Design and Development of Buccal Mucoadhesive Drug Delivery System for Perindopril

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ABSTRACT

The main objective of present study was to develop a buccal mucoadhesive drug delivery system for perindopril. Perindopril buccal mucoadhesive patches were developed by solvent casting technique using hydroxy propyl methylcellulose (HPMC), polycarbophil, sodium carboxymethylcellulose (SCMC) and sodium alginate as polymers for extended release of perindopril. Glycerine and DMSO were used as plasticizer and penetration enhancer respectively. Ethanol, methanol and dichloromethane were used as solvents. FTIR and DSC studies revealed no interaction between drug and polymers. The drug content in the perindopril patches was found to be uniform. The films exhibited good physical and mechanical properties. The surface pH of all the patches was within salivary pH range. Residual solvent content in patches are below the tolerated limits. The patches were found to have an extended release of the drug upto a period of 12 hours during ex vivo permeation studies with non-Fickian diffusion mechanism. The present study demonstrated the possibility of designing a buccal drug delivery system for perindopril.

Keywords: Ex vivo permeation, mucoadhesion, non Fickian diffusion, perindopril, polycarbophil.

1. INTRODUCTION

Within the oral cavity, delivery of drugs is classified into three categories: (a) sublingual delivery, which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth, (b) buccal delivery, which is drug administration through mucosal membranes lining the cheeks (buccal mucosa), and (c) local delivery, which is drug delivery into the oral cavity[(1)].

Within oral cavity, the buccal region offers an attractive route of administration for systemic drug delivery. Oral mucosa has rich blood supply and it is relatively permeable. Considering the low patient compliance of rectal, vaginal, sublingual and nasal drug delivery for controlled/sustained release, the buccal route of drug delivery is a good alternate as it offers many advantages [(2, 3)].

It enhances bioavailability for those drugs with bioavailability problems by increasing contact time, provides intimate contact between dosage form and absorbing tissue that may result in high drug concentration in a local area and hence high drug flux through the absorbing tissue and also bypasses the first pass metabolism.

If the prerequisite for efficient and prolonged drug absorption is considered, a bioadhesive dosage form should be the most appropriate delivery system. Because of the less flow of saliva in the buccal area, as compared to the sublingual region, the residence time of such a delivery system would be longer at the buccal tissue than on the sublingual mucosa, from which it would

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presumably be washed off quickly. Therefore, the buccal area is considered to be the best site for oral mucosal drug delivery [4].

Perindopril Eribumine is an orally active, angiotensin converting enzyme inhibitor. The terminal half-life of perindopril is about 0.8 to 1 hr [5]. Following oral administration, perindopril is well absorbed and undergoes substantial first-pass metabolism by cytochrome P450 enzymes; the systemic bioavailability of perindopril is about 20%. In view of these facts, this drug can be considered as a suitable candidate for buccal delivery.

MATERIALS & METHODS

Perindopril erbumine was a gift from Hetero Drugs Ltd., Hyderabad, India. Hydroxypropylmethylcellulose (Pharma coat, Pharma grade) and Sodium carboxymethylcellulose (Caramellose, Pharma grade) were gift samples from Tini Pharma Ltd., Tirupathi, India; Sodium alginate (analytical grade) was obtained from Loba Chemie PVT Ltd., Mumbai, India and polycarbophil (Noveon) was gifted by Aurobindo Pharma Ltd., Hyderabad, India. All reagents and solvents used were of analytical grade.

Investigation of drug–excipient interactions

Fourier transform infrared spectroscopy

Compatibility between drug and the polymers were studied by FTIR. FTIR studies were carried out for drug and its physical mixture (1:1). The sample was dispersed in KBr powder and the pellets were made by applying 6000 kg/cm^2 pressure and analyzed. FTIR spectra were obtained by diffuse reflectance on a FTIR spectrophotometer type FTIR 8400 (Schimadzu Corporation, Japan). The positions of FTIR bands of important functional groups of drug were identified and were cross checked in obtained spectra.

Differential scanning calorimetry (DSC)

DSC studies for drug and its physical mixture (1:1) were carried out using DSC-60 calorimeter (Schimadzu Corporation, Japan). The instrument was calibrated with an indium and zinc standard. The sample was heated from 10 to 300°C at a heating rate of 25°C/min to remove thermal history. The sample was then immediately cooled to 10°C and reheated from 10 to 300°C under the flow of nitrogen at a heating rate of 10°C/min.

Preparation of patches

Perindopril mucoadhesive buccal patches were prepared by solvent casting technique using chitosan, HPMCK4M, Sodium CMC, sodium alginate and polycarbophil as polymers. Glycerine and DMSO were used as plasticizer and penetration enhancer respectively. Ethanol, methanol and DCM were used as solvents. Composition of ingredients was given in table (1). Drug was dissolved in half of the solvent mentioned in table 1 and polymers were dissolved in remaining solvent/solvent mixture. Drug, polymer solutions along with plasticizer and permeation enhancer were sonicated for 30 min and examined for air entrapment. The solution was poured onto glass moulds of 10 × 5 cm^2 and air dried overnight at room temperature. An inverted funnel was kept on the mould for controlled evaporation. The dried film of the drug was peeled from the mould and packed in aluminium foil and kept in desiccator till further use. The backing layer was also prepared by the solvent casting method by dissolving 500 mg ethylcellulose in 15 ml of ethanol-toluene mixture (1:4). The drug loaded patches were laminated on one side with backing layer to provide unidirectional flow of drug across buccal mucosa.

Drug content

Drug content of patches was determined by dissolving five patches (1 cm^2) in 100 ml of 6.6 phosphate buffer. After suitable dilutions the resultant solution was filtered and analysed for perindopril content at 215 nm (Spectro UV 2060 Plus, Analytical technologies Limited, India) [6].

Thickness & weight variation

The thickness of patches was assessed using a micrometer screw gauge (Mitutoyo, Japan). From each

formulation, three randomly selected patches with surface area 1cm^2 were used. Twenty 1 × 1 cm^2 patches were weighed individually on an analytical balance (AX 200, Shimadzu, Japan) and the average weights were calculated [7, 8].

Table 1. Composition of perindopril buccal patches

Ingredients	Formulation			
	F 1	F 2	F 3	F 4
Perindopril (mg)	200	200	200	200
HPMCK4M (mg)	899	749	675	675
SCMC-H (mg)	--	150	--	--
Sodium alginate(mg)	--	--	225	--
Polycarbophil (mg)	--	--	--	225
Dimethylsulphoxide (ml)	0.2	0.2	0.2	0.2
Glycerine (ml)	0.4	0.4	0.4	0.4
Ethanol (ml)	--	5	7.5	5
Methanol (ml)	7.5	5	--	5
Dichloromethane (ml)	7.5	5	--	5
Water (ml)	--	--	7.5	--

Folding endurance

Folding endurance of patches was determined manually by repeatedly folding a film at the same place until it breaks. The number of foldings required to break or crack a patch was taken as the folding endurance [9].

Surface pH

Patches were placed in petri dishes containing 5 ml phosphate buffer (pH 6.6) and the pH at the surface was measured by placing the tip of glass microelectrode of a digital pH meter (Elico LI 120, India) close to the surface of patch and allowing it to equilibrate for 1 min prior to recording. Experiments were performed in triplicate [10].

Swelling index[11]

Swelling index of the patches was evaluated by placing them in petri dishes containing 4 ml of phosphate buffer pH 6.6 at room temperature. The patches were taken at regular intervals from petri dish and excess buffer was removed using filter paper. The swollen system was reweighed (w_2) The difference between the initial weight (w_1) and the weight gained at regular time interval (w_2) was used to determine swelling index which was calculated as S.I.= (w_2- w_1/ w_1)×100.

Preparation of porcine buccal mucosa

Buccal tissue was obtained from a local slaughterhouse from a freshly sacrificed porcine and used within 3 to 4 hr of sacrifice. The tissue was stored in isotonic phosphate buffer (pH 7.4) upon collection. Epithelium was separated from the underlying connective tissue using surgical blade and the membrane was used for the experiments [12].

***In vitro* residence time**

In vitro residence time was determined according to the method described by Nafee et al., The apparatus consists of disintegration apparatus with 800 ml of phosphate buffer pH 6.6 maintained at 37 ± 1°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 [10, 13].

***In vitro* mucoadhesion/bioadhesion test**

In vitro bioadhesion of the patches was determined by the procedure of Varsha et al using porcine buccal mucosa. A piece of porcine buccal mucosa was cut and glued with commercially available adhesive on the ground surface of a tissue holder made of thin plastic sheet. Similarly, the patch was glued to another tissue holder of the same size. Then the tissue holders with porcine buccal mucosa and patch were put in contact with each other by pressing with thumb for 5 min to facilitate adhesion. The tissue holder with porcine buccal mucosa was allowed to hang on an iron stand with the help of an

aluminium wire fastened with the hook provided on the back of the holder figure (1). A preweighed lightweight polypropylene bottle was attached to the hook on the back side of the formulation holder with aluminium wire. After a preload time of 5 min, water was added to the polypropylene bottle through an intravenous infusion set at constant rate of 100 drops per minute. The addition of water was stopped when buccoadhesive system was detached from buccal mucosa. The weight required to detach the system from buccal mucosa was noted [14].

The force of adhesion and the bond strength were calculated as[13].

$$Force\ of\ adhesion = Weight\ (gm) \times 9.81/1000 \quad \ldots\ldots(1)$$

$$Bond\ strength = Force\ of\ adhesion / Surface\ area\ of\ patch \quad \ldots\ldots(2)$$

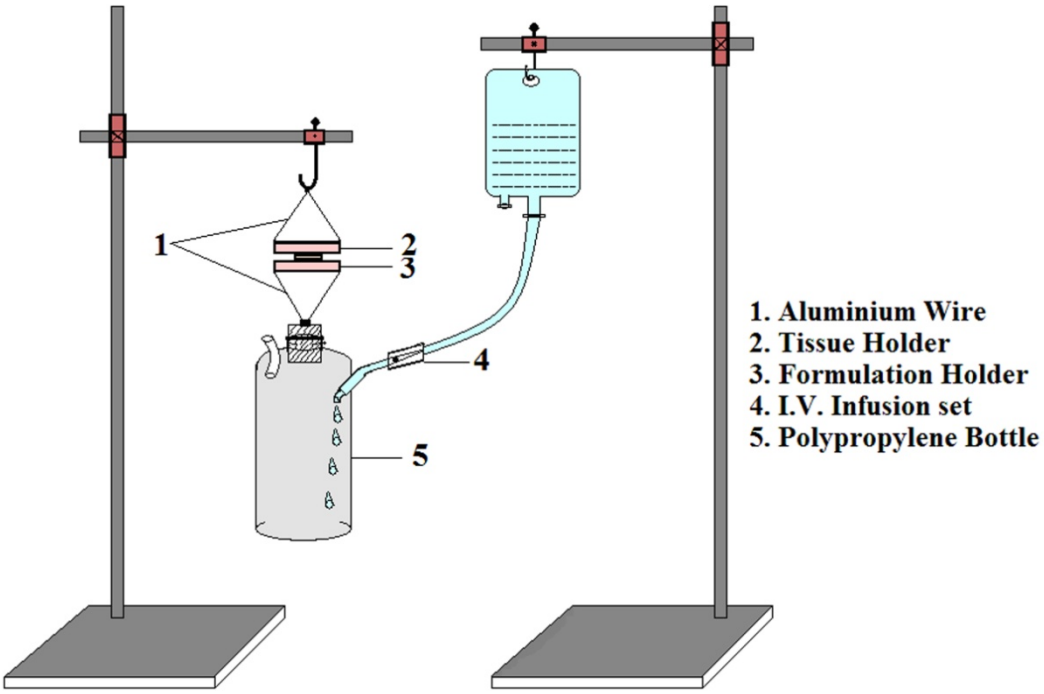

Figure 1. Apparatus for *in vitro* bioadhesion test

Determination of residual solvents

Methanol[15], ethanol[16] and dichloromethane[17] content in patches were determined by gas chromatography on an Agilent 7890 Gas Chromatograph, USA fitted with a flame ionization detector. For estimation of residual solvents, 1 cm^2 patch was dissolved in little amount of DMSO in a 10 ml volumetric flask and volume was made up to 10 ml with DMSO. The solution was filtered through 0.45 µm filter and degassed using sonicator. From the sample, 1µl was injected into injection port, the chromatogram was recorded and the peak area of solvent was measured. The concentration of residual solvent was calculated from calibration curve data.

***In vitro* release studies**

The apparatus consists of a receptor compartment (250 ml beaker), which is covered with a thin plastic sheet with three holes, one for a thermometer, second for sample collection tube and third for formulation holding ⊥ shaped glass rod shown in figure (2). Before starting the *in vitro* study, the patch was attached to glass rod and placed four inches above the receptor. The dissolution medium was 100 ml of phosphate buffer pH 6.6. The temperature was maintained at 37 ± 1°C on a heat controlled hot plate with a magnetic stirrer. Dissolution fluid was stirred at a constant speed of 50 rpm using a magnetic bead. Samples were withdrawn at regular

intervals and the same volume of fresh phosphate buffer pH 6.6 was replaced into the beaker to maintain sink condition. The samples were filtered through a 0.45 µm filter paper (Millipore) and drug concentration was analyzed spectrophotometrically [14].

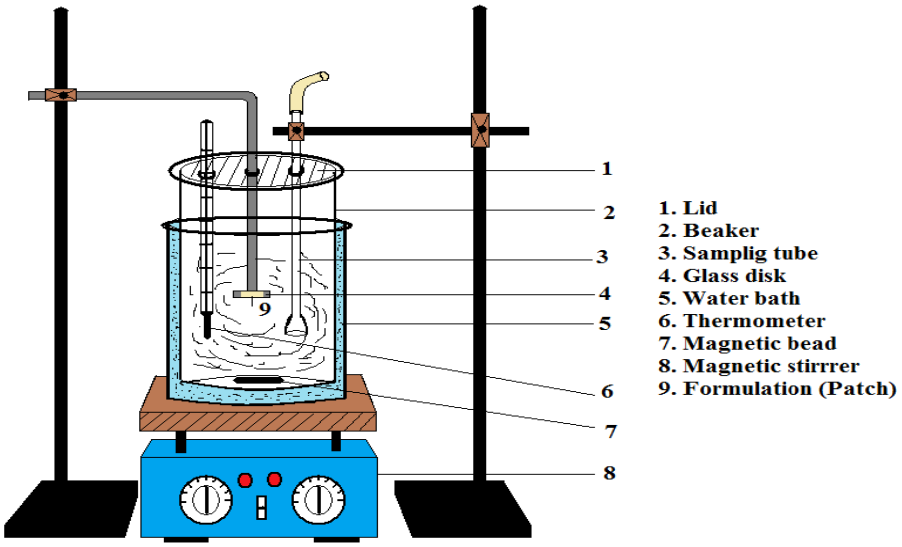

Figure 2. Modified dissolution apparatus used for *in vitro* release study

HPLC analysis

Analysis of samples was performed using a Schimadzu 10 AVP (Japan) HPLC system equipped with UV detector and a waters C-18 column (300 × 4.6 mm i.d) at ambient temperature. The mobile phase was mixture of phosphate buffer pH 3.0 and acetonitrile in the ratio 65:35 v/v. The solution was filtered through 0.45 µm filter and degassed by sonication. The flow rate was 1 ml per minute. The detection was carried on at 215 nm wavelength. A calibration curve was plotted for perindopril in the range of 20-100 µg/ml A good linear relationship was observed between the concentration of perindopril and its peak area (r^2 = 0.9981). Precision and accuracy of the HPLC method were estimated [18].

***Ex vivo* permeation studies**

1 cm^2 patch under study was placed in intimate contact with the excised porcine buccal mucosa and mounted between the two compartments of Franz diffusion cell. A teflon bead was placed in the receptor compartment filled with 25 ml of pH 6.6 phosphate buffer. The diffusion cell was thermo stated at 37±1ºC and at a rate of 50 rpm. The samples were withdrawn at regular intervals and the same volume of fresh phosphate buffer pH 6.6 was replaced into the diffusion cell to maintain sink condition. Samples were filtered through a 0.45 µm filter paper (Millipore) and analyzed for drug content using HPLC and the data was statistically analysed by one way ANOVA followed by turkey post hoc test for multiple comparison using graph pad prism[19]. Differences were considered to be significant at a level of $p<0.05$.

The different mathematical models may be applied for describing the kinetics of the drug release process from dosage forms the most suited being the one which best fits to the experimental results. The best models describe drug release from pharmaceutical dosage form resulting from a simple phenomenon, or when this phenomenon, by being the rate-limiting step, conditions all the process occurring in the system. The kinetics of release from formulations were determined by finding the best fit of the release data to zero order, first order, Higuchi and

Korsmeyer-Peppas plots [20]. The data was presented in the following graphical representation and regression analysis was performed.

Q_t versus t (zero order)

Log cumulative % of drug remained versus t (first order)

Q_t versus square root of t (Higuchi)

Log Q_t versus log t (Korsmeyer-Peppas)

Where, Q_t is the cumulative% of drug released/permeated at time t.

To examine the release mechanism of perindopril from the patches, the results were analyzed according to the following equation $Q_t/Q_\infty = k_t^n$, Where,

Q_t/Q_∞ is the fraction of drug released at time t,

k is a kinetic constant incorporating structural and geometrical characteristics of the drug/polymer system

n is the diffusional exponent that characterizes the mechanism of drug release [21].

The permeability coefficients (P) were calculated as follows [22]:

$$P = (dQ/dt)/ (CA)$$

Where

dQ/dt - Permeation rate,

C - Concentration of the donor chamber

A - Surface area of diffusion

Steady state fluxes (J_{ss}) were calculated by dividing the slope of cumulative amount permeated Vs time curve by the diffusional area.

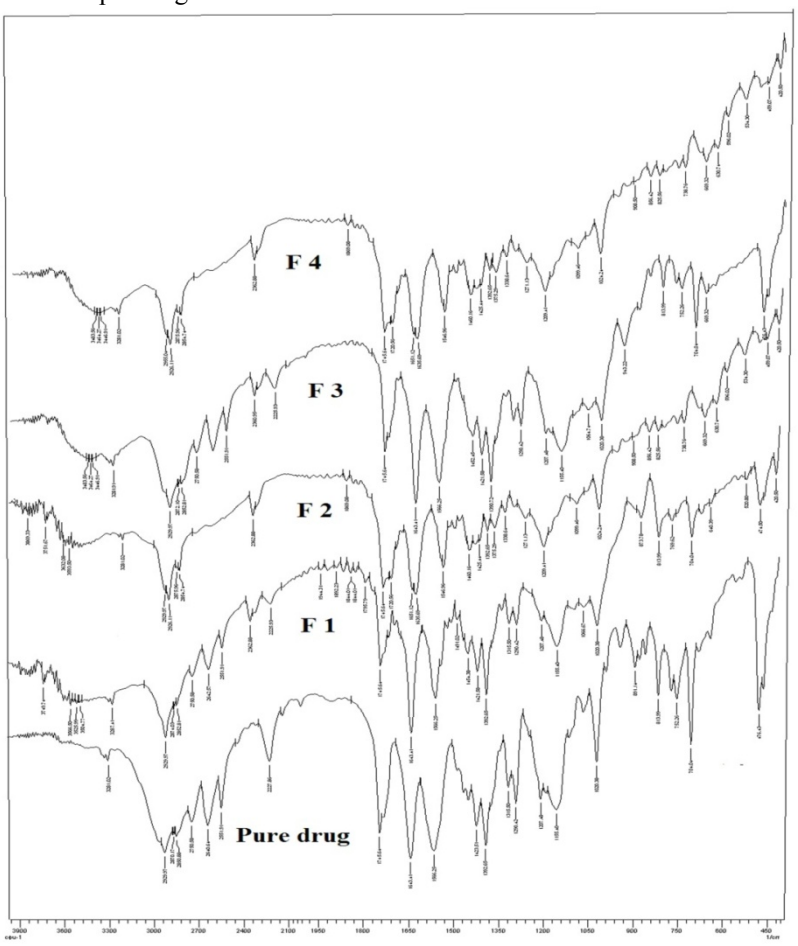

Figure 3. FTIR spectra of perindopril and its formulations

Drug release from backing layer

1 cm^2 patch was placed between the two compartments of a Franz diffusion cell at 37±1ºC with the backing layer facing the receptor compartment filled with 25 ml of pH 6.6 phosphate buffer. The samples were withdrawn at regular intervals and the same volume of fresh phosphate buffer pH 6.6 was replaced into the diffusion cell to maintain sink condition. Samples were filtered and analyzed for drug content [23].

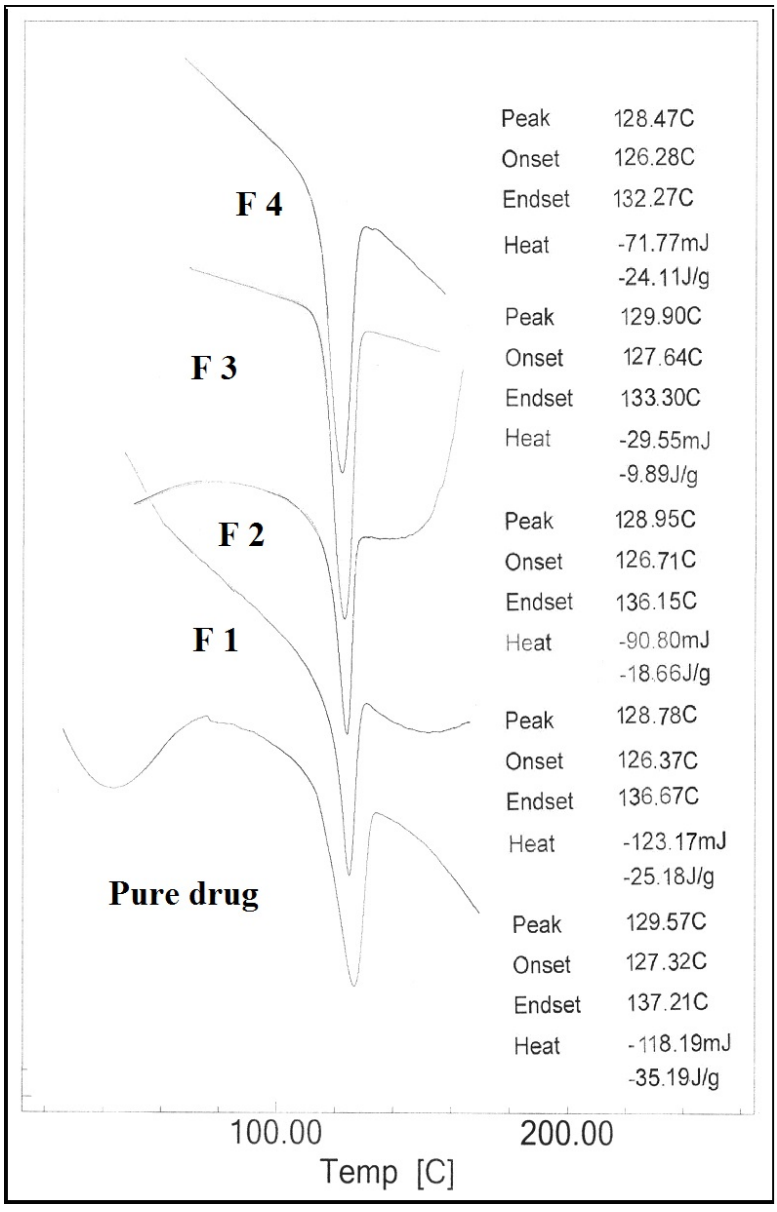

Figure 4. DSC thermograms of perindopril and its formulations

Stability in artificial saliva

Stability of the patches was assessed in artificial saliva. Patches were placed in petri dishes containing 5 ml of artificial saliva and kept in a temperature controlled oven at 37±1ºC for 6 h. The patches were examined for changes in texture and drug content [24, 25].

Stability studies

Stability studies were conducted according to the ICH Q1A (R2) guidelines. Patches were wrapped in aluminum foil and were kept in stability chamber at a temperature of 40±2ºC and 75±5% RH for 6 months. Samples were withdrawn at the end of 6 months and analyzed for drug content and *ex vivo* permeation through porcine buccal mucosa. The zero time samples were used as control for the study and the results were statistically analyzed by using t-test and $p < 0.05$ were considered as significant[26].

RESULTS & DISCUSSION

Investigation of drug–excipient interactions

The FTIR spectra of pure perindopril showed sharp characteristic peaks at 1020 (C–C stretch), 1207 (C-N stretch), 1392 (Carboxylate anion stretch), 1566 (N-H bending), 1745 (C=O stretch), 2870 (C–H stretch), 2929 (O-H stretch) and 3281 cm^{-1} (N–H stretch). All the above characteristic peaks appeared in the spectra of physical mixture at the same wave numbers indicating no modification or interaction between the drug and polymers.

The DSC thermo grams of perindopril showed an endothermic peak at 129.57ºC corresponding to its melting temperature, which was also detected in the thermo grams of physical mixture, signifying no interaction between perindopril and the polymers.

Physicochemical evaluation of perindopril buccal patches

Physicochemical evaluation data was shown in table (2). The drug content in all the patches was found to be uniform. The patches were weighing in between 28.59 mg to 29.92 mg. Patch thickness was in the range of 267 µm to 292 µm. The folding endurance of all the patches was optimum, exhibited good physical and mechanical properties. High alkaline or acidic pH of patches may cause irritation to the buccal mucosa and influence the degree of hydration of polymers [27, 28], so the surface pH of patches was determined to optimize release and adhesion. The surface pH of all formulations was in the range 5.9-7 pH, i.e close to buccal pH. Formulation F 3 showed highest swelling which may be due to presence of HPMC and sodium alginate. Addition of SCMC showed slight decrease in swelling index. Addition polycarbophil lead to more decrease in the swelling index due to formation of three dimensional network [29].

Higher residence time in F 4 may be due to the presence of polycarbophil, a good mucoadhesive polymer. Polycarbophil contains a weak polyacrylic acid, divinyl glycol which carries negative charges due to the presence of multiple carboxyl radicals (COO-) [30, 31]. This acid radical creates hydrogen bonding with the cell surface and creates strong bioadhesion. Where as addition of sodium alginate to HPMC lead to decrease in residence time of the patches which may be due to gelation nature of alginate.

In vitro mucoadhesion testing was carried using pork mucosal membrane, which gives indirect measurement of the bioadhesive strength in grams and the bond strength values were found to be 897.29, 965.01, 823.39 and 1052.29 N/m^2 for F 1, F 2, F 3 and F 4 respectively and significant difference was found in bioadhesive strength of patches. Formulation F 4 showed greater bioadhesive strength followed by F 2, F 1 and F 3. Addition of polycarbophil to HPMC was found to maximize the bioadhesive property; addition of SCMC also increases the bioadhesive property due to presence of hydroxyl and ether groups [32]. Where as addition of sodium alginate was found to minimize the bioadhesive property of patches. This may be due to gelation of sodium alginate[33].

Table 2. Physical evaluation of perindopril buccal patches

Formulation	Parameter						
	Drug content (mg)	**Weight variation (mg)**	**Thickness (µm)**	**Folding endurance**	**Surface pH**	**Swelling index**	***In vitro* residence time (min)**
F 1	3.98±0.14	29.92±0.47	287±1.53	298±2.64 (c***)	6.28±0.11 (b**, d***)	52.17±2 (b*, c*)	253±7.02 (b*, c*, d**)
F 2	4.08±0.13	28.59±0.59	292±3.61	285±6 (c***)	6.68±0.09 (a**, c*)	56.18±1.03 (a*, d**)	276±6.24 (a*, c***)
F 3	3.93±0.05	29.24±0.3	267±1.53	245±6.02 (a***, b***, d***)	6.43±0.04 (b*, d**)	57.50±0.75 (a*, d**)	228±8.74 (a*, b***, d***)
F 4	3.94±0.16	29.09±0.18	277±1.53	304±6.5 (b*, c***)	6.74±0.08 (a***, c**)	49.55±0.63 (b**, c**)	295±4.58 (a**, c***)

Mean ± SD, n = 3. a/b/c/d: Significantly different from F 1/F 2/F 3/F 4 respectively, */**/ ***: p<0.05/p<0.01/p<0.001 respectively.

According to guidelines for residual solvents Q3C (International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use) the residual solvents content in patches are largely below the tolerated limits.

In vitro release studies

In vitro release studies of patches were carried out in triplicate. After 6 h the release was found to be 94.24±0.94, 89.63±1.16, 88.42±1.85 and 80.38±1.04% for the formulations F 1, F 2, F 3 and F 4 respectively figure (5) and the data was analyzed by one way ANOVA and significant difference was observed between the means. *In vitro* release studies clearly showed that the percent release of perindopril was maximum i.e., 94.24% for formulation F 1.

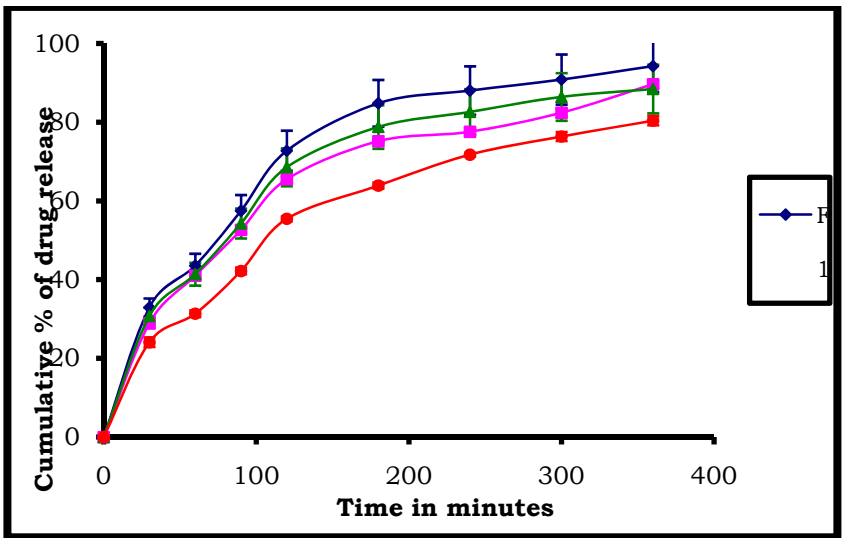

Figure 5. *In vitro* drug release profile of perindopril patches

***Ex vivo* permeation studies**

Ex vivo permeation studies for the patches were carried out in triplicate and after 12 hours the release was found to be 93.24±5.1, 87.62±4.73, 86.01±5.33 and 77.17±4.53% for the formulations F 1, F 2, F 3 and F 4 respectively figure (5) and significant difference was observed between means at 30, 120 & 240 minutes.

Formulation F 1 showed maximum release of drug from the patches which may due to formation of a thin gel (diffusion path length) by low viscous HPMCK4M. Addition of SCMC increases the gel strength of the patch which leads to slight decrease in the release [34]. Though formulation F 3 showed greater swelling index it shows the slow release which may be due to formation of a thick gel, which acts as a barrier for drug diffusion [35]. Presence of polycarbophil in formulation F 4 reduced the release of the drug. Polycarbophil having tendency to form a three dimensional network which controls the hydration and swelling of the formulation, leads to retardation of the drug release [29, 36].

In *ex vivo* permeation study formulation F 1 showed a maximum release of the drug, 93.24% in 720 min, this formulation was considered as optimized one and used for further study.

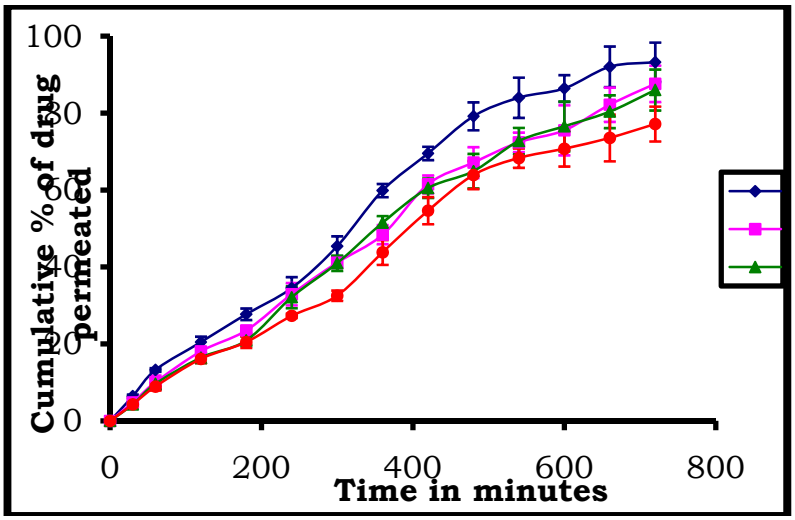

Figure 6. *Ex vivo* drug permeation profile of perindopril patches

Table 3. Correlation coefficient (r^2) and rate constant of different kinetic models for perindopril patches

Formulation	N value	Correlation coefficient (r^2)				Drug transport mechanism
		Zero order	First order	Higuchi	Peppas	
F 1	0.8372	0.9735	0.9618	0.9708	0.9782	Non-Fickian diffusion
F 2	0.9035	0.9888	0.9664	0.9783	0.9963	Non-Fickian diffusion
F 3	0.9592	0.9853	0.9775	0.9775	0.9939	Non-Fickian diffusion
F 4	0.9115	0.9782	0.977	0.9629	0.9918	Non-Fickian diffusion

The drug release data obtained were fitted in to various equations to know the mechanism of release. The *ex vivo* permeation profile of all formulations could be best expressed by Korsmeyer-Peppas model, as the plots showed highest linearity. All the formulations showed a non-Fickian release pattern as it was evidenced from the

release exponent (n > 0.5) table (3). This indicates coupling of the diffusion and erosion mechanism, called anomalous diffusion and shows that the drug release is controlled by more than one process.

The time taken for the permeation of 50% perindopril was found to be 300±8.6, 372±18.91, 349±11.67 and 385±24.69 minutes for the formulations F 1, F 2, F 3 and F 4 respectively. The mean steady state flux (J_{ss}) was found to be 0.326±0.01, 0.2953±0.01, 0.2959±0.00, 0.2719±0.01 mg/cm^2/hr and the permeability coefficient was found to be 0.0815±0.003, 0.0738±0.002, 0.0739±0.001, 0.0679±0.002 cm/hr for the formulations F 1, F 2, F 3 and F 4, respectively.

Stability studies

Stability study of formulation F 1 was conducted in artificial saliva to mimic the stability of drug and the formulation in the oral cavity. No color change was observed. Thickness of patches increased to 16.08% owing to swelling in artificial saliva over 6 h. The recovery of drug from the patches was 98.74% (3.92 mg) indicating maximum utilization of the drug incorporated. After accelerated stability studies, visual examination of the buccal patches did not show any change in morphology. Results revealed that there was no significant change in drug content and *ex vivo* permeation through porcine buccal mucosa. Shelf life of the formulation was calculated by using "Stab R" software [37] and it was found to be 18 months.

CONCLUSION

The present study indicates enormous potential of mucoadhesive buccal patches containing perindopril for systemic delivery with an added advantage of circumventing the hepatic first pass metabolism. The bioadhesive patches were displaying sufficient bioadhesive strength and *in vitro* drug release. The *ex vivo* permeation studies have shown that this is a potential drug delivery system for perindopril with considerably good stability and release profile. The release of drug was found to be combination of diffusion and erosion of polymers. So, it is possible to formulate mucoadhesive patches of perindopril with the intention of obtaining better therapeutic efficiency by sustaining drug release thereby improving patient compliance and increasing bioavailability with decreased dosing.

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تصميم وتطوير نظام إيتاء دواء فموي لدواء بيريندوبريل

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ملخص

الهدف الرئيس لهذه الدراسة: تطوير نظام إيصال دوائي شدقي لدواء بيريندوبريل. تم تطوير لصقات شدقية لدواء بيريندوبريل بتقنية صب المذيبات باستخدام هيدروكسي بروبيل ميثيل سيليلوز، بوليكاربوفيل، صوديوم كاربوكسيميثيلسيلولوسي وصوديوم الجينات على شكل بوليمرات لغرض التحرر الممتد لدواء بيريندوبريل. الغليسيرين وداي ميثيل صلفوكساید استخدما كمحسنات في التلدن والتغلغل على التوالي. واستخدم الإيثانول والميثانول وداي كلورو ميثان كمذيبات. وكشفت الدراسات باستخدام كل من FTIR وDSC بأنه لم يكن هناك تفاعل بين الدواء والبوليمرات. وقد وجدت محتويات لصقات بيريندوبريل متسقة. أظهرت الشرائح خصائص فيزيائية وميكانيكية جيدة. كانت حامضية السطح لجميع اللصقات ضمن معدل حامضية اللعاب. المحتوى المتبقي في اللصقات يقل إلى حد كبير عن حدود التحمل. وقد وجد أن للصقات مدة تحرر للدواء تصل إلى 12 ساعة خلال الدراسات التي تسبق التجارب الحيوية وذلك باستخدام آلية انتشار غير–فيكية. أظهرت هذه الدراسة إمكانية تصميم نظام إيتاء دوائي فموي لدواء بيريندوبريل.

الكلمات الدالة: الدراسات السابقة للتجارب الحيوية، موكوادهيجن، وانتشار غير فيكي، بيريندوبريل، بوليكاربوفيل.

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