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Formulation Optimization Of Mucoadhesive Buccal Tablets Of Carvedilol Using 3^2 Full Factorial Design

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Abstract

In present work attempt has been made to investigate the effect of two independent variables, concentration of HPMC K4M (X_1) and concentration of Carbopol 934p (X_2) at three different levels (-1, 0, +1) on parameters like percent drug released ($t_{50\%}$) and ($t_{70\%}$) and swelling index (after 06 hours) using 3^2 full factorial design. The conformity of derived polynomial equations was checked by preparing two check point formulations, C_1 and C_2. Good agreement was observed between predicted and observed profile for optimized formulation F_1. Majority of designed formulations displayed nearly zero order release kinetics releasing 70-80% drug in 8 hours. Optimized formulation F_1 exhibited 107.20% drug release in 10 hours, which provides zero order release kinetics hence considered for improved bioavailability of carvedilol. Short term stability studies of optimized formulation F_1 indicate that there

were no significant changes in drug content and dissolution parameters values after three weeks and when stored at 45± 1ºC. FTIR results showed no evidence of interaction between the drug and polymers. XRD study revealed that drug is in crystalline form in the polymer matrix. 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.

Keywords

Buccal tablets, carvedilol, hydroxypropyl methylcellulose (HPMC) K4M and carbopol 934P, factorial design

Introduction

Substantial efforts have recently been focused on giving the drug transmucosally to avoid rapid hepatic metabolism and there by increasing the bioavailability of drug.[1] Drug delivery via, the membranes of the oral cavity is traditionally divided into three categories buccal, sublingual and local delivery.[2,3] Different types of buccal formulations are buccal patches, tablets, gels etc. [4,5,6,7]

Carvedilol is non-selective β-adrenoceptor blocking agents used in treatment of hypertension and stable angina pectoris. It has low bioavailability of 25% due to extensive hepatic metabolism and elimination half–life of 6-10 hours. Hence need to be administered twice daily. Therefore, it is selected as suitable drug for the design of mucoadhesive buccal tablet with a view of improve its oral bioavailability and patient compliance.[8, 9, 10]

In present work, an attempt has been made to formulate buccal tablet of carvedilol using hydroxypropyl methylcellulose and carbopol. Optimization of designed buccal tablet will be performed using 3^2 full factorial experiments to evaluate all nine batches of carvedilol buccal tablet. The validity of derived polynomial equation for dependent variables will be verified by designing and evaluating two extra check point formulations.

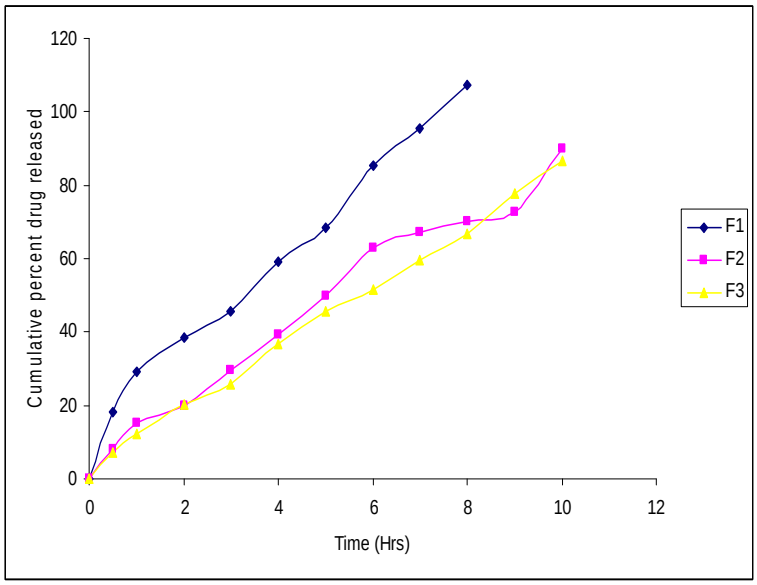

Figure 1:- Cumulative percent drug released Vs Time Plots of Formulations F_1, F_2 and F_3

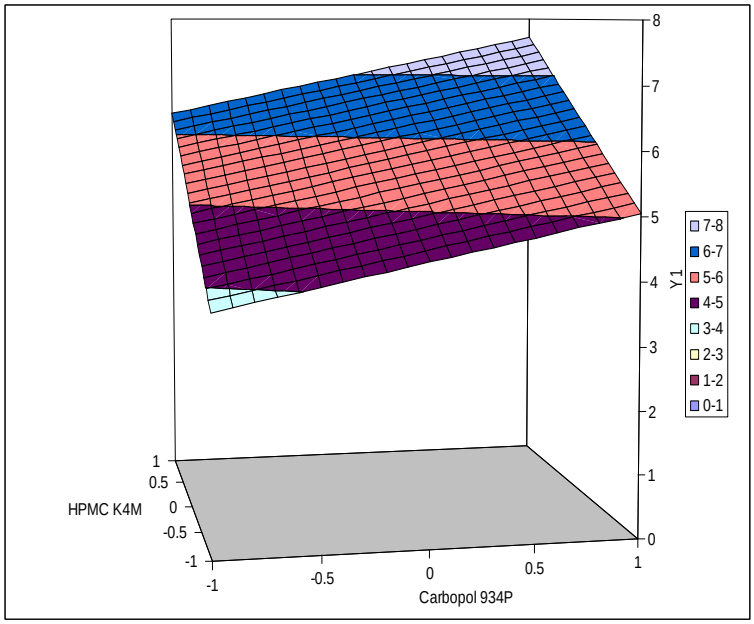

Figure -2: Response surface plot showing effect of variables on $t_{50\%}$

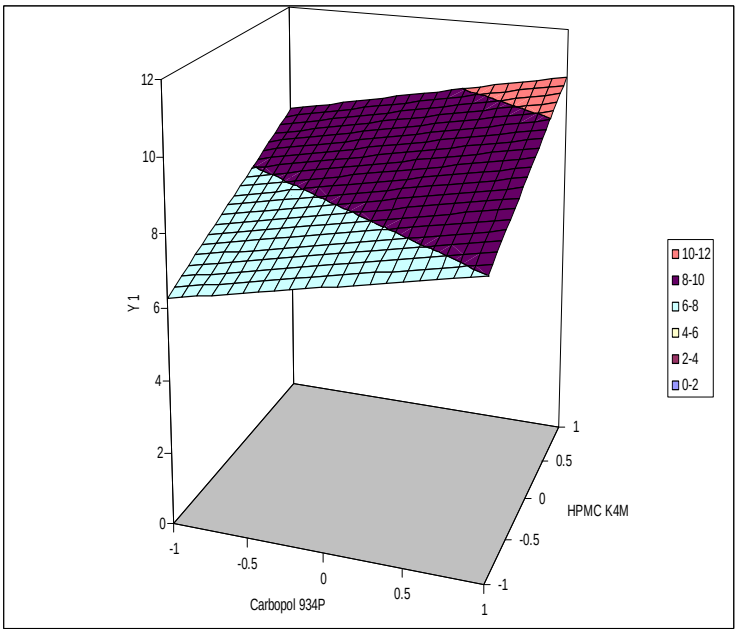

Figure -3: Response surface plot showing effect of factorial variables on $t_{70\%}$

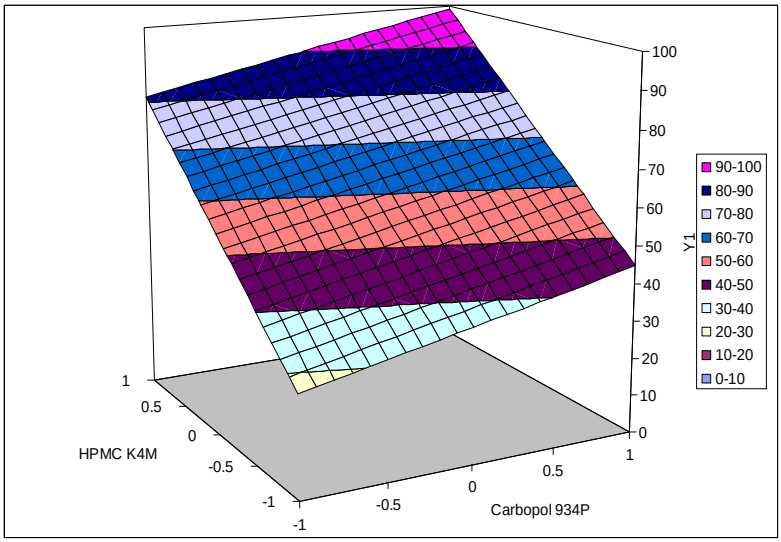

Figure -4: Response surface plot showing effect of factorial variables on SI

Table 1-: Preliminary trial of buccal tablets of carvedilol

Formulation code	HPMC K4M (mg)	Carbopol 934P (mg)	$t_{50\%}$ (hours)	$t_{70\%}$ (hours)	SI (after 6 h)	Cumulative percent drug release in 10 h
T_1	10	-	0.6 min	0.9 min	19.28	98.46
T_2	20	-	0.6 min	1.6	46.64	100.20
T_3	-	10	1.7	3.4	21.13	87.84
T_4	-	20	3.2	4.8	50.17	96.68
T_5	30	10	6.3	9.3	78.81	73.40
T_6	20	20	7.6	9.9	82.35	70.85
T_7	10	30	5.7	9.3	86.44	75.68

Total weight of each tablet:- 150mg, carvedilol:- 12.5mg, talc:- 1mg, magnesium stearate:- 1mg, lactose(DC):- filler(q.s.).

Table 2:- 3^2 full factorial Design Batches

Formulation code	Variable level in coded form		$t_{50\%}$ (hours)	$t_{70\%}$ (hours)	SI (after 6 hours)	Cumulative percent drug release in 10 h
	X_1	X_2				
F_1	-1	-1	3.4	5.5	21.78	107.20
F_2	-1	0	4.3	6.9	33.37	90.08
F_3	-1	+1	5.4	8.3	47.36	86.60
F_4	0	-1	5.8	8.5	58.50	73.44
F_5	0	0	5.8	8.9	64.00	71.04
F_6	0	+1	5.9	9.3	75.56	68.49
F_7	1	-1	6.2	8.8	82.35	69.94
F_8	1	0	6.9	9.4	89.47	67.51
F_9	1	+1	7.8	10.4* (extrapol.)	93.87	63.71
C_1	-0.5	-0.5	5.1	7.9	45	72.72
C_2	+0.5	+0.5	6.7	9.9* (extrapol.)	81.7	63.00

C_1, C_2 check point batches
$t_{50\%}$, $t_{70\%}$, swelling index analyzed by matrix model fitting using PCP disso V3 Software
*For HPMC K4M (X_1) transformed levels in mg are: -1 = 10, '0' = 20, + 1 = 30, - 0.5 = 15, + 0.5 = 25
For carbopol 934P (X_2) transformed level in mg are: -1= 5, '0' = 10, +1=15, -05 =7.5 + 0.5 = 12.5

Materials and Methods

Materials: Carvedilol was obtained as gift sample from Inogent labs, Hydrerabad. HPMC K4M donated by colorcon Asia Ltd. Goa. Corbopol 934P, Lactose DC, Magnesium stearate, talc were obtained from SD fine chem. Mumbai.

Preparation of Mucoadhesive tablets:

Preparation: Direct compression method has been employed to prepare buccal tablet with HPMC K4M and carbopol 934P as polymers.

Procedure: All the ingredients were accurately weighed and passed through mesh # 60. In order to mix all ingredients thoroughly drug, polymers, lactose DC were blended geometrically in mortar and pestle for 10 minutes then talc, magnesium stearate were mixed one by one for 1-2 min. tablets were compressed on Clit pilot press machine. The prepared tablets were coated with white bees wax from three sides as an impermeable layer.

Hardness test: The crushing strength (Kg/cm^2) tablets were determined by using Monsanto hardness tester. The results are given in table 3.

Table 3:- Evaluation of factorial design formulations

Formulation code	Mean Hardness Kg/cm^2	Friability % w/w	Average weight (mg)	Mean drug content % ± SD	SI ± SD (after 6 hrs)	Mucoadhesion (time of detachment hrs)
F_1	4.42	0.52	148.51	96.90 ± 1.56	21.78	>12
F_2	4.67	0.65	141.37	97.48 ± 1.08	33.37	>12
F_3	4.38	0.67	156.64	94.90 ± 0.81	47.36	>12
F_4	4.49	0.51	147.37	95.77 ± 0.08	58.50	> 12
F_5	4.66	0.63	148.87	95.14 ± 1.35	64	> 12
F_6	4.54	0.68	158.19	93.44 ± 0.68	75.56	> 12
F_7	4.69	0.53	153.96	96.09 ± 2.13	82.35	>12

F_8	4.62	0.50	143.54	97.18 ± 0.87	89.47	>12
F_9	4.32	0.61	140.98	95.87 ± 0.15	93.87	> 12
C_1	4.12	0.64	157.56	96.33 ± 1.88	45	>12
C_2	4.58	0.66	160.08	96.68±2.56	81.70	>12

Friability test: This was determined by weighing 10 tablets after dusting, placing them in the friabilator and rotating the plastic cylinder vertically at 25 rpm for 4 min. After dusting, the total remaining weight of the tablets was recorded and the percent friability was calculated according to:

$$\text{Percent friability} = \frac{\text{Weight}_{\text{final}} - \text{Weight}_{\text{original}}}{\text{Weight}_{\text{original}}} \times 100$$

The results are given in table 3.

Uniformity of weight: The weight (mg) of each of 20 individual tablets was determined by dusting each tablet off and placing it in an electronic balance. The weight data from the tablets were analyzed for sample mean and percent deviation. The results are summarized in table 3.

Uniformity of drug content: 5 tablets were powdered in a glass mortar and the powder equivalent to 50 mg of drug was placed in a stoppered 100 ml conical flask. The drug was extracted with 40 ml methanol with vigorous shaking on a mechanical gyratory shaker (100 rpm) for 1 hour. Then heated on water bath with occasional shaking for 30 minutes and filtered into 50 ml volumetric flask through cotton wool and filtrate was made up to the mark by passing more methanol through filter, further appropriate dilution were made and absorbance was measured at 242.5nm against blank (methanol).

Mucoadhesion study: The mucoadhesive performance of the buccal tablets was evaluated using sheep buccal tissue obtained from slaughter house. The fresh cut sheep buccal tissue was fixed on the side of the beaker with glue. Before addition of the buffer, the tablet was attached to sheep buccal tissue by applying light force with finger tip for 20 seconds. The beaker was then filled with 800ml of phosphate buffer and was kept at 37^0C. A stirring rate of 150 rpm was used to simulate buccal and saliva movement. The attachment of tablet was monitored until 24 hours. The time for tablet to detach from the sheep buccal tissue was recorded as the mucoadhesion time.

Tablet hydration study: [11] The tablet hydration studies were carried out in beaker with phosphate buffer (pH 6.8). Periodically, the tablets were withdrawn from the beaker and weighed on electronic balance after removal of surface water by light

blotting with a lab tissue. The sampling times of hydration studies were 0.5, 1, 2, 4, 6, 8, 12 and 24 hours. The rate of hydration was calculated according to the model describing the absorption of liquid into polymeric matrices via diffusion.

***In vitro* dissolution studies:**[12] *In vitro* dissolution studies of buccal tablets of carvedilol were carried out in USPXXIII tablet dissolution test apparatus-II (Electrolab), employing a paddle stirrer at 50 rpm using 900ml of 0.5% w/v SLS solution at 37 ±0.5°C as dissolution medium. One tablet was used in each test. At predetermined time intervals 5ml of the samples were withdrawn by means of a syringe fitted with a pre filter. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium maintained at 37±0.5°C. The samples were analyzed for drug release by measuring the absorbance at 242.5nrn using UV-Visible spectrophotometer after suitable dilutions.

FTIR and XRD study: The buccal tablets of optimized formulation F_1 were compressed and powdered. The palletized powder was used for FTIR studies. PXRD studies were performed on samples of polymers used and optimized formulation F_1.

Stability study: Short – term stability studies were performed at a temperature of 45° ± 1°C over a period of three weeks (21 days) on the promising buccal tablets of carvedilol formulation F_1. Sufficient number of tablets (15) were packed in amber colored screw capped bottles and kept in stability chamber maintained at $45^0 \pm 1^0$C. Samples were taken at weekly intervals for drug content estimation. At the end of three weeks period, dissolution test and drug content studies were performed to determine the drug release profiles and drug content. The data of drug content and dissolution studies are shown in tables 4 and 5.

Table - 4: Drug content Data of Stability Formulation (F_1)

Trial No.	1st Day (%)	7th day (%)	14th Day (%)	21st Day (%)
I	96.87	96.81	96.73	96.38
II	98.15	98.07	97.95	97.90
III	95.51	95.48	95.45	95.41
Mean $(\overline{X})$	96.84	96.78	96.71	96.56
SD	1.32	1.29	1.25	1.25

Table - 5: *In vitro* Release Data of the Stability Formulation (F_1)

Time (Hrs)	Cumulative* Percent Drug Released ± SD at 45 ± 1^0C

	1st Day	21st Day
01	18.04±0.47	17.35±1.25
02	29.08±0.68	28.15±0.97
03	38.24±0.67	36.69±0.08
04	45.67±0.53	43.19±0.42
05	59.08±0.91	58.38±0.76
06	68.36±0.80	65.26±0.58
07	85.17±0.44	83.48±0.90
08	95.50±0.28	92.67±0.84
09	107.20±0.14	104.73±1.58

*Average of three determinations

Result and Discussion

Hardness, Friability and Weight variation: The buccal tablets of carvedilol were evaluated hardness, friability and Weight variation. The hardness of tablets was found to be in the range of 4.12 to 4.69 kg/cm^2.The friability of tablets was less than 1% that is in the range of 0.50 to 0.68%. Hardness and Friability of optimized formulation was 4.42 kg/cm^2 and 0.52% respectively. Average weight of it was 148.51g (Table 3).

Drug content uniformity: The Drug content of all factorial formulations was found to be in the range of 93.44- 97.48% with SD of 0.08- 2.56%. Formulation F_1 recorded mean drug content of 96.90± 1.56%.

Mucoadhesion and Tablet hydration study: Mucoadhesion of tablet was found to be increased with increase in polymer content. Formulation F_1 showed mucoadhesion time greater than 12 hours. A tablet hydration study gives indication relative moisture absorption capacities of polymers and whether formulation maintains their integrity after moisture absorption. Swelling index calculated using this data. It was found to be increasing with increase in polymer concentration. Swelling index of F_1 after 6 hours was found to be 21.78.

3^2full Factorial Design: Optimization of formulations has been done by using 3^2 full factorial design after evaluating seven trial batches (T_1 to T_7).

In this study, two factors were evaluated each at three levels, and experimental trials were performed at all nine possible combinations. The amount of HPMC K4M(X_1) and amount of carbopol 934P(X_2) were selected as independent variables. Polynomial equations were derived for $t_{50\%}$, $t_{70\%}$ and swelling index (after 6 hou.) values by backward stepwise linear regression analysis using PCP Disso 2000 V3 software. Validity of derived equation was verified by preparing two check point formulations of intermediate concentrations (C_1 and C_2)[13, 14].

Polynomial equation for 32 full factorial designs is:

$$Y= b_0+b_1 X_1+b_2X_2+b_{12}X_1X_2+b_{11}X_1^2+b_{22}X_2^2 \quad \text{.....1}$$

Where Y is dependent variable, b_0 arithmetic mean response of nine batches, and b_1 estimated coefficient for factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction term (X_1X_2) shows how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity.

The equation derived for $t_{50\%}$ is:

$$Y_1=5.6889+1.3000X_1+0.6667X_2 \quad \text{…2}$$

The equation derived for $t_{70\%}$ is:

$$Y_2=8.4444+1.3167X_1+0.8667X_2 \quad \text{...3}$$

The equation derived for swelling index is:

$$Y_3 = 62.9178 + 27.1967X_1 + 9.0267 X_2 \quad \text{…4}$$

***In-Vitro* Drug Release Kinetics:** *In vitro* drug release data of all the buccal tablets of carvedilol formulations was subjected to goodness of fit test by linear regression analysis according to zero order equations, Higuchi's and Korsmeyer-Peppas models to ascertain the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in table 6.

Table 6:-Kinetic Data of Optimized Formulation

Batch		**Zero Order**	**First Order**	**Higuchi's Equation**	**Peppas Equation**
F_1	r	0.9971	-0.9004	0.9799	0.9817

	a	13.73	2.187	-16.73	1.4109
	b	11.58	16.265	40.966	0.6428

From the study it can be seen that in trial formulations except formulation T_1, T_2 and T_3 all the trial formulations containing combination of polymers HPMC and carbopol have displayed zero order release kinetics ('r' values in the range of 0.990 to 0.993). From Higuchi's and Peppas data, it is evident that the drug is released by non-Fickian diffusion mechanism (n=0.758 to 0.82) except formulation containing HPMC and carbopol alone. From the kinetic data of factorial formulations (table 6), it is evident that all the formulations have shown drug release by zero order kinetics.

The values of 'r' for Higuchi's equation of factorial formulations range from 0.961 to 0.998 and those of 'n' values of Peppas equation range from 0.632 to 0.911. This data reveals that drug release follows non-Fickian diffusion mechanism.

FTIR and XRD study: FTIR results showed no evidence of interaction between the drug and polymers. XRD study revealed that drug is in crystalline form in the polymer matrix.(Figure 5 and 6)

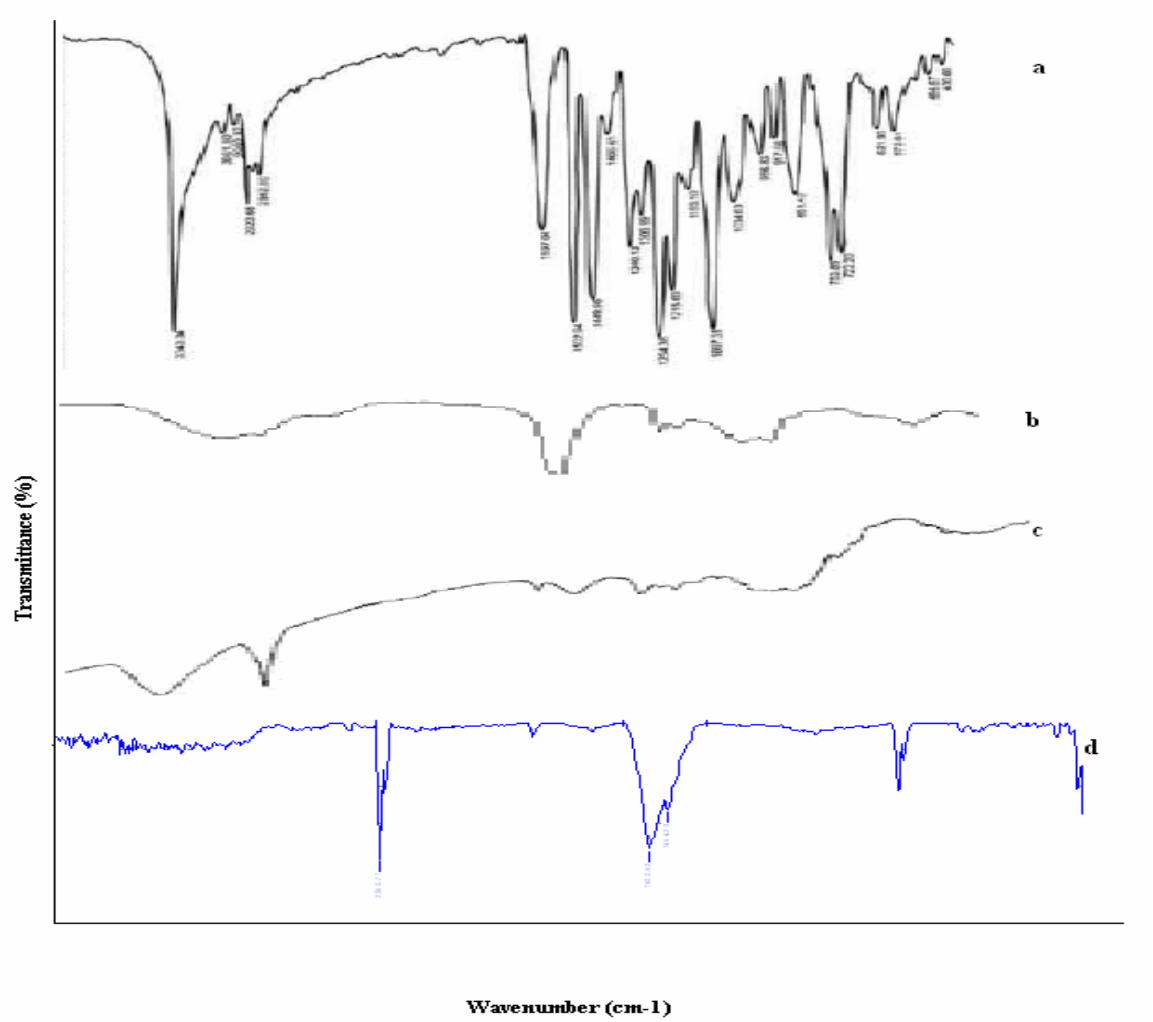

Figure 5: FTIR showing a- Carvedilol, b- Carbopol 934p, c- HPMC K4M, d- Optimized formulation F_1

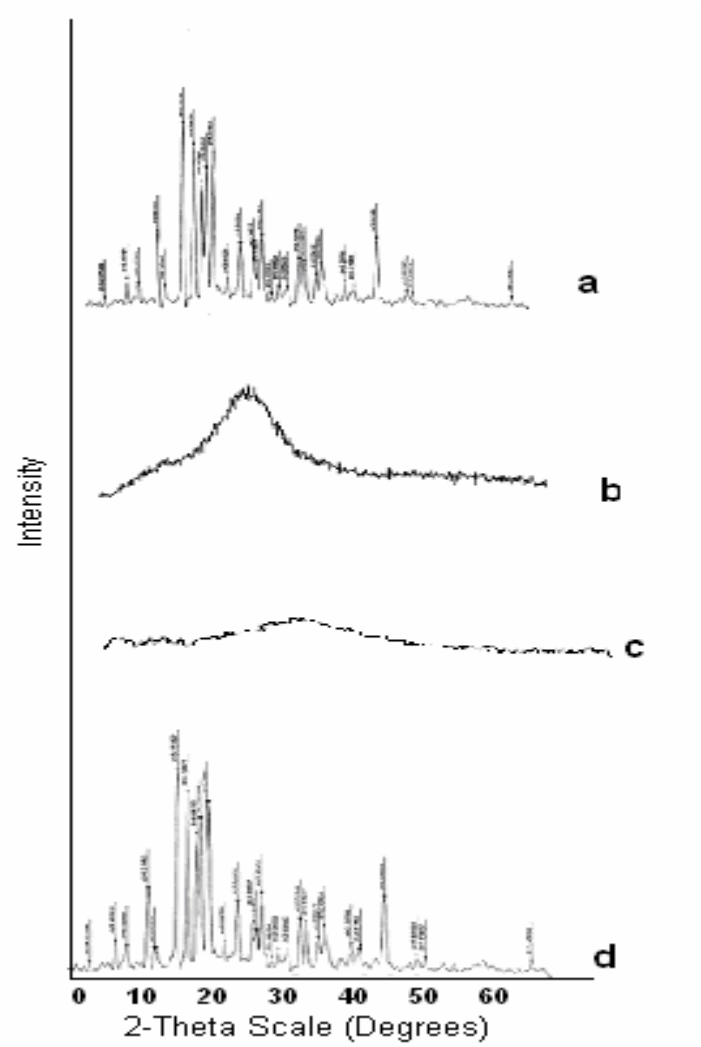

Figure 6: XRD showing a- Carvedilol, b- HPMC K4M, c- Carbopol 934p, d- Optimized Formulation F_1

Stability study: Short-term stability studies of optimized formulation F_1 indicate, that there are no significant changes in drug content and dissolution parameters values after 3 weeks and when stored at 45 $\pm 1^0$C.

CONCLUSION

This study proves BDDS of carvedilol can be prepared with HPMC K4M and carbopol 934P, which provides zero order release kinetics and thus bypasses hepatic metabolism with possibility of increased bioavailability of drug.

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