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Formulation and Evaluation of Sustained Release Tablets of Timolol Maleate

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ABSTRACT

Timolol maleate tablets were prepared by wet granulation method to study the effect of method of manufacture on the drug release. Drug and the diluent (MCC or Lactose) were sifted and mixed well to ensure the uniformity of premix blend. Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetic profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate-release dosage forms. In recent years, various modified-release drug products have been developed to control the release rate of the drug and the time for drug release.

Keywords: Minimum effective plasma concentration (MEC), Drug release, Wet granulation method, Lactose, Therapeutic effect.

Introduction

The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. 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". 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 [1,2]. Examples of extended-release dosage forms include controlled-release, sustained-release, and long-acting 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 dosage form that releases drug at or near the intended physiologic site of action [3,4,5]. Targeted-release dosage forms may have either immediate- or extended-release characteristics. 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. Pharmaceutical products designed for oral delivery are mainly

conventional drug delivery systems, which are designed for immediate release of drug for rapid/immediate absorption [6,7,8]. The administration of the conventional dosage form by extra vascular route does not maintain the drug level in blood for an extended period of time. The short duration of action is due to the inability of conventional dosage form to control temporal delivery.

The conventional dosage forms like solution; suspension, capsule, tablets and suppository etc. have some limitations such as

1) Drugs with short half-life require frequent administration, which increases chances of missing the dose of drug leading to poor patient compliance.

2) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult. The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the steady state concentration values fall or rise beyond the therapeutic range.

3) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overdosing occurs. In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits [9,10,11].

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 [12,13,14].

Oral controlled release drug delivery is a system that provides continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action.

First generation beta blockers such as propranolol, nadolol, timolol maleate, penbutolol sulphate, sotalol hydrochloride, and pindolol are non-selective in nature, meaning that they block both beta1 (β1) and beta2 (β2) receptors and will subsequently affect the heart, kidneys, lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle, and skeletal muscle and as an effect, could cause reduced cardiac output, reduced renal output amongst other actions [15,16,17].

Second generation beta blockers such as metoprolol, acebutolol hydrochloride, bisoprolol fumarate, esmolol hydrochloride, betaxolol hydrochloride, and acebutolol hydrochloride are selective, as they block only β1 receptors and as such will affect mostly the heart and cause reduced cardiac output.

Timolol maleate is a nonselective beta-adrenergic receptor blocking agent. It possesses an asymmetric carbon atom in its structure and is provided as the levo isomer. The mechanism of action like propranolol and nadolol, timolol competes with adrenergic neurotransmitters such as catecholamines for binding at beta (1)-adrenergic receptors in the heart and vascular smooth muscle and beta (2)-receptors in the bronchial and vascular smooth muscle [18,19,20]. Beta (1)-receptor blockade results in a decrease in resting and exercise heart rate and cardiac output, a decrease in both systolic and diastolic blood pressure, and, possibly, a reduction in reflex orthostatic hypotension. Beta (2)-blockade results in an increase in peripheral vascular resistance. The exact mechanism whereby timolol reduces ocular pressure is still not known. The most likely action is by decreasing the secretion of aqueous humour [21,22].

Materials and Methods

Timolol maleate was obtained from Neuland Laboratories, Hyderabad. HPMC K 15 M was obtained from Neuland Laboratories, Hyderabad. Polyethylene oxide was obtained from Neuland Laboratories, Hyderabad. Micro crystalline cellulose was obtained from Lobe Chemie Pvt. Ltd, Mumbai. Polyvinyl pyrrolidone was obtained from Lobe Chemie Pvt. Ltd, Mumbai. Isopropyl alcohol was

obtained from Lobe Chemie Pvt. Ltd, Mumbai. Magnesium stearate was obtained from S.D Fine Chem Ltd., Mumbai. Talc was obtained from S.D Fine Chem Ltd., Mumbai.

Standard Calibration Curve of Timolol maleate

Accurately weigh the 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 labelled as stock solution. 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 λmax (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.

Table 1: Standard Curve of Timolol maleate

Conc.(mcg/mL)	Absorbance at 295nm	
	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

Preparation of Timolol maleate sustained release tablets

All the matrix tablets, each containing 25 mg of timolol maleate, were prepared by wet granulation method to study the effect of method of manufacture on the drug release. In this Wet granulation method, the Drug and the diluent (MCC) along with PVP 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 (HPMC K15M and Polyethylene oxide), previously sifted through sieve No. 40, for 5 minutes. Premix blend was wet granulated with 5% w/v solution of iso propyl alcohol 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 blended granules were added 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.

Table 2: Composition of Timolol maleate tablets Containing HPMC K15M

Code	Timolol Maleate (mg)	HPMC K15M (mg)	Micro Crystalline Cellulose (mg)	Polyvinyl pyrrolidone (mg)	Isopropyl alcohol (ml)	Magnesium Stearate (mg)	Talc (mg)	Total (mg)
F1	25	12	72	6	q. s	2	3	120
F2	25	24	60	6	q. s	2	3	120
F3	25	37	47	6	q. s	2	3	120
F4	25	48	36	6	q. s	2	3	120

Table 3: Composition of Timolol maleate tablets Containing Polyethylene oxide

Code	Timolol Maleate (mg)	Polyethylene oxide (mg)	Micro Crystalline Cellulose (mg)	Polyvinyl pyrrolidone (mg)	Isopropyl alcohol (ml)	Magnesium Stearate (mg)	Talc (mg)	Total (mg)
F5	25	12	72	6	q. s	2	3	120
F6	25	24	60	6	q. s	2	3	120
F7	25	37	47	6	q. s	2	3	120
F8	25	48	36	6	q. s	2	3	120

Drug-Excipient compatibility

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.

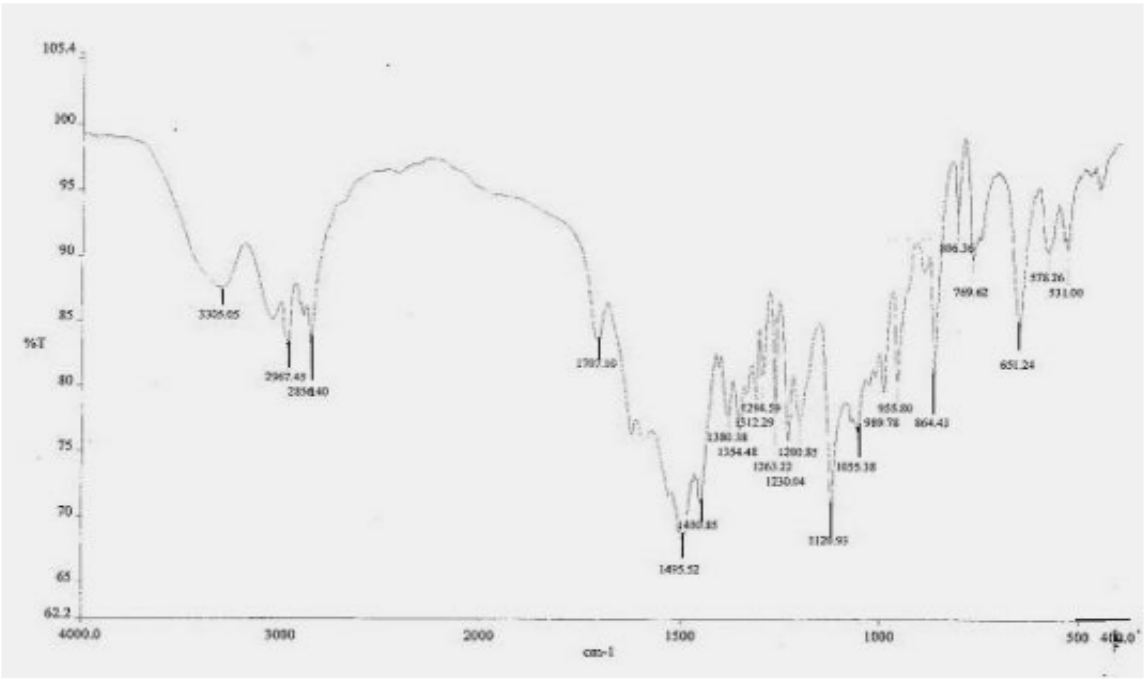

Figure 1: FTIR spectrum of Timolol Maleate

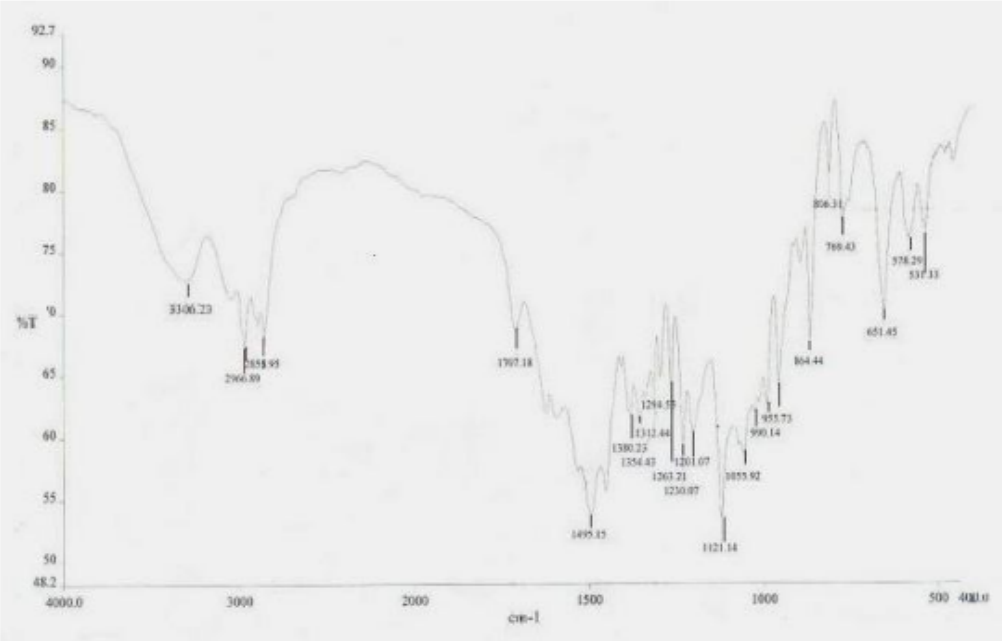

Figure 2: FTIR Spectrum of optimized formulation(F8)

Evaluation of powder blend

1. Angle of Repose: It is defined as the maximum angle that can be obtained between the free standing of powder heap and horizontal plane. It was determined by the following equation [23,24].

Tan θ=h/r

Where, θ = Angle of repose, h = powder heap, r =Radius of the powder cone.

2. Carr's Index: The carr's index or compressibility index was calculated from the bulk and tapped density value by following equation [25].

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

3. Hausner's Ratio: It is measurement of frictional resistance of tablet blend. The ideal range should be 1.2-1.5. It was determined by the ratio of tapped density and bulk density [26].

Hausner′s ratio=Tapped density/Bulk density

4. Bulk Density: Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape and the tendency of the particles to adhere to one another. Both loose bulk density (LBD) and tapped bulk density (TBD) were determined [27]. A quantity of accurately weighed powder (bulk) from each formula, previously shaken to break any agglomerates formed was introduced into a 25ml measuring cylinder and the initial volume was observed. It is given by the equation as

Bulk density=Mass of the powder/ bulk volume of the powder

5. Tapped density: Weighed quantity of tablet blend was introduced into a graduated cylinder. Volume occupied by the drug was noted down. Then cylinder was subjected to 100, 200 and 300 taps in tap density apparatus. According to USP, tapped density was given by

Tapped density=Mass of the powder/Tapped volume of the powder

Table 4: Specifications for flow properties

Flow Character	Carr's index (%)	Hausner's ratio	Angle of repose
Excellent	<10	1.00-1.11	25-30
Good	11-15	1.12-1.18	31-35
Fair	16-20	1.19-1.25	36-40
Passable	21-25	1.26-1.34	41-45
Poor	26-31	1.35-1.45	46-55
Very poor	32-37	1.46-1.59	56-65
Very, very poor	>38	>1.60	>66

Post Compression parameters of tablets

1. Weight variation test

Twenty Timolol maleate tablets were weighed individually, average weight was calculated and individual tablet weights were compared to the average weight [28]. The tablets met the USP test if no more than two tablets are outside the percentage limit and if no tablet differs by more than two times the percentage limit.

2. Hardness test

The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in kg/cm^2. Six tablets were randomly picked from each formulation and the mean values were calculated.

3. Friability

A friability test was conducted on Timolol maleate tablets using a Roche friabilator. Twenty tablets were selected from each batch and any loose dust was removed with the help of a soft brush. The tablets were initially weighed and transferred into friabilator. The drum was rotated at 25 rpm for 4 minutes after which the tablets were removed. Any loose dust was removed from the tablets as before and the tablets were weighed again. The percentage friability was then calculated by

$$\% \text{ Friability} = \frac{\text{Initial Weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

4. Drug content

The drug content of the tablets was determined according to invitro 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 Timolol maleate was transferred to a 100 mL volumetric flask containing 70 mL of 0.1N HCl. It was shaken by mechanical means for 1hour. Then it was filtered through a Whatman filter paper 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 by UV visible spectrometer.

5. Drug release studies

Drug release was assessed by dissolution test under the following conditions, USP type II dissolution apparatus (paddle method) at 100 rpm in 900 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 and drug content in each sample was analysed by UV-visible spectrophotometer at 295 nm.

Details of dissolution test:

Dissolution test apparatus: USP II

Speed: 100±0.1 rpm

Stirrer: paddle type

Volume of medium: 900 ml

Time interval: 1, 2, 3,4,6,8,10 and 12 hours

Medium used: 0.1N HCl for first 2 hours and the phosphate buffer pH 6.8 from 3 to 12 hours

Temperature: 37 ± 0.5^0C.

Results and Discussion

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 under λmax of 295nm, which suggests that it obeys the "Beer-Lambert's law". 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 of the uniformity of weight, hardness, thickness, friability, and drug content of the tablets are calculated. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 118 and 119 mg.

The hardness of the tablets ranged from 4 to 5 kg/cm^2 and the friability values were less than 0.7% indicating that the matrix tablets were compact and hard. All the formulations satisfied the content of the drug as they contained 90 to 98 % 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. All the formulations containing drug to polymer ratio 1:2 and MCC as a diluent extended the drug release for 8 to 12 hours.

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. It was revealed that polymers and diluent ratios had significant influence on drug release. Thus, it is summarized that stable dosage form can be developed by timolol maleate for sustained release matrix tablets.

Table 5: Pre-compression Parameters of Timolol maleate powder blend

Formulations Code	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	23.21	0.518	0.627	17.38	1.21

Table 6: Physical Evaluation of Timolol maleate tablets

Code	Hardness(kg/cm^2)	Weight (mg)	Friability (%)	Drug content (%)
F1	5.50	118.8	0.36	96.25
F2	5.50	118.4	0.39	95.28
F3	5.58	118.6	0.43	94.12
F4	5.66	118.8	0.12	91.22
F5	4.25	118.6	0.54	90.24
F6	4.08	119.2	0.58	97.53
F7	4.25	118.9	0.64	93.28
F8	5.41	119.9	0.07	98.35

Table 7: In-Vitro Release Data of Timolol Maleate from HPMC K15M

Time (hours)	F1	F2	F3	F4
1	41.94	39.96	37.12	36.78
2	53.82	50.99	50.20	48.13
3	74.58	67.43	63.09	62.99
4	82.35	80.50	77.61	75.35
6	94.28	89.47	86.23	83.30
8	-	92.55	93.83	91.15
10	-	-	-	92.4
12	-	-	-	-

Table 8: In-Vitro Drug Release Data of Timolol Maleate from Polyethylene Oxide

Time (hours)	F5	F6	F7	F8
1	32.90	28.81	25.56	22.38
2	44.14	40.35	37.36	35.23
3	58.23	55.46	54.48	51.66
4	73.74	69.38	66.55	63.48
6	92.30	84.68	82.43	79.57
8	-	91.19	92.57	98.77
10	-	-	-	-
12	-	-	-	-

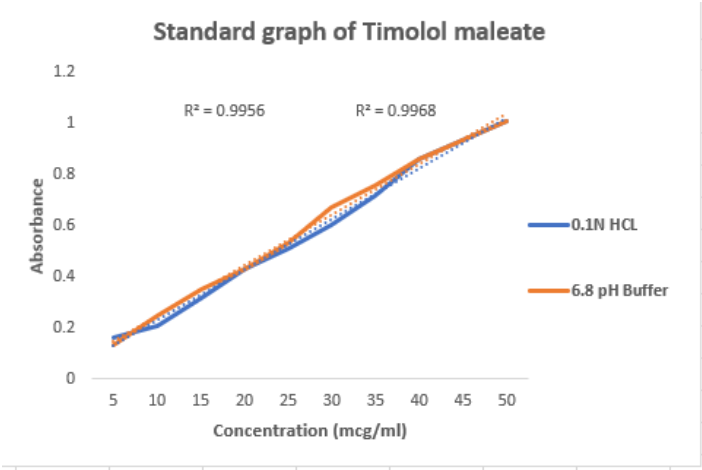

Figure 3: Standard graph of Timolol Maleate

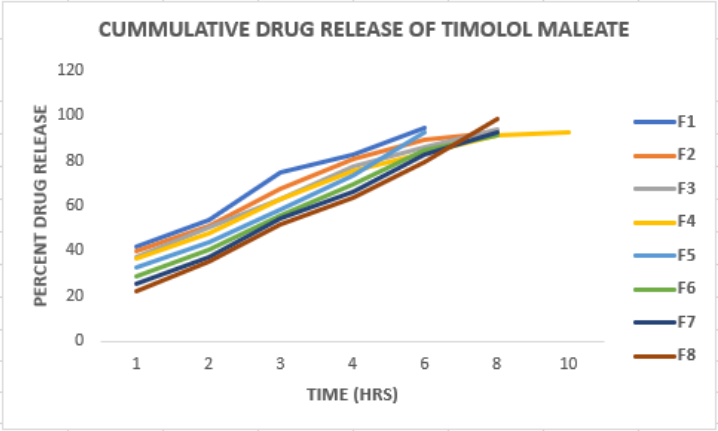

Figure 4: Cumulative drug release of Timolol maleate tablets (F1 to F8).

Conclusion

Timolol maleate is a nonselective beta-adrenergic receptor blocking agent. As the conventional doses release the Timolol maleate in just few minutes and therefore the therapeutic concentrations are maintained for a short period of time generating a need for administration of another dose Therefore, an attempt is made to maintain the therapeutic concentration for longer period of time. This is achieved by developing controlled release drug delivery system. These controlled release matrix tablets mainly prepared for release of the drug for longer period of time i.e., 12 hours and utilizing the drug to full extent avoiding unnecessary frequency of dosing.

For the formulation of sustained release tablet HPMC K 15M and polyethylene oxide were used as polymers. Other excipients used are microcrystalline cellulose (diluent), Magnesium stearate (lubricating agent). Fourier transform Infrared spectroscopy confirmed the absence of any drug/polymers/excipient's interactions. The prepared sustained release tablets were evaluated for hardness, Weight variation, thickness, friability, drug content uniformity and In-vitro dissolution studies. All the formulations containing drug to polymer ratio 1:2 and MCC as a diluent extended the drug release for 8 to 12 hours. The results of dissolution studies indicated that formulation F8, the most successful of the study, exhibited good drug release pattern. The designed tablets of F8 of timolol maleate of drug in the first hour and extend the release up to 12 hours, can overcome the disadvantages associated with conventional tablets formulation of Timolol Maleate. Hence it can be concluded that twice a daily sustained release tablet of Timolol maleate having satisfactory extended release profile which may provide an increased therapeutic efficacy.

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