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EFFECT OF DIFFERENT EXCIPIENTS ON IN VITRO RELEASE OF CARVEDILOL ER TABLETS

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ABSTRACT

Extended release matrix tablet formulation of carvedilol were developed and evaluated to observe the effect of different drug release retarding polymer i.e., (HPMC K4, Eudragit S100) on invitro drug release .Ten formulation (F1-F10) were prepared by direct compression technique. FTIR studies showed stable character of Carvedilol with polymer. The pre-formulation parameters such as bulk density, tapped density, angle of repose, compressibility index and hausner's ratio were analysed for prepared granules before compression. The thickness, hardness, friability, weight variation and drug content uniformity was evaluated for tablets. The effect of this variable on the drug release profile of carvedilol was also studied. In-vitro drug release is performed in USP apparatus-II(Paddle) at pH 7.4 phosphate buffer and at pH 1.2 in HCl medium at 37 °C for 16 hr. F3 has shown improved % cumulative drug release compared to others. Also F3 has satisfied the IP specifications of 81% within 16 hr. The stability study of the tablets F3 was carried out according to ICH guidelines at 40±˚C/75±5% RH for three months by storing the samples in stability chamber, No significant difference in % CDR was observed. The best fit of release kinetic was achieved with Higuchi model followed by zero order.

KEYWORDS: Carvedilol, Extended release tablets, HPMC K4, Eudragit S100.

INTRODUCTION

Hypertension is defined as blood pressure higher than 140 over 90mmHg (millimeters of mercury). High blood pressure is classified as either Primary high blood pressure or Secondary high blood pressure. Carvedilol is a non-selectiveβ-adrenergic blocking agent with α1-blocking activity. This is widely used as anti-hypertensive drug.[1] The use of extended release (SR) formulations offers many potential advantages, such as extended blood levels, attenuation of adverse effects and improved patient compliance. It is important especially in the case of antihypertensive agents to maintain constant blood levels, as otherwise dose dumping may cause hypotension. Carvedilol is chemically (+)-1-(carbazole-4-yloxy)-3-{[2-(O-methoxy phenoxy) ethyl] amino}-propan-2-ol with multiple mechanisms of action. It acts as a non-selective β and α-1 adrenergic receptor blocker and it also has vasodilating property that is attributed mainly to its α1 receptor antagonist activity. Its conventional dosage form is used to treat mild to moderate hypertension and angina pectoris. Carvedilol base is practically insoluble in water (0.583mg/L) and thus poorly absorbed from gastrointestinal tract its exhibits poor absolute bioavailability of 25-30%. The half-life of the drug is 6-8hr.The very poor aqueous solubility of carvedilol indicated that its absorption is dissolution rate- limited which results in irregular and delayed absorption.[2] The ER matrix tablet contains polymer like HPMC K4, Eudragit S100. Drug release was achieved with higuchi model followed by zero order kinetics. The extended release dosage form of carvedilol is evaluated for in vitro release by 'USP dissolution Test Apparatus' using rotating paddle test apparatus. Various excipients like diluents, binders, disintegrate and lubricants are dissolved in a suitable vehicle. Hydration of polymers shows formation of a gel layer that controls the release rate of drug from the core of matrix tablets. The aim of the present study was to develop the ER tablet of carvedilol for the treatment of hypertension.

MATERIAL AND METHODS

Materials

Carvedilol (micro labs), HPMC K4 (Rolex laboratory), Eudragit S100 (Polymer) [from Zydus Recon), Microcrystalline cellulose (Diluent) [from Sigma Aldrich], Magnesium stearate (Lubricant) [SD Fine Chem Ltd], Talc [SD finr Chem Ltd].

Methods

Calibration curve for carvedilol was prepared in 0.1N HCL using pH 1.2 acid buffer and phosphate buffer 7.4:[3]

Preparation of Hydrochloric acid ph 1.2: Preparation of Hydrochloric acid buffer (pH 1.2)
50ml of the KCl solution was mixed with 85ml of the Hydrochloric acid solution in a 200ml volumetric flask, and then water was added to make up the volume.

0.2M Hydrochloric acid
17ml Hydrochloric acid was added in 1000ml water.

0.2 M KCl solution
14.91g of KCl was dissolved in water, and diluted it with water to 1000ml.

Determination of λ max for Carvedilol in Hydrochloric acid buffer pH 1.2
A solution of Carvedilol in Hydrochloric acid buffer pH 1.2 was scanned in UV range between 200 to 400nm (Shimadzu UV-160, spectrophotometer, Japan) Carvedilol showed maximum absorbance at 241nm in Hydrochloric acid buffer pH 1.2.

Weigh accurately appropriate aliquots were pipetted out from the standard stock solution in to a series of 10ml volumetric flasks. The volume was made up to the mark with 0.1N Hydrochloric acid buffer to get a set of solution having the concentration range of 2, 4, 6, 8, 10 µg/ml for Carvedilol. Absorbance of the above solution was measured at 241nm and a calibration curve of absorbance against concentration was recorded. The regression equation and correlation coefficient was determined.

Determination of λ max of carvedilol in phosphate buffer pH 7.4
A solution of the carvedilol in phosphate buffer pH 7.4 was scanned in UV range between 200 to 400 nm using Shimadzu UV -1601 spectrophotometer, Japan. The drug showed maximum absorbance at 241nm in phosphate buffer pH 7.4.

Preparation of standard stock solution
Solution A: (1000µg/ml)- 100 mg of carvedilol was accurately weighed and transferred to a 100ml volumetric flask, dissolved and made up to the mark with phosphate buffer pH 7.4

Solution B: (100µg/ml)- from solution A, 10 ml was pipette and transferred in to a 100ml volumetric flask and made up to the mark with phosphate buffer pH 7.4. From this solution B aliquots of 2, 4, 6, 8, 10ml were transpired to 10ml volumetric flask and diluted to 10ml to obtained 20, 40, 60, 80, 100 and 100.

0.2M potassium dihydrogen orthophosphate solution
27.218 g of potassium dihydrogen phosphate solution was dissolved in 1000ml of water.

0.2M sodium hydroxide solution
8g of sodium hydroxide pellets were dissolved in 1000ml of water to give 0.2M sodium Hydroxide solution.

Compatability studies (Fourier Transform Infrared Spectroscopic studies)
The fourier transform infra-red analysis was conducted for the surface structure characterization.

FTIR spectrum of the formulated tablets, pure drug and polymers was recorded. The tablets were taken in a KBR pellet using Shimadzu, 8400s, Japan, FTIR Instrument. The Fourier Transform Infrared Spectroscopy study reveals that there is no interaction between the pure drug and polymers.[4]

Formulation of Carvedilol Matrix Tablet
ER matrix tablets of carvedilol (F1 to F6) were prepared by direct compression using Eudragit S100 and HPMC.

Preparation of Carvedilol Matrix Tablets by Direct Compression Method
The amount of Carvedilol and polymer required for batch of tablet formulation were weighed using electronic weighing balance. After weighing they were passing through #40 mesh to break agglomerates if any present in the raw materials for uniform distribution.

The polymer and drug mixed manually using a spatula in a mortar. The prepared blend was compressed in a D tooling single stage punching machine using 4mm punch and a compression force between 4.5-7kg/cm^3.

Table-1.

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug	20	20	20	20	20	20	20	20	20	20
HPMC K4	20	40	60	-	-	-	10	13.33	10	26.66
Eudragit S 100	-	-	-	20	40	60	10	26.66	10	13.33
MCC	107	87	67	107	87	67	107	87	107	87
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1	1	1
Total Weight	150	150	150	150	150	150	150	150	150	150

Evalution of the formulated carvedilol matrix tablets
The granules were evaluated for bulk density, tapped density, carr's index, Hausner's ratio and angle of repose. The tablets were evaluated for thickness, hardness, friability, weight variation test, drug content and in-vitro release rate studies.

Pre- Compression Parameters

A) Bulk Density (Db)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density was calculated according to the formula mentioned below. It is expressed in g/cc and is given by

Db=m/vo

Where, m= Mass of the powder
vo=bulk volume of powder

B) Tapped density (Dt)

It is the ratio of total mass of powder to the tapped volume of powder. the volume was measured by tapping the powder for 500 times then the tapping was done for 750 times and the tapped volume was noted (the difference between these two volumes should be less than 2%). If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. It is expressed in g/cc and is given by

Dt= m/vi

Where, M=Mass of the powder
vi=Tapped volume of powder.

C) Angle of repose(θ)

This is maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

The powders were allowed to flow through the funnel fixed to a stand at definite height (h). The Angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

Tanθ=h/r

$\theta = \tan^{-1}(h/r)$

where, θ= Angle of repose
h= height of the heap
r=Radius of the heap

D) Compressibility index

The flowability of powder can be evaluated by comparing the Bulk density (Db) and Tapped density (Dt) of powder and the rate at which it picked down. Compressibility index is calculated by-

$$\text{Compressibility index (\%)} = \frac{Dt-Db}{Dt} \times 100$$

Where,
Db= Bulk density
Dt= tapped density

E) Hausner's Ratio

It is the ratio of Tapped density to the Bulk density. It is given by-

Hausner's ratio= Dt-Db

Where, Dt= Tapped density
Db=Bulk density

Drug Content

Five tablets of each formulation were taken and amount of drug present in each tablet was determined. The individual tablets were crushed and required amount of buffer (Hydrochloric acid pH 1.2 and phosphate buffer pH 7.4) was added to extract the drug. Volumes make up to 100ml with buffer and filtered through whatman filter paper. From that 1ml filtrate were diluted to 10 ml with buffer.

The sample were analysed by UV-visible spectrophotometer at 241nm using buffer as a blank. The amount of drug present in one tablet was calculated.[5]

In-Vitro Release Rate Study

In-vitro release rate study of reference product (supermet XL 100) and prepared formulation (F1 to F10) was carried out according to USP method.

Procedure

The in-vitro release study for all the formulation was carried out by using USP type II (paddle Type) dissolution test apparatus in pH 1.2, 0.1N Hydrochloric acid and pH phosphate buffer 7.4. The water bath was thermo-stated at $37^{o}C \pm 0.5^{o}C$ and RPM for paddle was 50. Previously weighed tablet was kept in the 900ml dissolution media for 2 hr in 0.1N Hydrochloric acid and for 14 hr in pH 7.4 phosphate buffer. 10ml of dissolution media was pipetted out at each our hour up to 16 hr and the same volume of the fresh medium was replaced every time to maintain the necessary sink condition. The sample were analysed at a wavelength of 241nm using double beam UV-visible spectrophotometer. Amount of drug release was calculated using the equation generated from the standard curve. The percentage cumulative drug released was calculated and graph of %CDR vs. Time (hrs) was plotted.[6]

Acceptance Criteria For Dissolution Of Carvedilol As Per Usp.[7,8]

In-vitro Drug release study

Procedure

Six matrix tablets (equivalent to 150mg of Carvedilol) were taken for dissolution studies. Aliquots of sample were withdrawn at predetermined intervals of time and analysed for drug release by measuring the absorbance at 241 nm using 0.1 N Hydrochloric acid Buffer pH 1.2 as dissolution media for the first two hours and pH 7.4 phosphate buffer up to 16 hours. The volume withdrawn at each time interval was replaced with the same amount of fresh dissolution medium.

Treatment of dissolution data with different models

To analyse the mechanism of drug release from the matrix tablet, the data obtained from the drug release studies was analyzed according to the following equations.

1. Zero order model
Qt=Q0+ k0t
R^2 value near to 1 of plot amount of drug release vs time indicates zero order release mechanism.

2. First order model
Qt=Q0+ k1t
R^2 value near to 1 of plot log % ARR (Amount remaining to release) vs time indicates first order release.

3. Higuchi model
$Qt=Q0- kht^{1/2}$
R^2 value near to 1 of plot log % of drug release vs square root of time indicates anomalous release.

4. Korsmeyer-Peppa's model
log(Qt/Q∞)=log k+ n log t
N value of plot log (Qt/Q∞)vs log t indicates release mechanism.

The value of n=0.5 indicates fickian diffusion.
The value of n=0.5-1 indicates anomalous transport.

The value of n>1 indicates case 2 transport.

In all above equations, Qt is the amount of drug released at time t, Q∞ total amount of drug in the dosage form, k0 is the zero order release rate constant, k1 is the first order release rate constant, kh is the Higuchi square root of time release rate constant, k is constant which depends on the geometry of the dosage form and is the diffusion exponent indicating the mechanism of drug release.

Stability Studies
The stability study of the tablets F3 were carried out according to ICH guidelines at 40±2°C/75±5% RH for three months by storing the samples in stability chamber.

RESULTS AND DISCUSSION

Preformulation studies
Table 2: Organoleptic properties of Carvedilol.

Test	Specification	Observations
Colour	White	white
Taste	Bitter	Bitter
Odour	odourless	odourless

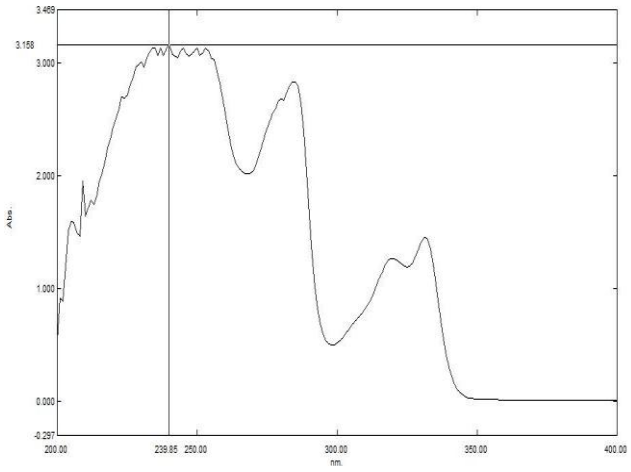


Fig 1:
Fig1: λ max for carvedilol in HCL of pH 1.2

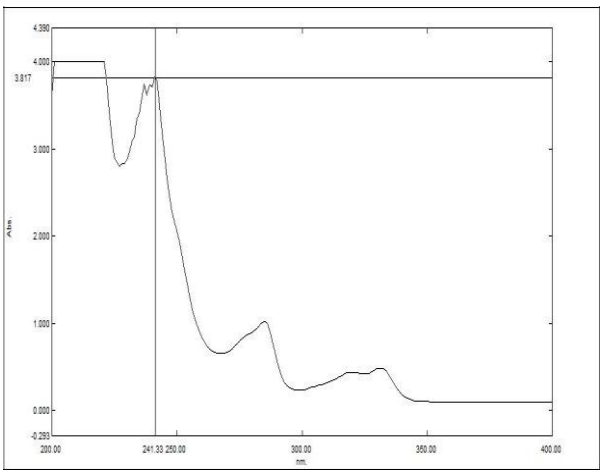


Fig 2:
Fig2: λ max of carvedilol in Phosphate buffer of pH 7.4

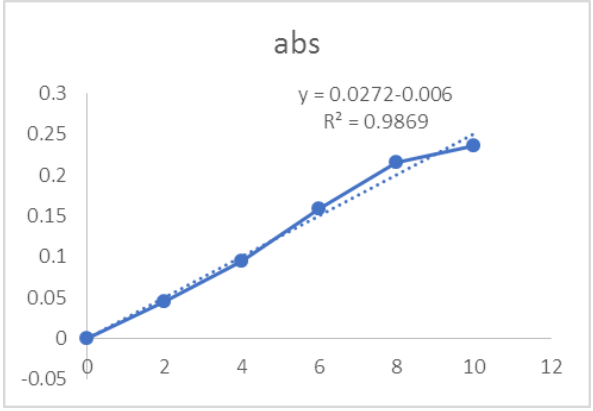


Fig 3:
Fig. 3: Standard curve of carvedilol in HCL of pH 1.2, buffer of pH 7.4.

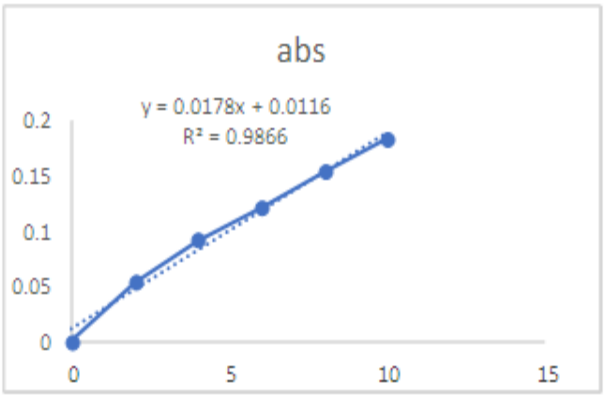


Fig 4:
Fig, 4: standard curve of carvedilol in phosphate

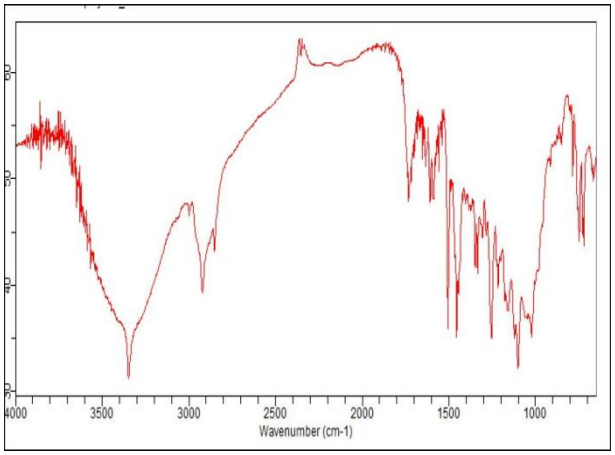


Fig-5.

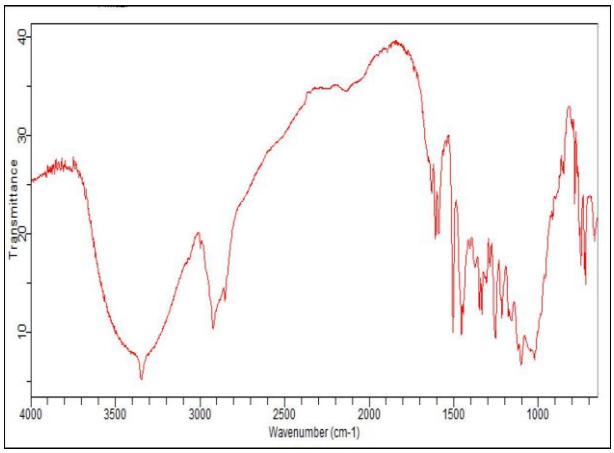


Fig-6.

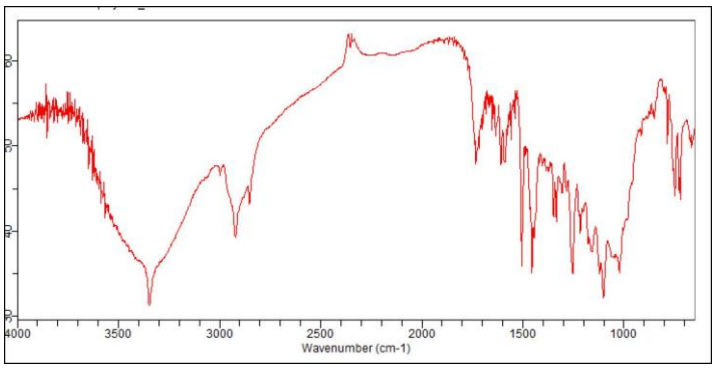


Fig-7.

FTIR study was performed to identify the purity and interaction of drugs and with excipients studies (given in fig no 5, 6, 7) the result of FTIR showed that, the sample comply with FTIR spectrum given in the BP. It is also concludes that there are no molecular interaction in drug and polymers.

Evaluation of Extended Release Tablets of Carvedilol

The flow properties of the granules for different formulation (F1-F10) were measured. The flow properties were studied by measuring the quality parameters like Bulk density, Tapped density, compressibility index and checked for the different formulation (F1-F10).

Table 3: Evaluation of pre-compression parameters of formulations of (F1-F6).

Sl. No.	Evaluation Parameters	F1	F2	F3	F4	F5	F6
1.	Bulk density (gm/ml)	0.401	0.363	0.363	0.398	0.384	0.361
2.	Tapped density (gm/ml)	0.46	0.447	0.447	0.498	0.576	0.444
3.	Carr's index	14.28	18.79	18.75	19.93	33.33	18.69
4.	Hausner's ratio	0.068	0.084	0.084	0.099	0.192	0.083
5.	Angle of repose	21..66	25.77	25.58	26.05	26.19	23.81

Table 4: Evaluation of pre-compression parameters of formulations of (F7-F10).

Sl. No.	Evaluation Parameters	F7	F8	F9	F10
1.	Bulk density (gm/ml)	0.345	0.336	0.351	0.323
2.	Tapped density (gm/ml)	0.394	0.413	0.401	0.372
3.	Carr's index	12.43	18.75	12.50	13.17
4.	Hausner's ratio	0.049	0.077	0.050	0.049
5.	Angle of repose	33.46	23.02	28.52	27.09

Pre-compression parameters are performed in order to evaluate the powder flow properties like bulk density, tapped density, hausner's ratio, cars index and angle of repose (given in Table no 3 and 4)

Table 5: Evaluation of post-compression parameters of formulations of F1-F6.

Sl. No.	Tests	F1	F2	F3	F4	F5	F6
1.	Hardness (kg/cm3)	4.5	4.7	4.9	5	5.3	5.6
2.	Thickness (mm)	2.16	2.30	2.24	2.36	2.29	2.28
3.	Friability (%)	0.480	0.4078	0.4065	0.341	0.4053	0.540
4.	Average weight (195-205mg)	148.9	145.16	149.2	144.67	148.35	149.92
5.	Weight variation ±5%	1.478	1.468	1.476	1.469	1.481	1.479

Table 6: Evaluation of post-compression parameters of formulations of F7-F10.

Sl. No	Tests	F7	F8	F9	F10
1.	Hardness (kg/cm3)	5.3	5.3	5.5	5.1
2.	Thickness (mm)	2.26	2.39	2.47	2.35
3.	Friability (%)	0.405	0.4742	0.542	0.405
4.	Average weight (195-205 mg)	148.23	149.91	145.6	149.12
5.	weight variation ±5%	1.481	1.476	1.476	1.478

In vitro dissolution profiles of Carvedilol

Table 7: In vitro release studies of Formulations F1 to F6.

Time (hr)	F1	F2	F3	F4	F5	F6	Dissolution media
1	14.396	25.303	17.019	18.9844	22.142	23.52	Hcl
2	15.662	27.195	22.086	23.4862	24.3012	25.811	
4	25.0330	51.859	36.038	41.377	42.927	41.629	
6	30.0299	58.055	39.7871	51.722	54.0653	44.17	PBS
8	34.19664	65.604	43.2329	58.75	62.1498	51.7	
10	38.3856	74.175	49.924	64.128	67.1627	56.282	
12	56.027	81.8072	57.296	69.541	73.1356	65.188	
14	64.623	89.150	69.87	76.324	80.3859	69.188	
16	77.84	96.8601	81.54	86.8585	87.6738	69.894	

Table 8: In vitro release studies of Formulations F7 to F10.

Time (hr)	F7	F8	F9	F10	Dissolution media
1	17.846	23.407	15.37	17.103	Hcl
2	19.398	26.592	17.3072	19.614	
4	30.323	43.902	33.6183	33.771	
6	36.082	49.984	38.1788	42.9509	PBS
8	39.794	51.290	42.7638	45.7875	
10	47.016	55.002	46.748	49.489	
12	51.476	58.737	52.6288	53.522	
14	55.605	61.4038	56.04	61.968	
16	59.4091	65.918	61.966	69.2102	

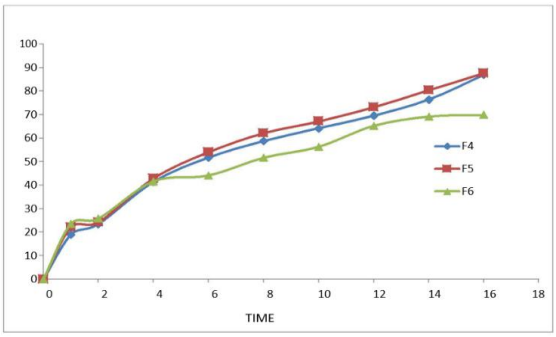


Fig. 6: Invitro release of formulations F1-F3.

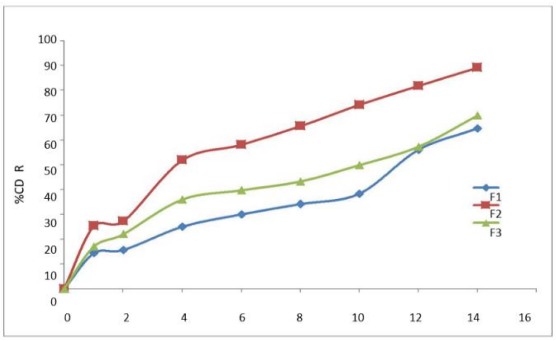


Fig. 7: Invitro release of formulations F7-F10.

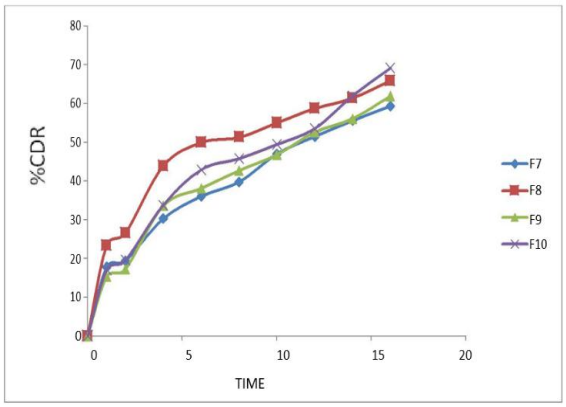


Fig. 8: Invitro release of formulations F7-F10.

Formulation F3 containing Drug: polymer (Drug: HPMC K4) 1:3 ration showed good release rate by the end of 16th hr. It was seen that as the polymer concentration increases, there was a decrease in dissolution release rate.

Table 9: Mathematical Model Fitting for obtained drug release Data Release Data for optimized formula.

Time (T)	Sqrt	Log T	%CDR	Log% CDR	% DRUG Remaining	Log % DR
0	0	0	0	0	100	2
1	1	0	17.019	1.23093	82.981	1.9189
2	1.414	0.3010	22.086	1.3441	77.914	1.8916
4	2	0.6020	36.038	1.5567	63.962	1.80592
6	2.44	0.7781	39.7871	1.5997	60.212	1.7796
8	2.828	0.9030	43.2329	1.6358	56.7671	1.75409
10	3.162	1	49.924	1.6983	50.076	1.6996
12	3.4641	1.0791	57.296	1.75812	42.704	1.6304
14	3.741	1.1461	69.87	1.8442	30.13	1.4789
16	4	1.2041	81.54	1.9113	18.46	1.2662

Fig 10 : First order kinetics.

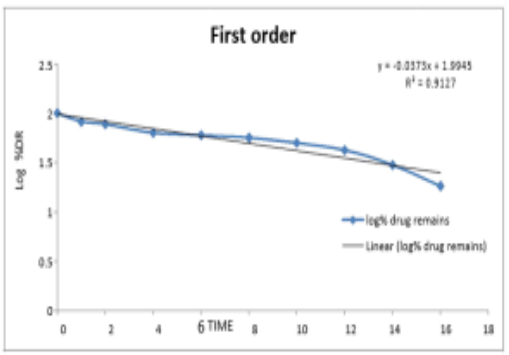


Fig 11 : Higuchi Model.

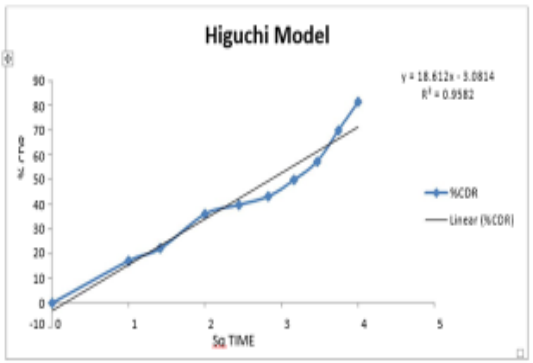


Fig 12 :Kors Peppas Model.

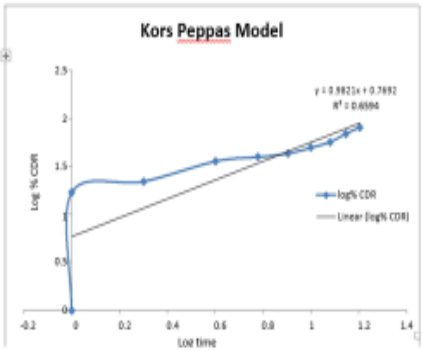


Fig 10: first order kinetics, Fig 11: Higuchi Model, Fig 12: Kors peppas Model

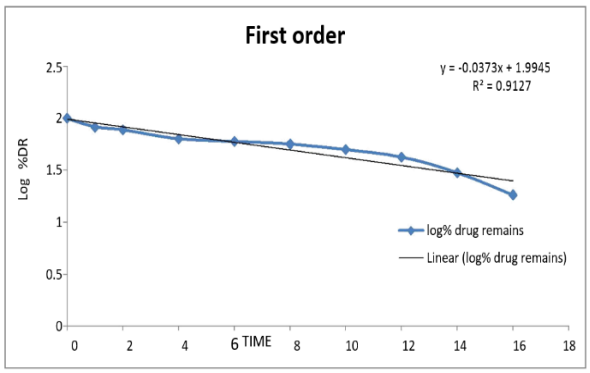


Fig. 10: First order kinetics.

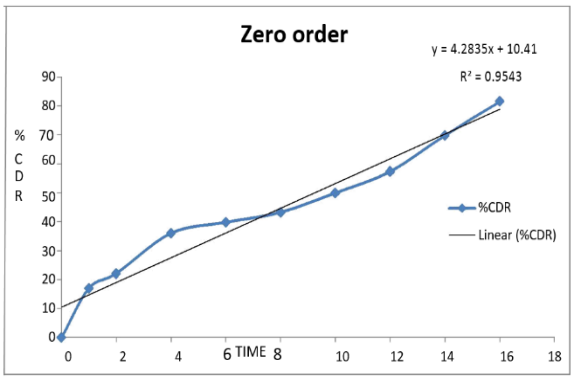


Fig 9: Zero order kinetics.

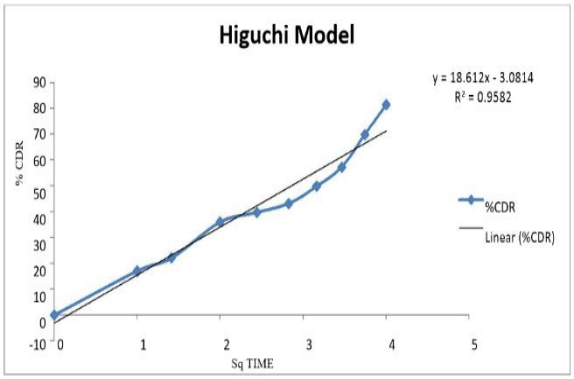


Fig. 11: Higuchi Model.

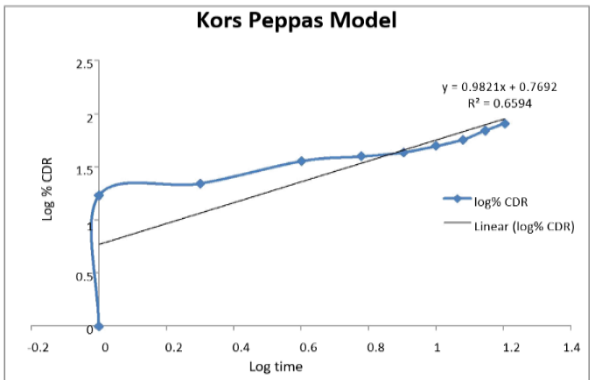
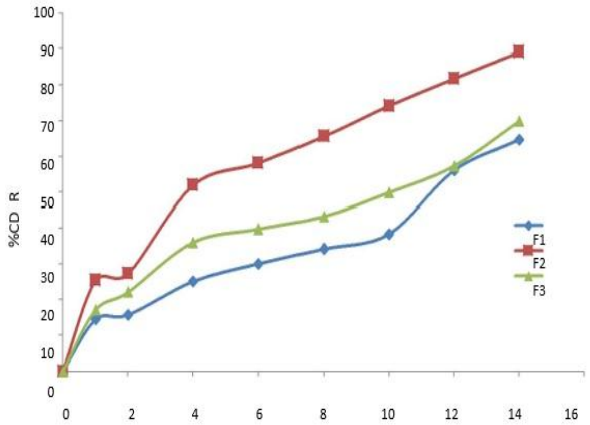
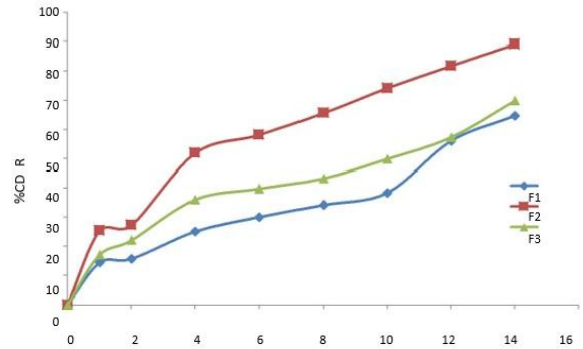


Fig. 12: Kors peppas Model.





Results from all above mentions pre-formulation, pre-compression, and post-compression parameters concluded that F3 is considered as best and optimized formulations among all The stability study of the tablets F3 were carried out according to ICH guidelines at 40±2°C/75±5% RH for three months by storing the sample in stability chamber. There were no major changes in the evaluated parameters like hardness, drug content and in-vitro dissolution pattern.

CONCLUSION

From the study, it is possible to conclude that the proposed tablet formulations were suitable for direct compression method. FTIR analysis reports of pure carvedilol, and physical mixture of carvedilol with formulation blend concludes there is no interaction between drug and polymer. According to the release studies, the decrease in the dissolution release rate was observed with an increase in the concentration of polymeric system. The result of in vitro release studies indicated that F3 formulation improved % cumulative drug release compared to others. Also F3 satisfied the IP specification of 81% with in 16hr. F3 was finalized as optimized formulation and was further subjected to stability studies. The stability study of the tablets F3 was carried out according to ICH guideline at 40±2˚C/75±5% RH for three month by storing the sample in stability chamber, No significant difference in % CDR was observed.

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