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FORMULATION, EVALUATION AND CHARACTERIZATION OF SUSTAINED-RELEASE MATRIX TABLETS OF TIMOLOL MALEATE USING HYDROPHILIC, HYDROPHOBIC AND PLASTIC POLYMERS

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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 F23 (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 (F23) 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 compared to lactose (water soluble) in the formulation of sustained release tablets of water soluble 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.

Key words: Hydrophilic, Hydrophobic polymers, sustained release, Timolol maleate, wet granulation.

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 infraction. 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 disentanglement 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 CR 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.

Methodology

CONSTRUCTION OF STANDARD GRAPH OF TIMOLOL MALEATE

Accurately weighed amount of 100 mg timolol maleate was transferred into a 100ml volumetric flask. 20 mL of 0.1N hydrochloric acid (HCl) was added to dissolve the drug and volume was made up to 100 mL with the same HCl. The resulted solution had the concentration of 1mg/ml which was labeled as 'stock'. From this stock solution 10ml was taken and diluted to 100 mL with 0.1N HCl which has given the solution having the concentration of 100 mcg/mL. Necessary dilutions were made by using this second solution to give the different concentrations of timolol maleate (5 to 50 mcg/mL) solutions.

The absorbances of above solutions were recorded at λ_{max} (295 nm) of the drug using double beam UV-Visible spectrophotometer. Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

Similarly, standard graph was plotted with 6.8 pH phosphate buffer.

PREPARATION OF 0.1 N HCL: Accurately measured 8.5 mL of concentrated hydrochloric acid was added to 1000 mL of distilled water.

PREPARATION OF PH 6.8 PHOSPHATE BUFFER: Accurately measured 50 mL of 0.2 M potassium dihydrogen orthophosphate was transferred to a 200mL volumetric flask and 22.4 mL of 0.2 M sodium hydroxide was added to it. Volume was made up to 200 mL with distilled water, mixed and pH was adjusted to 6.8 with 0.2 M sodium hydroxide or 0.2 M othophosphoric acid.

PREPARATION OF 0.2 M POTASSIUM DIHYDROGEN PHOSPHATE SOLUTION: Accurately weighed 27.218 g of monobasic potassium dihydrogen phosphate was dissolved in 1000 mL of distilled water and mixed.

PREPARATION OF 0.2 M SODIUM HYDROXIDE SOLUTION: Accurately weighed 8 g of sodium hydroxide pellets were dissolved in 1000 mL of distilled water and mixed.

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 or Lactose) 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 tabletting 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 HPMC K15M, Polyethylene oxide, Kollidon-SR, HPMC K100M CR and Ethyl cellulose. Diluents like MCC (water-insoluble) or lactose (water soluble) were used for the preparation of matrix tablets.

Table: 1 List of Different Formulations.

Formulae	Polymer (s)	Diluent	Method
F1 to F4	HPMC K15M	MCC	Wet granulation
F5 to F8	Polyethylene oxide	MCC	Wet granulation
F9 to F12	HPMC K 100M	MCC	Wet granulation
F13 to F16	Ethyl cellulose	MCC	Wet granulation
F17 to F20	Kollidon-SR	MCC	Direct compression
F21 to F25	HPMC K100M & EC	MCC	Wet granulation
F26 to F30	HPMC K 100M &HPMC K 15M	MCC	Wet granulation
F31 to F35	HPMC K100M & EC	Lactose	Wet granulation
F36 to F40	HPMC K100M & EC	MCC	Direct compression

Formulations

In the formulations prepared, the release retardants included were hydroxypropylmethylcellulose (HPMC K15M, HPMC K100M CR), polyethylene oxide (PEO), ethylcellulose (EC), and Kollidon-SR. Microcrystalline cellulose (MCC), lactose were used as diluents. Magnesium stearate (MS) 1% and talc 2 % were used as lubricants. 5% w/v solution of polyvinylpyrrolidone (PVP-K90) in isopropyl alcohol (IPA) was used as binder. Compositions of different formulations were given in the following Tables 2-10.

Table-2: Composition of Matrix Tablets Containing HPMC K15M*.

F.Code	TM (mg)	HPMC K15M (mg)	MCC (mg)	PVP-K90 (mg)	IPA (mL)	MS (mg)	Talc (mg)	Total (mg)
F1	25	12.5	72.9	6	qs	1.2	2.4	120
F2	25	25	60.4	6	qs	1.2	2.4	120
F3	25	37.5	47.9	6	qs	1.2	2.4	120
F4	25	50	35.4	6	qs	1.2	2.4	120

* qs = quantity sufficient; Drug to Polymer ratio is 1:0.5, 1:1, 1:1.5, and 1:2 for F1, F2, F3, and F4 respectively.

Table-3: Composition of Matrix Tablets Containing Polyethylene Oxide.

F.Code	TM (mg)	PEO (mg)	MCC (mg)	PVP-K90 (mg)	IPA (ml)	MS (mg)	Talc (mg)	Total (mg)
F5	25	12.5	72.9	6	qs	1.2	2.4	120
F6	25	25	60.4	6	qs	1.2	2.4	120
F7	25	37.5	47.9	6	qs	1.2	2.4	120
F8	25	50	35.4	6	qs	1.2	2.4	120

* qs = quantity sufficient; Drug to Polymer ratio is 1:0.5, 1:1, 1:1.5, and 1:2 for F5, F6, F7, and F8 respectively.

Table-4: Composition of Matrix Tablets Containing HPMC K100M CR*.

F.Code	TM (mg)	HPMC K 100M (mg)	MCC (mg)	PVP-K90 (mg)	IPA (ml)	MS (mg)	Talc (mg)	Total (mg)
F9	25	12.5	72.9	6	qs	1.2	2.4	120
F10	25	25	60.4	6	qs	1.2	2.4	120
F11	25	37.5	47.9	6	qs	1.2	2.4	120
F12	25	50	35.4	6	qs	1.2	2.4	120

* qs = quantity sufficient; Drug to Polymer ratio is 1:0.5, 1:1, 1:1.5, and 1:2 for F9, F10, F11, and F12 respectively.

Table-5: Composition of Matrix Tablets Containing Ethylcellulose*.

F.Code	TM (mg)	EC (mg)	MCC (mg)	PVP-K90 (mg)	IPA (mL)	MS (mg)	Talc (mg)	Total (mg)
F13	25	12.5	72.9	6	qs	1.2	2.4	120
F14	25	25	60.4	6	qs	1.2	2.4	120
F15	25	37.5	47.9	6	qs	1.2	2.4	120
F16	25	50	35.4	6	qs	1.2	2.4	120

* qs = quantity sufficient; Drug to Polymer ratio is 1:0.5, 1:1, 1:1.5, and 1:2 for F13, F14, F15, and F16 respectively.

Table-6: Composition of Matrix Tablets Containing Kolliodon-SR*.

F.code	TM (mg)	Kollidon-SR (mg)	MCC (mg)	PVP-K90 (mg)	MS (mg)	Talc (mg)	Total (mg)
F17	25	12.5	72.9	6	1.2	2.4	120
F18	25	25	60.4	6	1.2	2.4	120
F19	25	37.5	47.9	6	1.2	2.4	120
F20	25	50	35.4	6	1.2	2.4	120

* Drug to Polymer ratio is 1:0.5, 1:1, 1:1.5, and 1:2 for F17, F18, F19, and F20 respectively.

Table-7: Composition of Matrix Tablets Containing Combination of HPMC K100M and EC*.

F.Code	TM (mg)	HPMC K100M (mg)	EC (mg)	MCC (mg)	PVP-K90 (mg)	IPA (mL)	MS (mg)	Talc (mg)	Total (mg)
F21	25	40	10	35.4	6	qs	1.2	2.4	120
F22	25	30	20	35.4	6	qs	1.2	2.4	120
F23	25	25	25	35.4	6	qs	1.2	2.4	120
F24	25	20	30	35.4	6	qs	1.2	2.4	120
F25	25	10	40	35.4	6	qs	1.2	2.4	120

* qs = quantity sufficient; Drug to Polymer ratio is 1:2; HPMC to EC ratio is 4:1, 3:2, 1:1, 2:3, and 1:4 for F21, F22, F23, F24, and F25 respectively.

Table-8: Composition of Matrix Tablets Containing Combination of HPMC K100M and HPMC K15M*.

F.Code	TM (mg)	HPMC K100M (mg)	HPMC K15M (mg)	MCC (mg)	PVP-K90 (mg)	IPA (mL)	MS (mg)	Talc (mg)	Total (mg)
F26	25	40	10	35.4	6	qs	1.2	2.4	120
F27	25	30	20	35.4	6	qs	1.2	2.4	120
F28	25	25	25	35.4	6	qs	1.2	2.4	120
F29	25	20	30	35.4	6	qs	1.2	2.4	120
F30	25	10	40	35.4	6	qs	1.2	2.4	120

*qs = quantity sufficient; Drug to Polymer ratio is 1:2; HPMC K100M to HPMC K15M ratio is 4:1, 3:2,1:1, 2:3, and 1:4 for F26, F27, F28, F29, and F30 respectively.

Table-9: Composition of Matrix Tablets Containing Combination of HPMC K100M and EC (Lactose as a diluent).

F.Code	TM (mg)	HPMC K100M (mg)	EC (mg)	Lactose (mg)	PVP-K90 (mg)	IPA (mL)	MS (mg)	Talc (mg)	Total (mg)
F31	25	40	10	35.4	6	qs	1.2	2.4	120
F32	25	30	20	35.4	6	qs	1.2	2.4	120
F33	25	25	25	35.4	6	qs	1.2	2.4	120
F34	25	20	30	35.4	6	qs	1.2	2.4	120
F35	25	10	40	35.4	6	qs	1.2	2.4	120

qs = quantity sufficient; Drug to Polymer ratio is 1:2; HPMC to EC ratio is 4:1, 3:2, 1:1, 2:3, and 1:4 for F31, F32, F33, F34, and F35 respectively.

Table-10: Composition of Matrix Tablets Containing Combination of HPMC K100M and EC (Direct Compression Method).

F.Code	TM (mg)	HPMC K100M (mg)	EC (mg)	MCC (mg)	PVP-K90 (mg)	MS (mg)	Talc (mg)	Total (mg)
F36	25	40	10	35.4	6	1.2	2.4	120
F37	25	30	20	35.4	6	1.2	2.4	120
F38	25	25	25	35.4	6	1.2	2.4	120
F39	25	20	30	35.4	6	1.2	2.4	120
F40	25	10	40	35.4	6	1.2	2.4	120

Drug to Polymer ratio is 1:2; HPMC to EC ratio is 4:1, 3:2, 1:1, 2:3, and 1:4 for F31, F32, F33, F34, and F35 respectively.

EVALUATION OF PRE-COMPRESSION BLEND

A) 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]. $\tan \theta = h/r$

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.

B) 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.

Bulk density = W/V_0

Tapped density = W/V_f

where, W= Weight of the powder

V_0 = Initial volume

V_f = final volume

C) 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[13].

CI = (TD-BD) x 100/TD

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

Table-11: Carr's Index Values.

S.No.	Carr's Index	Properties
1	5-12	Free flowing
2	13-16	Good
3	18-21	Fair
4	23-35	Poor
5	33-38	Very poor
6	>40	Extremely poor

D) HAUSNER'S RATIO

It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties [13]. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index

EVALUATION OF MATRIX TABLETS

I) THICKNESS

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

II) 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.

III) 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.

IV) 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.

V) 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 70 mL of 0.1N HCl. It was shaken by mechanical means for 1h.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 0.1N HCl and absorbance was measured against blank at 295 nm.

VI) 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°C. An aliquot (5mL) was withdrawn at specific time intervals and replaced with the same volume of prewarmed (37°C ± 0.5°C) 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.

VII) 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[14]. 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).

$$C = K_0 t \quad (1)$$

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

$$LogC = LogC_0 - K_1 t / 2.303 \quad (2)$$

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

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

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

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

where, Q_t 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).

VIII) MECHANISM OF DRUG RELEASE[16]

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.

$$M_t / M_\infty = Kt^n \quad (5)$$

where M_t / $M\infty$ 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 Table12, 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 [17].

Table-12: Diffusion Exponent and Solute Release Mechanism for Cylindrical Shape.

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

IX) SIMILARITY FACTOR (F_2) ANALYSIS

In vitro release profiles of the selected batches (F12 and F21) of sustained release tablets were compared with the theoretical release profile which was calculated earlier. The data were analyzed by the following formula [18]

$$f_2 = 50 \log \{[1+ (1/N) \sum (R_i - T_i)^2]^{-0.5} \times 100\}$$

where N = number of time points, Ri and Ti = dissolution of reference and test products at time i. If f_2 is greater than 50 it is considered that 2 products share similar drug release behaviors.

X) 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

$$Q = 100(W_w - W_i) / W_i$$

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[19].

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.

XI) FTIR STUDIES

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

XII) 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 R^2 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:13,Figure:1&2)

Table-13: Standard Graph of Timolol Maleate.

Conc. (mcg/mL)	Absorbance	
	0.1N HCl	6.8 pH Buffer

5	0.159	0.135
10	0.208	0.248
15	0.318	0.352
20	0.428	0.433
25	0.512	0.535
30	0.605	0.671
35	0.718	0.759
40	0.860	0.858
45	0.932	0.934
50	1.009	1.011
R^2	0.9956	0.9968

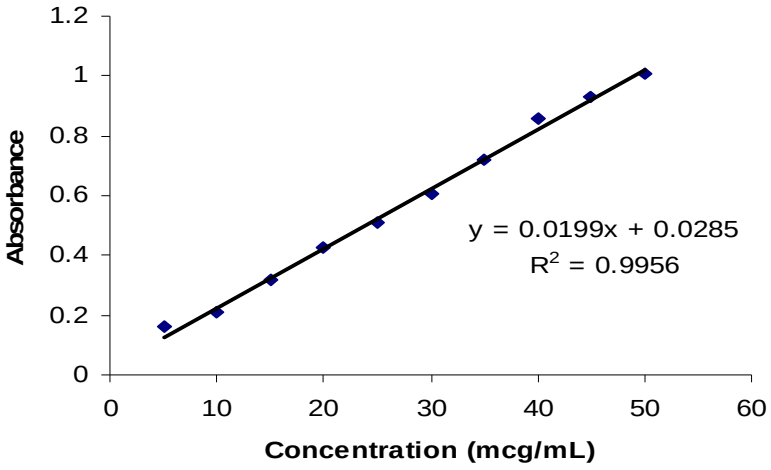

Figure-1: Standard graph of timolol maleate in 0.1 N HCl.

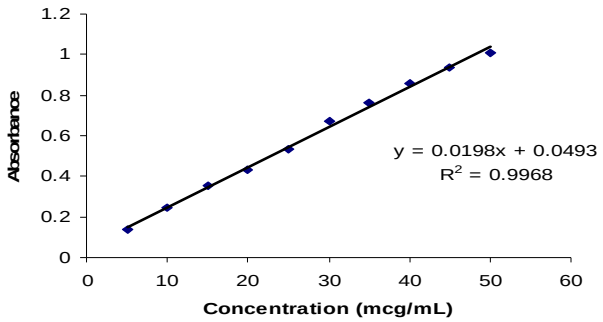

Figure-2: Standard graph of timolol maleate in 6.8 pH buffer.

DOSE CALCULATIONS AND THEORETICAL RELEASE PROFILE

As calculated before, the total dose required for twice-daily SR formulation of timolol maleate was found to be 25 mg and its theoretical release profile was given in Table.14.

Table-14: Theoretical Release Profile of Timolol Maleate from SR tablets.

Time (hours)	Cumulative % Release
1	26.16
2	33.08
3	40
4	46.92
6	60.76
8	74.6
10	88.44
12	> 90

CHARACTERIZATION OF GRANULES

The granules for matrix tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index, and drug content . Angle of repose was less than 35° and Carr's index values were less than 21 for the granules of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.25 for all the batches indicating good flow properties. The drug content was more than 90 % for all the granules of different formulations. The results are tabulated in table 15.

Table-15: Physical Properties of Precompression Blend.

Formulations	Angle of repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio
F1	25.49	0.214	0.251	14.74	1.17
F2	26.24	0.308	0.364	15.38	1.18
F3	29.05	0.276	0.322	14.28	1.16
F4	26.97	0.341	0.388	12.11	1.13
F5	29.25	0.324	0.376	13.82	1.16
F6	32.27	0.320	0.397	19.39	1.24
F7	33.65	0.521	0.629	17.17	1.20
F8	33.21	0.518	0.627	17.38	1.21
F9	26.56	0.422	0.506	16.60	1.19
F10	28.75	0.481	0.572	15.90	1.18
F11	27.33	0.475	0.566	16.07	1.19
F12	25.38	0.524	0.599	12.52	1.14
F13	26.43	0.412	0.483	14.69	1.17
F14	24.77	0.488	0.537	9.12	1.10
F15	26.42	0.439	0.521	15.73	1.18
F16	28.19	0.559	0.649	13.94	1.16
F17	29.58	0.331	0.393	15.77	1.18
F18	28.73	0.362	0.428	15.42	1.18
F19	30.45	0.386	0.473	18.39	1.22
F20	26.43	0.375	0.442	15.15	1.17
F21	19.29	0.434	0.497	12.67	1.14
F22	21.25	0.520	0.582	10.65	1.11
F23	26.27	0.487	0.561	13.19	1.15
F24	25.49	0.494	0.566	12.72	1.14
F25	27.88	0.544	0.643	15.39	1.18
F26	27.34	0.510	0.591	13.70	1.15
F27	28.77	0.533	0.617	13.61	1.15
F28	28.47	0.498	0.582	14.43	1.16
F29	32.51	0.539	0.652	17.33	1.20
F30	33.17	0.482	0.589	18.16	1.22
F31	28.42	0.399	0.468	14.74	1.17
F32	22.61	0.459	0.509	9.82	1.10
F33	26.79	0.480	0.554	13.35	1.15
F34	32.44	0.522	0.626	16.61	1.19
F35	34.12	0.531	0.633	16.11	1.19
F36	30.42	0.462	0.562	17.79	1.21
F37	26.17	0.439	0.507	13.41	1.15
F38	29.63	0.484	0.566	14.48	1.16
F39	30.24	0.468	0.562	16.72	1.20
F40	31.26	0.519	0.635	18.26	1.22

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 16. 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.

Table-16: Physical Evaluation of Matrix Tablets.

F.Code	Hardness (kg/cm^2) †	Thickness (mm) ‡	Weight (mg) ‡	Friability (%)	Drug content *
F1	5.50±0.44	3.22±0.17	119.8±1.48	0.36	98.25±1.37
F2	5.50±0.31	3.37±0.25	120.4±0.54	0.39	95.28±0.80
F3	5.58±0.40	3.14±0.80	118.6±0.41	0.43	99.12±2.47
F4	5.66±0.55	3.20±0.20	118.8±1.64	0.12	101.22±0.88
F5	4.25±0.57	3.08±0.66	120.6±1.14	0.54	100.24±1.25

F6	4.08±0.30	3.33±0.25	119.2±0.83	0.58	99.53±1.87
F7	4.25±0.57	3.24±0.71	119.9±0.67	0.64	93.28±1.99
F8	4.41±0.60	3.32±0.89	119.0±0.43	0.37	95.35±1.14
F9	5.00±0.44	3.38±0.73	120.5±0.80	0.77	96.34±2.18
F10	5.00±0.31	3.00±0.68	121.2±0.83	0.42	91.29±0.98
F11	5.08±0.37	2.98±0.88	122.1±0.93	0.48	97.35±0.43
F12	5.41±0.70	3.11±0.36	121.2±0.97	0.15	98.88±0.88
F13	4.33±0.50	3.06±0.46	119.2±0.83	0.27	94.57±1.22
F14	4.58±0.57	2.98±0.38	122.2±0.92	0.29	90.35±2.09
F15	4.75±0.77	3.25±0.37	122.0±1.22	0.53	99.54±2.15
F16	4.91±0.80	3.24±0.52	120.8±1.48	0.64	102.55±2.31
F17	5.08±0.86	3.15±0.56	118.4±1.04	0.71	93.78±1.56
F18	5.16±0.75	3.20±0.44	121.4±1.09	0.42	96.27±1.88
F19	5.25±0.67	3.11±0.55	120.7±0.65	0.66	92.55±1.56
F20	5.30±0.47	3.31±0.56	120.1±1.82	0.38	102.87±0.97
F21	5.41±0.69	2.95±0.75	122.3±0.84	0.86	100.68±1.39
F22	5.58±0.37	2.93±0.83	119.8±0.19	0.69	95.39±2.06
F23	5.66±0.65	3.33±0.59	119.8±0.38	0.37	98.90±2.31
F24	5.75±0.57	3.36±0.74	121.3±0.97	0.51	97.43±2.11
F25	6.16±0.70	3.32±0.65	122.9±0.90	0.59	97.66±2.04
F26	4.66±0.35	3.15±0.71	121.5±0.96	0.28	102.82±1.55
F27	5.08±0.37	3.26±0.43	120.2±0.76	0.35	100.44±1.21
F28	5.16±0.65	3.35±0.50	120.6±1.48	0.47	99.21±2.07
F29	5.25±0.57	3.31±0.44	120.9±0.99	0.21	91.99±2.81
F30	5.25±0.97	3.30±0.27	120.5±1.01	0.33	90.76±2.54
F31	4.58±0.60	2.93±0.34	122.1±0.51	0.57	94.86±2.41
F32	5.16±0.45	3.07±0.22	122.6±0.80	0.55	98.02±1.87
F33	5.25±0.77	3.30±0.54	120.7±1.35	0.72	96.72±2.66
F34	5.41±0.60	3.36±0.40	120.7±0.58	0.68	92.39±1.36

F35	5.33±0.45	3.40±0.71	121.6±1.81	0.43	95.64±1.93
F36	4.58±0.80	3.15±0.63	121.1±0.62	0.81	98.68±0.73
F37	4.66±0.65	2.86±0.59	120.9±2.74	0.64	98.03±0.96
F38	4.75±0.67	3.19±0.49	121.3±1.04	0.73	99.27±1.54
F39	4.83±0.55	3.32±0.65	122.0±0.70	0.66	91.38±2.42
F40	5.08±0.40	3.08±0.31	120.8±0.83	0.71	93.72±1.74

***** All values represent mean ± Standard Deviation (SD), n=3

† All values represent mean ± Standard Deviation (SD), n=6

‡ All values represent mean ± Standard Deviation (SD), n=20

IN-VITRO DRUG RELEASE STUDIES

DRUG RELEASE FROM HPMC K15M MATRICES

The release of drug depends not only on the nature of matrix but also upon the drug polymer ratio. As the percentage of polymer increased, the kinetics of release decreased. Formulation F1 composed of drug polymer ratio of 1:0.5, failed to sustain release beyond 6h. This formulation underwent erosion before complete swelling could take place. Formulations with drug polymer ratios 1:1 (F2), 1:1.5 (F3) have extended the drug release for 8h. Further increasing the ratio to 1:2 (F4), the release was sustained for 10 h. All these formulations have shown more than 30% release in the first 1 hour indicating burst release. This phenomenon may be attributed to surface erosion or initial disaggregation of the matrix tablet prior to gel layer formation around the tablet core[20] . It is reported in the literature that more than 30% release of drug in the first hour of dissolution indicates the chance of dose dumping [21]. Results of the same are tabulated in the Table:17, Figure:3.

Table-17: In-Vitro Release Data of Timolol Maleate from HPMC K15M Matrices*.

Time (hours)	F1	F2	F3	F4
1	41.94±0.87	39.96±0.93	37.12±1.22	36.78±1.53
2	53.88±0.44	50.99±0.68	50.20±0.37	48.13±1.12
3	74.58±1.10	67.43±0.49	63.09±0.96	62.99±0.84
4	82.35±1.35	80.50±1.77	77.61±0.42	75.35±0.59
6	94.28±1.79	89.47±1.35	86.23±1.49	83.30±0.97
8	-	97.55±0.21	93.83±0.74	91.15±0.68
10	-	-	-	98.47±0.81
12	-	-	-	-

*All **v**alues represent mean cumulative percent drug released ± SD (n=3)

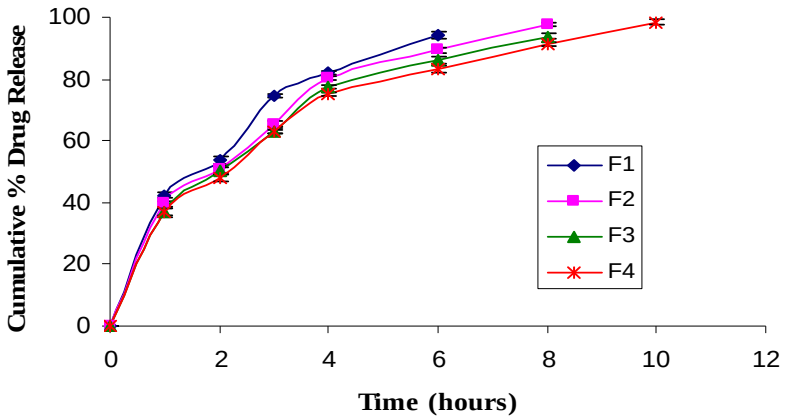

Figure-3: Release Profiles of Timolol Maleate from HPMC K15M Matrices.

DRUG RELEASE FROM POLYETHYLENE OXIDE MATRICES

High molecular weight polyethylene oxides have recently been proposed as an alternative to HPMC in controlled release matrix tablets. The drug release was extended up to 6h with initial burst release for the formulation F5. Further increase in the concentration of polymer the drug release was decreased slightly (97.19%, 92.57% and 90.77% at 8 hours for F6, F7 and F8, respectively). No burst release was observed during first hour for the

formulations F6, F7, and F8 with release of 28.81%, 25.56%, and 22.38% respectively. PEO matrices have shown faster drug release compared to HPMC containing formulations. Similar findings were reported by Maggi et al., 2000. They reported that slower release rates can be obtained from the matrices containing HPMC compared to PEO. Results of the same are tabulated in the Table:18, Figure:4.

Table-18: In-Vitro Drug Release Data of Timolol Maleate from Polyethylene Oxide Matrices*.

Time (hours)	F5	F6	F7	F8
1	32.90±1.25	28.81±0.79	25.56±0.47	22.38±0.96
2	44.14±0.58	40.35±0.43	37.36±1.68	35.23±0.88
3	58.23±0.97	55.46±0.74	54.48±1.53	51.66±0.91
4	73.74±1.19	69.38±0.95	66.55±1.49	63.48±0.65
6	92.30±0.58	84.68±0.52	82.43±1.27	79.57±0.85
8	-	97.19±1.43	92.57±1.36	90.77±0.64
10	-	-	-	-
12	-	-	-	-

*All **v**alues represent mean cumulative percent drug released ± SD (n=3)

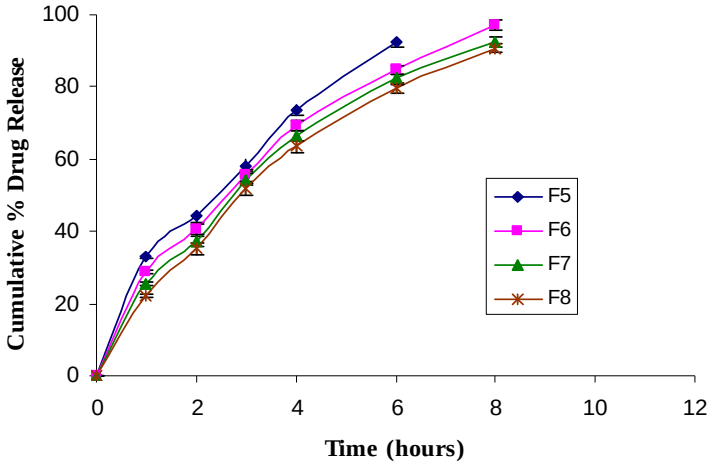

Figure:4 Release Profiles of Timolol Maleate from Polyethylene Oxide Matrices

DRUG RELEASE FROM HPMC K100M CR MATRICES

Low molecular weight HPMC is used predominantly for tablet film coating, while high molecular weight HPMC is used as rate-controlling polymer to retard the release of drugs from a matrix at levels of 10% to 80% w/w in tablets and capsules (Raymond and Paul, 2003).. Formulations containing HPMC K100M (F9 to F12) have shown initial burst release and extended the release for 8 to 12h. As the drug polymer ratio increased to 1:2 (F12), the kinetics of release decreased (98.97% at 12h). The drug release was slower from matrices containing HPMC K100M compared to HPMC K15M. This may be due to structural reorganization of HPMC. Increase in concentration and viscosity of HPMC may result in increase in the tortuosity or gel strength of the polymer. When HPMC is exposed to aqueous medium, it undergoes rapid hydration and chain relaxation to form viscous gelatinous layer (gel layer). Failure to generate a uniform and coherent gel may cause rapid drug release [22]. Results of the same are tabulated in the Table:19, Figure:5.

Table-19: In -Vitro Release Data of Timolol Maleate from HPMC K100M Matrices*.

Time (hours)	F9	F10	F11	F12
1	37.23±0.97	35.38±1.47	35.16±1.32	34.93±0.58
2	51.72±1.68	50.46±0.83	50.08±1.27	49.86±0.94
3	71.58±0.87	69.17±0.65	67.58±0.94	66.97±0.75
4	80.71±0.54	78.32±0.87	77.73±1.57	76.82±0.38
6	89.43±1.63	86.87±0.42	83.83±0.59	81.87±0.96
8	97.29±0.53	94.55±0.74	90.87±1.79	89.89±0.72
10	-	98.25±1.62	96.14±1.05	93.07±0.82
12	-	-	-	98.97±0.27

*All **v**alues represent mean cumulative percent drug released ± SD (n=3)

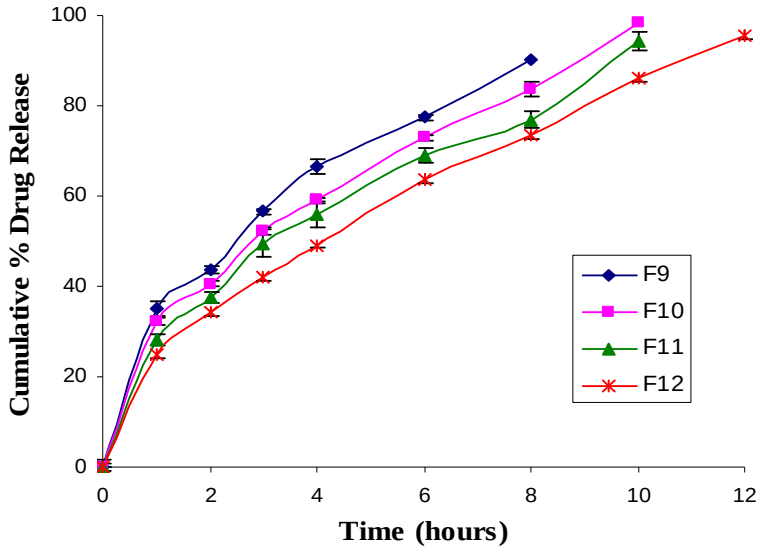

Figure-5: Release Profiles of Timolol Maleate from HPMC K100M Matrices.

DRUG RELEASE FROM ETHYLCELLULOSE MATRICES

Hydrophobic ethylcellulose can be used as a matrix former for the formulation of sustained-release dosage forms. Batches containing ethylcellulose (F13 to F16) as release retardant, extended the release up to 8 -10 hours with initial burst release. As drug polymer ratio increased, the release rate was decreased. During dissolution the erosion was observed. Results of the same are tabulated in the Table:20, Figure:6.

Table-20: In-Vitro Release Data of Timolol Maleate from Ethylcellulose Matrices*.

Time (hours)	F13	F14	F15	F16
1	42.27±0.57	38.7±0.82	35.62±0.71	32.42±0.62
2	52.47±0.67	47.28±0.69	46.34±0.54	42.83±0.81
3	64.86±0.73	59.73±0.87	56.84±0.37	54.86±0.42
4	77.27±0.84	74.95±0.31	72.92±0.84	68.03±1.57
6	86.63±0.79	81.62±0.64	79.72±0.53	76.26±0.46
8	98.31±0.52	96.59±0.63	94.56±0.83	85.92±0.75
10	-	-	-	97.56±0.71
12	-	-	-	-

*All values represent mean cumulative percent drug released ± SD (n=3)

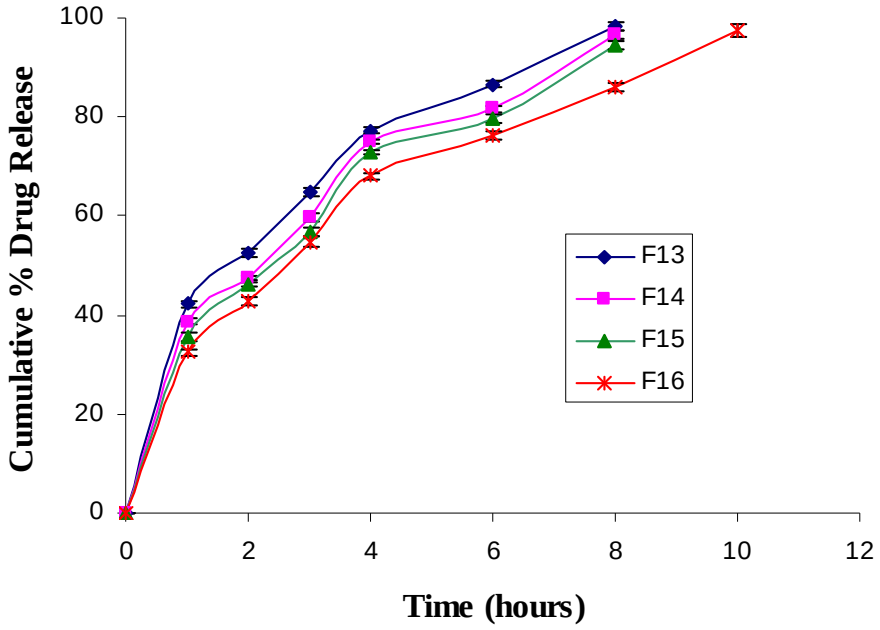

Figure-6: Release Profiles of Timolol Maleate from Ethylcellulose Matrices.

DRUG RELEASE FROM KOLLIDON-SR MATRICES

Kollidon-SR based formulations (F17 to F20) have shown initial burst release with sustaining the release up to 8-10 hours. The results of release studies were given in Table.21 and Figure7.

Table-21: In-Vitro Release Data of Timolol Maleate from Kollidon-SR Matrices*

Time (hours)	F17	F18	F19	F20
1	44.24±0.83	41.09±0.73	39.72±0.88	34.84±1.37
2	55.75±0.79	52.74±0.88	48.43±0.45	42.37±0.98
3	67.26±1.80	64.89±0.62	60.93±0.61	54.93±0.74
4	77.84±0.33	75.29±1.60	72.48±0.83	67.82±0.53
6	89.34±0.86	84.73±0.57	81.76±0.74	78.05±0.71
8	97.89±0.94	94.98±0.62	92.72±0.48	89.83±0.92
10	-	-	-	97.94±0.83
12	-	-	-	-

*All values represent mean cumulative percent drug released ± SD (n=3)

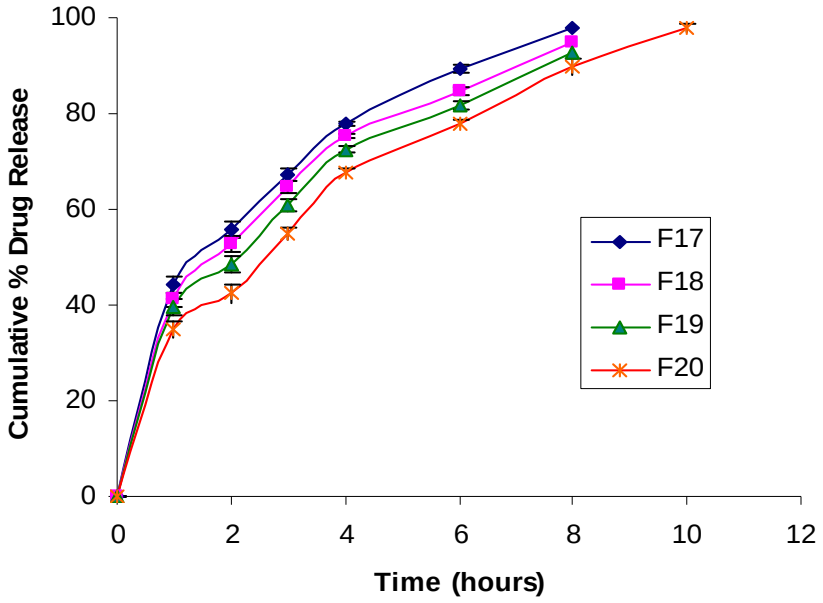

Figure-7: Release Profiles of Timolol Maleate from Kollidon-SR Matrices.

DRUG RELEASE FROM COMBINATION OF HPMC K100M AND EC MATRICES

Batches containing combination of HPMC K100M and ethylcellulose (F21 to F25) have shown better release profiles There was no burst release observed with formulations F21 to F23, and release was extended up to 10 to 12 hours. As the ethylcellulose concentration increases the drug release was decreased further in formulations F24 and F25. They prolonged the release for 8 hours only. Batch F23 was found to be optimum, as it shown similar release pattern as that of theoretical release profile. Results of the same are tabulated in the Table:22, Figure:8.

Table-22: In -Vitro Release Data of Timolol Maleate from Tablets Containing HPMC K100M CR and Ethylcellulose*.

Time (hours)	F21	F22	F23	F24	F25
1	27.06±0.85	28.73±0.97	25.38±1.54	31.86±1.37	32.23±1.15
2	40.68±0.93	42.24±0.89	35.09±1.65	44.35±1.52	47.67±1.73
3	54.27±1.29	55.85±1.17	51.93±1.69	59.83±1.46	64.83±1.58
4	66.82±1.48	66.38±1.42	62.15±1.99	70.82±1.04	75.38±1.01
6	80.72±1.79	83.35±1.73	73.88±2.01	87.43±1.96	89.25±1.90
8	88.25±1.88	90.10±1.92	81.09±2.92	94.64±1.09	98.63±0.97

10	95.17±2.38	98.43±2.05	87.04±2.48	-	-
12	-	-	97.21±2.59	-	-

*All **v**alues represent mean cumulative percent drug released ± SD (n=3)

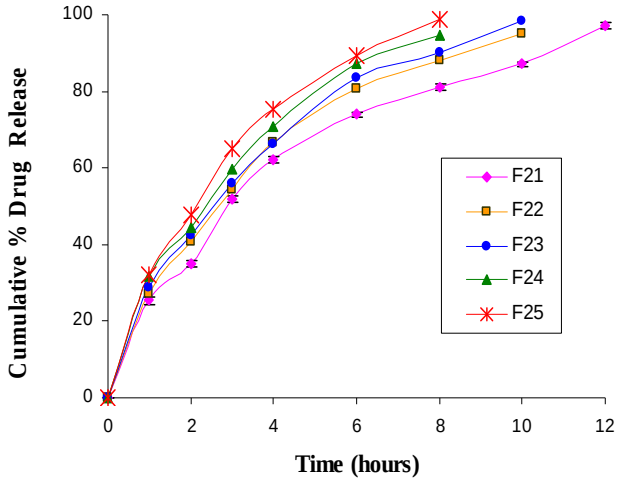

Figure-8 Release Profiles of Timolol Maleate from Tablets Containing HPMC K100M CR and Ethylcellulose

DRUG RELEASE FROM COMBINATION OF HPMC K100M AND HPMC K15M MATRICES

Combination of HPMC K100M and HPMC K15M was extended the release for 10 hours. No significant change in the drug release was observed with changing the ratio of polymers. All the batches (F26 to F30) have shown burst release also. Results of the same are tabulated in the Table:23, Figure:9.

DRUG RELEASE FROM COMBINATION OF HPMC K100M AND EC MATRICES (LACTOSE AS A DILUENT)

Lactose containing batches (F31 to F35) have increased the rate of drug release as compared to MCC containing formulations. This is due to water soluble nature of lactose and drug. Even though total concentration of polymers was 40%, more than 90% drug release was observed within 6 hours only. Results of the same are tabulated in the Table:24, Figure:10.

Table-23: In-Vitro Release Data of Timolol Maleate from Tablets Containing HPMCK100M and HPMC K15M*

Time (hours)	F26	F27	F28	F29	F30
1	31.25±0.83	32.82±0.95	32.86±0.64	33.55±0.86	34.20±0.38
2	38.28±0.76	42.71±0.88	44.83±0.58	45.91±0.77	47.04±0.46
3	53.88±0.58	56.36±0.72	57.73±0.37	59.45±0.73	61.37±0.39
4	66.46±0.87	67.83±0.46	69.38±0.74	71.24±0.56	74.27±0.48
6	74.25±0.56	76.25±0.55	76.54±0.83	79.83±0.49	81.38±0.64
8	83.89±0.58	85.93±0.74	86.25±0.57	88.28±0.68	89.36±0.56
10	90.63±0.63	93.06±0.67	95.84±0.68	96.09±0.47	97.23±0.84
12	-	-	-	-	-

*All values represent mean cumulative percent drug released ± SD (n=3)

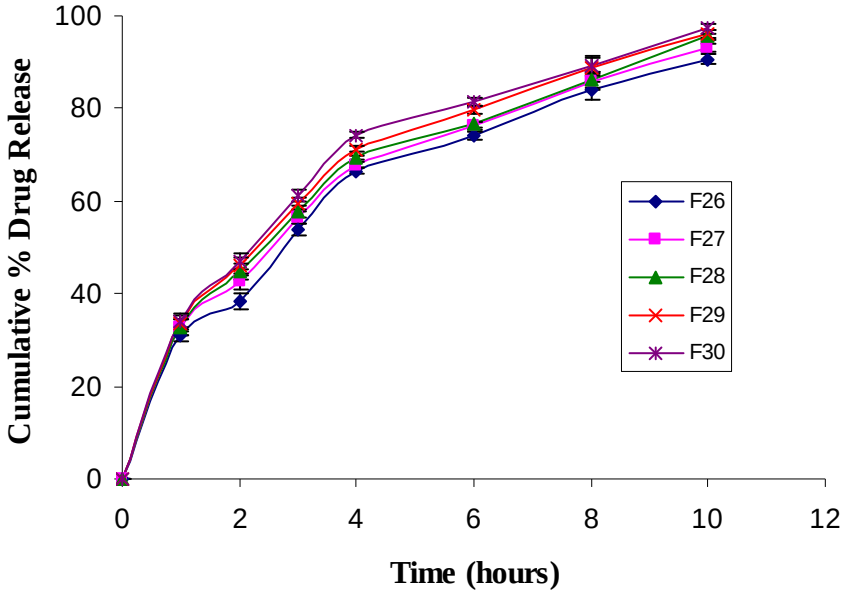

Figure-9: Release Profiles of Timolol Maleate from Tablets Containing HPMCK 100M and HPMC K15M

Table-24: In -Vitro Release Data of Timolol Maleate from Tablets with HPMC K100M and Ethylcellulose (Lactose as a diluent) *

Time (hours)	F31	F32	F33	F34	F35
1	31.35±0.75	33.63±0.38	33.98±0.84	35.46±0.57	37.89±0.63
2	42.75±0.66	44.74±0.89	44.95±0.65	48.97±0.39	52.87±0.88
3	53.47±0.58	56.83±0.58	59.47±0.88	62.84±0.48	67.37±0.73
4	65.78±0.49	68.58±0.44	68.86±0.59	71.97±0.73	77.85±0.93
6	77.57±0.84	80.05±0.86	81.87±0.83	92.83±0.68	94.76±0.68
8	91.36±.97	96.74±0.79	98.97±0.64	-	-
10	-	-	-	-	-
12	-	-	-	-	-

*All **v**alues represent mean cumulative percent drug released ± SD (n=3)

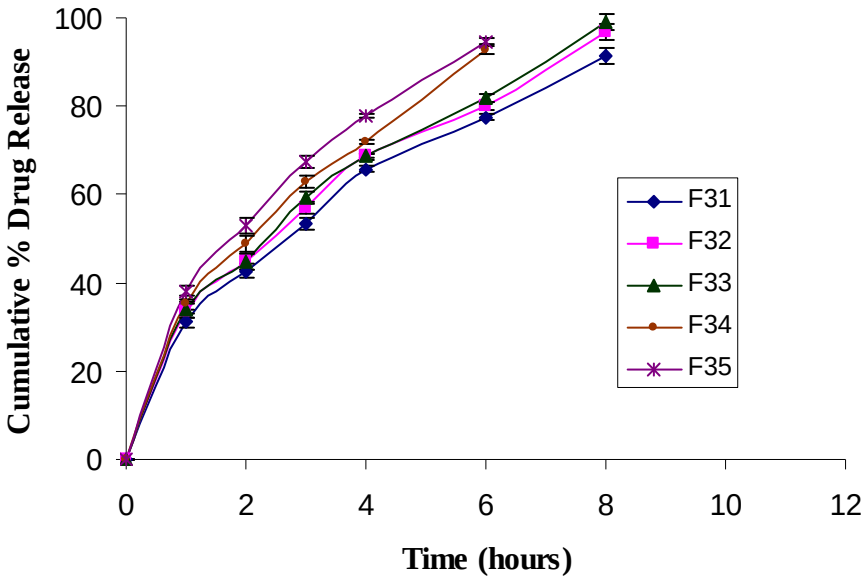

Figure:10 Release Profiles of Timolol Maleate from Tablets with HPMC K100M and Ethylcellulose (Lactose as a diluent).

DRUG RELEASE FROM COMBINATION OF HPMC K100M AND HPMC K15M MATRICES

Compared to wet granulation method, formulations prepared by direct compression (F36 to F40) have shown increased rate of drug release In the direct compression, the release was extended up to 8-10 hours with initial burst release, whereas with wet granulation method release was extended up to 10 -12 hours without burst release.

Table-25: In-Vitro Release Data of Timolol Maleate from Tablets with HPMC K100M and Ethylcellulose (direct compression)*.

Time (hours)	F36	F37	F38	F39	F40
1	32.87±0.83	35.24±0.82	37.12±0.64	39.83±0.53	41.24±0.77
2	40.63±0.37	45.52±0.73	48.83±0.58	51.52±0.65	53.53±0.74
3	53.74±0.49	56.38±0.55	59.43±0.37	63.82±0.42	65.97±0.53
4	65.09±0.43	69.28±0.78	73.35±0.48	76.89±0.64	77.72±0.53
6	77.26±0.82	82.75±0.66	85.98±0.74	89.52±0.62	89.88±0.69
8	88.57±0.64	92.86±0.54	95.42±0.63	98.76±0.59	97.35±0.52
10	97.93±0.89	-	-	-	-
12	-	-	-	-	-

*All values represent mean cumulative percent drug released ± SD (n=3)

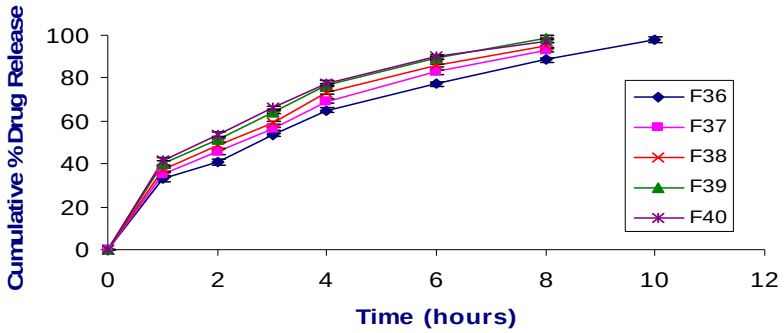

Figure-11: Release Profiles of Timolol Maleate from Tablets with HPMC K100M and Ethylcellulose (direct compression)

Out of total 40 batches, the drug release was extended up to 12 hours for the formulations F12 and F23. So, these two formulations selected for further studies like kinetic data analysis and similarity factor analysis.

KINETIC ANALYSIS OF DISSOLUTION DATA

The release rate kinetic data for the F12 and F23 is shown in Table:26&27 below and respectively. As shown in Figures:12-16, below, drug release data was best explained by first order equation, as the plots showed the highest linearity (r^2 = 0.9955), followed by Hixson-Crowell (r^2 = 0.9800) and Higuchi's equation (r^2 = 0.9661). As the drug release was best fitted in first order kinetics, indicating that the rate of drug release is concentration dependent. Higuchi's kinetics explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases. The applicability of the formulation to the Hixson –Crowell cube root law indicated a change in surface area and diameter of the tablets with the progressive dissolution of the matrix as a function of time.

MECHANISM OF DRUG RELEASE

As shown in Figure:13, the corresponding plot (log cumulative percent drug release vs time) for the Korsmeyer-Peppas equation indicated a good linearity (r^2 = 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.

Table-26: Drug Release Kinetics of Batch (F12) Matrix Tablets*

Zero order		First order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas		
r^2	$K_0 (h^{-1})$	r^2	$K_1 (h^{-1})$	r^2	$K_H (h^{-1/2})$	r^2	$K_{HC} (h^{-1/3})$	r^2	n	$K_{KP} (h^{-n})$
0.8461	5.188	0.8665	0.1890	0.9335	24.877	0.9695	0.2461	0.9911	0.56	0.4283

* r^2 = Correlation coefficient; K = Kinetic constant; n= Diffusional exponent.

Table-27: Drug Release Kinetics of Optimized (F23) Matrix Tablets*

Zero order		First order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas		
r^2	$K_0 (h^{-1})$	r^2	$K_1 (h^{-1})$	r^2	$K_H (h^{-1/2})$	r^2	$K_{HC} (h^{-1/3})$	r^2	n	$K_{KP} (h^{-n})$
0.8985	5.881	0.9955	0.2012	0.9661	27.839	0.9800	0.1997	0.9741	0.66	0.3238

* r^2 = Correlation coefficient; K = Kinetic constant; n= Diffusional exponent.

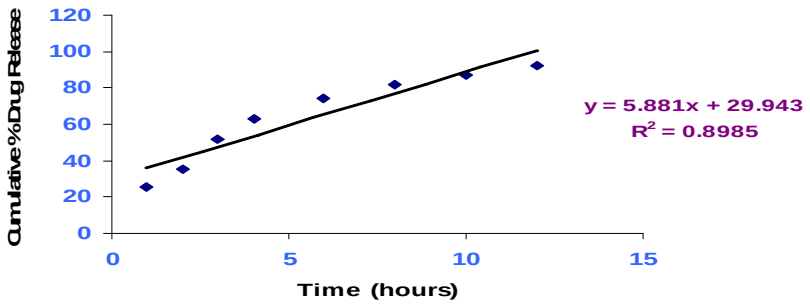

Figure-12: Zero Order Graph of Optimized Formulation (F23).

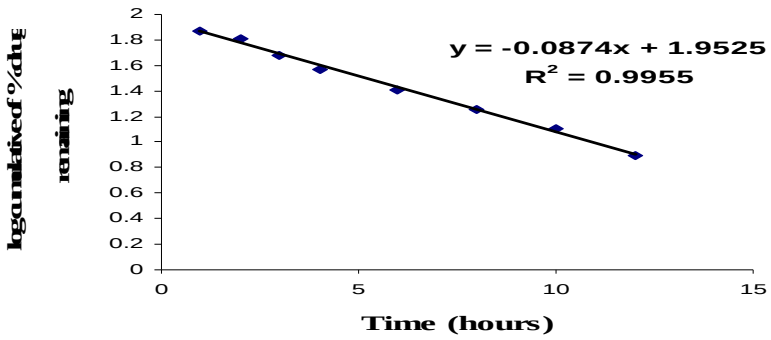

Figure-13: First Order Graph of Optimized Formulation (F23)

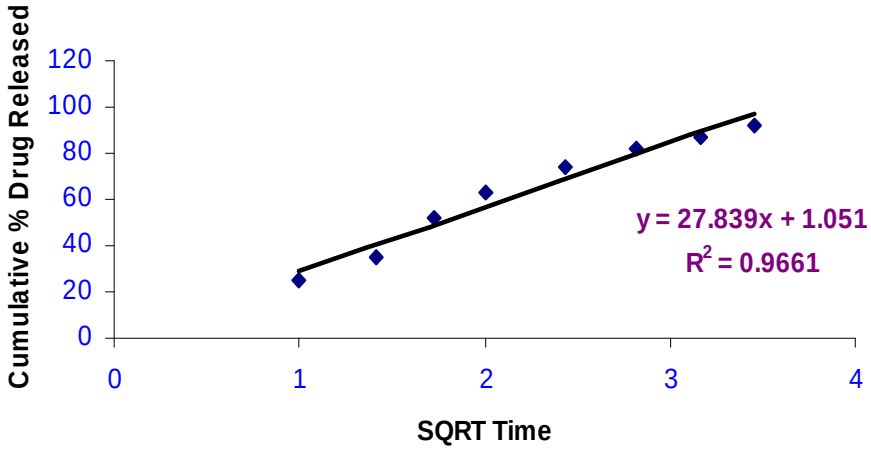

Figure-14: Higuchi Plot of Optimized Formulation (F23)

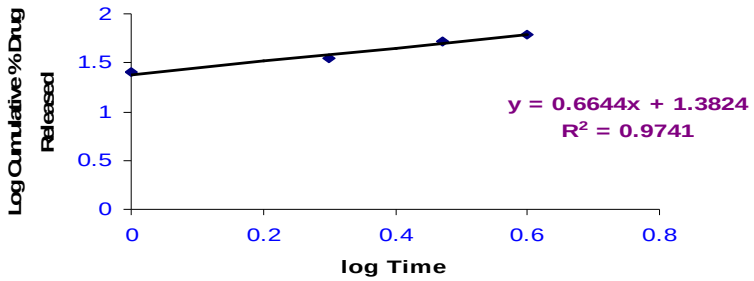

Figure-15: Korsmeyer-Peppas Graph of Optimized Formulation (F23)

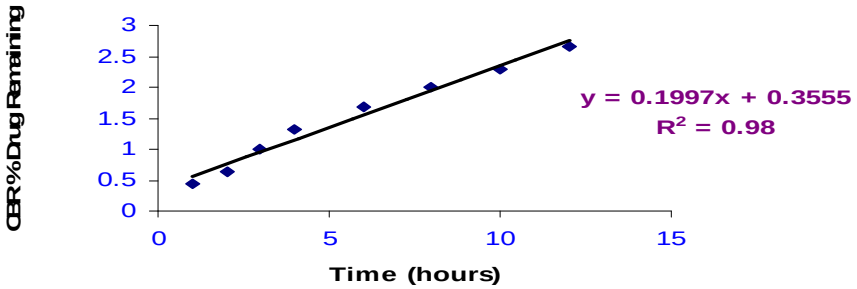

Figure-16: Hixson-Crowell Plot of Optimized Formulation (F23)

SIMILARITY FACTOR ANALYSIS

Similarity factor results for the batches F12 and F23 were given in Table 28. Similarity factor analysis between F23 tablets and theoretical release has shown an f_2 factor greater than 50 at each time point with an average value of f_2 factor 80.18. Incase of F12 tablets, an average value of f_2 factor was greater than 50, but at the 3rd and 4th hours f_2 factor was less than 50.

The in-vitro release behaviour of F12, F23 batches of tablets was compared with the theoretical release profile. A close relationship was observed between F23 formulation and theoretical release patterns, compared to a relationship between F12 and theoretical release patterns (Figure 17).

So, F23 was considered as optimized formulation, as these tablets did not show any burst release and extended the release for 12 hours with similar release pattern to that of theoretical release profile.

Table-28: Similarity Factor Analysis.

	Average % Drug Release			*f2 factor*	
Time (hrs)	**Theoretical release**	**F12**	**F23**	**F12**	**F23***
1	26.16	34.93	25.38	73.03	99.09
2	33.08	49.86	35.09	59.62	95.05
3	40.00	66.97	51.93	49.47	66.77
4	46.92	76.82	62.15	47.25	61.66
6	60.76	81.87	73.88	64.79	64.79
8	74.60	89.89	81.09	54.73	78.84
10	88.44	93.07	87.04	61.58	97.31
12	99.00	98.07	97.21	66.72	77.99

* Average value of *f2* factor = 80.18

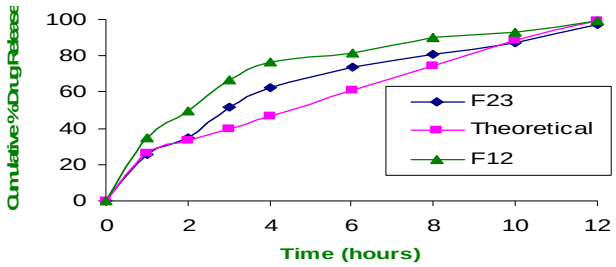

Figure-17: Comparative In-Vitro Drug Release Profile

Swelling and erosion behaviour, FTIR studies, and stability study were performed on optimized formulation (F23).

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 was shown in Figures18&19, and data was given in Table below. Maximum swelling was observed in first 2 hours and gradually it was decreased with simultaneous erosion of polymer. Results of the same are tabulated in the Table:29

Table-29: Swelling and Erosion Study of Optimized Formulation (F23).

Time (hours)	% Swelling	% Erosion
1	76.43	18.72
2	128.35	24.37
3	84.57	28.73
4	71.94	42.62
6	60.64	56.83
8	49.53	64.52
10	36.72	72.41
12	24.83	93.29

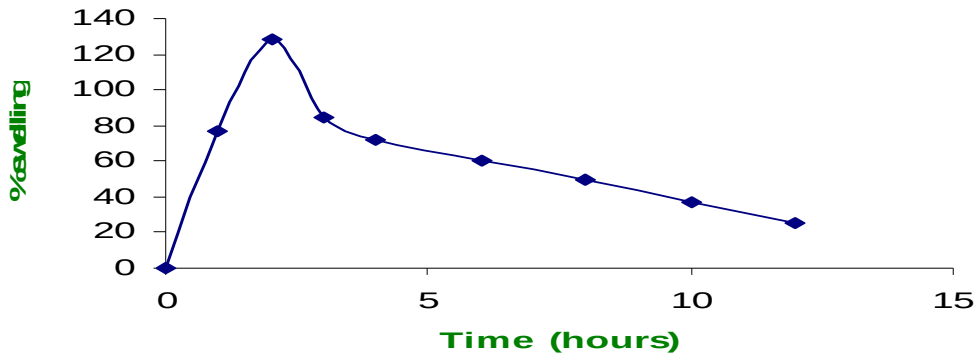

Figure-18: Swelling Study of Optimized Formulation (F23).

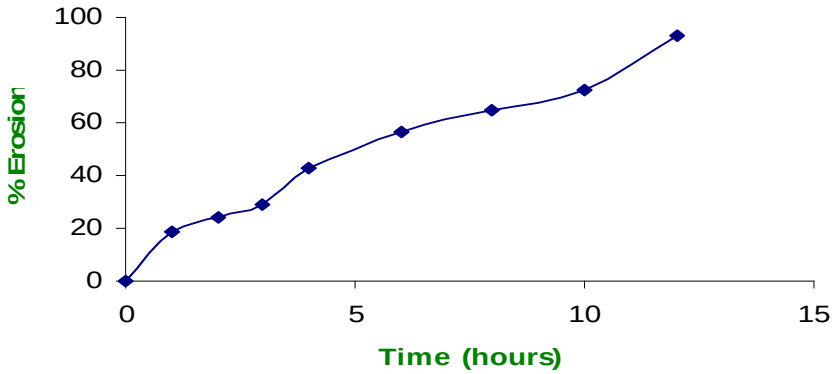

Figure-19: Erosion Study of Optimized Formulation (F23).

FOURIER TRANSFORM INFRARED SPECTROSCOPY (FTIR)

FTIR spectra of the drug and the optimized formulation were recorded in range of 4000-400 cm^{-1}. Timolol maleate showed some prominent and characteristic peaks. The peaks at 3305 and 1120 cm^{-1} were due to stretching

vibrations of O-H and C-O bond of secondary alcohol respectively. Peaks at 2967, 2856, and 1707 cm^{-1} could be assigned to the asymmetric C-H stretching of CH_3 group, symmetric C-H stretching of CH_2 group, and C=N stretching respectively. In the optimized formulation, the presence of all the characteristic peaks of the timolol maleate indicates that no interaction was occurred between the drug and the excipients.

STABILITY STUDIES

Stability studies of the optimized formulation did not reveal any degradation of the drug and there was no significant change in the physical properties, drug content, and in vitro release profiles of the optimized formulation after storage for 3 months.

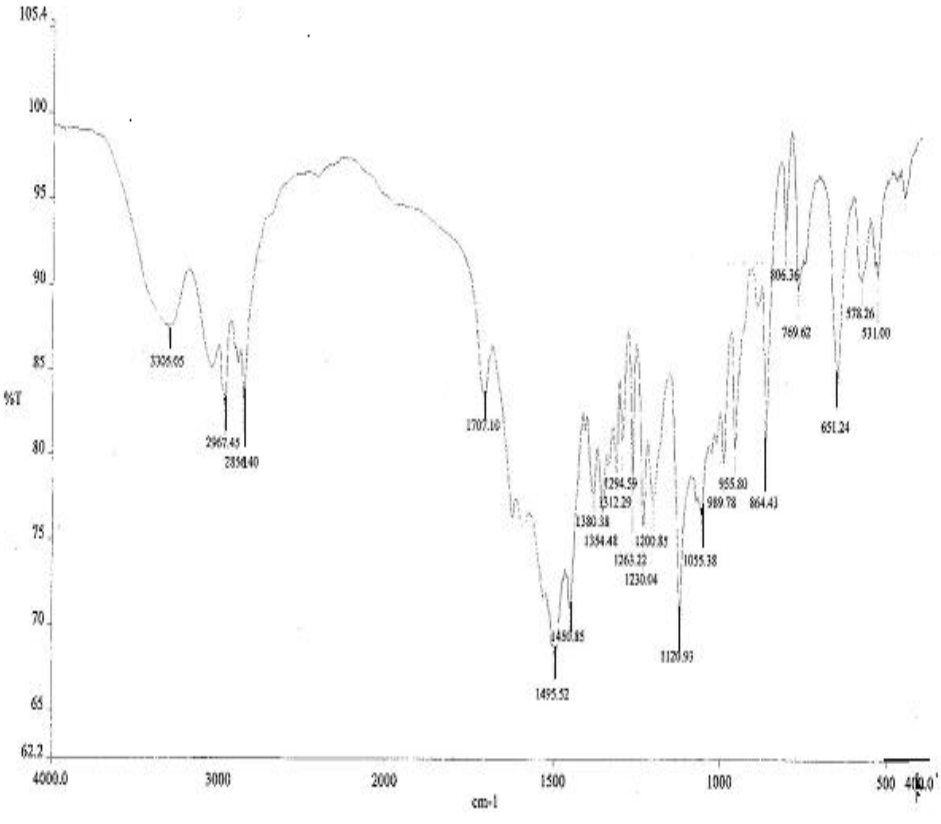

Figure-20: FTIR spectrum of Timolol Maleate.

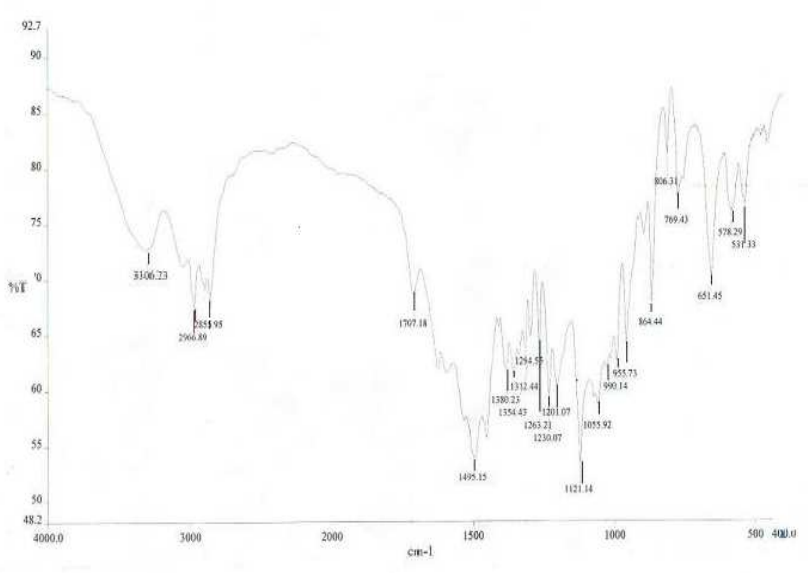

Figure-21: FTIR Spectrum of optimized formulation.

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. Lactose containing formulations have shown faster drug release.
- ✓ Among the hydrophilic matrix formers, the rate of drug release was in the following order
    - o PEO > HPMC K15M > HPMC K100M.
- ✓ PEO containing formulations (F6-F8) have did not show initial burst release.
- ✓ The drug release rate was almost similar with hydrophobic EC and plastic Kollidon-SR.
- ✓ The drug release rate was slower with the tablets containing combination of both hydrophilic HPMC K100M and hydrophobic EC polymers compared to with that of combination of 2 hydrophilic polymers (HPMC K100M and K15M).
- ✓ 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.
- ✓ Erosion was the dominating release mechanism for the formulations containing Kollidon-SR or EC.

Conclusion

Optimized formulation F23 (drug to polymer ratio 1:2) which includes both HPMC K100M 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 0.66 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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