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Research Article

Formulation and characterization of carvedilol buccal mucoadhesive patches

Arpita Choudhary*, Gulab Tiwari, Manisha Pandey, Koshy M. Kymonil, Shubhini A.Saraf

Department of Pharmaceutics, Faculty of Pharmacy, Babu Banarasi Das National Institute of Technology & Management, Lucknow-227105, India

ABSTRACT

Bioadhesive formulations have a wide scope of application for both systemic and local effects of the drug. The oral transmucosal drug delivery bypasses liver and avoids pre-systemic elimination. Carvedilol (Dose-3.125-25 mg) is β-adrenergic antagonist. Its oral bioavailability is 25-35% because of first pass metabolism. FTIR method revealed no interaction between carvedilol and polymers. Carvedilol patches were prepared using HPMC K15 and Carbopol 940.The patches were evaluated for their thickness, folding endurance, weight and content uniformity, swelling behaviour, mucoadhesive strength and surface pH. *In vitro* release studies were conducted for carvedilol-loaded patches in phosphate buffer (pH, 6.8) solution. The patches exhibited drug release in the range of 77.05 to 97.20% in 8 hours. Data of *in vitro* release from patches were fitted into kinetic models (Higuchi and Korsmeyer-Peppas models) to explain release profiles. The optimized formulation (patch V) showed first order release followed by zero order.

Keywords: Carvedilol; buccal patches; in vitro release; evaluation.

INTRODUCTION

Among the various transmucosal route, buccal mucosa has excellent accessibility, an expanse of smooth muscles and relatively immobile mucosa, hence suitable for administration of retentive dosage form. The oral cavity has rich blood supply that drains directly into the jugular vein and bypassing the liver. (Anders R and Merkle HP 1989; and Balamurugan K et al., 2001) Direct access to the systemic circulation through internal jugular vein (buccal mucosa) bypasses drugs from hepatic first pass metabolism, leading to high bioavailability. These factors make the oral mucosa a very attractive and feasible site for systemic drug delivery. Bioadhesion is the phenomenon between two materials which are held together for extended period of time by interfacial force. It is generally referred as bioadhesion when interaction occurs between polymer and epithelial surface. An ideal buccal patch should be flexible, elastic, soft yet adequate strong to withstand breakage due to stress from mouth activities. Moreover, it must also posses good mucoadhesive strength so that it can be retained in the mouth for a desired duration. (Choy et al., 1999)

Carvedilol is a non-selective beta blocker under various trade names including Coreg (GSK), Dilatrend (Roche), Eucardic (Roche), and Carloc (Cipla) as a generic drug (as of September 5, 2007 in the U.S.), and as a controlled-release formulation, marketed in the US as Coreg CR (GSK). Carvedilol blocks the binding to those receptors, which both slows the heart rhythm and reduces the force of the heart's pumping. This lowers blood pressure and reduces heart failure. Norepinephrine also binds to the α_1-adrenergic receptors on blood vessels, causing them to constrict and raise blood pressure. Carvedilol blocks this binding to the α_1-adrenergic receptors too, which also lowers blood pressure. Relative to other beta blockers, carvedilol has minimal inverse agonist activity. (Khanna R et al., 1997 and Michael V 1998) This suggests that carvedilol has a reduced negative chronotropic and inotropic effect compared to other beta blockers, which may decrease its potential to worsen symptoms of heart failure. Carvedilol is a weak base and its p*Ka* value is approximately 7.8, and its oral bioavailability is 25-35%, which satisfied the criterion for the selection of the drug for the buccal patch. (Mollendorff E.V. et al., 1987) The log PC (partition coefficient) value for carvedilol is about 3.967. (Noha AN et al., 2003 and Pavankumar GV et al., 2005) It indicates that carvedilol has sufficient lipophilicity to pass through the buccal membranes. The dose of carvedilol is 25 mg twice a day, however, a lower effective dose is reported to be approximately 3.125 mg. (Pavankumar 2005 and Siegel IA et al., 1981) By observing the above points, it is inferred that carvedilol has a need to formulate into buccal patches and the drug is suitable for it.

The purpose of this study was to develop formulation and systematically evaluate in vitro performance of

* Corresponding Author
Email: coolarpitachoudhary@rediffmail.com
Contact: +91-9997108445
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buccoadhesive patches of carvedilol using HPMC K15, carbopol 940, as polymers in order to provide the patch with bioadhesive property and to modify the rate of drug release.

MATERIALS AND METHODS

Materials

Carvedilol was obtained as a gift sample (Dr. Reddy's Labs, Hyderabad, India), Carbopol 940 and hydroxypropyl- methylcellulose K15 (HPMC K15) were obtained from Cadila Healthcare Ltd., (Ahmedabad, India). Other chemicals used were of analytical grade and procured from S.D. Fine Chemicals (Mumbai, India).

Methods

Preparation of the patches

Buccoadhesive patches of carvedilol were prepared by solvent casting technique (Pavankumar 2005 and Siegel 1981) using film forming polymers mentioned in table 1. HPMC K15 polymer was weighed accurately and dissolved in 2 ml of ethanol. The beaker containing polymer and ethanol was kept aside for 5 min for swelling of the polymer. Further 3 ml of ethanol was added to the above polymer solution and the dispersion was stirred. Then one drop of (0.0294 g) glycerin was added to the polymer solution. Accurately weighed carvedilol (15 mg) was dissolved in 1 ml of ethanol in another beaker. The drug solution was added to the polymer solution and was mixed thoroughly with the help of a magnetic stirrer. The glass mould of size 5×3 cm^2 was placed over a flat surface. The whole solution was poured into the glass mould. Inverted funnel was placed over the mould to avoid sudden evaporation. The mould containing polymeric solution of drug was kept for 12 hours at room temperature for drying. After drying, the patches were observed and checked for possible imperfections upon their removal from the moulds. They were covered with wax paper and preserved in desiccator till the evaluation tests were performed. The patches were examined in order to select the film having the best characteristics. Similarly, various patches (II to VI) were prepared. For preparing patches II, IV, V and VI carbopol 940 was placed in 4 ml of water and stirred for 60 min and HPMC K15 was dissolved in 3 ml of water, the two polymeric solutions were mixed. For preparing patch III carbopol 940 was placed in 4 ml of ethanol and stirred for 60 min and HPMC K15 was dissolved in 3 ml of ethanol, the two polymeric solutions were mixed. The moulds containing polymeric solutions of drug were kept aside for 12 h at room temperature for drying of patches II, III, and VI, whereas for patches IV and V, the drying time was 72 hours. Formulated patches were subjected to the evaluation tests. Patches with any imperfections, entrapped air, differing in thickness, or weight (or) content uniformity were excluded from further studies.

Table 1: Composition of different buccal mucoadhesive formulations containing Carvedilol

Formulations	Patch Code					
	I	II	*III*	IV	V	VI
Carvedilol, mg	15	15	15	15	15	15
HPMC K15, mg	200	100	150	66	134	50
Carbopol – 940, mg	-	100	50	134	66	150
Glycerin (1 drop), g	0.0294	0.0294	0.0294	0.0294	0.0294	0.0294
Ethanol, ml	7	-	7	-	-	-
Tween 80, g	-	0.0315	0.0315	-	-	-
Water, ml	-	7	-	7	7	7

HPMC = Hydroxy propyl methyl cellulose

Evaluation of the patches

Thickness uniformity of the patches

Three patches of each formulation were taken and the patch thickness was measured using micrometer screw gauge at three different places and the mean value was calculated.

Folding endurance

Three patches of each formulation of size (2x2 cm) were cut by using sharp blade. Folding endurance was determined by repeatedly folding a small strip of patch at the same place till it broke. The number of times, the patch could be folded at the same place without breaking gave the value of folding endurance. The mean value was calculated. (Barsuhn CL et al., 1988)

Uniformity of weight of the patches

Three patches of each formulation were taken and weighed individually on a digital balance. The average weight was calculated.

Drug content uniformity of the patches

Three patches (2×2 cm) of each formulation were taken in separate 100 ml volumetric flasks, 100 ml of pH 6.8 phosphate buffer was added and continuously stirred for 24 hrs. The solutions were filtered, diluted suitably and analyzed at 241 nm in a UV spectrophotometer. The average of three patches were taken as final reading. (Borodkin S and Tucker FE 1974).

Percent swelling

After determination of the original patch weight and diameter, the samples were allowed to swell on the surface of agar plate kept in an incubator maintained at 37±0.2 ^{o}. Increase in the weight of the patch (n=3) was determined at preset time intervals (1-5h). The percent swelling of the patches was calculated using the formula % S = $(X_t - X_0/X_0)$ x 100, where X_t is the weight of swollen patch after time t, X_0 is the initial patch weight at zero time. (Coutel-E. A et al., 1992 and Choy FW et al., 1999)

Surface pH of patches

For determination of surface pH, three patches of each formulation were allowed to swell for two hrs on the surface of a agar plate. (Vamshi VY et al., 2007) The surface pH was measured by using a pH paper placed on the surface of the swollen patch. A mean of three reading was recorded.

Ex- vivo mucoadhesive strength

Bioadhesive strength of the patch was measured on a modified physical balance. The fresh sheep buccal mucosa was cut in to pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the open mouth of a glass vial, which was filled completely with phosphate buffer pH 6.8. The glass vial was placed and tightly fitted in the center of glass beaker. The phosphate buffer (pH 6.8, 37±1^{0}C) was filled in the glass beaker just touches the mucosal surface. The patch was stuck to the lower side of rubber stopper with cyanoacrylate adhesive. Two pans of the balance were balanced with 5 gm weight on the right hand side pan. A weight of 5 gm was removed from the right hand side pan, which lowered the pan along with the patch over the mucosa. The balance was kept in this position for 5 min. contact time. The water (equivalent to weight) was added slowly with infusion set (100 drops/min.) to the right-hand side pan until the patch detached from the mucosal surface. The weight in grams required to detach the patch from the mucosal surfaces gave the measure of mucoadhesive strength. (Edith M et al., 1999 and Patil J.S. and Rao K.P.2003)

In vitro release studies of Carvedilol patches in phosphate buffer (pH 6.8.)

The USP XXIII rotating paddle method was used to study the drug release from buccal patch.(Thimmasetty J. et al., 2007) The dissolution media consisted of 200 ml of phosphate buffer pH 6.8. The release was performed at 37±0.5 ^{o}C, with a rotation speed 50 rpm. The one side of buccal patch was attached to the glass disc with instant adhesive (cyanoacrylate adhesive). The disc was allocated in the bottom of the dissolution vessel. Samples (5ml) were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through 0.45 µm Whatman filter paper, and assayed UV- spectrophotometrically at 241 nm. (Gua JH and Cooklock KM 1995)

Mechanism of release

The mechanism of release was determined by fitting the release data to the various kinetic equations such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas and finding the R^2 values of the release profile corresponding to each model. (Khanna 1997 and Michael JR et al., 1996)

Stability study

Medicated patches were subjected to stability testing. Patches were placed in a glass beaker lined with aluminium foil and kept in a humidity chamber maintained at 40 ± 2^{o}C and 75 ± 5% relative humidity for 1 month.(Guo J.H., 1994 and Beckett A.H. and Triggs E.J. 1967) Changes in the appearance and drug content of the stored patches were investigated at the end of every week. The data presented were the mean of three determinations.

RESULTS AND DISCUSSION

Drug-polymer compatibility

IR spectra of carvedilol alone and its combination with polymers are shown in fig. 1. An IR spectrum of pure carvedilol showed the peaks 3345.89 cm^{-1} (N-H, str), 2995.87 cm^{-1} (C-H, str, Sp^2), 2923.56 cm^{-1} (C-H, str, Sp^3), and 1106 cm^{-1} (C-O, str). These peaks can be considered as characteristic peaks of carvedilol and were not affected and prominently observed in IR spectra of carvedilol along with polymers as shown in the fig.1, indicated no interaction between carvedilol and polymers.

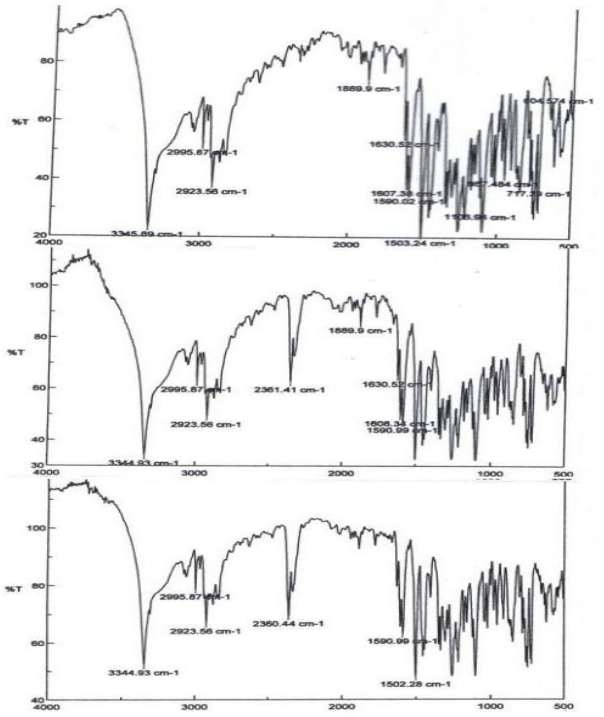

Figure 1: FTIR of a) carvedilol pure b) carvedilol with hydroxy propyl methylcellulose K15 c) carvedilol with carbopol 940 (from top to bottom)

Table 2: Characteristics of buccal mucoadhesive patches containing Carvedilol

Patch code	TN (mm) (mean*±Std)	WU (mg) (mean*±Std)	%swelling index (SI) (mean*±Std)	Surface pH (mean*±Std)	Mucoadhesive strength (MS) (mean*±Std)	CU (mean*±Std)	FE
I	0.205±0.001	22.53±1.17	47.00±1.52	6.75±0.130	6±0.47	88.20±0.061	>285
II	0.178±0.015	18.49±1.31	32.16±1.79	6.55±0.170	8±0.45	83.90±0.058	>285
III	0.188±0.002	16.38±1.35	35.13±1.49	6.86±0.170	5±0.47	86.75±0.062	>285
IV	0.251±0.002	29.34±1.25	49.34±1.05	6.85±0.125	9±0.30	93.25±0.047	>285
V	0.215±0.002	30.10±1.19	44.00±1.84	6.72±0.155	7±0.40	89.95±0.086	>285
VI	0.195±0.001	23.34±1.68	30.39±1.28	6.60±0.145	10±0.45	82.36±0.080	>285

PC = Patch code (I, II, III, IV, V and VI are formulations). TN= thickness, WU= weight uniformity, SI= percent swelling index, MS = mucoadhesive strength, CU = content uniformity, and FE = folding endurance respectively. *Each value is an average of three determinations.

Thickness uniformity

All the patches have uniform thickness throughout. Average thickness was found to be in the range of 0.178 to 0.251mm.

Folding endurance

Films did not show any cracks even after folding for more than 285 times. Hence it was taken as the end point. Folding endurance did not vary when the comparison was made between plain films and drug loaded films.

Weight uniformity

Drug loaded patches (1 x 1 cm^2) were tested for uniformity of weight. The patches were found to be uniform. The average weight of the patch was found to be in the range of 16.38 to 30.10 mg.

Content uniformity

The results of content uniformity indicated that the drug was uniformly dispersed. Recovery was possible to the tune of 82.36 to 93.25%.

Swelling studies

The swelling of the patches were observed via agar plate method and shown in table 2. These results were in agreement with the increase in area due to swelling. The swelling state of the polymer was reported to be crucial for its bioadhesive behavior. Swelling index was found to be proportional to HPMC K15 and inversely proportional to carbopol 940. Addition of certain amount of hydrophilic polymers increased surface wettability and consequently water penetration within the matrix. Patch I showed highest % swelling index (47%) due to higher amount of HPMC. Concentration of carbopol 940 had a negative effect on % swelling index, as the concentration of the carbopol is increased in the case of patch VI, the % swelling index get decreased (30%).

Surface pH

The surface pH of all formulations was within ± 0.5 units of the neutral pH and hence no mucosal irritation was expected and ultimately achieves patient compliance. All prepared formulation of carvedilol buccal patch posses surface pH within the range of salivary pH that is 6.5 to 6.8. The observed surface pH of the formulation I, II, III, IV,V and VI was 6.75±0.130, 6.55±0.17,6.86±0.17, 6.85±0.125, 6.72±0.157 and 6.60±0.145 respectively.

Ex-vivo mucoadhesive strength

Mucoadhesion may be defined as the adhesion between a polymer and mucus. In general, Mucoadhesion occurs in three major stages: wetting, interpenetration and mechanical interlocking between mucus and polymer. The strength of mucoadhesion is affected by various factors such as molecular weight of the polymer, contact time with mucus, swelling rate of the polymer and biological membrane used in the study. The ex-vivo mucoadhesive strength was found to be in the range of 5 to 10. Results indicated that the effect of carbopol 940 is more significant than HPMC K15 and the higher concentration of carbopol 940 had a positive effect on ex-vivo mucoadhesive strength in patch VI.

In vitro release

The release data of carvedilol from all the patches is shown in fig. 2. A perusal to fig. 2 indicated that the drug release was higher in HPMC (patch I) than HPMC-carbopol combinations (patches II to VI). At pH 6.8, carbopol is present in the ionized state and as a result the polymeric network gets loosened comparatively, attributing for the higher drug release. An increase in the polymer (Carbopol 940) content was associated with a corresponding decrease in the drug-release rate. (Michael V 1998) The drug release was observed to be sustaining with increasing the incorporation of higher amount of carbopol 940 in patch VI. This could be due to the extensive swelling of the polymers, which created a thick gel barrier for drug diffusion. The drug release was increased linearly with the increasing concentration of HPMC (Hydrophilic polymer), as it was observed in patch I which showed maximum release 97.2% in 8 hrs among other patches.

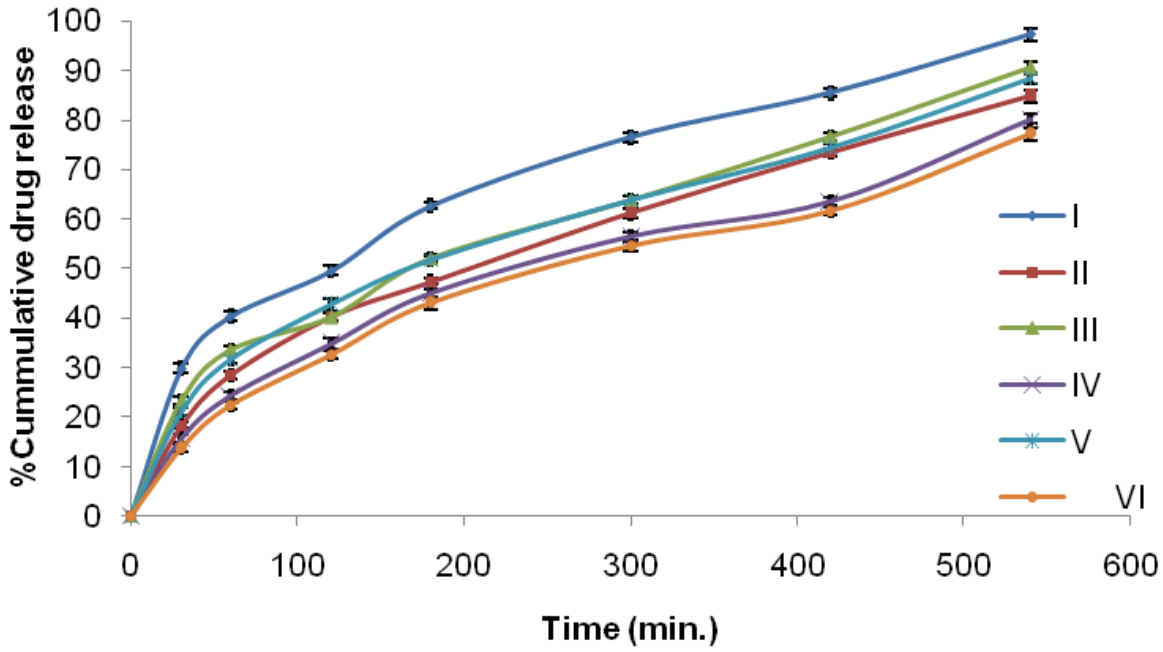

Figure 2: In vitro release of carvedilol from buccal mucoadhesive patches I to VI

Table 3: Released kinetics of Optimized formulation (Patch-V)

Zero order		First order		Higuchi model		Korsmeyer-peppas model	
R^2	K	R^2	K	R^2	K	R^2	n
0.909	0.141	0.455	0.002	0.997	3.684	0.723	0.067

Mechanism of release

Data of the *in vitro* release were fitted into different equations and kinetic models to explain the release kinetics of carvedilol from these buccal patches. The kinetic models used were zero-order equation, first order equation, Higuchi release, and Korsmeyer-Peppas models. The interpretation of data was based on the value of the resulting regression coefficients. The release kinetics of carvedilol followed zero order. To understand the mechanism of release of carvedilol from the patches the drug release data was fitted into Korsmeyer-peppas and Higuchi model and it showed the highest regression coefficient value ($R^{2=}$ 0.997) for Higuchi model, indicating diffusion to be the predominant mechanism of drug release.

Stability studies

Patches that were placed in humidity chamber for stability studies were withdrawn every week and analyzed for their drug content. Percentage drug present in the patches was determined spectrophotometrically. Drug content retained in the patches was to the extent of 61.15 to 80.13%. It was found that the drug loss was less though the patches were stored for one month. The patches were also observed for their appearance and texture. These properties did not change in patches II to VI during the period of study. The remaining patches I turned little rough probably due to decreased plasticizing property of the patches. Buccal mucoadhesive patches containing carvedilol using carbopol-940 and HPMC polymers showed satisfactory characteristics without being drastically influenced by ageing.

CONCLUSION

The HPMC K15 buccal adhesive patch showed satisfactory physicochemical properties. The ratio of hydrophilic polymers carbopol 940 to HPMC K15 had significantly influence on characteristics like swelling index, ex-vivo mucoadhesive strength and in-vitro drug release. Good correlation was observed between drug release and drug permeation study in-vitro. So, it can be concluded that such mucoadhesive patches of HPMC K15 and carbopol 940 could be a good carrier in buccal delivery of carvedilol.

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