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Mucoadhesive buccal patches based on interpolymer complexes of chitosan–pectin for delivery of carvedilol

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Abstract The study was designed to develop bioadhesive patches of carvedilol hydrochloride using chitosan (CH) and pectin (PE) interpolymer complexes and to systematically evaluate their *in vitro* and *in vivo* performances. Mucoadhesive buccal patches of carvedilol were prepared using solvent casting method. The physicochemical interaction between CH and PE was investigated by FTIR and DSC studies. The patches were evaluated for their physical characteristics like mass variation, content uniformity, folding endurance, *ex vivo* mucoadhesion strength, *ex vivo* mucoadhesion time, surface pH, *in vitro* drug release, *in situ* release study, and *in vivo* bioavailability study. The swelling index of the patches was found to be proportional to the PE concentration. The surface pH of all the formulated bioadhesive patches was found to lie between 6.2 and 7.2. The optimized bioadhesive patch (C1, CH:PE 20:80) showed bioadhesive strength of 22.10 ± 0.20 g, *in vitro* release of 98.73% and *ex vivo* mucoadhesion time of 451 min with in a period of 8 h. The optimized patch demonstrated good *in vitro* and *in vivo* results. The buccal delivery of carvedilol in rabbits showed a significant improvement in bioavailability of carvedilol from patches when compared to oral route.

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1. Introduction

Mucoadhesive drug delivery systems offer benefits over conventional delivery methods in terms of extended residence time of the drug at the site of application, a relatively large permeability of the mucus membranes that allow rapid uptake of a drug into the systemic circulation, and enhanced bioavailability of therapeutic agents resulting from the avoidance of some of the body's natural defense mechanisms. Mucoadhesion, defined as the ability to adhere to the mucus gel layer, is a key element in the design of these drug delivery systems (Lee et al., 2000). Buccal mucosa is an attractive route for systemic

delivery of drugs since it is relatively permeable, with rich blood supply (Hoogstraate et al., 1996). The problems such as high first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via the buccal route (Gu et al., 1988; Lehr et al., 1992) and, buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage form from the buccal cavity. Attempts have been made earlier to formulate various buccoadhesive devices, including tablets (Boyapally et al., 2010), films (Pongjaryakui and Suksri, 2009), patches (Morrow et al., 2010), disks (Darwish et al., 2008) and strips (Dixit and Puthil, 2009). However, buccal films are preferable over adhesive tablets in terms of flexibility and comfort (Gu et al., 1988). Natural polysaccharides have been widely used as bioadhesive polymers because of their biocompatibility and biodegradability properties. In this study chitosan (CH) and pectin (PE) were used as bioadhesive polymers to increase the residence time of the dosage form in buccal cavity. These polymers swell in aqueous media to form a gel through which the drug has to diffuse thus; they can also be used to control the rate of drug release.

Carvedilol is a non-selective, β-adrenergic antagonist with no intrinsic sympathomimetic activity and is widely used to treat essential hypertension and angina pectoris. Although it is completely absorbed from the gastrointestinal tract, the systemic availability is approximately 25–35% because of high first-pass metabolism. Carvedilol is metabolized primarily by aromatic ring glucuronidation. The oxidative metabolites are metabolized by conjugation via glucuronidation and sulfation (Morgan, 1994). Higher bioavailability of carvedilol has been observed following absorption from the buccal mucosa (Vamishi et al., 2007) and the lower parts of gastrointestinal tract GIT (Nolte et al., 1999). This suggests that the oral availability of carvedilol could be improved by formulating a buccoadhesive dosage form. Hence, buccoadhesive patches can be envisaged to ensure both enhanced oral availability as well as maintenance of effective plasma concentration over prolonged duration by extending the release of carvedilol. This in turn is expected to reduce the frequency of administration by maintaining effective plasma concentration over longer duration, providing better control of hypertension and thereby, improving patient compliance. In the present study, an attempt has been made to develop buccal patches of carvedilol hydrochloride using CH and PE. The in vitro release characteristics of the prepared systems were evaluated using USP type II dissolution apparatus, the adhesion measurement was conducted using modified balance method with porcine cheek mucosa and in vivo study was conducted in rabbits.

2. Experimental section

2.1. Materials

Carvedilol was received as a gift sample from Ranbaxy Laboratories, Gurgaon, India, chitosan was a gift sample from Central Institute of Fisheries Technology, India, Pectin was procured from Central Drug House, India and propylene glycol from Fine Chemicals, India. All other reagents and chemicals were of analytical grade and were used as such.

2.2. Methods

2.2.1. Formation of interpolymer complex between CH and PE
PE (80 mg) was dissolved in 50 ml of distilled water and CH (20 mg) was dissolved in 50 ml of 2% (v/v) acetic acid by magnetic stirring for 1 h. Upon addition of PE slowly in CH solution, while stirring continuously, a solid sticky mass was obtained. The admixture was kept at 37 °C for 48 h. The supernatant was decanted and the remaining solid complex was dried at 50 °C. The dried polymer complex of CH–PE was sieved first through sieve #22 and then through sieve #80. The powdered polymer complex of CH–PE was characterized using Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetric (DSC) studies.

2.2.2. Preparation of mucoadhesive buccal patches
Buccoadhesive patches were prepared by solvent casting method. CH and carvedilol were dissolved in 2% (v/v) glacial acetic acid solution containing ammonium acetate (5 M) and PE was dissolved in distilled water. CH solution was then added to PE solution with stirring. PG, 15% (v/v) was added as a plasticizer. The resulting viscous solution was poured in petri plates and dried in an oven at 50 °C for 48 h. The dried films were cut into square pieces of sides 1.5 cm containing 6–6.5 mg of drug per patch. The patches were packed in an aluminum foil and stored in an airtight glass container to maintain the integrity and elasticity of the patches. Table 1 shows the composition of formulated buccal patches.

2.2.3. Mass uniformity and folding endurance test
Mass uniformity of the patches was tested in 10 different randomly selected patches from each batch and the patch thickness was measured at five different randomly selected spots using a vernier caliper. Folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 200 times without breaking (Khurana et al., 2000).

2.2.4. Drug content uniformity
Drug content uniformity was determined by dissolving the patch by homogenization in 100 ml of an isotonic phosphate buffer (pH 6.6) for 2 h with occasional shaking. Aliquot (5 ml) was withdrawn and diluted with isotonic phosphate buffer pH 6.6 up to 20 ml, and the resulting solution was filtered through a 0.45 mm Whatman filter paper. The drug content was then determined spectrofluorometerically (Patel et al., 2007).

2.2.5. Surface pH determination
The surface pH of the patch was determined by the method similar to that used by Bottenberg et al. (1991). The patches were allowed to swell by keeping them in contact with 1 ml of distilled water for 2 h at room temperature, and pH was noted down by bringing the electrode in contact with the surface of the patch, allowing it to equilibrate for 1 min.

2.2.6. Measurement of bioadhesive strength
The bioadhesive strength of the bioadhesive patches was evaluated using the method reported by Gupta et al. (1992). Porcine cheek pouch (thickness 0.05 ± 0.01 mm) was used as

Table 1 Physical characteristics of bioadhesive carvedilol patches.

Patch code	CH:PE	Mass (mg)	Thickness (mm)	Drug content (%)	Folding endurance	Surface pH
A	100:0	49 ± 1	0.52 ± 0.11	97.84 ± 0.12	153 ± 13	3.3 ± 0.10
B	0:100	52 ± 1	0.66 ± 0.23	98.45 ± 0.23	175 ± 20	3.5 ± 0.11
C1	20:80	55 ± 0	0.58 ± 0.85	98.66 ± 0.15	205 ± 17	6.7 ± 0.30
C2	25:75	44 ± 1	0.45 ± 0.45	99.21 ± 0.45	179 ± 12	6.8 ± 0.15
C3	33:67	52 ± 1	0.52 ± 0.52	99.36 ± 0.650	188 ± 22	6.8 ± 0.17
C4	50:50	55 ± 1	0.69 ± 0.33	98.75 ± 1.12	186 ± 11	6.9 ± 0.16
C5	67:33	54 ± 0	0.78 ± 0.65	100.21 ± 0.63	198 ± 14	6.7 ± 0.30
C6	75:25	45 ± 1	0.65 ± 0.23	97.52 ± 0.98	201 ± 17	6.2 ± 0.15
C7	80:20	47 ± 1	0.57 ± 0.17	100.85 ± 0.85	152 ± 24	7.2 ± 0.15

All the experiments were carried out in triplicate.

the model membrane for the measurement of bioadhesive strength. The mucosal membrane was excised by removing the underlying connective tissue. The surface of the mucosal membrane was first blotted with filter paper and then moistened with 25 μl of buffer solution pH 6.6. The weight required to detach the film from the mucosal surface was determined and force of adhesion was taken as a measure of bioadhesive strength.

2.2.7. In vitro swelling studies of buccoadhesive patches
The degree of swelling of bioadhesive polymer is an important factor affecting adhesion. The swelling rate of buccoadhesive patch was evaluated by placing the films in phosphate buffer solution pH 6.6 at 37 ± 1 °C. Six patches of each batch were cut and weighed, and the average weight was calculated (W_1). The patches were placed in phosphate buffer and were removed at time intervals of 0.5, 1, 2, 3, 4, 5, 6 and 7 h, excess water on the surface was carefully absorbed using filter paper, and swollen patches were reweighed. The average weight W_2 was calculated, and the swelling index was calculated by the formula:

$$\text{Swelling index} = \frac{W_2 - W_1}{W_1}$$

All the experiments were carried out in triplicate.

2.2.8. In vitro release studies
In vitro drug release studies were carried out employing dissolution test apparatus type II (USP) paddle method using 900 ml of phosphate buffer (pH 6.6) as the dissolution medium at 50 rpm at 37 ± 0.5 °C for 8 h. To provide unidirectional release, one side of each patch was attached to a glass disk with the help of cyanoacrylate instant adhesive (Desai and Kumar, 2004). An aliquot of 5 ml was withdrawn at suitable time intervals and replaced with fresh phosphate buffer (pH 6.6) maintained at the same temperature. Samples were then analyzed spectrofluorometrically (limit of detection (LOD) was found to be 1 ng and limit of quantitation (LOQ) was found to be 2 ng).

2.2.9. Ex vivo mucoadhesion time
This study was performed on an optimized bioadhesive patch. The disintegration medium composed of 800 ml phosphate buffer pH 6.6 (IPB) maintained at 37 °C. A segment of porcine check mucosa, 3 cm long, was glued to the surface of a glass slab, vertically attached to the apparatus. The mucoadhesive patch was hydrated from one surface using 15 μl phosphate buffer and then the hydrated surface was brought into contact with the mucosal membrane.

The glass slab was vertically fixed to the apparatus and 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 necessary for complete erosion or detachment of the patch from the mucosal surface was recorded. All the experiments were carried out in triplicate (Nafee et al., 2004).

2.2.10. In situ release studies
The studies were carried out by using Keshary–Chein glass diffusion cells. Porcine cheek pouch was first given pretreatment by placing it between receptor and donor compartment for 3 h. The patch was then placed in the donor compartment. The whole assembly was maintained at 37 ± 1 °C and the medium stirred at 100 rpm. An aliquot of sample (1 ml) was taken at suitable time intervals from the receptor compartments and equal volume was replaced with fresh phosphate buffer (pH 6.6) maintained at the same temperature. Samples were analyzed spectrofluorometrically as for dissolution samples.

2.2.11. Pharmacokinetic studies
The pharmacokinetic studies were carried out in healthy rabbits. The animals selected for the study had no medication for 2 weeks prior to study. The rabbits were sedated with an intra muscular injection of ketamine (25 mg/kg) before application of test patch. The formulated test patch bonded directly to a backing layer made up of ethyl cellulose was placed in the buccal cavity. A gentle pressure was applied for 1 min and blood samples were taken from ear vein after regular intervals for 8 h, centrifuged at 4000 rpm for 10 min to separate plasma. The separated plasma was stored at −4 °C until analyzed. For the quantitative determination of carvedilol in rabbit plasma, 200 μl of plasma was taken into microcentrifuge tubes followed by addition of 100 μl of nimesulide (internal standard) and 100 μl of 5% (w/v) trichloroacetic acid as protein precipitant. The tubes were then centrifuged for 10 min at 4000 rpm. The supernatant was separated and 1 ml of chloroform was added and this solution was again centrifuged at 4000 rpm for 10 min. The chloroform layer was separated and dried. The residue was reconstituted with 1 ml of mobile phase, vortexed, filtered and 20 μl was injected into column. Similarly, rabbits were administered oral solution containing 6.25 mg of carvedilol in phosphate buffer.

2.2.12. Analysis of plasma samples by high performance liquid chromatography (HPLC) method

The analysis of the plasma samples was performed using Waters HPLC system equipped with a Waters 515 HPLC pump, Waters 2487, Dual λ Absorbance detector, and Waters spherisorb S5 C8 column. The mobile phase comprised of a mixture of acetonitrile and phosphate buffer pH 3.2 (60:40, v/v). The flow rate was 1 ml/min. The detection was carried out at wavelength 242 nm (LOD was found to be 4 ng and LOQ was found to be 5 ng). The data were acquired and processed using Empower 2 software.

2.2.13. Statistical analysis

Analysis of variance (ANOVA) followed by Tukey's test was used for statistical comparison of the data. Significance level was fixed at $p < 0.05$.

3. Results and discussion

In the present study, buccal patches of carvedilol were prepared using different ratios of CH:PE interpolymer complexes.

3.1. Characterization of CH–PE interpolymer complex

3.1.1. FTIR analysis

The FTIR spectra of CH (Fig. 1A) showed a sharp peak of strong intensity at 1580 cm^{-1} which is the characteristic peak of amino group in CH while in case of PE (Fig. 1B) sharp peaks at 1749.9 cm^{-1} and 1616.5 cm^{-1} indicated the presence of C=O stretching of the ester and carboxyl group, respectively. The FTIR spectra of CH–PE interpolymer complex (Fig. 1C–I) indicated changes in the range of 1800–1600 cm^{-1}, evident of interaction of amino and carboxylic groups. A strong peak at 1627.0 and 1412.9 cm^{-1} in C (CH:PE; 80:20), 1640.3 and 1402.7 cm^{-1} in D (CH:PE; 75:25), 1620.5 and 1403.6 cm^{-1} in E (CH:PE; 67:33), 1645.3 and 1417.3 cm^{-1} in F (CH:PE; 50:50), 1623.3 and 1403.1 cm^{-1} in G (CH:PE; 33:67), 16.22.3 and 1404 cm^{-1} in H (CH:PE; 25:75), 1621.0 and 1442.8 cm^{-1} in I (CH:PE; 20:80) indicated the presence of –COO$^-$ groups and –NH$_3^+$ in the patches indicating interpolymer complexes between CH and PE (Vasilyeva et al., 2004).

3.1.2. DSC studies

The DSC thermogram of CH or PE showed an endothermic transition at 70 and 95 °C, respectively. This could be attributed to water loss as all the powders were hydrated at 50% RH prior to thermal analysis. Further, an exothermic transition at 311 and 242.11 °C, respectively, was observed in the DSC thermograms of CH and PE. These exothermic transitions are indicative of degradation of these polymers. The complex prepared by interacting 20:80 or 80:20 ratio of CH:PE exhibited two endothermic transitions and an exothermic transition (Table 2). Two endothermic transitions were observed in thermograms of CH:PE complex prepared from ratio 50:50. However, no exothermic transition was observed in same CH–PE films. This might indicate that there is complete interaction between CH and PE. The second endothermic transition ranging from 210 to 220 °C could be attributed to the formation of carboxylate linkage between –COO of PE and –NH$_3^+$ of CH. Similar results have earlier been reported where
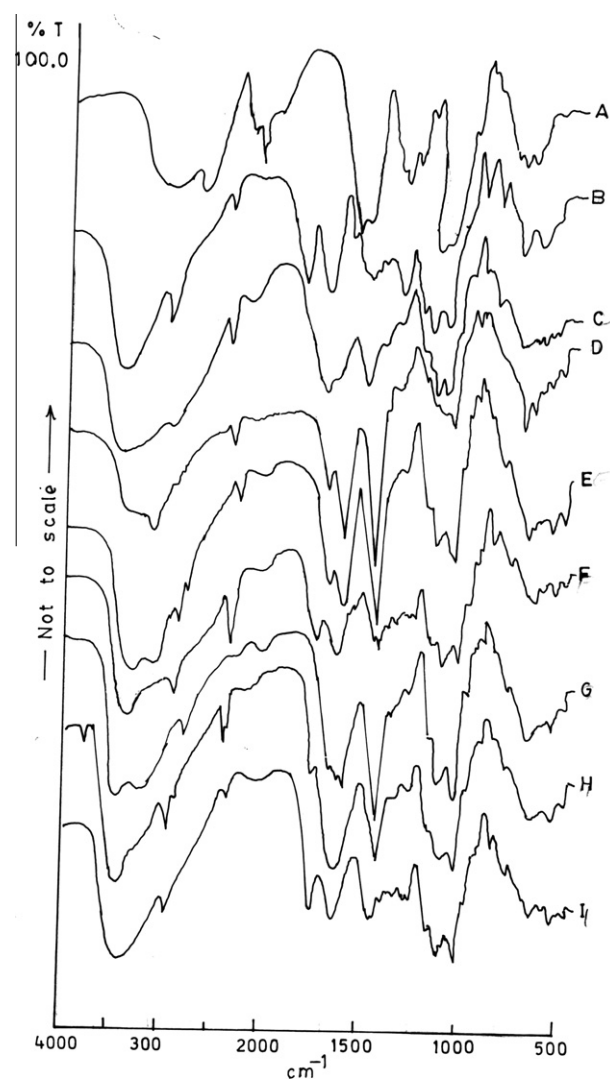

Figure 1 FTIR spectra of CH (A), PE (B), and interpolymer complex films comprising of 80:20 (C), 75:25 (D), 67:33 (E), 50:50 (F), 33:67 (G) 25:75 (H) or 20:80 (I) CH:PE ratios.

an additional endotherm at 210 °C was observed when chitosan and chondroitin sulfate interpolymer complexes were prepared (Kaur et al., 2010).

3.2. Physical characteristics of bioadhesive patches

The prepared patches were smooth in appearance, uniform in thickness, mass and drug content and showed no visible cracks. The patches were exhibiting good folding endurance (Table 1). The thickness of the patch ranged from 0.45 ± 0.45 to 0.78 ± 0.65 mm and mass ranged from 44 ± 1 to 55 ± 1 mg. The bioadhesive patches had a surface pH of 3.3 ± 0.10 to 7.2 ± 0.15 and the drug content in buccal patches was found to range from $97.52 \pm 0.98\%$ to $100.85 \pm 0.85\%$.

The surface pH of all the patches (C1–C7) was near 6 (Aframian et al., 2006) and hence, these patches should not cause any irritation in the buccal cavity.

Table 2 Thermal changes in interpolymer complexes prepared using different ratios of CH:PE.

Sample	Endotherms				Exotherm	
	First endotherm		Second endotherm			
	T_m (°C)	ΔH (J g^{-1})	T_m (°C)	ΔH (J g^{-1})	T_m (°C)	ΔH (J g^{-1})
CH alone	70.42	−246.00	*	*	311.32	116.46
PE alone	95.52	−21.61	*	*	242.11	43.31
CH:PE (20:80)	81.53	−142.13	278.21	−5.60	235.59	68.52
CH:PE (50:50)	81.04	−175.50	212.34	−132.62	*	*
CH:PE (80:20)	82.21	−189.13	209.83	−111.04	240.59	29.88

3.3. Swelling indices of bioadhesive patches

Patch A containing CH alone showed maximum swelling. However, patch B containing PE alone eroded after 30 min (Fig. 1). It has been demonstrated that when a patch comprising PE is placed in an aqueous medium, liquid penetrates into the patch and a gel is formed due to uncoiling of the structure of PE molecules and the formation of hydrogen bonds with water molecule. As a result, the diameter of the patch increases progressively and a distinct gel–sol boundary develops. Being hydrophilic in nature PE after hydration and swelling, goes into solution and erodes (Talukdar and Kinget, 1995). Due to the hydrophilic nature of PE batch B containing PE alone eroded within 30 min in phosphate buffer pH 6.6. The swelling index of the CH–PE complexed films was found to decrease as the concentration of PE decreases in patches C1–C4. However, an increase in the swelling index was observed in CH–PE patches C5–C7 when the CH concentration in the patch increases (Fig. 2). Ionically crosslinked films containing CH in cationic (protonated) forms have been reported to swell more. The swelling is favored by the protonation and repulsion of free ammonium groups of CH (Berger et al., 2004) thus leading to greater swelling of these patches.

3.4. Bioadhesive strength studies

The patches formulated using CH alone (patch A) were showing very less bioadhesive strength. The bioadhesive patch B

(PE alone) showed maximum bioadhesive strength (Fig. 2). The force required to detach the patches from the mucosal membrane decreased with a decrease in the PE concentration (C1–C4). PE being hydrophilic in nature forms a gel like structure at the buccal mucosa resulting in larger surface/contact area. The increase in the water uptake by capillary forces led to an increased bioadhesion (Park and Munday, 2004).

However, an increase in the bioadhesive strength was observed in patches C5–C7. This observation can be explained by the presence of CH in the cationic (protonated) form in the polymer complex. This led to electrostatic interactions between CH and negatively charged mucus (Lehr et al., 1992) thus resulting in increased bioadhesive strength as compared to CH alone. The formulated patches were showing statistically significant differences ($p < 0.05$) in their bioadhesive strength.

3.5. In vitro drug release studies

The patches A and B comprising CH and PE alone were either showing too high swelling index or they were eroding, therefore; in vitro studies were not carried out on these patches. A decrease in PE content in all the investigational patches (C1–C4) resulted in slower drug release (Fig. 2). This can be attributed to the swelling and erosion behavior of PE (Sujja-arrevath et al., 1998). The swelling and erosion of patches due to PE resulted in moving boundary condition thus modifying the effective diffusivity of the drug. The continued swelling of the
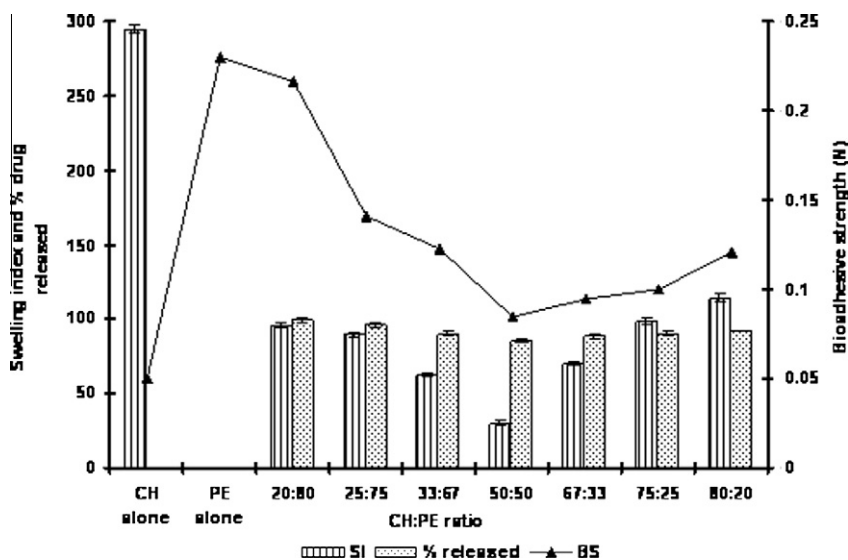

Figure 2 Swelling indices (SI), bioadhesive strength (BS) and % carvedilol released from formulated bioadhesive patches. Data are represented as mean ± SD.
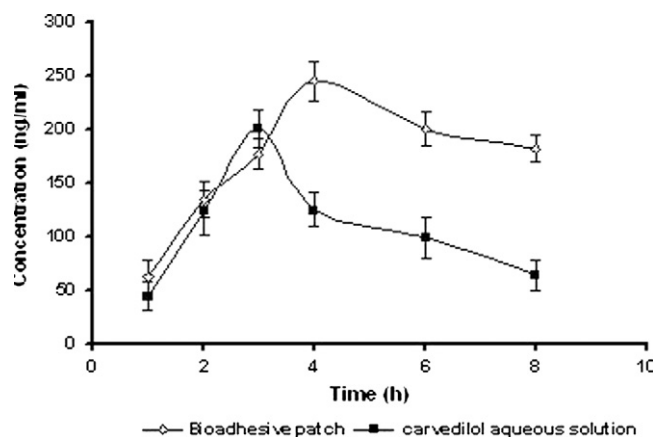
Figure 3 Plasma concentration profile of carvedilol bioadhesive patches and carvedilol aqueous solution ($n = 6$).

polymer matrix causes the drug to diffuse from the formulation at faster rate (Agarwal and Mishra, 1999).

Further, an increase in CH concentration (patches C5–C7) also showed an increase in drug release. This observation can be explained due to the increased swelling of CH in these patches leading to drug release in shorter period of time. Based on these studies patch C1 was selected for further studies.

Patch C1 showed a residence time of 7.5 h and *in situ* drug release studies showed that about 51.07% drug permeated through porcine buccal mucosa.

3.6. In vivo evaluation of bioadhesive buccal patch of carvedilol

The mean plasma concentration of carvedilol at different time intervals following the application of buccal patch and after oral administration of aqueous solution of carvedilol in rabbits is depicted in Fig. 3. The plasma concentration of carvedilol gradually increased and attained a maximum after which average steady-state level of drug declined upto 8 h ($n = 6$). The C_{max} obtained after application of buccal patch was 245 ng/ml and T_{max} 4 h. The AUC total obtained after application of buccal patch was 32.325 ng h/ml as compared to 15.05 ng h/ml obtained after the administration of carvedilol aqueous solution. The buccal formulation (C1) selected for *in vivo* study enhanced the bioavailability of carvedilol by 2.14 times with reference to an oral solution of carvedilol.

4. Conclusion

In the present investigation CH–PE interpolymer complexes were prepared and characterized using FTIR and DSC studies. Using these interpolymer complexes bioadhesive patches of carvedilol hydrochloride were formulated. The bioadhesive patches were displaying sufficient bioadhesive strength and *in vitro* drug release. The optimized patch C1 with interpolymer complex of CH–PE in ratio of 20:80 showed an increased bioavailability of about 2.14 times when compared to oral route. On the basis of the above results it can be concluded that CH–PE interpolymer complexes can be used to formulate bioadhesive buccal patches of carvedilol hydrochloride.

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