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Research Article

Formulation and *in-vitro in-vivo* characterization of buccoadhesive bilayer tablets of Carvedilol

Alagusundaram M*, Raju Rayyi, Ramesh Reddy K[1], Angala Parameswari S[1], Umasankar K[1], Jayachandra Reddy P[1], Bothiraj M[2]

[1]Krishna Teja Pharmacy College, Tirupati, Chittoor – District, Andhra Pradesh, India
[2]Ratnam Institute of Pharmacy, Pidathapolur, Nellore, Andhra Pradesh, India

ABSTRACT

An effort has been made to formulate buccoadhesive bilayered tablets comprising of Carvedilol containing bioadhesive layer and drug free backing layer to release the Carvedilol for extended period of time with reduction in dosing frequency. The buccoadhesive bilayer tablets of Carvedilol were prepared by most convenient direct compression method using various proportions of Bioadhesive polymers like HPMC K 100, SCMC, PVP K 30 and CP 934 in combination with EC as an impermeable baking layer provide unidirectional drug release towards the buccal mucosa. The drug-polymer interactions study through FTIR shows there is no significant reaction between the drug and polymer. The powder substances of drug and other excipients used for the formulation of Carvedilol buccal tablets were evaluated for derived and flow properties include bulk density, tapped density, angle of repose, Carr's index and Hausner's ratio before carry out the formulations. The prepared buccosdhesive bilayered tablets were evaluated for physicochemical characteristics, surface pH, swelling index, *ex-vivo* buccoadhesive strength, *in-vitro, in-vivo* drug release and *ex-vivo* permeation studies. The noticeable differences in the results were shown to be based on characteristics and combination of bioadhesive polymers used. Stability was performed in natural human saliva and accelerated temperatures showed no significant changes in physical appearance, drug content and buccoadhesive strength. *Ex-vivo* muco irritation by histological examination indicates the formulation should not cause any irritation and inflammation over the administration site. Amongst all formulation, the formulation C5 contains HPMC 25 mg, CP 12.5 mg, and PVP 12.5 mg was the best one in all the aspects. Good correlation was observed between *in-vitro* and *in- vivo* drug release profile of best formulation with correlation coefficient of 0.996, which reveals the ability of the formulation to reproduce the *in-vitro* release pattern through the biological membrane. The formulation was stable and non-significant from *p-value* obtained by one way ANOVA followed by Tukeys test.

Keywords: Carvedilol; buccoadhesive; bilayered tablet; *ex-vivo* permeation; histological examination; ANOVA

INTRODUCTION

The buccal region of the oral cavity is an attractive target for administration of the drug of choice. Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Unlike oral drug delivery, which presents a hostile environment for drugs, especially proteins and polypeptides, due to acid hydrolysis and the hepatic first-pass effect, the mucosal lining of buccal tissues provides a much milder environment for drug absorption (Alagusundaram M et al., 2009). The buccal mucosa is a useful route for the treatment of either local or systemic therapies overcoming the drawbacks of conventional administration routes. The sites of drug administration in the oral cavity include the floor of the mouth (sublingual), the inside of the cheeks (buccal) and the gums (gingival). Buccal and sublingual sectors are the most appropriate for drug delivery and they may be used for the treatment of local or systemic diseases (Nazila Salamat-Miller et al., 2005). In addition, the buccal mucosa is a well vascularized tissue and is easily accessible for both application and removal of a delivery device (Oliver A. Scholz et al., 2008). It's having facility to include permeation enhancer/enzyme inhibitor or pH modifier in the formulation and versatility in designing as multidirectional or unidirectional release systems for local or systemic actions. 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. Following buccal administration, the drug gains direct entry into the systemic circulation thereby by-

* Corresponding Author
Email: alagusundaram77@gmail.com
Contact: +91-9989530761
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passing the first pass effect (Alagusundaram M et al., 2011).

Carvedilol is a nonselective β-adrenergic blocking agent with selective α_1- adrenergic blocking activity (Goodman and Gilmans., 2006). It is chemically 1-(9H-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy) ethyl] amino]-2- propanol (The Merck Index., 2006). Carvedilol is a third generation β receptor antagonist that has a unique pharmacological profile. It blocks β_1, β_2 and α_1 receptors. It also has antioxidant and antiproliferative effects. It has membrane-stabilizing activity but it lacks intrinsic sympathomimetic activity. Carvedilol produces vasodilatation. The antihypertensive activity of carvedilol is characterized by a decrease in peripheral vascular resistance, resulting from the vasodilator activity of the compound, with no reflex tachycardia, as a result of beta-adrenoceptor blockade. Carvedilol improves ventricular function and reduces mortality and morbidity in patients with mild-to-severe congestive heart failure. The bioavailability of Crvedilol following oral administration is 25 – 30 % and has a shorter plasma half life 2 to 8 h due to first pass metabolism. The peak plasma concentration attains in 1 -2 h following oral administration which causes less in duration of therapeutic activity. Thus, the development of buccoadhesive dosage forms with controlled release patterns could provide a single dosing and ensure improvement of patient compliance.

MATERIALS AND METHODS

Carvedilol was obtained from Symed labs ltd. (Hyderabad, India); HPMC K 100, SCMC, PVP K 30, CP 934and EC procured from Drugs India (Hyderabad, India); fresh sheep buccal mucosa, for determining buccoadhesive strength and *ex-vivo* permeation studies was procured form a local slaughter house in Tirupati, India. All other materials used and received were of analytical grade. The buccoadhesive bilayer tablets were prepared by direct compression method.

DRUG –POLYMER COMPATIBILITY STUDIES BY FTIR

Drug polymer compatibility studies were performed by FTIR (Fourier transform infrared spectroscopy) (Giunchedi P et al., 2002). Infrared (IR) spectra were obtained on a Perkin Elmer 2000 IR system (Perkin Elmer, Norwalk, CT) using the KBr disk method (2 mg sample in 200 mg KBr). The scanning range was 400 to 4000 cm^{-1} and the resolution was 1 cm^{-1}. FTIR absorption spectra of pure drug and combination of drug and polymers were shows no significant interaction between drug and polymers. The obtained FTIR spectra have shown in figures 1 and 2.

Preparation of buccoadhesive bilayered tablets of Carvedilol

Bilayer buccoadhesive tablets containing Carvedilol were prepared by direct compression method (Prasad BK et al., 2008, Parvez N et al., 2002, Vamshi Vishnu Yamsani et al., 2007, Kashappa Goud H et al., 2004). Various batches were prepared by changing the ratio of HPMC, SCMC and PVP K 30 to identify the most effective formulation. The drug and polymer mixture was prepared by homogeneously mixing the drug with HPMC, SCMC, PVP K-30, CP (mucoadhesive polymers), Mannitol and lactose (diluents) in a glass mortar for 15 minutes. Before direct compression, the powder were screened through a 60 µm sieve and thoroughly blended. The blend was lubricated with magnesium stearate for 3-5 min. The mixture (100 mg) was then compressed using an 8 mm diameter die in a 9-station rotary punching machine (Ahmadabad, India). The upper punch was raised and the backing layer of EC was placed on the above compact; the two layers were then compressed into a buccoadhesive bilayer tablet. Each tablet weighed 150 mg and the compositions of Carvedilol bilayer buccal tablets were given in Table 1.

Physicochemical evaluation of buccoadhesive bilayered tablets

All the prepared formulation were evaluated for thickness, weight variation, hardness, friability and drug content were determined in a procedure as stated for conventional oral tablets in the accredited pharmacopoeia (Indian pharmacopoeia., 2010).

Surface pH

The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects in buccal environment. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible, The tablet was allowed to swell by keeping it in contact with 5 ml of phosphate buffer containing 2% w/v agar medium (pH 6.8±0.01) for 2 h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablets and allowing it to equilibrate for 1 minute. A mean of three readings were recorded (Samani SM et al., 2005, Nafee NA et al., 2003).

Swelling index

The swelling index of tablets was determined by gravimetry. The swelling rate of the bioadhesive tablet was evaluated by using 1 % agar gel plate. The average weight of the tablet was calculated (W1).The tablets were placed on gel surface in a petri dish placed in an incubator at 37.1^{0}C. Tablets was removed at different time intervals (1, 2, 3, 4, 5 and 6 h), wiped with filter paper and reweighed (W2) (Chidambaram N and Srivatsava AK., 1995, Pramod Kumar T M et al., 2004). The swelling index was calculated by the formula.

$$\text{Swelling Index (S.I)} = [(W2-W1)/W1] \times 100$$

Ex-vivo buccoadhesive strength

A modified physical balance method was used for determining the *ex vivo* buccoadhesive strength (Sahini J et al., 2008, Alagusundaram M et al., 2011). Fresh sheep buccal mucosa was obtained from a local slaugh-

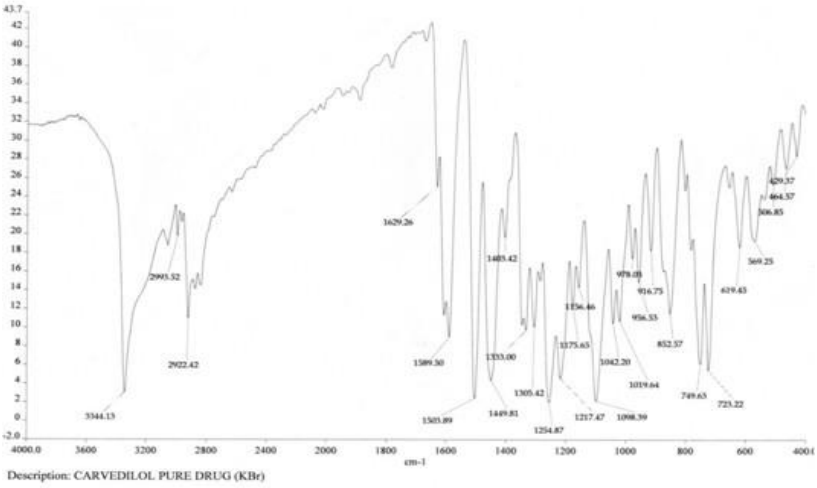

Figure 1: FTIR Spectra of Carvedilol

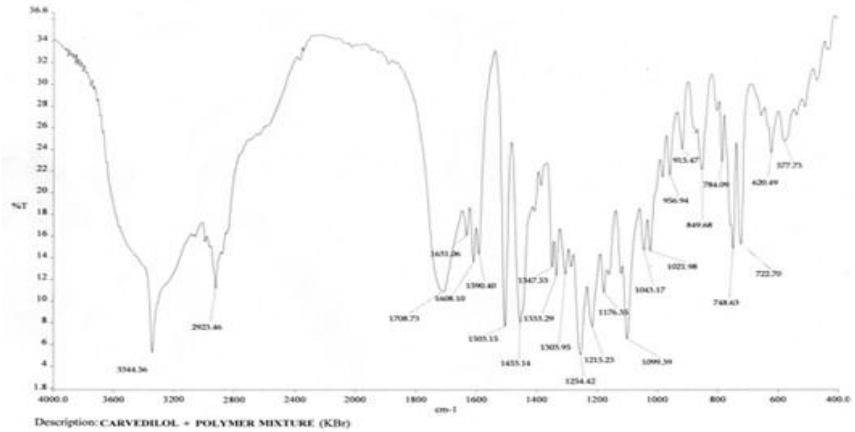

Figure 2: FTIR Spectra of Carvedilol and combination of polymers

Table 1: Composition of buccoadhesive bilayer tablets of Carvedilol

Formulation code		C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15
Ingredients (mg)	Carvedilol	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
	HPMC K 100	25	--	12.5	12.5	25	--	6.25	25	6.25	37.5	--	--	12.5	12.5	12.5
	SCMC	12.5	25	--	25	--	12.5	6.25	6.25	25	--	37.5	--	12.5	12.5	12.5
	PVP K 30	--	12.5	25	--	12.5	25	25	6.25	6.25	--	--	37.5	12.5	12.5	12.5
	CP 934	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
	Mg. stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
	Lactose	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	35	--
	Mannitol	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	--	35
	EC	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50

terhouse and used within 2 h of slaughter .The mucosal membrane was separated by removing underlying fat and loose tissues. The membrane was washed with distilled water and then with phosphate buffer pH 6.8. The two sides of the balance were made equal before the study, by keeping a 5 g saliva solution at 37^{o}C. The Sheep buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal muco---sa was tied to the glass vial, which was filled with phosphate buffer. The glass vial was tightly fitted into a glass beaker (filled with phosphate buffer pH 6.8 at 37^{o}c$\pm$1^{0}c) so that it just touched the mucosal surface. The buccal Tablet was stuck to the lower side of a rub---ber stopper with cyanocarylate adhesive and adds weight on the right-hand pan. A weight of 5 g was re---moved from the right hand pan. Which lowered the pan along with the Tablet over the mucosa.The balance was kept in this position for 5 minutes contact time. The water (equivalent to weight) was added slowly with an infusion set (100 drops/min). To the right-hand pan until the Tablet detached from the mucosal sur---face. This detachment force gave the mucoadhesive strength of the buccal tablet in grams.

Force of adhesion (N) = (Bioadhesive strength (g) ×9.8)/1000

Bond strength (N m–2) = Force of adhesion / surface area.

***In-vitro* drug release study**

The USP type II rotating paddle method was used to study the drug release from the bilayer tablet (Rafiee-

Table 2: Physicochemical evaluation of bilayer buccal tablets of Carvedilol

Formulation Code	Thickness (mm) ± SD	Weight varia---tion mg ± SD	Hardness (Kg/cm^2)	Friability (%)	Drug content in mg	Surface pH ± SD
C1	2.12 ±0.03	149±1.55	4.2±0.15	0.43±0.025	11.57±0.41	6.41±0.061
C2	2.19±0.02	147±0.94	4.1±0.25	0.54±0.03	11.85±0.19	6.73±0.03
C3	2.11±0.03	150±0.81	4.3±0.31	0.60±0.042	11.32±0.48	6.62±0.026
C4	2.15±0.05	148±0.72	3.9±0.21	0.48±0.036	12.26±0.41	6.79±0.040
C5	2.18±0.03	150±0.19	4.3±0.2	0.48±0.01	12.45±0.15	6.56±0.065
C6	2.19±0.04	147±0.84	4.2±0.26	0.51±0.02	11.19±0.01	6.77±0.066
C7	2.13±0.07	149±0.38	4.2±0.31	0.61±0.038	12.21±0.03	6.77±0.061
C8	2.16±0.02	148±0.52	4.5±0.25	0.54±0.025	12.15±0.65	6.56±0.066
C9	2.13±0.02	148±0.76	4.3±0.45	0.44±0.01	11.74±0.31	6.76±0.045
C10	2.15±0.02	150±0.41	4.2±0.41	0.44±0.026	11.43±0.15	6.72±0.04
C11	2.21±0.03	149±0.82	4.4±0.21	0.48±0.03	12.03±0.44	6.67±0.045
C12	2.13±0.03	147±0.48	4.1±0.15	0.69±0.025	12.35±0.61	6.64±0.077
C13	2.21±0.02	149±0.65	4.2±0.31	0.47±0.015	11.89±0.45	6.75±0.049
C14	2.15±0.01	150±0.23	4.0±0.41	0.44±0.036	12.13±0.35	6.60±0.056
C 15	2.16±0.02	149±0.57	3.7±0.15	0.52±0.041	11.65±0.28	6.76±0.080

Table 3: Swelling index data for all formulations

Formulation code	Swelling index ±S.D					
	Time in h					
	1	2	3	4	5	6
C1	26.09±0.76	38.61±1.08	55.58±0.80	64.96±0.70	71.27±0.76	74.84±0.27
C2	22.23±0.72	32.15±0.91	40.75±0.46	50.71±0.54	60.04±0.61	65.21±0.53
C3	19.19±0.64	24.48±0.63	37.81±0.67	45.84±0.68	51.8±0.66	55.77±0.51
C4	23.73±1.08	33.97±0.48	46.13±0.93	51.81±0.69	63.84±0.28	68.91±0.93
C5	27.39±1.03	41.62±0.90	57.67±0.53	66.68±0.75	71.25±0.61	78.6±1.04
C6	19.81±0.67	31.39±0.98	39.81±0.67	51.12±0.62	57.52±1.08	62.76±0.43
C7	16.01±0.84	25.64±0.75	32.76±0.54	41.10±0.88	46.46±0.87	51.76±0.64
C8	26.65±0.72	40.98±0.79	56.93±0.86	65.29±0.97	71.28±0.30	74.84±0.60
C9	23.35±1.12	31.43±0.64	41.91±0.93	51.66±0.57	61.44±0.63	65.69±0.64
C10	31.47±0.93	42.62±0.77	58.41±0.79	67.45±0.96	73.17±0.61	76.85±0.65
C11	24.72±0.38	33.98±0.81	44.19±0.91	51.81±0.67	61.52±1.06	67.85±0.51
C12	17.13±0.55	27.77±0.61	35.96±0.86	41.92±0.88	48.72±0.65	53.93±0.75
C13	21.48±0.94	32.18±0.82	42.18±0.37	50.91±0.82	57.80±0.99	64.26±0.78
C14	22.3±0.65	31.96±0.49	43.34±0.48	51.67±0.49	59.15±0.70	66.04±0.83
C15	20.47±0.76	31.11±0.75	42.01±0.86	48.12±0.62	57.2±0.40	64.08±0.63

Tehrani M et al., 2002, Agarwal V et al., 1999, Miyazaki S et al., 2000). The dissolution medium consisted of 900 ml of phosphate buffer pH 6.8. The release study was performed at 37 ± 0.5^0 C, with a rotation speed of 50 rpm. The backing layer of the buccal Tablet was at---tached to the glass slide with cyanoacrylate adhesive. The disk was placed at the bottom of the dissolution vessel. Aliquots (5ml each) were withdrawn at regular time intervals and replaced with fresh medium to maintain sink conditions. The samples were filtered, with appropriate dilutions with phosphate buffer pH 6.8 and were analyzed spectrophotometrically at 240 nm.

***Ex-vivo* permeation studies**

An *ex-vivo* diffusion study of Carvedilol tablets was carried out using a fresh sheep buccal mucosa using modified diffusion cell at 37^0 ± 1°C (Shanker G et al., 2009). Fresh sheep buccal mucosa was mounted be---tween the donor and receptor compartments. Sheep Buccal mucosa was tied to one end of an open-ended cylinder, which acts as a donor compartment. The tab---let should be placed in such a way that it should be stuck on the mucous membrane. The receptor com-partment was filled with isotonic phosphate buffer pH 6.8. The assembly was maintained at 37^{0}C and stirred magnetically. Samples were withdrawn at predeter---mined time intervals and analyzed using UV Spectro---photometer at 240 nm.

***Ex-vivo* muco irritation by histological examination**

Ex-vivo muco irritations of Carvedilol buccal tablets (C5) were performed by using a fresh sheep buccal mucosa was purchased from local slaughter house im-mediately after slaughter (sheep buccal mucosa was used for the histological examination within 2 h). Histo---logical examination was performed to evaluate the pathological changes in cell morphology and tissue

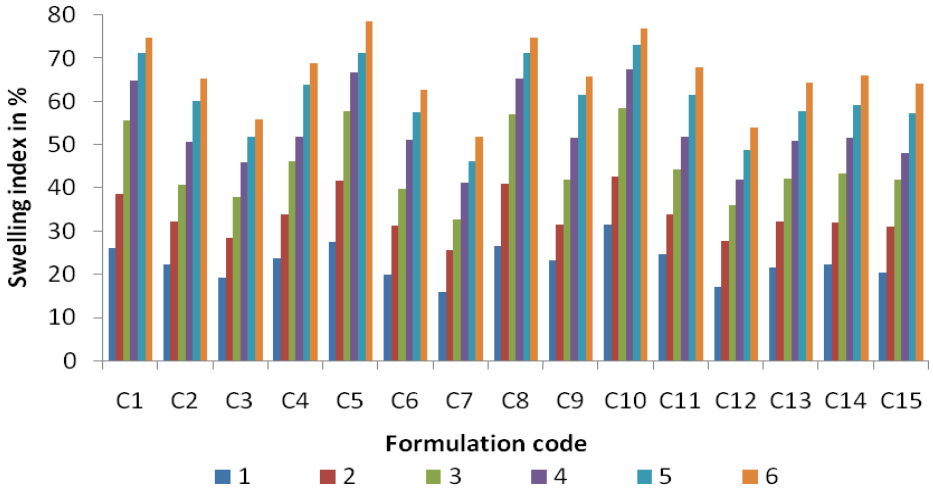

Figure 3: Swelling index of formulations C1-C15

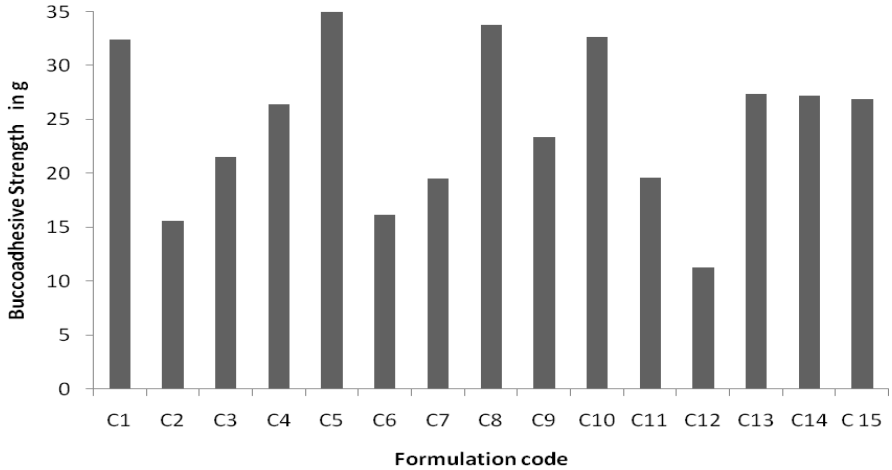

Figure 4: Buccoadhesive strength of formulations C1-C15

structure during administration of buccoadhesive tablets. The epithelial tissues of mucosa were fixed in 10 % neutral buffered formalin for 2 h, washed with distilled water upto 1 h and dehydrated with graded ethanol (60 %, 80 %, 90 %, 95 % and 100 %). Then it is treated with xylene for permeation and embedded with liquid paraffin using the standard procedures. After 8 h formalin fixed, paraffin embedded samples were cut in 4 µm thick sections on a microtome with a disposable blade and conveniently stained with eosin (Libero Italo Giannola et al., 2007).

***In-vivo* drug release study**

Six male New Zealand white Rabbits of 10 – 12 weeks old weighing 2.5 to 3 kg was selected. A healthy rabbit weight 2.5 to 3 kg was taken and checked for absence of any disease. The fore limbs and hind limbs were fixed, into the iron rod of mini operation table so rabbit was not dorsal position. The prepared buccoadhesive bilayer tablet was placed in a buccal membrane (Cheek pouch) with the help of forceps. Dextrose solution was given continuously throughout the period of study. Periodically 1 ml of blood sample was taken using a syringe which contained 1 ml of heparin solution to prevent blood clotting. These blood samples were centrifuged at 2500 rpm for about 30 mins. One ml of the supernatant was taken, and after suitable dilution, analyzed at 240 nm by spectrophotometrically. The value obtained is denotes amount of drug release from buccal mucosa of rabbits (Shin SC et al., 2000, Devarajan PV et al., 2001).

***In-vitro – in-vivo* correlation**

In-vitro and *in-vivo* correlation was carried out to compare the release of drug. It is governed by the factors related to both *in-vitro* and *in-vivo* characteristics of the drug. The cumulative percentage of drug release both in *in-vitro* and *in-vivo* was plotted (Alagusundaram M et al., 2011).

Stability study in human saliva

Samples of human saliva were collected from 10 humans (age 18-40 years) and filtered. The tablets from best batch were placed in separate Petri dishes containing 5 ml of human saliva and kept in a temperature controlled oven at 37±0.2°C for 6 hours. At regular time intervals the stability of the buccoadhesive tablets were evaluated for its appearance, such as color and shape, and concentration of Carvedilol (Patel VM et al., 2007).

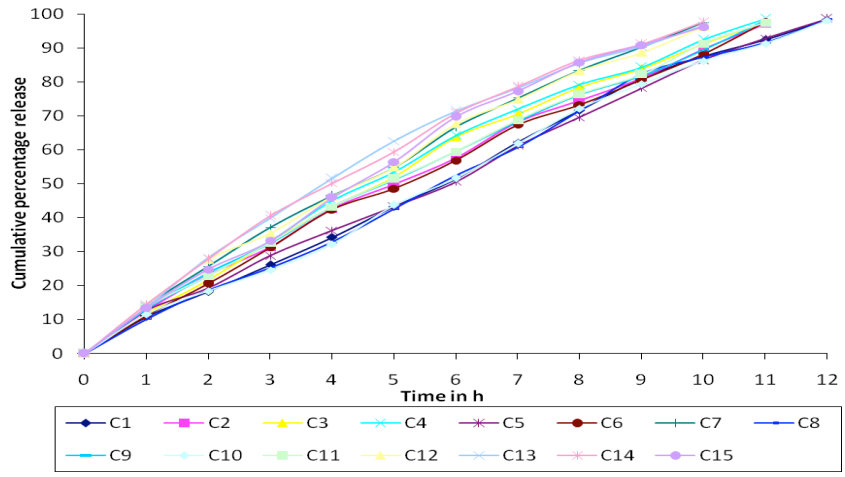

Figure 5: Cumulative % release of formulations C1-C15

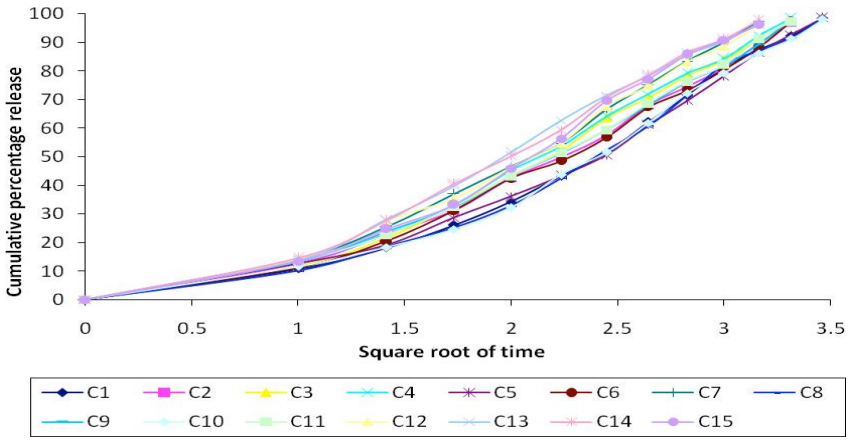

Figure 6: Higuchi's plot of formulations C1-C15

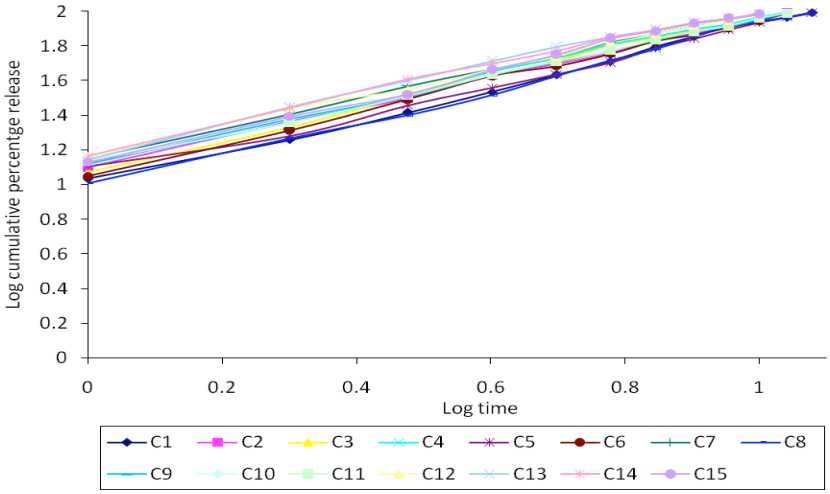

Figure 7: Peppa's plot of formulations C1-C15

Stability study

The formulation C5 was selected and the stability studies were carried out at accelerated condition of 40±2 ^{0}C, 75±5 % RH conditions, stored in desiccators, the tablets were packed in amber colour screw cap container and kept in above said condition for period of three months. The tablets were analyzed periodically for their physical appearance, buccoadhesive strength and *in-vitro* drug release. Results were analyzed by One-way ANOVA followed by Tukey's test. Differences were considered statistically significant at $p<0.05$ (Nakhat PD et al., 2007).

RESULTS AND DISCUSSIONS

The main objective of this research was to formulate buccoadhesive bilayer tablets to release the Carvedilol at site of administration in unidirectional pattern for extended period of time without wash of drug by saliva. The bilayer tablets were prepared by direct com-

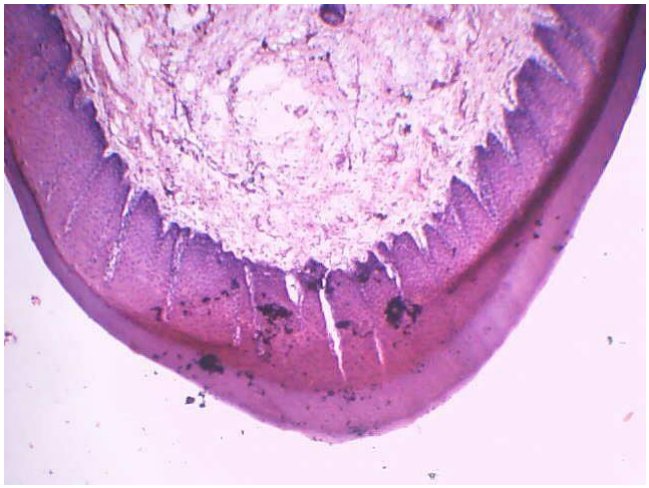

Figure 8: Controlled untreated sheep buccal mucosa

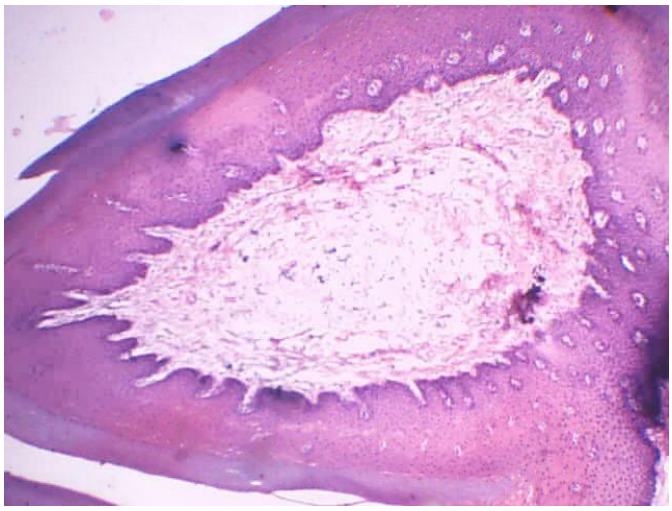

Figure 9: Carvedilol buccoadhesive tablet subjected to simple diffusion in sheep buccal mucosa

pression method using HPMC-K100, SCMC, PVP-K30 and CP 934. EC was chosen as a backing layer because of its low water permeability and flexibility in the buc---cal environment. The prepared buccoadhesive bilayer tablets were characterized for thickness, weight varia---tion, hardness, friability, drug content and surface pH. The results are shown in Table 2. All the formulation passes test for weight variation, showed acceptable drug content and friability.

Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa and influence the rate of hydration of the polymers, the surface pH of the tablets was determined. The observed surface pH of the formulations was found to be in the range of 6.56±0.065 to 6.79±0.040.The results are found that there is no significant difference of surface pH in all the formulations and the pH range lies within the range of salivary pH i.e. 6.5 to 6.8.

The swelling behavior of the polymer was reported to be crucial for its bioadhesive character. The adhesion occurs shortly after swelling but the bond formed is not very strong. The adhesion increases with the de---gree of hydration till the point of disentanglement at the polymer tissue surface, which leads to abrupt drop in adhesive strength due to over hydration. The formu---lation C5 shows maximum swelling index at the end of 6 h (78.6±1.04) due to the highest percentage of HPMC with Carbopol. The results were diagrammatically rep---resented in figure 3 and the values obtained shown in table3.

The observed buccoadhesive strength may be satisfac---tory in all formulations showing between the ranges 11.3 to 34.6 g. which ensures all the formulations was successfully maintaining in the buccal cavity. The re---sults were shown in the figure 4.

Distinguishable difference was observed in the release of Carvedilol in all formulations. The formulations C1, C2, C3, C4, C5 and C6 has shown release 98.3 %, 97.1 %, 97.4 %, 98.6 %, 98.6 % and 97.6 % respectively The *in-vitro* drug release and higuchi's plot has shown that the drug release followed by zero order kinetics, which was envinced from the regression value (R). The diffu---sion exponent (n) obtained by peppas plot showing 0.93067, 0.85066, 0.89323, 0.85197, 0.91961, 0.89929 respectively, which confirms that the diffusion mecha---nism involved in the drug release was Non fickian re---lease in case of formulations C2, and C4 and Super case II transport type in of case of formulations C1, C3, C5

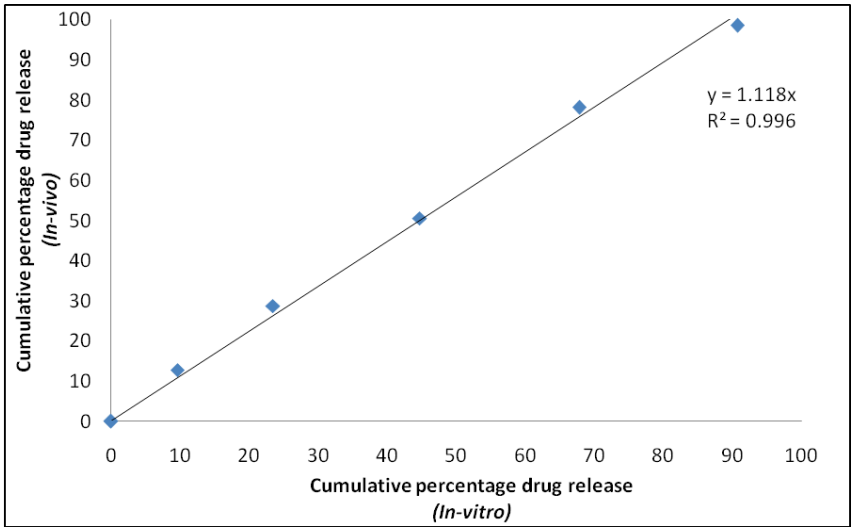

Figure 10: In vitro and in vivo correlation plot of optimized formulation

Table 4: Diffusion characteristics of Carvedilol buccal tablet formulations

Formulation code	Correlation coefficient values (r^2)		Diffusion exponent value (n) in Peppa's model
	Zero order	Higuchi's model	
C1	0.996	0.929	0.930671
C2	0.994	0.952	0.85066
C3	0.989	0.954	0.89323
C4	0.988	0.958	0.851974
C5	0.997	0.935	0.859561
C6	0.995	0.947	0.899291
C7	0.992	0.956	0.8421
C8	0.995	0.926	0.946998
C9	0.993	0.956	0.835221
C10	0.995	0.927	0.913316
C11	0.993	0.999	0.83572
C12	0.989	0.997	0.829072
C13	0.974	0.993	0.838346
C14	0.981	0.995	0.82543
C15	0.987	0.993	0.881046

and C6. The formulations C7, C8, C9, C10 and C11 has shown release 97.4% , 98.4% ,98.2 %, 98.1 %, and 97.4 % respectively The *in-vitro* drug release and higuchi's plot has shown that the drug release followed by zero order kinetics, which was envinced from the regression value (R). Peppa's plot was drawn which has shown slope value of 0.8421, 0.94699, 0.83522, 0.85655 and 0.83572 respectively, which confirms that the diffusion mechanism involved in the drug release was Non ficki-an release in case of formulations C7, C9, C10, C11and Super case II transport type in of case of formulations C8. Formulations C12, C13, C14 and C15 has shown release 96.2% , 96.6% ,97.8% and 96.2% respectively The *in-vitro* drug release and higuchi's plot has shown that the drug release followed by zero order kinetics, which was envinced from the regression value (R). Peppa's plot was drawn which has shown slope value of 0.82907, 0.83835, 0.82543, 0.88105 respectively, which confirms that the diffusion mechanism involved in the drug release was Non fickian release in case of formulations C12, C13, C14 and C15.

Data of *in-vitro* release were fit into different equations and kinetic models to explain the release kinetics of Carvedilol from the buccal tablet. The kinetic models used were a zero-order equation, higuchi's model and peppa's models. The obtained results in these formula---tions were plotted in various model treatment are as follows. I.e., zero order plot (Figure 5), Cumulative per---centage release of drug Vs Square root of time (Higu---chi's) (Figure 6) and Log cumulative percentage release Vs Log time (Peppas) (Figure 7). To know the mecha---nism of drug release of Carvedilol from the buccal tab---let the drug release data was fit into higuchi's models. To find out the mechanism of drug release from hy---drophilic matrices, the *in-vitro* dissolution data of each formulation with different kinetic drug release equa---tions. Namely Zero order: $Q=K_0t$; Higuchi's square rate at time: $Q=K_Ht^{1/2}$ and Peppas: $F=K_mt^n$, where Q is amount of drug release at time t, F is Fraction of drug release at time t, K_0 is zero order kinetic drug release constant, K_H is Higuchi's square root of time kinetic drug release constant, K_m is constant incorporating geomet---

ric and structural characteristic of the films and n is the diffusion exponent indicative of the release mecha---nism. The correlation coefficient values (r^2) indicate the kinetic of drug release was zero order. The mechanism of drug release was by peppas model indicates the su---per case II transport evidenced with diffusion exponent values (n).

The oral mucosa represents a barrier to drug permea---tion and it is intermediate between skin epidermis and the gut in its permeability characteristics. The effec---tiveness of the buccal barrier and whether buccal ab---sorption could provide means for Carvedilol admin---istration can be determined by *Ex-vivo* permeation studies. Permeation studies were carried out on formu---lation C5. The cumulative amount of drug permeated was 93.81 % maximum in 12 h.

Histological examination was performed to evaluate the pathological changes in cell morphology and tissue organization during administration of buccoadhesive tablets. The administration site of buccal tablet over the buccal mucosa should not cause any irritation, u|---ceration, inflammation and redness, and it resembles to controlled buccal mucosa.

In-vivo studies of buccal tablets of Carvedilol in rabbits did not show any inflammation or any other sensitiza---tion reactions at the buccal mucosa. *In-vitro* and *in-vivo* correlation were performed for the therapeutic effica---cy of carvedilol buccal tablets and the factors related to both *in-vitro* and *in-vivo* characteristics of the drug. A graph was plotted by taking cumulative % *in-vitro* re---lease on x-axis and cumulative % *in-vivo* drug release on y-axis for the same period of time and the release rate followed zero order with correlation coefficient value to be 0.996 shown in figure.

The stability studies of formulation C5 were carried out at Human saliva and accelerated condition of 40±2 ^{0}C, 75±5 % RH conditions, periodically checked for appear---ance, buccoadhesive strength and *in-vitro* drug release. A result was analyzed by One-way ANOVA followed by Tukey's test and indicates the formulation was stable and the p value as non-significant.

CONCLUSION

The Carvedilol buccoadhesive bilayer tablets were pre---pared by direct compression method using different polymers such as hydroxy propyl methyl cellulose 100K cps (HPMC), sodium carboxy methyl cellulose (SCMC), poly vinyl pyrrolidone K 30 (PVP) and carbopol 934 (CP) along with ethyl cellulose (EC) as an impermeable back---ing layer. Drug polymer compatibility studies by FTIR indicates there is no possible interaction between the drug and polymer and prepared tablets were charac---terized on their physico-chemical characteristics like surface pH, swelling percentage, thickness, weight var---iation, hardness, friability and drug content are lies within the limit of pharmacopoeia in all formulations. The *ex-vivo* buccoadhesive strength, *in-vitro* drug re---lease, *ex-vivo* permeation and *in-vivo* drug release in rabbit were produce reproducible results. *Ex-vivo* muco irritation by histological examination indicates the for---mulation should not cause any irritation and inflamma---tion over the administration site. Amongst all formula---tion, the formulation C5 contains HPMC 25 mg, CP 12.5mg, and PVP 12.5 mg was the best one in all the aspects. Good correlation was observed between *in-vitro* and *in- vivo* drug release profile of best formula---tion with correlation coefficient of 0.996, which reveals the ability of the formulation to reproduce the *in-vitro* release pattern through the biological membrane. The formulation was stable and non-significant from p val---ue obtained by one way ANOVA. Carvedilol buccoad---hesive bilayer tablets could be promising one as they, increase bioavailability, minimize the dose, reduces the side effects and improves patient compliance hence, Carvedilol might be a right and suitable candidate for oral controlled drug delivery via buccoadhesive bilayer tablets for the therapeutic use.

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