Optimization of Transmucosal Buccal Delivery of Losartan Potassium using Factorial Design

Monica RP Rao[1]*, Swati Taktode[1], Shivraj Sangappa Shivpuje[1], Shilpa Jagtap[1]

[1]Department of Pharmaceutics, AISSMS College of Pharmacy, Kennedy Road, Near R.T.O. Pune-411001, INDIA.

ABSTRACT

Objective: Buccal delivery is considered to be an important alternative to the peroral route for the systemic administration of drugs. Losartan potassium is an angiotensin II receptor antagonist with an oral bioavailability of only 33% due to extensive first pass metabolism. **Methodology:** Mucoadhesive buccal films of losartan potassium were prepared using solvent casting method with hydroxyl propyl methyl cellulose HPMC K100M and xanthan gum as retardant polymers xanthan gum and plasticizer as propylene glycol. FTIR analysis of drug and excipients binary mixtures showed no interactions. The films were subjected to physical investigations such as uniformity of thickness, weight, drug content, folding endurance, surface pH and mucoadhesive strength. **Results:** Flexibility of films were dependent on polymer and plasticizer concentration. The mucoadhesive force and swelling index was higher for formulations containing higher percentage of HPMC K100M. *Ex vivo* permeation studies revealed that all films exhibited sustained release in the range of 63.75 ± 1.08% to 89.95 ± 1.24 % for a period of 7 h. *Ex vivo* permeation studies through sheep buccal mucosa indicated that films containing higher percentage of the mucoadhesive polymer (HPMC K100M) showed higher permeation of the drug for duration of 6-7 h. **Conclusion:** Mucoadhesive buccal films of losartan potassium were successfully prepared and offers a promising alternative to oral delivery.

Key words: Losartan potassium, HPMC K100M, Xanthan gum, Buccal mucosa, Mucoadhesive, Permeation.

INTRODUCTION

Buccal drug delivery is an alternative to per-oral and parenteral administration of drug. To bridge the gap between the concept and the actual utilization of buccal delivery system in therapy, studies have been carried out which focus on assessing the feasibility of this delivery route and on developing delivery system for suitable drug candidates. The buccal mucosa lines the inner cheek and buccal formulations are positioned in the mouth, sandwiched between the gums and cheek to treat local and systemic conditions. The buccal route offers one of the potential routes for typically hydrophilic, large and unstable proteins, oligonucleotides and polysaccharides, as well as conventional small drug molecules. The oral cavity is the preferred site for local and systemic drug delivery. Adhesion of bioadhesive formulation leads to increased concentration gradient of drug across absorption site and improves dosage form bioavailability.[1,2]

The antihypertensive, losartan potassium (LP) is an angiotensin II receptor (type AT) antagonist, orally active and undergoes first-pass metabolism by cytochrome P450 enzymes.[3-5] The terminal half-life of LP is about 2 h. Its log P and pka is 5.08 and 5.5 respectively. The drug is orally administered as 25 mg tablets once or twice daily with total daily doses ranging from 25 to 100 mg. Following oral administration, LP is well absorbed and undergoes substantial first-pass metabolism; the systemic bioavailability of losartan is 33%. Thus to over-come extensive first-pass metabolism, LP was selected as a candidate for formulation in a bioadhesive buccal patch.[6]

Literature reveals alternative routes to improve the bioavailability of LP like transdermal delivery and sustained release

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tablets. The present study involved formulation of buccal films using a factorial design with propylene glycol (PG), hydroxyl propyl methyl cellulose (HPMC) K100M and xanthan gum (XG) as film formers and plasticizers and evaluating its *ex vivo* performance.

MATERIALS AND METHODS

LP was generously gifted to us by Calyx Chemicals and Pharmaceuticals Ltd. Dombivli, Thane. Xanthan gum and HPMC K100M were procured from Loba Chemie India Ltd., Mumbai. Organic solvents and other chemicals used were of analytical grade.

Preliminary studies

During preliminary studies, polymers viz. Eudragit S 100, HPMC K100M, xanthan gum, sodium alginate and carboxy methyl cellulose (CMC) and plasticizers like PG and glycerin were investigated for formulating buccal bioadhesive patches. Patches were prepared using each of these polymers with different ratios like 1:2, 2:2, 3:2 by solvent casting method.[7,8]

Experimental Design

A 3^2 factorial design was employed to investigate the effect of independent variables on flux and mucoadhesion. This design was carried out with Design Expert 9 software (State- Ease Inc, Minneapolis, USA) to study effect of ratio of polymer combination of HPMC K100M:XG and concentration of PG on flux and mucoadhesion. The two factors HPMC: XG ratio, PG and three levels -1, 0 and +1 were used for optimization and showed in Table 1.

Compatibility of drug and excipients

The binary mixtures of drug and various excipients like XG, HPMC K100M, propylene glycol and ethyl cellulose used in formulations were analyzed by FTIR (Shimadzu- FTIR- 460 plus) for determination of interactions. Drug was mixed with excipient in 1:1 ratio and samples were stored for 30 days at $40 \pm 2°/75 \pm 5\%$ RH. FT-IR spectra of these samples were then obtained after 30 days.

Preparation of films of XG and HPMC K100M

Films were prepared by the solvent casting method[7,8] using XG and HPMC K100M in the ratios of 1:2, 2:2 and 3:2. HPMC K100M and XG was dissolved in 25 ml of distilled water. This solution was kept overnight. LP was then added to this solution by calculating area of the petri plate so that final patch of 1 cm would contain 25 mg of drug. To this solution required volume of PG was added. The mixture was constantly stirred using magnetic stirrer (MS205 Eltek, Mumbai) until the polymers had completely gone into solution and a clear gel was obtained. The solution was then cast into a glass petri dish of 9.8 cm diameter and allowed to dry overnight at room temperature. The films were removed carefully and circular patches of 1 cm diameter were punched out so that each patch contained 25 mg of the drug (as per dose of the drug).

Preparation of backing membrane

Patch with backing membrane was prepared by pouring backing membrane solution on preformed patch. Backing membrane solution containing 500 mg of ethyl cellulose and 2% w/v propylene glycol in 10 ml acetone was poured into the glass petri plate and air dried for 1 h.[9,10]

Primary evaluation

All patches were visually inspected for color and clarity. Uniformity of weight and thickness were determined by using digital balance (Shimadzu Corporation, Kyoto, Japan) and thickness dial gauge (Mitutoyo, Japan) respectively.[10] The patches were tested for the content uniformity.[11] A patch of size 1×1 cm^2 was cut and placed in a beaker containing 10 ml of distilled water. The contents were stirred in mechanical stirrer to dissolve the patch. The absorbance of the solution was measured by proper dilution using distilled water as blank at 230 nm wavelength using UV spectrophotometer (Jasco Model no.V-530). The experiments were carried out in triplicate for the films of all formulations and average values were recorded.

Folding Endurance

The folding endurance[12] of the patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

Surface pH

The surface pH[12] of the drug loaded buccal patches was determined in order to investigate the possibility of any side effects *in vivo*. The buccal patch was allowed to swell by keeping it in contact with 1 ml of distilled water and readings were recorded after equilibration. Surface pH was measured by allowing the electrode of pH meter (VHS Electronics, Model no.101) to come in contact with the film for 1 min.

Measurement of Swelling Index

Patches of size of 1×1 cm^2 were weighed individually (designated as w_1) and placed separately in petridish containing 4 ml of phosphate buffer pH 6.8. At regular

intervals (0.5, 1, 2, 3, 4, 5 h), samples were taken from the petridish and excess water was removed carefully by using filter paper. The swollen patches were reweighed (w$_2$).[13,14] The swelling index of each system was the ratio of difference in final and initial weight of patch to the initial weight.

Ex vivo residence time

The residence time[15] of patch was evaluated by assessing the time for the patch to detach from sheep buccal mucosa in a well stirred beaker filled with 500 ml phosphate buffer pH 6.8 at 37°C. The mucosal membrane was fixed on the side of the beaker with cynoacrylate glue. The patch was attached to the membrane by applying light force with finger tip for 60 s. The beaker was then magnetically stirred at an approximate rate of 150 rpm to simulate buccal and saliva movement. The time necessary for complete erosion or detachment of the patches from the mucosal membrane was taken as an indication of the *ex vivo* residence time.

Mucoadhesion

Mucoadhesion[16] was evaluated using a texture analyzer (CEB Texture Analyzer, Make-Brookfield Engineering Labs, Inc., Model no. Texture Pro CT 3). Sheep buccal mucosa was utilized as the model membrane. A patch was carefully attached to a 10-mm cylindrical probe (TA probe) by a doubleface tape. The upper platform was moved downward manually near to the mucosa surface and then the polymer sample was brought toward the mucosa at a constant speed of 0.5 mm/s and predetermined compressive force of 1 N was applied for 60 s. The probe was then removed at 5 mm/s to a distance of 15 mm and maximum detachment force (kg) was determined for each sample.[8]

Ex vivo permeation study

Diffusion studies[17] were carried out to evaluate the permeability of drug across the sheep buccal mucosa by using Franz diffusion cell (Orchid scientifics). Sheep buccal mucosa was obtained from local slaughterhouse and used within 2 h of slaughter. The tissue was stored in phosphate buffered pH 7.4 solution upon collection. The epithelium was separated from underlying connective tissues with surgical scissors and clamped in between donor and receiver chambers of the diffusion cells for permeation studies. The patch was placed on the mucosal surface in donor compartment and 1 ml aliquots were removed at time intervals of 1, 2, 3, 4, 5, 6, 7 h from the receptor compartment while the solution was being stirred continuously using magnetic stirrer, replacing it with fresh 1 ml medium each time.

The experiment was carried out at 37°C. The amount of drug permeated was assayed using UV method of analysis. Flux is rate of mass transfer across a unit surface area of a barrier and it gives idea related to permeability. The flux (J) was calculated from the slope of a graph of percent permeation vs. time in hours.

Scanning electron microscopy (SEM)

Film morphology was characterized by scanning electron microscopy[18,19] (NOVA NANOSEM 450, Japan). SEM images of buccal films were obtained before and after swelling using scanning electron microscope. The films were mounted on the specimen stub. On the other hand, small sample of the coating membrane was carefully cut from the exhausted shell and dried at 50° for 12 h. The cross section of dried films were sputter coated for 5 to 10 min with barium using fine coat ion sputter and examined using a scanning electron microscope.

RESULTS AND DISCUSSION

Preparation of film formulations

Solvent casting method was used for the preparation of film because hot-melt extrusion method required melting of all excipients but the polymers used in the preparation of trial and design batches of the buccal patches had melting points greater than 200°C. Thus solvent casting was most suited for the present study. Selection of final polymers depended on physical examination of the patches and it was found that combination of Eudragit S100 and HPMC K100M caused precipitation of the drug while HPMC K100M-sodium alginate films were sticky. Films of HPMC K100M-CMC were found to be inferior and difficult to detach from the petri plate. In lieu of these facts HPMC K100M and XG combination as polymers and PG as plasticizer were chosen depending upon the physical properties like appearance, folding endurance of the patches and drug release studies.

Compatibility of Drug and Excipients

FTIR analysis of XG and HPMC K100M film formulations containing LP do not reveal any additional peak for the drug, indicated that the drug did not interact with excipients used in the films. FTIR spectra shows compatibility of LP with HPMC K100M, XG, EC and the functional group signals observed were -OH stretch (alcoholic), -CH stretch (aromatic), -CH stretch (aliphatic), C=O stretch (acid), C-O stretch at wave number 3735, 3224, 2957, 2425, 1640, 1459 cm^{-1} respectively.

Preliminary evaluation of films

The nine buccal patches, prepared as per factorial design, were subjected to preliminary evaluation. All the batches of films were found to be translucent, whitish and uniform in appearance. The thickness of formulated patches was found to be in ranges between 0.14 ± 0.0041 to 0.22 ± 0.0104 mm, while the average weight of patch ranged between 11 ± 0.47 to 24.43 ± 0.90 mg. The drug content was found to be in range of 95.45 ± 0.025 to 98.34 ± 0.093.

Folding endurance

An ideal buccal film should be flexible, elastic and soft with adequate strength to withstand breakage stress from mouth activities.[20] The films did not show any cracks even after folding for more than 300 times. This may also be important from point of view of drug release as a film which has low flexibility may crack during use and may alter the release profile of the drug causing release of higher amounts which may lead to higher systemic concentration or loss of drug due to swallowing. The reason for this may be the transport mechanism of the drug. Losartan is transported by active transport involving P glycoprotein (P-gp) in the gastrointestinal tract (GIT).[21] These transport mechanisms are saturable in nature. Though the levels of P-gp in buccal mucosa are much lesser than in GIT, losartan may be presumed to be transported by this mechanism.

Surface pH

An acidic or alkaline pH of administered dosage forms can irritate the buccal mucosa. The surface pH of a patch (i.e., 6.5-6.9) was close to that of saliva (i.e., 5.8–7.1) which means that they have less potential to irritate the buccal mucosa and therefore they should be fairly comfortable. Because any minor deviation from this pH range may lead to inflammatory reaction[22] and may cause detachment of film from its application site.

Swelling Index

Swelling index is related to bioadhesive itself and its environment. The swelling indices for all the films are represented in Figure 1. The swelling index of all the films was found to increase with time. The magnitude of swelling was higher at higher concentration of HPMC K100M, XG and PG. Whenever film comes in contact with phosphate buffer, liquid penetrates into the film and a gel like structure is formed due to uncoiling of PG molecules. Polymer and plasticizer increased the surface wettability and consequently water penetration within the matrix, hence led to increased weight. The swelling reached a plateau after 4 h. Formulation F9
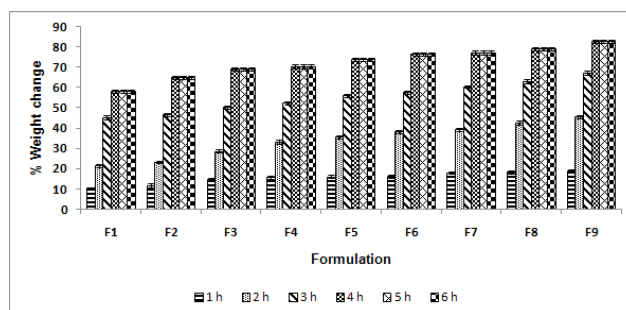

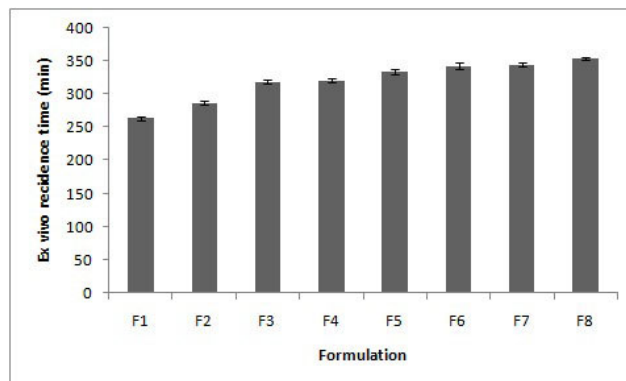**Figure 1: Swelling study of losartan potassium buccal films**
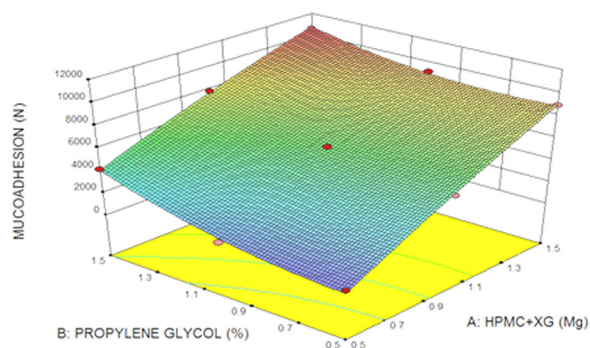

Figure 2: *Ex-vivo* residence time
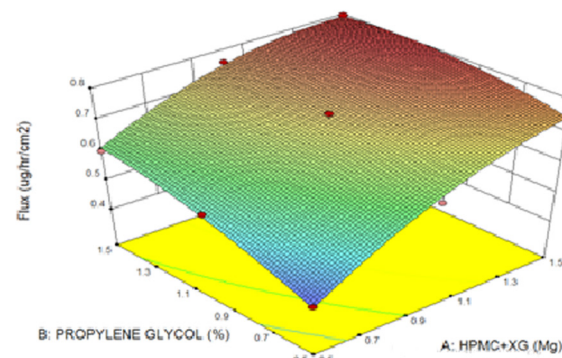

Figure 3: 3D surface graph of mucoadhesion

Figure 4: Permeation study–Flux
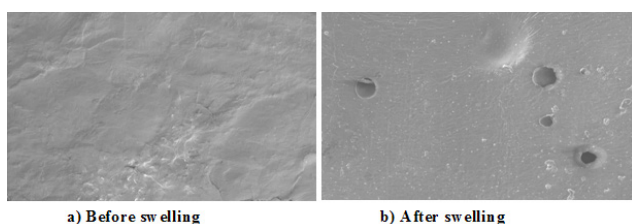
a) Before swelling   b) After swelling

Figure 5: Scanning electron microscopy a) before swelling b) after swelling

showed higher swelling index than the other because these formulations contained higher amount of polymer and plasticizer.[23]

Ex-vivo residence time

Residence time of formulation in the buccal cavity depends upon the mucoadhesive strength of polymers. This test reflects the mucoadhesive capacity of polymers used in formulations. HPMC K100M was used as mucoadhesive polymer and xanthan gum was used as retardant polymer which has hydrophilic properties. Mucoadhesion can be attributed to the ionization of HPMC K100M and XG at salivary pH and formation of secondary bonding with mucin[21] and entanglement and interpenetration of polymeric chain with mucin.[24] *Ex-vivo* residence time was found to increase as polymer concentration increased and reason might be higher ionization due to the higher concentration of HPMC K100M and XG. *Ex-vivo* residence time was in the range of 245 ± 2.72 to 354 ± 2.94 min showed in Figure 2.

Statistical analysis

A 3^2 factorial design was employed to investigate the effect of independent variables on flux and mucoadhesion. This design carried out with Design Expert 9 software (State-Ease Inc, Minneapolis, USA) to study effect of polymer combination of HPMC K100M**:** XG and plasticizer as PG. The two factors HPMC: XG ratio and PG were used at three levels -1, 0 and +1 for optimization. A 3^2 factorial design with measured responses showed in Table 2.

Mucoadhesion

The mucoadhesion of a buccal film is a critical parameter affecting its performance.[15] Both concentration of polymer (HPMC K100M: XG) and plasticizer (PG) significantly affected the mucoadhesion, which was tested on sheep buccal mucosa. The 3D graph of mucoadhesion (Figure 3) showed a direct relationship between polymer concentration and mucoadhesion. This might be due to the formation of hydrogen bonds, hydrophobic interaction and electrostatic interactions between carbo-

xylic group of polymer and lipoidal molecules of mucin. Increase in mucoadhesion due to increased PG concentration may be attributed to its hydrophilic nature which causes it to form a gel like structure at the buccal mucosa resulting in larger surface area. The increase in the water uptake by capillary forces may be the reason for increased bioadhesion.[7]

ANOVA analysis revealed that the F-value of 160.72 implied that the quadratic model was significant. Values of "Prob > F" less than 0.0500 indicated that the model terms were significant. The "Predicted R-Squared" 0.9584 was in agreement with the Adjusted R-Squared" of 0.9901; i.e. the difference was less than 0.2 showing that model has no block effect. Coded equation for response was found to be as follows:

Mucoadhesion = 5498.56 + 3850.33 A + 1447 B + 503 AB − 302 A2 + 825.67 B2   (1)

Where, A-Polymeric ratio (HPMC K100M: XG), B-plasticizer concentration (PG)

Above equation showed that polymer and plasticizer concentration had a pronounced effect on mucoadhesion. Sign on the coefficient indicated the nature of relationship between the response variable and independent variables with the positive sign indicating a direct relationship and negative sign indicating an inverse relationship.

Permeation study

Ex vivo permeation studies of LP film formulation showed slow and sustained permeation of the drug for 6-7 h. The rank order of drug permeation from films was found to be F9 > F8 > F7 > F6 > F5 > F4 > F3 > F2 >F1. The patches containing higher concentration of XG than HPMC K100M showed lower flux values as XG is a retardant polymer as it forms a thick gel on swelling which affects the diffusion of drug through the film.[25,26]

Permeation study revealed that drug release increases as plasticizer and mucoadhesive polymer concentration increases which gave maximum release $89.95 \pm 1.24\%$ in 7 h among other patches. This could be due to the extensive swelling of the hydrophilic polymers and plasticizer which created a gel barrier for drug diffusion.

Flux is rate of mass transfer across a unit surface area of a barrier and it gives idea related to permeability.[27] The 3D graph of permeation (Figure 4) showed that the flux across the membrane increased with increase in polymer and plasticizer concentration. This could be due to the extensive swelling of the hydrophilic polymer and plasticizer. Swelling is indicative of entrapment of large amount of water in the polymer network which

Table 1: Variable and their levels in 3^2 factorial design			
Independent variables	**Levels**		
	Low (-1)	**Medium (0)**	**High (+1)**
Polymer–HPMC K100M: XG	1:2	2:2	3:2
Plasticizer - PG (%)	0.5	1	1.5
Dependent variables	**Responses**		
	1. Flux 2. Mucoadhesion		

Table 2: 3^2 factorial experimental design with measured responses				
Formulation code	**HPMC:XG**	**PG (%)**	**Flux (µg/hr/cm^2)**	**Mucoadhesion (Dynes)**
F1	-1	-1	0.4385	490
F2	-1	0	0.5573	981
F3	-1	+1	0.5991	4218
F4	0	-1	0.6177	4610
F5	0	0	0.7384	5689
F6	0	+1	0.7589	7884
F7	+1	-1	0.7646	8927
F8	+1	0	0.7716	9221
F9	+1	+1	0.7958	10643

Table 3: Comparison of the observed responses with that of the predicted responses				
Response variables	**Predicted**	**Observed**	**%Error**	**Desirability**
Mucoadhesion (Dyne)	9046.58	8988.24	0.6448	0.918
Flux (*µg/hr/cm*^{2})	0.7949	0.7857	1.15	

may be presumed to act as a solvent for LP which is able to diffuse out through the disentangled chains of the polymer.[28] PG was used as plasticizer which has additional property of penetration enhancer[29] this may results enhancement of permeation and flux.

ANOVA analysis revealed that the quadratic model with F-value of 36.60 was significant. The "Predicted R-Squared" 0.8239 was in agreement with the Adjusted R-Squared" of 0.9570; i.e. the difference was less than 0.2 showing that model has no block effect. Coded equation for response was found to be as follows:

Flux = 0.72 + 0.12 A + 0.055 B + 0.033 AB - 0.050 A2 + 0.026 B2 (2)

Where, A-Polymeric ratio (HPMC K100M: XG), B-plasticizer concentration (PG)

Equation (3) showed that the high levels of factor A gave high value of flux as evident by the higher coefficient. Factor B has did not have a significant effect on flux. These results confirm the interpretation of response surface graphs.

Validation

Design Expert 9 version software was used to generate the optimum formulation by desirability approach. The process was optimized for response variables i.e. mucoadhesion and flux. The optimized formula was arrived by setting maximum mucoadhesion with propylene glycol being targeted at the middle level. The optimized formulation contained 1.5% of HPMC K100M: XG and 1% PG as plasticizer. The percent error between the predicted and observed values was found to be insignificant (Table 3).

Drug content of optimized batch was found as 98.34 ± 0.093.

Scanning electron microscopy of optimized batch

Scanning electron microscopy was used to study of changes in surface morphology of the optimized film (Figure 5a). The micrographs, before swelling showed smooth surface of optimized formulation which confirmed the uniform dispersion of drug molecules in polymeric solution. The micrographs of the swollen

films (Figure 5b) showed presence of microporous matrix which allows diffusion of the drug.

CONCLUSION

This study shows that mucoadhesive films of losartan potassium gives better therapeutic efficiency by controlling drug release and it may increase bioavailability leading to decreased dosing and fewer side effects. The use of retardant polymers retards drug release and higher percentage mucoadhesive polymer increases the mucoadhesive properties. *Ex vivo* permeation studies through sheep buccal mucosa revealed the possibility of permeation through human oral mucosa.

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CONFLICTS OF INTEREST

The authors report no conflict of interest, financial or otherwise associated with this project.

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SUMMARY

- Buccal delivery of Losartan potassium can improve its bioavailability.
- Mucoadhesive films were prepared with hydroxypropyl methyl cellulose and xanthan gum.
- Factorial design revealed dependence of mucoadhesion on concentration of polymers and plasticizer.
- Flux was found to be influenced by polymer concentration.

PICTORIAL ABSTRACT
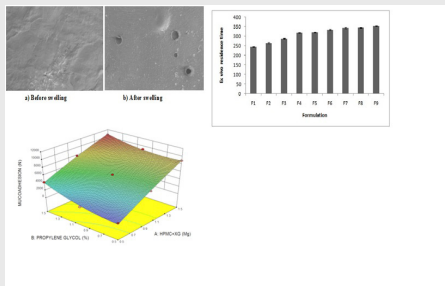
ABBREVIATIONS USED

HPMC: Hydroxyl propyl methyl cellulose; **LP:** Losartan potassium; **XG:** Xanthan gum; **CMC:** Carboxy methyl cellulose; **PG:** Propylene glycol.

About Authors

Dr. Monica Rao: Is an Associate Professor at Department of Pharmaceutics, AISSMS College of Pharmacy with 18 years experience. She has to her credit more than 40 publications in national and international journals. Her fields of interest include nanosponges and solubility enhancement.

Swati Shivaji Taktode: Has completed her Masters in Pharmaceutics from AISSMS College of Pharmacy and is presently working as a medical coder with Episource at Mumbai.