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Research Article

Formulation, optimization and evaluation of controlled release matrix tablets of Carvedilol using response surface methodology

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ABSTRACT

The modified release matrix dosage form is preferred in order to avoid fluctuations in the blood levels, which was observed in the drug Carvedilol. The objective of the present research was to formulate a controlled release matrix dosage form of Carvedilol, a potent therapeutic agent for cardiovascular disease, which primarily reduce the occurrence of steep rises in plasma concentration of drug, by using different polymers to achieve better bioavailability and also to reduce dosing frequency and side-effects employing response surface methodology by incorporating a 3-factor, 3-level Box-Behnken statistical design using direct compression technique. Dependent variables are the release retardant polymers such as HPMC K15M (X1), Ethyl cellulose (X2), and Sodium carboxy methyl cellulose (X3) and Independent variables are the percentage drug release at 24 h (Y1), drug content (Y2) and regression analysis (Y3) were studied. Box-Behnken response surface plots were drawn, statistical validity of the second order and quadratic models were established and the optimized formulations was chosen based on feasibility and grid search. The physical evaluation and *in-vitro* release studies were performed and the data were fitted to different release kinetic equations such as Zero order, First order, Higuchi and Korsemeyer-peppas in terms of r^2 and n-value. Validation of the optimization study with 17 confirmatory runs indicated high degree of prophetic ability of response surface methodology. From the confirmatory runs, the optimized formulation showed gradual controlled release (best fit model–Zero order, n=4.029) by Super case - 2 transport process**.** This design facilitated optimization of Carvedilol controlled release matrix dosage form to achieve better bioavailability.

Key words : *Carvedilol, Controlled release, Response surface methodology, Box-Behnken design, Responses.*apoptosis.

INTRODUCTION

Despite of the advancements in other drug delivery systems, oral sustain/controlled release drug delivery systems is dominating the market and have an increased safety and patient compliance. By the controlled release method, a sufficient amount of drug is initially made available to the body to cause a desired pharmacological response. The remaining fraction is released periodically and is required to maintain the maximum initial pharmacological activity for some desirable period of time in excess of time expected from usual single dose[1].

To control the release of drug from a controlled release dosage forms, polymers are used, which release the drug in a slow and nearly constant manner to obtain nearly constant peak plasma level[2]. At lowest concentrations of the HPMC and EC, compressed matrices showed increased drug release initially. This is due to decrease in hydrated gel layer formation, but at the high concentration of HPMC and EC initially tablet shows increased in the diffusion layer formation probably due to the increased concentration of HPMC followed by erosion of tablet was observed[3.] In this study, an effort has been made to formulate controlled release matrix tablets of Carvedilol, a nonselective beta-adrenergic blocking agent with alpha1-blocking activity and is indicated for the treatment of hypertension and mild or moderate heart failure[4] using different hydrophilic and hydrophobic polymers like HPMC, SCMC and EC. The main effect & the interactions of polymers on drug release & drug content analysis were studied. The effect of various critical processing variables

on the dissolution of controlled release matrix tablets is evaluated. For better response on optimization of the parameters, statistical techniques like response surface methodology is used with the help of software "Stat-Ease Design-Expert 8.0.7.1" [5,6].

MATERIALS AND METHODS

Carvedilol was obtained as a generous gift sample from Aurobindo Pharma India Ltd. HPMC K15M, EC were obtained from Colorcon, India, SCMC from Simla industries, Mumbai, PVP K30 from Elegant Drugs Pvt Ltd, Hubli & lactose from Himedia laboratories. Pvt Ltd, Mumbai. Magnesium stearate and talc from S.D. Fine chemicals, Mumbai. All other chemicals used were of analytical grade.

Preformulation studies:

Determination of λmax of Carvedilol:

Stock solution (100 µg/ml) of Carvedilol was prepared in phosphate buffer pH 6.8 containing dimethyl sulfoxide [4,6]. This solution was appropriately diluted to 10 µg/ml. The resultant solution was scanned in the range of 200nm to 400 nm on UV Visible spectrophotometer. The drug exhibited a λmax at 286 nm[7].

Construction of standard graph of Carvedilol:

Carvedilol (10 mg) was dissolved in 10 ml of dimethyl sulfoxide (stock solution). From the above solution samples of concentrations 2, 4, 6, 8 and 10 µg/ml are prepared and standard graph was plotted [8].

Drug excipients compatibility studies:

There is a possibility of drug - excipient interaction in any formulation due to their intimate contact of active drug with inactive excipients used in the formulation of a dosage form which may influence drug safety and efficacy through its detrimental effect on drug stability and bioavailability. So, it is necessary to determine any possible interaction between excipients.

FTIR (Fourier transform infra red spectroscopy) studies:

IR spectrum with high quality is acquired with KBr (pellet) method. The sample powder of drugs, excipients and mixture of they were prepared and placed on glass plate and apply the infra red beam to record the IR spectrum between 4000 cm^{-1} and 400 cm^{-1}. The mixture spectra were compared with that of the original spectra [9].

Differential Scanning Calorimetry (DSC) studies:

The sample were sealed in aluminum pans and heated at a constant rate 10°C/min over a temperature range of 50-400°C. An inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/min [10,11].

Formulation of Controlled Release Matrix Tablets:

The active ingredient i.e. Carvedilol [10 mg] with the mixture of two hydrophilic swellable polymers, for e.g. HPMC K15M, SCMC and hydrophobic polymers EC at different concentrations according to response surface methodology, Lactose as a diluent, PVP K30 as binding agent, magnesium stearate and talc as lubricant and glidant respectively were used in the formulation. The mixture was compressed by using 8 mm standard flat round punch and die set of single station tablet punching machine. Total tablet weight is maintained at 250 mg.

Formulation development:

The better formulation is developed in the formulation development phase by selecting the polymeric concentration. A computer-aided optimization technique was employed to investigate the formulation design by using Design Expert Software version 8.0.7.1.[12]. RSM and the effects of critical formulation variables i.e., independent variables concentration of HPMC K15M, SCMC and EC on dependent variables i.e., Percentage drug release at the end of 24 hours, % drug content and regression analysis are studied and the optimized concentrations are selected for the optimized formulation of Carvedilol controlled release matrix tablets. The software designs 17 formulations in different polymer concentrations are obtained in the Box-Behnken Design [5].

Pre compression parameters:

***Physical characterization of the blend*[13]:**

Determination of Bulk Density, Tapped density, Compressibility index & Angle of repose:

A weighed quantity of the powder sample passed into 50 ml graduated cylinder. The measuring cylinder was subjected to taps and the change in volume was noted. The bulk density, Tapped density, Compressibility index, Angle of repose were calculated by using the formula:

$$\text{Bulk density} = \frac{weight\ of\ powder\ blend}{bulk\ volume}$$

$$\text{Tapped density} = \frac{weight\ of\ powder\ blend}{tapped\ volume}$$

$$\text{Compressibility index} = \frac{tapped\ \ density\ -bulk\ \ density}{tapped\ density} \times 100$$

$$\text{Angle of repose, } \theta = \tan^{-1} h/r$$

***Post compression parameter*[13]:**

Weight variation test:

Not more than two of the individual weights of the 20 tablets should deviate from the average weight by more than the percentage shown in the table and none should deviate by more than twice the percentage.

Hardness test: The tablet was held between the edges of the fixed and movable part of the instrument. The hardness was measured in N/cm^2.

Thickness test:

Thickness of the tablets are measured by using the Digital Vernier Calipers and can be read by in metric and imperial by pressing the inch/mm button.

Friability:

Friability is the measure of tablet strength.

$$\text{Friability} = \frac{(w1 - w2)}{w1} \times 100$$

Where: w_1= weight of the tablet before test., w_2 = weight of the tablet after test.

Content uniformity of tablet formulations:
20 tablets were weighed and powder equivalent to 100 mg of drug was dissolved in 100 ml of 6.8 pH phosphate buffer. The absorbance was measured at 286 nm. The concentration of the drug was computed from the standard curve.

Swelling index of tablet formulations:
One tablet from each formulation was kept in a petridish containing 20 ml 0.1 N HCl for first 2 hrs and later in phosphate buffer pH 6.8. At the end of 1hr, 2hrs the tablet was withdrawn, wiped with tissue paper, and weighed. The process was continued till the end of 24 hrs.

$$\% \text{ Swelling index} = \frac{w2 - w1}{w1} \times 100$$

Where: w_2 = Final weight of tablet after swelling.
w_1 = Initial weight of tablet

In-vitro dissolution test:
In-vitro dissolution test is carried under USP dissolution paddle apparatus using 6.8 pH phosphate buffer as the dissolution medium.

Characterization of release kinetics[14,15,16]**:**
Model-Dependent methods:
The release kinetics of the drug was described by fitting the data obtained from *in-vitro* drug release in various kinetic models.

Zero-order kinetic model:
The zero-order kinetic describes the systems as a one in which the drug-release rate is independent of its concentration It defines a linear relationship between the fractions of drug release versus time. The equation that describes zero order kinetics is

$$Q = K_0 t, \ldots \times 100 \quad \ldots..\text{Eq(5)}$$

Where: Q is the fraction of drug release at time t, K_0 is the zero order release rate constant.

Table 1: Variable Factors with ranges

Factor	Name	Minimum	Maximum	Coded Values	Mean	Std. Dev
A	HPMC	60.00	140.00	1.000=60.001.000=140.00	100.0	27.4
B	EC	20.00	40.00	-1.000=10.001.000=40.00	30.00	6.86
C	SCMC	20.00	40.00	-1.000=20.001.000=40.00	30.00	6.86

Type - Numeric and Subtype - Continuous

Table 2: formulation table

Ingredient	Quantity per tablet (mg/tab)																
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17
Drug	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
HPMC K15M	60	60	100	100	100	100	140	100	100	100	100	140	60	60	140	140	100
EC	30	40	20	30	40	30	20	30	30	40	30	30	30	20	40	30	20
SCMC	20	30	20	30	40	30	30	30	30	20	30	20	40	30	30	40	40
PVP K30	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
Talc	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mg.Stearate	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Lactose	105	85	75	55	35	55	25	55	55	55	55	25	85	105	5	5	55
Total wt	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

Table 3: Limits of weight variation

S.No.	**Average weight of the tablet,** mg	**% Deviation allowed**
1.	130 or Less	± 10
2.	From 130 – 324 mg	± 7.5
3.	More than 324 mg	± 5

First-order kinetic model:

According to first-order kinetic rate of release is concentration dependent. The equation that describes first order kinetics is

$$\ln(1 - Q) = -K_1 t, \ldots \ldots \text{Eq(6)}$$

Where: Q is the fraction of drug released at time t, K_1 is the first order release rate constant.

Higuchi kinetic model:

Higuchi kinetic model explains release of drugs from an insoluble matrix as a square root of time dependent process based on Fickian diffusion. The equation that describes Higuchi kinetics is

$$Qt = K_H t_{1/2}, \ldots\ldots \text{Eq(7)}$$

Where: Qt is the amount of drug released in time t, K_H is the release rate constant for Higuchi model, $t_{1/2}$ is the square root of time.

Korsemeyer-Peppas model:

This model describes solute release behavior from controlled release polymer matrices. Here, a plot of the logarithm of the cumulative percentage of the drug released against the logarithm of time and the slope, 'n' and the regression line values (R^2) were extracted from the graph. The equation used is

$$F = (Mt/M) = kt^n \ldots\ldots \text{Eq(8)}$$

Where: F = fraction of drug released, Mt = amount of drug released at time t, M = total amount of drug in dosage form, k = kinetic constant, t = release time, n = the diffusional exponent for drug release.

Table 4: Diffusion exponent and release mechanism

Diffusion exponent (n)	Diffusion mechanism
< 0.45	Fickian diffusion
0.45-0.89	Non- Fickian Transport
0.89	Case-II transport
> 0.89	Super Case-II transport

Model-Independent methods:

The similarity factor (*f2*) given by SUPAC guidelines for controlled release dosage form was used as a basis to compare dissolution profile. The dissolution profiles are considered to be similar when *f2* is between 50 and 100. The release profiles are considered as insignificant of difference factor *f1* is > 15.

RESULTS

***Preformulation studies*:**

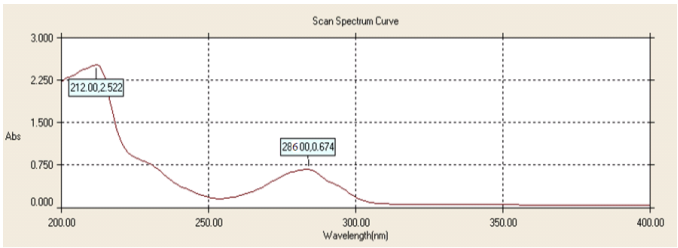

Figure 1 : UV spectrum of Carvedilol in pH 6.8 buffer

Table 5: Calibration curve of Carvedilol at 286 nm

Concentration (µg/ml)	Absorbance	
	0.1N HCl solution	6.8 pH buffer solution
0	0	0
2	0.142	0.151
4	0.287	0.276
6	0.394	0.429
8	0.541	0.577
10	0.676	0.698
Regression	0.9985	0.999
Slope	0.0667	0.0708

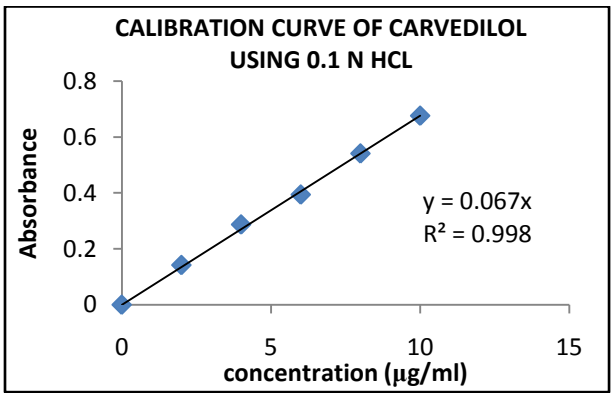

Figure 2: Calibration curve in 0.1 N HCl

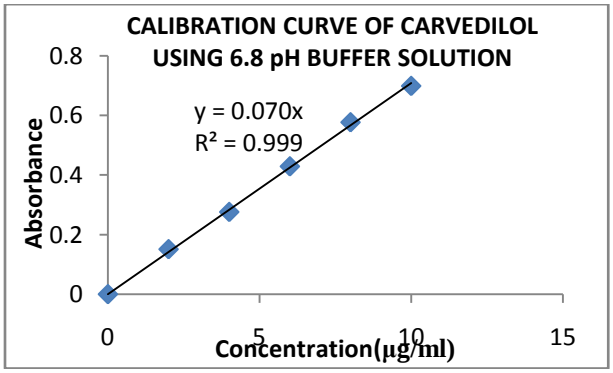

Figure 3: Calibration curve in 6.8 pH buffer

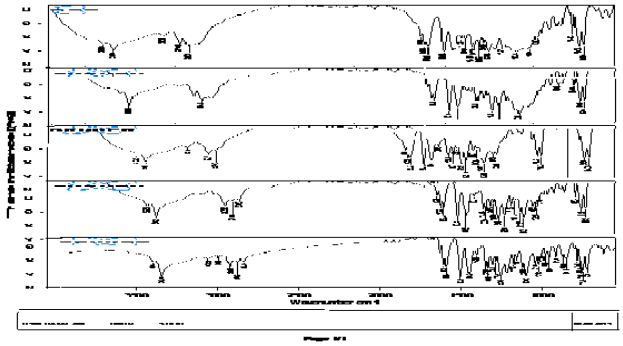

Figure 4: Drug excipients compatibility studies by FTIR

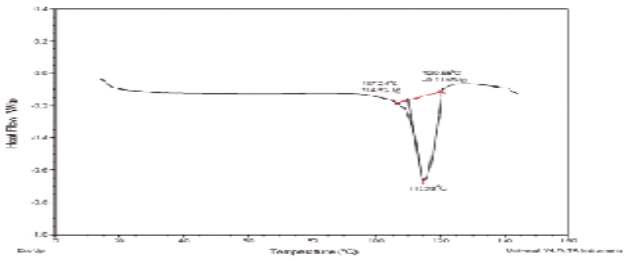

Figure 5: DSC thermogram of Carvedilol pure drug showing Melting point at 115.59 ^{0} C.

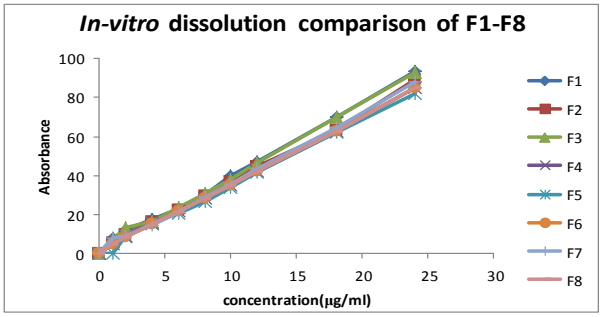

Figure 7: *In-vitro* Dissolution Profile of F1-F8.

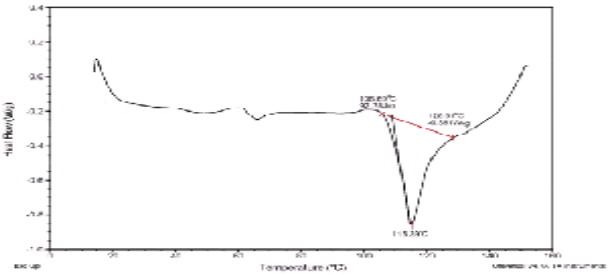

Figure 6: DSC thermogram of Carvedilol formulation showing Melting point at 115.39 ^{0} C.

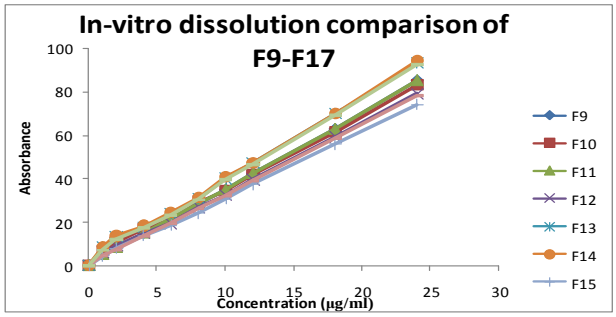

Figure 8: *In-vitro* Dissolution Profile of F9-F17.

Table 6: Results of Compressibility Index, Hausner's Ratio & Angle of repose

Formulations	Bulk density	Tapped density	Carr's index	Hausner's ratio	Angle of repose
F1	0.46±0.0177	0.583±0.024	21.5±0.336	1.273±0.05	23.69±1.20
F2	0.43±0.007	0.52±0.015	17.22±0.25	1.207±0.03	26.2±0.99
F3	0.459±0.004	0.604±0.008	23.98±0.25	1.315±0.04	25.82±0.04
F4	0.428±0.046	0.551±0.06	22.25±0.14	1.285±0.02	27.22±0.63
F5	0.398±0.004	0.513±0.005	22.4±0.086	1.288±0.01	29.65±0.42
F6	0.428±0.046	0.551±0.06	22.25±0.14	1.285±0.02	27.22±0.63
F7	0.423±0.007	0.52±0.015	18.63±0.20	1.228±0.03	24.35±0.24
F8	0.428±0.046	0.551±0.06	22.25±0.14	1.285±0.02	27.22±0.63
F9	0.428±0.046	0.551±0.06	22.25±0.14	1.285±0.02	27.22±0.63
F10	0.462±0.085	0.583±0.01	20.74±0.22	1.261±0.03	25.6±1.03
F11	0.428±0.046	0.551±0.06	22.25±0.14	1.285±0.02	27.22±0.63
F12	0.411±0.007	0.49±0.01	15.98±0.85	1.189±0.01	25.96±0.54
F13	0.438±0.007	0.547±0.006	19.86±0.67	1.247±0.01	24.01±0.74
F14	0.528±0.016	0.657±0.017	19.71±0.64	1.245±0.09	24.3±1.46
F15	0.384±0.006	0.462±0.008	16.92±0.23	1.203±0.03	27.81±0.58
F16	0.39±0.006	0.48±0.009	18.8±0.357	1.231±0.05	27.93±0.67
F17	0.43±0.075	0.568±0.013	24.19±0.41	1.318±0.07	24.48±0.53

All the values are calculated as (Mean ±SD,n=3).

Table 7: Results of Weight variation, Hardness (N/cm^2), Thickness (mm), Friability & % drug content:

Formulations	Tablet wt. (mg) n=10	Hardness(kg/cm^2)	Thickness (mm)	Friability	% Drug content
F1	250.8±0.599	7.0±0.11	3.20±0.17	0.079±0.011	99
F2	250.5±0.46	6.36±0.28	3.53±0.05	0.1941±0.01	95.75
F3	250.74±0.52	7.36±0.20	3.16±0.05	0.225±0.033	102
F4	249.68±0.42	7.16±0.32	3.53±0.05	0.115±0.03	97.5
F5	251.02±0.27	7.06±0.25	3.60±0.10	0.131±0.016	104.75
F6	249.68±0.42	7.16±0.32	3.53±0.05	0.115±0.03	97.5
F7	251.10±0.21	7.06±0.11	3.50±0.10	0.1783±0.01	98.75
F8	249.68±0.42	7.16±0.32	3.53±0.05	0.115±0.03	97.5
F9	249.68±0.42	7.16±0.32	3.53±0.05	0.115±0.03	97.5
F10	250.27±0.62	6.63±0.23	3.23±0.20	0.026±0.011	98
F11	249.68±0.42	7.16±0.32	3.53±0.05	0.115±0.03	97.5
F12	250.78±0.49	7.26±0.20	3.50±0.10	0.279±0.013	99
F13	250.12±0.9	6.73±0.15	3.26±0.11	0.1502±0.03	99
F14	249.68±0.32	6.53±0.15	3.23±0.15	0.341±0.019	98.6
F15	249.98±0.49	6.8±0.1	3.56±0.20	0.238±0.045	101.5
F16	249.15±1.17	6.7±0.1	3.56±0.05	0.434±0.028	103.25
F17	249.78±0.77	7.16±0.25	3.46±0.05	0.182±0.012	102.75

All the values are calculated as (Mean ±SD,n=3).

Table 8: Swelling index of tablet formulations:

F.CODE	TIME IN HRS									
	1	2	4	6	8	10	12	18	22	24
F1	5.3±2	14.6±2	26.6±2	40±4	52±4	64±4	72±4	110.6±6	134.6±6	116±4
F2	12±4	21.3±4	36±4	52±4	62.6±6	76±4	85.3±4	120±4	144±4	150.6±6
F3	16±4	20±4	36±4	44±4	52±4	60±4	68±4	96±4	118.6±6	104±4
F4	9.3±2	17.3±2	28±4	42.6±6	56±4	68±4	80±4	104±4	124±4	132±4
F5	4±0	9.3±2	20±4	32±4	40±4	52±4	64±4	88±4	112±4	120±4
F6	9.3±2	17.3±2	28±4	42.6±6	56±4	68±4	80±4	104±4	124±4	132±4
F7	8±0	16±4	28±4	40±4	52±4	54±4	76±4	108±4	132±4	144±4
F8	9.3±2	17.3±2	28±4	42.6±6	56±4	68±4	80±4	104±4	124±4	132±4
F9	9.3±2	17.3±2	28±4	42.6±6	56±4	68±4	80±4	104±4	124±4	132±4
F10	9.3±2	17.3±2	24±4	36±4	48±4	62.6±8	74.6±8	98.6±8	118.6±8	126.6±8
F11	9.3±2	17.3±2	28±4	42.6±6	56±4	68±4	80±4	104±4	124±4	132±4
F12	6.6±2	10.6±2	18.6±2	25.3±2	32±4	40±4	52±4	80±4	104±4	112±4
F13	14±2	20±4	32±4	44±4	52±4	60±4	72±4	104.6±3	128±4	113.3±2
F14	12±4	17.3±2	32±4	48±4	64±4	76±4	88±4	124±4	144±4	132±4
F15	2±2	5.3±2	13.3±2	20±4	24±4	32±4	40±4	68±4	88±4	96±4
F16	4±0	9.3±2	17.3±2	21.3±2	28±4	36±4	44±4	76±4	100±4	108±4

All the values are calculated as (Mean ±SD,n=3).

Table 9: *In-vitro* Dissolution Profile of F1-F8.

TIME (hrs)	% CUMULATIVE DRUG RELEASE						
	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
1	7.67±0.39	5.51±0.3	7.54±0.39	5.1±0.33	5. 47±0.2	8.16±0.33	6.83±0.33
2	12.26±0.4	9.41±0.4	13.09±0.4	8.35±0.38	9.037±0.2	9.39±0.33	10.48±0.3
4	17.38±0.3	16.52±0.3	16.31±0.37	15.0±0.31	15.47±0.1	14.68±0.3	16.78±0.4
6	23.19±0.3	22.3±0.37	23.3±0.37	21.62±0.3	20.42±0.3	21.16±0.3	21.22±0.4
8	30.25±0.4	29.53±0.4	31.0±0.44	28.48±0.3	26.72±0.5	28.9±0.31	29.27±0.3
10	39.91±0.4	36.74±0.4	37.96±0.44	34.89±0.3	33.96±0.3	35.9±0.31	34.48±0.3
12	47.1±0.37	44.52±0.3	46.45±0.37	42.50±0.2	41.41±0.3	43.27±0.2	41.67±0.3
18	69. 8±0.3	63.69±0.3	69.8±0.37	62.84±0.2	62.24±0.1	64.55±0.3	61.58±0.2
24	93.31±0.3	89.19±0.3	93.07±0.37	85.28±0.2	82.24±0.3	88.02±0.1	83.07±0.3

Table 10: *In-vitro* Dissolution Profile of F9-F17.

TIME (hrs)	% CUMULATIVE DRUG RELEASE								
	F9	F10	F11	F12	F13	F14	F15	F16	F17
0	0	0	0	0	0	0	0	0	0
1	5.1±0.33	6.83±0.33	5.1±0.33	6.0±0.33	8.11±0.46	8.55±0.53	4.5±0.53	4.58±0.53	7.19±0.53
2	8.35±0.38	10.48±0.33	8.35±0.38	8.97±0.46	13.01±0.5	13.50±0.47	7.72±0.47	7.59±0.47	12.3±0.47
4	15.0±0.31	16.78±0.44	15.0±0.31	14.93±0.38	17.56±0.4	18.19±0.44	13.71±0.4	13.70±0.44	17.30±0.44
6	21.62±0.3	21.22±0.44	21.62±0.3	19.41±0.37	23.73±0.4	24.15±0.51	18.4±0.51	19.65±0.51	23.19±0.51
8	28.48±0.3	29.27±0.31	28.48±0.3	26.79±0.44	30.63±0.2	31.30±0.44	24.16±0.4	26.24±0.44	30.38±0.44
10	34.89±0.3	34.48±0.31	34.89±0.3	32.29±0.37	39.96±0.5	40.71±0.37	30.64±0.3	32.20±0.37	39.70±0.37
12	42.50±0.2	41.67±0.31	42.50±0.2	39.56±0.31	46.94±0.3	47.19±0.37	37.42±0.3	39.22±0.37	46.39±0.37
18	62.84±0.2	61.58±0.25	62.84±0.2	59.26±0.31	69.72±0.5	69.89±0.37	55.95±0.3	58.76±0.37	69.17±0.37
24	85.28±0.2	83.07±0.37	85.28±0.2	79.20±0.44	93.1±0.44	93.9±0.22	74.24±0.2	78.11±0.22	92.42±0.22

Statistical optimization:

Statistical Optimization at the formulation development step involves finding a best possible result for the responses from the existing concentrations of the polymeric ranges. The % Cumulative Drug Release, % Drug Content and Regression Analysis data is entered into the generated design model, and then the software generates Model graphs to interpret and evaluate the given data to find out the best response. With the help of Factors tool the variable factors are adjusted in the software to show the maximum predicted response.

Table 11: Formulation Development Results

RUN	Response 1: % CDR	Response 2: %DC	Response 3: REG r^2
1	93.31	99	0.998
2	89.19	95.75	0.997
3	92.72	102	0.995
4	85.28	97.5	0.999
5	82.24	104.75	0.998
6	85.28	97.5	0.999
7	88.02	98.75	0.996
8	85.28	97.5	0.999
9	85.28	97.5	0.999
10	83.07	98	0.995
11	85.28	97.5	0.999
12	79.02	99	0.997
13	93.1	99	0.995
14	93.9	98	0.996
15	74.24	101.5	0.998
16	78.11	103.25	0.999
17	92.42	102.75	0.996

Response:1 %CDR

Table 12: ANOVA for Response Surface Linear Model-1

Source	df	F Value	Prob >F	Significance
Model	3	49.78	< 0.0001	Significant
A-HPMC	1	*93.43*	< 0.0001	Significant
B-EC	1	*55.64*	< 0.0001	Significant
C-SCMC	1	*0.25*	*0.6244*	
Lack of Fit	9			Valid
Pure Error	4			Valid

Response: 2 % DC

Table 13: ANOVA for Response Surface Linear Model-2

Source	df	F Value	Prob > F	Significance
Model	9	28.24	0.0001	Significant
A-HPMC	1	*36.98*	0.0005	Significant
B-EC	1	*0.72*	0.04242	Significant
C-SCMC	1	*44.18*	0.0003	
Lack of Fit	3			Valid
Pure Error	4			Valid

Response: 3 Regression

Table 14: ANOVA for Response Surface Linear Model-3

Source	df	F Value	Prob > F	Significance
Model	9	4.47	0.0306	Significant
A-HPMC	1	*2.33*	*0.01705*	Significant
B-EC	1	*2.33*	*0.01705*	Significant
C-SCMC	1	*2.33*	*0.01705*	
Lack of Fit	3			Valid
Pure Error	4			Valid

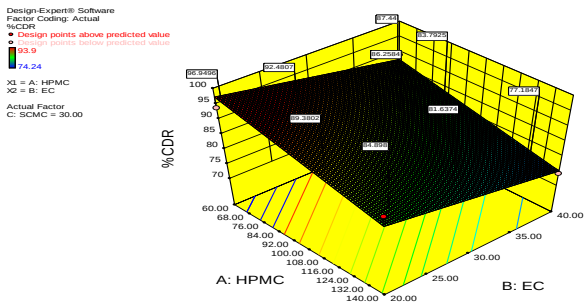

Figure 9: 3D Graph for % CDR

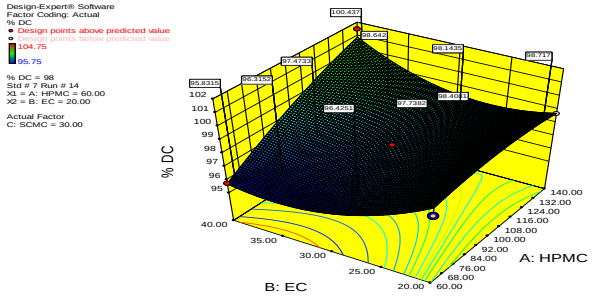

Figure 10: 3D Graph for % DC

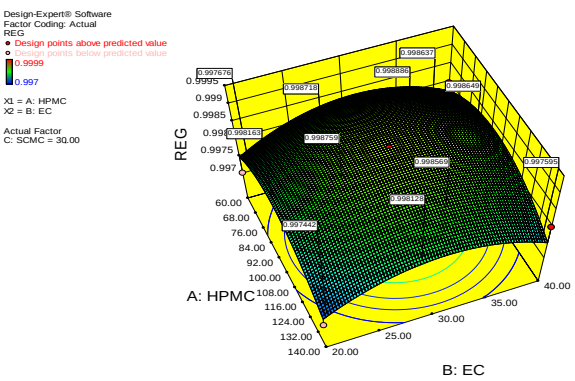

Figure 11: 3DGraph of Regression analysis

Confirmation Report:
Two-sided Confidence = 95% (n = 1)

Table 15,16: Predicted polymeric concentrations for maximum predicted response.

Factor	Name	Level	Low Level	High Level	Std. Dev.	Coding
A	**HPMC**	**60.00**	60.00	140.00	0.000	Actual
B	**EC**	**24.00**	20.00	40.00	0.000	Actual
C	**SCMC**	**20.94**	20.00	40.00	0.000	Actual

Response	Prediction	Std Dev	SE Pred	95%PI low	95%PI high
%CDR	**95.6988**	1.83286	2.11481	91.1301	100.268
% DC	**100**	0.625	0.837681	98.0194	101.981
REG	**0.9992**	0.0006554	0.000878522	0.997171	1.00133

The tablets produced with the predicted values of variable factors showed 95.698% drug release, 100% drug content and regression of 0.999.

Experiment results of the predicted response generated by software are as follows:
Based on these predictions a new batch of formulation optimized has been prepared with the predicted variable factors and analyzed for dissolution data, drug content and regression analysis. After the formulation from the predicted polymeric concentrations generated from the software the following results were obtained:

- % Cumulative Drug Release - 96.145±0.509.
- % Drug Content - 100.06±0.719.
- Regression -0.9997.

Optimized Formulation:

Table 17: Evaluation of Optimized formulation

Pre compression Evaluations:		**Post compression Evaluations:**	
Bulk density	0.39±0.01	**Weight variation test**	250.16±0.08
Tapped density	0.436±0.02	**Hardness test**	7.46±0.35
Carr's index	10.95±1.908	**Thickness Test**	3.33±0.25
Hausner's ratio	1.119±0.02	**Friability**	0.0893±0.013
Angle of repose(θ)	23.791±1.406	**Content uniformity**	100.06±0.79

From the above studies it was revealed that the flow properties of the optimized formulation were found to be excellent and results of evaluations of optimized formulation were found to be within the range.

Table 18: Dissolution profiles of Optimized formulation and Marketed formulation

Time(hrs)	% Cumulative Drug Release Avg ± SD (n=3)	
	Optimized formulation	Marketed formulation
0	0	0
1	5.17±0.059	4.29±0.053
2	9.05±0.79	8.91±0.47
4	17.10±0.32	16.55±0.44
6	24.64±0.62	24.97±0.55
8	33.02±0.56	33.06±0.19
10	41.69±0.25	41.28±0.62
12	48.29±0.63	49.32±0.24
18	71.32±0.25	74.20±0.52
24	96.14±0.26	98.71±0.50

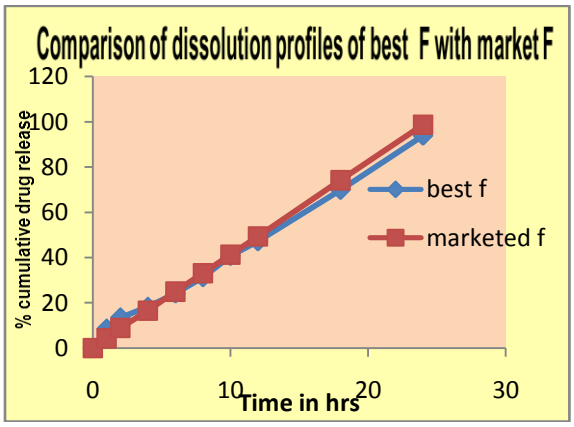

Figure 12: Comparison of dissolution profiles of Best formulation from the design i.e., F14 with Marketed formulation

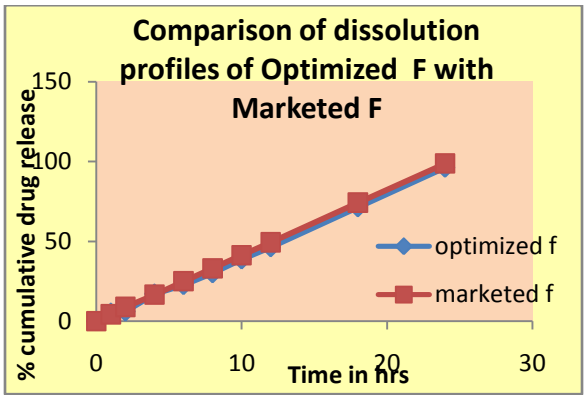

Figure 13: Comparison of dissolution profiles of optimized formulation with Marketed formulation.

Table 19: Similarity & Difference Factors

	F14 with Marketed formulation	Optimized formulation with Marketed formulation.
Similarity factor f_2	66	83
Difference factor f_1	7	3

DISCUSSION

Preformulation Studies:

The drug Carvedilol exhibited UV spectrum in pH 6.8 buffer, i.e., λmax at 286 nm. Calibration curve of Carvedilol using 0.1N HCl solution showed a linear plot of drug absorbance with r^2 = 0.9987, slope of 0.0669. Using 6.8 pH buffer solution showed a linear plot of drug absorbance with r^2 = 0.999 , slope of 0.0708. Based on results of FTIR no changes in structure of drug & no significant change in the position of peaks in the IR spectra of drug with excipients compared to spectra of pure drug. The DSC thermo gram of pure drug & of the formulation showed no interaction of the drug with polymer and other excipients in the formulation. Percentage purity of Carvedilol was found to be 98.4 % pure.

Pre compression Evaluations:

The Compressibility Index was found to be good to fair i.e. 16.92 to 24.19 %, Hausner's Ratio was found to be Excellent to fair i.e. 1.1 to 1.31 and Angle of repose was found to be excellent to good i.e., 23.69 to 29.65.

Post compression parameters:

Weight variation, Hardness, Thickness, Friability, Drug content test were found to be within the range. On observing, it is found that the viscosity of the polymer had major influence i.e., a linear relationship exists on swelling process and the matrix integrity of the prepared tablets. *In-vitro* Dissolution Studies revealed that among all the formulations [F1-F17] developed in the formulation development phase **F-14** has shown a maximum dissolution of 93.90 % at the end of 24 hrs. From all the 13 formulations are subjected to dissolution, at the end of 24 hrs the % cumulative drug release (CDR) is calculated which ranges from **72.24±0.35** to **93.90±1.11.** Formulation F-15 shows least CDR among all formulations i.e., 74.24. Among all F1 and F10 formulations releases maximum CDR by the end of 24 hrs. F1 has HPMC K15M, EC and SCMC in the range of 60, 30 and 20 mg respectively where as F14 has HPMC K15M, EC and SCMC in the range of 60, 20, 30 mg concentrations. From the above results it can be confirmed that the maximum of HPMC K15M (60mg) and minimum of SCMC and EC (20mg) concentrations have significant effect on the % CDR. The drug release kinetics of all the formulations showed Zero order release mechanism with the super case-2 type of diffusion.

Formulation development:

The predicted parameters of the maximum response were found to be Hydroxy Propyl Methyl Cellulose K15M: 60.00 mg, Ethyl Cellulose: 24.00 mg, Sodium Carboxy Methyl Cellulose: 20.94 mg. The tablets produced with the predicted values of variable factors showed 95.698% drug release, 100% drug content and regression of 0.999. The release kinetics of the optimized formula also followed Zero order release mechanism with the super case-2 type of diffusion.

CONCLUSION

The present works aims to prepare and evaluate Controlled Release Matrix Tablets of Carvedilol using a combination of hydrophilic and hydrophobic polymers by direct compression method and the effect of formulation variables i.e., the polymeric concentrations on the tablet *in-vitro* dissolution(% CDR), % DC, Regression analysis is studied. The results, showed a better dissolution in the formulation development phase. Compatibility study showed are no physicochemical changes and interaction. Evaluation tests shown the results within the satisfactory limits. Using the stat-ease design expert 8.0.7.1 helped to find out the maximum response. The investigation the *in-vitro* dissolution data of tablets revealed that increase in the % CDR, % DC and Regression analysis in the predicted results generated by the software. Once daily dose with improved patient compliance was formulated.

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