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PRE-CLINICAL STUDIES OF TIMOLOL MALEATE MATRIX TABLET FORMULATED WITH DIFFERENT POLYMERS AND RATIOS

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ABSTRACT

The purpose of the present study was to prepare and characterize twice-daily sustained-release matrix tablets of timolol maleate (TM) using different concentrations of hydrophilic, hydrophobic, and plastic polymers. The effect of nature of the diluents and method of preparation were also studied. Formulations were evaluated for the release of TM over a period of 12 hours using United States Pharmacopoeia (USP) type-II dissolution apparatus. Along with physical properties, the dynamics of water uptake and erosion degree of tablets were also studied. The *in-vitro* drug release study revealed that the most successful formulation of the study F28 (drug to polymer ratio 1:2) which includes both HPMC K100M and EC (1:1), extended the drug release up to 12 hours, exhibited satisfactory drug release in the initial hours, and the total release pattern was close to the theoretical release profile with similarity factor (*f*2) above 50. The drug release from optimized formulation (F28) followed first-order kinetics via non-Fickian anomalous) diffusion. FTIR studies revealed that there was no interaction between the drug and excipients. Microcrystalline cellulose (water insoluble) was found to be better diluent in the formulation of sustained release tablets of water insoluble drug like TM. Compared to direct compression, wet granulation was found to be method of choice for the preparation of these matrix tablets. In conclusion, the results indicated that the prepared sustained-release tablets of TM could perform therapeutically better than conventional tablets with improved efficacy and better patient compliance.

KEYWORDS

Hydrophilic, Hydrophobic polymers, Sustained release, Timolol maleate and Wet granulation.

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INTRODUCTION

Timolol maleate is a non-selective beta-adrenergic receptor blocker used in the treatment of essential hypertension, glaucoma, migraine, and for prophylaxis after myocardial infarction. It is rapidly and nearly completely (about 90%) absorbed from the gastrointestinal tract (GIT) following oral ingestion, showing 60% bioavailability. Detectable plasma levels occur within one-half hour and peak plasma levels occur in about 1-2 hours. A plasma

half life is 4 hours. In the treatment of hypertension the usual initial dosage is 10 mg twice a day, whether used alone or added to diuretic therapy. Dosage may be increased or decreased depending on heart rate and blood pressure response. The usual total maintenance dosage is 20-40 mg per day. Increases in dosage to a maximum of 60 mg per day divided into two doses may be necessary[1].

Although conventional tablets of timolol maleate available in the market commercially, no study has been done so far for preparing the timolol maleate sustained-release tablets. To improve the oral bioavailability and to reduce the dose dependent toxicity there is a need for the development of sustained-release formulations. Many patent technologies also indicated that timolol maleate is suitable for the sustained-release[2,3]. The most commonly used method of modulating the drug release is to include it in a matrix system[4]. An effort was therefore made to develop simple and effective sustained-release timolol maleate tablets using a polymer matrix system. The drug is freely soluble in water and hence judicious selection of matrix formers is essential for achieving constant release. HPMC is the most commonly and successfully used hydrophilic retarding agent for the preparation of oral controlled drug delivery systems[5]. Upon contact with the gastrointestinal fluid, HPMC swells, gels, and finally dissolves slowly[6]. The gel becomes a viscous layer acting as a protective barrier to both the influx of water and the efflux of the drug in solution[7,8]. As the proportion of the polymer in the formulation increases, the gel formed is more likely to diminish the diffusion of the drug and delay the erosion of the matrix[9]. The dissolution can be either is entanglement or diffusion controlled depending on the molecular weight and thickness of the diffusion boundary layer. The rate of polymer swelling and dissolution as well as the corresponding rate of drug release are found to increase with either higher levels of drug loading or with use of lower viscosity grades of HPMC[10]. However, the use of hydrophilic matrix former alone for sustaining drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs it is necessary to include hydrophobic polymers in the matrix system[11]. Hence, in the present study, an attempt has been made to develop the sustained-release matrix tablets of TM using hydrophilic HPMC K100M in combination with hydrophobic ethylcellulose, and the sustained pattern of timolol maleate was evaluated by *in-vitro* drug release for 12 hours. The drug release data were plotted using various kinetic equations (zero-order, first-order, Higuchi's kinetics, Korsmeyer's equation, and Hixson-Crowell cube root law) to evaluate the drug release mechanism and kinetics. *In-vivo* drug release, biopharmaceutical evaluation, and *in-vitro/ in-vivo* correlations were beyond the scope of this study and will be considered in future work.

MATERIALS AND METHOD

MATERIALS

Timolol Maleate was obtained as a gift samples from Ven Petro-Chem. and Pharma Pvt. Ltd, Mumbai. HPMC K100, HPMC K200, Xanthan gum, Ethyl cellulose and Polyethylene glycol were a Gift sample from Cadila Pharma. Magnesium stearate, PVP K-90, Isopropyl alcohol and Talc were obtained as a gift samples from Lifeline pharma, Puducherry. All other chemicals and reagents used were of analytical grade.

METHOD

Preparation of Timolol Maleate Matrix Tablets

All the matrix tablets, each containing 25 mg of timolol maleate, were prepared by wet granulation method and some of the formulations were prepared by direct compression method also to study the effect of method of manufacture on the drug release.

Wet Granulation

Drug and the diluent (MCC) were sifted through sieve No.40 manually and mixed well to ensure the uniformity of premix blend. Several drug-diluent premixes were then mixed with the selected ratio of polymer(s), previously sifted through sieve No. 40, for 5 minutes. Premix blend was wet granulated with 5% w/v solution of PVP K-90 in a mortar. The wet mass was passed through No.18 sieve. The wet granules were dried at 55°C ± 5°C for 1 hour in a

hot-air oven and the dried granules were sieved through No.22 sieve. These granules were blended with lubrication mixture (1% w/w magnesium stearate and 2% w/w talc) and compressed using 16 station rotary tableting machine, equipped with flat-faced, round punches of 6-mm diameter.

Direct compression

Accurately weighed amounts of drug, polymer, and diluent were mixed geometrically in a mortar. This mixture was passed through No.40 sieve and thoroughly mixed in a polythene bag for 15 minutes. The powder blend was then lubricated with magnesium stearate and talc for 2 minutes and compressed into tablets on a 16-station rotary tableting machine using 6-mm round, flat-faced punches. The drug polymer ratio was developed to adjust drug release as per theoretical release profile and to keep total weight of tablet constant for all the fabricated batches under experimental conditions of preparations. The total weight of the matrix tablets was 120mg with different drug polymer ratios like 1:0.5, 1:1, 1:1.5, 1:2. The various polymers used were Xanthan gum, Polyethylene oxide, HPMC K100 and Ethyl cellulose. Diluents like MCC (water-insoluble) were used for the preparation of matrix tablets (Table No.1).

EVALUATION OF PRE-COMPRESSION BLEND

Angle of Repose

The angle of repose of granules was determined by the funnel-method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a manner that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone measured and angle of repose was calculated using the following equation[12].

$$\mathbf{Tan\ \theta = h/r}$$

where h and r are the height and radius of the powder cone, **θ** is the angle of repose.

Angle of repose values less than 25, 25-30, 30-40, and more than 40 indicates excellent, good, passable, and poor flow properties respectively.

Determination of Bulk Density and Tapped Density

An accurately weighed quantity of the granules/ powder (W) was carefully poured into the graduated cylinder and volume (V_0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 100 tabs and after that the volume (V_f) was measured and continued operation till the two consecutive readings were equal[13.]

The bulk density and the tapped density were calculated using the following formulae.

$$\mathbf{Bulk\ density = W/V_0}$$

$$\mathbf{Tapped\ density = W/V_f}$$

Where, W= Weight of the powder

V_0 = Initial volume

V_f = final volume

Compressibility Index (Carr's Index)

Carr's index (CI) is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is[14].

$$\mathbf{CI = (TD\text{-}BD) \times 100/TD}$$

Where, TD is the tapped density and BD is the bulk density.

Hausner's Ratio

It is the ratio of tapped density and bulk density. Hausner's found that this ratio was related to Interparticle friction and, as such, could be used to predict powder flow properties[14.] Generally a value less than 1.27 indicates good flow properties, which is equivalent to 20% of Carr's index.

EVALUATION OF MATRIX TABLETS

Thickness

Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using digital vernier calliper. Average thickness and standard deviation values were calculated.

Hardness

Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations.

Friability Test

From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, dedusted and reweighed. The friability was calculated as the percentage weight loss.

Note: No tablet should stick to the walls of the apparatus. If so, brush the walls with talcum powder. There should be no capping also.

% friability was calculated as follows

$$\% \text{ Friability} = (W_1 - W_2) \times 100/W_1$$

Where, W_1 = Initial weight of the 20 tablets.

W_2 = Final weight of the 20 tablets after testing. Friability values below 0.8% are generally acceptable.

Weight Variation Test

To study weight variation individual weights (W_I) of 20 tablets from each formulation were noted using electronic balance. Their average weight (W_A) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

$$\% \text{ weight variation} = (W_A - W_I) \times 100/ W_A$$

As the total tablet weight was 120 mg, according to IP 1996, out of twenty tablets ±7.5% variation can be allowed for not more than two tablets.

According to USP 2004, ±10% weight variation can be allowed for not more than two tablets out of twenty tablets.

Drug Content (Assay)

The drug content of the matrix tablets was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 90% to 110% of the standard amount. Ten tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to about 100 mg of TM was transferred to a 100 mL volumetric flask containing 70mL of 0.1N HCl. It was shaken by mechanical means for 1hr.Then it was filtered through a Whatman filter paper (No.1) and diluted to 100 mL with 0.1N HCl. From this resulted solution 1 mL was taken, diluted to 50 mL with 0.1NHCl and absorbance was measured against blank at 295 nm.

***In Vitro* Drug Release Characteristics**

Drug release was assessed by dissolution test under the following conditions: n=3, USP type II dissolution apparatus (paddle method) at 100 rpm in 500 mL of 0.1N HCl for first 2 hours and the phosphate buffer pH 6.8 from 3 to 12 hours, maintained at 37°C ± 0.5^0C. An aliquot (5mL) was withdrawn at specific time intervals and replaced with the same volume of prewarmed (37^0C ± 0.5^0C) fresh dissolution medium. The samples withdrawn were filtered through Whatman filter paper (No.1) and drug content in each sample was analyzed by UV-visible spectrophotometer at 295 nm.

Kinetic Analysis of Dissolution Data

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration[15]. The first order Eq. (2) describes the release from system where release rate is concentration dependent[15]. Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq.(3). The Hixson-Crowell cube root law Eq.(4) describes the release from systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931).

$$C = K_0 t \text{ ---------- (1)}$$

Where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$\text{Log}C = \text{Log}C_0 - K_1 t / 2.303 \text{---------- (2)}$$

Where, C_0 is the initial concentration of drug and K_1 is first order constant.

$$Q = K_H t^{1/2} \text{ ---------- (3)}$$

Where, K_H is the constant reflecting the design variables of the system.

$$Q_0^{1/3} - Qt^{1/3} = K_{HC} t \text{ ---------- (4)}$$

Where, Qt is the amount of drug remained in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation. The following plots were made using the in-vitro drug release data

Cumulative % drug release vs. time (Zero order kinetic model); Log cumulative of % drug remaining vs. time (First order kinetic model); Cumulative % drug release vs. square root of time (Higuchi model); and Cube root of initial concentration minus the cube root of percentage of drug remaining in the matrix vs. Time (Hixson-Crowell cube root law).

MECHANISM OF DRUG RELEASE[17]

Korsmeyer *et al* (1983) derived a simple relationship which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer-Peppas model.

$$Mt / M\infty = Ktn \text{ ---------- (5)}$$

Where, $Mt / M\infty$ is fraction of drug released at time t, K is the release rate constant incorporating structural and geometric characteristics of the tablet, and n is the release exponent. The n value is used to characterize different release mechanisms.

A plot of log cumulative % drug release vs. log time was made. Slope of the line was n. The n value is used to characterize different release mechanisms as given in Table No.2, for the cylindrical shaped matrices. Case-II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release[18].

Similarity Factor (*F*2) Analysis

In vitro release profiles of the selected batches (F15 and F20) of sustained release tablets were compared with the theoretical release profile which was calculated earlier. The data were analyzed by the following formula[19].

$$f2 = 50 \log \{[1+ (1/N) \Sigma (Ri – Ti)2]-0.5 \times 100\}$$

Where N = number of time points, Ri and Ti = dissolution of reference and test products at time i. If f2 is greater than 50 it is considered that 2 products share similar drug release behaviours.

Swelling and Erosion Studies

The dissolution jars were marked with the time points of 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours. One tablet was placed in each dissolution jar containing 500 mL of 0.1 N HCl at 37°C±0.5°C, and the apparatus was run at 100 rpm using paddle. After 2 hours, 0.1 N HCl was replaced with 500 mL of phosphate buffer pH 6.8. The tablets were taken out after completion of the respected stipulated time span as mentioned above and weighed after the excess of water at the surface had been removed with filter paper. The wetted samples were then dried in an oven at 40°C up to constant weight. The increase of the weight on the tablet reflects the weight of the liquid uptake. It was estimated according to following equation

$$Q = 100(Ww – Wi) / Wi$$

where Q is the percentage swelling, and Ww and Wi are the masses of the hydrated samples before drying and the initial starting dry weight, respectively[20].

The degree of erosion (expressed as percentage erosion of the polymer content, E) was determined using following equation.

$$E = 100(W_i – W_f) / W_i$$

Where,

W_f is the final mass of the same dried and partially eroded sample.

FTIR Studies

FTIR studies were performed on drug and the optimized formulation using Shimadzu FTIR (Shimadzu Corp., India). The samples were analyzed between wave numbers 4000 and 400 cm-1.

Stability Studies

The optimized matrix tablets were subjected to stability studies at 25°C ± 2°C / 60% ± 5% RH and 40°C ± 2°C / 75% ± 5% RH The products were evaluated for their physical characteristics, drug content, and in-vitro drug release profiles over a period of 3 months

RESULTS AND DISCUSSION

Standard Graph of Timolol Maleate

The standard graph of Timolol maleate) has shown good linearity with R2 values 0.9956 and 0.9968 in 0.1 N HCl and pH 6.8 buffer respectively, which suggests that it obeys the “Beer-Lambert’s law” (Table No.3, Figure No.1 and 2).

Evaluation of Pre-Compression Blend

The results of the uniformity of Pre-Compression Blend. The results are given in Table No.4.

Physical Evaluation of matrix tablets

The results of the uniformity of weight, hardness, thickness, friability, and drug Content of the tablets are given in Table No.5. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 118.4 and 122.3 mg. The hardness of the tablets ranged from 5.08 to 6.16 kg/cm^2 and the friability values were less than 0.8% indicating that the matrix tablets were compact and hard. The thickness of the tablets ranged from 2.88 to 3.40 mm. All the formulations satisfied the content of the drug as they contained 90 to 103 % of timolol maleate and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practically within control.

***In vitro* Drug Release Studies**

Mechanism of Drug Release

The corresponding plot (log cumulative percent drug release vs time) for the Korsmeyer-Peppas equation indicated a good linearity (*r2* = 0.9741). The diffusion exponent n was 0.66, which appears to indicating a coupling of the diffusion and erosion mechanism (Anomalous diffusion) and may indicate that the drug release was controlled by more than one process.

Determination of Swelling and Eroding Behavior

Since the rate of swelling and erosion is related and may affect the mechanism and kinetics of drug release, the penetration of the dissolution medium and the erosion of the hydrated tablets were determined. Simultaneously with the swelling study, the percentage erosion of polymer was determined. The percentage swelling and erosion of optimized tablet. Maximum swelling was observed in first 2 hours and gradually it was decreased with simultaneous erosion of polymer.

SUMMARY

Matrix tablets were compressed without any problem and do not require any change in ratio of excipients in formulation. Results of the present study demonstrated that combination of both hydrophilic and hydrophobic polymers could be successfully employed for formulating sustained-release matrix tablets of timolol maleate all the formulations containing drug to polymer ratio 1:2 and MCC as a diluent extended the drug release for 8 to 12 hours (Figure No.3-10). Lactose containing formulations have shown faster drug release. The drug release rate was slower with the tablets containing combination of both hydrophilic HPMC K100 and hydrophobic EC polymers compared to with that of combination of 2 hydrophilic polymers (HPMC K100 and HPMC K200). Compared to direct compression, wet granulation method was found to be better choice to extend the drug release for 12 hours. Majority of formulations have released the drug by non-Fickian diffusion (Table No.6).

Table No.1: List of Different Formulations

S.No	Formulae	Polymer (s)	Diluent	Method
1	F1 to F4	Xanthan gum	MCC	Wet granulation
2	F5 to F8	HPMC K 100M	MCC	Wet granulation
3	F9 to F12	HPMC K 200M	MCC	Wet granulation
4	F13 to F16	EC	MCC	Wet granulation
5	F17 to F20	PEO	MCC	Wet granulation
6	F21 to F25	Xanthan gum and EC	MCC	Wet granulation
7	F26 to F30	HPMC K 100M and EC	MCC	Direct compression
8	F31 to F35	HPMC K200M and EC	MCC	Direct compression
9	F36 to F40	HPMC K100M and HPMC K200M	MCC	Wet granulation

S.No	Composition	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	TM	25	25	25	25	25	25	25	25	25	25	25	25
2	Xanthan gum	12.5	25	37.5	50	-	-	-	-	-	-	-	-
3	HPMC K100	-	-	-	-	12.5	25	37.5	50	-	-	-	-
4	HPMC K200	-	-	-	-	-	-	-	-	12.5	25	37.5	50
5	MCC	72.5	60.25	47.75	35.25	72.5	60.25	47.75	35.25	72.5	60.25	47.75	35.25
6	PVP K 90	6	6	6	6	6	6	6	6	6	6	6	6
7	IPA	qs	qs	qs	qs	qs	qs	Qs	qs	qs	qs	qs	qs
8	MS	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
9	Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
10	Av. Wt.(mg)	120	120	120	120	120	120	120	120	120	120	120	120

S.No	Composition	F13	F14	F15	F16	F17	F18	F19	F20
1	TM	25	25	25	25	25	25	25	25
2	Ethyl Cellulose	12.5	25	37.5	50	-	-	-	-
3	PEO	-	-	-	-	12.5	25	37.5	50
4	MCC	72.5	60.25	47.75	35.25	72.5	60.25	47.75	35.25
5	PVP K 90	6	6	6	6	6	6	6	6
6	IPA	qs	Qs	qs	qs	qs	qs	qs	qs
7	MS	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
8	Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
9	Av. Wt.(mg)	120	120	120	120	120	120	120	120

S.No	Composition	F21	F22	F23	F24	F25	F26	F27	F28	F29	F30
1	TM	25	25	25	25	25	25	25	25	25	25
2	Xanthan gum	10	20	25	30	40	-	-	-	-	-
3	Ethyl Cellulose	40	30	25	20	10	40	30	25	20	10
4	HPMC K100	-	-	-	-	-	10	20	25	30	40
5	MCC	35.25	35.25	35.25	35.25	35.25	35.25	35.25	35.25	35.25	35.25
6	PVP K 90	6	6	6	6	6	6	6	6	6	6
7	IPA	qs	qs	qs	qs	qs	Qs	qs	qs	qs	qs
8	MS	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
9	Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
10	Av. Wt.(mg)	120	120	120	120	120	120	120	120	120	120

S.No	Composition	F31	F32	F33	F34	F35	F36	F37	F38	F39	F40
1	TM	25	25	25	25	25	25	25	25	25	25
2	HPMC K200	10	20	25	30	40	40	30	25	20	10
3	HPMC K100	-	-	-	-	-	10	20	25	30	40
4	Ethyl Cellulose	40	30	25	20	10	-	-	-	-	-
5	MCC	35.25	35.25	35.25	35.25	35.25	35.25	35.25	35.25	35.25	35.25
6	PVP K 90	6	6	6	6	6	6	6	6	6	6
7	IPA	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
8	MS	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
9	Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
10	Av. Wt.(mg)	120	120	120	120	120	120	120	120	120	120

Table No.2: Diffusion exponents and solute release mechanism for cylindrical shape

S.No	Diffusion exponent (n)	Overall solute diffusion mechanism
1	0.45	Fickian diffusion
2	$0.45 < n < 0.89$	Anomalous (non-Fickian) diffusion
3	0.89	Case-II transport
4	$n > 0.89$	Super case-II transport

Table No.3: Standard Graph of Timolol Maleate

S.No	Concentration (mcg/mL)	Absorbance	
		0.1N HCL	6.8 pH Buffer
1	5	0.112	0.148
2	10	0.217	0.234
3	15	0.320	0.342
4	20	0.432	0.443
5	25	0.525	0.549
6	30	0.620	0.640
7	35	0.721	0.770
8	40	0.819	0.834
9	45	0.904	0.918
10	50	0.994	0.998

Table No.4: Physical Properties of Pre-compression Blend

S.No	Formulations	Angle of Repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio
1	F1	24.43	0.314	0.255	14.84	1.27
2	F2	26.54	0.311	0.354	15.15	1.21
3	F3	29.00	0.290	0.331	16.04	1.14
4	F4	28.14	0.432	0.391	12.20	1.20
5	F5	29.15	0.334	0.386	13.62	1.22
6	F6	32.57	0.341	0.381	19.52	1.25
7	F7	33.55	0.522	0.639	17.47	1.24
8	F8	33.24	0.528	0.617	17.28	1.23
9	F9	26.62	0.422	0.510	16.60	1.19
10	F10	28.72	0.481	0.568	15.90	1.20
11	F11	27.36	0.476	0.548	16.07	1.18
12	F12	25.41	0.538	0.584	12.52	1.16
13	F13	26.29	0.416	0.468	14.69	1.19
14	F14	24.40	0.488	0.542	12.42	1.15
15	F15	26.36	0.452	0.524	15.73	1.18
16	F16	28.74	0.562	0.654	13.94	1.17
17	F17	29.36	0.321	0.384	15.77	1.21
18	F18	28.18	0.352	0.428	15.42	1.19
19	F19	30.52	0.366	0.473	18.39	1.17
20	F20	26.44	0.365	0.442	15.15	1.18
21	F21	27.88	0.544	0.643	15.39	1.19
22	F22	25.49	0.494	0.566	12.72	1.14
23	F23	26.27	0.487	0.561	13.19	1.15
24	F24	21.25	0.520	0.582	10.65	1.11
25	F25	19.29	0.434	0.497	12.67	1.14
26	F26	33.17	0.482	0.589	18.16	1.22

27	F27	32.51	0.539	0.652	17.33	1.20
28	F28	28.47	0.498	0.582	14.43	1.16
29	F29	28.77	0.533	0.617	13.61	1.15
30	F30	27.34	0.510	0.591	13.70	1.15
31	F31	34.12	0.531	0.633	16.11	1.19
32	F32	32.44	0.522	0.626	16.61	1.19
33	F33	26.79	0.480	0.554	13.35	1.15
34	F34	22.61	0.459	0.509	14.24	1.10
35	F35	32.44	0.522	0.626	16.61	1.19
36	F36	31.26	0.519	0.635	18.26	1.22
37	F37	30.24	0.468	0.562	16.72	1.20
38	F38	29.63	0.484	0.566	14.48	1.16
39	F39	22.61	0.459	0.509	9.82	1.10
40	F40	30.42	0.462	0.562	17.69	1.21

Table No.5: Physical Evaluation of Matrix Tablets

S.No	Formulation Code	Hardness (kg/cm^2)	Thickness (mm)	Weight (mg)	Friability (%)	Drug content (%)
1	F1	3.41±0.18	3.21±0.18	119.6±1.38	0.46	98.84±1.36
2	F2	5.50±0.31	3.36±0.24	120.1±0.54	0.49	96.98±0.64
3	F3	5.54±0.40	3.14±0.80	118.6±0.41	0.43	99.12±2.47
4	F4	5.62±0.55	3.20±0.20	118.8±1.64	0.22	100.22±0.88
5	F5	4.24±0.57	3.08±0.66	120.6±1.14	0.44	99.24±1.25
6	F6	4.12±0.30	3.33±0.25	119.2±0.83	0.68	98.53±1.87
7	F7	4.28±0.57	3.24±0.71	119.9±0.67	0.54	97.81±1.99
8	F8	4.36±0.60	3.32±0.89	119.0±0.43	0.47	96.35±1.14
9	F9	4.84±0.44	3.38±0.73	120.5±0.80	0.67	98.34±2.18
10	F10	5.00±0.31	3.00±0.68	121.2±0.83	0.44	97.29±0.98
11	F11	5.04±0.37	2.98±0.88	122.1±0.93	0.31	99.35±0.43

12	F12	5.30±0.70	3.11±0.36	121.2±0.97	0.36	99.88±0.88
13	F13	4.34±0.50	3.06±0.46	119.2±0.83	0.30	97.57±1.22
14	F14	4.51±0.57	2.98±0.38	122.2±0.92	0.34	94.35±2.09
15	F15	4.78±0.77	3.25±0.37	122.0±1.22	0.54	99.54±2.15
16	F16	4.92±0.80	3.24±0.52	120.8±1.48	0.49	100.55±2.31
17	F17	5.08±0.86	3.15±0.56	118.4±1.04	0.52	98.78±1.56
18	F18	5.12±0.75	3.20±0.44	121.4±1.09	0.48	98.27±1.88
19	F19	5.14±0.67	3.11±0.55	120.7±0.65	0.58	97.55±1.56
20	F20	5.12±0.47	3.31±0.56	120.1±1.82	0.50	100.87±0.97
21	F21	5.16±0.69	2.95±0.75	122.3±0.84	0.68	100.68±1.39
22	F22	5.42±0.37	2.93±0.83	119.8±0.19	0.59	97.39±2.06
23	F23	5.32±0.65	3.33±0.59	119.8±0.38	0.54	98.90±2.31
24	F24	5.24±0.57	3.36±0.74	121.3±0.97	0.57	99.43±2.11
25	F25	5.58±0.70	3.32±0.65	122.9±0.90	0.61	98.66±2.04
26	F26	4.84±0.35	3.15±0.71	121.5±0.96	0.32	101.82±1.55
27	F27	5.12±0.37	3.26±0.43	120.2±0.76	0.52	100.44±1.21
28	F28	5.16±0.65	3.35±0.50	120.6±1.48	0.47	99.21±2.07
29	F29	5.24±0.57	3.31±0.44	120.9±0.99	0.48	95.99±2.81
30	F30	5.32±0.97	3.30±0.27	120.5±1.01	0.42	94.76±2.54
31	F31	4.62±0.60	2.93±0.34	122.1±0.51	0.50	97.86±2.41
32	F32	5.22±0.45	3.07±0.22	122.6±0.80	0.54	98.02±1.87
33	F33	5.25±0.77	3.30±0.54	120.7±1.35	0.61	98.72±2.66
34	F34	5.44±0.60	3.36±0.40	120.7±0.58	0.52	99.39±1.36
35	F35	5.28±0.45	3.40±0.71	121.6±1.81	0.48	96.64±1.93
36	F36	5.30±0.80	3.15±0.63	121.1±0.62	0.58	98.78±0.73
37	F37	4.92±0.65	2.86±0.59	120.9±2.74	0.66	98.43±0.96
38	F38	4.98±0.67	3.19±0.49	121.3±1.04	0.62	99.47±1.54
39	F39	5.12±0.55	3.32±0.65	122.0±0.70	0.69	94.38±2.42
40	F40	5.08±0.40	3.08±0.31	120.8±0.83	0.71	93.72±1.74

Table No.6: Similarity factor

S.No	Time (Hr)	Log Time	SQRT Time	Conc.	Amt. Release	% Cumulative drug Release	Log % Release	% Drug remaining	Log % Drug remaining
1	0	0.000	0	0	0	0	0	100	2
2	1	0.000	1.000	1.125	10.125	29.22	1.466	70.78	1.850
3	2	0.301	1.414	1.729	15.561	35.95	1.5557	64.05	1.807
4	3	0.477	1.732	2.364	21.276	41.47	1.6177	58.53	1.767
5	4	0.602	2.000	3.158	28.422	48.86	1.6890	51.14	1.709
6	6	0.778	2.449	3.974	35.766	62.87	1.7984	37.13	1.570
7	8	0.903	2.828	5.421	48.789	76.97	1.8863	23.03	1.362
8	10	1.000	3.162	6.875	61.875	89.57	1.9522	10.43	1.018
9	12	1.079	3.464	7.621	68.589	99.87	1.9994	0.13	-0.886
$K_{0(Slope)}$						**Zero order**	**Peppas**	**Higuichi**	**First Order**
						7.418344	0.5156	0.484	-0.179
R^2						0.9537	0.9713	0.9859	0.7023

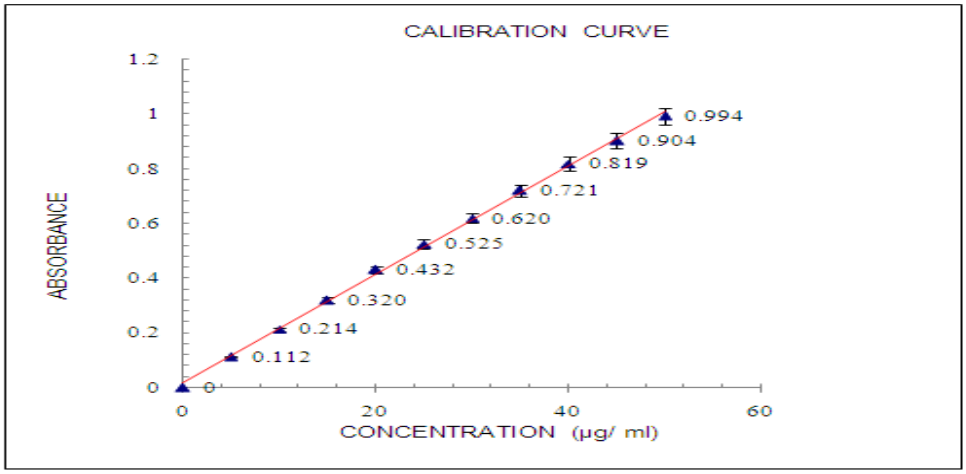

Figure No.1: Standard graph of timolol maleate in 0.1 N HCl

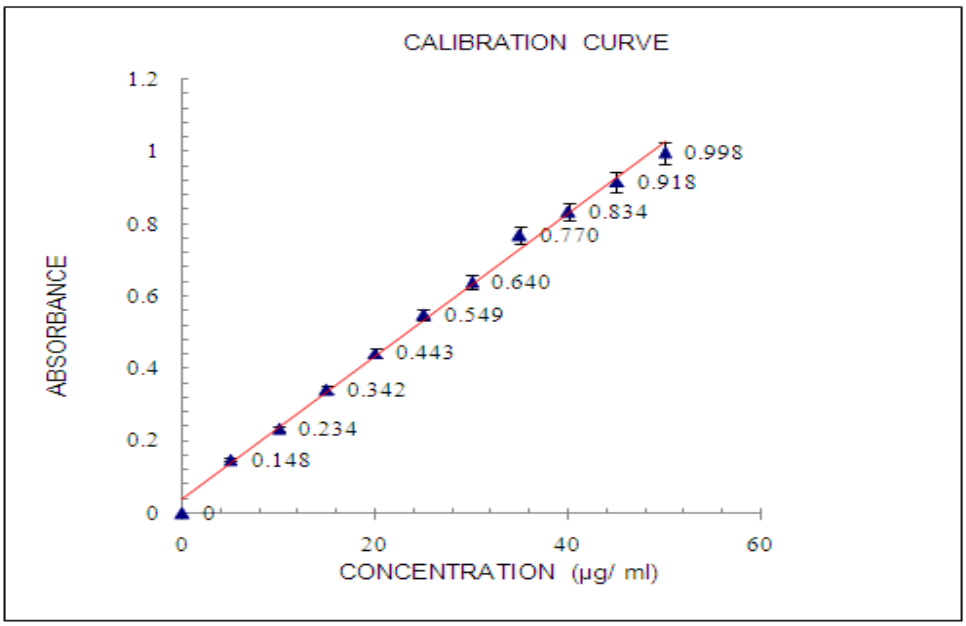

Figure No.2: Standard graph of timolol maleate in 6.8 pH buffer

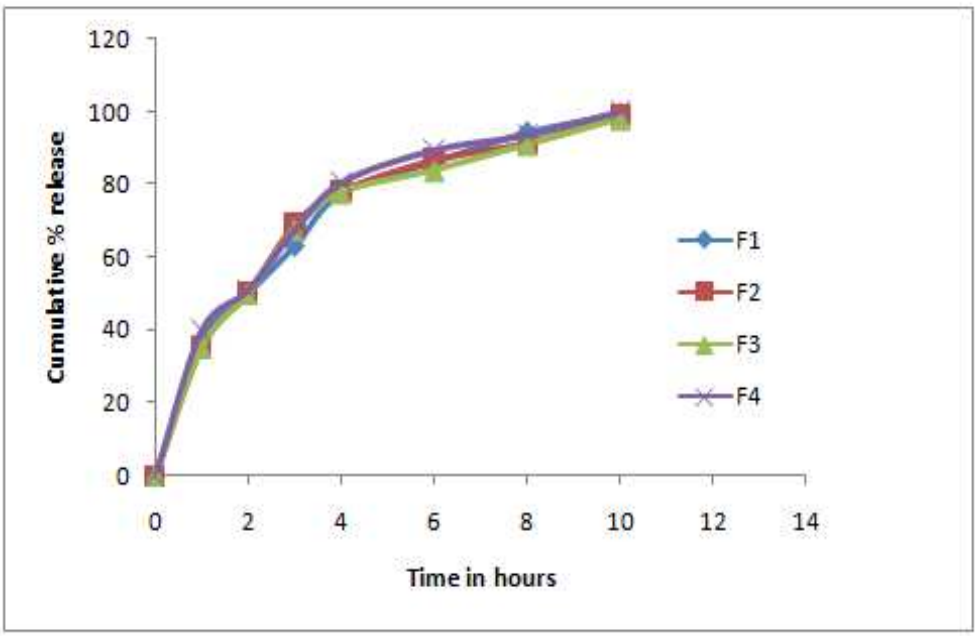

Figure No.3: Release profile of Timolol Maleate from tablets containing Xanthan gum

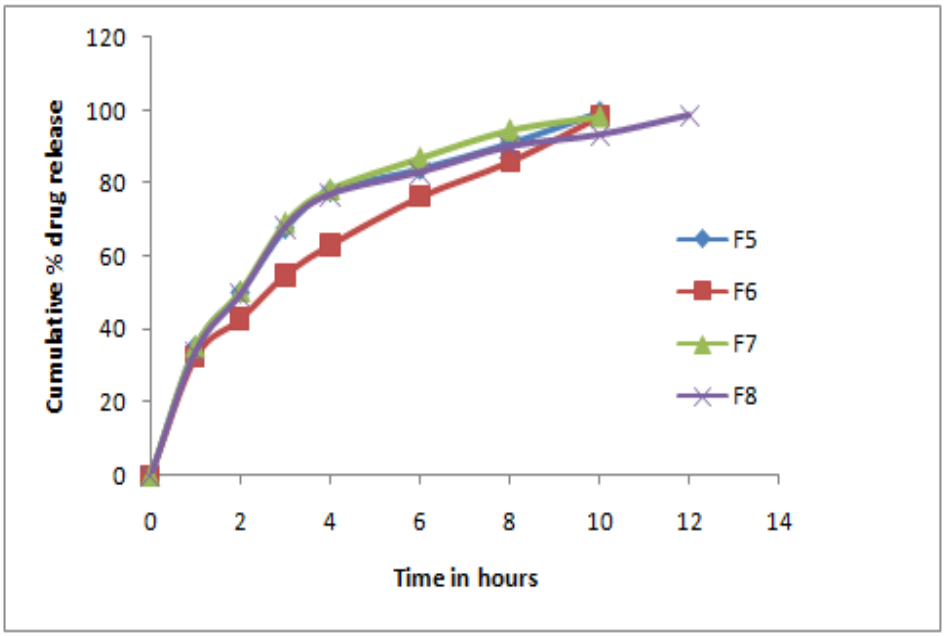

Figure No.4: Release profile of Timolol Maleate from tablets containing HPMC K100

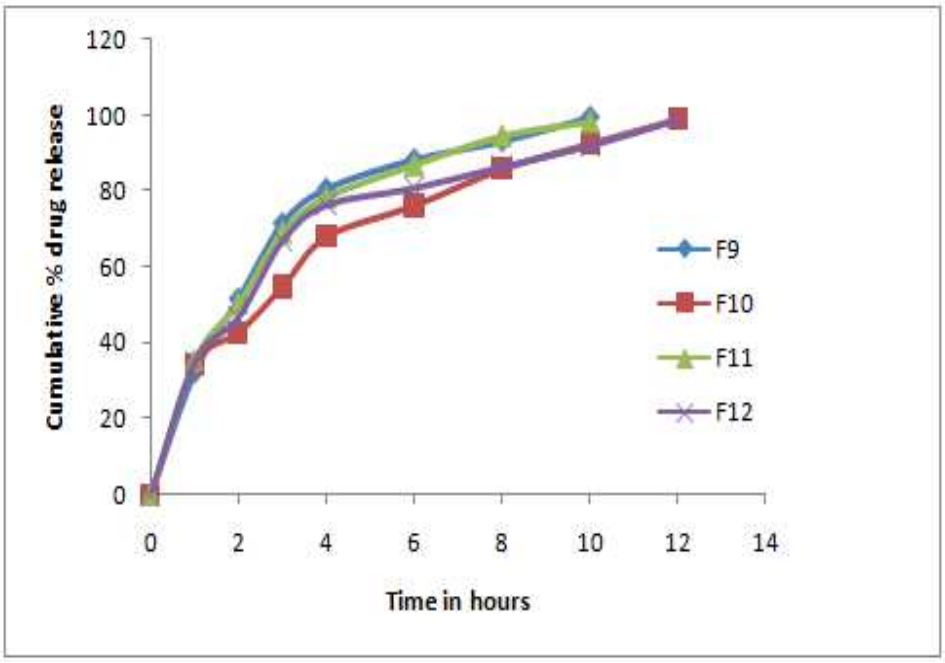

Figure No.5: Release profile of Timolol Maleate from tablets containing HPMC K200

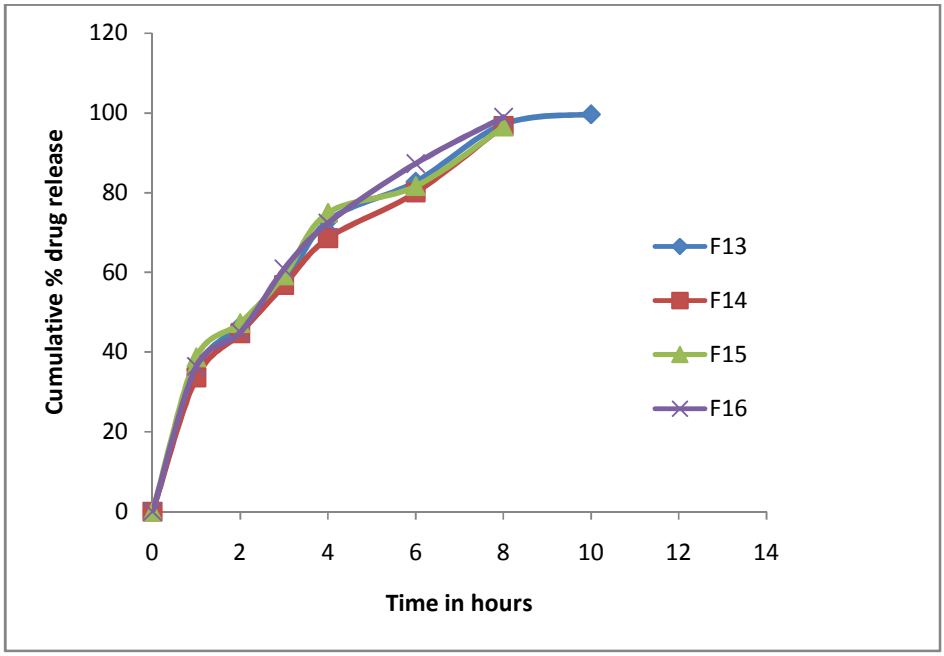

Figure No.6: Release profile of Timolol Maleate from tablets containing Ethyl cellulose

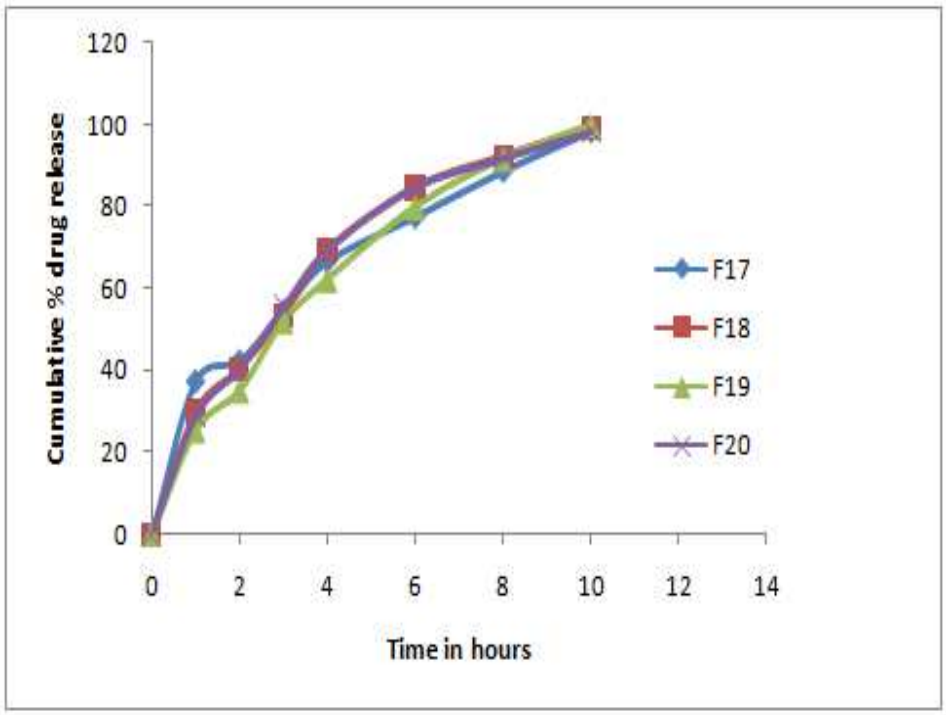

Figure No.7: Release profile of Timolol Maleate from tablets containing PEO

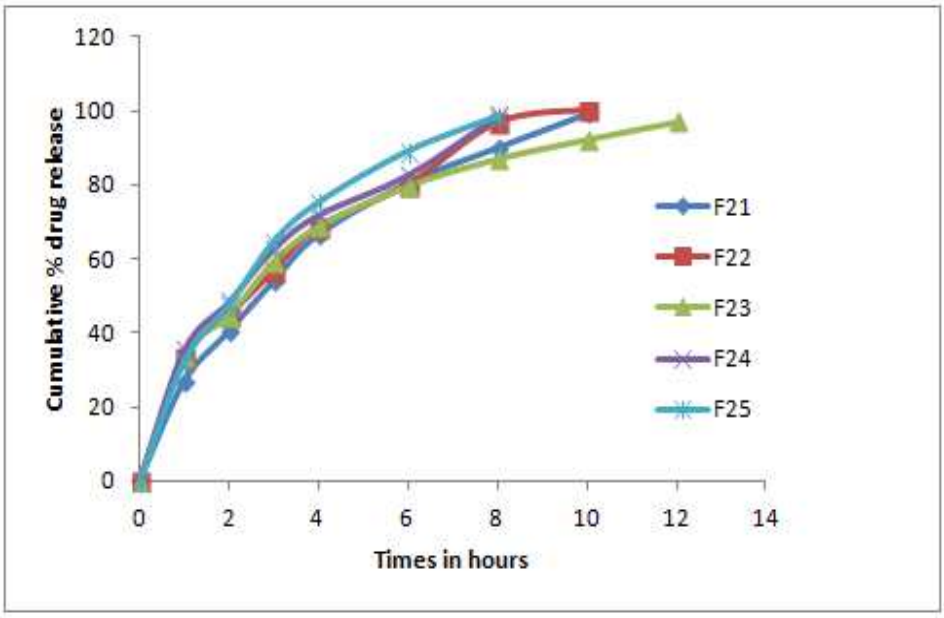

Figure No.8: *In Vitro* Release data of Timolol Maleate from Tablets Containing Xanthan gum and Ethyl cellulose

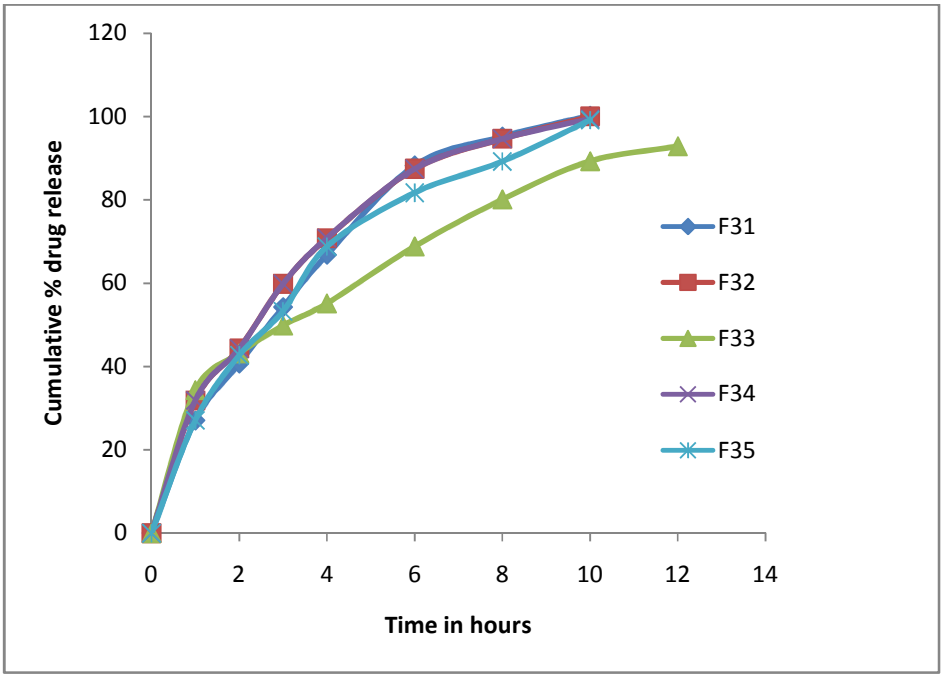

Figure No.9: Release profile of Timolol Maleate from tablets containing HPMC K100 and EC

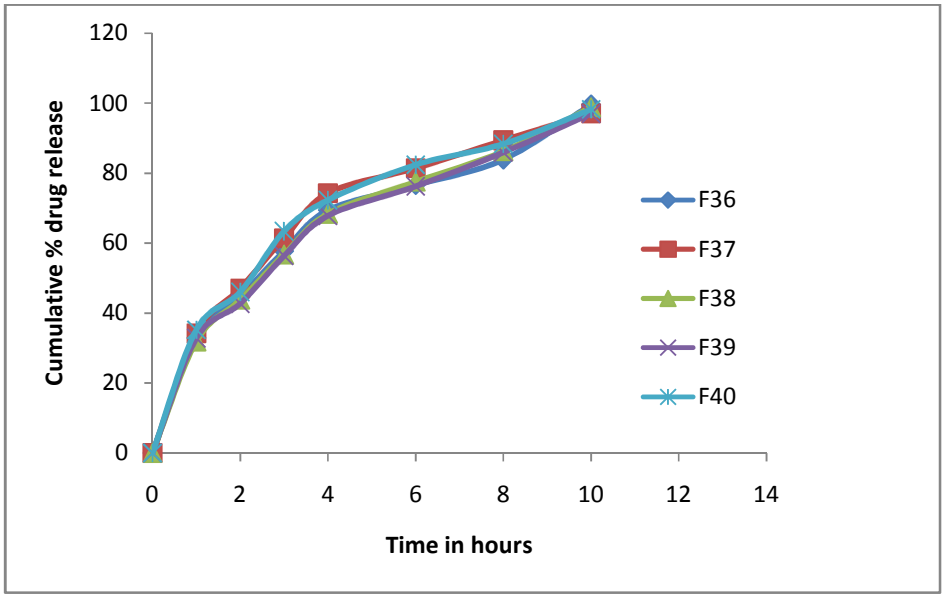

Figure No.10: Release profile of Timolol Maleate from tablets containing HPMC K100 and HPMC K200

CONCLUSION

Optimized formulation F28 (drug to polymer ratio 1:2) which includes both HPMC K100 and EC (1:1) has successfully sustained the drug release for 12 hours and the drug release pattern was similar to theoretical release profile. The release process involves anomalous diffusion mechanism or diffusion coupled with erosion, as indicated by the n value of 0.67 in Korsmeyer's plot. There was an alteration in the surface area and diameter of the tablets with the progressive dissolution of the matrix as a function of time, as indicated in Hixson-Crowell plot. FTIR studies combined with stability studies proved the integrity of the developed matrix tablets.

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