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Original Research Article

FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF CARVEDILOL PHOSPHATE

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ABSTRACT

The objective of the present research work was to develop sustained release matrix tablets of Carvedilol phosphate (40 mg) using Sodium Carboxy Methyl Cellulose polymer in different ratios, to reduce the dosing frequency. The drug polymer interaction was investigated by FTIR and their results directed further course of formulation. The tablets were prepared by employing direct compression method and were evaluated for various pre compression parameters and post compression studies like weight variation, hardness, friability, thickness, disintegration, drug content and in vitro dissolution studies. In vitro dissolution studies were performed using USP apparatus II (paddle) over a period of 24 hours in 0.1N HCl. The release kinetics was analyzed as per Zero-order, First-order, Higuchi and Peppas equations**.** The invitro dissolution studies of optimized formulation (F3) showed percentage drug release of about 92.45 % up to 24hrs and showed First-order release kinetics with Fickian diffusion model. The optimized formulation F3 showed similar drug release when compared with innovator (COREG). The result of stability studies (40±2°C/75±5% RH), showed no change in physical properties and in vitro dissolution profile of F3. As per release profile, a decrease in release rate was observed with increase in the viscosity of polymer.

Key words: Carvedilol phosphate, Sustained release, Sodium Carboxy Methyl Cellulose, COREG.

INTRODUCTION

In the recent years of development in pharmaceutics, increasing attention is being given for administering drugs in a more challenging and controlled manner for better therapeutic end point[1, 2]. Oral ingestion has long been the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, least sterility constraint and flexibility in the design of the dosage form. The goal of any drug delivery system is to provide a therapeutic amount of the drug at the target site in the body and maintains the desired drug concentration for prolong period of time. Over the past decade an entirely new technique for the delivery of a drug and other biologically active agents has been developed.

Sustained release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology. They are also referred to as "long acting" or "delayed release" when compared to "rapid" or "conventional" release preparations. Sustained release (SR) formulations offer many potential advantages, such as sustained 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. Matrix tablets is one of the most widely used approaches. One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Both hydrophilic and hydrophobic polymer matrix was widely used for formulating sustained release dosage forms[3- 5].

Carvedilol, chemically (2 RS) - 1- (9H-Carbazol-4yloxy) - 3- [[2- (2- methoxy phenoxy) ethyl] amino] propan- 2- ol is a non selective β and α1 adrenergic receptor blocking agent [6- 8]. It also has multiple spectrums of activities such as antioxidant property, inhibition of smooth muscle proliferation and calcium antagonistic blocking activity [8-10]. Its conventional tablet dosage form is used to treat mild-to-moderate hypertension and angina pectoris. It exhibits poor absolute bioavailability of 25-35%. The half-life of the drug is 6 h. Therefore conventional tablets are required to be administered 3 - 4 times a day. A suitable sustained release dosage form of carvedilol should provide prolonged action and better compliance of the patient. The aim of this work was to prepare sustained release matrix tablets containing Carvedilol, sodium carboxy methyl cellulose (SCMC) as matrix former to control drug release and thereby reducing dosing frequency.

MATERIALS AND METHODS

MATERIALS

Carvedilol phosphate was obtained as a gift sample from Hetero labs. Sodium carboxy methyl cellulose, Lactose monohydrate USP, magnesium stearate BP, Talc was obtained from SD Fine chemicals, Mumbai. All the ingredients used were of analytical grade.

METHOD

Preparation of matrix tablets:

Matrix embedded sustained release tablets of Carvedilol phosphate were prepared by direct compression technique using sodium carboxy methyl cellulose as release retarding polymer. All ingredients except magnesium stearate were blended in glass mortar uniformly. After the sufficient mixing of drug as well as other components, magnesium stearate were added and mixed for additional 5 minutes and finally compressed on a rotary tabletting machine using 7.96mm punches.

Table.1. Formulation of Carvedilol phosphate with different ratios of SCMC

Ingredients(mg/tablet)	F1 (10%)	F2 (15%)	F3 (20%)	F4 (25%)
Carvedilol phosphate	40	40	40	40
Sodium carboxy methyl cellulose	20	30	40	50
Lactose monohydrate	136	126	116	106
Magnesium stearate	2	2	2	2
Talc	2	2	2	2
Total(mg)	200	200	200	200

EVALUATION PARAMETERS[11-13]

Pre-formulation Studies Fourier Transform Infrared Spectroscopy:

The Fourier transform infra-red analysis was conducted for the structure characterization. FTIR spectra of the pure drug, polymers and formulations were recorded by using Alpha Brooker FTIR instrument. Approximately 5mg of samples were mixed with 50mg of spectroscopic grade KBr; samples were scanned in the IR range from 4000 to 400 cm-1.

Pre-compression studies of Sustained Release tablets:

Bulk density:

Bulk density is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve #20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. It is expressed in g/ml and is given by

Bulk density (D_b) = Mass of powder(M)/ bulk volume of powder(Vb)

Tapped Density:

It is the ratio of the total mass powder to the tapped volume of the powder. It was determined by placing a graduated cylinder, containing a known mass of drug-excipient blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10cm. The tapping was continued until no further change in volume was noted.

$$Dt = M / Vt$$

Where, M is the mass of powder Vt is the tapped volume of the powder.

Angle of Repose :

It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The angle of repose was determined by the funnel method suggested by Newman. Angle of repose is determined as

$$\tan \theta = h/r$$

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

Where, θ = Angle of repose, h = height of the cone, r = Radius of the cone base.

Compressibility Index :

It is an indirect measure of bulk density, size, shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index.

$$\text{Carr's compressibility index (\%)} = [(Dt-Db) \times 100] / Dt$$

Where, Dt is the tapped density Db is the bulk density

Hausner's ratio: Tapped density and bulk density were measured and the Hausner's ratio was calculated using the formula,

$$\text{Hausners ratio} = \rho t / \rho o$$

Where, ρt = Tapped density

ρo = Bulk density

Post compression parameters:

Weight variation test :

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets from each formulation was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.

Hardness: Tablets should be sufficiently hard to resist breaking during normal handling, packaging and shipping, and yet soft enough to disintegrate properly after swallowing. Hardness is an important criterion, since it can affect disintegration and dissolution. The test measures crushing strength property defined as the compressional force applied diametrically to a tablet which just fracture (break) it. A force of about 4 Kg is considered the minimum requirement for a satisfactory tablet. Hardness of tablets from each formulation was determined by Monsanto hardness tester.

Friability:

The friability of the tablet was determined using Roche Friabilator. It is expressed in percentage (%). 10 tablets were initially weighed (W initial) and transferred into the friabilator and were operated at 25 rpm per min for 4 mins (100 revolutions). The tablets were weighed again (W final). The % friability was then calculated by

$$\text{\% Friability} = (\text{loss in weight} / \text{Initial weight}) \times 100$$

Drug content uniformity: Five tablets were selected randomly and average weight was calculated. Tablets were crushed in a mortar and accurately weighed amount of average tablet was taken from the crushed blend. Then, the samples were transferred to three 100 ml volumetric flasks and were diluted up to the mark with 0.1 N HCl. The content was shaken periodically and kept for 24 hours for dissolution of drug completely. The mixtures were filtered and appropriate dilutions were made. The drug content in each tablet was estimated at λ_{max} 241 nm against blank reference and reported.

Disintegration studies:

Tablets were randomly selected and one tablet was introduced in each tube of disintegration apparatus and placed in 1litre beaker containing water at $37^0 \pm 2^0$C and disintegration time was recorded. The study was done at room temperature without disc being added.

In Vitro Drug Release:

In vitro drug release was carried out using USP – type II dissolution apparatus (paddle type). The dissolution medium, 900 ml of 0.1N HCl was placed into the dissolution flask maintaining the temperature of $37^0 \pm 0.5\ ^o$C at 50rpm. One carvedilol phosphate tablet was placed in each flask of dissolution apparatus. The apparatus was allowed to run for 24 hours. An aliquot (5ml) Samples were withdrawn after every hour up to 24 hours and simultaneously the samples were replaced with fresh dissolution medium. Then samples were filtered through 10 µm membrane filter and diluted to a suitable concentration with pH 1.2 HCL buffer. The obtained samples were analyzed at 241 nm using a UV/Visible spectrophotometer with dissolution medium as blank. The cumulative percentage drug release was calculated.

Release Mechanisms: To study the release mechanisms of Carvedilol phosphate the data of in vitro drug release was verified using Higuchi's model, Korsmeyer-Peppas model, and Hixson-Crowell cube root law models

Similarity study: Similarity study has been done for the prepared tablets with innovator formulation COREG and similarity factor has been calculated.

Stability study:

Stability studies were performed by preparing blends at different ratios of different excipients with the drug, based on tentative average weight. These blends were stored at accelerated condition of 40°C/75% RH. Control samples were stored at 40°C. The ratio of drug to excipients varies from 1:1 to 1:10 depending on the purpose of use, and the samples were kept in double lined poly-bags. The samples were evaluated for any change in the physical characteristics with reference to its controlled sample stored at 40^0C for a period of 15 days.

RESULTS AND DISCUSSION

The present study was done to formulate sustained release tablets of Carvedilol

phosphate. Matrix tablets each containing 40 mg of Carvedilol Phosphate could be prepared employing different proportions (10, 15, 20 and 25 % concentrations in the formulae) of Sodium carboxymethylcellulose polymer by direct compression technique method. All the formulations prepared showed the angle of repose less than 30^0, which reveals good flow properties (Table-2). The loose bulk density and tapped density for the entire formulation varied from 0.434gm/cm^2 to 0.494gm/cm^2 and 0.497 gm/cm^2 to 0.566 gm/cm^2 respectively (Table-2). The results of Compressibility index (%) varied from 12.67-13.19.Post compression parameters was given in Table-3.Hardness of the tablets was in the range of 7.2 - 7.9 kg/ Sq. cm. Weight loss in the friability test was less than 0.1% in all the cases. All the matrix tablets prepared contained Carvedilol phosphate within 97±1% of the labeled claim. All the tablets were found to be non – disintegrating in water and aqueous acidic (pH 1.2) and alkaline (pH 7.4) fluids. As such the prepared tablets were of good quality with regard to drug content, hardness and friability. As the tablets formulated employing Carvedilol Phosphate were non – disintegrating in acidic and alkaline fluids, they are considered suitable for oral sustained release. Release parameters of the tablets (F3) are summarized in Table 4. Carvedilol Phosphate release from the prepared tablets was slow and spread over 24 h and depended on the concentration of Sodium carboxy methyl cellulose polymer. When the release data were analyzed as per zero and first order kinetic models, it was observed that first order is applicable to describe the release data (Table-6). The correlation coefficient (r) values were found to be 0.9908. When the release data were analyzed as per Peppas equation, the release exponent 'n' was found to be 0.9887 indicating fickian diffusion as the release mechanism from all the matrix tablets prepared. Plots of percent released versus square root of time were found to be linear ($r > 0.8805$) with all tablets prepared indicating that the drug release from the tablets was diffusion controlled.

For comparison, Carvedilol Phosphate release from commercial controlled release tablets was also studied (Table-4). Drug release profiles of formulation F3 and COREG Tablets were compared by calculating similarity factor f_2. A value of $f_2 > 50$ indicates similarity of the two drug release profiles. The values of f_2 were found to be 67.51 indicating that the release profiles of these two products are similar. Hence matrix tablets formulated employing Sodium carboxy methyl cellulose (F3) is considered suitable for sustained release of Carvedilol Phosphate over 24 h.

The drug release profile of F3 (20%) complies with innovator product. All the results were found to be satisfactory. Short term accelerated stability studies were conducted for Carvedilol Phosphate 40mg matrix tablets for the best formulation F3, were carried out at 40 $\pm$ 2 ^oC and 75 $\pm$ 5% RH for one month (Table-7). There were no significant changes found during the study period. Hence the designed and developed formula of Carvedilol phosphate was stable.

Table.2. Pre compression parameters of tablet blends F1 to F4

Formulation Code	Bulk density (gm/cc)	Tapped density (gm/cc)	Compressibility index (%)	Hausner's ratio	Angle of repose (θ)
F1	0.486	0.562	13.12	1.15	24.67
F2	0.487	0.561	13.19	1.15	24.56
F3	0.434	0.497	12.67	1.142	25.34
F4	0.494	0.566	12.72	1.14	27.15

Table.3.Post compression studies for prepared tablets F1 to F4

Formulation Code	Hardness (kg/cm2)	Thickness (mm)	Drug content (%)	Friability (%)	Weight variation	DT
F1	7.56 ± 0.2	3.40 ± 0.01	96.4 ± 0.01	0.054	200 ± 7.5	ND
F2	7.26 ± 0.2	3.40 ± 0.04	96.1 ± 0.05	0.032	200 ± 7.5	ND
F3	7.94 ± 0.2	3.41 ± 0.04	98.6 ± 0.10	0.086	200 ± 7.5	ND
F4	7.61 ±0.2	3.40 ± 0.02	96.4 ± 0.06	0.154	200 ± 7.5	ND

DT – Disintegration Time
ND – Non Disintegrating

Table.4. In vitro release profiles of Carvedilol phosphate from tablets of F1 -F4

Time (hrs)	Innovator profile (COREG)	Cumulative percentage of drug released* AM ± SD			
		F-I	F-II	F-III	F-IV
0	0	0.0 ± 0.0	0.0 ± 0.0	0.0± 0.0	0.0 ± 0.0
1	10	38.07± 0.46	30.27± 0.66	25.20± 2.02	18.43± 0.78
2	20	60.27± 1.15	55.21± 3.18	34.20 ± 3.63	27.45± 0.54
4	40	79.11± 0.85	68.21± 0.95	39.03 ± 3.93	35.54± 1.52
6	53	88.53± 0.98	76.53± 0.88	50.39 ± 3.06	46.38± 0.67
8	65	95.26± 0.45	84.26± 0.45	61.85 ± 1.09	52.65± 0.78
12	81	--	96.34± 0.78	70.57 ± 1.57	61.72± 0.56
18	94	--	--	83.34± 1.59	72.45± 1.34
24	96	--	--	92.45± 1.67	84.34± 1.45
F2 factor		**20.25**	**20.49**	**67.51**	**52.64**

AM- Average Mean
SD-Standard Deviation

Table.5.Kinetic treatments of dissolution data for optimized formulation F3

Time (hrs)	$\sqrt{T}$	Log T	C%DR*	Log C%DR*	C%DR**	Log C %DR**	Q01/-Qt1/3
0	0	0	0	0	0	0	0
1	1	0	25.2	1.401	74.8	1.874	0.428
2	1.414	0.301	34.2	1.534	65.8	1.818	0.604
4	2.000	0.602	41.03	1.615	58.76	1.769	0.754
8	2.828	0.903	61.85	1.791	38.15	1.581	1.275
12	3.464	1.079	70.57	1.840	29.43	1.469	1.555
18	4.243	1.301	83.34	1.946	16.66	1.222	2.088
24	4.899	1.380	92.45	1.990	7.55	0.878	2.680

T – Time
Cumulative% Drug Released – C%DR*
Cumulative% Drug Remaining – C%DR**

Table.6. Zero order, First order, Higuchi, Peppas and Hixson Crowell data for prepared Carvedilol phosphate tablet F3

KINETICS	Regression Coefficient (R^2)
ZERO	0.9435
FIRST	0.9908
HIGUCHI	0.9864
PEPPAS	0.9887
HIXSON-CROWELL	0.9953

Table.7. In Vitro release of Carvedilol phosphate from tablets of F3 on zero Day and samples after Three month accelerated stability studies

Time (hours)	Cumulative percentage of drug released* from Tablets AM ± SD			
	Zero day	After one month	After two months	After Three months
0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
1	13.07 ± 0.57	12.08 ± 0.63	12.08 ± 0.63	12.08 ± 0.63
2	24.33 ± 0.68	23.12 ± 0.67	23.12 ± 0.67	23.12 ± 0.67
4	37.24 ± 1.55	36.34 ± 0.98	36.34 ± 0.98	36.34 ± 0.98
6	49.46 ± 2.23	50.45 ± 0.12	50.45 ± 0.12	50.45 ± 0.12
8	57.63 ± 1.99	56.92 ± 1.35	56.92 ± 1.35	56.92 ± 1.35
12	74.13 ± 0.84	73.17 ± 1.86	73.17 ± 1.86	73.17 ± 1.86
18	89.29 ± 0.97	88.23 ± 0.69	88.23 ± 0.69	88.23 ± 0.69
24	96.14 ± 0.65	94.95 ± 0.80	94.95 ± 0.80	94.95 ± 0.80

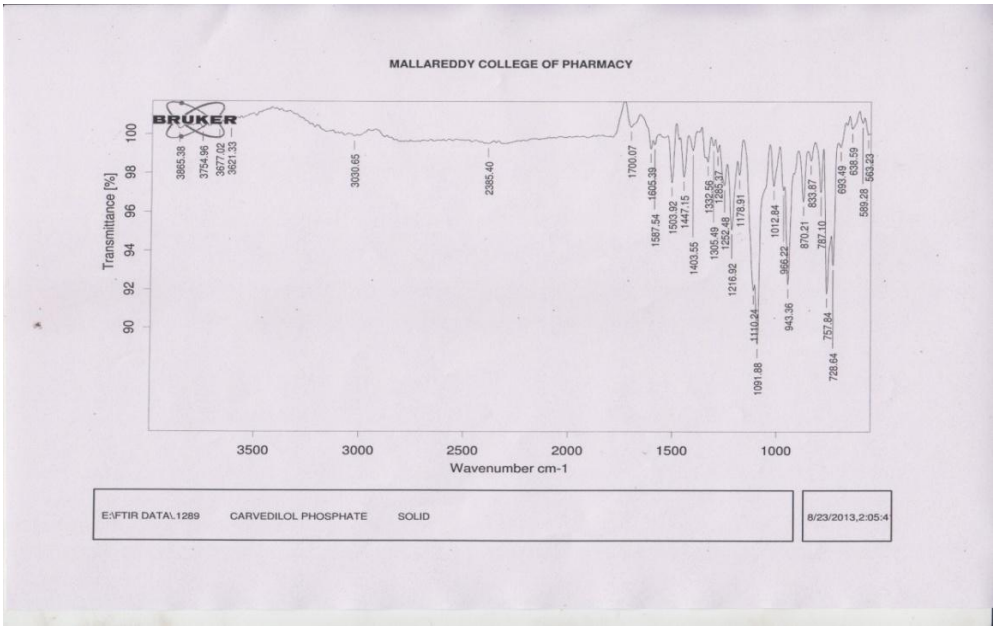

Fig.1. FT-IR spectrum of pure Carvedilol phosphate

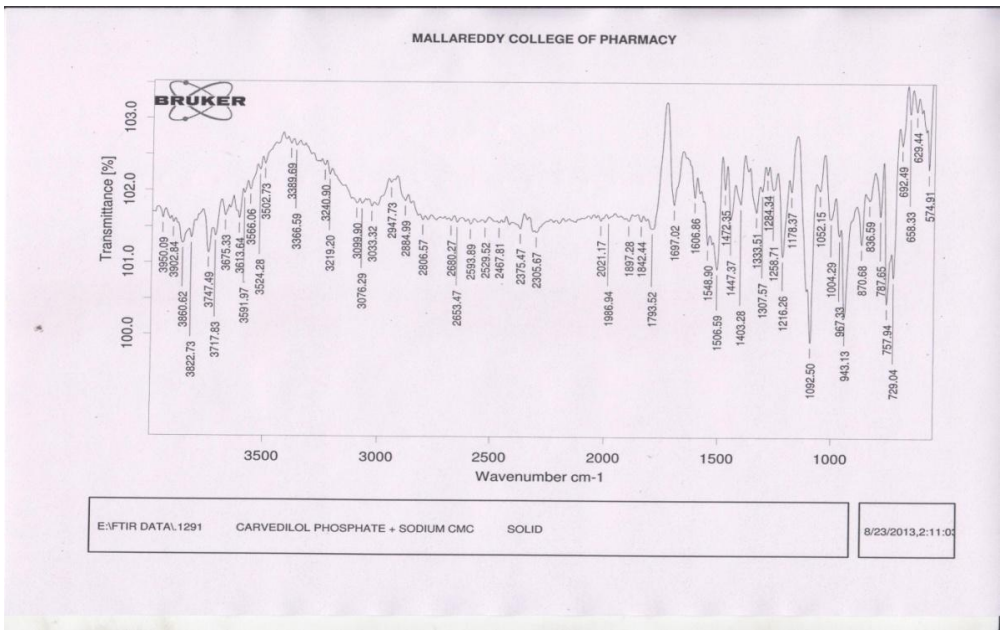

Fig.2. FT-IR spectrum of physical mixture of Na CMC and Carvedilol phosphate

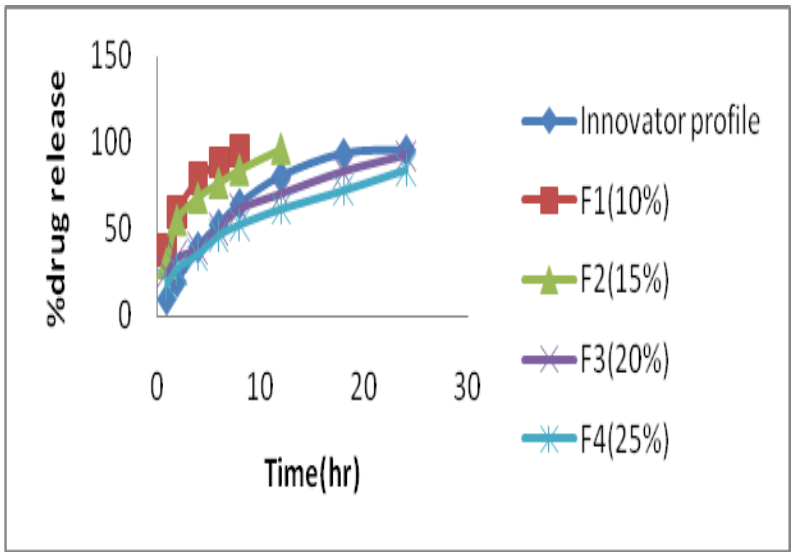

Fig.3. Comparison of dissolution profiles of formulation F1 to F4

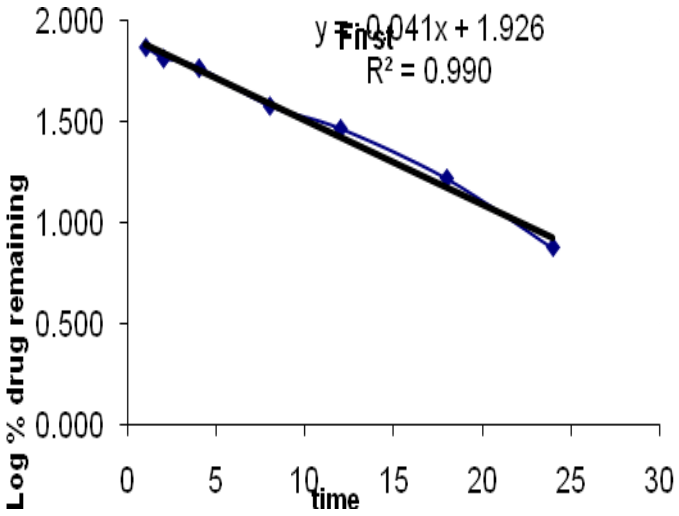

Fig.4.Zero order release plot for optimized formulation (F3) of Carvedilol phosphate

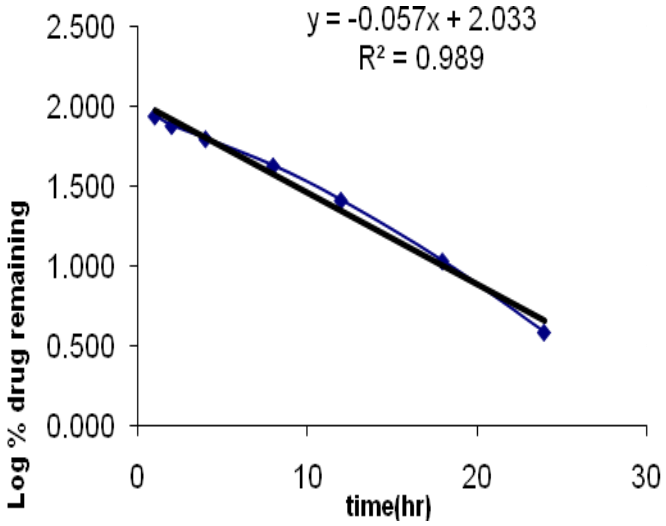

Fig.5.First order release plot for optimized formulation (F3) of Carvedilol phosphate

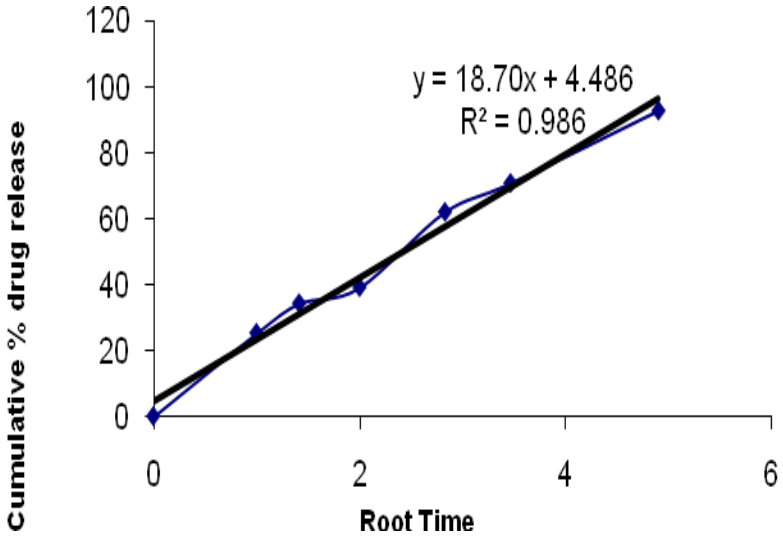

Fig.6. Higuchi's Plot for optimized formulation (F3) of Carvedilol phosphate

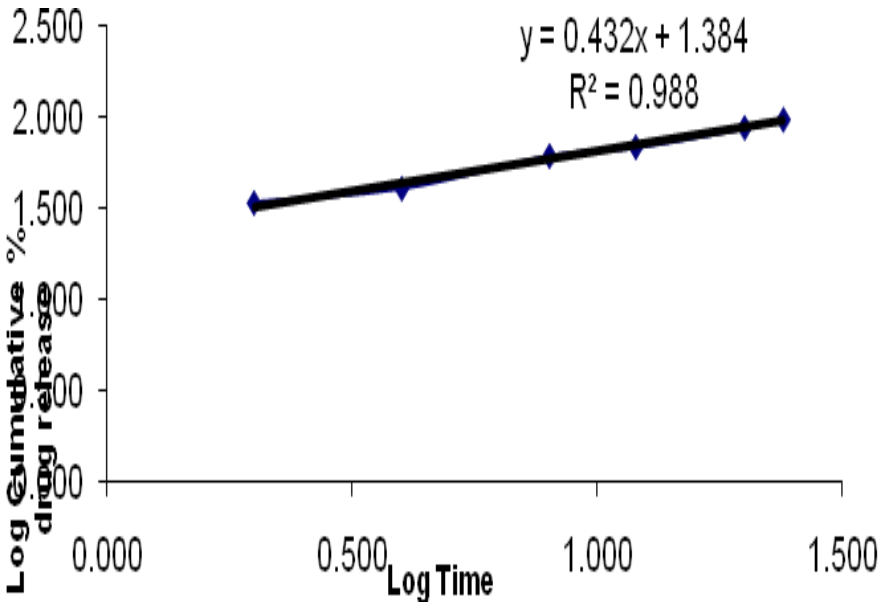

Fig.7. Korsmeyer's Plot for optimized formulation (F3) of Carvedilol phosphate

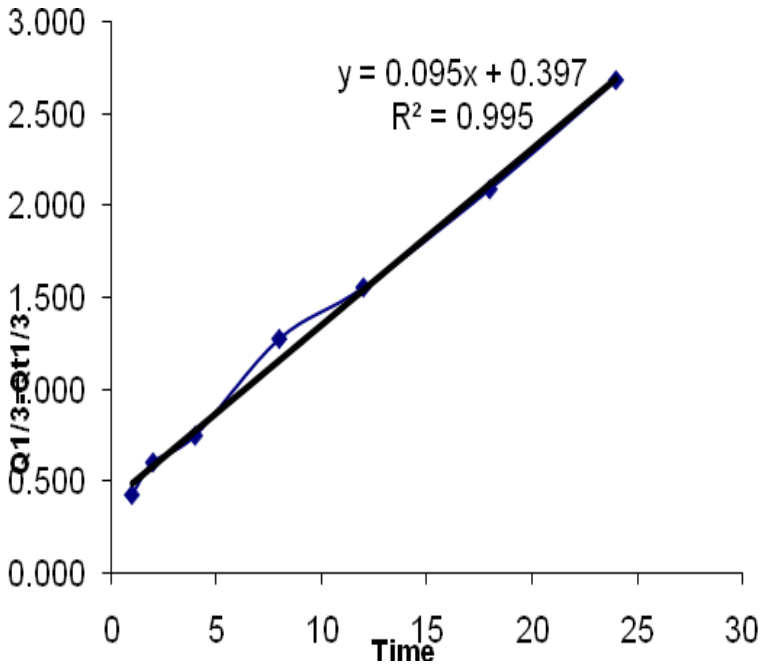

Fig.8.Hixson-Crowell plot for optimized formulation (F3) of Carvedilol phosphate

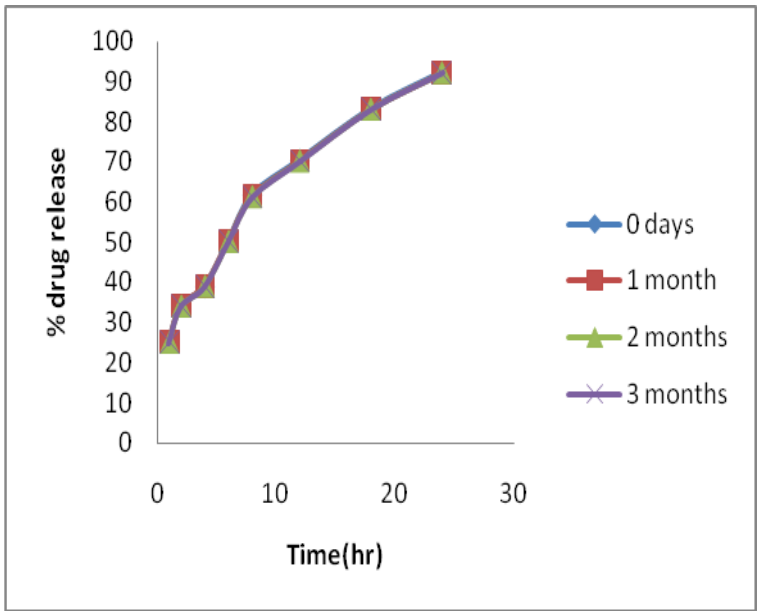

Fig.9. Accelerated stability studies for formulation F3

CONCLUSION

- Matrix tablets formulated employing sodium carboxy methyl cellulose polymer is suitable for oral sustained release of Carvedilol phosphate. Carvedilol phosphate release from the formulated tablets was slow and spread over 24 h and depended on percent polymer in the tablet. Fickian diffusion was the drug release mechanism from the formulated tablets. Carvedilol phosphate release from matrix tablets F3 formulated employing 20 % cross carmellose sodium was similar to that from COREG Tablets, a commercial controlled release formulation of Carvedilol phosphate. Drug-excipient interaction and stability studies were carried out and was observed that there was no interaction. Crosscarmellose sodium polymer is suitable for the design of oral sustained release tablets.

REFERENCES

1. Langer R. drug delivery and targeting. Nature. 1998; 392:5-10.
2. Vekataraman S, Jie P, Min F, Freddy B Y C, Leong-huat G. Micelle-like nanoparticles of PLGA PEG PLA triblock copolymer as chemotherapeutic carrier. Int. J. Pharm. 2005; 298:219-232.
3. Vidyadhara.S, PR.Rao, Prasad JA. Formulation and evaluation of Propranolol hydrochloride oral controlled release matrix tablets. Indian J Pharm Sci. 2004; 66: 188-192.
4. Reddy KR, Mutalik S, Reddy S. Once daily sustained release matrix tablets of nicorandil: formulation and in vitro evaluation. AAPS Pharm. Sci Tech.2003; 4:1-9.
5. Mohammed AD, James LF, Michael HR, John EH. Rajabi- Siahboomi AR. Release of propranolol hydrochloride from matrix tablets containing sodium carboxy methyl cellulose

and Hydroxypropyl methyl cellulose. Pharm Dev Tech. 1999; 4: 313-324.
6. Nicholas AJ, Sulpizio AC, Ashton DJ, Hieble JP, Ruffolo RR Jr. In vitro pharmacologic profile of the novel beta-adrenoreceptor antagonist and vasodialator, carvedilol. Pharmacology. 1989; 39:327-336.
7. Ruffolo RR, Gellai M, Hieble JP, Willette RN, Nicholas AJ. The pharmacology of carvedilol. European Journal of Clinical Pharmacology. 1990; 38:S82-88.
8. Nicholas AJ, Gellai M, Ruffolo RR Jr. Studies on the mechanism of arterial vasodialation produced by the novel anti hypertensive agent, carvedilol. Fundamental Clinical Pharmacology. 1991; 5:25-38.
9. Feuerstein GZ, Rufflo RR Jr. Carvedilol, a novel multiple action antihypertensive agent with antioxidant activity and the potential for myocardial and vascular protection. European Heart Journal. 1995; 16:38-42.
10. Sung CP, Arleth AJ, Ohlstein EH. Carvedilol inhibits vascular smooth muscle cell proliferation. Journal of Cardiovascular Pharmacology.1993; 21:221-27.
11. Raju D B, Sreenivas R and Varma M M. Formulation and evaluation of floating drug delivery system of Metformin Hydrochloride. *J. Chem. Res.* 2010; 2(2): 274-278.
12. Arunachalam A, Sudhakar Babu A M S, Varatharajan P. Preparation and *in vitro* evaluation of sustained release tablets of Aceclofenac. International Journal of Research in Pharmaceutical and Nano Sciences. 2012; 1(1): 1-10.
13. M. Suvarchala, A.M.S. Sudhakar babu, P. Venkateswararao, G. Lakshmi Devi. Formulation and *in vitro* evaluation of Sumatriptan Succinate fast dissolving tablets. International Journal of Research in Pharmaceutical and Nano Sciences. 2012; 1(2): 111-123.