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International Journal of Current Research
Vol. 7, Issue, 03, pp.13316-13337, March, 2015

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

FORMULATION AND EVALUATION OF BISOPROLOL FUMARATE EXTENDED RELEASE TABLETS

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ARTICLE INFO

Article History:
Received 20th December, 2014
Received in revised form
16th January, 2015
Accepted 23rd February, 2015
Published online 17th March, 2015

Key words:

Bisoprolol fumarate.
Extended release tablets,
Hydroxy propyl methyl cellulose,
Eudragit L100.

ABSTRACT

Bisoprolol is a cardio selective β-blocker. It is given as the fumarate in the management of hypertension and angina pectoris. On oral administration, the drug undergoes extensive first pass metabolism. The purpose of this study was to develop and evaluate Bisoprolol extended release tablets by the wet granulation method using different proportions of polymers and binder. Pre-formulation studies were done initially and the results were found to be within the limits. All the mentioned batches were prepared and granules were evaluated for pre-compression parameters such as loss on drying, bulk density, tapped density and compressibility index. Tablets were evaluated for weight variation, thickness, hardness, friability; disintegration time and assay were found to be within the limits. In vitro dissolutions were performed with 0.05M 6.8 PH phosphate buffer and effect of various polymers were explored. Final selection of formulation was based on dissolution profile, from dissolution studies, formulation 9 showed 80% drug release within 20 hours, so it will be compared with innovator. Similarity and difference factors which revealed that formulation (F 9) containing HPMC K 200, Eudragit L100 and binder are most successful as it exhibited in vitro drug release that matched with innovative products. In vitro drug release profile reveals that with increased concentration of Eudragit L 100. Accelerated stability studies were performed for the optimized batch, which indicated that there were no changes in drug content and in vitro dissolution.

INTRODUCTION

An extended release dosage form, which contains several times the therapeutic dose for maintaining the reached blood level concentration. The main concept of the extended drug delivery system is the use of the system and techniques for changing and controlling the absorption, blood levels, metabolism, organ distribution and cellular uptake of pharmaceutically active agents (Juliano, 1980). The main aim of the extended or controlled dosage form is to produce an improved therapy by producing a uniform plasma concentration of drug at steady state and by reducing the ratio of maximum and minimum plasma levels. This could be achieved if the release of drug from the dosage form is slow, first order or slow zero order absorption of the drug occurs from the gastrointestinal tract (Robinson, 1978). The term "extended release" is known to have existed in the medical and pharmaceutical literature for many decades. It has been constantly used to describe a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed and prolonged and its plasma profile is extended in duration. The onset of its pharmacological action is often delayed and duration of its therapeutic effect is extended (Yie W. Chien, 1992). Extended release systems include any drug delivery system that achieves slow release of drug and maintain the effective therapeutic concentration over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue or organ, it is considered as a controlled-release system. If it is unsuccessful at this, but nevertheless extends the duration of action over that reached by conventional delivery, it is considered as a prolonged release system (Gennaro, 1995).

Drug release period restricted to residence time in the gastrointestinal tract (Peter *et al.,* 1991). For dissolution or diffusion sustaining forms, much of the drug will reach in the small intestine in solid form (Shargel *et al.,* ?). That means the solubility of the drug is likely to change several orders of magnitude during its release (Andrasi *et al.,* 2007). The biological half-life and duration of action of drug obviously play a major role in the process of considering a drug for sustained release (Leo *et al.,*1997). The rate at which drug enters the circulation must be approximately equivalent to the rate of its elimination. The elimination rate is quantitatively described by the half-life (Jantez *et al.,* 1996). A heterogeneous

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dispersion or solution of the drug in water swellable hydrogel matrix controls drug release by slow surface to center swelling of the matrix. Liquid-liquid encapsulation of the drug in a viscous solution of polymer, which controls drug release by slow diffusion. Pumps that either mechanically or chemically release drug in a controlled manner. Drug coated micropellets, which have an apparent density lower than that of gastric juice. The final product floats on gastric juice for an extended period, while slowly releasing the drug. Drug containing bio-adhesive polymer that adheres to the gastrointestinal mucosal layer and release drug slowly at a constant rate (Robinson *et al.,*1987).

MATERIAL AND METHODS

Bisoprolol fumarate taken gift sample from Eros Pharma, Bangalore and Microcrystalline cellulose pH 101, Eudragit L 100 purchased from Rohm Pharma, Bombay. Lactose monohydrate from Kelco Pharma. HPMC E 3LV, Povidone K 90, HPMC K4M, HPMC K 200, MCC 112, Aerosil 200, Stearic acid, Cross carmellose purchased from SD Fine Chem., Bombay.

Drug-Excipients compatibility studies

FT-IR STUDY: One part of the sample and three parts of potassium bromide were taken in a mortar and triturated. A small amount of triturated sample was taken into a pellet maker and was compressed at 10kg/cm2 using a hydraulic press. The pellet was kept on to the sample holder and scanned from 4000cm-1to 400cm-1 in Bruker IR spectrophotometer. Then it was compared with original spectra (Pavia *et al.,* 2002).

DSC Study

Differential Scanning Calorimetry of Bisoprolol fumarate and optimized formulations was recorded between 30.0°C to 300.0°C at the rate of 20.0°C per minute under the environment of nitrogen (Beckett *et al.,* 2004).

Preparation of calibration curve for Bisoprolol fumarate

Preparation of stock solution 1:

Bisoprolol fumarate equivalent to 100 mg was weighed and transferred to 100 ml volumetric flask, dissolved in few ml of methanol and the final volume was made up to 100ml with 6.8 pH Phosphate buffer. The resulted solution had the concentration of 1mg/ml (1000µg/ml) which was labeled as "stock solution 1"

Preparation of stock solution 2:

From the stock solution 1, 1 ml was pipette out in 100ml volumetric flask and the final volume was made up to 100ml with 6.8 pH Phosphate buffer. The resulted solution had the concentration of 0.1mg/ml (100µg/ml) which was labeled as "stock solution 2". From the second stock solution, various volumes of solution were pipette into different 25 ml volumetric flasks as shown in Table 1 given below:

Table 1. Standard calibration curve values

S.No	Concentration (µg/ml)	Absorbance At 260nm
1	10	0.016
2	20	0.034
3	30	0.062
4	40	0.083
5	50	0.112
6	60	0.133

The volume in each 25 ml volumetric flask was made up to 25 ml with 6.8 pH Phosphate buffer and the absorbance was measured at the λ_{max} of 260 nm for Bisoprolol fumarate. Absorbances of different concentrations were measured against a blank that is distilled water using Shimadzu spectrophotometer. A standard graph was obtained by plotting concentration of Bisoprolol fumarate per ml versus absorbance value at (260 nm). The standard graph obtained is shown below in Figure 1.

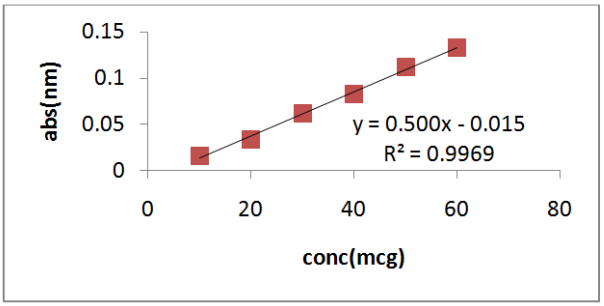


Fig. 1. Calibration curve of bisoprolol fumarate

Preparation of the matrix tablets

In this work, the wet granulation method is used to prepare matrix tablets of Bisoprolol fumarate. Combination of polymers, i.e. HPMC 3LV and HPMC K4M was used in different concentration along with the drug. In other formulations, different types of diluents were used, i.e. microcrystalline cellulose, and binder like PVP K90. Talc and Magnesium stearate and stearic acid were used as lubricant and glidant respectively as shown Tables 2-3.10 batches were prepared and the method details are given below (Dr. Jave *et al.,* 2008).

Table 2. Formula for the matrix tablets of bisoprolol fumarate for 1 tablet (F1-F5)

Name of the Ingredients	F1	F2	F3	F4	F5
	Mg/tab	Mg/tab	Mg/tab	Mg/tab	Mg/tab
Intragranular	0.38	0.38	0.38	0.38	0.38
Bisoprolol fumarate	17.22	-	17.22	17.22	41.22
Lactose monohydrate	40	40	85.6	73.6	67.6
Microcrystalline	-	-	12	12	6
cellulose PH 101	2.4	-	-	-	-
Eudragit L 100	-	19.62	-	-	-
HPMC E 3LV	-	-	4.8	4.8	4.8
Povidone K 90	q.s	q.s	q.s	q.s	q.s
HPMC K4M					
Purified water	120	100	100	100	100
Extragranular	52.8	72.8	12.8	12.8	12.8
HPMC K 200	4.8	4.8	4.8	4.8	4.8
MCC 112	2.4	2.4	2.4	2.4	2.4
Aerosil 200					
Stearic acid	240	240	240	240	240
TOTAL					

Table 3. Formula for the matrix tablets of bisoprolol fumarate for 1 tablet (F6-F9)

Name of the ingredients	F6	F7	F8	F9
	Mg/tab	Mg/tab	Mg/tab	Mg/tab
Intragranular	0.38	0.38	0.38	0.38
Bisoprolol fumarate	41.22	41.22	41.22	41.22
Lactose monohydrate	6	6	6	12
Eudragit L 100	-	-	-	-
HPMC 3LV	4.8	4	3.6	3.5
Povidone K 90	-	-	-	-
HPMC K4M	q.s	q.s	q.s	q.s
Purified water				
Extra granular	100	100	100	100
HPMC K 200	40.6	41.2	41.6	35.7
MCC 112	4.8	4.8	4.8	4.8
Aerosil 200	2.4	2.4	2.4	2.4
Stearic acid	240	240	240	240
Total				

Bisoprolol fumarate 9 formulations were prepared by the wet granulation method.

↓

Accurately weighed quantity of drug and excipients were passed through sieve no. 40 # and mixed thoroughly

↓

(PVP: Water) 1: 9 solution was added and which forms mass and mass passed through from mesh #16

↓

The granules were dried at 65 ^{o}C for 1 hr

↓

Then passed through mesh # 20 and # 40 (#20 for granules and #40 for fines)

↓

Then glidant and lubricant were passed through # 80

↓

Then excipients added to the granules and mix for 5 min

↓

These granules are ready for compression

Evaluation of powder blend

Blend was evaluated for flow properties by following parameters (Agro food industry Hi-tech 2008 , Science alert 2008):

Angle of repose: 20gms of the sample was taken and it was passed through the funnel from a certain height to obtain the heap. The height of the sample heap formed was measured. The circumference formed was drawn with a pencil on the graph paper The radius was measured and the angle of repose was determined. This was repeated three times for a sample and calculated by following formula(Satyabrathabhanja.et.al 2010).

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

Where, h = height, r = radius.

Tapped density: Tapped Density was determined by the USP method II apparatus. A known quantity of powder was transferred to a graduated cylinder and volume V_0 was noted. The cylinder was fixed to apparatus and tapped for 200 times, then reading was observed. After observing the initial volume the cylinder was mechanically tapped and volume reading was taken until little further volume changes was observed and calculated by following equation (Satyabrathabhanja.et.al 2010).

$$\rho_t = M / V_t$$

Where, M = mass of the powder,V_t= final tapping volume of the powder.

Hausner ratio: Hausner ratio is the ratio between the tapped density and bulk density as shown in following equation (Satyabrathabhanja *et al.,* 2010).

$$\text{Hausner ratio} = \rho_t / \rho_b$$

Where, ρ_t= tapped density, ρ_b= bulk density.

Bulk density: Bulk density was determined by measuring the volume of known mass of powder sample that has been passed through the screen into a graduated cylinder and calculated by the following equation (Owens *et al.,* 2005).

$$\rho b = M / Vb$$

Where, M= mass of the powder;V_b=bulk volume of the powder.

Compressibility index: The procedure is to measure the unsettled apparent volume, (V_0), and the final tapped volume, (V_t), of the powder after tapping the material until no further volume changes occur. The compressibility index was calculated as follows (Owens *et al.,* 2005):

$$I = (\rho_t - \rho_b)/ \rho_t \times 100$$

Where, ρ_t= tapped density,ρ_b= bulk density.

EVALUATION OF TABLETS

The important parameters in the evaluation of tablets can be divided into following:

Weight Variation: Twenty tablets were weighed individually and the average weight calculated. The individual weights were then compared with the average weight. The tablets passes the test if not more than two tablets fall outside the percentage limit and none of the tablets differ by more than double the percentage limit given below (Satyabrathabhanja *et al.,* 2010).

Average of the tablet Percentage deviation
80 mg or less ± 10
More than 80 mg and less than 250 mg ± 7.5
250 mg or more ± 5.0
Percentage deviation = (Difference between Average weight and tablet weight/ Average tablet weight) X 100

Friability: A definite quantity (20 tabs.) of weighted tablets were placed in the friabilator and then operated at 25 rpm for four minutes. The tablets were then removed and weighed. The difference in the two weights is used to calculate friability (F) following equation (Martin Physical pharmacy):

$$F = 100 [1 – W / Wo]$$

Where, Wo= Initial weight, W=Final weight.

Hardness: The tablet was held between a fixed and moving jaw, the body of the Monsanto hardness tester carries an adjustable scale which was set to zero against an index mark fixed to the compression plunger, when the tablet was held between the jaws. The load was gradually increased until the tablet fractured. The value of the load at the point gave a measure of the tablet (M.Aulton, Pharmaceutics, Indian Pharmacopeia, 2007).

Thickness: Control of physical dimensions of the tablets such as thickness is essential for consumer acceptance and tablet uniformity (Lachman *et al.,* 1991; JSIR 2007; Biotechnology and Applied biochemistry-2002).

***IN – VITRO* DISSOLUTION STUDIES**

900ml of dissolution media was taken. The Paddle rotation was adjusted to 100 rpm, the temperature being maintained at 37± 0.5ºC throughout the study. Phosphate buffer pH 6.8 was used as a Dissolution medium. 5 ml of the sample of dissolution medium was withdrawn and replaced with the dissolution medium. Samples were filtered through What man filter paper 41 and were analyzed 1 hour interval spectrophotometrically at 260nm (Shimadzu). The results of in vitro release profile obtained for all the formulations were plotted in modes of data treated as follows (Taylan *et al.,* 1996; Labot *et al.,* 2002; Indian pharmacopoeia, 2010; Korsemeyer *et al.,* 1983). Zero Order Kinetics: Zero order release would be predicted by the following equation:

$$\mathbf{A_t = A_o \text{ --- } K_o t}$$

Where, At=Drug release at time‘t’,A_o=Initial drug concentration, K_o=Zero-order rate constant (hr^{-1})

First Order Kinetics: First – order release would be predicted by the following equation:

$$\text{Log } C = \text{Log } C_o – Kt / 2.303$$

Where, C = Amount of drug remained at time ‘t’,C_o = Initial amount of drug, K = First –order rate constant (hr^{-1}).

Higuchi’s Model: Drug released from the matrix devices by diffusion has been described by following Higuchi’s classical diffusion equation:

$$\mathbf{Q = [D\varepsilon / \tau (2A - \varepsilon Cs) Cst]^{1/2}}$$

Where Q = Amount of drug released at time ‘t’, D = Diffusion coefficient of the drug in the matrix, A = Total amount of drug in unit volume of matrix, Cs = the solubility of the drug in the matrix, ε = Porosity of the matrix, τ = Tortuosity, t = Time (hrs) at which ‘q’ amount of the drug is released., Above equation may be simplified if one assumes that D, Cs and A are constant. Then equation becomes:

$$\mathbf{Q = Kt ½}$$

Peppa’s Model: In order to understand the mode of release of drug from swelleable matrices. The data were fitted to the following peppa’s law equation.

$$\mathbf{Mt / M\propto = Kt^n}$$

Where Mt / M∝ = the fraction of drug released at time ‘t’, K = Constant incorporating the structural and geometrical characteristics of the drug / polymer system., N = Diffusion exponent related to the mechanism of the release.

Hixon- Crowell erosion equation: Hixson-Crowell cube root law, as the *cube root of percentage drug remaining vs. time* correlated the release from systems with polymer erosion/dissolution resulting in a change in surface area and diameter of particles or tablets and calculated following equation:

$$\mathbf{Q_0^{1/3} – Q_t^{1/3} = k_{HC} t}$$

Where, Q_t = the amount of drug released in time t,Q_0 = the initial amount of the drug in the tablets
k_{HC} i=the rate constant for the Hixson-Crowell rate equation.

Stability studies: Stability studies were performed at two temperatures Viz, 25°C ± 2ºC / 60% RH ± 5% RH and 30°C ± 2ºC / 65% RH ± 5% RH over a period of one month on the matrix tablet formulation F-9 and marketed drug Mirapex ER. Sufficient number of tablets (Ten) were packed in amber colored capped bottles and kept in stability chamber maintained at 25°C and 30°C. Samples were taken at weakly intervals for drug content estimation. At the end of one month period, dissolution test was performed to determine the drug release profiles.

RESUTLS AND DISCUSSION

Preformulation Studies

Drug – Excipient Compatibility Studies

FT-IR studies

As described in the methodology section the FT-IR studies were carried out for the pure drug alone and along with polymers. The results are summarized as follows. An FT-IR spectrum of pure Bisoprolol fumarate is shown in the Figure 2 and Drug and excipients compatibility are listed in the Table 4. Similarly FT-IR spectra of Bisoprolol fumarate dihydrochloride monohydrate in combination with polymers. . These peaks were not affected and prominently observed in FT-IR spectra given in Figures 3 to7. This indicates that there is no interaction between Bisoprolol fumarate and polymers and the drug was compatible with the formulation components.

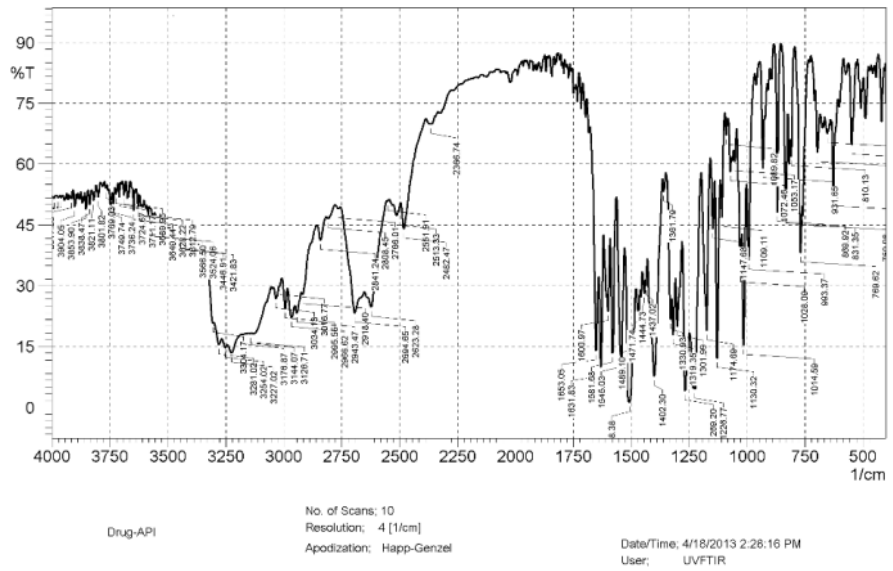


Fig. 2. FTIR graph of pure drug of Bisoprolol fumarate

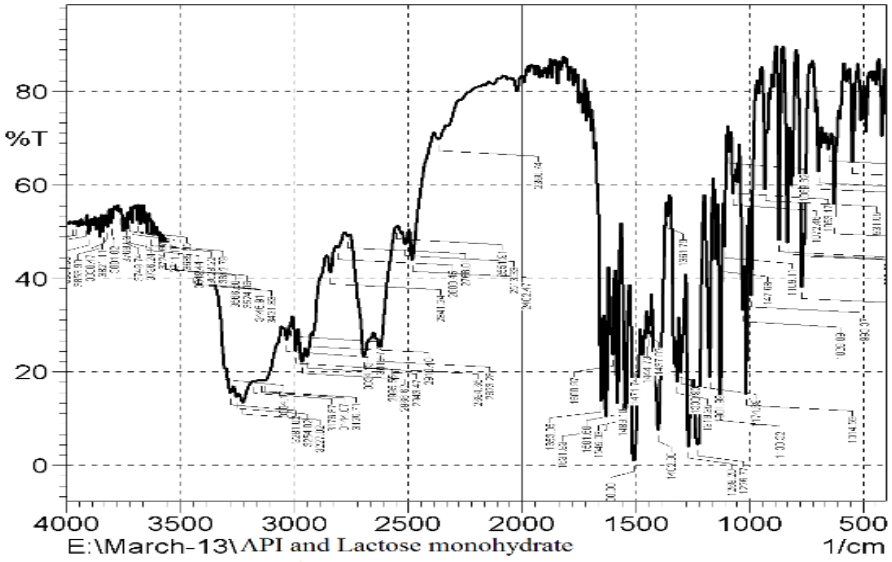


Fig. 3. FTIR graph of pure drug of Bisoprolol fumarate

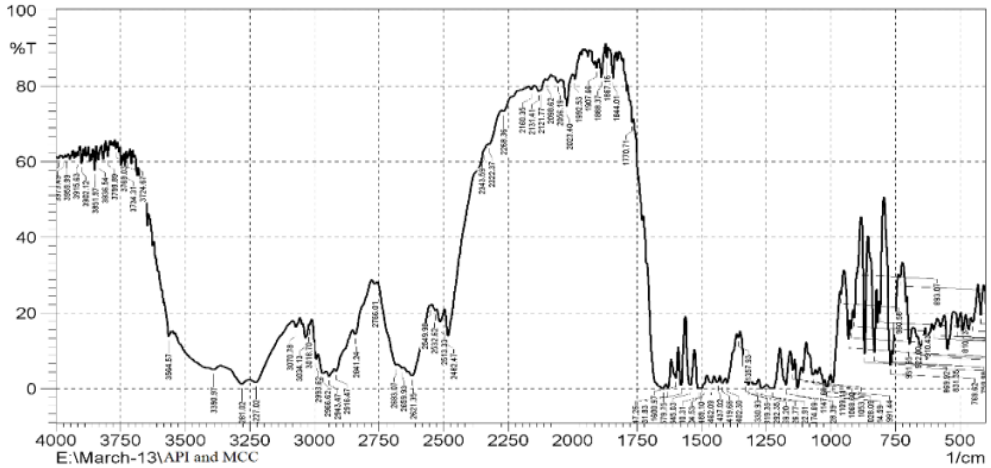


Fig. 4. FTIR Graph of Bisoprolol fumarate +MCC

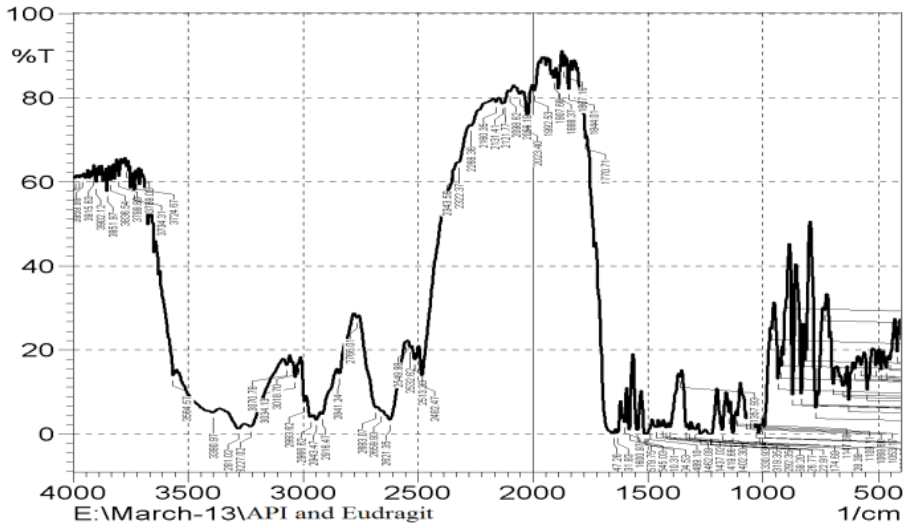


Fig. 5. FTIR Graph of Bbisoprolol fumarate + Eudragit

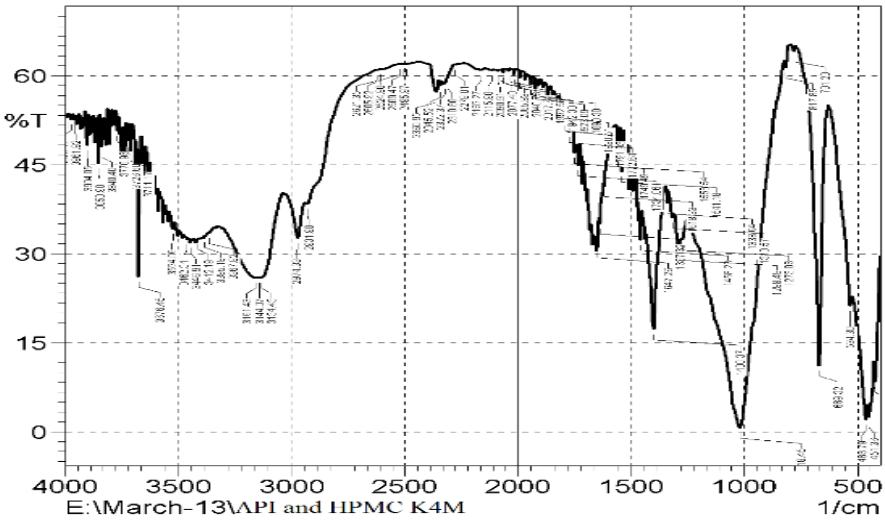


Fig. 6. FTIR Graph of bisoprolol fumarate + HPMCK4M

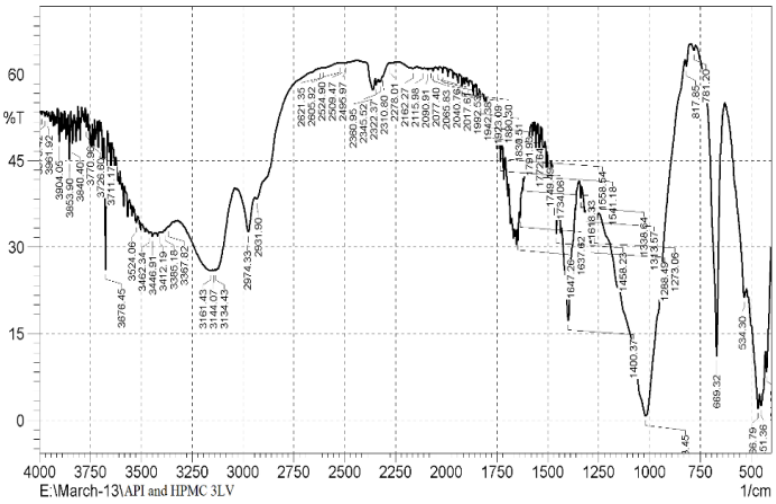


Fig. 7. FTIR Graph of Bisoprolol fumarate+ HPMC3LV

Table 4. Results of drug and excipients compatibility study

S.No	Drug and excipients	Ratio	Observation
1	API and lactose monohydrate	1:5	NCC
2	API and MCC	1:5	NCC
3	API and Eudragit	1:5	NCC
4	API and HPMC 3LV	1:5	NCC
5	API and HPMC K4M	1:5	NCC

DSC STUDY

The compatibility and interactions between drugs and polymer were checked using differential scanning calorimetry (DSC) results obtained were shown Figures 8-9. DSC thermogram showed that there was no any major difference in onset temperature and peak temperature, when compared with pure drug thermogram. No interaction was found between drug and polymers. From the DSC results it was observed that the characteristic peak of drug is not observed in the formulation. Hence it indicates the physical nature of the drug is not changed in the formulation.

Formulation and evaluation of extended release tablets

Precompression Parameters

Table 5 represents the physical properties of the granules used for the preparation of tablets. The flow properties such as angle of repose, Hausner's ratio, Carr's index, Bulk density and Tapped density are considered as indirect measurements of powder flowability. Hausner's ratio is indicative of inter-particular friction; the Carr's index shows the propensity of a material to diminish in volume. As the values of these indices increase, the flow of the powder decreases. All parameter values are within the satisfactory limit compared with the standard values.

Evaluation of tablets

The weighed quantities of the drug and polymer were mixed thoroughly in different combination and compressed into tablets of appropriate dimensions by wet granulation method.

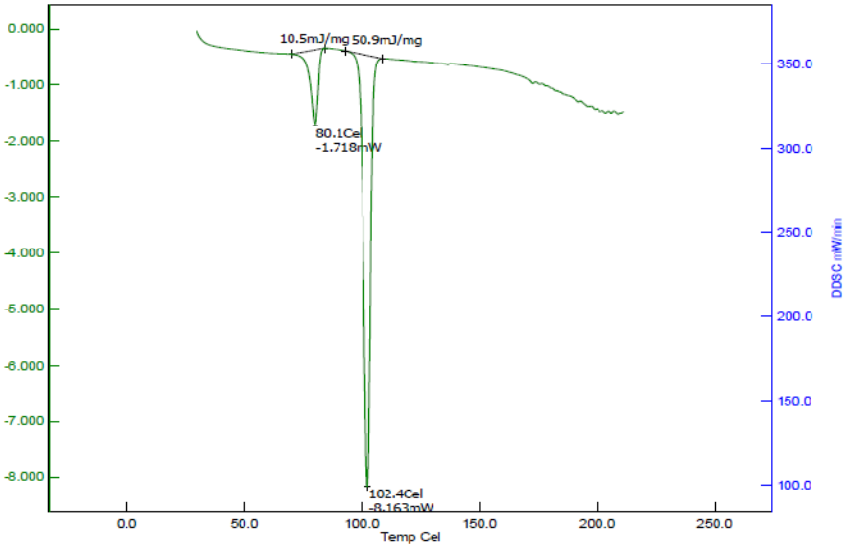


Fig. 8. DSC of Bisoprolol fumarate

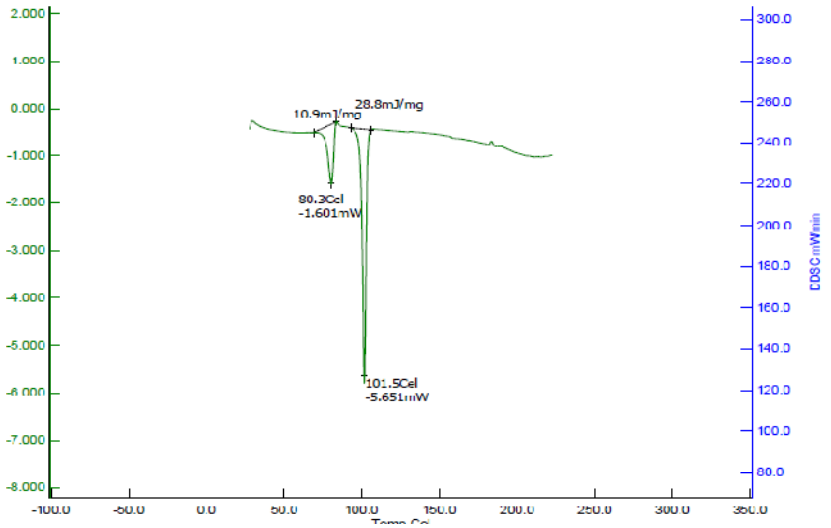


Fig.9. DSC of optimized formulation

Table 5. Evaluation of mixed blend of drug and excipients

Formulation code	% of fines	Angle of repose (θ)	Bulk density (gm /cm ^{3})	Tapped density (gm /cm^3)	Carr's index	Hausner's Ratio
F-1	18.45	24.62	0.416	0.454	1.338	1.09
F-2	18.63	27.40	0.454	0.500	9.100	1.10
F-3	17.71	27.11	0.416	0.454	8.330	1.09
F-4	20.79	28.30	0.357	0.400	10.72	1.12
F-5	20.09	29.21	0.454	0.476	4.536	1.04
F-6	20.62	27.29	0.416	0.454	8.330	1.09
F-7	20.26	26.95	0.384	0.416	7.678	1.08
F-8	19.29	27.75	0.330	0.362	8.004	1.08
F-9	19.15	28.39	0.458	0.500	8.250	1.09

The compressed tablets were tested for physical parameters like hardness, weight variation, friability, thickness, evaluated for the drug content uniformity and In–vitro drug release profiles and stability studies. The prepared tablets were evaluated for weight variation and the results are given in Table 6-8, the percentage deviation from the average weight was found to be within the prescribed official limits.

The tablet hardness was found to be in the range of NLT 15 kgs Kg/cm2 and results, also the friability was found to be in the range of 0.013-0.41, fulfilling official requirements (not more than 1%) as shown in Table 9.

Table 6. Weight variations for tablet formulation F-1, F-2 and F-3

S.No	F-1			F-2			F-3		
	Wt in Mg	Difference in Wt	%Deviation	Wt in Mg	Difference in Wt	% Deviation	Wt in Mg	Difference in Wt	% Deviation
1	238	1.75	0.73	240	-0.25	0.10	240	-0.25	0.10
2	238	1.75	0.73	238	1.75	0.73	238	1.75	0.73
3	238	1.75	0.73	241	-1.25	0.72	241	-1.25	0.93
4	240	-0.25	0.10	242	-2.25	0.92	240	-0.25	0.10
5	238	1.75	0.73	241	1.75	0.72	241	-1.25	0.93
6	240	-0.25	0.10	238	1.75	0.73	238	1.75	0.73
7	238	1.75	0.73	238	1.75	0.73	238	1.75	0.73
8	241	-1.25	0.93	238	1.75	0.73	238	1.75	0.73
9	242	-2.25	0.92	240	-0.25	0.10	240	-0.25	0.10
10	241	1.75	0.93	238	1.75	0.73	238	1.75	0.73
11	241	1.75	0.93	240	-0.25	0.10	239	0.75	0.31
12	241	1.75	0.93	238	1.75	0.73	237	2.75	1.16
13	242	-2.25	0.92	241	-1.25	0.72	238	1.75	0.73
14	238	1.75	0.73	242	-2.25	0.92	240	-0.25	0.10
15	241	-1.25	0.93	241	1.75	0.72	238	1.75	0.73
16	241	-1.25	0.93	237	2.75	1.16	240	-0.25	0.10
17	240	-0.25	0.10	238	1.75	0.73	238	1.75	0.73
18	237	2.75	1.10	238	1.75	0.73	241	1.75	0.73
19	238	1.75	0.73	240	-0.25	0.10	242	-2.25	0.92
20	242	-2.25	0.92	238	1.75	0.73	241	1.75	0.73
	Average of 20 Tablets= 239.4			Average of 20 Tablets= 239.35			Average of 20 Tablets =239.85		

Table 7. Weight variations for tablet formulation F-4, F-5 AND F-6

S.No	F-4			F-5			F-6		
	Wt in Mg	Difference in Wt	%Deviation	Wt in Mg	Difference in Wt	% Deviation	Wt in Mg	Difference in Wt	%Deviation
1	238	1.35	0.56	239	0.4	0.16	238	1.85	0.77
2	239	0.35	0.14	240	0.6	0.25	238	1.85	0.77
3	238	1.35	0.56	240	0.6	0.25	238	1.85	0.77
4	240	0.65	0.27	242	-2.6	1.07	240	0.15	0.62
5	238	1.35	0.56	241	-1.6	0.66	238	1.85	0.77
6	239	0.35	0.14	238	1.4	0.58	239	0.85	0.35
7	240	0.65	0.27	238	1.4	0.58	240	0.15	0.62
8	240	0.65	0.27	238	1.4	0.58	240	0.15	0.62
9	239	0.35	0.14	240	0.6	0.25	242	-2.15	0.88
10	241	-1.65	0.68	238	1.4	0.58	241	-1.15	0.47
11	238	1.35	0.56	240	0.6	0.25	239	0.85	0.35
12	238	1.35	0.56	240	0.6	0.25	240	0.15	0.62
13	238	1.35	0.56	242	-2.6	0.25	240	0.15	0.62
14	240	0.65	0.27	241	-1.6	0.66	242	-2.15	0.88
15	238	1.35	0.56	239	0.4	0.16	241	-1.15	0.47
16	241	-1.65	0.68	238	1.4	0.58	238	1.85	0.77
17	240	0.65	0.27	238	1.4	0.58	240	0.15	0.62
18	242	-2.65	1.09	238	1.4	0.58	240	0.15	0.62
19	241	-1.65	0.68	240	0.6	0.25	242	-2.15	0.88
20	239	0.35	0.14	238	1.4	0.58	241	-1.15	0.47
	Average of 20 Tablets= 239.35			Average of 20 Tablets= 239.4			Average of 20 Tablets =239.85		

Table 8. Weight variations for tablet formulation F-7, F-8, F-9

S.No	F-7			F-8			F-9		
	Wt in Mg	Difference in Wt	% Deviation	Wt in Mg	Difference in Wt	% Deviation	Wt in mg	Difference in Wt	% Deviation
1	238	2.25	0.94	240	0.1	4.16	238	2	0.84
2	240	0.25	0.10	240	0.1	4.16	240	0	0
3	240	0.25	0.10	242	-1.9	0.78	240	0	0
4	242	-1.75	0.72	241	0.9	0.37	242	-2	-0.82
5	241	-0.75	0.31	239	1.1	0.46	241	-1	-0.41
6	240	0.25	0.10	240	0.1	4.16	238	2	0.84
7	240	0.25	0.10	240	0.1	4.16	239	1	0.41
8	242	-1.75	0.72	242	-1.9	0.78	240	0	0
9	241	-0.75	0.31	241	0.9	0.37	241	-1	-0.41
10	239	1.25	0.52	239	1.1	0.46	238	2	0.84
11	241	-0.75	0.31	242	-1.9	0.78	239	1	0.41
12	239	1.25	0.52	241	0.9	0.37	240	0	0
13	240	0.25	0.10	238	2.1	0.88	240	0	0
14	240	0.25	0.10	239	1.1	0.46	242	-2	-0.82
15	242	-1.75	0.72	240	0.1	4.16	241	-1	-0.41
16	241	-0.75	0.31	241	0.9	0.37	238	2	0.84
17	239	1.25	0.52	241	0.9	0.37	240	0	0
18	241	-0.75	0.31	238	2.1	0.88	240	0	0
19	239	1.25	0.52	239	1.1	0.46	242	-2	-0.82
20	240	0.25	0.10	241	0.9	0.37	241	-1	-0.41
	Average of 20 Tablets= 240.25			Average of 20 Tablets =240.1			Average of 20 Tablets= 240		

Table 9. Physical properties of the tablet formulations

FORMULATION CODE	FRIABILITY(%)	THICKNESS (mm)	HARDNESS (kg/cm^2)
F-1	0.225	3.7	NLT 15 kgs
F-2	0.218	3.7	NLT 15 kgs
F-3	0.094	3.7	NLT 15 kgs
F-4	0.312	3.7	NLT 15 kgs
F-5	0.318	3.7	NLT 15 kgs
F-6	0.230	3.7	NLT 15 kgs
F-7	0.148	3.7	NLT 15 kgs
F-8	0.178	3.7	NLT 15 kgs
F-9	0.178	3.7	NLT 15 kgs

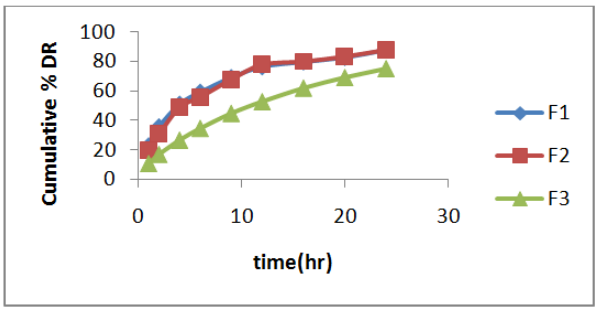


Fig.10. Comparison of drug release profile of F1, F2 AND F3

Table 10. Dissolution profile and F_1, F_2 matching of formulations F-1, F-2, AND F-3

Time (Hours)	RLD- Dissolution	F1	F2	F3
1	21.2	22.5	19.8	10.8
2	28.4	35.4	30.7	17
4	37.8	50.8	49	26.7
6	46.7	58.9	56	34.7
9	50.6	68.8	67.9	44.9
12	59	76.2	78	52.9
16	72.5	79.5	80.1	62.1
20	80.7	82.5	83.5	69.3
24	94.5	87.6	88.0	75.3
f_2	-	48	48.69	47
f_1	-	17	16	20

Table 11. Dissolution profile and F_1, F_2 matching of formulations F-4, F-5 and F-6

Time (Hours)	RLD- Dissolution	F4	F5	F6
1	21.2	7.9	14.9	19.3
2	28.4	12.8	20.6	29.5
4	37.8	20.6	22.5	47.8
6	46.7	27.1	27.1	59.2
9	50.6	35.6	35.6	70.2
12	59	49.9	42.3	77.2
16	72.5	55.9	53.8	82.5
20	80.7	60.2	58.8	85.3
24	94.5	67.1	67.1	87.5
f_2	-	37	38	47.22
f_1	-	31	30	17

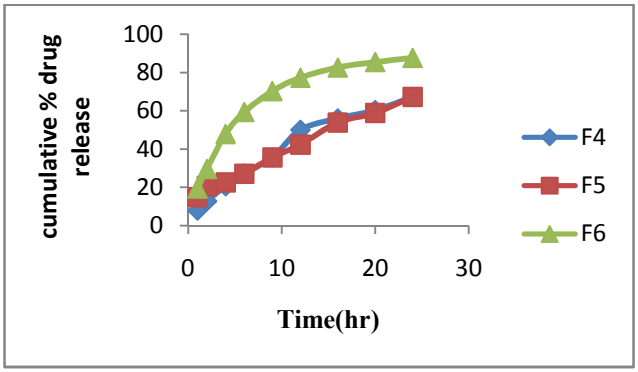


Fig.11. Comparison of drug release profile of F4, F5 AND F6

Table 12. Dissolution profile and F_1, F_2 matching of formulations F-7, F-8, AND F-9

Time (Hours)	RLD- Dissolution	F7	F8	F9
1	21.2	10.9	13	15.2
2	28.4	17.7	20.9	23.6
4	37.8	27.6	32.1	37.2
6	46.7	36.7	41.2	47.3
9	50.6	47.4	53	54
12	59	57.1	61.6	66
16	72.5	69.8	71.5	74
20	80.7	74.6	78.6	86
24	94.5	81.7	81.7	99
f_2	-	53	59	67
f_1		14	10	7

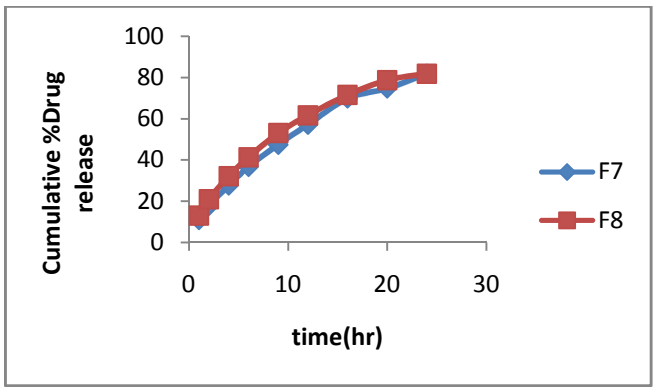


Fig.12. Comparison profile of drug release of F7 AND F8

Table 13. Comparision of drug release profile of F9 and mirapex ER

Time (hrs)	F9	Marketed ER
1	15.2	21.2
2	23.6	28.4
4	37.2	37.8
6	47.3	46.7
9	54	50.6
12	66	59
16	74	72.5
20	86	80.7
24	99	94.5

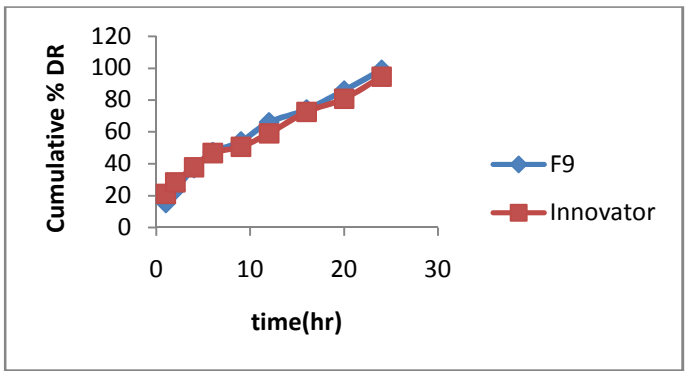


Fig. 13. Comparison profile of drug release of F9 and marketed ER

Dissolution profile of the extended release tablets for the batches f-1tof-9

After getting all the physical parameters satisfactory for batches F-1 to F-9, the dissolution of these batches was tested. The details of the dissolution study for the tablets of the batches F-1 to F-9 are given in the Table 10-13.

The In –vitro dissolution studies were performed for all the formulation of tablets including commercial formulation using USP II tablet dissolution tester employing Paddle type at 100 rpm using 900 ml. of 6.8 pH phosphate buffer as dissolution medium and drug release profiles were shown in Figures 10-13, it was observed that among the different combination of polymers used, formulation with drug and polymer (HPMC K4M and HPMC 3LV) F-9 has shown higher drug release rates when compared to other formulation and marketed formulation.

Kinetics of *In vitro* drug release

The dosage forms most commonly release the drug either in the zero order or in the first order pattern. Extended release dosage forms of Bisoprolol fumarate were prepared and studied for their dissolution behavior. The release profiles of Bisoprolol fumarate from the tablets of the formulation F-1 to F-9 were processed into graphs for comparison of different orders of drug release and to understand the linear relationship, i.e., kinetic principles. The data were processed for regression analysis using MS-Excel statistical functions and drug release profile given satisfactory manner compared with official standards as shown in Tables 14- 23 and Figures 14-63.

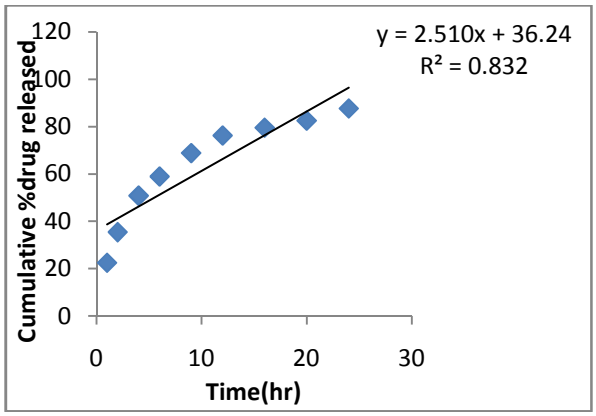


Fig.14. *In-vitro* drug release profile of F-1 fitted in zero order

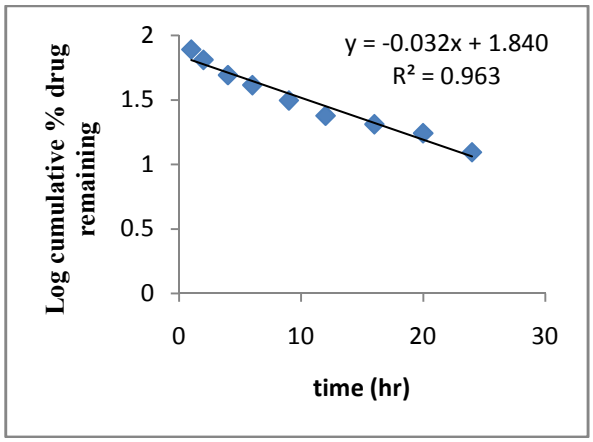


Fig.15. *In-vitro* drug release profile of F-1 fitted in first order

Table 14. Dissolution rates of Bisoprolol fumarate from formulation F-1

S.No	Time (hrs)	Square root of time	Log time	Cumulative %t drug Released (±SD)	Log Cumulative %t drug Released	Cumulative % drug Remaining	Log cumulative % drug remaining
1	1	1.000	0.000	22.5	1.352	77.5	1.889
2	2	1.414	0.301	35.4	1.549	64.5	1.809
3	4	2.000	0.602	50.8	1.705	49.2	1.691
4	6	2.449	0.778	58.9	1.770	41.1	1.613
5	9	3.000	0.954	68.8	1.837	31.2	1.494
6	12	3.464	1.079	76.2	1.881	23.8	1.376
7	16	4.000	1.204	79.5	1.9	20.5	1.31
8	20	1.301	1.301	82.5	1.91	17.5	1.24
9	24	4.898	1.380	87.6	1.942	12.4	1.093

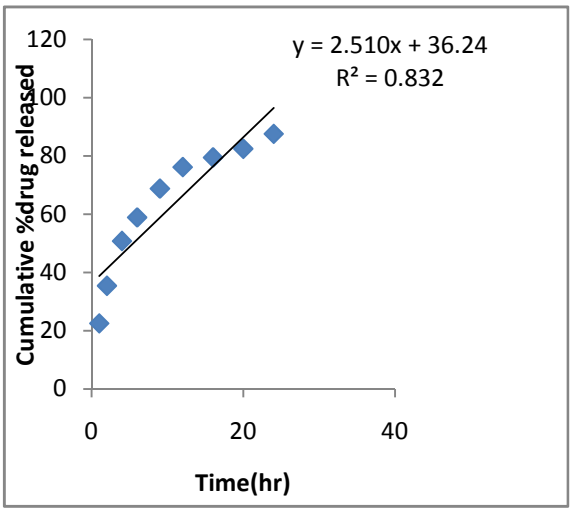


Fig.14. *In-vitro* drug release profile of F-1 fitted in zero order

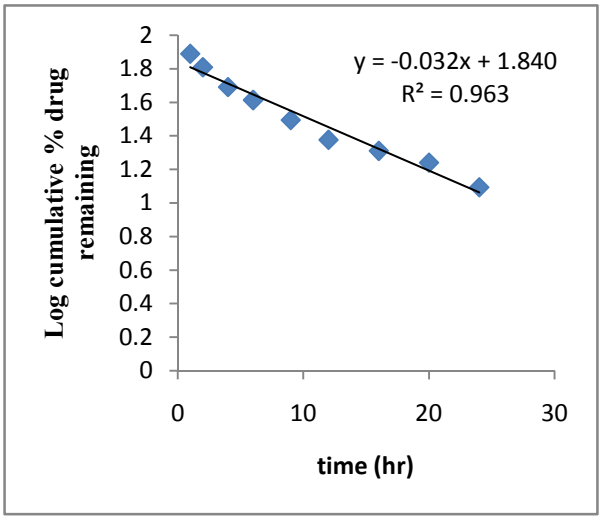


Fig.15. *In-vitro* drug release profile of F-1 fitted in first order

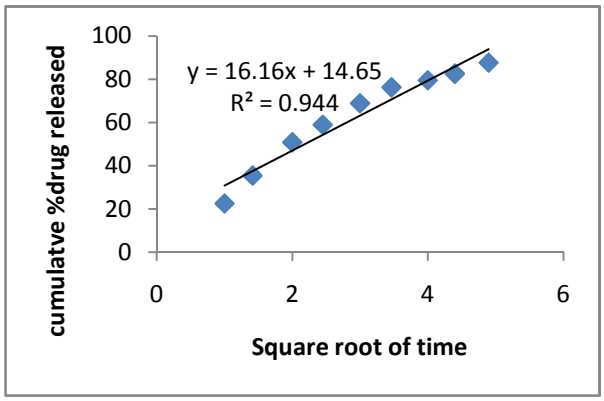


Fig.16. F-1 Formulation drug release profile fitted in higuchi model

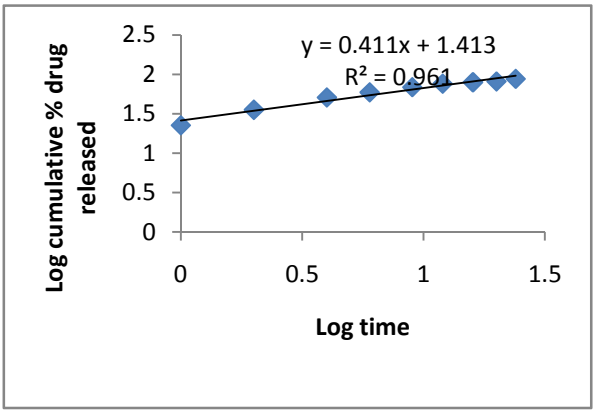


Fig.17.F-1 Formulation drug release profile fitted in korsmeyer-peppas

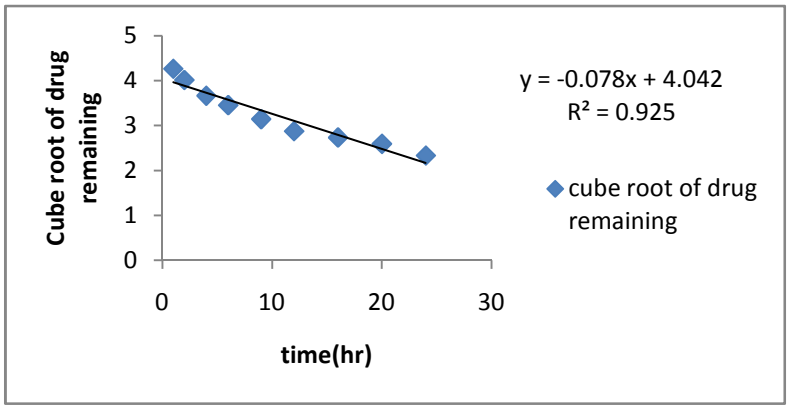


Fig.18. F-1 Drug release fitted in hixon- crowel cube root law

Table 15. Dissolution rates of Bisoprolol fumarate from formulation F-2

S.No	Time (hrs)	Square root of time	Log time	Cumulative % drug Released (±SD)	Log Cumulative % drug released	Cumulative % drug Remaining	Log cumulative % drug remaining
1	1	1.000	0.000	19.8	1.296	80.2	1.904
2	2	1.414	0.301	30.7	1.417	69.3	1.840
3	4	2.000	0.602	49	1.69	51	1.707
4	6	2.449	0.778	56.0	1.748	44.0	1.643
5	9	3.000	0.954	67.9	1.831	32.1	1.506
6	12	3.464	1.079	78	1.881	22	1.378
7	16	4.000	1.204	80.1	1.903	19.9	1.298
8	20	1.301	1.301	83.5	1.921	16.5	1.217
9	24	4.898	1.380	88.0	1.944	12	1.079

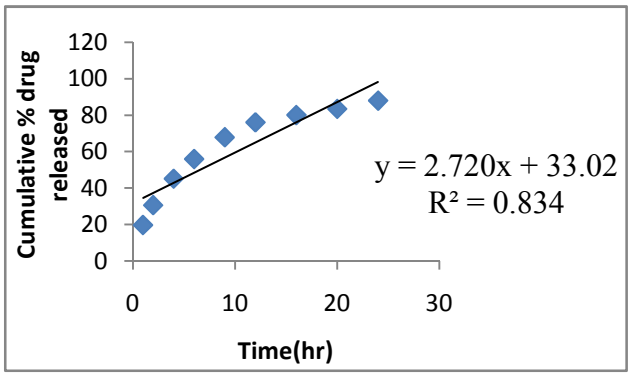


Fig.19. F-2 Drug release fitted in zero order

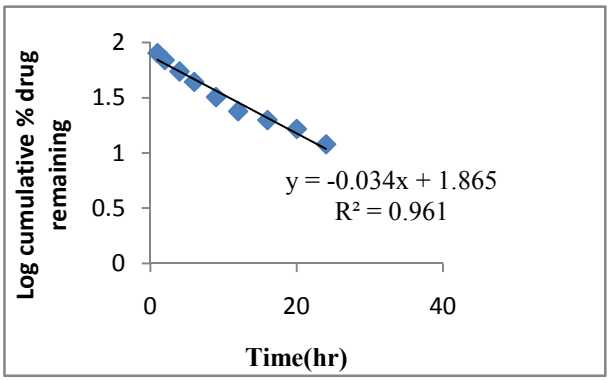


Fig.20. F-2 Drug release fitted in first-order

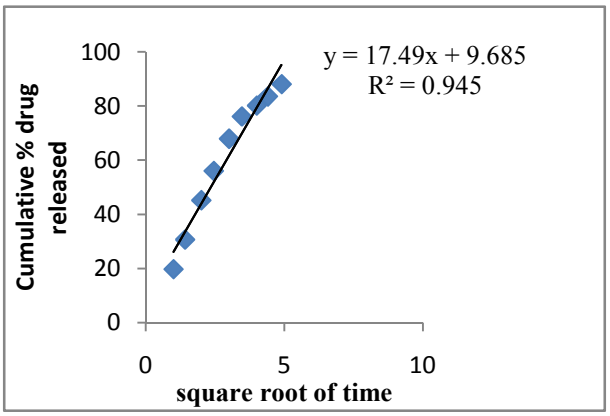


Fig.21. F-2 Drug release profile fitted in higuchi model

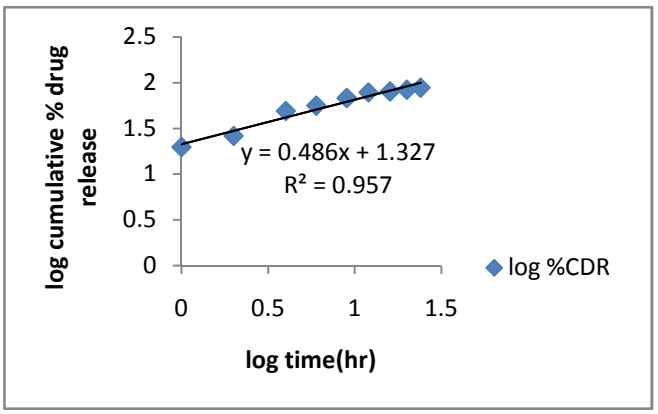
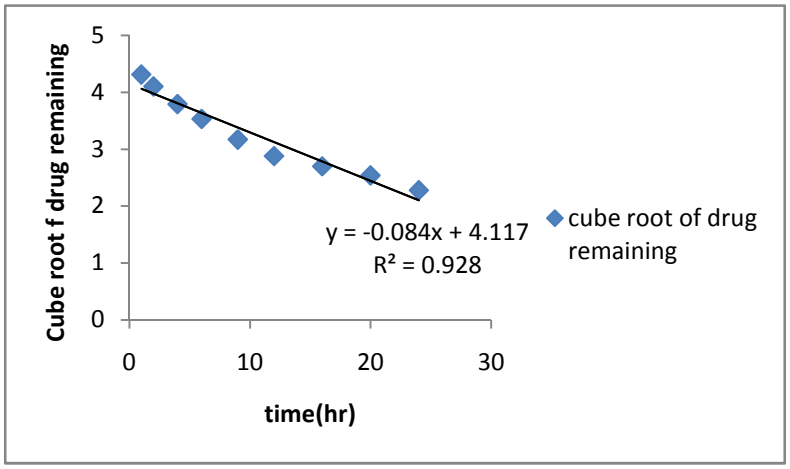


Fig.22. F-2 Drug release fitted in korsmeyer-peppas model



FIig.23. F-2 Drug release fitted in hixon- crowel cube root law

Table 16. Dissolution rates of Bisoprolol fumarate from formulation F-3

S.No	Time (hrs)	Square root of time	Log time	Cumulative %drug Released (±SD)	Log Cumulative % drug released	Cumulative % drug Remaining	Log cumulative % drug remaining
1	1	1.000	0.000	10.8	1.033	89.2	1.950
2	2	1.414	0.301	17	1.230	83.0	1.919
3	4	2.000	0.602	26.7	1.426	73.3	1.865
4	6	2.449	0.778	34.7	1.540	65.3	1.814
5	9	3.000	0.954	44.9	1.652	55.1	1.741
6	12	3.464	1.079	52.9	1.723	47.1	1.673
7	16	4.000	1.204	62.1	1.793	37.9	1.578
8	20	1.301	1.301	69.3	1.840	30.7	1.487
9	24	4.898	1.380	75.3	1.876	24.7	1.392

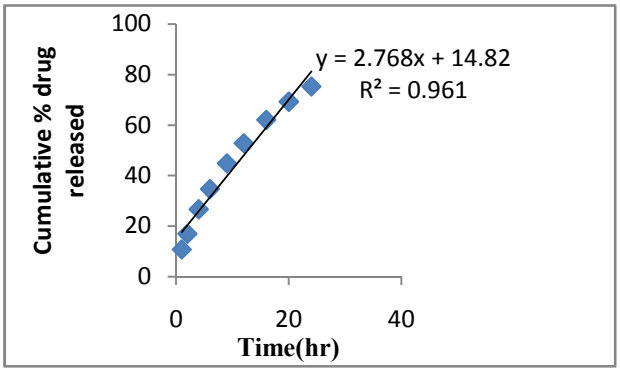


Fig.24. F-3 Drug release fitted in zero order

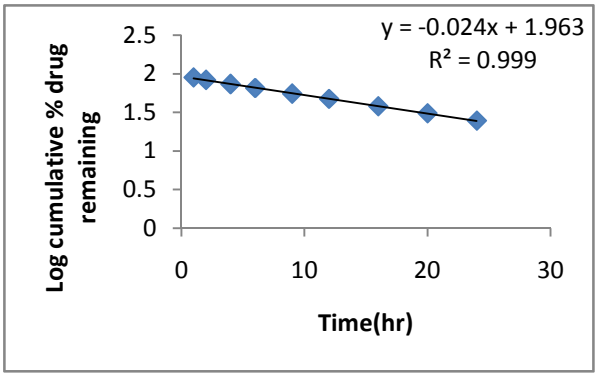


Fig.25. F-3 Drug release fitted in first-order

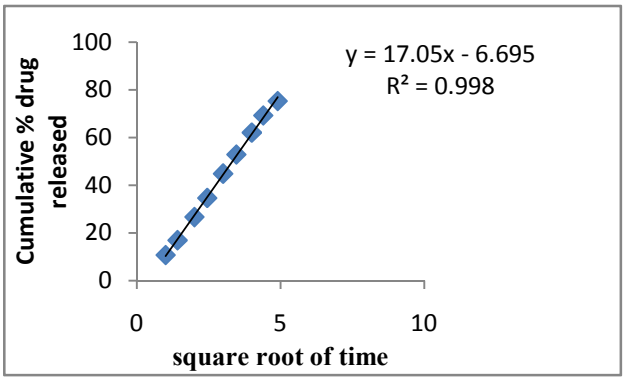


Fig.26. F-3 Drug release profile fitted in higuchi model

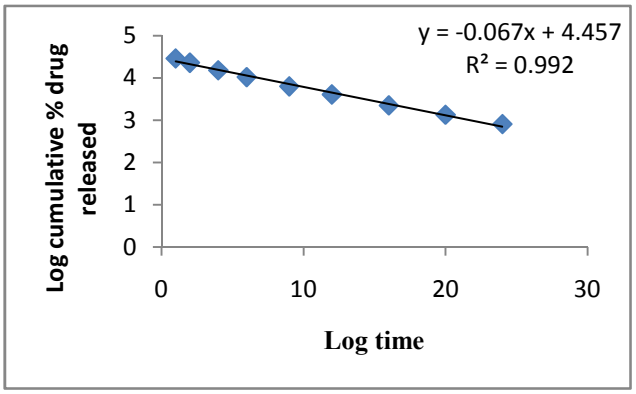


Fig. 27. F-3 Drug release profile fitted in korsmeyer-peppas model

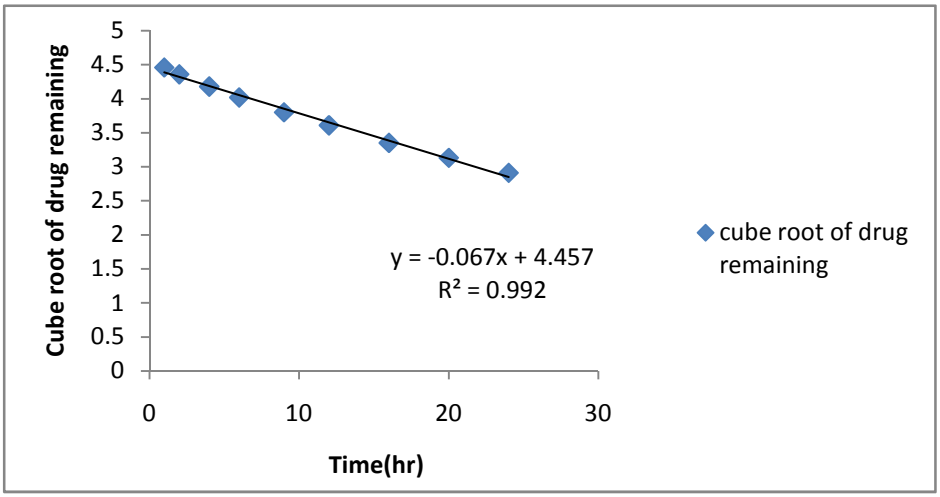


Fig.28. F-3 Drug release fitted in hixon- crowel cube root law

Table 17. Dissolution rates of bisoprolol fumarate from formulation F-4

S.No	Time (hrs)	Square root of time	Log time	Cumulative % drug Released (±SD)	Log Cumulative %drug Released	Cumulative %drug Remaining	Log cumulative % drug Remaining
1	1	1.000	0.000	7.9	0.897	92.1	1.964
2	2	1.414	0.301	12.8	1.107	87.2	1.940
3	4	2.000	0.602	20.6	1.313	79.2	1.898
4	6	2.449	0.778	27.1	1.432	72.9	1.862
5	9	3.000	0.954	35.6	1.551	64.4	1.808
6	12	3.464	1.079	49.9	1.698	50.1	1.699
7	16	4.000	1.204	55.9	1.747	44.1	1.644
8	20	1.301	1.301	60.2	1.779	29.8	1.474
9	24	4.898	1.380	67.1	1.826	22.9	1.359

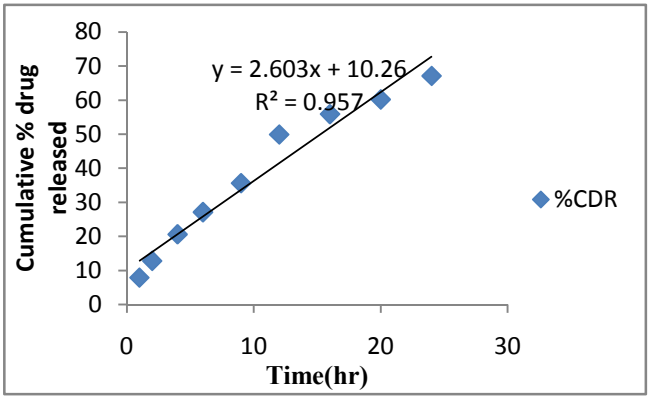


Fig.29. F-4 Drug release fitted in zero order

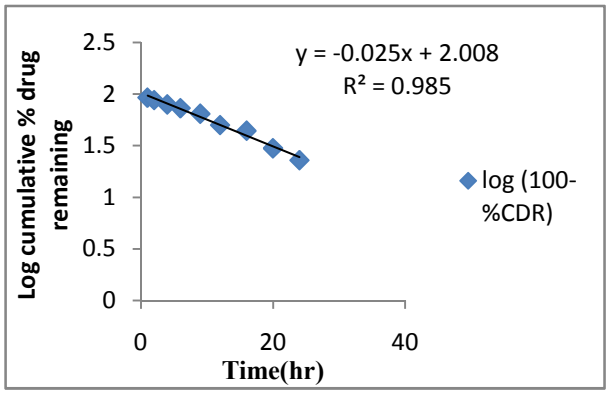


Fig.30. F-4 Drug release fitted in first-order

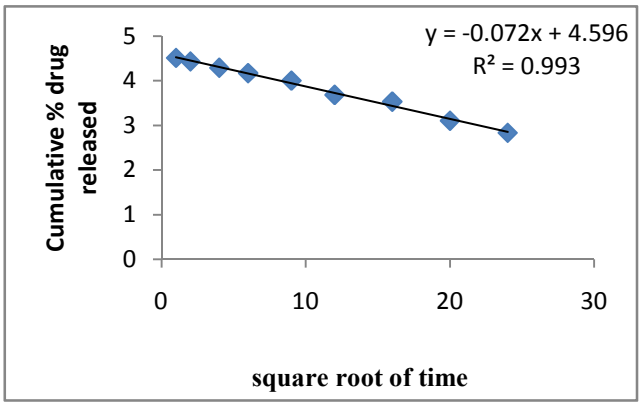


Fig. 31. F-4 Drug release profile fitted in higuchi model

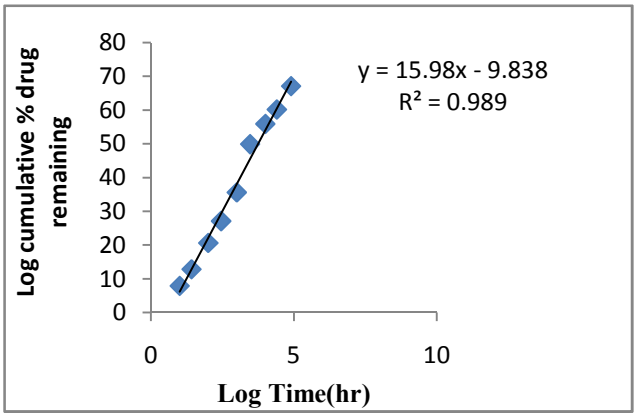


Fig.32. F-4 Drug release profile fitted in korsmeyer-peppas model

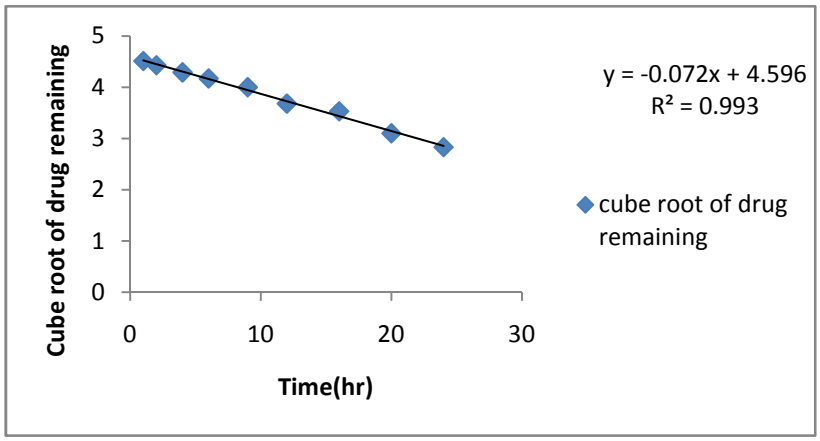


Fig.33. F-4 Drug release fitted in hixon- crowel cube root law

Table 18. Dissolution rates of bisoprolol fumarate from formulation F-5

S.No	Time (hrs)	Square root of time	Log time	Cumulative % drug Released (±SD)	Log Cumulative %drug Released	Cumulative % drug Remaining	Log cumulative % drug Remaining
1	1	1.000	0.000	14.9	1.173	85.1	1.929
2	2	1.414	0.301	22.8	1.357	77.2	1.887
3	4	2.000	0.602	20.6	1.313	79.4	1.899
4	6	2.449	0.778	27.1	1.432	72.9	1.857
5	9	3.000	0.954	35.6	1.551	64.4	1.808
6	12	3.464	1.079	42.3	1.626	57.7	1.76
7	16	4.000	1.204	53.8	1.73	46.2	1.66
8	20	1.301	1.301	58.8	1.769	41.2	1.614
9	24	4.898	1.380	67.1	1.826	32.9	1.517

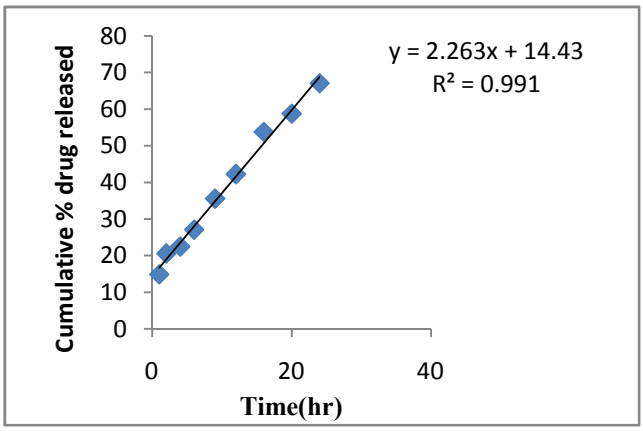


Fig.34. F-5 Drug release fitted in zero order

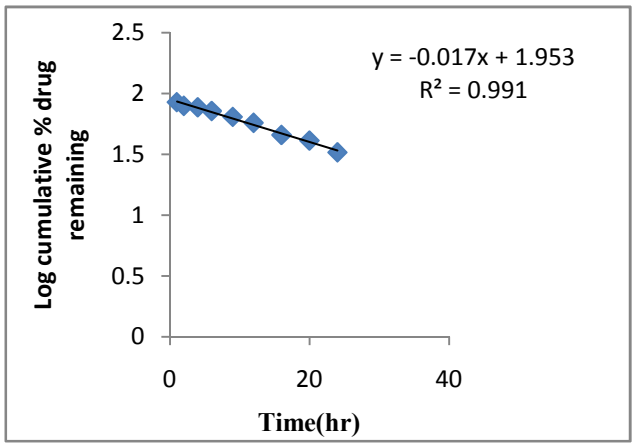


Fig.35. F-5 Drug release fitted in first-order

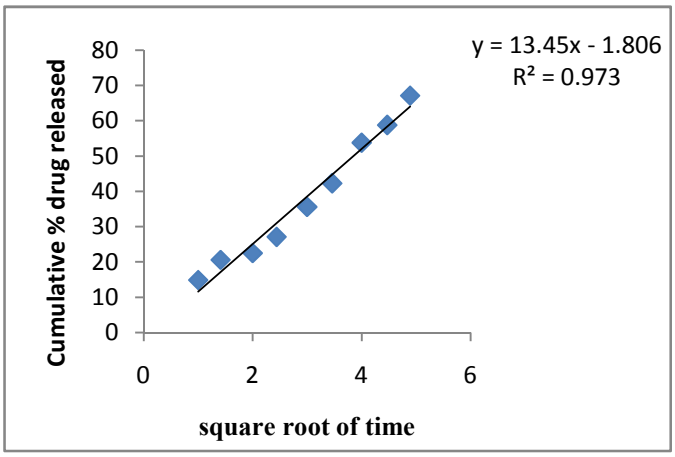


Fig. 36. F-5 Drug release profile fitted in higuchi model

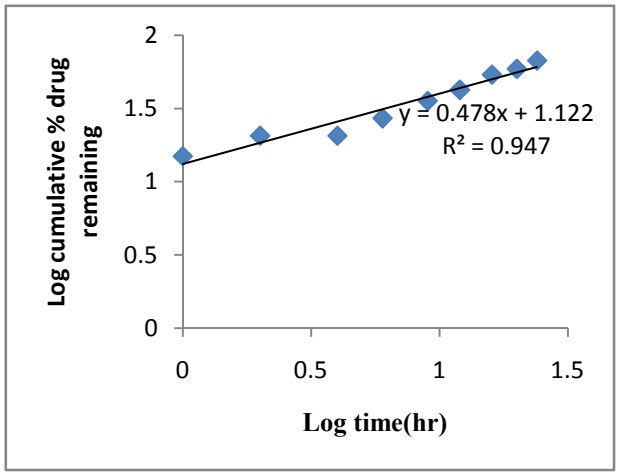


Fig.37. F-5 Drug release profile fitted in korsmeyer-peppas model

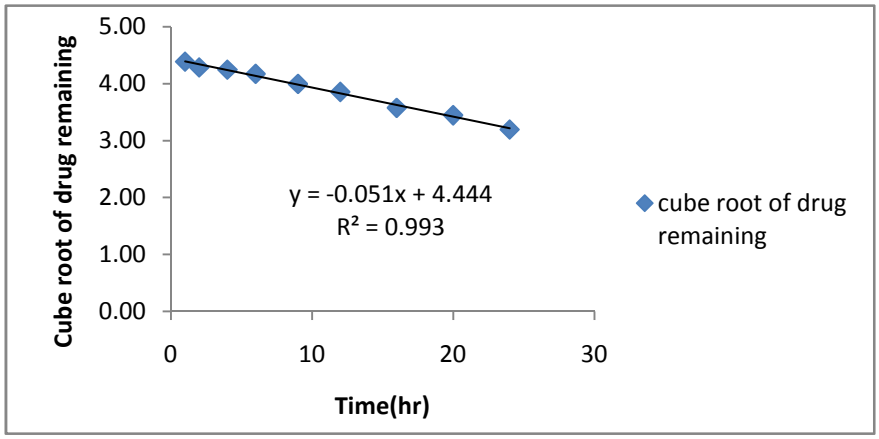


Fig.38.F-5 Drug release fitted in hixon- crowel cube root law

Table 19. Dissolution rates of bisoprolol fumarate from formulation F-6

S.No	Time (hrs)	Square root of time	Log time	Cumulative %drug Released (±SD)	Log Cumulative %drug released	Cumulative %drug Remaining	Log cumulative % drug remaining
1	1	1.000	0.000	19.3	1.285	79.7	1.901
2	2	1.414	0.301	29.5	1.469	70.5	1.848
3	4	2.000	0.602	47.8	1.679	52.2	1.717
4	6	2.449	0.778	59.2	1.772	40.8	1.610
5	9	3.000	0.954	70.2	1.846	29.8	1.474
6	12	3.464	1.079	77.2	1.887	22.8	1.357
7	16	4.000	1.204	82.5	1.916	17.5	1.243
8	20	1.301	1.301	85.3	1.930	14.7	1.167
9	24	4.898	1.380	87.5	1.942	12.5	1.096

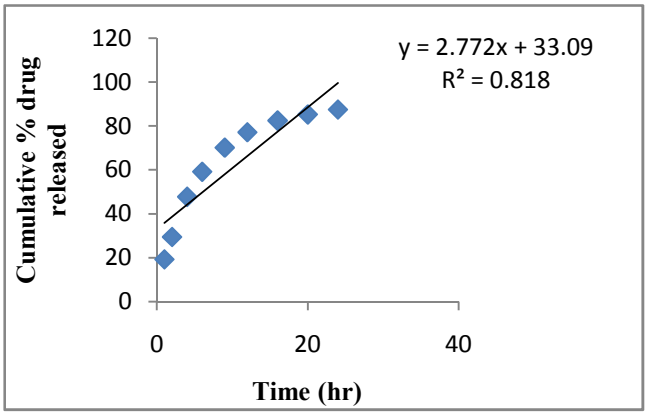


Fig.39.F-6 Drug release fitted in zero order

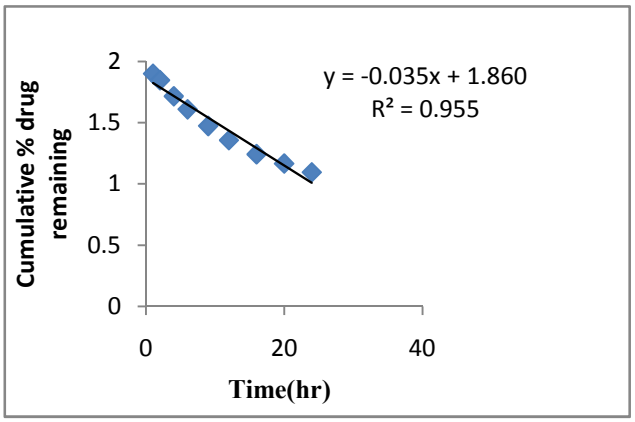


Fig.40.F-6 Drug release fitted in first-order

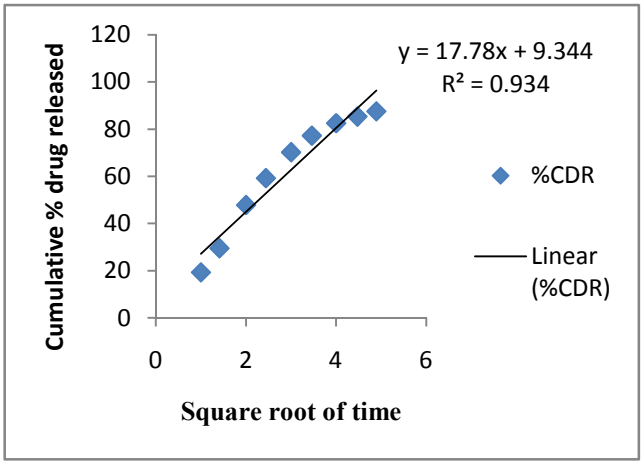


Fig.41. F-6 Drug release profile fitted in higuchi model

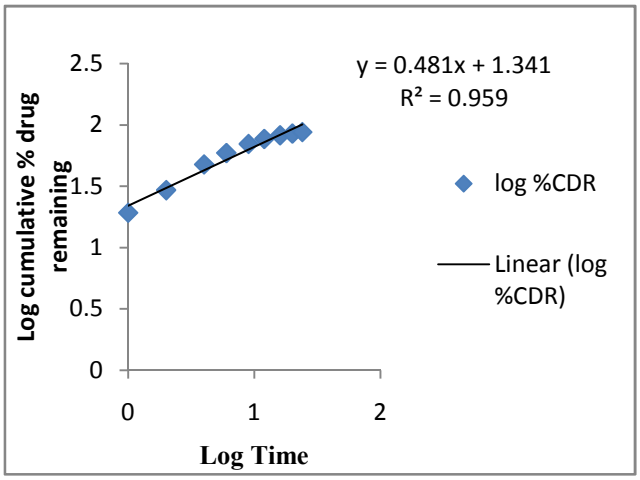


Fig.42. F-6 Drug release profile fitted in korsmeyer-peppas model

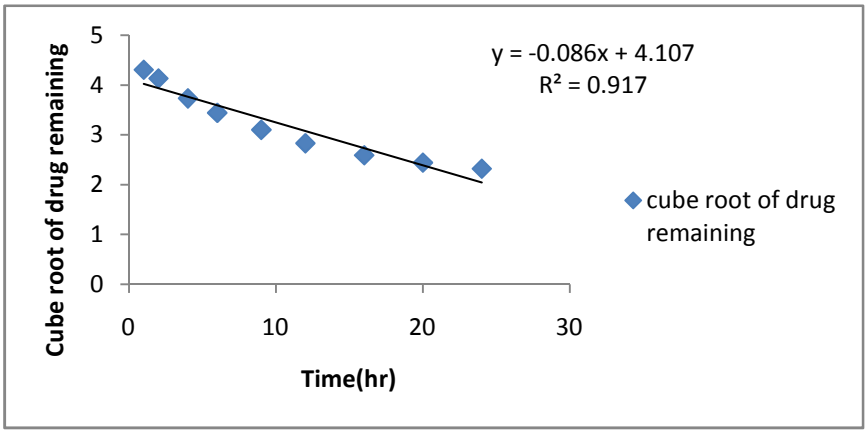


Fig.43. F-6 Drug release fitted in hixon- crowel cube root law

Table 20. Dissolution rates of bisoprolol fumarate from formulation f-7

S.No	Time (hrs)	Square root of time	Log time	Cumulative %drug Released (±SD)	Log Cumulative % drug released	Cumulative %drug Remaining	Log cumulative % drug remaining
1	1	1.000	0.000	10.9	1.037	89.1	1.949
2	2	1.414	0.301	17.7	1.247	82.3	1.915
3	4	2.000	0.602	27.6	1.440	72.4	1.859
4	6	2.449	0.778	36.7	1.564	63.3	1.801
5	9	3.000	0.954	47.4	1.675	52.6	1.720
6	12	3.464	1.079	57.1	1.756	42.9	1.632
7	16	4.000	1.204	69.8	1.843	30.2	1.480
8	20	1.301	1.301	74.6	1.872	25.4	1.404
9	24	4.898	1.380	81.7	1.912	18.3	1.262

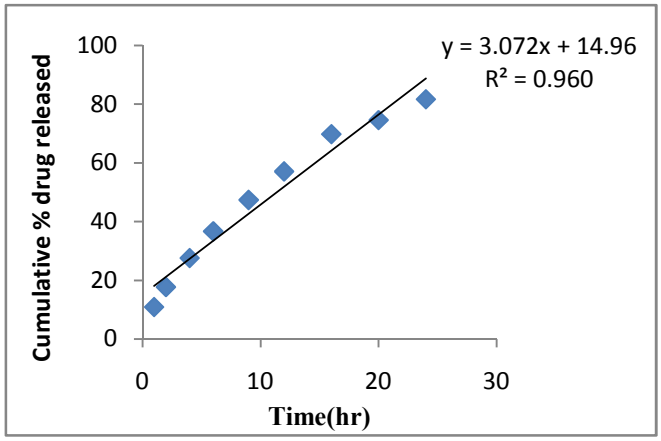


Fig.44.F-7 Drug release fitted in zero order

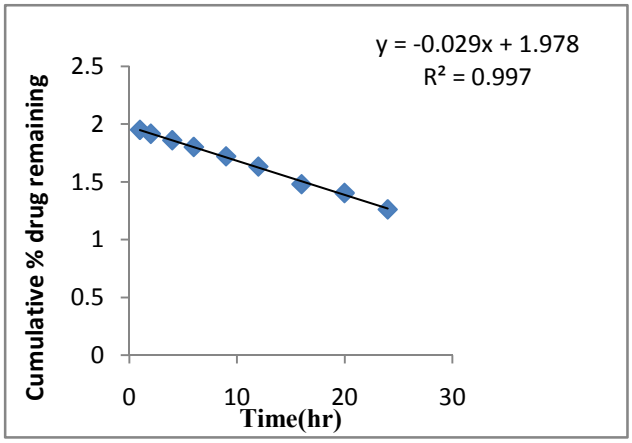


Fig.45.F-7 Drug release fitted in first-order

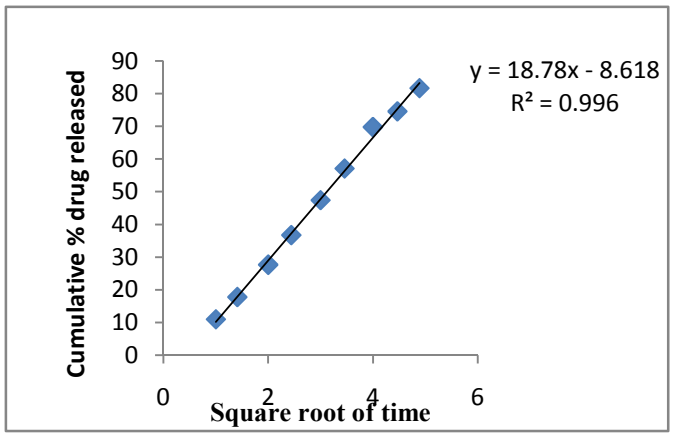


Fig.46. F-7 drug release profile fitted in higuchi model

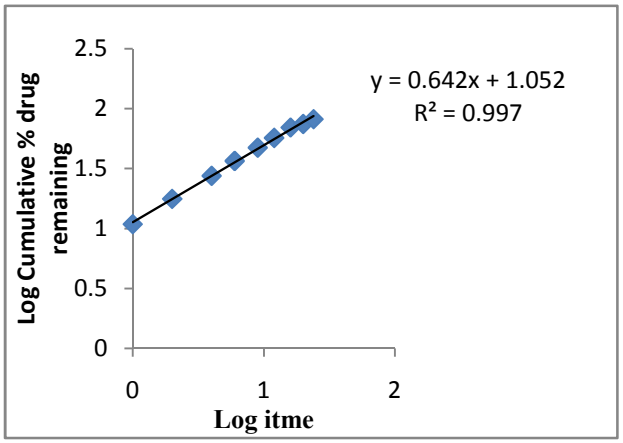


Fig.47. F-7 Drug release profile fitted in korsmeyer-peppas model

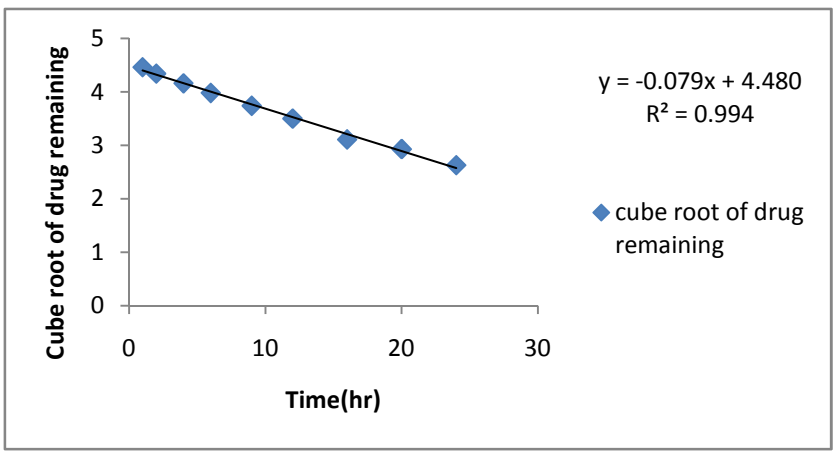


Fig.48. F-7 Drug release fitted in hixon- crowel cube root law

Table 21 Dissolution rates of bisoprolol fumarate from formulation F-8

S.No	Time (hrs)	Square root of time	Log time	Cumulative %drug Released (±SD)	Log Cumulative %drug Released	Cumulative %drug Remaining	Log cumulative % drug remaining
1	1	1.000	0.000	13	1.11	87	1.939
2	2	1.414	0.301	20.9	1.320	79.1	1.898
3	4	2.000	0.602	32.1	1.506	67.9	1.831
4	6	2.449	0.778	41.2	1.614	58.2	1.764
5	9	3.000	0.954	53	1.724	47	1.672
6	12	3.464	1.079	61.6	1.789	38.4	1.584
7	16	4.000	1.204	71.5	1.854	28.5	1.454
8	20	1.301	1.301	78.6	1.895	21.4	1.330
9	24	4.898	1.380	81.7	1.912	18.3	1.262

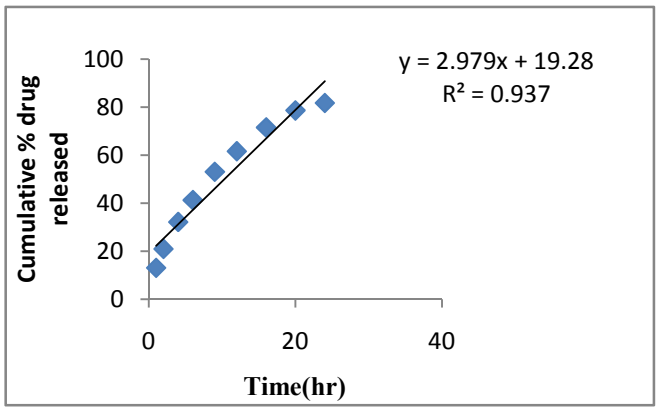


Fig.49. F-8 Drug release fitted in zero order

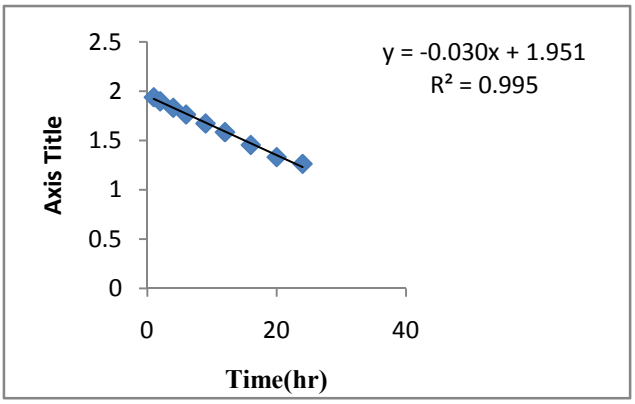


Fig.50. F-8 Drug release fitted in first-order

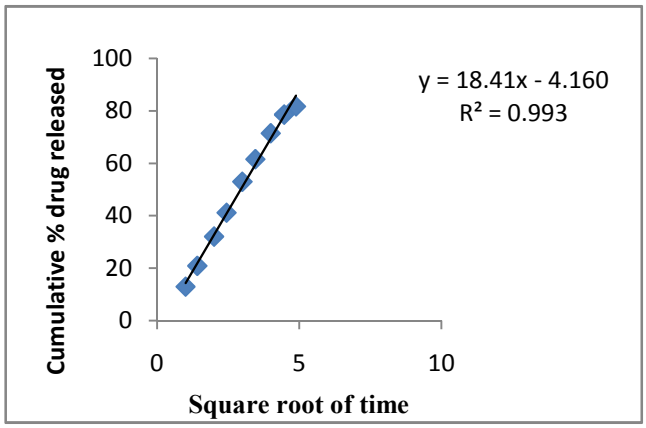


Fig.51. F-8 Drug release profile fitted in higuchi model

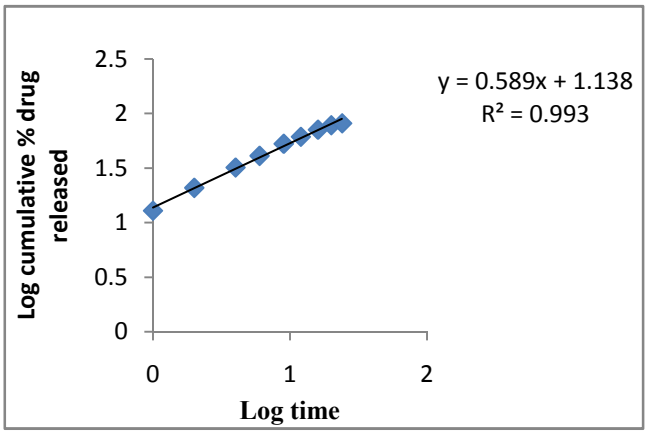


Fig.52. F-8 Drug release profile fitted in korsmeyer-peppas model

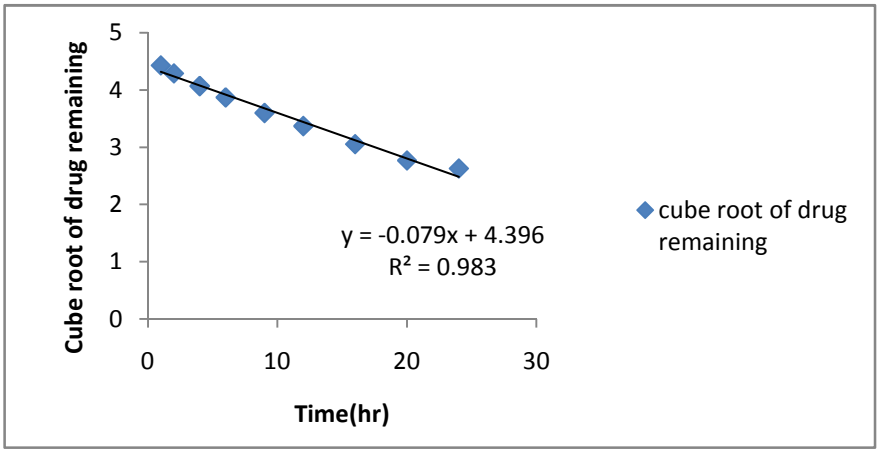


Fig.53. F-8 Drug release fitted in hixon- crowel cube root law

Table 22. Dissolution rates of bisoprolol fumarate from formulation F-9

S.No	Time (hrs)	Square root of time	Log time	Cumulative % drug Released (±SD)	LogCumulative % drugreleased	Cumulative% drug Remain in g	Log cumulative % drug Remain in g
1	1	1.000	0.000	15.2	1.181	84.8	1.928
2	2	1.414	0.301	23.6	1.372	76.4	1.883
3	4	2.000	0.602	37.2	1.570	62.8	1.797
4	6	2.449	0.778	47.3	1.674	52.7	1.721
5	9	3.000	0.954	54	1.785	39	1.591
6	12	3.464	1.079	66	1.851	29	1.462
7	16	4.000	1.204	74	1.909	18.9	1.276
8	20	1.301	1.301	86	1.959	9	0.954
9	24	4.898	1.380	99	1.995	1	0

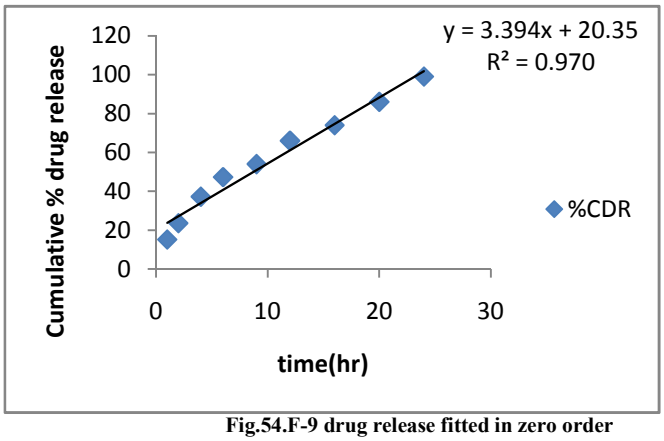


Fig.54.F-9 drug release fitted in zero order

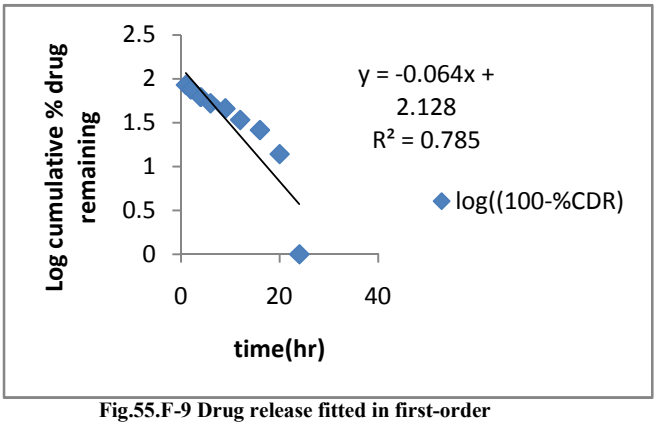


Fig.55.F-9 Drug release fitted in first-order

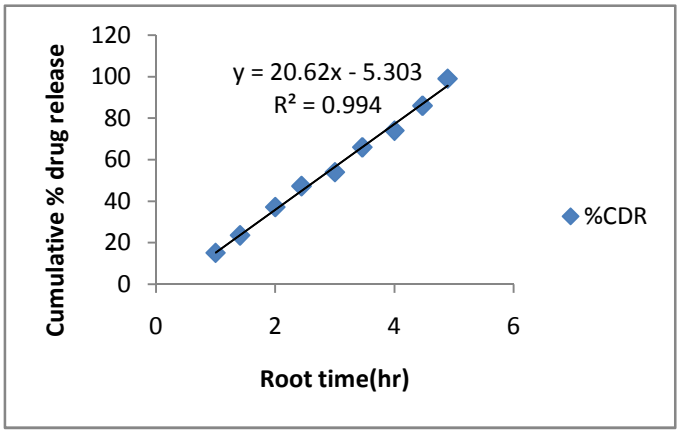


Fig.56.F-9 Drug release profile fitted in higuchi model

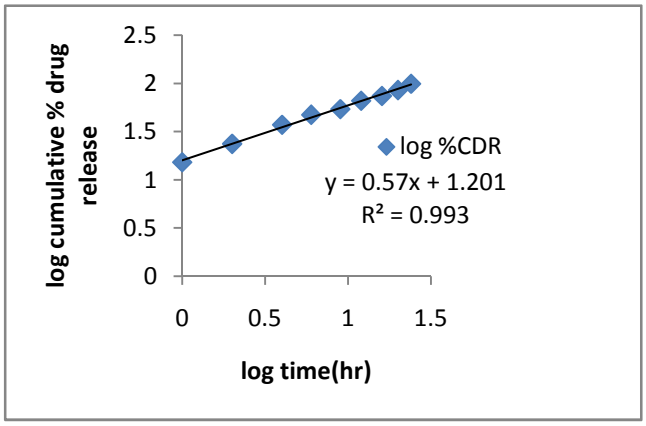


Fig.57.F-9 Drug release profile fitted in korsmeyer-peppas model

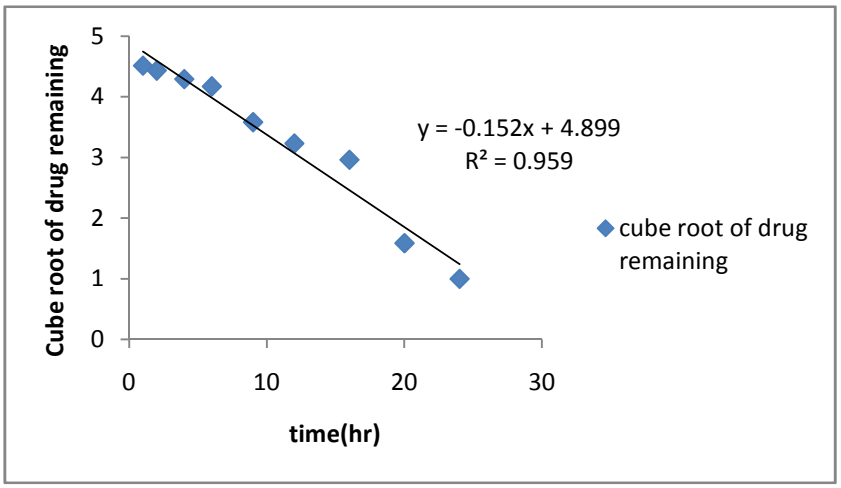


Fig.58. F-9 Drug release fitted in hixon- crowel cube root law

Table 23. Dissolution rates of bisoprolol fumarate commercial formulation mirapex XR

S.No	Time (hrs)	Square root of time	Log time	Cumulative% drug Released(±SD)	Log Cumulative% drug released	Cumulative% drug Remain in g	Logcumulative% drug remain in g
1	1	1.000	0.000	21.2	1.326	78.8	1.896
2	2	1.414	0.301	28.4	1.453	71.6	1.854
3	4	2.000	0.602	37.8	1.577	62.2	1.793
4	6	2.449	0.778	46.7	1.669	53.3	1.726
5	9	3.000	0.954	50.6	1.704	49.4	1.693
6	12	3.464	1.079	59	1.770	41	1.612
7	16	4.000	1.204	72.5	1.860	27.5	1.493
8	20	1.301	1.301	80.7	1.906	19.3	1.285
9	24	4.898	1.380	94.5	1.975	5.5	0.740

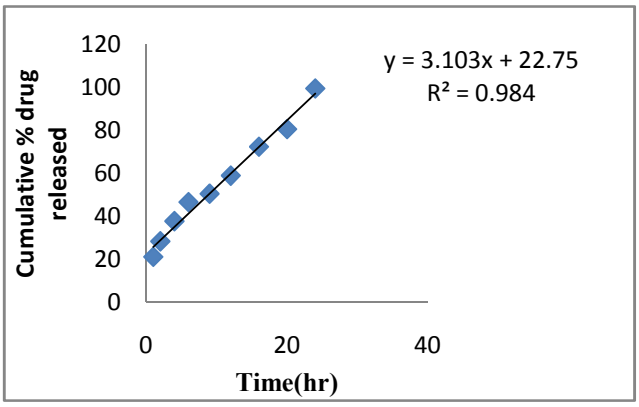


Fig.59 In-vitro drug release profile of marketed ER fitted in zero-order

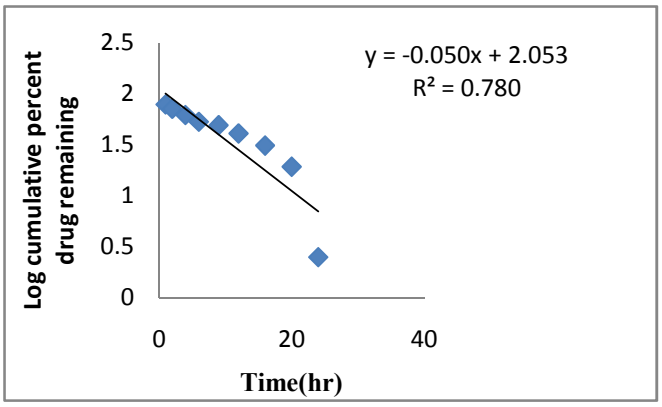


Fig.60 In-vitro drug release profile of marketed ER fitted in first order

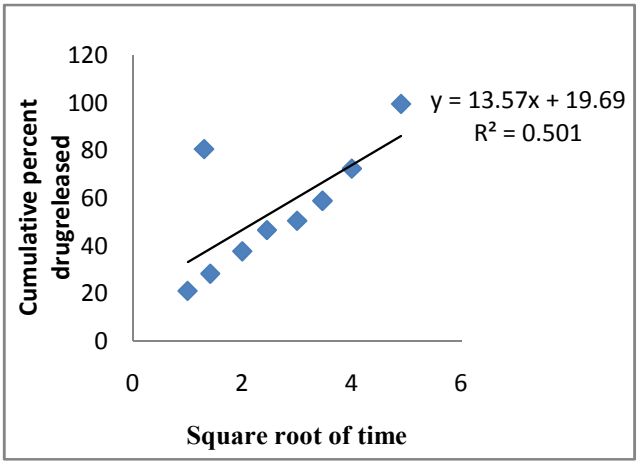


Fig.61.In-vitro drug release profile marketed ER Fitted in higuchi model

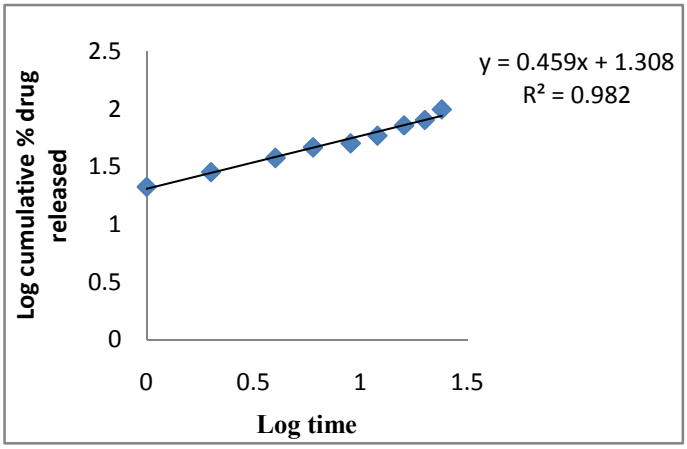


Fig.62. In-vitro drug release profile of marketed ER fitted in korsmeyer-peppas

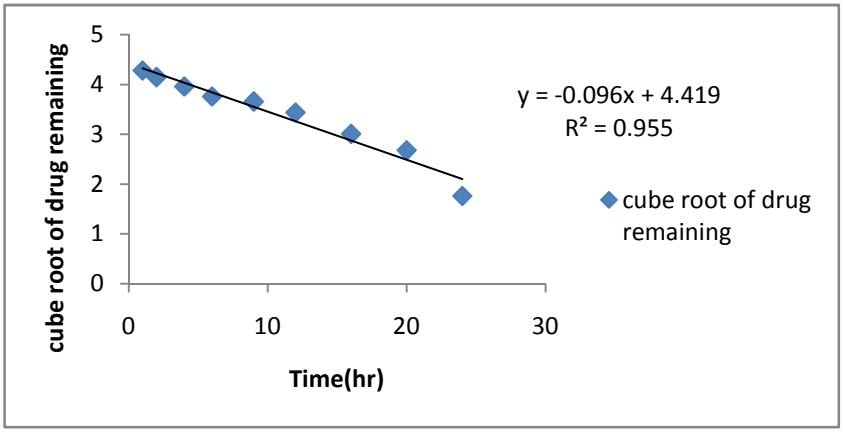


Fig.63. Marketed er drug release profile fitted in hixon-cube root law

Table 24. Stability study of marketed product

S.No	Time in days	Physical changes	25˚C	30˚C
			Mean % drug content (±SD)	Mean % drug content (±SD)
1	01	No change	Marketed-ER	Marketed-ER
2	07	No change	99.13± 1.41	99.01± 0.99
3	14	No change	99.02± 0.69	98.97± 0.48
4	21	No change	98.91± 0.98	98.55± 0.28
5	30	No change	98.84± 0.36	97.12± 0.21
			98.56±0.32	97.21±0.32

Table 25. Stability study of formulation F-9

S.No	Time in days	Physical changes	25˚C	30˚C
			Mean%drug content (±SD)	Mean % drug content (±SD)
1	01	-	Formulation F9	Formulation F9
2	07	No change	98.40± 1.31	98.11± 0.12
3	14	No change	98.21± 1.08	98.02± 0.88
4	21	No change	97.98± 0.69	97.25± 042
5	30	No change	99.52± 0.77	97.12± 0.21
			99.445±0.66	97.11±0.54

Stability studies

Stability studies were performed at two temperatures Viz, 25°C ± 2ºC/ 60% RH ± 5% RH and 30°C ± 2ºC / 65% RH ± 5% RH over a period of one month. The matrix tablet formulation F-9 and marketed drug Marketed ER. Sufficient number of tablets (Ten) were packed in amber colored capped bottles and kept in stability chamber maintained at 25°C and 30°C. Samples were taken at weekly intervals for drug content estimation. At the end of one month period, dissolution test was performed to determine the drug release profiles. The data of dissolution after stability studies was Tables 24 and 25.

Conclusion

Suitable analytical method based on UV-Visible spectrophotometer was developed for Bisoprolol fumarate λ_{max} of 260 nm was identified in pH 6.8 Phosphate buffer. From the FT-IR spectra the interference was verified and found that Bisoprolol fumarate did not interfere with the excipients used. Procedure to manufacture extended tablets by Wet granulation method was established. The tablets were evaluated for pharmacopoeial and non-pharmacopoeial (industry specified) tests. Based on the results, F-9 was identified as better formulation amongst all formulations developed for matrix tablets. Tablets of the formulation F-9 passed all official and unofficial quality control tests.

In vitro release profiles of optimized formulations of Bisoprolol fumarate Tablets (F-9) were found to be similar to that of the theoretical drug release profile. The f_1 and f_2 values for the comparison of release of drugs from the formulation F-9 with the theoretical drug release profile were found to be 7, 67 in 6.8 Phosphate buffer. Bisoprolol fumarate release from the tablets of F-9formulation follows zero- order kinetics. Bisoprolol fumarate release from the tablets of F-9 formulation follows Higuchi model. The release mechanism of Bisoprolol fumarate monohydrate from Tablets of F-9 formulation follows Diffusion-rate limited mechanism.

According Korsmeyer-Peppas the mechanism was Anomalous (Non-Fickian) diffusion. After one month of accelerated stability studies developed formulation was found to be stable. The conclusions arrived in this thesis indicated that the Extended release formulation of Bisoprolol fumarate developed in this investigation releases drug equivalent to theoretical drug release, based on *in vitro* release studies. The result of the study indicates that extended release tablets of Bisoprolol fumarate can be successfully prepared.

REFERENCES

Andrasi M., P. Buglyo, L. Zekany, A. Gaspar, 2007. *J. Pharm. Biomed. Anal.,* 44,1040.

Aulton M. Pharmaceutics- The Science of Dosage form design, 2ndedition, page no:457.

Beckett A.H. and Stenlake J.B. 2004. Practical Pharmaceutical Chemistry, Part II. CBS Publishers, Delhi, Fourth Edition: 72-75.

Dr. Jave A., Dr. Khar R.K., Dr. Alka A. A Text book of Dosage form Design. 1-31. Agro food industry Hi-tech 2008, volume 19, 9, 1-31.

Gennaro, AR. 1995. The Science and Practice of Pharmacy, Vol–II, 19th edition (2):1662.

In:Banker GS, Rhodes CT, editors.Modern Pharmaceutics,3rd ed.New York : Marcel Dekker Inc.

Indian Pharmacopeia, 2007, volume II, pageno 1217-18.

Indian pharmacopoeia. Vol 2. Controller of publications. Ministry of health and family welfare. Delhi; 2010.p. 48-52.

Jantez GM, Robinson JR 1996, Sustained-and Controlled-release drug delivery systems.

Juliano R. 1980. Drug Delivery Systems. Oxford University Press, New York., Page No.84-91.

Korsemeyer RW, Peppas NA. Macromolecular and modeling aspects of swelling – controlled systems. In Mansdrofsz, rosemann TJ, ad, Controlled Release Delivery systems. New York, Ny

Labot J.M., R.H. Manzo, A. Allemandi, Double layered Mucoadhesive Tablets Containing Nystatin, AAPS PharmSciTech., 2002, 3(3), 5-22.

Lachman L, Liberman HA, Joseph CK. Pharmaceutical Dosage Forms, 3rd Ed., Varghese Publishing House, Bombay, 1991; p.317-50.

Leo A., C.Hansch and D. Elkins, "Partition Coefficients and Their Uses", *Chem. Rev.,* 71(6), 525-616 (1997).

NISCAIR online periodical repository (NOPR) *Research Journals of Scientific Andindustrial Research* (JSIR), July 2007, 11. Biotechnology and Applied Biochemistry, Feb-2002.

Owens T.S., Dansereau R.J. and Sakr, A. 2005. Development and evaluation of extended release bio adhesive sodium fluoride tablets, *Int J Pharm.,* 288:109-122.

Pavia, D.L., Lampman G.M. and Kriz, G.S. 2002. Introduction to Spectroscopy. Washington: library of congress catalogue, 26-27.

Peter G. Welling; Francis L. S. Tse; Shrikant V. Dighe. 1991, Pharmaceutical Bioequivalence, Drugs and the Pharmaceutical Sciences 48., New York, NY: Marcel Dekker. ISBN 978-0-8247-8484-3.

Physical pharmacy by Alfred Martin, 4thedition, page no. 447.

Robinson JR and Lee HL 1987. Controlled Drug Delivery fundamentals and application; Marcel Dekker Inc New York, 2nd edition:373.

Robinson JR. 1978. Sustained and Controlled Drug Delivery System; Marcel Dekker Inc-New York and Basel, Page No.37-40.

Satyabrathabhanja, PEllaiah, sujitkumar Martha 2010, Formulation & Invitro evaluation of mucoadhesivebuccal tablets of timololmeleate, *Int J pharm biomed Res.,* I(4),129-134.

Science alert 2008, (An open access publisher) Journal of biological sciences, page no; 288-99).

Shargel L and Andrew BC. Applied Biopharmaceutics & Pharmacokinetics (4th Edn.),174.

Taylan, B., Y. Capan, O. Güven, S. Kes, A.A. Hincal, Design and evaluation of sustained-release and buccal adhesive propranolol hydrochloride tablets*, J. Control. Res.,* 1996,38, 11-20. 22.

Yie W. Chien 1992. Novel Drug Delivery Systems, Marcel Dekker Inc New York, 2nd edition: 1-2

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