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Research Article

FORMULATION AND EVALUATION OF SUSTAINED-RELEASE MATRIX TABLETS OF TIMOLOL MALEATE

S. Ramu*, S. Rambabu, D. Srinivasa Rao and G. Rama Krishna

Department of Pharmaceutics, K.C. Reddy Institute of Pharmaceutical Sciences, JamgamaguntlaPallem, Medikondur, Guntur, Andhra Pradesh, India.

ABSTRACT

The objective of the present study is to "optimize, formulate and evaluate sustained-release (SR) matrix tablets of timolol maleate''. A controlled drug delivery system is usually designed to deliver the drug at particular rate, safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. The present work is aimed at preparing and evaluating sustained-release (SR) matrix tablets of timolol maleate (TM). The Preparation contains 40 formulations of timolol maleate (TM) by using different polymers like 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. The sustained-release (SR) matrix tablets of timolol maleate (TM) were prepared by wet granulation and direct compression methods. The prepared batches of matrix tablets of timolol maleate can be evaluated forpre compression parameters like bulk density, tapped density, carr's index, hausner`s ratio, and angle of repose and physical evaluation of tablets like weight variation, thickness, hardness test, drug content, *In -Vitro*dissolution studies,swelling and erosion studies. Among all the formulations 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.

Keywords: Sustained-Release (SR),Hydroxy Propyl Methyl Cellulose (HPMC).

INTRODUCTION

A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized"[1].

Extended-release drug products: A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release, and long-acting drug products. Delayed-release drug products: A dosage form that releases a discrete portion or portions of drug at a time or at times other than promptly after administration, although one portion may be released promptly after administration. Enteric-coated dosage forms are the most common delayed-release products. A targeted drug release product is defined "as a dosage form that releases drug at near the intended physiologic site of action. Targeted-release dosage forms may have either immediate- or extended-release characteristics[2].

The term controlled-release drug product was previously used to describe various types of oral extended-release-rate dosage forms, including sustained-release, sustained-action, prolonged-action, long-action, slow-release, and programmed drug delivery.

A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. This predetermined rate of drug release is based on the desired therapeutic concentration and the drug's pharmacokinetics[3].

Advantages of Controlled Drug Delivery System

1. Overcome patient compliance problems.
2. Employ less total drug

a) Minimize or eliminate local side effects
b) Minimize or eliminate systemic side effects
c) Obtain less potentiation or reduction in drug activity with chronic use.
d) Minimize drug accumulation with chronic dosing.

3. Improve efficiency in treatment[4]

a) Cures or controls condition more promptly.
b) Improves control of condition i.e., reduced fluctuation in drug level.
c) Improves bioavailability of some drugs.
d) Make use of special effects, e.g. Sustained-release aspirin for morning relief of arthritis by dosing before bed time.

4. Economy i.e. reduction in health care costs. The average cost of treatment over an extended time period may be less, with lesser frequency of dosing, enhanced therapeutic benefits and reduced side effects. The time required for health care personnel to dispense and administer the drug and monitor patient is also reduced[5].

Disadvantages

1) Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc[6].
2) Poor in vitro – in vivo correlation.
3) Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
4) Reduced potential for dose adjustment of drugs normally administered in varying strengths (Hoffman, 1998).

MATERIALS AND METHODS

Timolol Maleate was obtained as a gift sample fromVen Petro-Chem&Pharma Pvt. Ltd, Mumbai. HPMC K15M, *HPMC K100M CR* from CadilaPharma, Ahmedabad. *Polyethylene Oxide,*Kollidon Gift sample from Glenmark Pharmaceuticals Ltd, Mumbai. Ethylcellulose from Vilin Biomed, New Delhi. All other chemicals used were of analytical grade.

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[7].

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[8].

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 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[9].

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

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 forF1, 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 ofHPMC 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 HPMCK15M 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 Precompression 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 [10].

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

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.

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. The bulk density and the tapped density were calculated using the following formulae [11].

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

Where, W= Weight of the powder
V_0 = Initial volume V_f = final volume

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[11].

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

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 [11]. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index

Evaluation of Matrix Tablets[1]

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.

RESULTS AND DISCUSSION

Table 12: 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

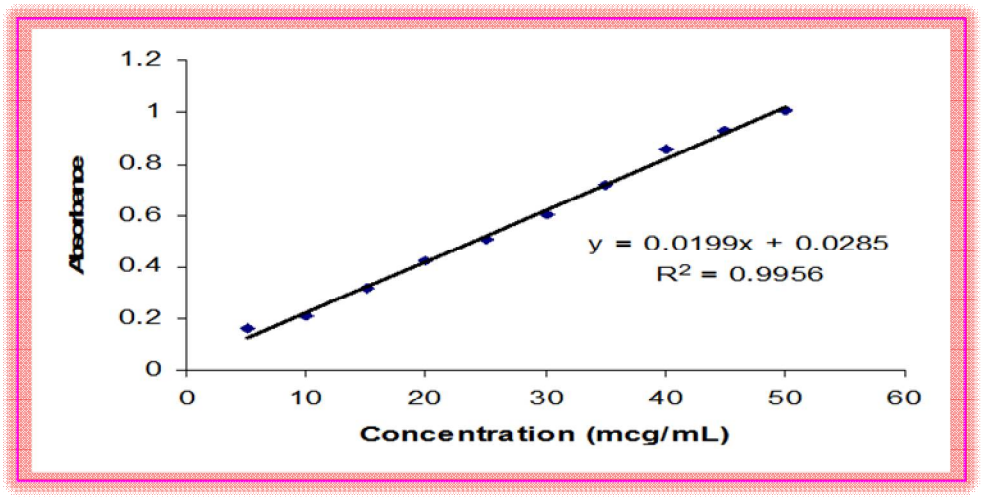

Fig. 1: Standard graph of timolol maleate in 0.1 N HCl

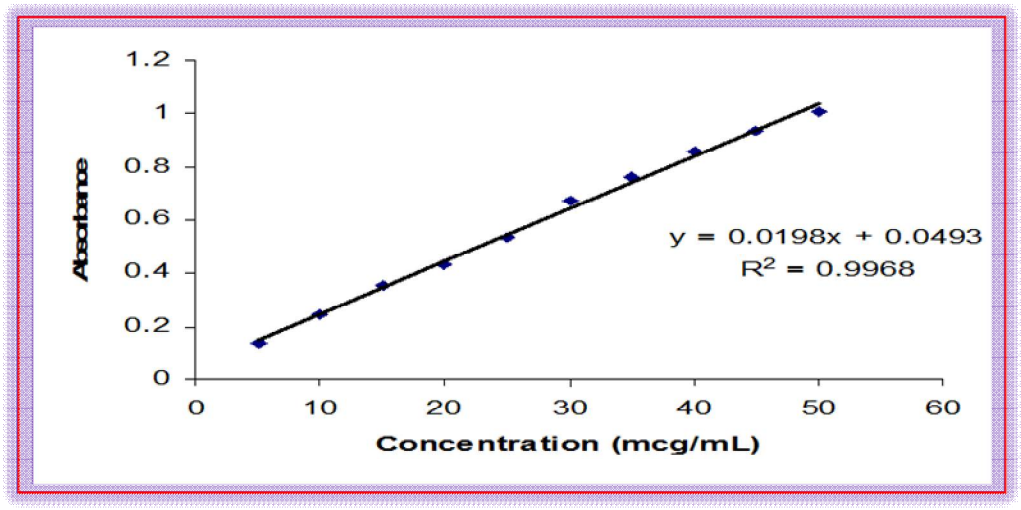

Figure 2Standard graph of timolol maleate in 6.8 pH buffer

Table 13: 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

Table 14: Physical Evaluation of Matrix Tablets

F.Code	Hardness (kg/cm²) †	Thickness (mm) ‡	Weight Variation	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

Table 15: 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 values represent mean cumulative percent drug released ± SD (n=3)

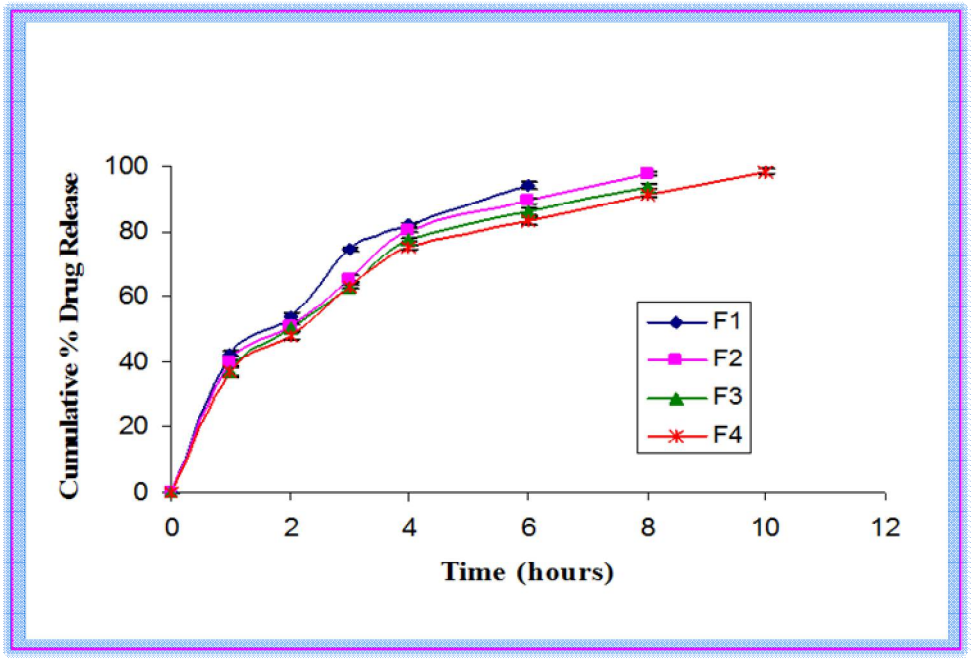

Fig. 3: In-Vitro Release Data of Timolol Maleate from HPMC K15M Matrices*

Table 16: In-Vitro Drug Release Data of TimololMaleate 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 values represent mean cumulative percent drug released ± SD (n=3)

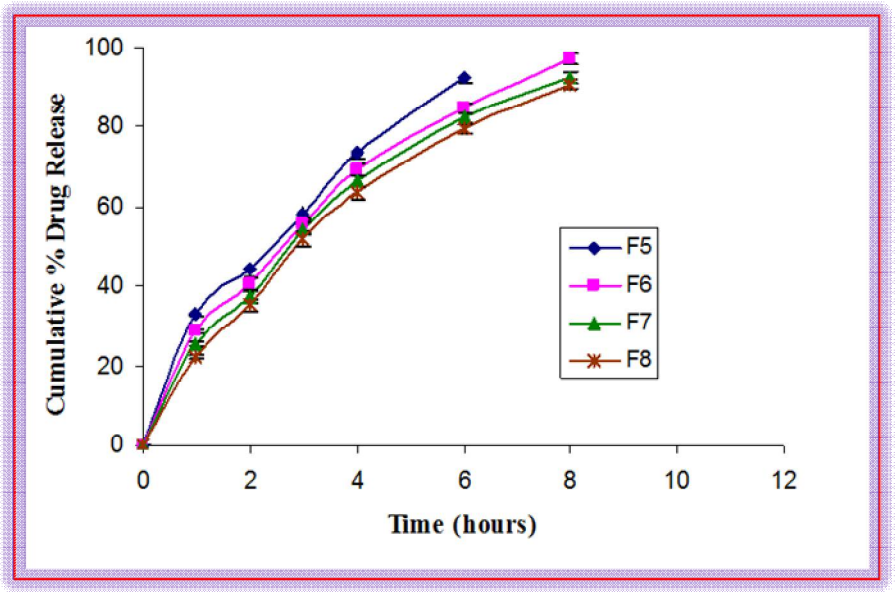

Fig. 4: Release Profiles of Timolol Maleate from Polyethylene Oxide Matrices

Table 17: 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 values represent mean cumulative percent drug released ± SD (n=3)

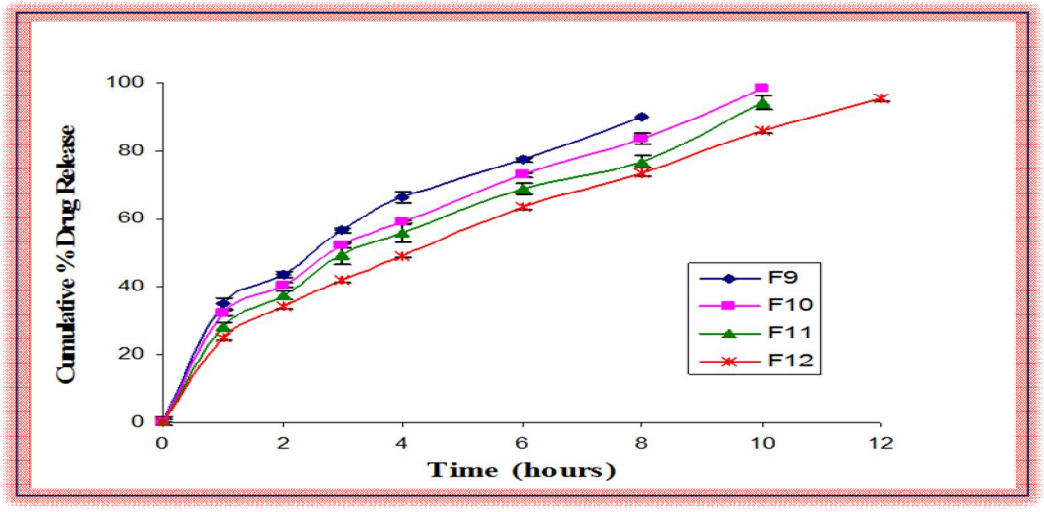

Fig. 5: Release Profiles of Timolol Maleate from HPMC K100M Matrices

Table 18: 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)

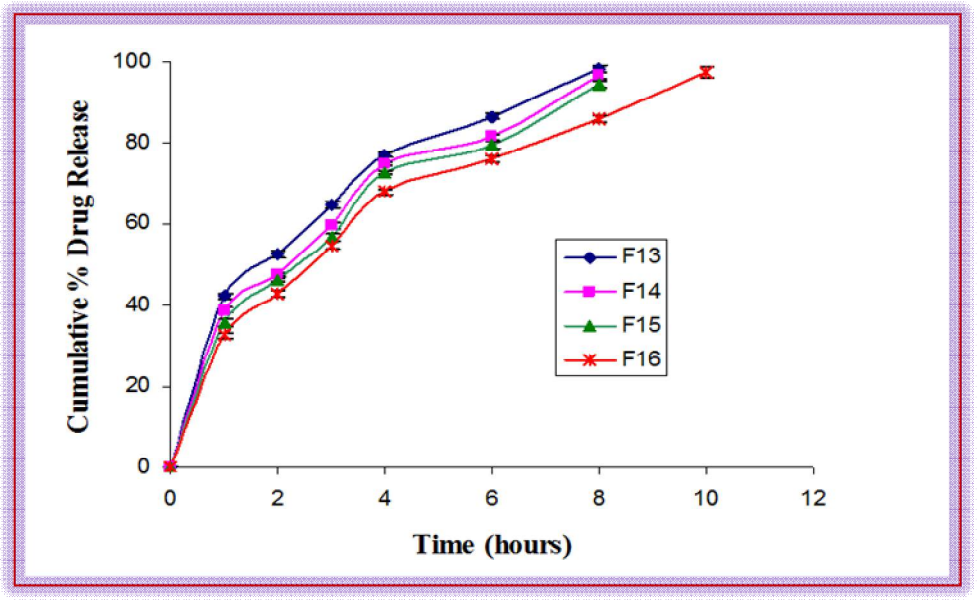

Fig. 6: Release Profiles of Timolol Maleate from Ethylcellulose Matrices

Table 19: 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)

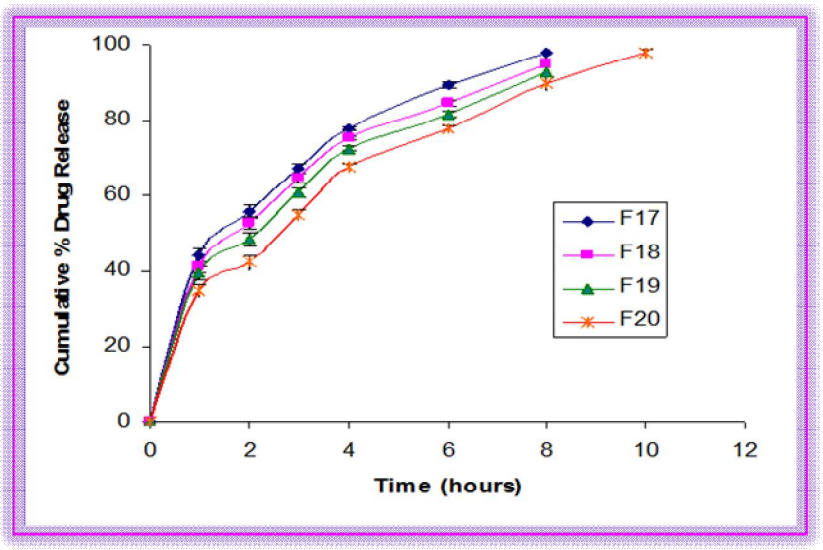

Fig. 7: Release Profiles of Timolol Maleate from Kollidon-SR Matrices

Table 20: 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 values represent mean cumulative percent drug released ± SD (n=3)

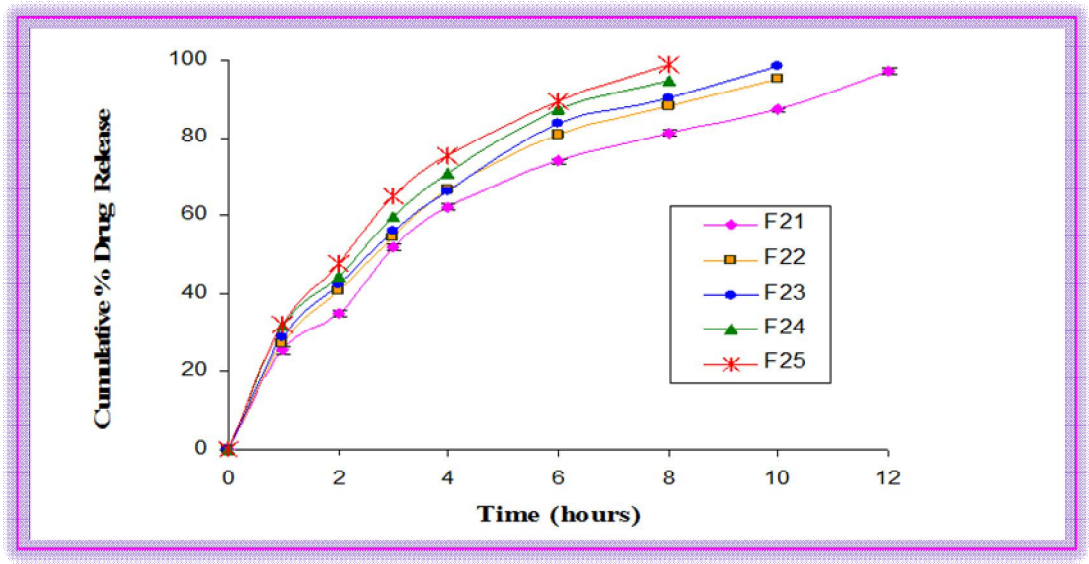

Fig. 8: Release Profiles of Timolol Maleate from Tablets Containing HPMC K100M CR and Ethylcellulose

Table 21: 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)

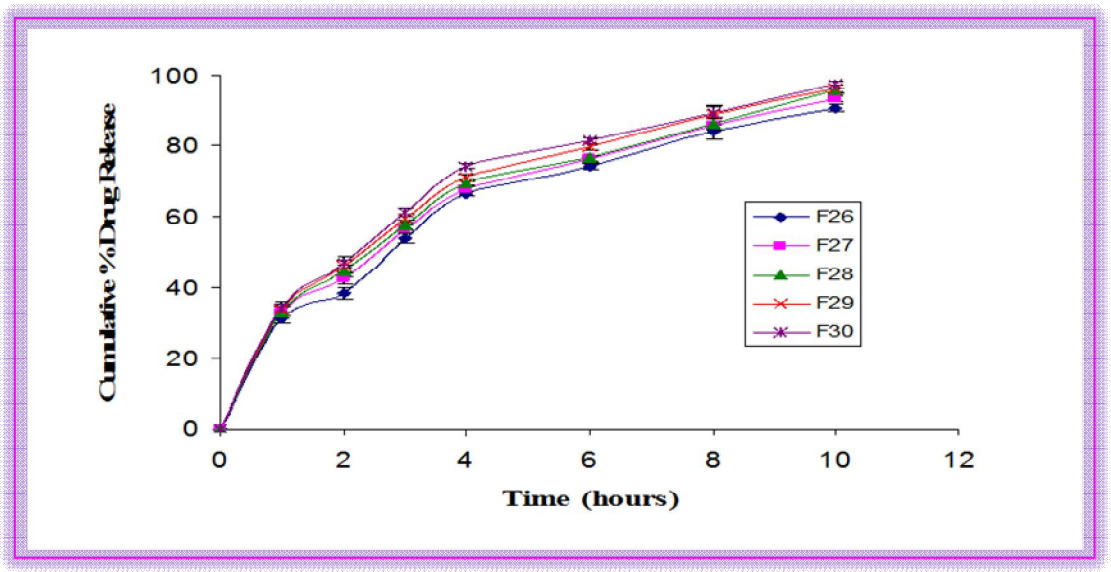

Fig. 9: Release Profiles of Timolol Maleate from Tablets Containing HPMCK 100M and HPMC K15M

Table 22: 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 values represent mean cumulative percent drug released ± SD (n=3)

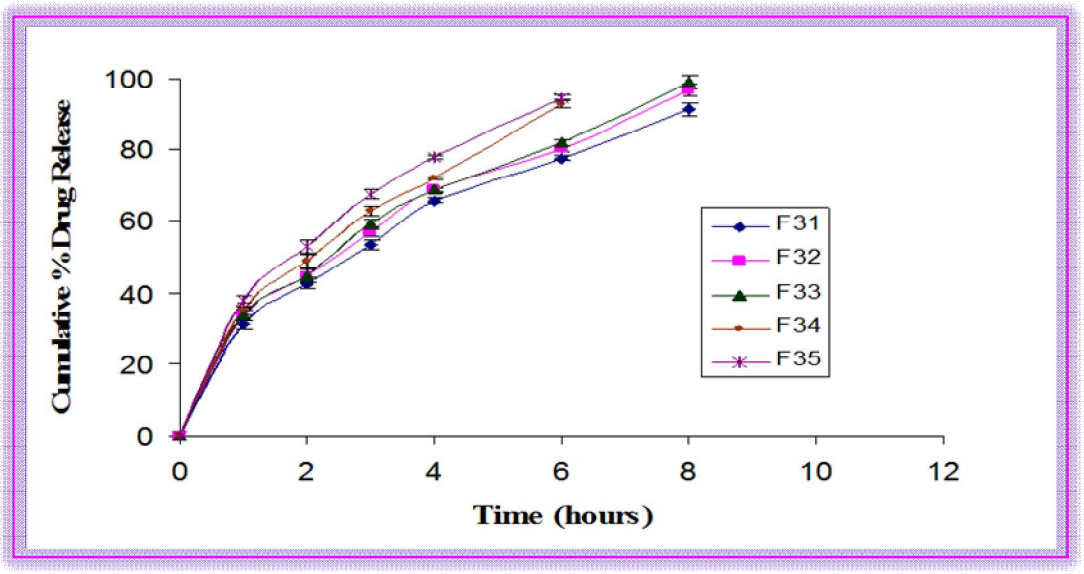

Fig. 10: Release Profiles of Timolol Maleate from Tablets with HPMC K100M andEthylcellulose (Lactose as a diluent)

Table 23: 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)

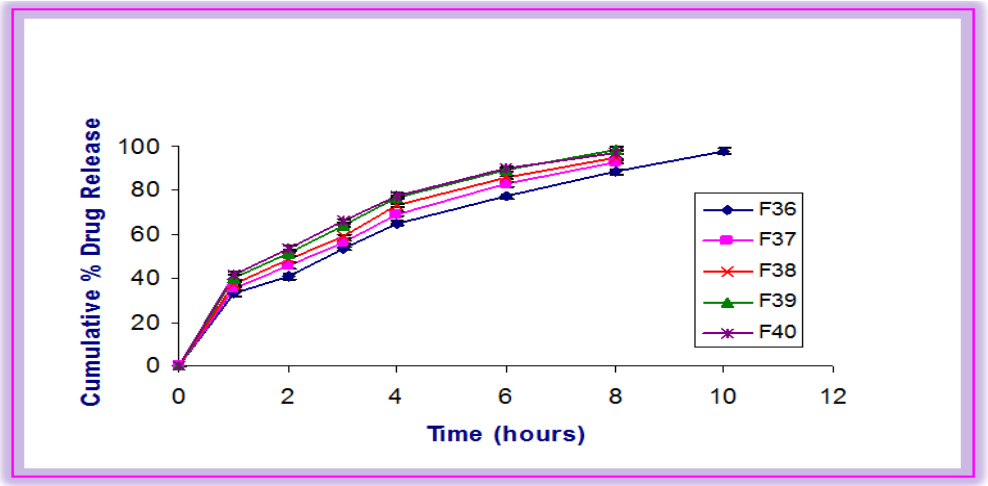

Fig. 11: Release Profiles of Timolol Maleate from Tablets with HPMC K100M and Ethylcellulose (direct compression)

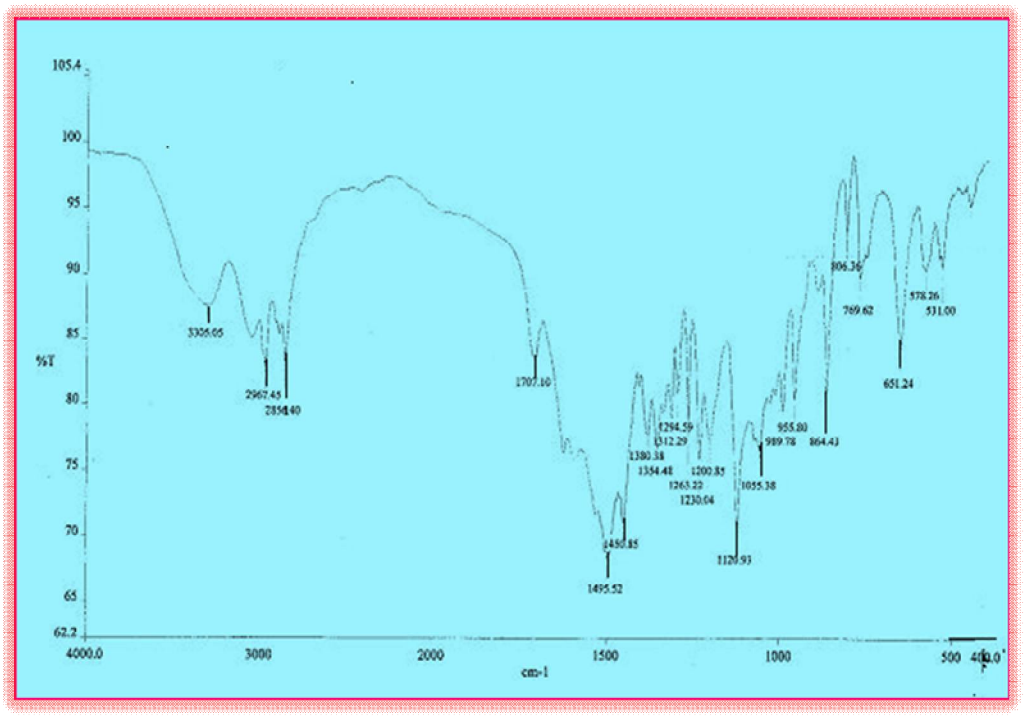

Fig. 12: FTIR spectrum of Timolol Maleate

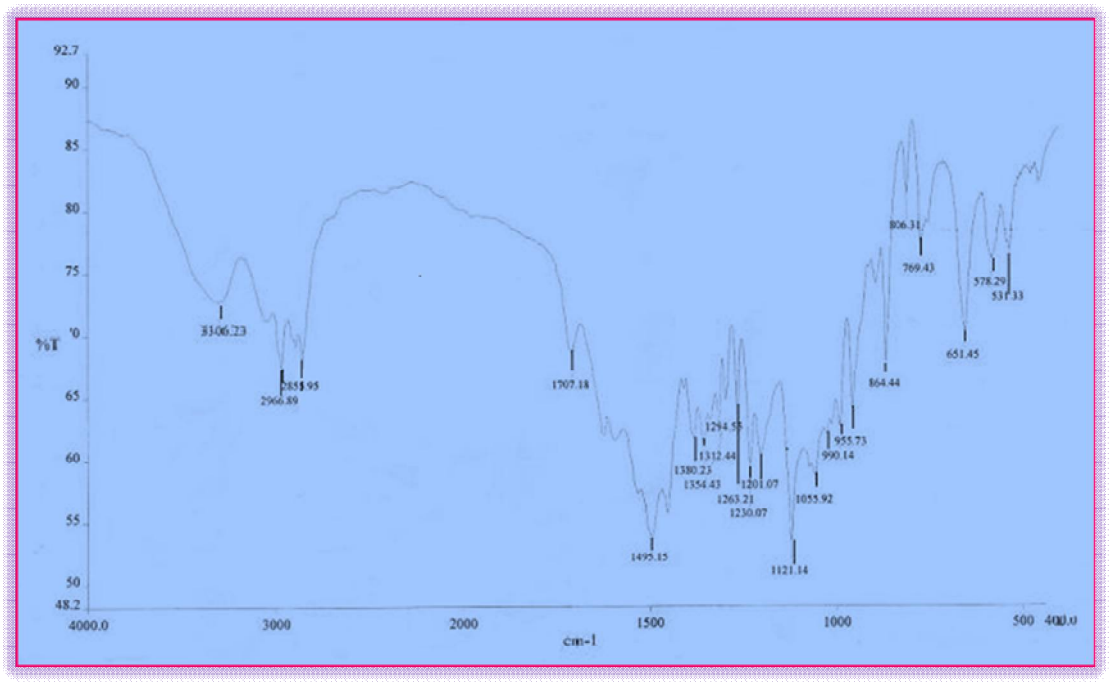

Fig. 13: FTIR Spectrum of optimized formulation

DISCUSSION

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 (Table 13). 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.

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 14. 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

Drug Release from HPMC K15M Matrices

The results of release studies of formulations F1 to F4 are shown in Table 15. 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 [12]. 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 [5].

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 [13]. They reported that slower release rates can be obtained from the matrices containing HPMC compared to PEO.

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 [14]. Results for the drug release from HPMC K100M matrices. 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.

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.

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.

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.

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.

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.

Drug Release from Combination of HPMC K100M and HPMC K15MMatrices

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.

SUMMARY AND CONCLUSION

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

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.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.

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