IJPSR (2014), Volume 5, Issue 11 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 13 February 2014; received in revised form, 04 July 2014; accepted, 31 July 2014; published 01 November 2014

FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL TABLETS BY USING NATURAL POLYMER

Anna Balaji, Vaddepalli Radhika * and Vishnuvardhan Goud

Centre for Biopharmaceutics and Pharmacokinetics, Trinity College of Pharmaceutical Sciences, Peddapally, Karimnagar - 505172, Andhra Pradesh, India.

Keywords:

Buccal tablets, Carvedilol, Casein, Hydroxypropylmethyl cellulose K4M, Factorial design

Correspondence to Author:
V. Radhika

Trinity College of Pharmaceutical Sciences, Peddapally, Karimnagar - 505172, Andhra Pradesh, India.

E-mail: radhika.vaddepalli291@gmail.com

ABSTRACT: The study was aimed at developing mucoadhesive buccal tablet containing Carvedilol. The effect of two independent variables, Casein (X_1) and hydroxypropylmethyl cellulose (HPMC K4M) (X_2) at three different levels (-1, 0, +1) on dependent variable including hardness (Y_1), cumulative percentage drug release at 6 h (Y_2) and 12 h (Y_3) using 3^2 full factorial design. FTIR and DSC results showed no evidence of interaction between the drug and polymers. All physicochemical parameters were within permissible Pharmacopoeial limits. The concentrations of independent variables had profound effect on dependent variables. The hardness of the optimized formulation F3 was 5.43 kg/cm^{2,} and the drug release was found to be 53.32% at the end of 6 hrs (Q6) and 95.16% at the end of 12 h (Q12). The optimized formulation followed zero-order release kinetics with non-fickian drug release mechanism. The study revealed that mucoadhesive buccal tablets could be successfully formulated using Casein and HPMC K4M using 3^2 full factorial design in the buccal delivery of Carvedilol. The result indicates that suitable innovative mucoadhesive buccal tablets may be prepared with desired bioavailability and mucoadhesion and it can be better option to by-pass hepatic metabolism.

INTRODUCTION: Buccal route of drug delivery is a good alternative amongst the various routes of drug delivery. The oral route is perhaps the most preferred for the patients. Buccal routes of drug delivery offer distinct advantages over oral administration for systemic drug delivery. These advantages include a bypass of first-pass effect and avoidance of pre-systemic elimination within the GI tract. These factors make the oral mucosal cavity a very attractive and feasible site for systemic drug delivery [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.5(11).4699-08

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.5(11).4699-08

Carvedilol is a nonselective β-adrenergic blocking agent with α1-blocking activity; It has vasodilating activity at alpha-1-receptors; at higher doses calcium channel blocking activity may contribute. Carvedilol is used in the management of hypertension and angina pectoris, and as an adjunct to standard therapy in symptomatic heart failure. The absolute bioavailability is about 25%, and the elimination half-life is about 6 h.

This is because of undergoing of the drug to first-pass metabolism in liver and gut wall. The buccal mucosa is an attractive route for systemic delivery of many drugs since it is relatively permeable with a rich blood supply. The mucoadhesive buccal drug delivery system offers several advantages as compared to traditional methods of systemic drug administration [2, 3]. Casein, the major milk protein, comprises about 80 % total protein content of milk.

Casein forms an integral part of the daily diet in many parts of the world. It is in soluble in water, and organic solvents. Casein possesses a number of interesting properties that make it a good candidate for conventional and novel drug delivery systems. It has a mucoadhesive property. Industrially it is used in sizing of textile and as an adhesive, in preparation of Casein plastic and Casein paints.

MATERIALS AND METHODS: Carvedilol pure drug was obtained as a gift sample from M/s Dr. MACS Bio-Pharma Private limited, Kukatpally, Hyderabad, Andhra Pradesh India. Hydroxypropyl-methyl cellulose K4M (HPMC-K4M) and Casein was obtained from S.D. Fine Chemicals Limit, Mumbai, India, Polyvinylpyrolidine K30 (PVP-K30) was obtained from Himedia Laboratories, Mumbai, India. Isopropyl alcohol and Dicalcium Phosphate was obtained from Finar chemicals limited, Ahmedabad, India. Magnesium stearate was obtained from Himedia Laboratories, Mumbai, India. All other chemicals used were of analytical grade.

Formulation of Mucoadhesive Tablets: Wet granulation method was employed to prepare buccal tablets of Carvedilol using, HPMC-K4M, Casein, PVP-K30.

Factorial Design: A 3^2 full factorial design was constructed, where the amounts of Casein (X_1) and HPMC K4M (X_2) selected as the independent factors. Hardness (Y_1), cumulative % drug release at 6 h (Q_6, Y_2) and 12 h (Q_{12}, Y_3) were selected as dependent variables. The levels of the two factors were selected on the basis of studies carried out before implementing the experimental design. **Table 1** summarizes the experimental runs, their factor combinations and the translation of the coded levels to the experimental units used in the study.

TABLE 1: TRANSLATION OF CODED LEVELS IN ACTUAL UNITS

Factor	Name	Units	Low (-)	Medium (0)	High (+)
X_1	Casein	mg	10.00	25	40
X_2	HPMC K4M	mg	60.00	35	60

Preparation: Mucoadhesive Buccal tablet each containing 6.25mg of Carvedilol were prepared by wet granulation method (using isopropyl alcohol). All the ingredients except lubricants were mixed in the order of ascending weights and blended for 10 min in an inflated polyethylene pouch. Carvedilol was added in this mixture and mixed for 2 min. Granulation was done with binder solution of PVP-K30 which was previously dissolved in isopropyl alcohol, and the damp mass passed through sieve no 10.

The granules were dried in air and passed through sieve no. 16, magnesium stearate & talc were added and mixed and compressed using a 10-station rotary compression machine (Karnavati Engineering Hd, Gujarat, India) into 150 mg tablet, using 6.5 mm punch. Composition of the different bioadhesive buccal tablet formulations of Carvedilol [4] is as shown in **Table 2.**

TABLE 2: COMPOSITION OF CARVEDILOL MUCOADHESIVE BUCCAL TABLETS

Formulation Code	Ingredients							
	Carvedilol (mg)	Casein (mg)	HPMCK4M (mg)	PVP-K30 (mg)	Dicalcium Phosphate (mg)	Magnesium Stearate (mg)	Talc (mg)	Isopropyl alcohol
F1	6.25	25	35	15	65.75	3	3	q.s
F2	6.25	25	35	15	65.75	3	3	q.s
F3	6.25	40	60	15	22.75	3	3	q.s
F4	6.25	25	35	15	65.75	3	3	q.s
F5	6.25	40	35	15	47.75	3	3	q.s
F6	6.25	40	10	15	72.75	3	3	q.s
F7	6.25	25	10	15	87.25	3	3	q.s
F8	6.25	25	60	15	37.75	3	3	q.s
F9	6.25	25	35	15	65.75	3	3	q.s
F10	6.25	10	35	15	77.75	3	3	q.s
F11	6.25	25	35	15	65.25	3	3	q.s
F12	6.25	10	60	15	52.75	3	3	q.s
F13	6.25	10	10	15	102.75	3	3	q.s
S1	6.25	24.97	54.3	15	43.48	3	3	q.s
S2	6.25	25.10	54.29	15	43.36	3	3	q.s

All the weights are taken in mg, except isopropyl alcohol is taken in q.s; the total weight of tablet is 150 mg.

Evaluation of Mucoadhesive Buccal Tablets Compatability Studies:

Fourier Transform Infrared (FTIR) Spectroscopy: The drug-polymer compatibility was confirmed by carrying out FTIR and DSC studies. Drug, polymer, and physical mixture of drug-polymer were subjected to FTIR analysis using FTIR 8400 Shimadzu, Japan. Samples were prepared in KBr disks and scanned between 450-4000cm^{1} with a resolution of 4 cm^{-1}. FTIR studies were carried out for Carvedilol pure drug, physical mixture of optimized formulation and optimized formulation.

Differential Scanning Calorimetry (DSC): DSC analysis using DSC-60 Shimadzu, Japan. Differential scanning calorimetry was performed for pure drug, physical mixture of optimized formulation, and optimized formulation. Accurately weighed samples were placed on aluminum plate sealed with aluminum seals and heated at a constant temp. of 5 °C/min over a temp. range of 0 - 400 °C in an inert (nitrogen) atmosphere.

Thickness: The thickness of buccal tablets was determined using vernier calipers. Ten tablets from each batch were evaluated and the results averaged.

Weight Variation Test: Twenty tablets from each formulation were weighed using an electronic digital balance and the average weight was calculated.

Hardness: Hardness was determined by compressing the tablets diametrically on six tablets from each batch using Monsanto hardness tester and average values were calculated.

Friability: Friability is the measure of tablet strength. Roche type friabilator (Tropical Equipment Pvt. Ltd. Mumbai, India) was used for testing the friability the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with revolution. After 4 min, the tablets were weighed and the percentage loss was determined [5, 6].

Drug Content Uniformity: Ten tablets were weighed and grounded in a glass mortar with a pestle to obtain fine powder. Powder equivalent to the mass of one tablet from each batch was taken in separate 100 ml volumetric flask containing 100 ml of 6.8 phosphate buffer, 20% of methanol and kept for 15 mins constant stirring. The solution was filtered, diluted and analyzed at 244 nm using UV spectrophotometer (UV Spectrophotometer 1800, Shimadzu, Japan).

Surface pH: The microenvironment pH (surface pH) of the buccal tablets was determined in order to investigate the possibility of any side effects *in-vivo*. 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 method adopted by Battenberg *et al*. was used to determine the surface pH of the tablet. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 5 ml of distilled water (pH 7.0 ± 0.05) 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 min [9].

Mucoadhesion Studies: The apparatus used for testing bioadhesion was assembled in the laboratory. Mucoadhesion strength of the tablet was measured on a modified physical balance employing the method described by using sheep buccal mucosa as model mucosal membrane. A double beam physical balance was taken, the left pan was removed. To left arm of balance a thick thread of suitable length was hanged. To the bottom side of thread a glass vial of 30 ml capacity with uniform surface was tied. A clean 500 ml glass beaker was placed below hanging glass vial within which was placed another glass beaker of 100 ml capacity in inverted position. The temperature control system involves placing the thermometer in 500 ml beaker and intermittently adding hot simulated saliva (pH 6.8) into 500 ml beaker containing simulated saliva (pH 6.8) maintained at 37.0 ± 0.5 °C. The balance was so adjusted that right-hand-side was exactly 5 g heavier than the left [10-12].

Swelling Studies: The tablets were individually weighed (W_1) and placed separately in Petri dishes

with 5 ml of simulated saliva of pH 6.8. At the time interval of 0.5, 1, 2, 4, 6, 8, 10 and 12 hrs, tablet was removed from the petri dish and excess water was removed carefully using the filter paper. The swollen tablet was then reweighed (W_2) and the percentage hydration was calculated using the following formula [13, 14].

$$\% \text{ Swelling Index (S.I)} = [(W_2-W_1)/ W_1] \times 100$$

W_1 = initial weight; W_2= final weight

***In-vitro* Drug Release Study from Carvedilol Loaded Tablets:** *In -vitro* study was carried out in USP II apparatus (Electro lab TDT 08L USP), employed paddle stirrer at 50 rpm and 900 ml of phosphate buffer pH 6.8 as dissolution medium maintained at 37 ± 0.5 ℃. The tablets were designed to release drug from one side only, therefore, one side of tablet was fixed to a glass disk with cyanoacrylate adhesive [15, 16].

The disk was placed at the bottom of the dissolution vessel. Aliquots of 5 ml were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through Whatman filter paper and analyzed it at 240 nm using UV-Visible spectroscopy (UV-1800 Shimadzu Corporation, Japan).

Statistical and Kinetic Analysis: The data obtained from all the formulations were fitted into various mathematical models including zero order, first order, Higuchi, Hixon Crowell, and Korsmeyer - Peppas release models. The Korsmeyer - Peppas model is widely used, when the release mechanism is not well known or more than one type of release could be involved. For non-fickian release, the value of n falls between 0.5 and 1.0; while in case of fickian diffusion, $n \leq 0.5$; for zero-order release (case II transport), $n = 1$; and for super case II transport, $n > 1$[17, 18].

RESULTS AND DISCUSSION:

Compatibility Studies:

Fourier Transform Infrared (FTIR) Spectroscopy: FTIR studies were carried out for the pure drug – Carvedilol, formulation F3 and their spectra are as shown in **Fig. 1** and **Fig. 2** respectively. The characteristic peaks of the pure drug – Carvedilol were assigned from standard literature. These included O-H stretching, =C-H stretching, N-H stretching.

The spectra for carvedilol exhibits a broad peak at 344.68 cm^{-1} due to alcohols and phenols (O-H) stretching vibration, 3061.13 cm^{-1} due to alkenes (=C-H) stretching vibration and 2956.97 cm^{-1} due to alkanes (C-H) stretching vibration **Fig. 1**.

The FTIR results from formulation F3 exhibited broad peaks at 3527.29 cm^{-1} due to alcohols and phenols (O-H) stretching vibration, 3066.92 cm^{-1} due to alkenes (=C-H) stretching vibration, 2837.31cm^{-1} due to alkanes (C-H) stretching vibration **Fig. 1**.

The intensity and position of these characteristic peaks permit easy interpretation of any possible interaction between the drug and the excipients in the formulation. The results clearly showed that there was no interaction between the drug and the excipients in the prepared formulation F3. Carvedilol was intact, and there was no sign of any degradation due to preparative processes adopted during the loading of the drug into buccal tablets.

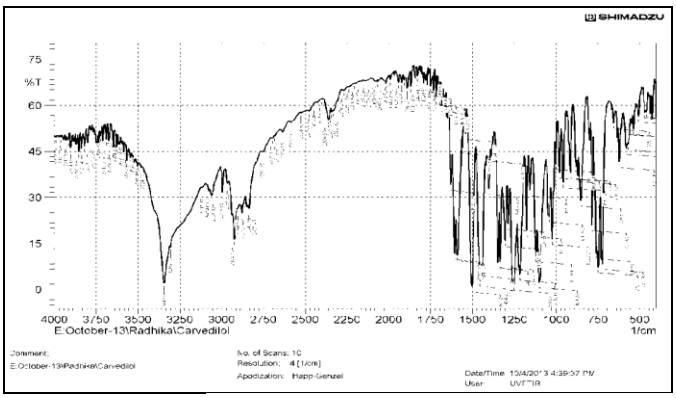

FIG. 1: FTIR SPECTRA DATA FOR PURE DRUG CARVEDILOL

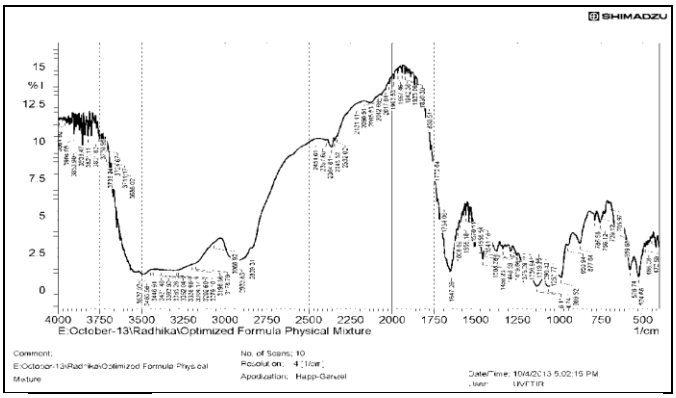

FIG. 2: FTIR SPECTRA OF OPTIMIZED PHYSICAL MIXTURE (FORMULATION F3)

Differential Scanning Calorimetry (DSC): Thermal characterization and analysis of DSC curves of the pure drug, physical mixture of formulation F3 were carried out. The studies provided thermal behavior of the pure drug, its physical mixture with Casein, HPMC K4M, PVP K-30, Dicalcium phosphate. Carvedilol showed an endothermic peak at 117 ºC and an exothermic peak at 118.9 ºC. A physical mixture of Formulation F3 showed an endothermic peak at 19 ºC and exothermic peaks at 186 ºC. The above results indicated that the characteristic peaks of Carvedilol appeared in the physical mixture of Formulation F3 indicating that there was no possible interaction between the drug and the excipients in the mucoadhesive buccal formulation. The drug in all probability was present in its stable form without any possible degradation.

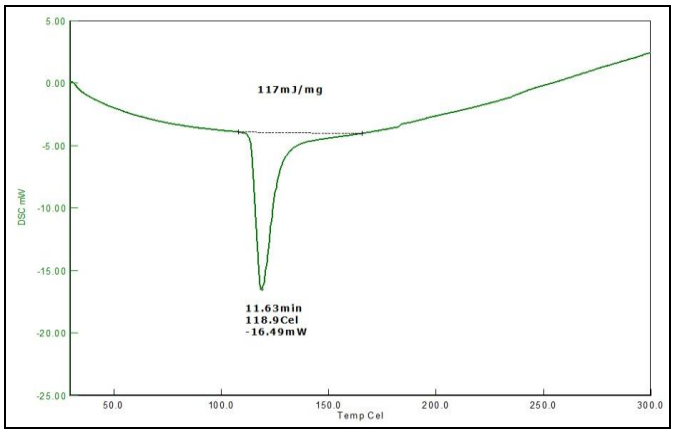

FIG. 3: DSC THERMOGRAM OF PURE DRUG CARVEDILOL

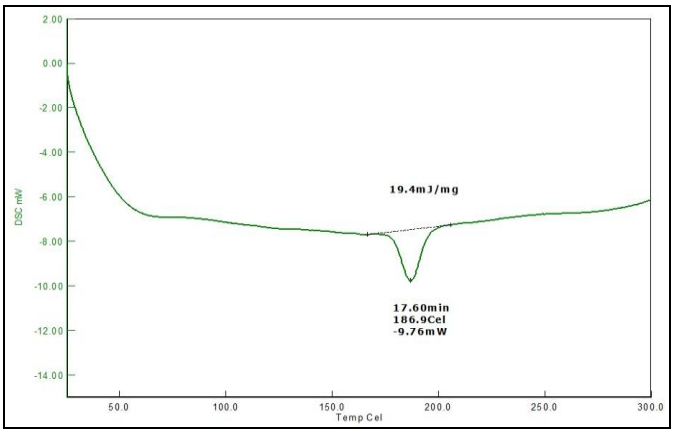

FIG. 4: DSC THERMOGRAM OF PHYSICAL MIXTURE OF FORMULATION F3

Factorial Design: Experimental trials were performed for all 13 possible combinations by 3^2 randomized full factorial design. The quadratic model was fitted to the data for two responses simultaneously using Design-Expert software 7.0.0 and adequacy and good fit of the models was tested using analysis of variance (ANOVA). Data were analyzed using Design expert 7.0.0 software. The formulation layout for the factorial design batches F1–F13 is shown in **Table 3**.

TABLE 3: OBSERVED RESPONSES FOR 3^2 FULL FACTORIAL DESIGN WITH RESPONSE SURFACE METHODOLOGY

Formulation Code	Casein	HPMC-K4M	Hardness (kg/cm^2)	Q_6 at 6hrs	Q_{12} at 12 hrs
1	25	35	5.53	35.59	78.03
2	25	35	5.45	36.89	77.05
3	40	60	5.42	53.26	95.16
4	25	35	5.49	35.75	77.79
5	40	35	4.71	26.62	44.76
6	40	10	5.82	21.63	37.27
7	25	10	4.94	37.22	62.14
8	25	60	5.33	51.82	94.17
9	25	35	5.40	36.55	78.01
10	10	35	5.63	31.83	70.83
11	25	35	5.41	37.01	77.25
12	10	60	5.70	46.58	82.08
13	10	10	5.72	23.14	46.09

Thickness: The thickness of the tablets was found to be almost uniform in all formulations F1 to F13. The thickness was found to be in the range of 2.1 to 3.3 mm. None of the formulations (F1 to F13) showed a deviation. Hence, it is concluded that all the formulations compiled the thickness test and the results are shown in **Table 4**.

Weight Variation Test: The weight variation test was conducted for each batch of all formulations F1 to F13 as per I.P, and the results are shown in **Table 4**. The weight variation test for all the formulations complies with the IP limit (± 10%).

TABLE 4: EVALUATION CHARACTERISTICS OF MUCOADHESIVE BUCCAL TABLETS

Formulation Code	Weight variation* (mg)	Thickness* (mm)	Hardness (kg/cm^2)	Friability %	Drug content estimation %
F1	150.13±0.05	2.62±0.01	5.53±0.17	0.85±0.08	98.72±0.02
F2	150.25±0.04	2.93±0.05	5.45±0.16	0.78±0.07	96.96±0.01
F3	150.88±0.26	2.55±0.03	5.42±0.11	0.96±0.08	97.44±0.05
F4	148.25±0.35	2.12±0.03	5.49±0.14	0.95±0.07	95.68±0.04
F5	150.28±0.25	2.43±0.04	4.71±0.13	0.69±0.06	97.61±0.02
F6	151.87±0.34	3.35±0.07	5.82±0.19	0.66±0.09	96.80±0.03
F7	149.99±0.23	3.23±0.09	4.94±0.17	0.56±0.06	93.91±0.03
F8	151.65±0.26	3.14±0.06	5.33±0.11	0.73±0.05	96.73±0.03
F9	150.22±0.16	2.56±0.03	5.40±0.16	0.54±0.02	95.12±0.03
F10	149.22±0.17	2.83±0.13	5.63±0.13	0.64±0.08	98.88±0.05
F11	150.26±0.12	2.53±0.04	5.41±0.18	0.59±0.02	97.28±0.05
F12	150.3±0.28	2.94±0.02	5.70±0.18	0.84±0.01	97.44±0.02
F13	150.35±0.18	2.92±0.01	5.72±0.15	0.88±0.03	94.13±0.01
S1	149.87±0.25	3.22±0.08	5.23±0.15	0.92±0.06	98.56±0.07
S2	150.55±0.22	3.21±0.08	5.43±0.18	0.69±0.02	97.12±0.02

*Mean ± SD; n = 3

Hardness: Adequate tablet hardness is a necessary requisite for consumer acceptance and handling. The hardness of tablets of all formulations (F1 to F13) ranged between 3.0 to 7.0 kg/cm^{2,} and the results are shown in Table 4. As the Casein and HPMC K4M ratio increased, the hardness of the tablet increased. The lowest hardness value of 4.5 kg/cm^2 was obtained for Formulation F1 and highest of 5.7 kg/cm^2 h for Formulation F3. For hardness two-dimensional contour plot and three-dimensional surface response plots are shown in **Fig. 5** and **Fig. 6**. Hardness v increased with increase in concentration of Casein (X_1) and HPMC K4M. The low-level factor of X_1 and a high level of X_2 predicted. The regression coefficient for Y_1 (hardness) is as follows.

$$Y_1 = +5.33+0.017X_1+0.20X_2-0.040X_1 X_2 .....1$$

Two-dimensional contour plot and three-dimensional surface response plots are shown in **Fig. 5** and **Fig. 6** for hardness. Hardness values increased with increase in concentration of Casein (X_1). Median level factor (0) of X1 and X2 predicted an optimal hardness value which would impart adequate mechanical properties and desired rate of drug release.

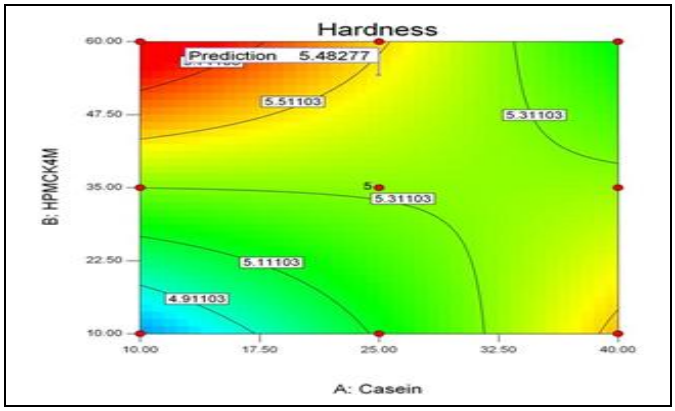

FIG. 5: TWO-DIMENSIONAL CONTOUR PLOT FOR HARDNESS

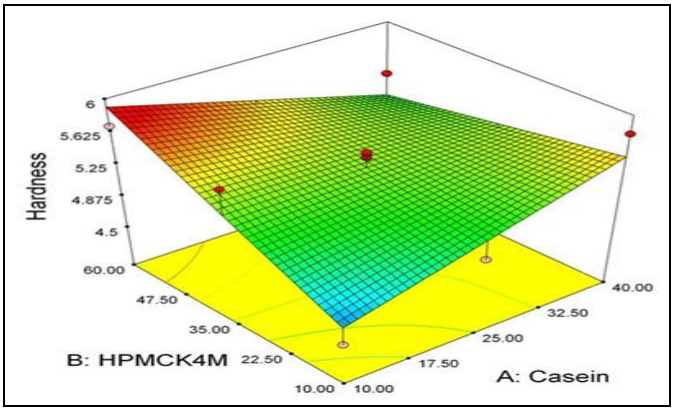

FIG. 6: THREE DIMENSIONAL RESPONSE SURFACE PLOT FOR HARDNESS

Friability: The friability test for all the formulations was done as per the standard procedure in I.P. The results of the friability test are tabulated in **Table 4**. The results indicated that the friability was less than 1% for all formulations ensuring that the tablets were mechanically strong.

Drug Content: The drug content of each batch of all the formulations (F1 to F13) was evaluated as per the standard protocol maintained in I.P and the results are as shown in **Table 4**. The results indicate that the percentage of drug content was found to be 6.06 to 6.18 hence it was concluded

that all the formulations were within the acceptable limits as per Indian Pharmacopeia, *i.e.* ± 5 %.

Surface pH: Surface pH of all the formulations F1 to F13 was found to be 7.01 ± 0.25 to 7.23 ± 0.33 **Table 5**. Hence, it can be expected that there would be no local irritation to the mucosal surface, and all the formulation can be used safely.

Bioadhesive Strength: The *In-vitro* bioadhesion study was performed using a modified physical balance and measure the force (N) required to detach the tablet was noted. The bioadhesion characteristics were affected by the concentration of bioadhesive polymers used.

Increase in concentration of polymer increased the bioadhesive strength of the formulation shown as **Table 5**. The strength of bioadhesion was between 23.12 ± 0.17 to 33.52 ± 0.03 N.

TABLE 5: EVALUATION PARAMETERS OF MUCOADHESIVE BUCCAL TABLETS

Formulation code	Surface pH	Mucoadhesive strength (N)	Cumulative % drug release	
			6 h	12 h
F1	7.10 ± 0.33	29.66 ± 0.07	35.59	78.03
F2	7.20 ± 0.21	25.49 ± 0.02	36.82	77.05
F3	7.20 ± 0.11	33.52 ± 0.03	53.32	95.16
F4	7.11 ± 0.22	32.19 ± 0.27	35.74	77.79
F5	7.09 ± 0.32	27.89 ± 0.28	26.63	44.76
F6	7.01 ± 0.25	23.97 ± 0.22	21.63	62.14
F7	7.11 ± 0.66	26.03 ± 0.27	21.63	62.14
F8	7.13 ± 0.33	31.21 ± 0.05	37.14	94.17
F9	7.11 ± 0.32	30.52 ± 0.05	51.90	78.01
F10	7.10 ± 0.22	27.17 ± 0.29	31.78	70.83
F11	7.11 ± 0.15	23.12 ± 0.17	37.08	77.25
F12	7.23 ± 0.33	31.52 ± 0.21	46.50	82.08
F13	7.21 ± 0.11	25.30 ± 0.17	23.15	46.09
S1	7.13 ± 0.17	29.39 ± 0.29	50.46	92.15
S2	7.21 ± 0.30	27.38 ± 0.15	53.38	95.11

*Mean ± SD; n = 3

Swelling Studies: The swelling studies were conducted for all formulations, *i.e.* F1 to F13 and the results are as shown in **Table 6**. All the formulations were hydrated generally by keeping the tablets in contact with water for 1 h to 12 h. The highest hydration (swelling), *i.e.* 80 was observed with the formulation F3. This may be due to the quick hydration of polymers (Casein and HPMC K4M). The swelling rate of tablets increased in case of formulation F3 containing Casein and HPMC K4M in the ratio of 40:60.

TABLE 6: SWELLING INDEX OF MUCOADHESIVE BUCCAL TABLETS

	Swelling Index							
Formulation code	0.5 hrs	1 hrs	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs	12 hrs
F1	22	27	32	35	38	40	43	45
F2	17	23	35	37	42	44	47	48
F3	23	29	33	48	54	62	74	80
F4	27	31	35	39	41	44	49	51
F5	29	31	34	37	41	48	52	57
F6	24	28	30	31	33	37	40	43
F7	25	27	30	32	35	39	43	47
F8	29	31	37	40	44	47	52	55
F9	29	33	44	49	53	55	61	64
F10	33	39	41	43	47	49	51	53
F11	25	27	31	38	39	41	48	58
F12	38	41	47	49	51	52	57	60
F13	29	33	35	39	41	45	57	61
S1	25	33	39	43	46	53	54	66
S2	27	28	33	38	48	55	64	79

***In-vitro* Drug Release Studies**: *In-vitro* drug release experiments were performed at 37 ± 0.5 °C in the USP II dissolution apparatus. The results showed that all formulations released the drug within 12 h. It was found that the rate of drug release was different for formulations with different proportions of Casein (X_1) and HPMC K4M (X_2) which were used as independent variables in low (-1), median (0) and high (+1). At low levels of Casein (formulations F10, F12 & F13), Q6 was ranging from 23.25 to 46.57% and Q12 was between 46.09 to 82.08 at the end of 6 and 12 h respectively **Table 5** and **Fig. 11**. At median levels of Casein (formulations F1, F2, F4, F7, F8, F9 & F11), Q6 was ranging from 21.66 to 51.95 % and Q12 was between 42.14 to 94.17% at the end of 6 and 12 h respectively **Table 5** and **Fig. 11**. At high levels of Casein (formulations F3, F5 & F6), Q6 was ranging from 21.67 to 53.39 % and Q12 was between 44.76 to 95.16% at the end of 6 and 12 h respectively **Table 5** and **Fig. 11**.

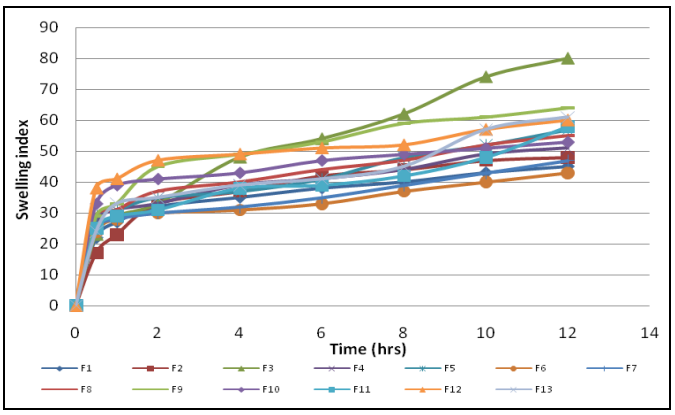

FIG. 7: SWELLING INDEX OF BUCCAL TABLETS

In all the formulations the effect of HPMC K4M (X_2) had a profound effect on drug release. As its concentration increased the rate of drug release increased. The *in-vitro* release data of F1 to F13 formulations fitted into zero-order, first-order, Higuchi, Hixon Crowell and Korsmeyer - Peppas release models and evaluated Co-efficient of regression values (r^2) suggested the best fit kinetic model indicating zero-order release for all the formulations with an exception of formulations F5 & F6 which followed first-order **Table 9**.

The release exponent (n) value of the optimized formulation F3 was 0.5143 confirming the release mechanism to follow anomalous transport *i.e.*, drug release is being governed by both diffusion and erosion mechanism. The regression coefficient for Y_2 and Y_3 are as follows.

$$Y_2 = 36.53 - 6.667E-0.03\ X_1 + 11.61\ X_2 + 2.05\ X_1 X_2 - 27.73\ X_1^2 + 7.57\ X_2^2 \quad .....2$$

$$Y_3 = 76.56 - 3.03\ X_1 + 21.59\ X_2 + 6.38\ X_1 X_2 - 16.10\ X_1^2 + 4.26\ X_2^2 \quad .....3$$

All the 13 formulations were optimized, and the results were entered and analyzed using Design-Expert software trial version 7.0.0 (Stat-Ease Inc., Minneapolis, USA) in 3 level factorial design using quadratic model. Two formulations were developed with a predicted set of values **Table 8** whose quadratic model was found to be significant Q6 (F=18.83, p<0.06) and Q12 (12.03, p<0.25). Two-dimensional contour plot and three-dimensional response surface plots for Q6 (Y_2) and Q12 (Y_3) in **Fig. 8, 9, 10** & **11** respectively. The actual values of formulations S1 and S2 were close to the predicted Q_6 & Q_{12} values **Table 8**.

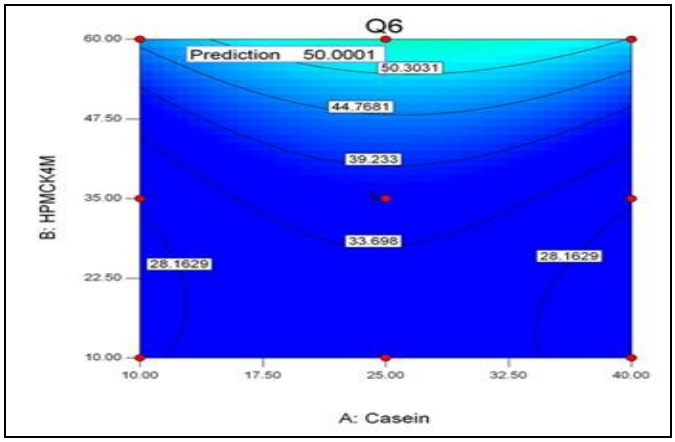

FIG. 8: TWO-DIMENSIONAL CONTOUR PLOT FOR Q_6

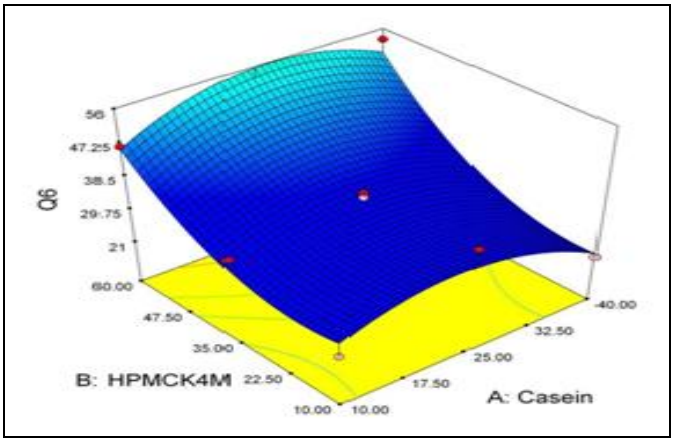

FIG. 9: THREE DIMENSIONAL RESPONSE SURFACE PLOT FOR Q_6

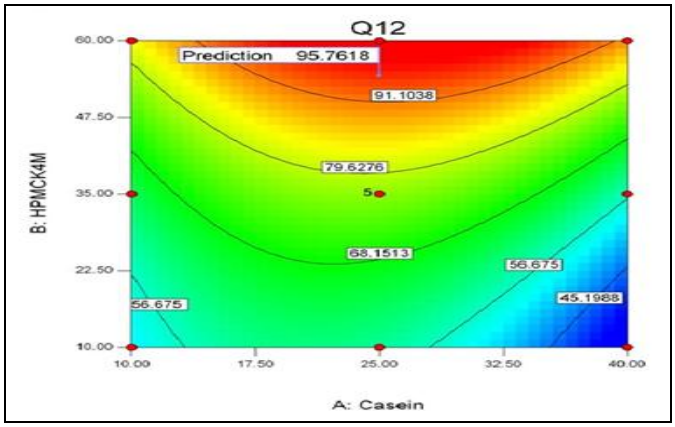

FIG. 10: TWO-DIMENSIONAL CONTOUR PLOT FOR Q_{12}

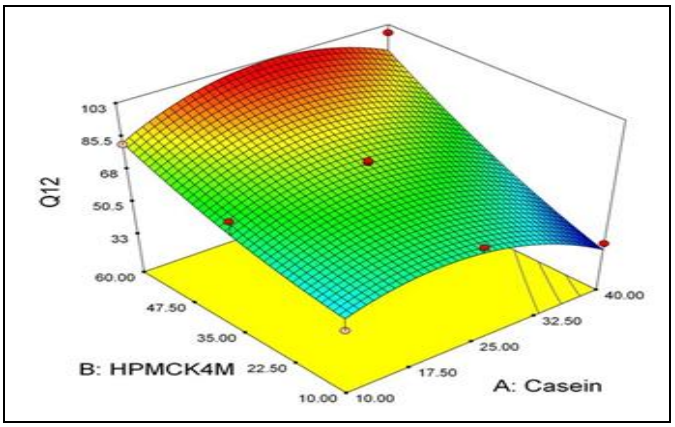

FIG. 11: THREE DIMENSIONAL RESPONSE SURFACE PLOT FOR Q_{12}

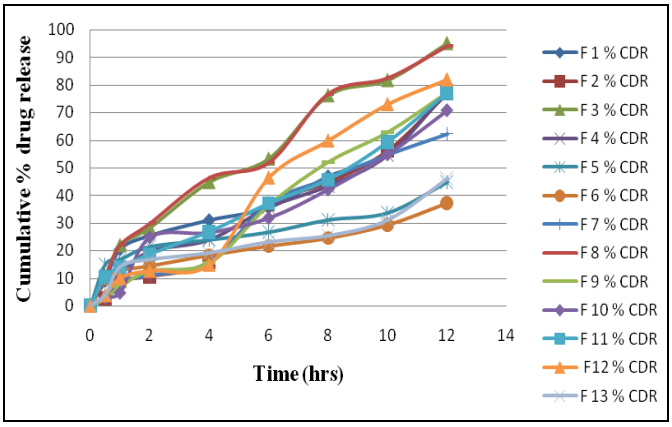

FIG. 12: *IN-VITRO* DRUG RELEASE PROFILE FORMULATION F1 - F13

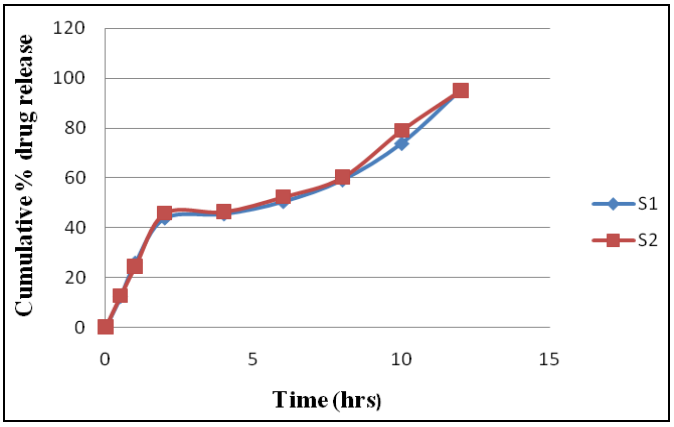

FIG. 13: *IN-VITRO* DRUG RELEASE PROFILE FORMULATION S1 AND S2

TABLE 8: PREDICTED AND ACTUAL VALUES OF FORMULATIONS S1 AND S2

Parameters	Hardness		Q_6		Q_{12}	
Formulation code	Predicted value	Actual value	Predicted value	Actual value	Predicted value	Actual value
S1	5.482	5.2	50.0	50.40	95.76	95.25
S2	5.480	5.4	50.0	52.38	95.76	95.11

Drug Release Kinetics: The data of drug release from different formulations of buccal tablets were processed to understand the linear relationship. The data were processed for regression analysis using MS EXCEL Statistical functions. The parameters and equations are given in **Table 9**. The release kinetics of carvedilol found to follow zero-order and mechanism is Korsmeyer Peppas.

TABLE 9: KINETICS VALUES OBTAINED FROM DIFFERENT PLOTS OF FORMULATIONS F1-F13

Formulation code	Zero-order	First-order	Higuchi	Hixon-Crowell	Korsmeyer-Peppas	
	r^2	r^2	r^2	r^2	r^2	*n value*
F1	0.9409	0.8467	0.9224	0.2078	0.9993	0.3055
F2	0.9790	0.8979	0.8834	0.2859	0.8209	0.7174
F3	0.9734	0.9004	0.9774	0.3847	0.9853	0.5143
F4	0.9717	0.8703	0.9118	0.2568	0.9588	0.6072
F5	0.8554	0.9296	0.9316	0.0107	0.9748	0.2491
F6	0.9181	0.9623	0.9561	0.0096	0.9700	0.2936
F7	0.9822	0.9803	0.9228	0.2451	0.8389	0.7354
F8	0.9674	0.9215	0.9772	0.3802	0.9878	0.5024
F9	0.9860	0.9472	0.8939	0.3148	0.8992	0.8300
F10	0.9585	0.9169	0.9192	0.2386	0.7647	0.9863
F11	0.9805	0.8987	0.9282	0.2450	0.9849	0.5330
F12	0.9720	0.9535	0.8921	0.3447	0.7174	0.7297
F13	0.8970	0.897	0.9016	0.0483	0.9717	0.2598
S1	0.9075	0.7483	0.9397	0.2967	0.8208	0.3452
S2	0.9109	0.7938	0.9464	0.3127	0.7912	0.3889

CONCLUSION: In the present study, an attempt to formulate mucoadhesive buccal tablets of Carvedilol for treatment of hypertension using novel polymer (Casein) obtained from milk protein and HPMC K4M was made by an optimization technique. Using 3^2 full factorial design, the effect of interaction of independent variables Casein (X_1) and HPMC K4M (X_2) on dependent hardness (Y_1) and cumulative % drug release at 6 h (Q_6, Y_2) and 12 h (Q_{12}, Y_3) were studied and optimized.

The optimal formulation had the approximated percentage drug release which met the required rate of drug release for a period of 12 h through the buccal mucosa thus preventing first-pass hepatic metabolism. Casein showed the good mucoadhesive property. The optimized formulation followed zero-order release kinetics with non-fickian drug release mechanism. From the results it can be concluded that mucoadhesive buccal tablets can be successfully formulated using Casein.

ACKNOWLEDGEMENT: The authors would like to thank the management of Trinity College of Pharmaceutical Sciences for their support and encouragement.

CONFLICT OF INTEREST: Nil

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How to cite this article:
Balaji A, Radhika V and Goud V: FOrmulation and evaluation of mucoadhesive buccal tablets by using natural polymer. Int J Pharm Sci & Res 2014; 5(11): 4699-08. doi: 10.13040/IJPSR.0975-8232.5(11).4699-08.