ORIGINAL ARTICLE

Effect of novel mucoadhesive buccal patches of carvedilol on isoprenaline-induced tachycardia

Navneet Verma, Pronobesh Chattopadhyay[1]

Department of Pharmacy, IFTM University, Moradabad, Uttar Pradesh, [1]Defence Research Laboratory, DRDO, Tezpur, Assam, India

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ABSTRACT

The main aim of the study was designed to develop bioadhesive buccal patches of carvedilol (CR) and evaluate for isoprenaline-induced tachycardia. Buccal patches of carvedilol were prepared by using chitosan (CH), sodium salt of carboxy methyl cellulose (NaCMC), and polyvinyl alcohol (PVA) as mucoadhesive polymers. The solvent evaporation method was used for the preparation of buccal patches. The patches were evaluated for their physical characteristics like patch thickness, weight variation, content uniformity, folding endurance, surface pH, residence time, *in vitro* drug release, and *in vivo* pharmacodynamic study. The swelling index of the patches was found to be proportional to the polymer concentration, whereas surface pH of all the formulated bioadhesive patches was found to lie between neutral ranges. *In-vitro* release study shows that 94.75% drug was release in 8 hours from the patch, which containing 2% w/v chitosan. The folding endurance result shows good elasticity in all the patches. Application of buccal patches on buccal mucosa of rabbit shows a significant result in % inhibition of isoprenaline-induced tachycardia. Prepared buccal patches of chitosan, NaCMC, and PVA containing Carvedilol meet the ideal requirement for the delivery of cardiovascular drugs and inhibit the isoprenaline tachycardia.

Key words: Buccal, carvedilol, folding endurance, tachycardia

INTRODUCTION

The buccal mucosa offers many advantages because of its smooth and relatively immobile surface and its suitability for the placement of controlled-release system, which is well-accepted by patients. The buccal mucosa is a useful route for the treatment of either local or systemic therapies overcoming the drawbacks of conventional administration routes.[1-3] These routes can bypass the first-pass effect and exposure of the drugs to the gastrointestinal fluids.[4-6] Bioadhesive polymer can significantly improve the performance of many drugs, as they are having prolonged contact time with these tissues.[7-9] These patient compliance controlled drug delivery products have improved drug bioavailability at suitable cost.[10,11]

The oral mucosa has a rich blood supply. Drugs are absorbed from the oral cavity through the oral mucosa, and transported through the deep lingual or facial vein, internal jugular vein, and braciocephalic vein into the systemic circulation.[12,13]

Carvedilol is a non-selective beta blocker used in the treatment of mild to moderate congestive heart failure (CHF). It blocks β_1 and β_2 adrenergic receptors as well as the α_1 adrenergic receptors. Carvedilol is rapidly and extensively absorbed following oral administration. The absolute bioavailability of carvedilol is approximately 25%. Plasma levels peak approximately one hour after an oral dose.[14,15]

Chitosan is a natural polymer obtained by de-acetylation of chitin. Chitin is the second most abundant polysaccharides in nature after cellulose. It is a biologically safe, non-toxic, biocompatible, and biodegradable polysaccharide.[16] Being a bioadhesive polymer and having antibacterial activity, chitosan is a good candidate for site-specific drug delivery.[17]

Address for correspondence:
Dr. Navneet Verma,
Department of Pharmacy, IFTM University, Moradabad,
Uttar Pradesh, India.
E-mail: navneet28jan@yahoo.com

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Buccal device of carvedilol is also used in case of tachycardia produced by isoprenaline, and examine the usefulness of the device in suppressing isoprenaline-induced tachycardia in rabbits.[18]

MATERIALS AND METHODS

Phenobarbitone (Samarth life Sci. Pvt. Ltd., Mumbai), Carvedilol (Aurobindo Pharma Ltd. Medak), Isoprenaline (Samarth life Sci. Pvt. Ltd., Mumbai), Chitosan (Sigma Aldrich, Mumbai), polyvinyl alcohol (Qualigens fine chemicals, Mumbai), sodium carboxymethyl cellulose (Qualigens fine chemicals, Mumbai) were used. Other chemicals were of analytical grade.

Drug-polymer compatibility study

Drug-polymer interaction was observed by IR spectrophotometry and differential scanning microscopy (DSC). An FTIR study of pure carvedilol and physical mixture of carvedilol and polymers were recorded. For DSC study, thermogram was recorded from 38°C to 450°C at the heating rate 10°C/min under a constant flow of an inert nitrogen gas atmosphere with the flow rate of 20 ml/min.[19]

Preparation of mucoadhesive buccal patches of carvedilol

Patches of carvedilol containing different polymer proportions were prepared by the solvent casting method. For chitosan patches, calculated amount of chitosan was dissolved in 1.5% (v/v) acetic acid, and for sodium carboxy methyl cellulose patches, calculated amount of sodium carboxy methyl was dissolved in purified water under constant stirring for 12 h. For polyvinyl alcohol patches, PVA was dissolved in hot water (80-100° C) under constant stirring for 08 h. In resultant viscous solution 5% glycerol as plasticizer and calculated amount of drug solution was added [Table 1]. The resultant viscous solution was left to stand until all air bubbles disappeared.[20] The solution was poured into a clean, dry, glass petri dish and left to dry at room temperature. The dried films were carefully removed from the petri dish, checked for any imperfection or bubbles, and cut into 10 mm (1.0 cm) diameter patches. The samples were packed in aluminum foil and stored in a glass container maintained at room temperature.[21]

Table 1: Compositions of different buccal patches containing carvedilol

Patch code	Chitosan (%)	NaCMC (%)	PVA (%)	Glycerol (%)
CC-1	1.0	-	-	5.0
CC-2	2.0	-	-	5.0
CC-3	3.0	-	-	5.0
SC-1	-	1.0	-	5.0
SC-2	-	2.0	-	5.0
SC-3	-	3.0	-	5.0
PC-1	-	-	8.0	5.0
PC-2	-	-	10.0	5.0
PC-3	-	-	12.0	5.0

Each formulation contained 2% w/v carvedilol

Content uniformity

Drug content uniformity was determined by dissolving the CR patch by homogenization in 100 ml of phosphate buffer (pH 6.8) for 8 h under occasional shaking.[22] The drug content was then determined after proper dilution at 285 nm using a UV-spectrophotometer (Shimadzu, Japan).

Patch thickness and weight variation

The thickness of the patch was measured using screw gauge with a least count of 0.01 mm at different spots of the patch. Weight variation was tested in 10 different randomly selected patches using electronics single pan balance.[23]

Surface pH

For determination of surface pH, three buccal patches of each formulation were allowed to swell for 2 h on the surface of agar plate (2% w/v). The surface pH was measured by using a pH paper placed on the surface of swollen patch.[24]

% Swelling

After determination the initial patch weight, the samples were allowed to swell on the surface of agar plate (2% w/v) kept in an incubator at 37 ± 1°C.[25] At regular interval of one-hour (for 6 h), the weight of the patch was determined, and radial swelling was calculated as

$$S_D\ (\%) = [(Wt - Wo)/Wo] \times 100$$

S_D (%) is the percent swelling obtained by the weight method, Wt is the weight of the swollen patch after time t, Wo is the initial patch weight at time zero.

Folding endurance

For the determination of folding endurance, the patches were folded repeatedly at the same place till it broken; the number of times the film could be folded at the same place without breaking gave the value of the folding endurance.[26]

Residence time

The *in vitro* residence time was determined by a locally modified USP disintegration apparatus using phosphate buffer of pH 6.8 maintained at 37 ± 0.5°C as medium. A segment of pig intestinal mucosa was glued to the surface of glass slab, vertically attached to the apparatus. The buccal patch was hydrated from one surface using 10 µl isotonic phosphate buffer, and then hydrated surface was brought into contact with the mucosal membrane.[27] The glass slab was allowed to move up and down, and then the time necessary for complete erosion or detachment of the patch from the mucosal surface was recorded.

In vitro release study

Drug release from the buccal patches was studied using USP type I dissolution test apparatus. Patches (10 mm diameter) were cut, and an impermeable backing membrane on one side of the patch. The assembly for release studies was prepared by placing the patch in contiguity with cellulose acetate dialysis membrane such that the drug release from the patch diffuses through dialysis membrane. This assembly was placed in dissolution apparatus containing 500 ml of phosphate buffer (pH 6.8) and rotating at 50 rpm at 37 ± 0.5^0 C. Eight samples (5 ml) were collected after every one hour and diluted with phosphate buffer (pH 6.8), 2 ml of which was analyzed spectrophotometrically (UV-1800, Shimadzu, Japan) at 285 nm.[27] The volume of sample collected was replaced by same volume of fresh phosphate buffer to maintain the sink condition.

Scanning electron microscopy

Optimized formulations (CC-2, SC-3, and PC-2) morphology was characterized by scanning electron microscopy. The images were captured on a black and white 35 mm film.[28]

Pharmacodynamic study

Healthy albino rabbits of either sex (2.5 to 5.0 kg) were selected for the study. Institution's animal ethics committee (IAEC) permission was obtained prior to start the study. Rabbits were anaesthetized by intraperitoneal administration of 30 mg/kg of phenobarbitone sodium in sterile normal saline, and the anesthesia was maintained by administering additional phenobarbitone sodium at a dose of 6 mg/kg per hour. Electrocardiograph electrodes (stainless steel needles) were set subcutaneously (one each in right and left forelegs, and right and left hind legs). Lead I or Lead II was used for recording ECG on a physiograph. The chart speed was kept at 5 mm/sec. Heart rate was determined by counting the "R-waves" of the ECG.[29]

Administration of carvedilol (i.v, oral and buccal patch)

Normal heart rate of the rabbit was recorded before administration of isoprenaline. Two i.v slow infusion of a standard dose of isoprenaline (0.25 µg/kg) were given at interval of 30 min, and heart rate was recorded. For i.v route[30] study, 100, 200 and 300 µg/kg body weight of carvedilol was administered for 30 sec through central or marginal ear vein. For oral dose, 1, 2 and 4 µg/kg body weight was administered as a bolus via an oral catheter, and similarly for the buccal route, the patch was stuck in the upper oral mucosa after wiping the site with tissue paper. In all the cases, the dose of isoprenaline (0.25 µg/kg) was administered at 5, 30, 60, 120, 180, and 240 min after every CR administration. Heart rate (beats/min) was recorded at 30 sec before and 20 min (4 × 30 sec) after isoprenaline administration. The difference in heart rate before and after each isoprenaline injection was determined.

Analysis of % inhibition of Isoprenaline-induced tachycardia

The percentage inhibition of isoprenaline-induced tachycardia was calculated by:

$$\% \text{ Inhibition} = (HR_0 - HR/HR_0) \times 100$$

Where HR_0 was number of heart beats increased by isoprenaline before CR administration, and HR was the number of heart beats increased by isoprenaline after CR administration.

RESULTS

Fourier transform infra red analysis

In FTIR, spectrum of pure carvedilol shows peaks at 3346.11 of N-H stretching. 3169.05 and 3061.08 peaks are due to C-H and O-H of aromatic ring. Peak of C-O appeared at 1022.80. In case of chitosan, the peaks at 3448.22 and 2876.80 were due to O-H and O-H stretching. The carbonyl C = O-NHR band observed at 1654.87. For PVA, the peaks at 3352 were due to O-H stretching, at 2796 due to $-CH_2$, while at 1415 and 1097 were due to C-O group of PVA. In the spectra of NaCMC, the peaks at 3470 were due to O-H stretching, at 2923 due to C-H stretching, at 1415 due to CH_2 stretching, at 1310 due to O-H bending vibration, and at 1080 due to CH_2-O- CH_2.

The IR spectra of carvedilol, chitosan, NaCMC, PVA, and drug loaded patches showed no evidence of interaction as all the major peaks were found intact or exhibited very minor shift in frequencies.

Differential scanning calorimetric

Thermogram of carvedilol showed a broad endothermic peak at 117^{o}C suggesting the melting of the drug, whereas the peak at 317^{o}C indicated the thermal degradation of drug. In the DSC thermogram of chitosan, the endothermic peak at 61^{o}C, for PVA endothermic peak at 215^{o}C and for NaCMC exothermic peak at 332^{o}C was observed.

Physiochemical properties

In case of physiochemical properties of CR, loaded patches were presented in Table 2. The content uniformity of chitosan patch was found to be 99.25 ± 2.01, 98.97 ± 1.52, 98.50 ± 1.20, while for NaCMC and PVA patches, it was 97.88 ± 0.05, 98.65 ± 1.40, 98.74 ± 1.57 and 97.12 ± 1.06, 99.00 ± 1.10, 98.20 ± 0.22, respectively. The patch thickness of the patches was measured with the help of screw gauge and was in the range 1.01-1.07 mm, 0.85-0.89 mm, and 1.07-1.09 mm for Chitosan, NaCMC, and PVA patches. The weight of the patches also varies, and it was 117 ± 0.22 - 123 ± 0.19, 107 ± 0.05 - 114 ± 0.04, and 134 ± 0.87 - 138 ± 0.28 for chitosan, NaCMC, and PVA patches. Surface pH of the all formulations was found to be between 5.5 and 7.0. The folding endurance of all the patches was found more than 300.

% Swelling

Swelling of CR-loaded patches is presented in Figure 1. The values are as CC-1 >CC-2 >CC-3, SC-1 >SC-2 >SC-3, PC-1 >PC-2 >PC-3, for chitosan, NaCMC, and PVA patches.

Residence time study

Residence properties of CR patches on mucosa are presented in Table 3 and Figure 2. The residence time for CC-1, CC-2, and CC-3 was 10.0 ± 2.44, 12.0 ± 0.63, and 12.5 ± 0.18. While for SC-1, SC-2, SC-3 and PC-1, PC-2, PC-3 was 6.5 ± 3.1, 8.0 ± 0.55, 11.0 ± 0.42 and 7.0 ± 2.3, 11.5 ± 0.11, 13.5 ± 0.58, respectively.

In vitro release study

The values of CR *in vitro* release study are shown in Figure 3. In 8 hrs, maximum 94.75 ± 0.70%, 85.50 ± 0.20%, and 89.65 ± 3.30% CR was released from CC-2, SC-3, and PC-2 patches, and the minimum amount was release from CC-3 (65.30 ± 3.80%), SC-1 (64.12 ± 2.50%), and PC-1 (51.28 ± 1.35%), respectively. Release kinetics of drug of different formulation follows zero order (R^2 = 0.950-0.997), first order (R^2 = 0.8505-0.9524), Higuchi model (R^2 = 0.8570-0.9469), and Koresmeyer-Peppas equation. Different formulations and their release kinetic models with regression co-efficient and n values are reported in Table 4.

Scanning electron microscopy study

The Scanning Electron Microscopy (SEM) study of optimized batch was found at different set. The SEM photographs of optimized patches (CC-2, SC-3, and PC-2) are shown in Figure 4.

Pharmacodynamic study

In-vivo pharmacodynamic study was conducted in rabbit by measuring the inhibition of isoprenaline-induced tachycardia. The normal heart rate of rabbit was 180 ± 20 beats per minutes. Injection of isoprenaline at a dose of 0.25 µg/kg increases the heart rate by 85 ± 20 beats per minutes above the normal heart rate. Administration of CR reduces the increased heart rate through competitive antagonism.

Table 2: Physiochemical properties of mucoadhesive buccal patches containing carvedilol

Patch code	Content uniformity (%)*	Patch thickness (mm)**	Weight variation (mg)**	Surface pH*	Folding endurance*
CC-1	99.25±2.01	1.02±0.01	117±0.22	5.5	>300
CC-2	98.97±1.52	1.01±0.01	119±0.15	5.5	>300
CC-3	98.50±1.20	1.07±0.02	123±0.19	5.5	>300
SC-1	97.88±0.05	0.89±0.011	107±0.05	5.5	>300
SC-2	98.65±1.40	0.87±0.045	111±0.44	5.5	>300
SC-3	98.74±1.57	0.85±0.01	114±0.04	5.5	>300
PC-1	97.12±1.06	1.09±0.013	134±0.87	7.0	>300
PC-2	99.00±1.10	1.07±0.027	136±0.021	7.0	>300
PC-3	98.20±0.22	1.09±0.019	138±0.28	7.0	>300

*All values represent mean±SD (*n*=3), **All values represent mean±SD (*n*=10), >more than

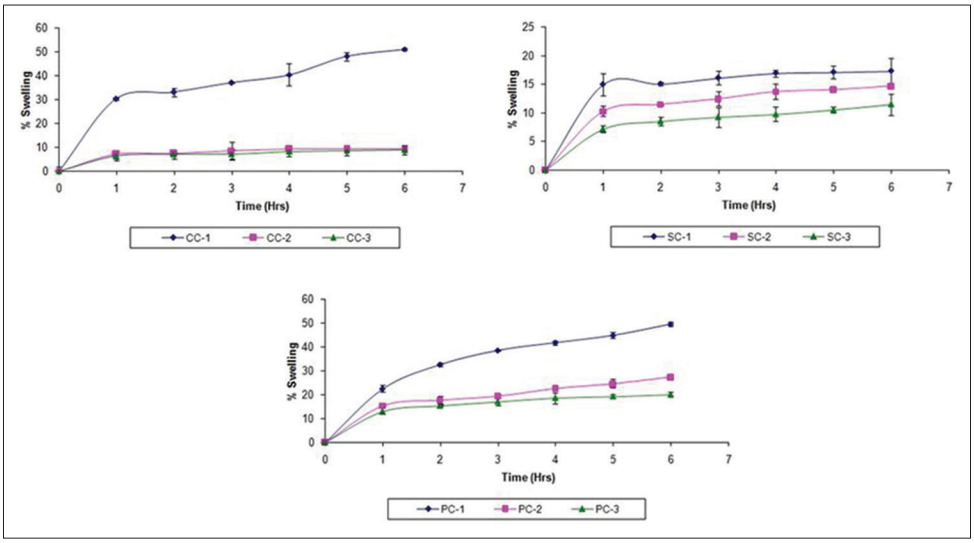

Figure 1: % Swelling of chitosan, NaCMC, and PVA patches containing carvedilol

Intravenous administration of CR

The effect of intravenous (i.v.) CR on the isoprenaline-induced tachycardia in rabbits and the pharmacodynamic parameters such as Emax, Tmax, and T50% were derived from the time versus percent inhibition in heart rate curves and are summarized in Table 5.

The results indicated the dose-dependent increase in the magnitude of % inhibition and duration of effect of CR after IV administration. CR at a dose of IV-1 (100 µg/kg) and IV-2 (200 µg/kg) produced a maximum of 52.75 ± 5.40 and 72.33 ± 1.20 percent inhibition of isoprenaline-induced tachycardia at 5 min, respectively, after IV injection, whereas CR at a dose of IV-3 (300 µg/kg) produced almost total inhibition of isoprenaline-induced tachycardia i.e. 89.80 ± 2.50 at 5 mins.

The inhibitory effect of IV CR gradually decreases, and at the end of 4 hrs, the effect observed was 6.55 ± 2.11% and 15.00 ± 1.30% for IV-2 and IV-3 of CR, respectively, whereas IV-1 showed negligible inhibition (1.32 ± 1.10%) in heart rate at the end of 4 hrs. E_{max} attained by IV-1 and IV-2 were significantly lower than that of IV-3 ($P < 0.05$). A significant decrease in $T_{50\%}$ values was observed for IV-3 when compared with IV-2 and IV-1 ($P < 0.05$), whereas IV-1 and IV-2 showed a difference in $T_{50\%}$ values, which was not significant ($P > 0.05$). Time to produce maximal percent inhibition in isoprenaline effect by IV-3 was identical with the IV-1 or IV-2.

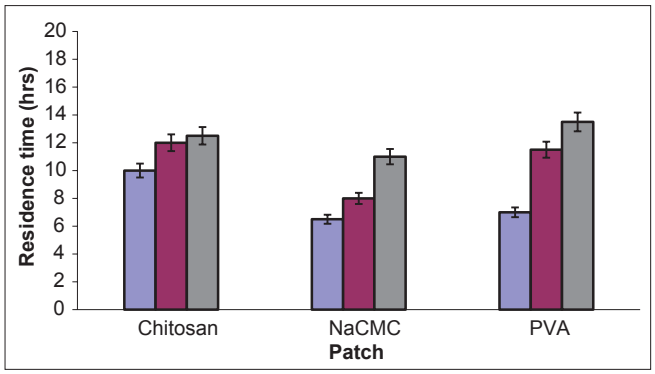

Figure 2: Residence time of mucoadhesive buccal patch containing carvedilol

Table 3: Residence time of mucoadhesive buccal patch containing carvedilol

Patch code	Residence time (hrs)
CC-1	10.0±2.44
CC-2	12.0±0.63
CC-3	12.5±0.18
SC-1	6.5±3.1
SC-2	8.0±0.55
SC-3	11.0±0.42
PC-1	7.0±2.3
PC-2	11.5±0.11
PC-3	13.5±0.58

Table 4: Calculated CR release kinetic parameters of all formulations containing carvedilol

Patch code	r^2 value				*N* value
	Zero order	First order	Higuchi model	Korsmeyer-peppas model	
CC-1	0.950	0.9524	0.9038	0.9733	0.3620
CC-2	0.995	0.9160	0.9280	0.9832	0.2960
CC-3	0.980	0.9519	0.9469	0.9938	0.3407
SC-1	0.987	0.8556	0.8814	0.940	0.3747
SC-2	0.986	0.8505	0.8570	0.9839	0.4716
SC-3	0.968	0.9496	0.9188	0.9905	0.3378
PC-1	0.997	0.8916	0.8948	0.9915	0.4404
PC-2	0.993	0.8836	0.8749	0.9932	0.419
PC-3	0.989	0.8641	0.8740	0.9984	0.5287

CR: Carvedilol

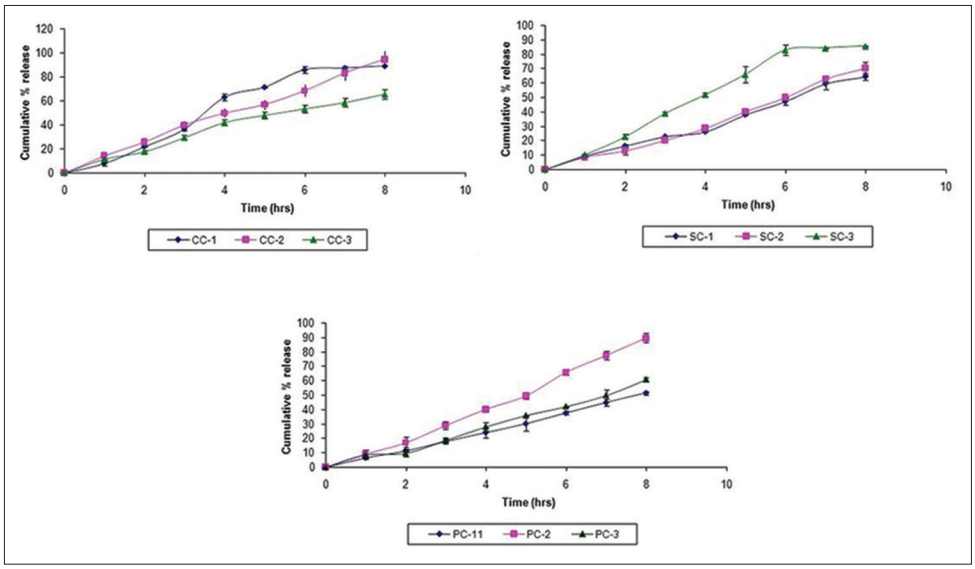

Figure 3: *In-vitro* cumulative % release of CR from various buccal patches in phosphate buffer pH 6.8 at 37 ± 0.5°C

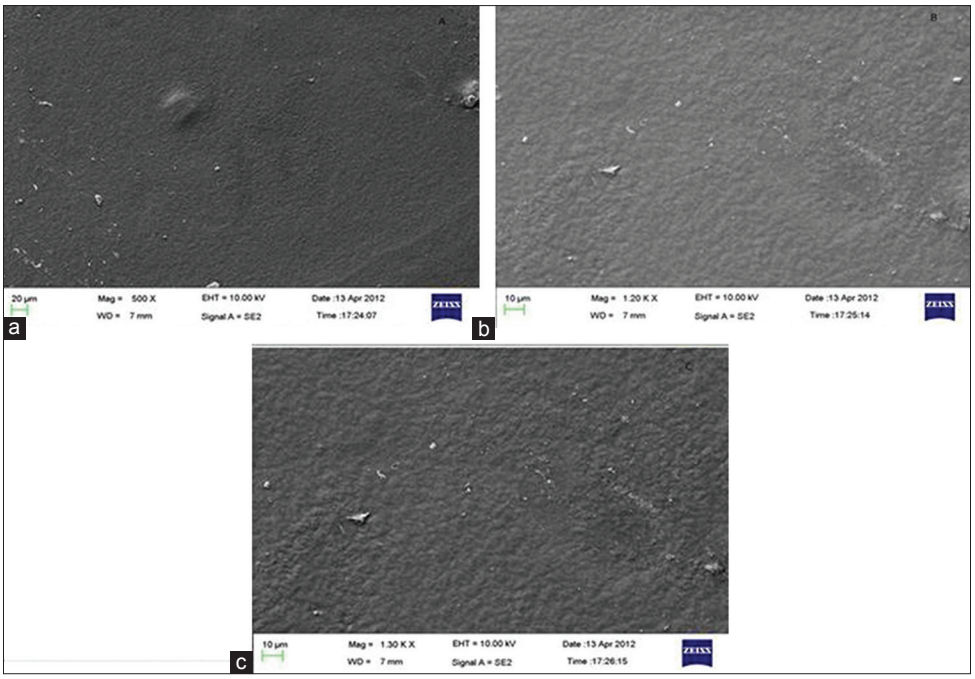

Figure 4: Scanning electron micrographs of optimized buccal patches (a) CC-2 (b) SC-3 (c) PC-2

Table 5: Percent inhibition in isoprenaline-induced heart rate after intravenous administration of CR

Route of administration	Batch code	Dose (μg/kg)	Percent inhibition in heart rate (mean±SD) (*n*=3)					
			Time (min)					
			5	30	60	120	180	240
i.v	IV-1	100	52.75±5.40	39.65±2.20	16.02±1.65	8.41±0.89	2.89±2.44	1.32±1.10
i.v	IV-2	200	72.33±1.20	58.70±4.40	33.88±1.02	17.38±2.10	9.85±2.48	6.55±2.11
i.v	IV-3	300	89.80±2.50	75.42±3.02	56.24±1.90	40.25±3.42	29.27±2.72	15.00±1.30
Placebo i.v.	IV	Normal Saline	−4.75	−5.25	−1.75	2.00	−2.75	−2.25

CR: Carvedilol, SD: Standard deviation

Oral administration of CR

The effect of oral (OS) CR on the isoprenaline-induced tachycardia in rabbits is shown in Table 6. Like IV, oral solution of CR also showed dose-dependent percent inhibition in isoprenaline-induced heart rate. CR oral solution at doses of 1 mg/kg (OS-1), 2 mg/kg (OS-2), and 4 mg/kg (OS-3) produced 69.95 ± 1.24, 85.10 ± 0.90, and 96.40 ± 2.20% inhibition, respectively, at 15 min. About 76% inhibition was observed with OS-3 dose at the end of 2 hrs, whereas about 68% and 28% inhibition was observed at the end of 2 hrs with OS-2 and OS-1, respectively. The inhibitory effect gradually decreased, and at the end of 8 hrs, the effect observed was 37.50 ± 0.95 and 29.72 ± 1.28 for OS-2 and OS-3 doses of CR, respectively, whereas with OS-1, the inhibitory effect (4.85 ± 1.85) was observed at the end of 6 hrs. The calculated pharmacodynamic parameters after oral administration of CR show that the T_{max} values for all oral doses of CR were found to be 15 min. T_{max} values for OS-1, OS-2, and OS-3 showed a difference that was not statistically significant ($P < 0.05$).

Buccal administration of CR

Table 7 presents the pharmacodynamic effect of buccal patches (CC-2, SC-3, and PC-2). The patches CC-2, SC-3, and PC-2 showed maximum inhibitory effect i.e. 50.52 ± 2.44, 27.02 ± 2.82, and 32.92 ± 2.80% within one hour and reached steady state inhibitory effect after 2 hrs. The steady state inhibitory effect was maintained around 35% (CC-2), 21% (SC-3), and 28% (PC-2) until the device was removed at the end of 6 hrs. After removal of the device, the effect started to decline and reached 3.70 ± 1.32%, 3.90 ± 1.20%, and 6.57 ± 1.42% for CC-2, SC-3, and for PC-3, 2 hrs after removal of device. $T_{50\%}$ inhibitory effect was not reached by the different patches. The relative % bioavailability of patches CC-2, SC-3, and PC-2 when compared to oral dose 2 mg/kg (OS-1) was found to be 160.72, 164.50, and 162.65%, respectively.

DISCUSSION

The FTIR spectra of carvedilol, chitosan, NaCMC, PVA, and drug-loaded patches showed no evidence of interaction as all the major peaks were found intact or exhibited very minor shift in frequencies. In the DSC study, the thermal peak of carvedilol shows that the drug was in pure form. The peak

Table 6: Percent inhibition in isoprenaline-induced heart rate after oral administration of CR

Route of administra-tion	Batch code	Dose (mg/kg)	Percent inhibition in heart rate (mean±SD) (*n*=3) Time (min)							
			15	30	60	120	180	240	360	480
Oral	OS-1	1.0	69.95±1.24	49.30±0.72	40.82±3.08	28.15±2.15	11.52±1.32	6.21±1.40	4.85±1.85	-
Oral	OS-2	2.0	85.10±0.90	79.31±1.40	77.87±1.88	68.05±1.28	62.72±2.08	50.82±1.20	39.45±2.57	37.50±0.95
Oral	OS-3	4.0	96.40±2.20	89.55±2.30	86.28±1.75	76.33±1.65	57.70±2.88	48.90±1.28	41.80±2.15	29.72±1.28
Placebo oral	OS	Water	−3.00	−3.00	3.00	−3.00	−4.00	−3.00	3.00	−3.00

CR: Carvedilol, SD: Standard deviation

Table 7: Percent inhibition in isoprenaline-induced heart rate after buccal patch administration of CR

Patch code	Percent inhibition in heart rate (mean±SD) (*n*=3) Time (hrs)							
	1	2	3	4	5	6	7	8
CC-2	50.52±2.44	37.20±0.82	34.10±1.90	32.57±2.30	29.73±2.32	27.11±0.21	6.72±1.52	3.70±1.32
SC-3	27.02±2.82	22.95±2.90	21.50±1.50	20.77±1.20	18.63±1.25	17.25±0.80	5.70±2.80	3.90±1.20
PC-2	32.92±2.80	29.90±0.30	28.70±1.22	27.85±2.85	25.98±2.26	24.70±0.80	8.80±2.30	6.57±1.42
Placebo	1.80±0.55	−5.40±1.33	−2.40±1.20	1.02±0.40	1.50±2.45	−2.70±3.20	2.85±2.80	1.2±1.30

CR: Carvedilol, SD: Standard deviation

61°C of chitosan is due to presence of moisture in the polymer. For PVA 215°C and for NaCMC 332°C was the melting point of polymer. The DSC thermogram of carvedilol, chitosan, NaCMC, PVA, and drug-loaded patches showed no evidence of interaction as all the major peaks were found intact or exhibited very minor shift in frequencies.

In evaluation of physiochemical properties, it was found that the content of drug present in the entire patch and thickness of all the patches was almost same. On the bases of weight variation results, it was observed that the weight of the patches increases as the concentration of the polymer increased. The pH of the patches was almost same as of salivary pH (5.5 - 7.0); they did not produce any local irritation on mucosal surface. All the patches show good flexibility because the folding endurance of all the patches was more than 300.

The values of % swelling decrease as the concentration of the polymer increase. The maximum value was 51.00 ± 0.47 for CC-1, and the least value was 8.7 ± 0.21 for CC-3 patch.

Residence time property was polymer-dependent because, as the concentration of the polymer increases, the residence time also increases.

By using the Korsmeyer-Peppas model equation, the *n* values were obtained between 0.2316 and 0.5000 for all formulations. These values are characteristic of Fickian diffusion. In this context, the results obtained from fitting the data in Koresmeyer-Peppas and zero order kinetics also supported the theory that the release of the drug from the patches was by a diffusion dominated.

The SEM photograph indicates the uniform dispersion of polymeric solution with drug molecules. We compared the i.v, oral, and buccal administration of drug in case of *in-vivo* bioavailability study; the buccal patches showed significantly greater inhibitory effect on isoprenaline-induced tachycardia.

CONCLUSION

Overall, from the present study, carried out on carvedilol buccal patches prepared from variable amount of chitosan, NaCMC, and PVA, we concluded that the buccal patches prepared using chitosan, NaCMC, and PVA were found to have good physical characteristics. In the present study, patches showed significantly greater inhibitory effect on isoprenaline-induced tachycardia.

Lastly, we concluded that, buccal patches of chitosan, NaCMC, and PVA containing Carvedilol meet the ideal requirement for the delivery of cardiovascular drugs and inhibits the isoprenaline tachycardia.

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