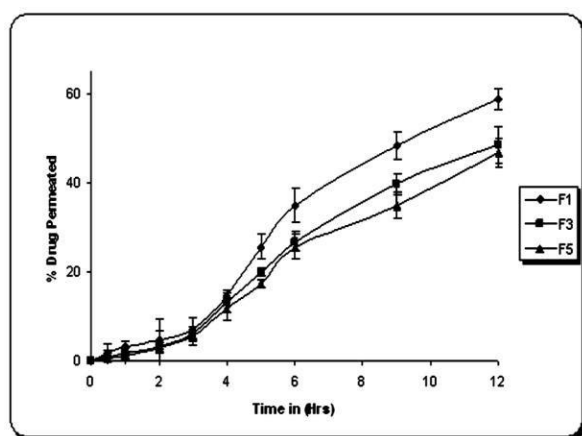


Figure 7: Cumulative % drug permeated from formulations F1, F3 and F5

CONCLUSION

The present work indicates a good potential of mucoadhesive buccal patches containing trandolapril for systemic delivery with an added advantage of circumventing the hepatic first pass metabolism. It exhibited well controlled and delayed manner and results shown that therapeutic levels of trandolapril can be delivered through buccal route.

ACKNOWLEDGEMENTS

The authors are thankful to Jyothi Karan, Vice President, Granules India, Hyderabad, India for the gift sample of Trandolapril, MNR Educational Trust, Hyderabad and Dr. V. Alagarsamy, Professor and Principal, MNR College of Pharmacy, Sangareddy for their valuable support to carry out this research. We also thank the Quality Assurance Deputy Manager, Macleods Pharmaceuticals, Vapi, Gujarat for gas chromatographic analysis.

REFERENCES

- Chang H.S., Park H., Kelly P. and Robinson J.R., Bioadhesive polymers as platform for oral controlled drug delivery: II, synthesis and evaluation of some swelling, water insoluble bioadhesive polymers, *J. Pharm. Sci.*, vol.74(4), 1985, pp.399-405.
- Cheng Li., Padmanabh P., Bhatt B. and Johnston T.P., In Vitro Release and Permeation of Oxytocin from a Mucoadhesive Buccal Patch, *Pharm. Dev. Technol.*, vol.1(4), 1996, pp. 357-364.
- Di Martino P., Di Cristofaro R., Barthelemy C., Joiris E., Pal Mieri Filippo G. and Sante M., Improved compression proper-ties of propyphenazone spherical crystals, *Int. J. Pharm.*, vol.197(1-2), 2000, pp.95-106.

- Guay D.R., Trandolapril: a newer angiotensin-converting enzyme inhibitor. *Clin. Ther.*, vol.25 (3), 2003, pp.713-775.
- Khan T.A., Peh K.K. and Chang H.S., Mechanical bioadhesive strength and biological evaluations of chitosan patches for wound dressing, *J. Pharm. Pharmaceut. Sci.*, vol. 3 (3), 2000, pp.303-311.
- Khanna R., Agrawal S.P. and Ahuja A., Preparation and evaluation of buccal films of clotrimazole for oral Candida infections, *Ind. J. Pharm. Sci.*, vol.59 (6), 1997, pp.299-305.
- Kim C.K., Choi H. G., Development of omeprazole buccal adhesive tablets with stability enhancement in human saliva, *J. Control. Rel.*, vol.68 (3), 2000, pp.397-404.
- Laha T.K., Adhikari L., Sannigrahi S. and Sen S., RP-HPLC Analysis of trandolapril in pharmaceutical dosage forms, *Asian J. Chem.*, vol.20 (1), 2008, pp.352-356.
- Llabot J.M., Palma S.D., Manzo R.H. and Allemandi D.A., Design of novel antifungal mucoadhesive films Part II. Formulation and in vitro biopharmaceutical evaluation, *Int. J. Pharm.*, vol.336 (2), 2007, pp.263-268.
- Murthy T.E.G.K. and Kishore V.S., Effect of casting solvent and polymer on permeability of propranolol hydrochloride through membrane controlled transdermal drug delivery systems, *Ind. J. Pharm. Sci.*, vol. 69 (5), 2007, pp.646-650.
- Nafee N.A., Ismail F.A., Boraie N.A. and Mortada L.M., Mucoadhesive buccal patches of miconazole nitrate: in vitro/in vivo performance and effect of ageing, *Int. J. Pharm.*, vol.264 (1-2), 2003, pp.1-14.
- Nafee N.A., Ismail F.A., Boraie N.A. and Mortada L.M., Mucoadhesive delivery systems II. Formulation and in-vitro/in-vivo evaluation of Buccal Mucoadhesive tablets containing water-soluble drugs, *Drug Dev. Ind. Pharm.*, vol.30 (9), 2004, pp.995-1004.
- Noha A.N., Nabila A.B., Ismail F.A. and Lobna M.M., Design and characterization of muco-adhesive buccal patches containing cetylpyridium chloride, *Pharm. Acta Helvetiae.*, vol.53 (3), 2003, pp.199-212.
- Park H. and Robinson J.R., Physico chemical properties of water insoluble polymers important to mucin epithelial adhesion. *J. Control. Rel.*, vol.2, 1985, pp.47-57.
- Samal A., Mona B., Bhatt G. K., Gupta G. D. and Shrivastava A. K., Design and evaluation of mucoadhesive buccal films of Diltiazem hydrochloride, *Ind. J. Pharm. Sci.*, vol.67 (5), 2005, pp. 548-552.
- Smart J.D., An *in vitro* assessment of some mucoadhesive dosage forms, *Int. J. Pharm.*, vol.73 (1), 1991, pp.69-74.

Vamshi Vishnu Y., Chandrasekhar V., Ramesh G. and Madhusudan Rao Y., Development of mucoadhesive patches for buccal administration of carvedilol, *Curr Drug Deliv.*, vol.4 (1), 2007, pp.27-39.

Yehia S.A., Elgazayerly O.N. and Basalious E.B., Fluconazole mucoadhesive buccal films: *in vitro/in vivo* performance, *Curr. Drug Deliv.*, vol.6 (1) 2009, pp.17-27.