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Research Article

IMPROVEMENT OF DISSOLUTION RATE OF RAMIPRIL BY SOLID DISPERSION TECHNIQUE AND DEVLOPEMENT OF BUCCAL PATCH

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ABSTRACT

Ramipril is an ACE inhibitor mainly used for management of mild to severe hypertension and myocardial infarction. The poor solubility and wettability of Ramipril leads to poor dissolution and hence showing variations in bioavailability. The present study is aimed to increase solubility and dissolution of the drug using solid dispersion techniques. The formulations were characterized by solubility studies, X-Ray Diffractometry studies, differential scanning calorimetry, Fourier transform infrared spectroscopy and in vitro dissolution rate studies. The solubility of drug increased linearly with increase in polymer concentration showing A_L type solubility diagrams. The solid dispersions of the drug demonstrated higher drug dissolution rates than physical mixtures and pure Ramipril. The kneaded complex method showed higher dissolution rate than other complex method and it was incorporated into buccal Patches. The patches were prepared by solvent casting method using HPMC K15 and Poloxomer WSR205NF.

The patches were found to be smooth in appearance, uniform in thickness, weight uniformity, drug content, swelling index, folding endurance, surface pH and in vitro diffusion study using Keshery chien diffusion cell. The Patch of 0.5% HPMC K15 exhibit in vitro release of 78.16% through cellophane membrane and 72.16% release through egg membrane and the patch of 0.5% Poloxomer WSR205 NF exhibit in vitro release of 74.24% through cellophane membrane and 69.44% release through egg membrane in 8 hrs showing good mucoadhesive strength and mucoadhesive time. The optimised patch was subjected to ex vivo studies through goat buccal mucosa showed 60.47% release in 8 hrs.

Keywords: Ramipril, Solid dispersion, Buccal patch, HPMC K15, Poloxomer WSR205NF.

INTRODUCTION

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of dosing. Problems such as first pass metabolism and drug degradation in the GIT environment can be circumvented by administering the drug via buccal route. Buccal delivery offers a safer mode of drug utilization, since drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal cavity. A suitable buccal drug delivery system should possess good bio adhesive properties, so that it can be retained in the oral cavity for the desired duration[1-3].

Ramipril is practically insoluble in water (3.5 mg/L). The poor solubility and wettability of Ramipril leads to poor dissolution and hence, variations in bioavailability. Ramipril, ACE inhibitor mainly used for management of mild to severe hypertension and myocardial infarction, suffers from low bioavailability of 28%. Two main reasons for low bioavailability being its poor aqueous solubility and high first pass metabolism. Thus, increasing the aqueous solubility and dissolution of Ramipril is of therapeutic importance[4]. The solid dispersion method is one of the selective approaches to achieve this ideal therapy particularly for drugs with poor aqueous solubility by incorporating them into a water-soluble polymer matrix (PEG 6000 & Pluronic F127). After assessing the drug content in the solid dispersions, the products were characterized by differential scanning Calorimetry, Fourier transform infrared spectroscopy, powder X ray diffraction and in vitro dissolution rate studies. The drug polymer interactions in aqueous solutions were investigated by phase solubility analysis[5].

Drugs administered by buccal route offers several advantages such as rapid absorption through oral mucosa and high blood level due to high vascularisation of the region; thereby avoiding first pass effect. The present study aims to improve dissolution rate of Ramipril by Solid Dispersion technique and to prepare buccal patches incorporating the SD to possibly improve the bioavailability.

MATERIALS AND METHODS

Materials

Ramipril was obtained as gift sample form Cipla ltd. Mumbai. The Polyethylene glycol 6000 & Pluronic F127 were purchased from Colorcon, Mumbai. HPMC K15 and Poloxomer WSR205NF were procured from Oxford chemical, Mumbai. All other chemicals and solvent used were of Pharmaceutical and analytical grade.

Phase solubility studies[6]

Phase solubility studies were carried out at room temperature, in triplicate according to method reported by Higuchi and Connors. Excess amount of Ramipril was added to double distilled water containing various concentration of PEG 6000 & Pluronic F127 (0-5%) in a series of stoppered conical flasks and shaken for 48 hr on a rotary flask shaker. The suspensions were filtered through whatman filter paper and assayed for Ramipril using UV spectrophotometer (Varian Cary 100, Australia) at 210 nm against blank prepared using same concentration of Peg 6000 and Pluronic F127 in double distilled water.

Preliminary Study (Selection of appropriate ratio of drug and carrier)

Preliminary study was carried out to select the appropriate ratio of drug and carrier for maximum improvement in drug solubility. For that various ratios (1:1, 1:3, 1:5, and 1:7) had been tried and saturation solubility study was performed.

Preparation Methods of SD

The two carries selected for the study i.e. PEG 6000 and Pluronic F127. All SD were prepared with both the carries and at 1:1, 1:3, 1:5 and 1:7 ratios, by methods as described in detail below. All prepared SDs were pulverized with pestle and mortar, sieved (<250 µm), dried in oven for at least 48 hrs and then stored at room temperature in a screw-capped glass vial until use.

Physical mixtures (PM)

For the comparative study, physical mixtures of Ramipril were prepared by mixing accurately weighed amounts of Ramipril with carriers in mortar and passed through sieve.

Preparation of Solid dispersions

Solvent evaporation method (SE)

SD was prepared by dissolving accurately weighed amounts of Ramipril and carrier in methanol. After complete dissolution

sonicate the solution for 20 minutes and then solvent was evaporated under reduced pressure at room temperature in desiccators.

Co-grinding method (CG)

Ramipril was triturated with minimum quantity of methanol in a glass mortar until it dissolved. The carrier was then added and suspension was triturated rapidly at room temperature until the solvent evaporated

Kneading method (KN)

A mixture of carrier and Ramipril was wetted with water and kneaded thoroughly for 30 minutes in a glass mortar.

Closed Melting method (CM)

One gram of PM was weighed in to glass ampoules, sealed and heated for 30 min. in water bath at 80^0C temperature to prepare the SDs. After slow cooling the ampoules caps were opened and collect the SDs.

Spray drying method (SD)

The Ramipril and Pluronic F127 were dissolved in methanol and solution was kept to run from spray drier (Labultima LU 222). The inlet temperature maintained was at 65^0C and outlet temperature at 40^0C. The aspiration rate was 50-55. The feed pump speed was 10ml/min. The cooling temperature was maintained at 35^0C. The powder was collected from collector and stored.

Freeze –Drying Method (FD)

Physical mixtures of drug and carrier in a molar ratio of were added to 500 ml double distilled water and stirred for 5 days. The suspension was freeze dried (ilshin® freeze Dryer), and obtained freeze-dried complex was pulverized and sieved through (<38μm).

Evaluation of Solid Dispersion

Determination of drug content

SD equivalent to 10 mg of drug was stirred with 100ml of methanol for 60 minutes, and then the solution was filtered and treated as stock solution containing 100 μg/ml drugs. From this stock solution the concentration of 10μg/ml was prepared and the drug content was determined using the calibration curve of pure drug in methanol spectrophotometrically at 210 nm using methanol as blank.

Saturation Solubility Studies

The saturation solubility study was carried out to determine increase in the solubility of pure Ramipril as compared with the physical mixture and SD. Excess amount of drug, physical mixture and SD were added to the 250 ml conical flasks containing 25 ml of double distilled water. The sealed flasks were shaken for 24hr at room temperature followed by equilibrium for three days. Then, the aliquots were withdrawn through whatman filter paper. The concentration of Ramipril was determined by UV spectrophotometer at 210 nm.

Characterization of the Physical mixture and SD

UV spectroscopic study[7]

This was performed by spectral shift method weighing Ramipril, all SDs accurately, dissolved in methanol, volume made with DW to produce a final concentration of 10μg/ml. It was then filtered, degassed by sonication for 30 min. and analyzed spectrophotometrically in UV region and absorbance was measured at 210 nm.

Fourier Transform Infrared spectrophotometry [FT-IR]

FTIR spectra of pure Ramipril and carries and SDs were recorded with FTIR spectrophotometer using KBr disks. The scanning range used was 4000 to 400 cm^{-1} at a scan period of 1 minute. Then the spectra were comparatively analyzed for drug-carrier interaction.

Powder X-ray Diffractometry [PXRD]

XRD (Philips PW 1729, Netherlands) was employed for tracing XRD patterns of Ramipril and SDs, using Ni filter, Cu K (α) radiation, a voltage of kV, a current of 20 mA and receiving slit of 0.2 in. The samples were analyzed over 2θ range of 5° to 50°, with scan step size of 0.020° (2θ) and scan step time of 1 second.

Differential Scanning Calorimetry [DSC]

DSC (Lab Mettler Stare SW 9.20, Switzerland) was used to obtain the curves of Ramipril, carriers and SDs representing the rates of heat uptake. About 2-5mg of sample was weighed in a standard open aluminium pans, were scanned from 40-250°C, at a heating rate of 10°C/min while being purged with dry nitrogen. The instrument was calibrated prior to sample analysis, using an indium standard.

In-vitro dissolution studies

Drug release studies were performed in triplicate at 37 ± 0.5 0C employing USP apparatus II at 75 rpm. Dissolution study was carried out in two dissolution media (Phosphate buffer of pH 6.8 and double distilled water). Dissolution studies were performed on pure drug (10 mg) and the SD containing an equivalent amount of the drug. Aliquots of the periodically withdrawn samples (5 ml) were analyzed spectrophotometrically at 210 nm, and were replaced with an equal volume of plain dissolution medium8.

Formulation of buccal patches

Kneading complex of SD was selected for the formulation of buccal patch. The buccal patches were prepared by solvent casting method. HPMC K15 and Poloxomer WSR205NF polymers in ratio of 0.5 to 1 % were incorporated in different buccal patches. The concentration of plasticizer was finalized differently for the two polymers from the plasticity of the film. It is varied from 10% to 20% for the patch. The composition of different formulation is shown in Table no.1.

The component of each formulation were mixed and poured in the mould and dried in oven then removed from the mould and cut in to pieces of 1 × 1 cm and finally packed in aluminium foil.

Table 1: Composition of Mucoadhesive buccal patch

Formulation batch	SD/CD equivalent to Ramipril (mg)	HPMC K15 (%)	Poloxomer WSR205NF (%)	Propylene glycol (%)
A1	10	0.5	-	10
A2	10	1	-	10
A3	10	-	0.5	13
A4	10	-	1	13
B1	10	0.5	-	10
B2	10	1	-	10
B3	10	-	0.5	13
B4	10	-	1	13

*A- PEG6000, B- Pluronic F127

Evaluation of buccal patch

Folding Endurance

Folding endurance was determined by repeatedly folding at the same place until it broke. The number of times the film folded at the same place without breaking was the folding endurance value.

Patch thickness

Patch thickness measured at five different randomly selected spots using screw gauge.

Content uniformity

The buccal Patch dissolved in phosphate buffer pH 6.8. The n solution is diluted and filtered through whattman filter paper, and analyzed at 210 nm using a UV Double beam spectrophotometer.

Surface pH study

The Patch was allowed to swell by keeping it in contact with 2% agar gel plate for 2 hrs at room temperature. The pH was measured by bringing the electrode in contact with the surface of the patch and allowing it to equilibrate for 1 min.

Swelling study

Buccal patches were weighed individually (W1) and placed separately in 2% agar gel plates with the core facing the gel surface and incubated at 37 ± 1°C. At regular intervals (1, 2, 3, 4, 5& 6 hours) the patches were removed from Petri dishes and excess water removed carefully using filter paper. The swollen patch was then reweighed (W2) and the swelling index (SI) were calculated using the formula given in equation no.1.

$$SI = [(W2-W1) \div W1] \times 100 \text{ ---------- (1)}$$

Where, W1 = initial weight of the patch;

W2 = final weight of the patch[9].

In Vitro Drug Release

The in vitro drug permeation study was carried out using Keshery chien diffusion glass cell. The upper and lower compartment was filled with saline phosphate buffer solution. Cellophane membrane was kept in between two compartment and whole assembly kept at 37 ± 0.2°C. The amount of drug permeated was determined by removing an aliquot of 1ml sample at appropriate time interval and stirred at 50 rpm on magnetic stirrer.

In vitro mucoadhesive strength[10]

The strength of bond formed between the patch and mucosa membrane excised from goat mucosa was determined using two-arm balance method. Fresh goat mucosa section was fixed on the plane surface of glass slide (3×5 cm) attached (with adhesive tape) to bottom of smaller beaker, kept inverted in 500 ml beaker attached to the bigger beaker. Isotonic phosphate buffer (pH 6.8) was added to the beaker up to the upper surface inverted beaker with goat mucosa. The patch was stuck to the lower side of the upper clamp with cyanoacrylate adhesive. The exposed patch surface was moistened with phosphate buffer (pH 6.8) and left for 30s for initial hydration and swelling. Then the platform was slowly raised until the patch surface came in contact with mucosa. Two sides of the balance were made equal before study. After a preload (50 gm) time of 2 minutes, water was added to the polypropylene bottle present in another arm, until the patch was detached from the mucosa. The water collected in the bottle was measured and expressed as weight (gm) required for the detachment. The force measurement was repeated 3 times for each formulation. The following parameters were calculated from the bio adhesive strength using equation 2&3.

Force of adhesion (N) = (Bio adhesive strength (gm) * 9.81) / 1000 ---------- (2)

Bond strength (Nm^{-2}) = Force of adhesion / Disk surface area ---------- (3)

Ex-Vivo drug permeation studies

Permeation studies were carried using the Keshery chien diffusion glass cell. Goat oral mucosa was used as the model membrane. The buccal pouch of the freshly sacrificed goat was procured from the local slaughter house. The buccal mucosa was excised and trimmed evenly from the sides and then washed in phosphate buffer of pH 6.8 and used immediately. The membrane was stabilized before mounting in order to remove the soluble components. The mucosa was mounted between the donor and receptor compartments. The receptor compartment was filled with Phosphate buffer of pH 6.8 which was maintained at 37 ± 0.2º C and the hydrodynamics were maintained by stirring with magnetic bead at 50 rpm.

FT-IR study of buccal Patch

The sample of Ramipril with HPMC K15 was prepared by simple blending with KBr. The scanning range used was 4000 to 400 cm^{-1}. Then the spectra were comparatively analyzed for drug-carrier interaction.

RESULTS AND DISCUSSION

Phase Solubility Analysis

Phase solubility diagrams for Ramipril with PEG 6000 and Pluronic F127 in distilled water are shown in fig.1 and fig.2. The solubility of Ramipril increased in linear fashion as a function of the concentration of PEG 6000 and Pluronic F127, showing A_L –type phase solubility diagram with slopes of less than unity. According to Higuchi and Connors, these A_L type solubility curves indicate the first order dependency of the interaction on the concentration of SD and the formation of soluble Ramipril-PEG 6000 and Ramipril-Pluronic F127 complexes with Stoichiometric ratio of 1:5. The value of the stability constants for PEG 6000 was 111.53, while $K_{1:5}$ value of Pluronic F127 was 77.5.

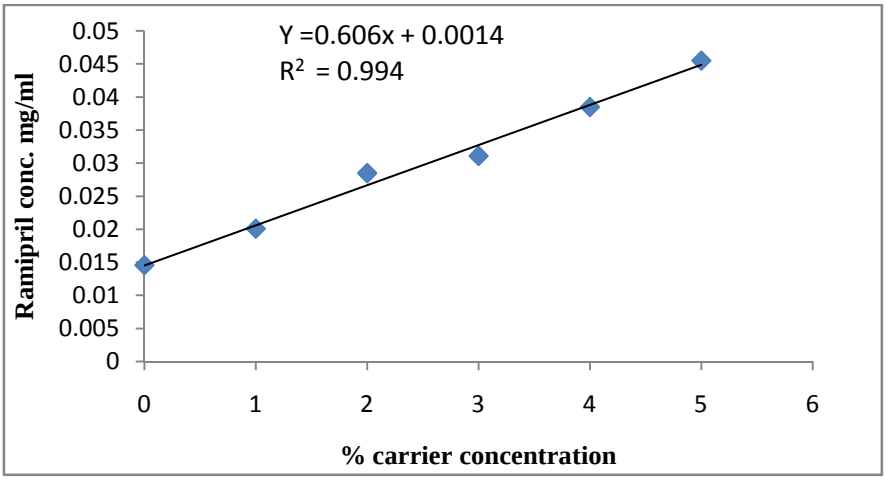

Fig. 1: Phase solubility analysis plot for inclusion complexes (Drug: PEG6000)

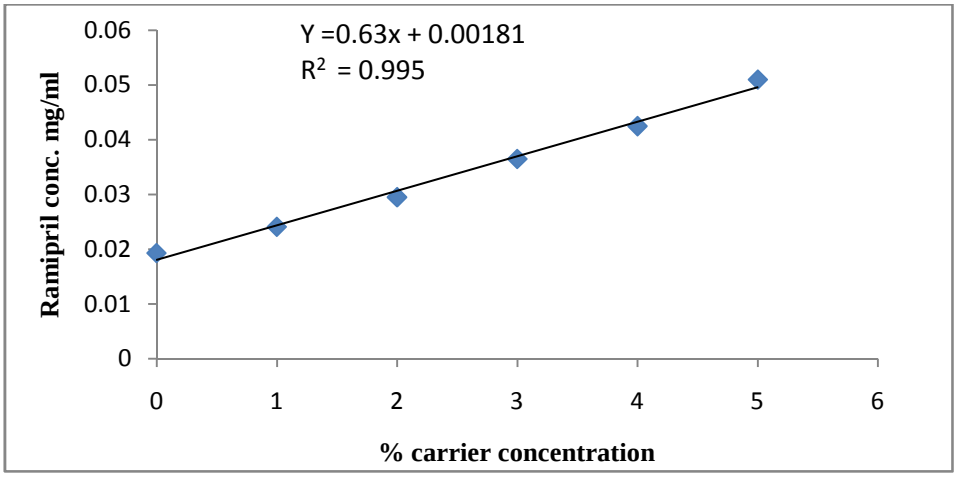

Fig. 2: Phase solubility analysis plot for inclusion complexes (Drug: PluronicF127)

Evaluation of Solid dispersion

Drug Content in drug: PEG6000 (1:5) and Drug: PluronicF127 (1:5) complex

Percentage drugs content of the complexes are shown in Table 3 was found within the range of 87 to 98%. The maximum percent drug content was found to be 97.9±0.21% and 98.8±0.3% in the drug: PEG6000 (1:5) and drug: Pluronic F127 (1:5) spray-dried complex.

Saturation solubility study

The saturation solubility data for drug and complexes are presented in Table 4&5. It is confirmed that the enhancement of solubility of Ramipril from ratio 1:5, 1:3 and 1:1 was maximum in comparison to other ratio. Similar result was obtained with carrier Pluronic F127. This improvement solubility was might be due to good result of binding of drug and carrier in ratio up to 1:5, further increment of carrier concentration did not affect the binding capacity of carrier but release of drug form carrier mass may be hindered, hence shows the lower solubility. Thus, selected final ratio was 1:5.

FTIR

FTIR spectroscopy has been used to assess the interaction between drug and cyclodextrin molecules in the solid state. Fig.3&4 illustrates the FT-IR spectra of the samples under study. The chemical interaction between the drug and the cyclodextrin often leads to identifiable changes in the infrared profile of dispersion. Drug spectrum shows prominent peaks at IR spectra of Ramipril showing the peaks at 3400 cm^{-1} for –NH and -OH, 2900 cm^{-1} for –CH aromatic streaching,1730 cm^{-1} for -C=O, 1320 cm^{-1} for –CH aliphatic bending. Physical mixture of drug with PEG6000 (1:5) and drug: Pluronic F127 complexes shows the prominent peaks of drug, but there was reduction in peak intensity of drug peak which was obscured by cyclodextrin peak indicating formation of complexes.

Table 3: Percentage drug content of drug: PEG6000 (1:5) and drug: PluronicF127 (1:5) complex.

Complexes	% Drug Content	
	PEG6000	PluronicF127
Physical mixture	87.5±0.12%	88.39±0.13%
Kneading	98.05±0.34%	97.2±0.23%
Co-grinding	97.7±0.32%	95.9±0.31%
Solvent evaporation	94.3±0.15%	93.69±0.43%
Closed melting	92.14±0.09%	93.01±0.17%
Spray Drying	97.9±0.21%	98.8±0.3%
Freeze Drying	95.4±0.13%	97.8±0.08%

Table 4: Preliminary saturation solubility of PEG6000

Preparation Methods	Saturation Solubility on Various Ratio of PEG6000 (µg/ml)			
	1:1	1:3	1:5	1:7
Physical mixture (PM)	64.2± 0.78	68.1± 1.25	87.3± 0.87	72.8± 0.69
Solvent evaporation (SE)	98.4± 0.36	138± 0.22	174.3± 1.11	158.5± 0.55
Co-Grinding (COG)	122.1± 0.75	218.3± 0.80	387± 0.91	340± 1.02
Kneading (Kn)	234.3± 0.88	260± 1.12	317± 0.42	284.2± 0.93
Closed Melting (CM)	190.2± 1.03	222± 0.49	251.4± 0.62	230± 0.39
Spray Drying (SPD)	121.3± 1.19	214.6± 1.07	267.1± 0.36	254.3± 0.91
Freeze drying (FD)	180.4± 0.27	251.4± 0.84	312.2± 0.41	284.7± 0.80

Table 5: Preliminary saturation solubility of PluronicF127

Preparation Methods	Saturation Solubility on Various Ratio of PluronicF127 (µg/ml)			
	1:1	1:3	1:5	1:7
Physical mixture (PM)	94.11± 0.41	98.21± 0.55	105.3± 1.58	95.7± 1.82
Solvent evaporation(SE)	107.7± 0.64	187.2± 0.47	214.7± 0.64	197.3± 0.67
Co-Grinding (COG)	125.7± 0.69	192.8± 0.37	284.7± 1.44	221.3± 0.97
Kneading (Kn)	172.9± 0.19	212.7± 0.49	321.9± 0.65	272± 0.48
Closed Melting (CM)	103± 0.97	142.7± 0.78	178.4± 0.66	133.7± 0.82
Spray Drying (SPD)	167.8± 1.06	198.8± 0.88	237.8± 1.67	210± 1.48
Freeze drying (FD)	195.7± 1.56	274.3± 1.16	317.3± 0.69	282.5± 1.01

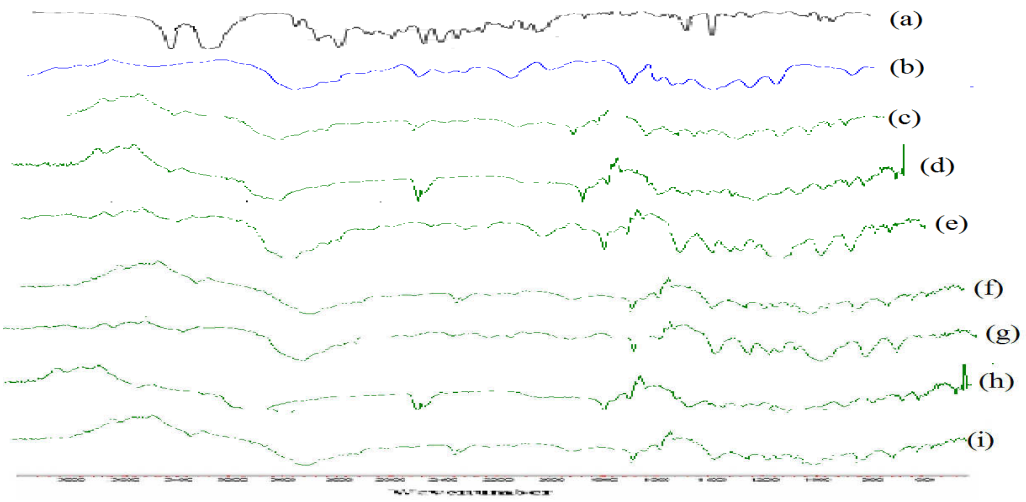

Fig. 3: IR Spectral analysis of a) Ramipril b) PEG6000 c) Physical mixture d) Kneading method e) Solvent evaporation method f) Co-grinding, g) Closed melting method, h) Spray drying, i) Freeze drying.

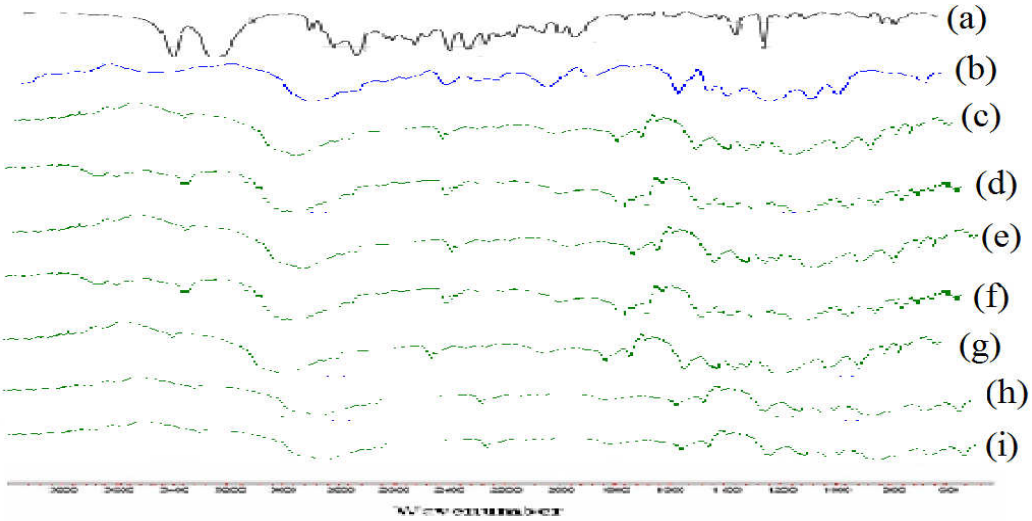

Fig. 4: IR spectral analysis of a) Ramipril b) PluronicF127 c) Physical mixture d) Kneading method e) Solvent evaporation method f) Co-grinding, g) Closed melting, h) Spray drying, i) Freeze drying.

X-ray Diffractometry [XRD]

Powder X-ray diffraction spectroscopy has been used to assess the degree of crystallinity of the given sample. When complex of drug and Peg6000 / PluronicF127 are formed, the overall number of crystalline structure is reduced and the number of amorphous structures is increased. The final product sample shows less number as well as less intensity of peaks. This shows that overall crystallinity of complexes is decreased and due to more amorphous nature, the solubility is increased. The PXRD spectra of Ramipril, cyclodextrin and its complex are shown in Fig.5&6. Ramipril showed its highly crystalline nature, as indicated by the numerous distinctive peaks at 2θ values are 8.26, 10.13, 12.4, 13.2, 17.8, 19.1, 19.9, 21.1, and 21.6. The powder X-ray diffractogram of pure Ramipril showed numerous distinctive peaks that indicated a high crystallinity. The diffractogram of complexes were found to be more diffuse compared to drug, there is no characteristic peak i.e formation of amorphous solid state (inclusion complex formation).

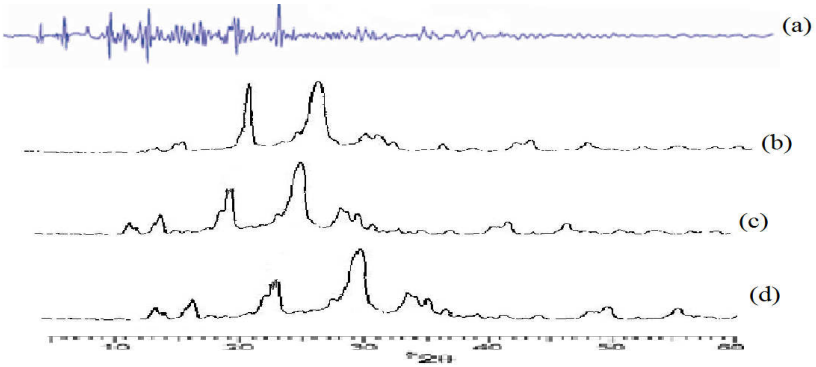

Fig. 5: X-Ray Diffraction of a) Ramipril, b) PEG6000, c) Kneading method d) Co-grinding.

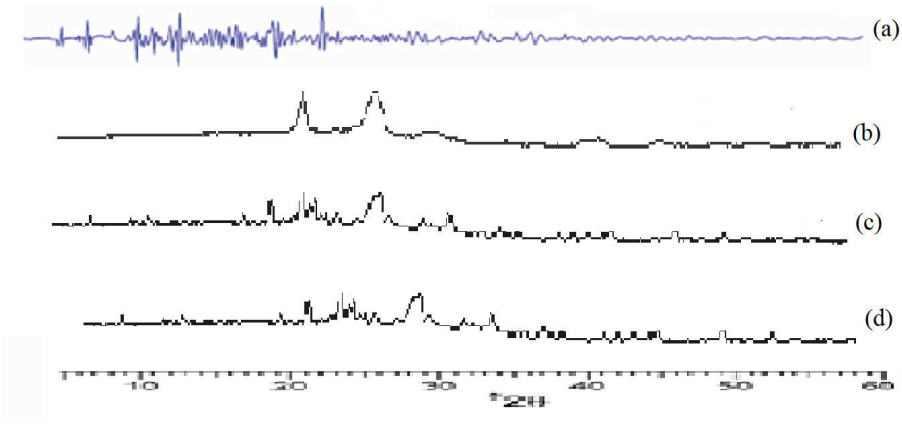

Fig. 6: X-Ray Diffraction of a) Ramipril, b) PluronicF127, c) Kneading method, d) Co-grinding.

DSC

DSC enables the quantitative detection of all processes in which energy is required or produced (i.e., endothermic or exothermic phase transformations). Thermo-grams for drug and complexes are shown in Fig.7&8. DSC studies showed that endothermic peaks for pure Ramipril, PEG6000 and PluronicF127 were obtained at 112°C, 62.7°C and 58.7°C respectively. Thermo gram of drug: PEG600 (1:5) and drug: PluronicF127 (1:5) complex showed complete disappearance of peak of Ramipril and shift of endothermic peak of PEG6000 and PluronicF127. These indicate successful complexation with PEG6000 and PluronicF127. Thus, DSC studies confirm the SD of drug with PEG6000 and PluronicF127.

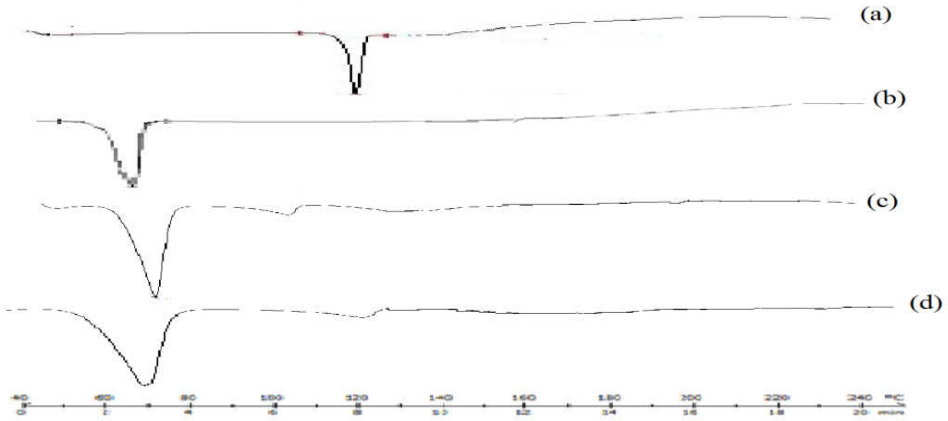

Fig. 7: DSC study of a) Ramipril, b) PEG6000, c) Kneading complex, d) Co-grinding complex.

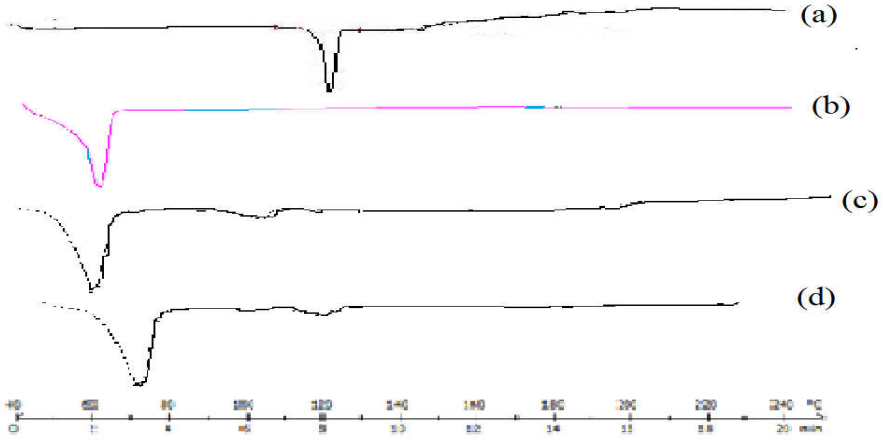

Fig. 8: DSC study of a) Ramipril, b) PluronicF127, c) Kneading complex, d) Co-grinding complex.

In vitro release profile of complexes

Dissolution profiles of pure Ramipril and SD are presented in Fig.9, Fig.10, Fig.11 and Fig.12. It is evident that the complexation technique has improved the dissolution rate of Ramipril to a great extent. From in vitro release study, Fig.9, Fig.10, Fig.11 and Fig.12, it was found that the complex prepared as 1:5 by kneading method of drug:PEG6000 and drug:PluronicF127 has shown improve in dissolution behaviour as compare to drug and other complexes. This might be due to the inclusion complex formation, which indicates the improved solubility phenomenon.

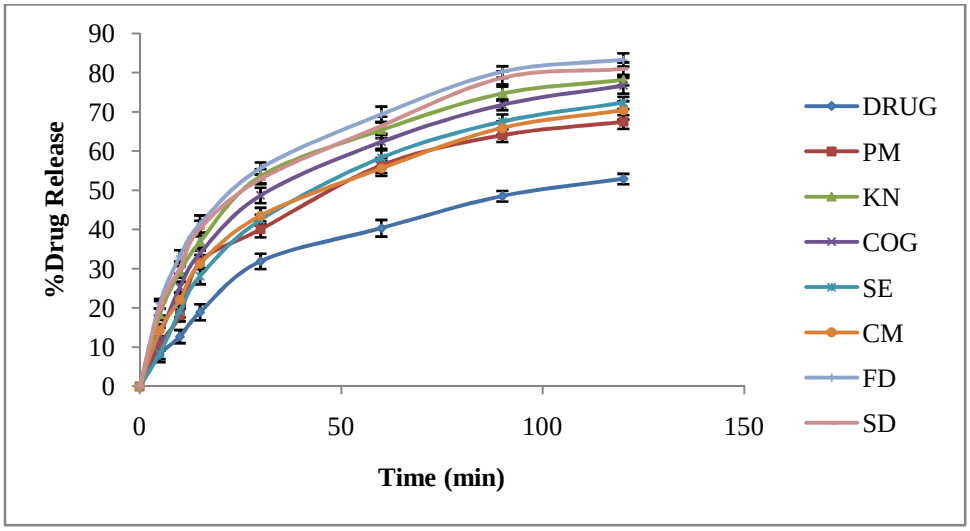

Fig. 9: % drug release of drug and its SD in Distilled Water (Drug: PEG6000 complex).

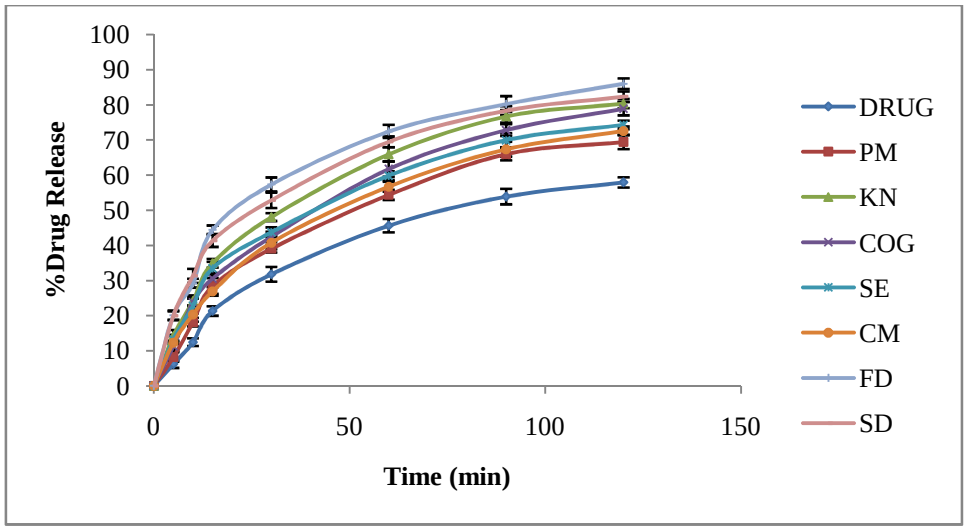

Fig. 10: % drug release of drug and its SD in Phosphate buffer pH 6.8 (Drug: PEG6000 complex).

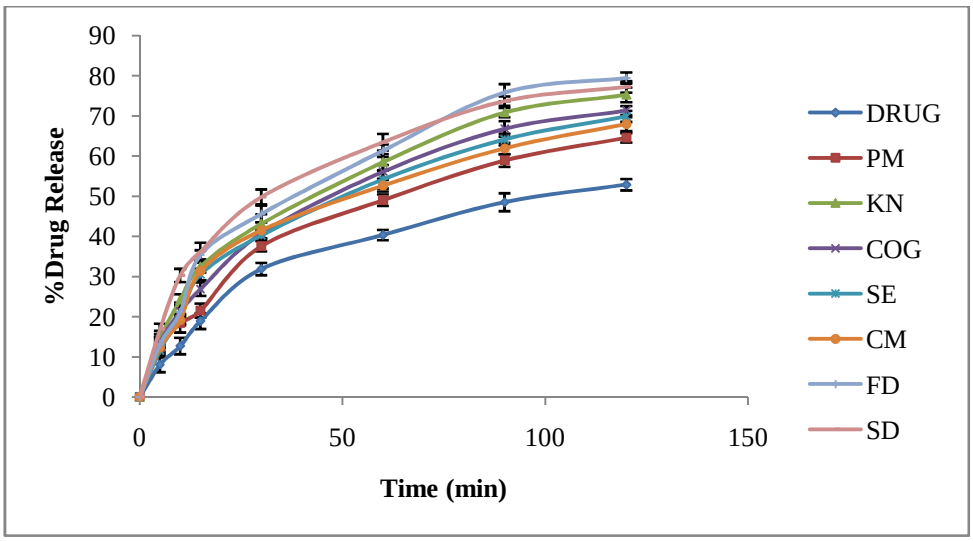

Fig. 11: % drug release of drug and its SD in Distilled Water (Drug: PluronicF127 complex).

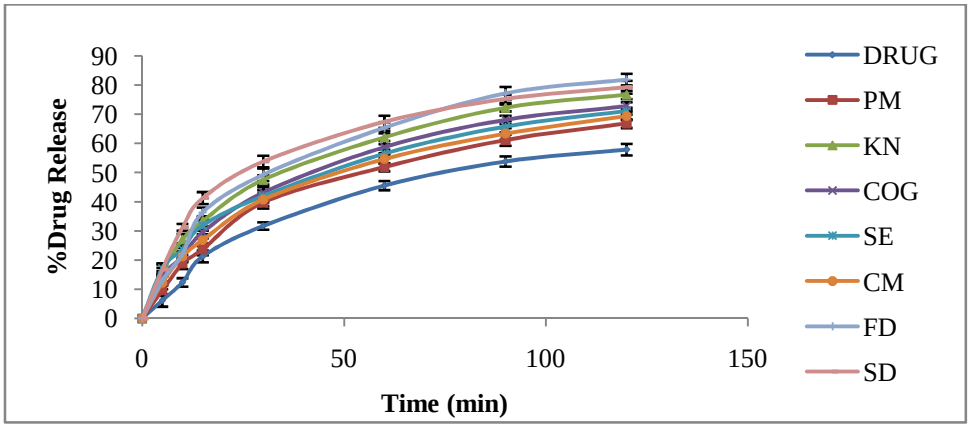

Fig. 12: % drug release of drug and its SD in Phosphate buffer pH 6.8 (Drug: PluronicF127 complex).

Evaluation of Buccal patches

To formulate a buccal patch of Ramipril, the Kneaded complex of PEG6000 and Kneaded complex of PluronicF127 was selected based on its saturation solubility and in-vitro dissolution performance. The patches were prepared by solvent casting method using hydroxyl propyl methyl cellulose (HPMC K15) and Poloxomer WSR205NF.

Table 6: Characteristics of mucoadhesive buccal patches containing PEG6000

Batch code	A1	A2	A3	A4
Patch Thickness	0.91±0.15	1.17±0.36	0.86±0.03	1.22±.17
Surface pH	6.9	7.23	6.34	6.1
Folding Endurance	252	281	279	287
Swelling Index	47±0.12	34±0.45	39±0.32	31±0.21
%Drug content	96.4±0.21	95.64±0.18	97.51±0.14	96.23±0.02
Mucoadhesive strength (gm)	8.91±0.034	6.8±0.12	9.13±0.042	7.93±0.23
% Drug release after 8 hrs	78.16±1.21	71.72±1.34	74.24±1.37	62.08±2.23

Table 7: Characteristics of mucoadhesive buccal patch containing PluronicF127

Batch code	B1	B2	B3	B4
Patch Thickness	0.93±0.17	1.09±0.02	0.89±0.21	1.14±0.11
Surface pH	6.78	6.43	7.13	6.65
Folding Endurance	267	252	311	285
Swelling Index	43±0.23	35±0.1	39±0.4	31±0.5
%Drug content	97.51±0.18	95.35±0.03	98.1±0.14	96.13±0.17
Mucoadhesive strength	9.12±0.021	7.34±0.098	10.01±0.03	8.35±0.1
% Drug release after 8 hrs	73.8±2.23	68.52±1.19	65.24±2.22	60.44±1.21

Table 8: Best fit model for diffusion study of optimized batches of buccal patch of Ramipril

Sr. no.	Formulation code	Best Fit model	n	R^2=
1	A1cel	Matrix	0.3763	0.9897
2	A3cel	Matrix	0.3766	0.9901
3	A1egg	Matrix	0.3776	0.9902
4	A2egg	Matrix	0.3748	0.9885
5	A1goat	Matrix	0.3635	0.9878

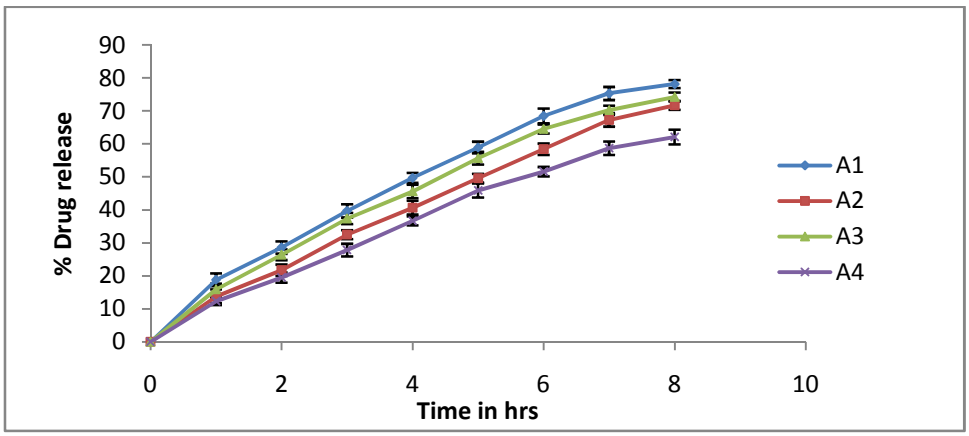

Fig. 13: Release profile of Ramipril from buccal patches containing PEG6000 on cellophane membrane.

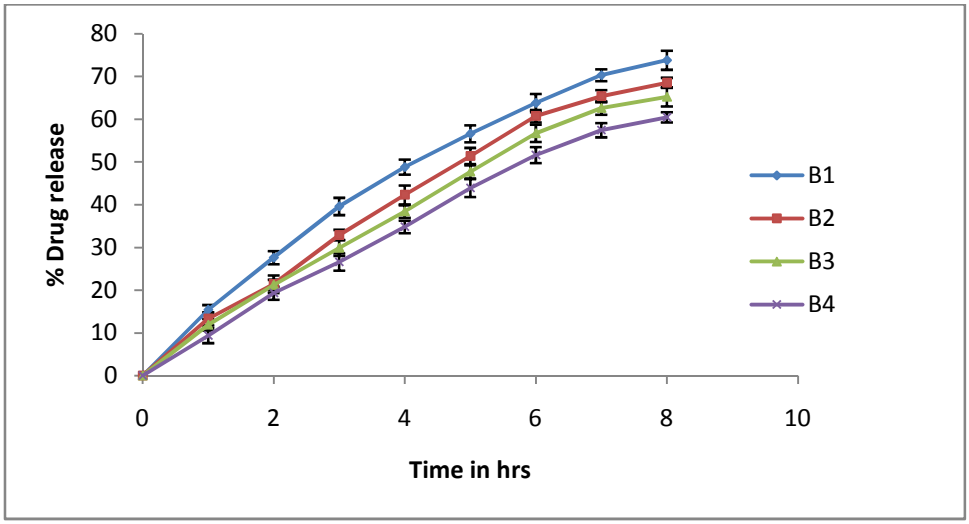

Fig. 14: Release profile of Ramipril from buccal patches containing PluronicF127 on cellophane membrane.

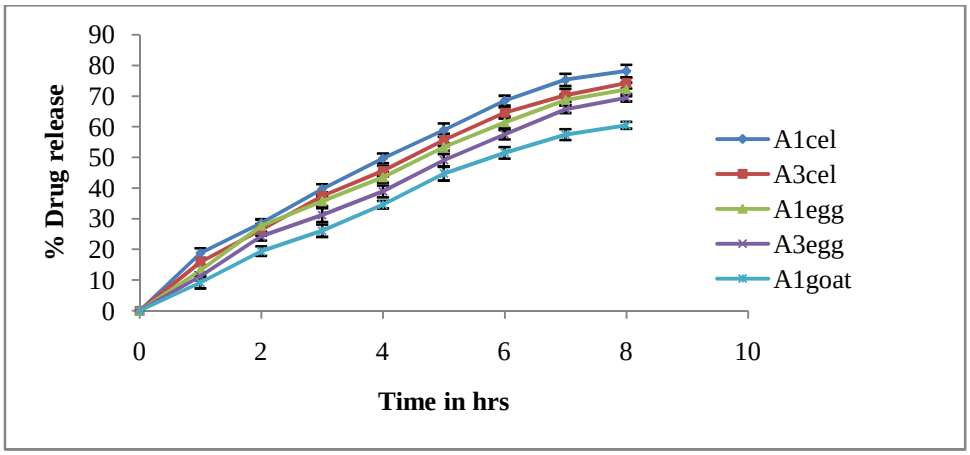

Fig. 15: Release profile of Ramipril optimised buccal patch on cellophane, egg membrane and goat mucosal membrane.

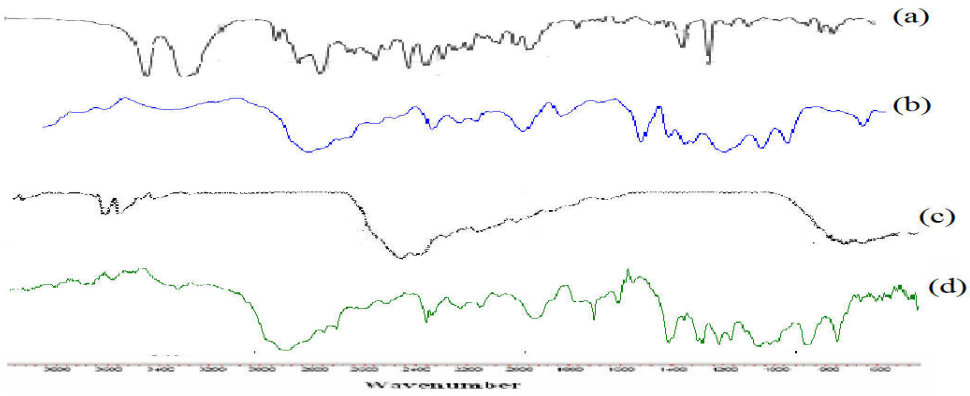

Fig. 16: IR spectral analysis of a) Ramipril b) PEG6000 c) HPMC K15 d) Optimised formulation.

CONCLUSION

The present work demonstrated the preparation of solid dispersions of Ramipril with PEG6000 and PluronicF127 by solvent method, with the improved solubility and dissolution properties. The solubility, DSC, FT-IR, XRD and SEM studies clarified the physical state of both the drug and the carrier in the samples. A eutectic system was obtained in which the contribution of the PEG and Pluronic crystals was concentration dependent. The higher dissolution rates exhibited by solid dispersions may imply enhanced oral bioavailability due to the increased wetting properties and solubility of drug in the hydrophilic polymer.

Buccal patches of Ramipril using polymers like HPMC K15 and Poloxomer WSR205NF in various proportions and combinations showed satisfactory Physico-mechanical and mucoadhesive

characteristics. From the present investigation, it can be concluded that such buccal patches of Ramipril may provide sustained buccal delivery for prolonged periods in the management of hypertension, which can be a good way to bypass the extensive hepatic first-pass metabolism.

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