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RESEARCH ARTICLE

Formulation of Timolol Maleate Sustained-release Matrix Tablets

B. Lakshmi Satya[1]*, C. Soujanya[1], Nayudu Teja[2], R. Pradeep[3], B. Karthik[3]

[1]Department of Pharmaceutics, Vishnu Institute of Pharmaceutical Education and Research, Tuljaraopet, Telangana, India, [2]Department of Pharmaceutics, Jawaharlal Nehru Technological University, Kakinada, Andhra Pradesh, India, [3]Department of Pharmacy, Vishnu Institute of Pharmaceutical Education and Research, Tuljaraopet, Telangana, India

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ABSTRACT

Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid/immediate absorption. 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 drugs pharmacokinetics. An controlled release formulation of Timolol maleate to maintain constant therapeutic levels of the drug for over 10 h. Timolol maleate-controlled release matrix tablets are prepared by wet granulation method with different grades of HPMC. An efficient extended release formulation of Timolol maleate could be designed as controlled release tablets. Combination of HPMC K100M and HPMC K15M was extended the release for 10 h. 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. The release process involves anomalous diffusion mechanism or diffusion coupled with erosion.

Keywords: Timolol, Maleate, drug

INTRODUCTION

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 to 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, 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/or the time for drug release.

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

***Corresponding Author:**
B. Lakshmi Satya,
E-mail: lakshmisatya.b@viper.ac.in

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."

Conventional drug delivery system

Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid/immediate absorption [Figure 1].

As shown in graph [Figure 1], 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.

Controlled release drug delivery systems

More precisely, controlled delivery can be defined as follows:

1. Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects
2. Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue
3. Targeted drug action using carriers or chemical derivatives to deliver drug to a particular target cell type
4. Provide a physiologically/therapeutically based drug release system. In other words, the amount and the rate of drug release are determined by the physiological/therapeutic needs of the body.

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 drugs pharmacokinetics [Table 1].

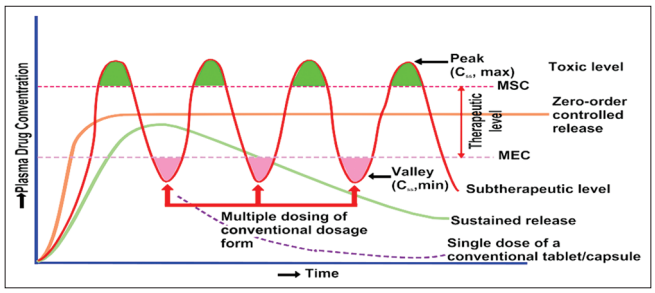

Figure 1: A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations. (MSC = maximum safe concentration, MEC = minimum effective concentration).

METHODOLOGY

The materials used in the present investigation were either AR/LR grade or the best possible Pharma grade.

Formulae	Polymer (s)	Diluent	Method
F1 to F4	HMPC K 15M	MCC	Wet Granulation
F5 to F8	Polyethylene	MCC	Wet Granulation
F9 to F12	HMPC K 15M	MCC	Wet Granulation
F13 to F16	Ethyl cellulose	MCC	Wet Granulation
F17 to F20	Kollidon-SR	MCC	Direct Compression
F21 to F25	HMPC K 100M &EC	MCC	Wet Granulation
F26 to F30	HMPC K 100M &HPMC K15M	MCC	Wet Granulation

Materials used

S. no	Material	Supplied by
1	Timolol maleate	Neuland Laboratories, Hyderabad
2	HPMCK 15 M	Neuland Laboratories, Hyderabad
3	HPMCK 100 M	Neuland Laboratories, Hyderabad
4	Polyethylene Oxide	LobaChemie Pvt. Ltd, Mumbai.
5	Ethylcellulose	LobaChemie Pvt. Ltd, Mumbai
6	Kollidon-SR	Neuland Laboratories, Hyderabad
7	Microcrystalline cellulose	LobaChemie Pvt. Ltd, Mumbai
8	Polyvinylpyrrolidone	LobaChemie Pvt. Ltd, Mumbai
9	Isopropylalcohol	LobaChemie Pvt. Ltd, Mumbai
10	Magnesiumstate	S.D FineChem Ltd., Mumbai
11	Talc	S. D FineChem Ltd., Mumbai

Equipments used

Details of equipments used

S. No.	Instrument	Manufacturer
1.	Electronic Weighing Balance	Sartoriousbt 2235, Japan
2.	Tap Density Tester (U.S.P.)	Electrolab, ETD-1020, India
3.	Sieves	Rolex standard sieves, India

4.	Tablet punching machine	Cadmach-cmd4
5.	Dissolution apparatus (U.S.P.)	Distek–2100c
6.	Dissolution sampler	HPLC Waters 2666
7.	Mill	Quardo
8.	pH Meter	LI120, Elico Pvt. Ltd, India
9.	Loss on drying tester	Sartorious102
10.	Hardness Tester	Varian-vk200
11.	UV Spectrophotometer	Varian21cfr-11
12.	Electromagnetic Sieve Shaker	EMS– 8

RESULTS

Standard graph of Timolol maleate

The standard graph of Timolol maleate [Table 2] has shown good linearity with R^2 values 0.9956 and 0.9968 in 0.1 N HCl [Figure 2] under λ max of 295 nm, which suggests that it obeys the "Beer-Lambert's law."

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.

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 3]. Angle of repose was <35° and Carr's index values were <21 for the granules of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was <1.25 for all the batches indicating good flow properties. The drug content was more than 90% for all the granules of different formulations.[1-10]

Evaluation of matrix tablets

The results of the uniformity of weight, hardness, thickness, friability, and drug content of the tablets

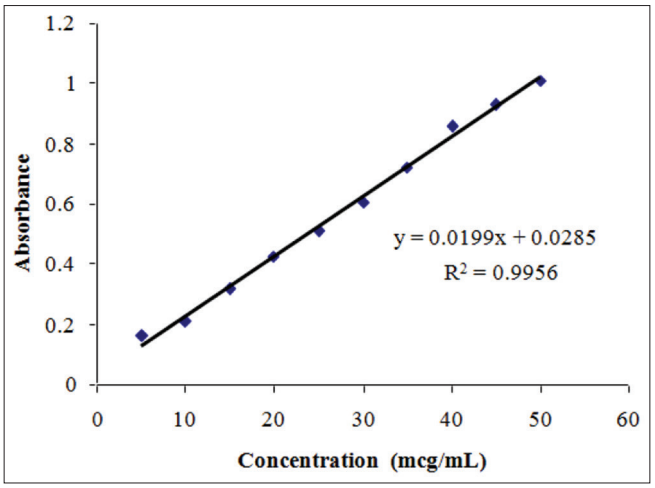

Figure 2: Standard graph of Timolol maleate in 6.8 phosphate buffer

Table 1: Technologies used for CRDDS

S. No.	Design or type of the system	Release mechanism
1	Dissolution controlled CR systems Encapsulation (including microencapsulation) a. Barrier coating b. Embedment into a matrix of fatty materials) c. Repeat action coatings d. Coated plastic materials or hydrophilic materials e. Matrix dissolution control	The dissolution of drug from system
2	Diffusion Controlled CR systems Reservoir devices (fatty polymer coated systems) Matrix devices (Fatty polymer dispersed systems)	The diffusion of the drug solution through a water-insoluble, permeable polymeric film
3	Dissolution and diffusion controlled CR systems • Non-disintegrating polymeric matrix • Hydrophilic matrices	Diffusion of a drug solution through a porous matrix
4	Ion-exchange resin CR systems	Ion-exchange between the resin-drug complex and ions in the GI tract
5	pH-Independent formulations	Influenced by change in pH and ionic permeability of the membrane coating
6	Osmotically controlled CR systems	They contain the buffering agents in a system which maintains constant pH throughout the GIT, so the drug release from the device is not affected by variable pH of GIT. Water entering by Osmosis dissolves the drug, and the drug solution is forced out through a laser drilled orifice
7	Altered-density systems	Diffusion from high-density pellets or from floating

CRDDS: Controlled release drug delivery systems

Table 2: Standard graph of Timolol maleate

Conc.(mcg/mL)	Absorbance at 295 nm	
	0.1NHCl	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

are given in Table 2. 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 <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 90–103% of Timolol maleate and good uniformity in drug content was observed.[11-19] Thus, all the physical attributes of the prepared tablets were found be practically within control [Table 4].

Table 3: 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

Table 4: 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

*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

Drug release from combination of HPMC K100M and HPMC K15M matrices

Combination of HPMC K100M and HPMC K15M was extended the release for 10 h. 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. Data are given in Table 5 and Figure 3.

Out of total 30 batches, the drug release was extended up to 10 h for the formulations F26 and F30.

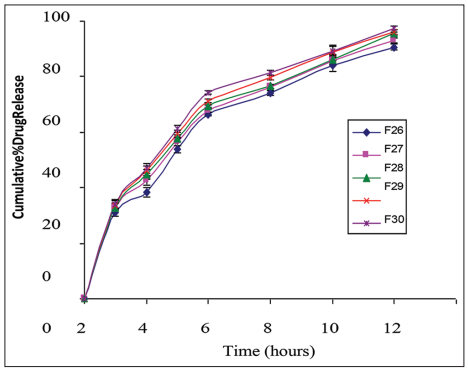

Figure 3: Release profiles of Timolol maleate from tablets containing HPMCK100M and HPMCK15M

Table 5: *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)

CONCLUSION

The aim of the present study was to develop an controlled release formulation of Timolol maleate to maintain constant therapeutic levels of the drug for over 10 h. Timolol maleate-controlled release matrix tablets are prepared by wet granulation method with different grades of HPMC. An efficient extended release formulation of Timolol maleate could be designed as controlled release tablets. The optimized formulation (F26) was developed using HPMCK50M and Ethylcellulose (1:1). There sults of dissolution studies indicated that formulation F-26, the most successful of the study, exhibited drug release pattern very close to theoretical release profile. The designed matrix tablets F-26 of Timolol maleate, which release 25.38%, respectively, of drug in the 1st h and extend the release up to 10 h, can overcome the disadvantages associated with conventional tablets formulation of Timolol maleate tablets. Regulated drug release in zero order kinetics attained with this formulation.

The release process involves anomalous diffusion mechanism or diffusion coupled with erosion, as indicated by the $n = 0.66$ 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.

Hence, it can be concluded that twice a daily controlled release matrix tablet of Timolol maleate having sat is factory extended release profile which may provide an increased therapeutic efficacy. The developed formulation overcomes and alleviates the drawback and limitation of extended release preparations.

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