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RESEARCH PAPER

DESIGN AND EVALUATION OF SUSTAINED RELEASE TABLETS OF TIMOLOL MALEATE

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The goal of the research work was to design and characterize sustained-release tablets of a model drug Timolol maleate. The tablets were formulated employing mixture of hydrophilic and hydrophobic polymers by using wet granulation technique. The tablets prepared with drug to polymer ratio 1:2 (HPMC K100M:Ethyl cellulose) exhibited best drug release profile. The *in vitro* dissolution study was performed by USP type II dissolution apparatus (paddle method) at 100 rpm in 900 ml of 0.1 N HCl (pH 1.2) for first 2 hr and the phosphate buffer (pH 6.8) from 3 to 12 hr, maintained at temperature of 37°C±0.5°C and the sample was analyzed by UV-visible spectrophotometer at 295 nm. The optimized formulation (F9) showed 99.21% drug release at the end of 12 hr. The drug release followed zero order kinetics and best fit with Higuchi model *via* non-Fickian (anomalous) diffusion.

Key words: Sustained-release, Timolol maleate, In vitro dissolution, Kinetic release analysis.

INTRODUCTION

Sustained release dosage forms are designed to release a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects (Brahmankar and Jaiswal 2009; Vyas and Khar, 2012; Zalte and Saudagar, 2013). The design of oral sustained release delivery systems is subjected to several interrelated variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. Sustain release system includes any drug delivery systems that achieves slow release of drug over prolong period of time (Qiu and Zhang, 2000). Timolol maleate is salt form of Timolol, a propanol amine derivative and a non-selective beta-adrenergic antagonist (**Figure 1**). It is a beta-blocker effective in the treatment of hypertension. Timolol is also used to prevent migraine headache and widely used for the therapy of angina pectoris and prevention of vascular headache. It is rapidly and nearly completely (about 90%) absorbed from the gastrointestinal tract (GIT) following oral ingestion, showing 60% bioavailability. The plasma levels occur within one-half hour and peak plasma levels occur in about 1-2 hr (Mortazavi *et al* 2014). It has a plasma half life of 4 hr. In the treatment of hypertension, the usual initial dosage is 10 mg twice a day, whether used alone or added to diuretic. Dosage may be increased or decreased depending on heart rate and blood pressure response. The usual total maintenance dosage is 10-20 mg per day. An increase in dosage to a maximum of 30 mg per day divided into two doses may be necessary (Saleem *et al* 2012). Therefore, in the present investigation, the strength of Timolol maleate drug chosen was 25 mg to improve the oral

bioavailability and to decrease the dose dependent toxicity to develop the sustained-release formulations.

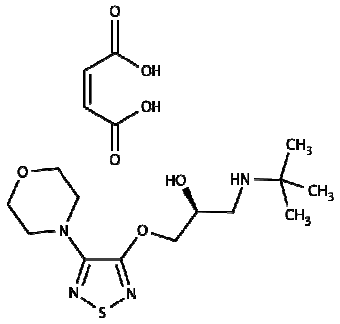

Fig. 1. Chemical structure of Timolol maleate

MATERIALS AND METHODS

Preparation of Timolol maleate matrix tablets

Timolol maleate sustained release tablets were prepared by wet granulation technique. The drug and excipients were shifted through mesh size 60# and 40#.

Accurately weighed drug, polymers HPMC K4M, HPMC K100M, HPC and diluent MCC (selected different formulations) were mixed properly in glass mortar pestle for 5 min. The mixture was then granulated by using required quantity of PVP K90 dissolved in sufficient quantity of isopropyl alcohol and the resulting wet mass was passed through No. 24 sieve. The wet granules were dried at 60°C ± 5°C for 1 hr in a hot-air oven and the dried granules were sieved through No. 24 sieve. The moisture content was not more than 1%. The under size and oversized products can be reprocessed to achieve the desired size range. These granules were blended with Aerosil and Talc. The blend was compressed by using 16 station multi station tablet punching machine using 6 mm flat punches as shown in **Table 1**.

Table 1. Preparation of different formulation of sustained release tablets of Timolol maleate

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Timolol maleate	25	25	25	25	25	25	25	25	25
HPMCK 100M	-	-	-	30	25	20	20	25	30
Ethyl cellulose	-	-	-	-	-	-	30	25	20
HPMC K 4 M	20	25	30	20	25	30	-	-	-
HPC	30	25	20	-	-	-	-	-	-
MCC	33	33	33	33	33	33	33	33	33
PVPK-90	6	6	6	6	6	6	6	6	6
Aerosil	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4
Isopropyl alcohol (ml)	qs	qs	qs	qs	qs	qs	qs	qs	qs
Total weight (mg)	120	120	120	120	120	120	120	120	120

Evaluation of pre-compression blend

Angle of repose

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 (Brahma and Gali, 2012). The diameter of the powder cone was measured and angle of repose was calculated using the following equation

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

where h and r are the height and radius of the powder cone, θ is the angle of repose. The results are shown in **Table 2**.

Bulk density and tapped density

The bulk density denotes the total density of the material as it exists. The bulk volume includes true volume, volume of interparticle spaces and intra particle pores.

The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample. The tapped density is obtained by mechanically tapping a graduated measuring cylinder or vessel containing the powder sample (Agarwal and Khanna, 2006; Janakiraman and Ramasamy, 2014).

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 the volume (V_f) was measured. Operation was continued till the two consecutive readings were equal. The results are shown in the **Table 2**.

Table 2. Characterization of Timolol maleate powder blend

Formulation code	Angle of Repose (Θ)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio	Bulkiness
F1	26.56	0.422	0.506	16.6	1.19	2.37
F2	33.21	0.518	0.627	17.38	1.21	1.93
F3	33.65	0.521	0.629	17.17	1.2	1.92
F4	25.49	0.214	0.252	14.74	1.17	4.67
F5	26.24	0.308	0.364	15.38	1.18	3.25
F6	29.05	0.276	0.322	14.28	1.16	3.62
F7	26.27	0.487	0.561	13.19	1.15	2.05
F8	25.49	0.494	0.566	12.72	1.14	2.02
F9	24.25	0.52	0.582	10.65	1.11	1.92

The bulk density and the tapped density were calculated using the following formula:

Bulk density = W/V_0

Tapped density = W/V_f

where, W= Weight of the powder,

V_0 = Initial volume, V_f = final volume

Compressibility index (Carr's index)
Carr's index (CI) is an significant measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material, the more flowable it is (Ventakata Ramana Reddy *et al* 2014).

Carr's index is calculated by the equation:

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

where, TD is the tapped density and BD is the bulk density (**Table 2**).

Hausner's ratio (HR)
It is the ratio of tapped density and bulk density. This ratio is related to interparticle friction and, as such, can be used to predict powder flow properties (Brahma and Gali, 2012). All the preformulation results are shown in the **Table 2**.

HR = TD/BD

Bulkiness
Bulkiness = 1/BD

Evaluation of matrix tablets
Shape and size
Shape, size and diameter of the all the tablets were controlled by compression machine and tablets were flat-faced, round in shape and all the tablets were 6 mm ± 0.5 mm in diameter.

Thickness
Five tablets were chosen from the formulation batch and individual tablet thickness was measured by using digital Vernier Caliper. Average thickness and standard deviation values were calculated. The tablet thickness should be controlled within a ± 5% variation of standard value. The results are shown in the **Table 3**.

Table 3. Post formulation study of Timolol maleate sustained release tablets

Formulation code	Weight variation (mg)	Thickness (mg)	Hardness (kg/cm^2)	Friability (%)	Drug Content (%)
F1	119.0±0.43	3.32±0.89	4.41±0.60	0.37	95.35±1.14
F2	119.9±0.67	3.24±0.71	4.25±0.57	0.64	93.28±1.99
F3	119.2±0.83	3.33±0.25	4.08±0.30	0.58	99.53±1.87
F4	120.9±0.99	3.31±0.44	5.25±0.57	0.21	91.99±2.81
F5	120.6±1.48	3.35±0.50	5.16±0.65	0.47	99.21±2.07
F6	120.2±0.76	3.26±0.43	5.08±0.37	0.35	100.44±1.21
F7	119.8±0.19	2.93±0.83	5.58±0.37	0.69	95.39±2.06
F8	119.8±0.38	3.33±0.59	6.66±0.65	0.37	98.90±2.31
F9	120.3±0.97	3.36±0.74	6.75±0.57	0.51	97.43±2.11

Weight variation
Twenty tablets were chosen from each formulation batch. Weighed the individual weights (WI) of 20 tablets from each formulation and their average weights (WA) were calculated by using electronic balance. The % of weight

variation was calculated and average weights of the tablets along with standard deviation values were calculated.
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 (Gupta and Ray, 2012). The results are shown in **Table 3**.

Hardness
The tablet hardness of different formulations was measured using the Monsanto hardness tester, along with standard deviations. The force of fracture was recorded and the zero force reading was deducted from it. Generally, a minimum hardness of 5-7 kg/cm^2 is considered acceptable for uncoated tablets. The hardness for sustained release tablets should be preferably 4-6 kg/cm^2. The results are shown in **Table 3**.

Friability test
From each batch, 10 tablets were accurately weighed and placed in the Roche friabilator apparatus which was operated at 25 rpm for 4 min while rotating. The tablets were taken after 100 rotations, dedusted and reweighed. The friability was calculated as the percentage weight loss. Friability values below 1% are generally acceptable (Lachman *et al* 1987). % Friability was calculated as follows:

$$\% \text{ Friability} = (W1 - W2) \times 100/W1$$

where, W1 = Initial weight of the 20 tablets,
W2 = Final weight of the 20 tablets after testing.

Drug content (Assay)
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 Timolol maleate was transferred to a 100 ml volumetric flask containing 70 ml of 0.1 N HCl. It was shaken by mechanical means for 1 hr. Then, it was filtered through a Whatman filter paper (No. 1) and diluted to 100 ml with 0.1 N HCl. From this resulted solution, 1 ml was taken, diluted to 50 ml with 0.1 N HCl and absorbance was measured against blank at 295 nm. 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. The results are shown in **Table 3**.

Compatibility study of Timolol Maleate
FT-IR studies
The peaks obtained in the spectras of physical mixtures correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components. The results are shown in **Figure 2**. The procedure consisted of dispersing a sample (drug alone, polymers alone *i.e.* HPMC K4M, Ethyl cellulose mixture of drug and polymers) in KBr to prepare 10% of mixture and grounded generally in mortar-pestle with KBr compressed into granules. These granules were placed in light path and spectrum was recorded at a resolution of 2 cm over a frequency range of 4000 to 400 cm^{-1} (**Figure 2, 3**).

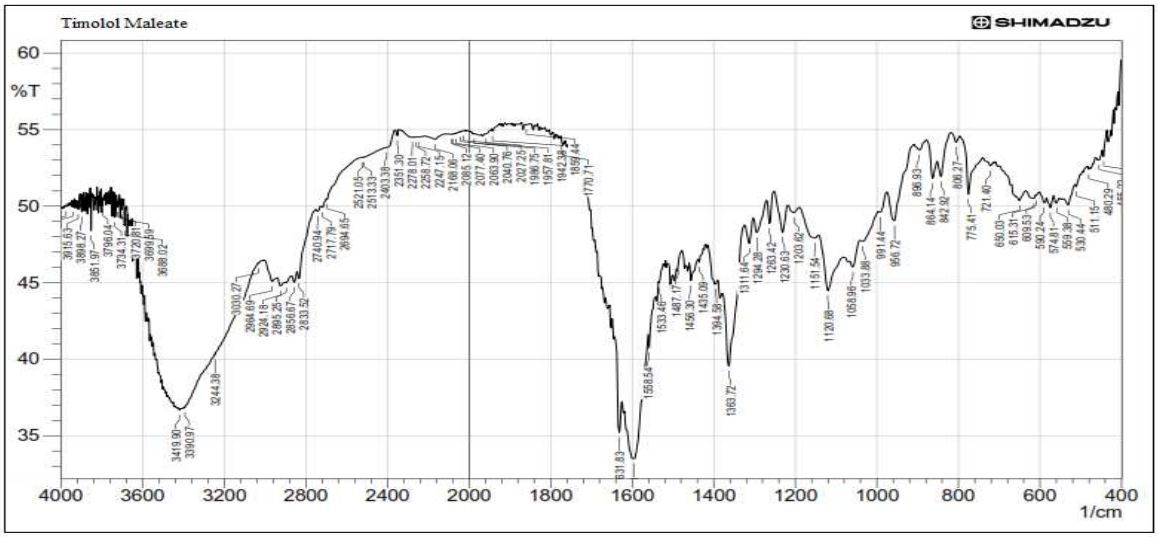

Fig. 2. FTIR of Timolol maleate

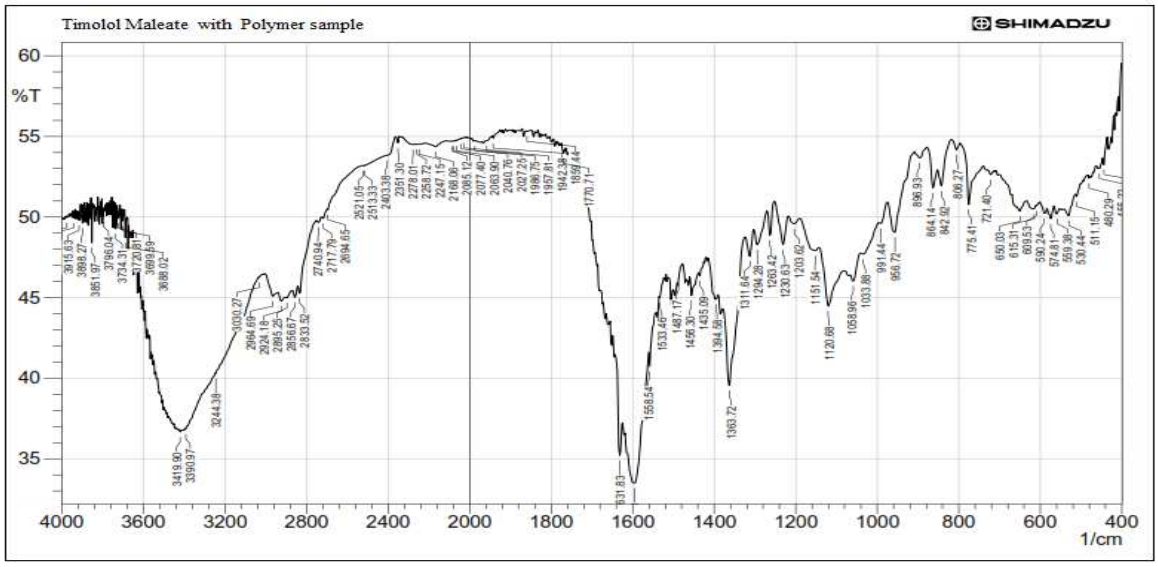

Fig. 3. FTIR of Timolol maleate with excipients

In the present study, it has been observed that there is no chemical interaction between drug and the polymers used. It was observed that there were no changes in these main peaks in FT-IR spectra of mixture of drug and polymers, which showed that there were no physical interactions because of some bond formation between drug and polymers (**Table 4**).

Table 4. FTIR data for estimation of Timolol maleate

S. No.	Functional group with types of vibration	Peak (cm^{-1})
1	Alcohols O-H stretch	3200-3400
2	Aromatic C-H stretch	3000-2800
3	Carboxylic acid C=O stretch	1630-1760
4	Aliphatic C-H stretch	2970-2840
5	Aromatic C=C stretch	1550-1600
6	Aliphatic C-H bend	1300-1500
7	Alcohols C-O stretch	1000-400

Construction of standard graph of Timolol maleate

Preparation of stock solution

Accurately weighed 100 mg of Timolol maleate was transferred into a 100 ml volumetric flask. 20 ml of 0.1 N hydrochloric acid 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 1 mg/ml which was labeled as 'stock'. From this stock solution, 10 ml was taken and diluted to 100 ml with 0.1 N HCl which has given the solution a 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 absorbance of above solutions were recorded at 295 nm 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. The standard curve of different buffers is shown in the **Figure 4, 5**.

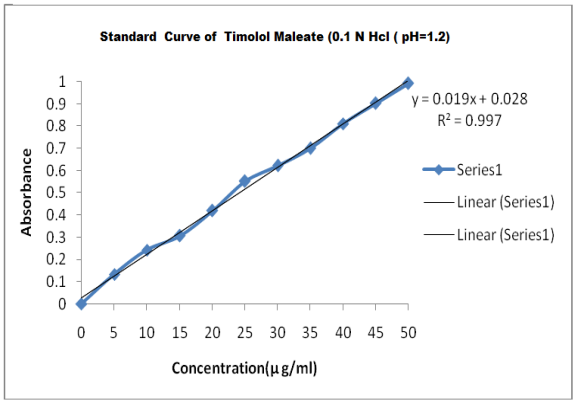

Fig. 4. Standard curve of Timolol maleate at 0.1 N HCl

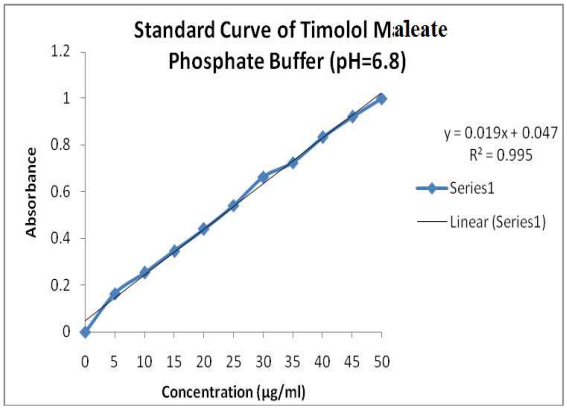

Fig. 5. Standard curve of Timolol maleate at phosphate buffer 6.8

In vitro drug dissolution study

Drug release was assessed by dissolution test using USP type II dissolution apparatus at 100 rpm in 900 ml of 0.1 N HCl for first 2 hr and the phosphate buffer pH 6.8 from 3 to 12 hr, maintained at 37°C ± 0.5°C. An aliquot (5 ml) was withdrawn at specific time intervals and replaced with the same volume of pre warmed (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. Each time, % of drug release was calculated. The results are shown in the **Table 5** and **Figure 6**.

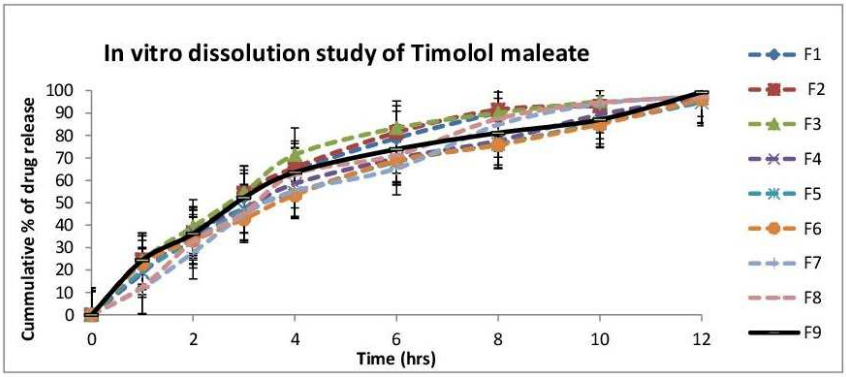

Fig. 6. *In vitro* dissolution study of sustained release tablets Timolol maleate (F1-F9)

Table 5. In vitro dissolution study of Timolol maleate sustained release tablets (F1-F9)

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	23.32	24.66	24.31	18.66	19.54	22.73	11.94	12.54	24.37
2	34.63	36.38	39.37	37.15	33.26	33.18	27.83	32.77	36.19
3	52.46	54.43	54.49	47.38	46.93	42.71	44.74	45.38	52.23
4	64.38	65.66	71.38	58.44	54.43	53.36	55.24	62.83	63.48
6	78.77	81.34	83.33	69.74	68.31	68.73	65.32	71.22	73.88
8	90.19	91.52	93.49	77.64	76.14	75.65	84.75	87.43	81.09
10	-	93.15	95.19	89.28	85.45	84.93	94.1	94.64	87.04
12	-	-	-	96.46	94.74	96.06	97.43	97.15	99.21

Kinetic release analysis

Zero order release model

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly and describes the dissolution of various dosage form. The pharmaceutical dosage forms following this profiles release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action (Dash *et al* 2010). The equation for zero order release is $Q_t = Q_0 + K_0 t$ where Q_0 = initial amount of drug, Q_t = cumulative amount of drug release at time 't', K_0 = zero order release constant, t = time (in hrs).

Plot: % CDR *vs* Time (**Figure 7**).

First order release kinetics

This model describes drug dissolution in pharmaceutical dosage form such as containing water soluble drugs in porous matrices. The first order release equation is:

$\text{Log } Q_t = \text{Log } Q_0 + K_t/2.303$

where Q_0 = initial amount of drug, Q_t = cumulative amount of drug release at time 't', K = first order release constant, t = time (in hr).

Plot: log of % drug remaining *vs* time (**Figure 8**).

Higuchi's model

The release of a drug from a drug delivery system (DDS) involves both dissolution and diffusion (Higuchi, 1963). The equation for Higuchi's for drug release through matrix is:

$Q = KH\ t^{1/2}$

where Q = cumulative amount of drug release at time 't', KH = Higuchi constant, t = time (in hrs)

Plot: Amount of drug released *vs* square root of time (**Figure 9**).

Korsmeyer-peppas model

To find out the mechanism of drug release, first 60% data is fitted in this model (Siepmann and Siepmann, 2008) to predict the effect of the device design parameters (e.g. shape, size and composition of HPMC-based matrix tablets on the resulting drug release rate), thus facilitating the development of new pharmaceutical products. Simple empirical or semi-empirical models such as the classical Higuchi equation and the so-called power law, as well as more complex mechanistic theories, consider diffusion, swelling and dissolution processes (Siepmann and Peppas, 2001). This equation is:

$F = (M_t / M) = K_m$

where F = Fraction of drug released at time 't', M_t = Amount of drug released at time 't', M = Total amount of drug in dosage form, K_m = Kinetic constant, n = Diffusion or release exponent, t = time (in hr)

Plot: log % CDR *vs* log time taken (**Figure 10**).

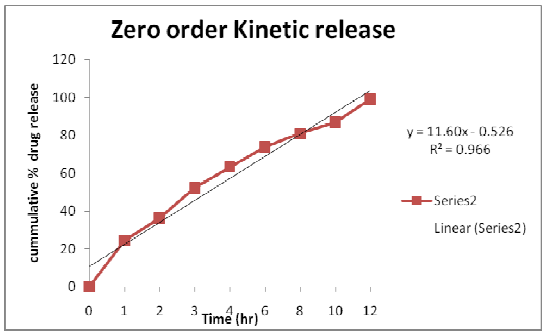

Fig. 7. Zero order kinetic model

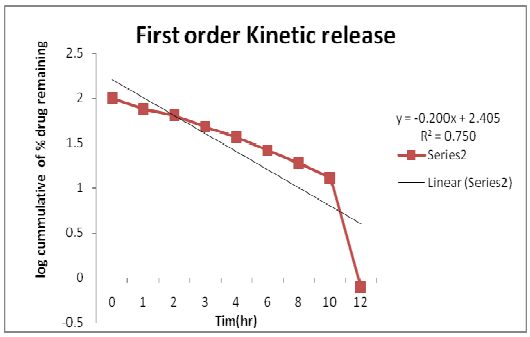

Fig. 8. First order kinetic model

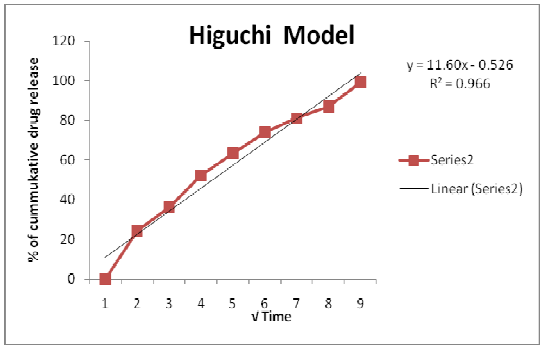

Fig. 9. Higuchi kinetic model

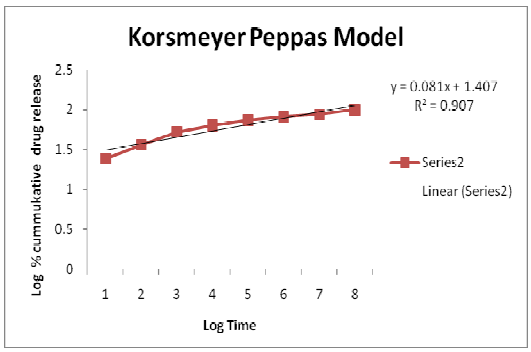

Fig. 10. Korsmeyer-Peppas kinetic model

RESULTS AND DISCUSSION

The drug release rate was slower with the tablets containing combination of both hydrophilic HPMC K100M and hydrophobic EC polymers. Wet granulation method was found to be better choice to extend the drug release for 12 hrs. The combination of polymer HPMC K4M and HPC was used as polymer in a ratio of Drug to polymer as 1:0.67, 1:1, 1:1.5. Formulation F1 composed of drug polymer ratio of 1:0.5, failed to sustain release beyond 10 hrs. This formulation underwent erosion before complete swelling could take place. Formulations with drug polymer ratios (F2) have extended the drug

Table 6. Kinetic release analysis of Timolol maleate SR tablets

Kinetic release model	Zero order Kinetic	First order kinetic	Higuchi Model	Korsmeyer-Peppas Model
Coefficient of regression	0.966	0.75	0.996	0.907
Slope	11.6	-2	11.6	0.081
Intercept	0.526	2.45	0.526	1.47

release for 10 hrs. All these formulations have shown more than 30% release in the first 1 hr indicating burst release. For formulation F4 to F6, HPMC K100M and HPMC 4M was used as polymer in a ratio of Drug to polymer as 1:1.5, 1:1, 1:0.67. Formulations containing HPMC K100M (F4 to F6) have shown initial burst release and extended the release for 12 hr. As the drug polymer ratio increased to 1:2, the kinetics of the release decreased (98.97% at 12 hr). The drug release was slower from matrices containing HPMC K100M compared to HPMC K4M. For formulation F7 to F9, ethyl cellulose was used as polymer in a ratio of Drug to polymer as 1:067, 1:1, 1:1.5. Batches containing ethyl cellulose (F7 to F9) as release retardant, extended the release up to 12 hr with initial burst release. The optimized formulation (F9) showed better release profiles.

CONCLUSION

The optimized Timolol maleate sustained release tablets were successfully formulated with help of HPMC K100M and ethyl cellulose by wet granulation method. The physical mixture of blend of optimized formulation of F9 were evaluated, which showed micrometric properties. The post formulation study was conducted which are with in specification range. The % drug release of Timolol maleate sustained release tablets were 99.21 % over the end of 12 hr. The drug release pattern was similar to theoretical release profile. The drug release of successful batch followed Zero order kinetics and best fit with Korsmeyer's Peppas kinetic release model.

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