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Original Article

FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL TABLETS OF CARVEDILOL

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ABSTRACT

Objective: The aim of the study was to formulate and evaluate mucoadhesive buccal tablets of carvedilol to avoid the first-pass metabolism.

Methods: Mucoadhesive Buccal tablets of carvedilol were prepared by direct compression techniques using a combination of bioadhesive polymers such as hydroxypropyl cellulose (HPC) and polyethlyelne oxide WSR-1105 (PEO WSR-1105). In order to improve solubility of carvedilol, solid dispersion was prepared using poloxamer 188. A 3^2 Full factorial design was applied to investigate the combined effect of the two independent variables i.e. concentration of HPC (X_1) and concentration of PEO WSR-1105(X_2) on the dependent variables, % *in vitro* drug release at 1 h (Y_1), % *in vitro* drug release at 4 h (Y_2), mucoadhesive strength (Y_3) and mucoadhesion time (Y_4).

Results: Optimized mucoadhesive buccal tablets shows *in vitro* drug release of 96.23±2.45 in 8 h, mucoadhesive strength of 18.20±1.44 g, mucoadhesion time 420±2.6 min and surface pH 6.75±0.015. Drug excipients compatibility study by FTIR showed no interaction between drug and excipients.

Conclusion: From all parameters and experimental design evaluation, it was concluded that the drug release rate decreased with an increase the concentration of HPC and PEO WSR-1105 and mucoadhesion property increased with increase the concentration of PEO WSR-1105. The *in vitro* release kinetics revealed the Korsmeyer-Peppas model is followed and drug release is by anomalous diffusion.

Keywords: Carvedilol, Mucoadhesive buccal tablets, Solid dispersion, Hydroxypropyl cellulose, Polyethylene Oxide WSR-1105, Factorial design

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INTRODUCTION

Bioadhesive buccal delivery of drugs is one of the alternatives to the oral route of drug administration, particularly to those drugs that undergo first pass metabolism [1, 2]. Problems accompanied with oral route of administration such as extensive metabolism by liver, drug degradation in the gastrointestinal tract due to harsh environment, and invasiveness of parenteral administration can be solved by administering the drug through the buccal route [1, 3, 4].

Buccal drug delivery systems offer a promising route for drug delivery not only to the buccal mucosa for the treatment of oral conditions but also for systemic delivery by absorption through the mucosa to the systemic circulation at a predetermined and controlled rate [5, 6]. In addition, the buccal mucosa permits prolonged retention of a dosage form, especially with the use of mucoadhesive polymers without much interference in activities such as speech or mastication unlike the sublingual route [5, 7]. Buccal drug delivery allows interruptions at any time in the case of toxicity or adverse effects. It is also possible to administrate drugs to patients who have difficulties in swallowing [8].

Carvedilol is a non-selective β-adrenergic antagonist used in the treatment of hypertension and stable angina pectoris. It also possesses antioxidant and antiproliferative effects, which may enhance its ability to combat the deleterious effects of sympathetic nervous system activation in heart failure [9, 10]. It is rapidly absorbed after an oral administration, the bioavailability of carvedilol is 25%–35% as it undergoes stereo-selective first-pass metabolism. Carvedilol is a weak base with pKa value 7.7–7.9 and log PC (partition coefficient) value of 3.967, which indicates sufficient lipophilicity to pass through any biological membrane, including buccal membranes [5]. In the present study, mucoadhesive buccal tablets of carvedilol were developed using a combination of bioadhesive polymers such as hydroxypropyl cellulose (HPC) and polyethylene oxide WSR-1105 (PEO WSR-1105) to avoid first-pass metabolism.

MATERIALS AND METHODS

Materials

Carvedilol was obtained a gift sample from Cadila Pharmaceutical Ltd, Dholka, Ahmedabad. Poloxamer 188, hydroxypropyl cellulose, polyethylene oxide WSR-1105, pearlitol 200 SD, magnesium stearate, aerosil and polyvinylpyrrolidone (PVP K-30) were purchased form Yarrow chem Product, Mumbai. Aspartame was procured from Forbes Pharmaceutical, Mumbai.

Drug-excipient interaction study by FTIR

FTIR study carried out to identify the drug sample and to establish drug-polymer compatibility in physical mixture of drug and polymers. Fourier Transform Infrared Spectroscopy carried out by diluting the sample with dried potassium bromide and acquiring IR spectrum in the range of 400-4000 cm^{-1}. FTIR spectra of pure drug, and physcial mixture (drug+poloxamer 188+HPC+PEO) were taken [11].

Preparation of solid dispersion by melting method

Accurately weigh the drug and poloxamer 188. In this method, poloxamer 188 was melted to a temperature slightly above its melting point and the drug is incorporated into the matrix to ensure a homogenous dispersion of the drug in the matrix. The dispersion was cooled rapidly in an ice bath. The obtained dried mass is pulverized and sieved through # 40 [12-14].

Characterization of solid dispersion by differential scanning calorimetry (DSC) study

Differential Scanning Calorimetry (DSC) spectra of (i) carvedilol (ii) poloxamer 188 (iii) drug+poloxamer 188 physical mixture (iv) solid dispersion of all these were recorded using DSC instrument of the institute (DSC-60, Shimadzu Corporation, Japan). The samples were heated in sealed aluminum pans under airflow (30 ml/min) at a scanning rate of 10 °C/min from 30 to 300 °C. Empty aluminum pan was used as a reference. The heat flow as a function of temperature was measured for the samples [15].

Preparation of buccal tablet

Carvedilol buccal tablets were prepared by direct compression techniques. All ingredients and carvedilol solid dispersion were accurately weighed. All ingredients and carvedilol solid dispersion was passed through sieve # 40 and mixed thoroughly for 10 min. The blend was lubricated with aerosil and magnesium stearate for 2

min. The lubricated blend was compressed using 8 mm punch in single rotary tablet compression machine (Karnavati Engineering, Mehsana) [11, 16].

Experimental design

In this design, two factors were evaluated each at three levels and experimental trials was performed using all possible nine combination. In this present study, concentration of HPC (X_1) and concentration of PEO WSR-1105 (X_2) were selected as independent variables. The % *in vitro* drug release at 1 h, (Y_1), *in vitro* drug release at 4 h (Y_2), mucoadhesive strength (Y_3) and mucoadhesive time (Y_4) were selected as dependent variables. A statistical model, incorporating interactive and polynomial terms, was used to evaluate the response.

Table 1: Variables in 3^2 factorial designs

Independent variables	Levels		
	-1	0	+1
X_1: HPC	17.5 mg (10 %)	35 mg (20 %)	52.5 mg (30%)
X_2: PEO WSR-1105	17.5 mg (10 %)	35 mg (20 %)	52.5 mg (30%)

Dependent variables: Y_1: *in vitro* drug release at 1 h, Y_2: *in vitro* release drug 4 h, Y_3: mucoadhesive strength (g), Y_4: mucoadhesion time (min)

Table 2: Composition of factorial batches

Ingredients	Batches (Qty. in mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Carvedilol solid dispersion equivalent to 6.25 mg carvedilol	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75
HPC	17.5	35	52.5	17.5	35	52.5	17.5	35	52.5
PEO WSR-1105	17.5	17.5	17.5	35	35	35	52.5	52.5	52.5
Pearlitol 200 SD	103.25	85.75	68.25	85.75	68.25	50.75	68.25	50.75	33.25
PVP K-30	10	10	10	10	10	10	10	10	10
Aspartame	1	1	1	1	1	1	1	1	1
Aerosil	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Magnesium stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Average weight of tablets	175	175	175	175	175	175	175	175	175

Evaluation of buccal tablets

Tablet thickness and diameter

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using vernier calipers [17].

Hardness

This test is used to check the hardness of a tablet, which may undergo chipping or breakage during storage, transportation and handling. In these five tablets will select at random and the hardness of each tablet will measure with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm^2 [17].

Friability

The friability test will carried out in Roche friabilator. Ten tablets weighed ($W_{initial}$) initially and put in a rotating apparatus drum. Then, they are subjected to fall from 6 inches in height. After completion of 100 rotations, the tablets again weighed (W_{final}). The percent loss in weight or friability (f) calculated by the formula given below [17].

$$F = \frac{(W_{initial}) - (W_{final})}{(W_{initial})} X\ 100$$

% Drug content

Uniformity of drug content was determined according to the following procedure. 10 tablets crushed in mortar pestle. Equivalent powder to dose 6.25 mg carvedilol was taken from the powder and dissolved in 10 ml of methanol. The volume was made up to 100 ml with phosphate buffer pH 6.8 and sonicate for 20 min and then 1 ml was transferred to 10 ml volumetric flask and the volume was adjusted with phosphate buffer pH 6.8. The absorbance was measured on a UV-Vis spectrophotometer at 240 nm. A concentration of carvedilol was calculated from a standard calibration curve of carvedilol [18].

Uniformity of weight

This test is performed to maintain the uniformity of weight of each tablet, which should be in the prescribed range; this is done by sampling and weighing 20 tablets at random and average weight is calculated. The weight variation test was performed according to Indian Pharmacopeia [17].

***In vitro* drug release**

In vitro drug release was performed on buccal tablets using USP rotating paddle apparatus (Electrolab Dissolution Tester (USP) TDT-08L). The dissolution medium consisted of 500 ml of phosphate buffer pH 6.8. The experiment was performed at 37±0.5 °C, with a rotation speed of 50 rpm. Buccal tablet was attached to the glass slide with instant adhesive (cyanoacrylate adhesive). The slide was placed at the bottom of the dissolution vessel. Samples (5 ml) were withdrawn at predetermined time intervals and the equivalent amount was replaced with fresh medium. The samples were filtered through Whatman filter (0.45 µm) paper and analyzed by UV spectrophotometer at 240 nm [18].

***Ex vivo* mucoadhesive strength**

A modified balance method was used for determining the *ex vivo* mucoadhesion strength. Porcine buccal mucosa was used as the model substrate and phosphate buffer pH 6.8 was used as the moistening fluid. Freshly excised porcine buccal mucosa was obtained from the local slaughterhouse used within three hours of slaughter. A preload of 50 gm was placed on the clamp for 5 min to establish an adhesive bond between the tablet and buccal mucosa. After completion of preload time, preload was removed from the clamp and water was added into the beaker from the burette at a constant rate. Mucoadhesive strength was measured in terms of weight in g of water required to detach the tablet from the buccal mucosa. The addition of water was stopped when tablet was detached from porcine buccal mucosa. The weight of water required to detach the tablet from buccal mucosa was noted as *ex vivo* mucoadhesive strength. Mucoadhesive strength was performed in triplicate and average mucoadhesive strength was determined [19].

Surface pH study

The surface pH of the buccal tablet was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may irritate the buccal mucosa, we sought to keep the surface pH as close to neutral as possible. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 1 ml of phosphate buffer pH 6.8 for 2 h at room temperature. The pH was identified by bringing the electrode into contact with the tablet surface and allowing it to equilibrate for 1 min [11].

***Ex vivo* mucoadhesion time**

The *ex vivo* mucoadhesion time of mucoadhesive buccal tablets was determined using a modified USP dissolution apparatus. The dissolution medium was composed of 500 ml of phosphate buffer pH 6.8 maintained at 37 °C. A segment porcine buccal mucosa each of 3 cm length, was tied to the surface of glass slide, which was then vertically attached to the apparatus. The buccal tablet was hydrated using 15µl of pH 6.8 phosphate buffer on one side and a hydrated surface was brought into contact with the mucosal membrane for 30 sec. The glass slide was vertically fixed to the apparatus and allowed to run in such way that the tablet completely immersed in the buffer solution at the lowest point and was out at the highest point. Tablet adhesion was monitored for 12 h. The time necessary for complete erosion or detachment of the carvedilol buccal tablet from the mucosal surface was recorded. The experiments were performed in triplicate (n = 3) and the mean of triplicate was determined [1].

***Ex vivo* drug permeability**

Ex vivo drug permeation study was carried out by using Franz diffusion apparatus. Porcine buccal mucosa was mounted on a diffusion cell between the donor and receptor compartment. The mucoadhesive tablet was fixed on the mucosal membrane. One milliliter phosphate buffer pH 6.8 in the donor compartment and 50 ml of the same phosphate buffer in the receptor compartment was filled as dissolution fluid. The fluid was maintained at 37±0.5 °C and stirred continuously at very low speed i.e. 50 RPM with the help of a magnetic stirrer. The external jacket was connected with a water bath so as to maintain the temperature in the Franz diffusion cell. Aliquots of 1 ml were collected at a pre-specified time interval for 8 h, filtered through 0.45 µm membrane filter and the amount of drug was determined by measuring the absorbance of the aliquots at 240 nm using UV–VIS spectrophotometer. Pre warmed (37±0.5 °C) phosphate buffer was added to the diffusion cell after each withdrawal of the sample. The experiment was carried out in triplicate (n = 3) and the mean value was taken for the determination of ex vivo drug permeation [5].

***In vitro* release kinetic study**

The drug release data of buccal tablets were fitted to kinetics models, that is, zero order, first order, higuchi and Korsmeyer-Peppas to find out drug release pattern and mechanisms [15].

RESULTS AND DISCUSSION

Drug–excipients compatibility study by FTIR

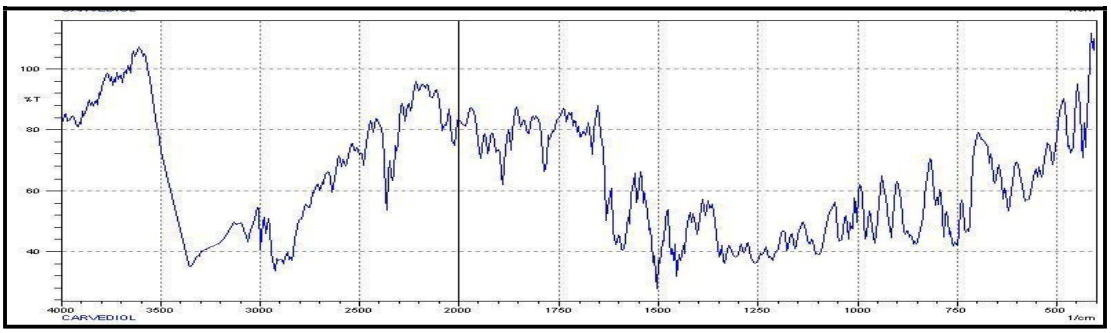

Fig. 1: IR spectra of carvedilol

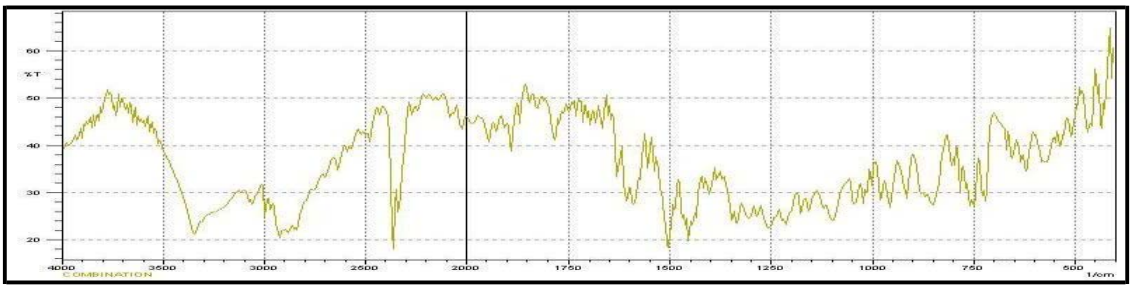

Fig. 2: IR spectra of the physical mixture (Carvedilol+Poloxamer 188+HPC+PEO)

Table 3: IR spectra peaks

S. No.	Functional group	Wave no (cm^{-1})
1	C=C stretching	1590
2	N-H stretching	3350
3	C-H stretching	3050
4	C-N stretching	1100
5	O-H stretching	3200-3300

From the IR studies, important function group IR bands of pure drug and physical mixture were identified. Characteristic IR bands of carvedilol includes the presence of peaks at 1590 cm^{-1} (C=C stretching),, 3350 cm^{-1} (N-H stretching), 3050 cm^{-1} (C-H stretching), 1100 cm^{-1}(C-N stretching) and 3200-3300 cm^{-1}(O-H stretching) which remained unaltered in IR spectrum of the physical mixture of drug and polymers. IR analysis revealed that there is no interaction between drug and polymers [14].

Characterization of solid dispersion by differential scanning calorimetry (DSC) study

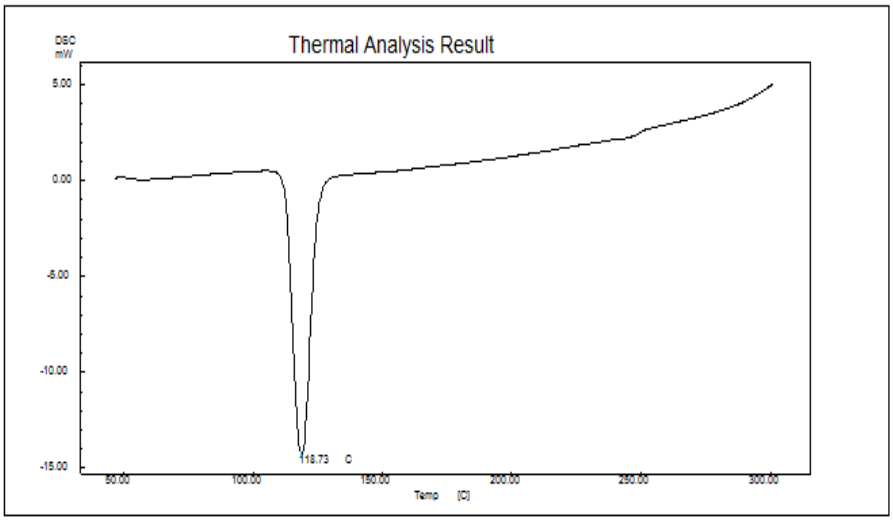

Fig. 3: DSC study of carvedilol

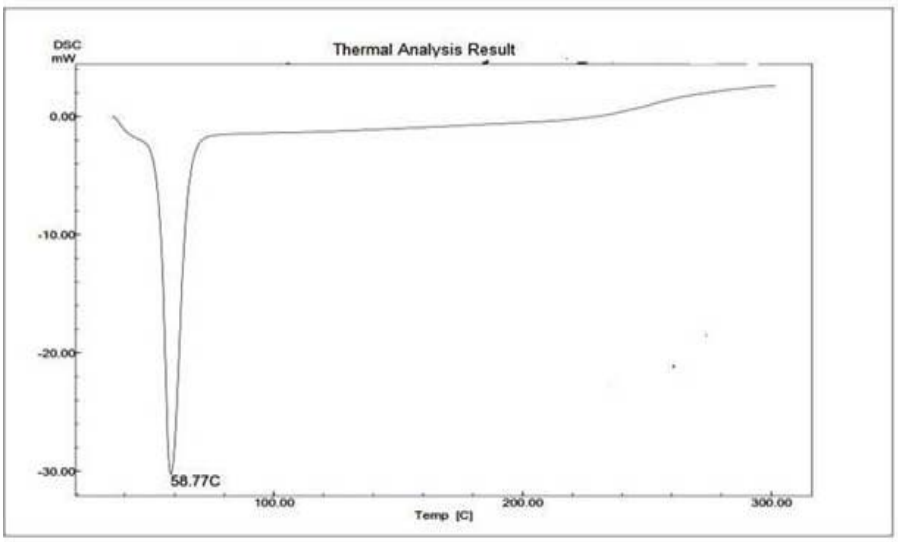

Fig. 4: DSC study of poloxamer 188

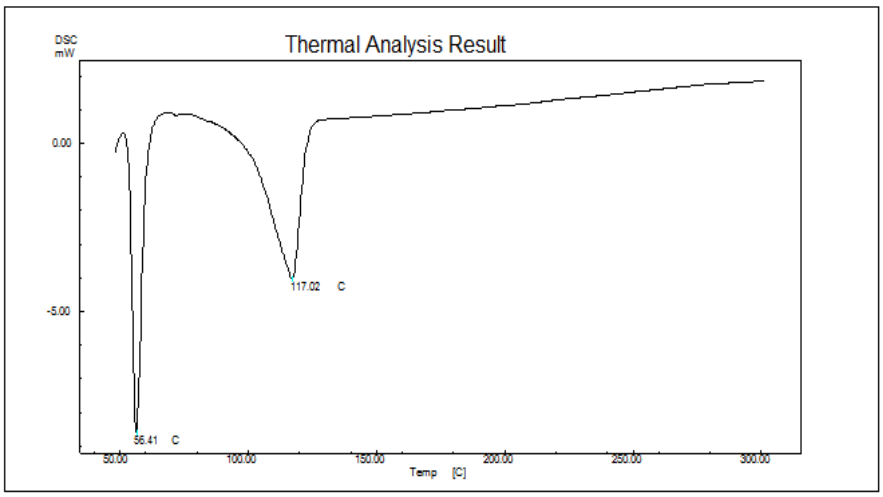

Fig. 5: DSC study of carvedilol and poloxamer-188

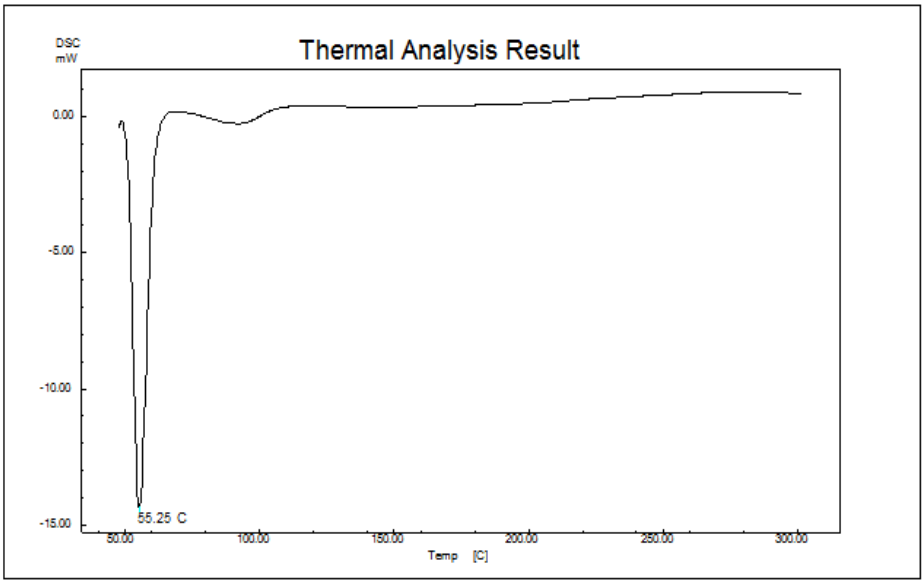

Fig. 6: DSC study of carvedilol solid dispersion

DSC analysis was employed to evaluate the phase of transformation during the formation of solid dispersions. DSC thermogram of carvedilol showed an endothermic peak at 118.73 °C, corresponding to its melting point. Poloxamer 188 showed an endothermic peak at 58.77 °C. The DSC thermogram of the physical mixture and solid dispersion showed endothermic peaks corresponding to the melting point of poloxamer 188. The intensity of carvedilol peak is decreased in the physical mixture could be explained by a lower amount of carvedilol in physical mixtures and dissolving of carvedilol in melted carriers. The absence of carvedilol's endothermic peak in case of solid dispersion suggests molecular dispersion of the drug in poloxamer 188. Thus, the crystalline drug could not be detected with DSC in these systems and converted in the amorphous state [20, 21].

Factorial design batches tablets evaluation parameters

Prepared tablets of all batches were evaluated for weight variation, hardness, thickness, % drug content and friability. Results of all batches are shown in table 4.

Table 4: Results of factorial design batches tablets evaluation

Batch code	Weight variation (mg)*	Hardness (kg/cm²)#	Thickness (mm)#	% Drug content $	% Friability $
F1	174.2±2.40	5.54±0.18	1.98±0.02	101.82±0.92	0.34±0.10
F2	175.5±1.82	5.82±0.25	2.02±0.05	101.63±1.23	0.32±0.15
F3	175.4±1.43	5.78±0.17	2.04±0.03	102.82±2.21	0.28±0.05
F4	175.8±2.12	6.21±.0.18	2.14±0.023	101.84±1.28	0.19±0.12
F5	175.4±1.54	6.43±0.15	2.03±0.024	101.92±1.92	0.17±0.05
F6	175.3±1.92	5.98±0.15	2.01±0.023	99.82±1.82	0.30±0.15
F7	175.9±1.21	6.01±0.14	1.93±0.043	100.22±1.98	0.12±0.15
F8	175.3±1.32	6.08±0.17	1.94±0.03	99.87±1.94	0.17±0.08
F9	175.8±1.83	5.79±0.20	1.92±0.01	99.54±1.90	0.28±0.05

*n=20, # n=5, $= 10. (mean±SD)

The prepared tablets were smooth and white in color. Weight variation in case of all tablets was acceptable. The weight variation in case of all the tablets was within±2.5% of theoretical tablet weight. This falls well within the acceptance criteria. Hardness value of all the formulation was in the range of 5.54-6.43 kg/cm². The prepared tablets showed in range thickness of 1.92-2.14 mm. Percentage of drug content for all formulations was found to be between 99.54% and 102.82%. Friability in case of all the designed tablets was less than 1% indicating suitability of the method used for manufacturing the tablets.

***Ex vivo* mucoadhesive strength, mucoadhesion time and surface pH**

The *ex vivo* mucoadhesive strength and mucoadhesion time of the tablets were determined for all formulations using porcine buccal mucosa, which are shown in table 5. *Ex vivo* mucoadhesive strength was found between 11.82±0.82 g to 30.28±1.09 g. Highest Mucoadhesive strength was found in batch F9. *Ex vivo* mucoadhesion time was found between 220±1.2 min to 580±2.2 min. The maximum and minimum surface pH of the formulations found to be 6.78±0.035 and 6.23±0.015, respectively. The surface pH was determined in order to investigate the possibility of any side effects, in the oral cavity as acidic or alkaline pH is bound to cause irritation to the buccal mucosa. The acceptable pH of saliva is in the range of 5 to 7. So these formulations may not produce any mucosal irritation in buccal mucosa [16, 22]. The surface pH of all the formulations is shown in table 5.

***In vitro* drug release**

The drug release of carvedilol buccal tablets was found between 101.02±2.12 to 53.14±1.34. Batch F5 showed the drug release was 96.23±2.45 after 8 h. *In vitro* release study data indicate that duration of release of drugs is dependent on the percentage of selected polymer used in the formulations. An increase in the polymer concentration not only causes increase in the viscosity of the gel but also leads to formation of gel layer with a longer diffusion path. This leads to a decrease in the diffusion of the drug and therefore a reduction in the drug release rate [22-24].

Table 5: E*x vivo* mucoadhesive strength, time and surface pH

Batch code	Mucoadhesive strength (g)	*Ex vivo* mucoadhesion time (min)	Surface pH
F1	11.82±0.82	220±1.2	6.23±0.015
F2	15.28±0.85	300±1.4	6.28±0.017
F3	16.44±0.92	440±2.3	6.34±0.015
F4	16.72±0.79	240±1.5	6.54±0.030
F5	18.20±1.44	420±2.6	6.75±0.015
F6	20.23±1.11	460±2.5	6.54±0.015
F7	24.23±1.09	470±2.5	6.57±0.005
F8	25.24±1.75	540±2.3	6.59±0.043
F9	30.28±1.09	580±2.2	6.78±0.035

*n = 3. (mean±SD)

Table 6: *In vitro* drug release

Time (h)	% Cumulative release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	35.24±1.21	31.15±1.32	28.48±1.43	30.45±2.12	28.77±1.65	25.88±1.45	25.19±1.43	21.37±1.89	17.00±1.34
2	51.52±1.67	46.24±2.56	42.42±1.56	43.82±1.32	47.54±2.56	35.65±2.67	36.43±2.12	32.2±1.56	26.22±1.32
3	68.42±1.34	63.29±2.12	54.62±1.67	62.45±1.26	59.66±1.56	50.25±1.32	42.54±1.34	41.65±1.67	32.95±1.54
4	81.4±2.12	75.5±1.34	64.78±2.12	69.24±1.52	70.52±1.32	61.45±1.34	52.65±1.52	49.52±1.72	39.69±1.32
5	97.23±2.12	90.12±1.56	75.45±1.43	85.23±1.56	84.66±1.43	65.22±2.12	63.43±1.43	56.43±	44.71±1.32
6	101.02±2.12	95.64±2.12	90.65±2.56	93.12±1.67	89.32±2.58	69.54±1.67	74.53±1.62	62.43±1.32	48.33±1.45
7	-	100.21±1.2	95.34±1.34	98.12±1.39	94.4±1.56	71.45±1.45	78.64±2.45	65.34±2.12	52.45±1.67
8	-	-	98.54±2.52	101.45±1.69	96.23±2.45	72.07±1.59	80.28±1.92	69.42±1.67	53.14±1.34

*Values are expressed as mean±SD (n=6)

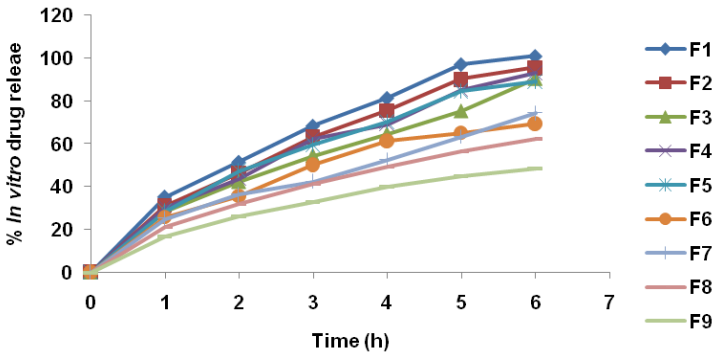

Fig. 7: *In vitro* drug release data of F1-F9 batches (n=6)

Regression analysis for the effect of X_1 (HPC) and X_2 (PEO WSR-1105) on Y_1 (*in vitro* drug release at 1 h

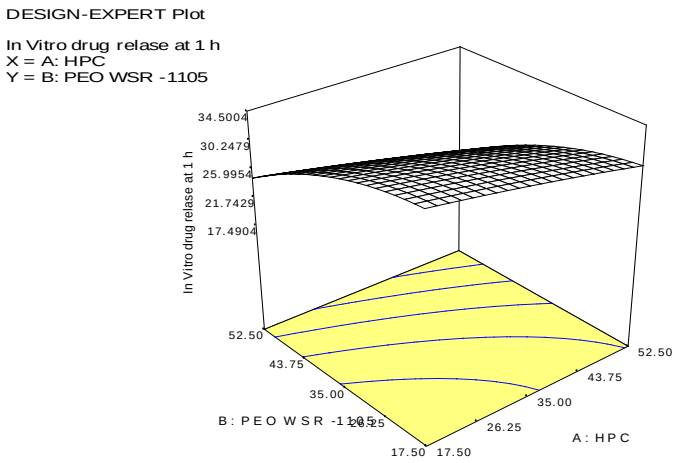

Fig. 8: Surface response plot of Y_1

Table 7: Regression analysis for Y_1 (*in vitro* drug release at 1 h)

Regression statistics Y_1		
R Square	0.9864	
Adjusted R square	0.9767	
Source		
Source	**Sum of squares**	**P-value**
Model(Quadratic)	244.73	<0.0001
X_1	63.51	<0.0001
X_2	165.48	<0.0001
X_1X_2	0.51	0.3376
$X1^2$	0.18	0.5593
$X2^2$	11.43	0.0017

Full model equation

$$Y_1 = 28.67-3.25X_1-5.25X_2-0.36X_1X_2-0.26X_1^2-2.06\ X_2^2 \ldots\ldots (1)$$

Reduced model equation on the basis of p value

$$Y_1 = 28.67-3.25X_1-5.25X_2--2.06\ X_2^2 \ldots\ldots (2)$$

Higher values of correlation coefficients for drug release at 1 h indicate a good fit. The polynomial equations can be used to draw conclusions after considering the magnitude of the coefficient and the mathematical sign it carries. Here p-Value for X_1 and X_2 was less than 0.05. So HPC and PEO WSR-1105 both had a significant effect on % cumulative drug release. HPC and PEO had a negative effect on % cumulative release so it was concluded that % drug release decreased with an increase the concentration of HPC and PEO WSR-1105. The coefficients b_1, b_2 and b_2^2 were found to be significant at p is less than 0.05 and thus, were retained in the reduced model equation [17, 25]. Here b_2 value is more negative than b_1, which indicated that PEO had more release retardant effect compare to the HPC at 1 h.

Regression analysis for the effect of X_1 (HPC) and X_2 (PEO WSR-1105) on Y_2 (*in vitro* drug release at 4 h

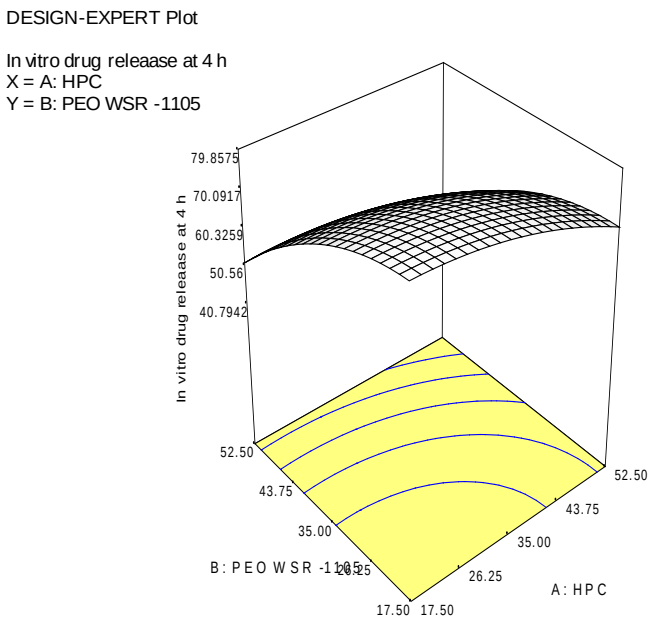

Fig. 9: Surface response plot of Y_2

Table 8: Regression analysis for Y_2 (*in vitro* drug release at 4 h)

Regression statistics Y_2		
R Square	0.9877	
Adjusted R square	0.9788	
Source		
Source	**Sum of squares**	**P-value**
Model (**Quadratic)**	1525.08	<0.0001
X_1	232.75	<0.0001
X_2	1061.87	<0.0001
X_1X_2	3.35	0.3040
$X1^2$	34.76	0.0092
$X2^2$	112.15	0.0004

Full model equation

$$Y_2 = 69.32-6.23X_1-13.30X_2+0.91X_1X_2-3.54X_1^2-6.37X_2^2 \text{ ..... (3)}$$

Reduced Model Equation on the basis of p value

$$Y_2 = 69.32-6.23X_1-13.30X_2-3.54X_1^2-6.37X_2^2 \text{ ..... (4)}$$

Higher values of correlation coefficients for drug release at 4 h indicate a good fit. The polynomial equations can be used to draw conclusions after considering the magnitude of the coefficient and the mathematical sign it carries. Here p-Value for X_1 and X_2 was less than 0.05. So HPC and PEO WSR-1105 both had a significant effect on % cumulative drug release. HPC and PEO WSR-1105 had a negative effect on % cumulative release so it was concluded that % drug release decreased with an increase the concentration of HPC and PEO WSR-1105. The coefficients b_1, b_2, $b_1^2$and b_2^2 were found to be significant at p is less than 0.05 and thus, were retained in the reduced model equation [17, 25]. Here b_2 value is more negative than b_1, which indicated that PEO had more release retardant effect compare to the HPC at 4 h.

Regression analysis for the effect of X_1 (HPC) and X_2 (PEO WSR-1105) on Y_3 (mucoadhesive strength)

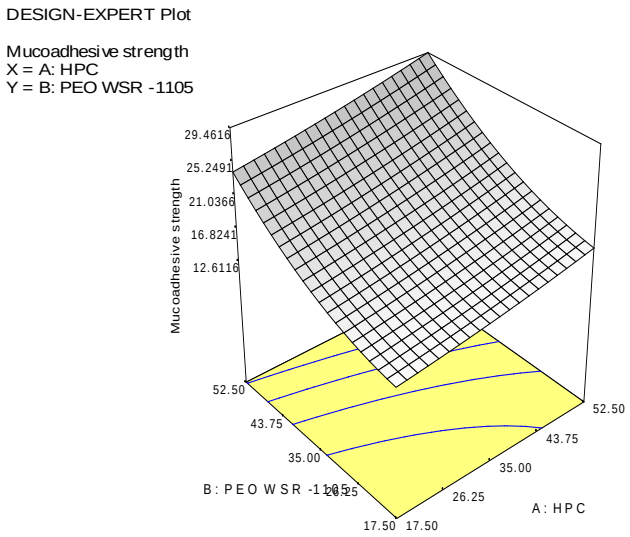

Fig. 10: Surface response plot of Y_3

Table 9: Regression analysis for Y_3 (mucoadhesive strength)

Regression statistics Y_3		
R Square	0.9851	
Adjusted R square	0.9744	
Source		
Source	**Sum of squares**	**P-value**
Model (Quadratic)	271.79	<0.0001
X_1	33.51	0.0001
X_2	220.46	<0.0001
X_1X_2	0.51	0.3826
$X1^2$	0.27	0.5205
$X2^2$	13.09	0.0022

Full model equation

$$Y_3 = 18.19+2.36X_1+6.06X_2+0.36X_1X_2+0.31X_1^2+2.18X_2^2 \text{ (5)}$$

Reduced Model Equation on the basis of p value

$$Y_3 = 18.19+2.36X_1+6.06X_2+2.18X_2^2 \text{(6)}$$

Higher values of correlation coefficients for mucoadhesive strength indicate a good fit. Here p-Value for X_1 and X_2 was less than 0.05 so HPC and PEO WSR-1105 both had a significant effect on mucoadhesive strength (Y_3). HPC and PEO WSR-1105 had a positive effect on mucoadhesive strength. This may be due to fact that positive charges on the surface of HPC and PEO WSR-1105 could give rise to strong electrostatic interaction with mucous or negatively charged mucous membranes. In equation (5) show that PEO WSR-1105 (X_2) had higher positive value than HPC (X1). So, it was concluded that PEO WSR-1105 has more superior mucoadhesive property compare to HPC. This can be attributed due to higher flexibility of polymeric chains of PEO resulting in better interaction with mucins [16, 23].

Table 10: Regression analysis for Y_4 (mucoadhesion time)

Regression statistics Y_4		
R Square	0.8941	
Adjusted R square	0.8730	
Source		
Source	**Sum of squares**	**P-value**
Model (Linear)	1166000	<0.0001
X_1	50416.67	0.0001
X_2	66150	<0.0001

Regression analysis for the effect of X_1 (HPC) and X_2 (PEO WSR-1105) on Y_4 (mucoadhesion time)

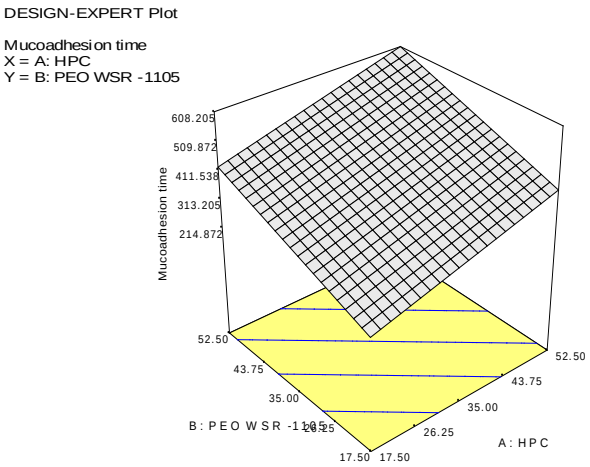

Fig. 11: Surface response plot of Y_4

Full model equation

$$Y_4 = 411.54+91.67X_1+105.00X_2 \ldots\ldots (7)$$

Here p-Value for X_1 and X_2 was less than 0.05 so HPC and PEO WSR-1105 both had a significant effect on Mucoadhesive time (Y_4). Above equation (7) showed that HPC and PEO WSR-1105 had a positive effect on mucoadhesive time but PEO WSR-1105 (X_2) has a higher positive value than HPC (X1) so it was concluded that mucoadhesive time increased with an increase the concentration of PEO WSR-1105 compare to HPC.

Validation of design model by checkpoint batches

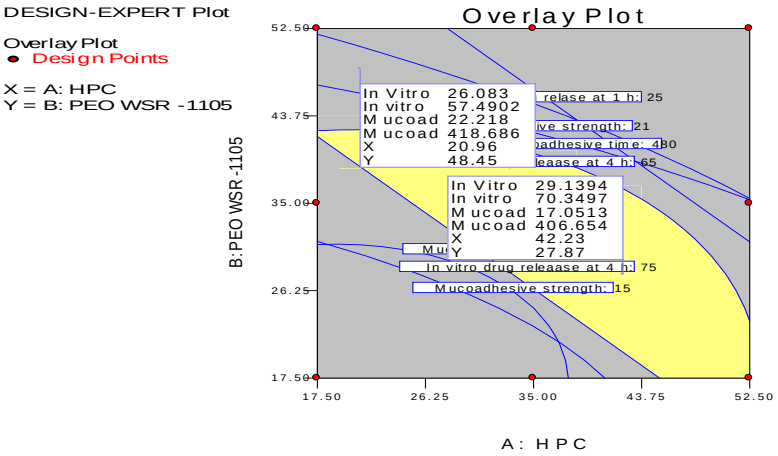

Fig. 12: Overlay plot of response variables

Preparation of checkpoint batches from overlay plot

Checkpoint batch C1 and C2 were selected from the overlay plot of responses. The amount of HPC and PEO WSR-1105 and according to their amounts, the predicted responses were given in the Overlay plot flag or in the solution of overlay data. From that, any two batches C1 and C2 were selected for the verification of the model [17].

Table 11: Formulation for checkpoint batch

Ingredients	Quantity taken (mg)	
	C_1	C_2
Carvedilol solid dispersion equivalent to 6.25 mg carvedilol	18.75	18.75
HPC	20.96	42.23
PEO WSR-1105	48.45	27.87
PVP K30	10	10
Aspartame	1	1
Pearlitol 200 SD	68.84	68.15
Magnesium Stearate	3.5	3.5
Aerosil	3.5	3.5
Total (mg)	175	175

Table 12: Validation of model by comparing predicted response to actual response

Predicted response and the actual response of checkpoint batch						
Evaluation parameters	**Batch C1**			**Batch C2**		
	Predicted value	**Actual value**	**% Error**	**Predicted value**	**Actual value**	**% Error**
% drug release at 1 h	26.083%	27.18%	4.20%	29.1394%	28.75%	1.33%
% drug release at 4 h	57.49%	58.89%	2.43%	70.349%	69.10%	1.77
Mucoadhesive strength	22.218 gm	21.5 gm	4.59%	17.051 gm	16.4 gm	3.81%
Mucoadhesion time	418.686 min	422 min	0.79%	406.654 min	400 min	1.63%

Actual response of C1 and C2 batch was measured and compared with the predicted response of checkpoint batch. % error was found to be less than 5 of all the responses. Hence, this model was valid and an optimized batch can be selected from the overlay plot of this model.

Optimized batch from overlay plot

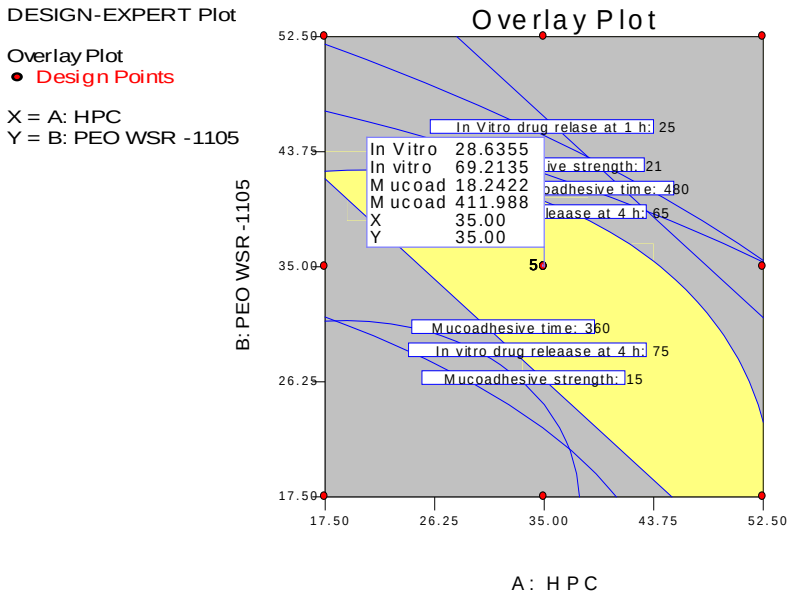

Fig. 13: Optimized batch from overlay plot

The contour plots are evolved for each response, which divides the plot surface into a desirable and not desirable zone. A contour for each response is then superimposed to locate the area where the targets for the all response are achieved. Here in above fig. 13 shows the yellow area was the optimized area and Batch F5 was fall in the yellow region [15].

***Ex vivo* permeation study**

Optimized batch was selected for the *ex vivo* permeation study. The buccal mucosa of pigs resembles that of humans more closely than any other animal in terms of structure and composition and therefore, porcine buccal mucosa was selected for drug permeation studies. The drug permeation slow and 83.24 % of carvedilol permeated through buccal mucosa after 8 h [26]. The result of *ex vivo* permeation study is shown in table 13.

***In vitro* release kinetic study**

Dissolution profiles were fitted to various model and release data were analyzed on the basis of Koresmeyer-Peppas, zero order, first order and higuchi models. The best fit model was selected on the basis of R^2 values. Thus, it may be concluded that from the above data Korsmeyer-Peppas model was followed by formulation n value between 0.5-0.85, which showed that anomalous (non-Fickian) diffusion [27]. The *in vitro* release kinetic data is shown in table 14.

Table 13: *Ex vivo* permeation study

Time(h)	Cumulative % drug permeated
1	20.32±1.22
2	32.63±2.14
3	44.23±2.13
4	51.36±1.68
5	60.24±1.80
6	70.15±2.10
7	77.25±2.37
8	83.24±2.30

*Values are expressed as mean±SD (n=3)

Table 14: *In vitro release* kinetic study

Batch code	Zero order	First order	Higuchi	Korsmeyer-peppas	
	R^2	R^2	R^2	R^2	n
F1	0.9497	0.9380	0.9668	0.9912	0.611913
F2	0.9432	0.9540	0.9655	0.9872	0.628234
F3	0.9542	0.8064	0.9618	0.9899	0.621277
F4	0.9338	0.9532	0.9705	0.9843	0.607026
F5	0.9543	0.9830	0.9747	0.9932	0.592808
F6	0.8629	0.9051	0.9470	0.9492	0.526823
F7	0.9488	0.9692	0.9599	0.9826	0.589123
F8	0.9287	0.9564	0.9876	0.9939	0.576665
F9	0.9158	0.8715	0.9872	0.9895	0.562149

CONCLUSION

The mucoadhesive buccal tablets of carvedilol were successfully prepared by direct compression techniques using polymer like HPC and PEO WSR-1105 to avoid the first-pass metabolism. Solubility of carvedilol was improved by solid dispersion technique using poloxamer 188. From all Parameters and experimental design evaluation, it was concluded that the drug release rate decreased with an increase the concentration of HPC and PEO WSR-1105. Here PEO had a more significant effect in mucoadhesive property of tablet compare to HPC. So, mucoadhesion time and mucoadhesive strength of formulation was increased with increasing the concentration of PEO WSR-1105. The *in vitro* release kinetics revealed Korsmeyer-Peppas model is followed and drug release is by anomalous diffusion.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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