Research Article

Design and Evaluation of Mucoadhesive Buccal Patch of Ramipril

Anjana Anil*, Preethi Sudheer
Department of Pharmaceutics, Krupanidhi College of Pharmacy, Chikkabellandur, Carmelaram Post, Varthur (H), Bangalore, India.
***Corresponding author's E-mail:** anjanaanilattupurathu@gmail.com

Received: 13-05-2018; **Revised:** 28-05-2018; **Accepted:** 12-06-2018.

ABSTRACT

Ramipril is an antihypertensive drug - angiotensin converting enzyme (ACE) inhibitor, which exhibits a bioavailability of 28% due to the extensive hepatic first pass metabolism. So the present work is aimed to develop an alternative drug delivery system in the form of mucoadhesive buccal patch. In this study, mucoadhesive buccal patch of ramipril was prepared using poly vinyl alcohol (PVA), sodium alginate and hydroxy propyl methyl cellulose (HPMC-5) as mucoadhesive polymers and poly ethylene glycol (PEG 400) was used as plasticizer. The patches were studied for its physical parameters, drug content, mucoadhesive strength, in-vitro diffusion, *in vitro* dissolution and *ex vivo* permeation studies. The percentage drug content of the formulations (F1- F8) was found to be in the range of 81.6% ±0.086 to 98.4% ±0.027. Fourier transforms infrared spectroscopy (FTIR) and Differential scanning calorimetry (DSC) studies showed that there was no considerable interaction between the drug and polymers used. Surface property of the selected formula by scanning electron microscopy found to be slightly uneven. The release of drug from all the formulations (F1-F8) in phosphate buffer solution pH 6.8 was found to be in a sustained manner during the 8 hour study. The *ex vivo* permeations of ramipril from selected formulation (f4) of buccal patches showed that the drug permeated well across porcine buccal mucosa over 6 hour time period. It may be concluded that mucoadhesive buccal patch of ramipril is an alternate way to bypass hepatic first pass metabolism therefore it is expected to improve the bioavailability of ramipril.

Keywords: Ramipril, HPMC 5, PVA, sodium alginate, buccal patch.

INTRODUCTION

Oral administration of drugs has been the most common and preferable route for delivery of most therapeutic agents. The major obstacle for per oral administration of drug is the extensive hepatic first pass metabolism and stability problems within the gastrointestinal environment such as instability in gastric pH and complexation with mucosal membrane. These obstacles can be overcome by altering the route of administration as parenteral, transdermal or trasmucosal etc.[1]

Transmucosal delivery of therapeutic agents is an important method in pharmaceutical technology that offer many benefits compared to other methods of drug delivery. Mucoadhesive polymers are water soluble and insoluble, and have the capability to form swellable networks, jointed by cross-linking agents by the processes such as wetting, mutual adsorption and by processes interpenetration of polymer and mucus. [2]

The attractive target for administration of the drug of choice is the buccal region in the oral cavity. Buccal mucosa is rich with blood supply, which acts as an ideal site for the absorption of drugs. Different from oral drug delivery, which presents a hostile environment for drugs, due to hepatic first-pass effect and acid hydrolysis, the mucosal lining of buccal tissues provides a much milder environment for drug absorption. This results in reduction of the drug dose and consequent minimization of systemic side effects.[3]

Bucoadhesive dosage forms are used to prolong drug retention in the oral cavity, which includes ointments, gels, disks, patches, films and tablets. Among these formulations, buccal patches are preferred over mucoadhesive disks and tablets, in terms of patient compliance, flexibility, and also in ensuring higher accurateness in drug dosing and longer residence time in comparison to ointments and gels. [4]

Buccal patches are designed for attachment to the buccal mucosa; they can be formulated to exhibit local as well as systemic action. Due to direct entry of buccal patch to the systemic circulation through the internal jugular vein, which bypasses the drug from the hepatic first pass metabolism leading to high bioavailability. The main property of the buccal patch is having large surface area, it allows quick wetting of the patch which accelerates absorption of the drug quickly when compared to tablets.[5]

Ramipril is a sparingly soluble drug with a log p value of 3.32. After oral administration, drug exhibits bioavailability of 28% due to its high first pass metabolism. The biological half life of drug is reported to be 2 to 4 hours. Ramipril is 73% bound to human plasma proteins. Initial dose of ramipril is 2.5-5 mg and maximum daily dose reported to be 20 mg.[6] Therefore in this paper, we did an attempt to prepare and evaluate the buccal patch of ramipril, which could overcome the above mentioned drawbacks of drug.

MATERIALS AND METHODS

Materials

Ramipril is obtained as a gift sample from United Biotech (p) Ltd. All other polymers and chemicals were procured from SD fine chemicals, Mumbai. All the ingredients used throughout the study were of analytical grade.

Methods

Method for the preparation of mucoadhesive buccal patch

Polymer was soaked in 10 ml of water and stirred at a rotation of 80 – 90 rpm using magnetic stirrer for 30min. Drug was added to the above polymer solution and stirring was continued for 5 min. Polyethylene glycol 400 was added as plasticizer to the above drug polymer mixture and under magnetic stirring for 2 min. Teflon coated Petri plate with surface area of 41.83 cm^2 was used for solvent casting method. An amount of (52mg) was incorporated Into the surface area of 41.83cm^2, in such a way that 2 cm^2 area of patch contains a dose of 2.5mg of drug. The solution was then poured into a Petri plate slowly and solvent was allowed to evaporate at a temperature 40 – 60°C using hot air-oven for overnight and slowly peeled after drying.

Table 1: Formulation chart of mucoadhesive buccal patch of ramipril

Sl.No	Ingredients	Formulation code							
		F1	F2	F3	F4	F5	F6	F7	F8
1	Ramipril (mg)	**52**	**52**	**52**	**52**	**52**	**52**	**52**	**52**
2	PVA (mg)	**300**							
3	Sodium alginate (mg)		**100**						
4	HPMC 5 (mg)			**300**					
5	PVA: Sodium alginate: HPMC 5 (mg)				**125:50:125**				
6	PVA: Sodium alginate (mg)					**250:50**			
7	HPMC 5: Sodium alginate (mg)						**250:50**		
8	HPMC 5: Sodium alginate (mg)							**150:50**	
9	PVA: Sodium alginate (mg)								**150:50**
10	PEG 400 (ml)	**0.2**	**0.2**	**0.2**	**0.2**	**0.2**	**0.2**	**0.2**	**0.2**
11	Water (ml)	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**

Calibration curve of Ramipril in Phosphate buffer solution pH 6.8

A stock solution of 1 mg/ml ramipril was prepared by dissolving 100 mg of ramipril in 100 ml PBS pH 6.8. The stock solution was Diluted suitably using PBS pH 6.8 to Beer's range. The absorbance of dilutions was taken at observed λmax using UV spectrophotometer and the calibration curve was prepared by plotting the absorbance v/s concentration.

Solubility studies of ramipril

Excess quantity of ramipril was added to dimethyl sulphoxide (DMSO), distilled water, phosphate buffer solution (PBS) pH 6.8 and ethanol in a series of stoppered tubes and shaken for 72 hr on a vortex shaker. The suspensions were filtered through Whatman filter paper and analyzed for ramipril using UV spectrophotometer at 210 nm.

Compatibility studies by FTIR

A Fourier transform infrared spectrum (FTIR) was used to identify if any interaction exist between ramipril and excipients used. Samples were analyzed by potassium bromide pellet method in an IR spectrophotometer (Thermo-Nicolet 6700) in the region between 4000-400 cm^{-1}.

Evaluation of buccal patch

Thickness

The thickness of the patch was measured using screw gauge at three different points and an average was taken.[7]

Drug content uniformity

An area containing 2.5 mg of ramipril was cut. It was then added to 100 ml volumetric flask and diluted using PBS pH 6.8. It was then sonicated for 15 to 20 minutes. From that solution, 1 ml was taken and diluted to 10 ml with PBS pH 6.8 and absorbance was measured using UV-spectrophotometer at 210 nm. [8]

Folding endurance

A dimension of 4x2 cm was cut from the patch uniformly and repetitively folded at the same place till it broke. The number of times the patch could be folded at the similar position without breaking gives the correct same of folding endurance. [8]

Swelling index

It is determined by placing a patch in a Petri plate containing 5ml of PBS pH 6.8. Hydrated patches were detached at each observation points at a time interval of 10, 15, 30, 60, 90, 120 min, when the patch surface was gently dried using blotting filter paper and reweighed again.[9]

Mass uniformity

The mass of each patch (2×3 cm^2) was measured using a digital balance from different positions of the patch and average was calculated.[10]

Surface pH

The Patches were moistened with 3 drops of water on a Petri plate and an electrode was attached to the surface of the patch and the pH was noted.[11]

Mucoadhesive strength

Mucoadhesion studies were carried out using physical balance. The porcine buccal mucosa was obtained from slaughterhouse excised and washed, was tied tightly to the upper part of glass vial, which was filled with PBS (pH 6.8) to keep the mucosal surface moist. This was then placed below left hand arrangement of the balance. The patch was then fixed with a little moisture; on to the lower surface of a rubber closure hanging from the left hand side of the balance and was brought in contact with the mucosa. The balance was kept in this position for 3 to 4 min and then gradually weights were added on the right pan, till the patch separated from the mucosal surface.[12]

***In vitro* diffusion studies**

Franz diffusion cell was used for the determination drug release from buccal patch. Buccal patch was placed on a treated cellophane membrane between donor and receptor compartment of the Franz diffusion cell assembly. The whole unit was maintained at 37°C, donor compartment was filled with 2ml of PBS pH 6.8 and receptor compartment was filled with phosphate buffer pH 7.4 under magnetic stirring. At predetermined intervals, 1 ml sample was removed from donor compartment and analyzed at 210 nm by UV spectrophotometric analysis to check release of drug from the patch. [13]

***In vitro* release studies**

An area of patch containing equivalent amount of ramipril (2.5 mg) was added to 900 ml of phosphate buffer pH 6.8 (USP-II dissolution apparatus) at 37°C using at a rotation speed of 50 rpm. Sample volume of 2ml was withdrawn at an interval of 5, 10, 15, 30, 45, 60, 90, 120 minutes. An equal amount of fresh dissolution medium was added at each time intervals after withdrawal of the sample. Samples were filtered through Whatman filter paper and diluted accordingly. The amount of ramipril released was analyzed by measuring in UV-spectrophotometer at 210 nm. [14]

***Ex vivo* permeation studies**

Franz diffusion cell was used to determine the permeability of drug across the porcine buccal mucosal membrane. Porcine buccal mucosa was obtained from local slaughterhouse and used within 2 h of slaughter. The porcine buccal mucosa was stored in phosphate buffer solution (PBS) pH 7.4. The epithelium was separated from underlying connective tissues with surgical scissors and placed between donor and receptor compartment of the Frantz diffusion cell. Receptor compartment was filled with 50 ml phosphate buffer pH 7.4 and donor compartment was filled with 2 ml PBS of pH 6.8. The patch was placed on the mucosal surface in donor compartment. Aliquots of 1ml were removed at time intervals of 1, 2, 3, 4, 5, 6, 7 hrs from the receptor compartment and replacing it with 1 ml fresh medium followed by stirring. The assembly was maintained at 37°C. The amount of drug permeated was determined by using UV visible spectrophotometer at 210 nm.[15]

Scanning electron microscopy (SEM)

The morphologic properties of the best patch formulation (f4) were characterized by Scanning electron microscopy. The patches were coated with gold sputter and then examined under scanning electron microscope.[16]

Differential Scanning Calorimetry (DSC)

The thermal activities of ramipril, physical blend and the patch formulation (f4) was studied using Differential Scanning Calorimetry. The samples were heated from 0 to 300°C at a heating rate of 5°C/min under a nitrogen flow, flowing at a rate of 40cc/min through the DSC cell.[17]

RESULTS AND DISCUSSION

Drug incorporated patches of ramipril was prepared by solvent casting technique. Petri plates having radius of 3.6 cm was used for solvent casting, in which 52 mg of drug in the calculated surface area of 41.83 cm^2. Thus patch of 2cm^2 area should have 2.5 mg of drug. Total eight formulations were prepared.

Solubility studies

The saturation solubility of ramipril was found to be 40.4 mg/ml in dimethyl sulphoxide, 20.8 mg/ml in water, 37.8 mg/ml in ethanol and 35.4 mg/ml in phosphate buffer solution pH 6.8 respectively and is shown in figure 1.

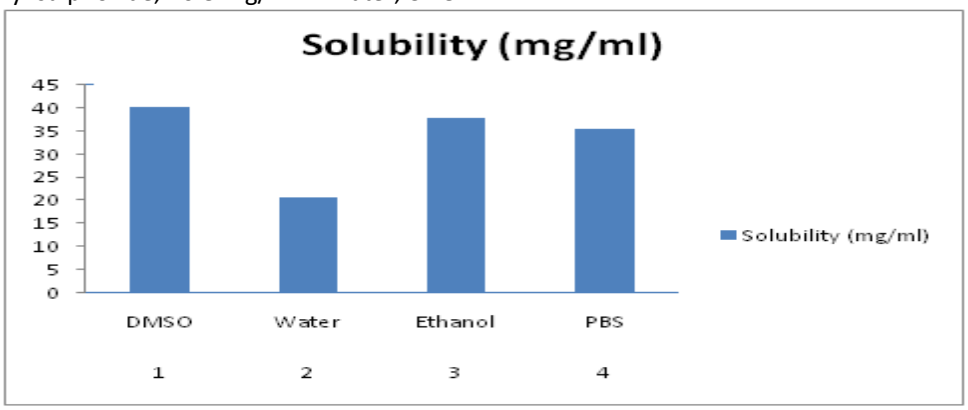

Figure 1: Solubility analysis of ramipril

FTIR

The result of FTIR is shown in figure 2. Ramipril showed characteristics peak in the range of 3000-2500 cm^{-1} for OH (stretching), 3300-3200 cm^{-1} for NH (stretching), 1700-1600 cm^{-1} for C=C (aromatic), 2964-2860 cm^{-1} for CH (aliphatic), 1750-1735 cm^{-1} for C=O (ester). Ramipril showed characteristics peak of 2865.50 cm^{-1} for OH (stretching), 3277.20 cm^{-1} for NH (stretching), 1650.27 cm^{-1} for C=C (aromatic), 2962.31 cm^{-1} for CH (aliphatic), 1741.52 cm^{-1} for C=O (ester). All the above distinctive peaks appeared in the spectra of physical mixtures. Compatability studies by FTIR showed that there is no interaction between drug and excipients used.

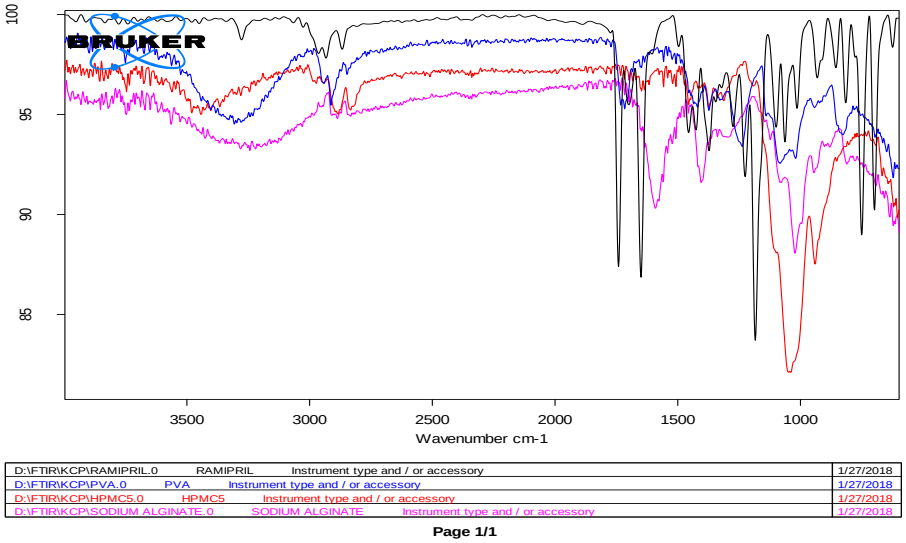

Figure 2: FTIR overlay spectrum physical mixture of Ramipril, sodium alginate, HPMC 5 and PVA

UV spectroscopy

A 10 µg/ml solution of drug in PBS pH 6.8 was scanned over UV range of 400 to 200 nm to determine λmax. The maximum absorbance of drug was found to be at 210 nm. Standard calibration curve of the drug in PBS showed linear range from 2 to 30 µg/ml, showed a regression co-efficient of 0.998.

Drug content

Drug content for patch formulations (F1 – F8) was found to be 89.6%±0.086 to 98.4% ±0.027. It was observed from the drug content data; there was no considerable difference in uniformity of the drug content. In case of formulation (f2) drug content was relatively low the reason may due to low concentration (1%) of sodium alginate.

Thickness

Thickness of all patch formulations was found to be 100µm±0.012 to 180µm±0.018.

Folding endurance

Folding endurance of the patch formulations was found to be 86±2786 to 290±4.906. The patches (F2, F6, F7) having low folding endurance, the reason may be due to the absence of polymer PVA in these formulations. Higher tensile strength and larger molecular weight of this polymer might have contributed to high folding capacity compared to other polymers.[18] Folding endurance was

found to be more for (F4) 290 ±4.906 this may due to polymer combinations such as PVA, HPMC 5 and sodium alginate.

Swelling index

Swelling index for patch formulations was found to be 16%±2.160 to 38%±2.068. Swelling index of the prepared patches were found to be moderate and varied between formulations. Formulation (F3) found to have high swelling index due to the presence of hydrophilic polymer HPMC 5. The influence of drug on the swelling properties of polymer matrices is primarily depending on the substituted groups of polymer. The hydroxyl groups take part an important role in matrix integrity of the swollen hydrophilic cellulose matrix. The amount and properties of drug determines the matrix integrity. [19] (table 2)

Table 2: Drug content, thickness, folding endurance, swelling index

Sl.No.	Formulation	Drug Content (%) ±SD (n=3)	Thickness(µm) ± SD (n=3)	Folding Endurance (no) ±SD (n=3)	Swelling index(%) ±SD(n=3)
1	**F1**	95.4 ± 0.012	150 ± 0.091	250 ± 2.389	20 ± 1.707
2	**F2**	89.6 ± 0.086	170 ± 0.010	88 ± 4.281	17 ± 4.546
3	**F3**	94.6 ± 0.054	140 ± 0.017	104 ± 5.235	38 ± 2.068
4	**F4**	98.4 ± 0.027	100 ± 0.012	290 ± 4.906	25 ± 1.674
5	**F5**	96.8 ± 0.114	120 ± 0.019	240 ± 3.123	16.9 ± 2.129
6	**F6**	92.8 ± 0.081	180 ± 0.018	86 ± 2.786	28 ± 2.041
7	**F7**	90.9 ± 0.099	160 ± 0.098	88 ± 5.139	26.2 ± 2.389
8	**F8**	96 ± 0.035	130 ± 0.047	270 ± 2.098	16 ± 2.160

Mass uniformity

Mass uniformity for patch formulations was found to be 100mg±0.094 to 130mg±0.036. No significant variation in average weight was observed for different formulations.

Surface pH

Surface pH of patch formulations was found to be 6.37±0.017 to 6.81±0.026. The pH at the mucosal surface approximately 6.8, all the formulated patch observed that it was safe enough for the continuous application in the mucosal surface.

Mucoadhesive strength

Mucoadhesive strength of patch formulations was found to be 10gm±4.082 to 20gm±3.741. The strength of mucoadhesion is affected by various factors like molecular mass, swelling rate of polymers, biological membrane used in the study etc. The patches formulated with a mixture of PVA, HPMC 5, sodium alginate showed good mucoadhesive strength. However incorporation of PEG 400 produces significant increase in mucoadhesion that could have been associated to the plasticization of polymer network. Incorporation of plasticizers reduces the intra chain polymer interaction, thereby raising the relaxation possibilities of the chain. So this higher flexibility can enhance the interpenetration and entanglement of bioadhesive polymer chain with mucous polymer, leading to the strengthing of mucoadhesive interaction.[20] (table 3)

Table 3: Surface pH, mass uniformity, mucoadhesive strength

Sl.No.	Formulation	Surface pH ±SD (n=3)	Mass uniformity (mg) ± SD (n=3)	Mucoadhesive strength (gm) ±SD (n=3)
1	**F1**	6.40±0.012	100±0.081	16±2.160
2	**F2**	6.37±0.017	110±0.014	12±2.764
3	**F3**	6.75±0.005	100±0.057	17±2.943
4	**F4**	6.81±0.026	130±0.036	20±3.741
5	**F5**	6.73±0.021	120±0.094	15±4.082
6	**F6**	6.46±0.034	120±0.010	13±2.685
7	**F7**	6.62±0.029	110±0.012	10±4.082
8	**F8**	6.50±0.035	100±0.094	14±2.160

In vitro diffusion studies of patches

An *in vitro* diffusion study was carried out for 8 hour duration with fixed sampling intervals of 1 hr. The release of drug depends on the hydration properties and swelling behavior of the polymer combination used. Based on *in vitro* release studies formulation (F4) with 1.25% PVA, 0.5% sodium alginate, 1.25% HPMC 5 and 2% PEG 400 exhibited a sustained drug release of 97.02% ±0.023 within 8 hrs. The reason may be due to combined property of HPMC 5 with the other two polymers in the patch would enhance hydration and channel formation leading to maximum drug release with a sustained effect could be contributed by polymers, PVA and sodium alginate.[19] (table 4 and figure 3).

Table 4: *In vitro* diffusion studies of ramipril buccal patch in PBS pH 6.8

Time (hr)	% Cum. Drug release ± SD (n=3)							
	F1	F2	F3	F4	F5	F6	F7	F8
1	39.41±0.11	36.62±0.32	28.97±0.23	41.83±0.51	40.15±0.18	34.05±0.03	27.33±0.03	30.23±0.09
2	47.80±0.23	49.87±0.56	38.12±0.26	55±0.26	53.38±0.32	45.18±0.25	44.59±0.02	39±0.32
3	54.23±0.03	57±0.24	50.84±0.48	68.77±0.45	63.23±0.15	53.72±0.32	53.98±0.02	51.32±0.25
4	64.76±0.42	60.29±0.35	57.78±0.55	75.86±0.26	65.79±0.21	59.96±0.43	60.18±0.14	59.80±0.06
5	75±0.56	72.45±0.21	67.96±0.03	78.82±0.32	75.66±0.36	67.56±0.02	69.73±0.25	66.82±0.25
6	80.28±0.42	86.65±0.54	77.91±0.36	86.45±0.15	82.48±0.03	77.13±0.09	78.22±0.06	75±0.02
7	87.13±0.62	89.23±0.23	86.67±0.25	94.96±0.28	91.37±0.09	83.77±0.412	81.56±0.36	85.39±0.12
8	94.65±0.23	90±0.28	93.69±0.09	97.02±0.02	95.50±0.20	89.15±0.06	87.23±0.05	93.50±0.13
9	93.33±0.56	86±0.17	91.03±0.31	96.14±0.14	93.91±0.14	79.80±0.12	83.94±0.19	88.31±0.03

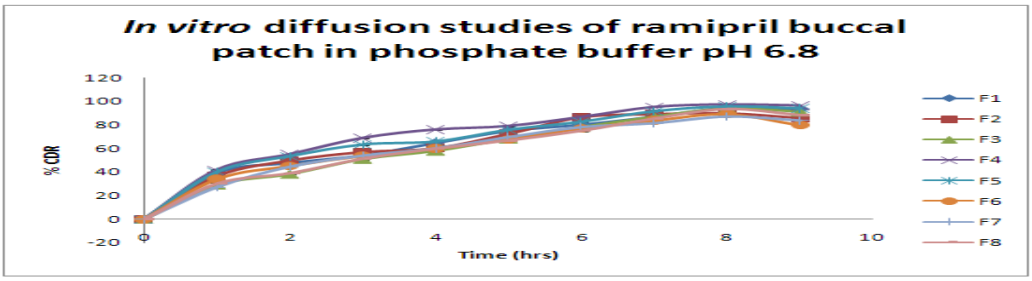

Figure 3: *In vitro* diffusion studies of ramipril buccal patch

In vitro dissolution studies of patches

Percentage drug release of patches was found to be 86.69% ±0.064 to 98% ±0.298 with maximum release of 98% ±0.298 from patch formulation F4. The maximum release of 98% ±0.298 within 2 hour (figure 4). During dissolution combinations of polymer HPMC 5, PVA, sodium alginate swelled and forming a gel layer on exposed patch surface. The slackly bound polymer molecules were easily eroded allowing the release of drug in a higher rate compared to other formulations.[19, 20]

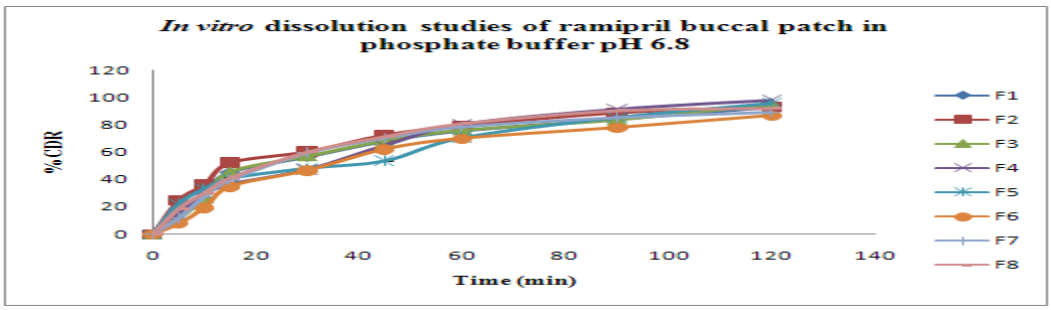

Figure 4: *In vitro* dissolution studies of ramipril buccal patch in PBS pH 6.8

Ex vivo permeation studies of patches

The *ex vivo* permeation of ramipril through buccal patch formulation showed that the drug permeated well across porcine buccal mucosa over 6 hour time period. Maximum drug permeation of 94.87%±0.398 from patch formulation F4 (table 5). It was seen that, there was a good correlation of *in vitro* diffusion profile with *ex vivo* permeation. (Figure 5)

Table 5: *Ex vivo* permeation of ramipril from buccal patch through porcine buccal mucosa

Sl.no	Time (hr)	% cumulative drug release ± SD (n=3)			
		F1	F3	F4	F5
1	1	40.60 ± 0.239	37.82 ± 0.094	45.12 ± 0.054	48.36 ± 0.322
2	2	54.72 ± 0.398	48.10 ± 0.241	59.25 ± 0.322	57.81 ± 0.054
3	3	60.61 ± 0.187	55.22 ± 0.399	64.02 ± 0.411	66.78 ± 0.097
4	4	71.32±0.286	60.29±0.197	69.36±0.069	71.67±0.397
5	5	77.35±0.311	77.81±0.581	79.89±0.087	83.56±0.211
6	6	93±0.411	88.12±0.314	94.87±0.398	93.57±0.088
7	7	80.08±0.387	75.24±0.067	89.99±0.027	88.59±0.065

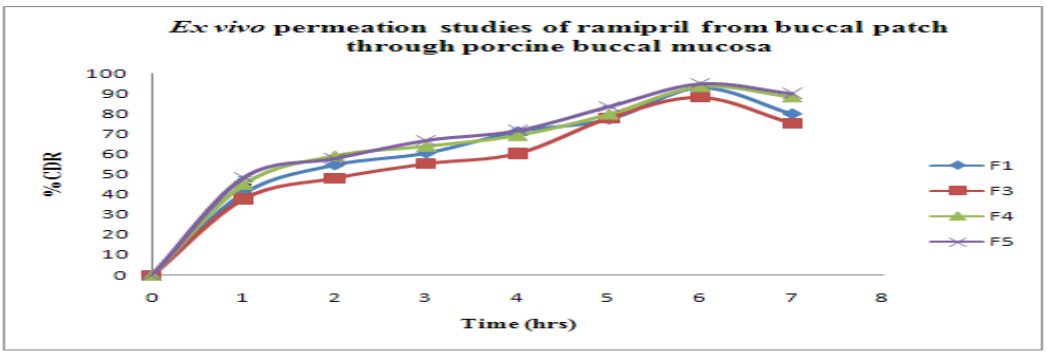

Figure 5: *Ex vivo* permeation of ramipril from buccal patch through porcine buccal mucosa

In vitro ex vivo correlation of selected formulation (F4)

Table 6: *In vitro ex vivo* correlation of selected formulation (F4)

Time (hr)	% cumulative drug release ± SD (n=3)	
	In vitro diffusion (f4)	*Ex vivo* permeation(f4)
1	41.83±0.512	45.12 ± 0.054
2	55±0.264	59.25 ± 0.322
3	68.77±0.453	64.02 ± 0.411
4	75.86±0.264	69.36±0.069
5	78.82±0.324	79.89±0.087
6	86.45±0.158	94.87±0.398

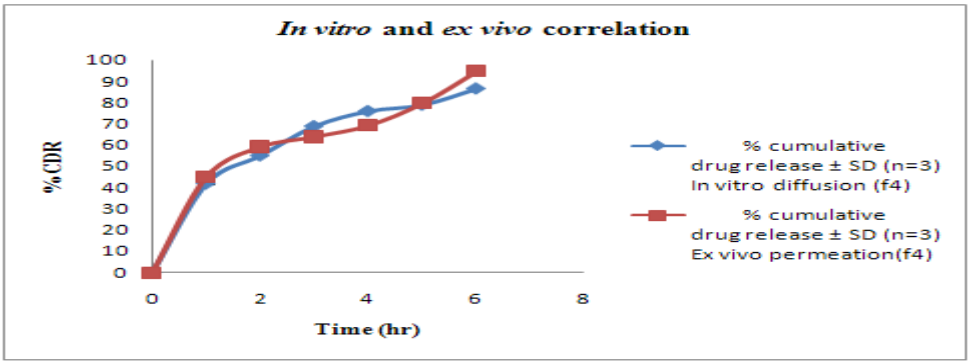

Figure 6: *In vitro ex vivo* correlation of selected formulation (F4)

Surface morphology

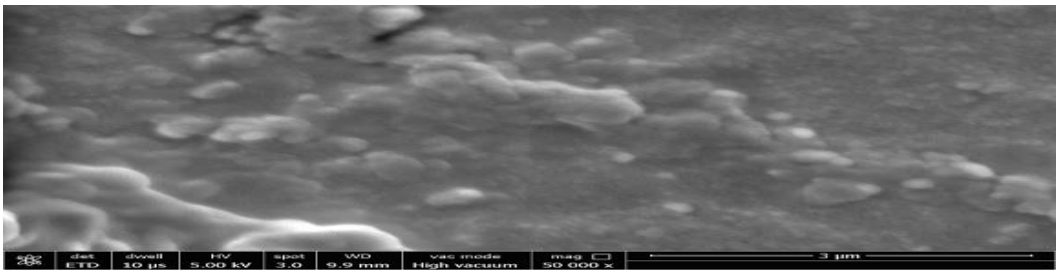

Figure 7: SEM photograph of patch (F4)

DSC studies

DSC studies showed that there was no significant interaction between drug and the excipients used. Thermogram of pure drug ramipril revealed that the pure drug has a sharp endotherm at 114.28°C whereas ramipril in F4 patch formulation has broad peaks shifted to lower range of 63.79°C. The peaks of drug have changed to broad peaks with reduction of height (figure 8). Effect of plasticizer and combined properties of polymers that leads to reduction of melting point.[21]

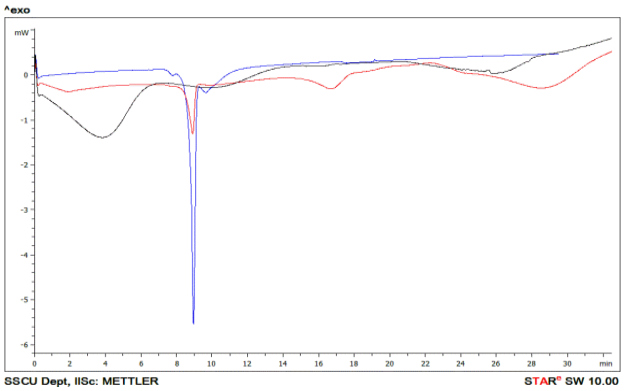

Figure 8: DSC Thermogram of ramipril, physical mixture and patch

CONCLUSION

The concept of formulating mucoadhesive buccal patch of ramipril offers a practical approach to achieve sustained release of drug. In present investigation, mucoadhesive buccal patch of ramipril were prepared to bypass the extensive hepatic first pass metabolism and improve the bioavailability of drug. This was achieved successfully by solvent casting method using HPMC-5, PVA, and sodium alginate as mucoadhesive polymers. Out of the total 8 formulations, best formulation was found to be F4 on the basis of mucoadhesive strength, *in vitro* diffusion profile and *ex vivo* permeation. Prepared patches exhibited a sustained drug release up to 8 hrs. There was no drug polymer interactions exhibited in FTIR and DSC analysis. Buccal patch was found to an alternate drug delivery to bypass hepatic first pass metabolism and to release the drug in a sustained manner.

Acknowledgement: The authors thank the management and Principal of Krupanidhi College of Pharmacy.

REFERENCES

1. Puratchikody A, Prasanth VV, Mathew ST, Kumar A, Buccal drug delivery: past present and future-a review, Int J Drug Dev, 3(2), 2011, 171-175.
2. Miller NS, Chittchang M, Johnston TP. The use of mucoadhesive polymers in buccal drug delivery, Adv drug deli rev, 4(2), 2005, 1666-1691.
3. Khobragade PK, Puranik PK, Suradkhar SS, Literature studies on preparation and evaluation of buccal patches, Int J Pharm Rev Res, 25(2), 2014, 83-91.
4. Kresmer C, Albrecht K, Greindl M, Wolf C, Debbage P,Schnurch AB, *In vivo* determination of the time & location of mucoadhesive drug delivery systems disintegration in the gastrointestinal tract, Magnetic resonance imaging, 26(5), 2008, 638-43.
5. Gawas S, Dev A, Deshmukh G, Rathod S, Current approaches in buccal drug delivery system, Pharmaceutical and Biological Evaluations, 3(2), 2016, 165-77.
6. Ramipril - DrugBank [Internet]. Drugbank.ca, 2018. Available from: https://www.drugbank.ca/drugs/DB00178. [Accessed on: 24 March 2018].
7. Reddy RJ, Anjum M, Hussain MA, A comprehensive Review on Buccal drug delivery system, J Adv Drug Deliv, 1(3)2013, 300-12.
8. Woertz C, preis M, Breitkreutz J, Kleinebudde P, Assesment of test methods evaluating mucoadhesive polymers and dosage forms: an over view, Eur J Pharm Biopharm, 6(2),2013,843-853.
9. Fiza F, Sudir B,, Priyanka A, Garima S, Deepthi R, Imran K, Rahul T, Arvind RS, Buccal patches a review, Indo Ame J Pharm Res, 3(4), 2013, 3324-3335.
10. Yamsani VV, Chandrasekhar Kolli CS, Gannu R, Yamsani MR, Development of mucoadhesive patches for buccal administration of carvedilol, Curr Drug Deliv, 4(1), 2007, 27-39.
11. Pendekal MS, Tegginamat PK, Formulation and evaluation of bioadhesive patch for buccal delivery of Tizanidine, Acta Pharm Sin B, 2(3), 2012, 318-324.
12. Li X. *et al,* Mucoadhesive buccal films of tramadol for effective pain management, Rev Bras Anesteesiol, 10(8), 2016, 1-7.
13. Semalty A, Semalty M, Nautival U, Formulation and evaluation of mucoadhesive buccal films of enalapril maleate, Ind J Pharm Sci, 72(5), 2016, 571-575.

14. Patel V, Prajapati B, Patel M, Effect of hydrophilic polymers on buccoadhesive eudragit patches of propranolol hydrochloride using factorial design, AAPS Pharmscitech, 8(2), 2007, 38-45.
15. Semalty M, Semalty A, Kumar, Formulation and characterization of mucoadhesive buccal films Glipizide, Indian J Pharm Sci, 70(1), 2008, 43-8.
16. Ramana MV, Nagda C, Himaja M, Design and evaluation of mucoadhesive buccal drug delivery system containing metoprolol tartrate, Indian J Pharm Sci , 69(4), 2007, 515-18.
17. Singh S, Jain S, Muthu MS, Tiwari S, Tilak R, Preparation and evaluation of buccal bioadhesive film containing Clotrimazole, AAPS Pharm Sci Tech , 9(2), 2008, 660-7.
18. Armstrong NA, Hyprpmellose in In: Rowe RC, Sheskey PJ, Quinn ME, Handbook of pharmaceutical excipients, 6th ed. London, Pharmaceutical Press, 2009, 326-330.
19. Nafee NA, Ismail FA, Boraie NA, Mortada LM, Mucoadhesive buccal patch of miconazole nitrate *in vitro in vivo* perfomance & effect of ageing, Int J Pharm Sci, 4(5), 2003, 1-14.
20. Vasantha P, Puratchikody A, Mathew ST, Balaraman AK, Developement and characterization of eudragit based mucoadhesive buccal patch of salbutamol sulfate, Saudi Pharm J, 19(4), 2011, 207-214.
21. Bazigha K, Abdul Rasool, Khan SA, *In Vitro* Evaluation of Miconazole mucoadhesive buccal films, Int J Appl Pharm, 4(2), 2010, 23-6.

Source of Support: Nil, **Conflict of Interest:** None.