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DESIGN AND IN-VITRO EVALUATION OF SUSTAINED-RELEASE MATRIX TABLETS OF TIMOLOL MALEATE

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ABSTRACT

The aim of the present study was to prepare and characterize twice-daily sustained-release matrix tablets of Timolol maleate (TM) using different concentrations of hydrophilic Hydroxypropylmethylcellulose (HPMC K100M CR) alone and its combination with hydrophobic ethyl cellulose (EC). Formulations prepared by the wet granulation technique and were evaluated for the release of TM over a period of 12 hours using United States Pharmacopoeia (USP) type-II dissolution apparatus. Along with physical properties, the dynamics of water uptake and erosion degree of tablets were also studied. The in-vitro drug release study revealed that formulation F3 (40% wt/wt HPMC K100M) could extend the drug release up to 8 hours. The most successful formulation of the study, F5 (HPMC to EC, 1:1), extended the drug release up to 12 hours, exhibited satisfactory drug release in the initial hours, and the total release pattern was close to the theoretical release profile. The drug release from optimized formulation (F5) followed first-order kinetics via Non-Fickian (anomalous) diffusion. FTIR studies revealed that there was no interaction between the drug and excipients. In conclusion, the results indicated that the prepared sustained-release tablets of TM could perform therapeutically better than conventional tablets with improved efficacy and better patient compliance.

Key words: Timolol maleate; Matrix tablets; Sustained-release; Ethyl cellulose; Hydroxypropylmethylcellulose; In-vitro drug release.

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INTRODUCTION

Timolol maleate is a non-selective beta-adrenergic receptor blocker used in the treatment of essential hypertension, glaucoma, migraine, and for prophylaxis after myocardial infarction. It is rapidly and nearly completely (about 90%) absorbed from the gastrointestinal tract (GIT) following oral ingestion. The absolute bioavailability after oral administration has been reported to be approximately 60%. Detectable plasma levels occur within 0.5 hours and peak plasma levels occur in about 1-2 hours. A plasma half-life is 4 hours. In the treatment of hypertension the usual initial dosage is 10 mg twice a day, whether used alone or added to diuretic therapy. Dosage may be increased or decreased depending on heart rate and blood pressure response. The usual total maintenance dosage is 20-40 mg per day. Increases in dosage to a maximum of 60 mg per day divided into two doses may be necessary.[1]

Although conventional tablets of Timolol maleate available in the market, no study has been done so far for preparing the Timolol maleate sustained-release tablets. To improve the oral bioavailability and to reduce the dose dependent toxicity there is a need for the development of sustained-release formulations. Many patent technologies also indicated that Timolol maleate is suitable for the sustained-release.[2-3]

The most commonly used method of modulating the drug release is to include it in a matrix system.[4]An effort was therefore made to develop simple and effective sustained-release Timolol maleate tablets using a polymer matrix system. The drug is freely soluble in water and hence judicious selection of matrix formers is essential for achieving constant release. HPMC is the most commonly and successfully used hydrophilic retarding agent for the preparation of oral controlled drug delivery systems.[5]Upon contact with the gastrointestinal fluid, HPMC swells, gels, and finally dissolves slowly.[6] The gel becomes a viscous layer acting as a protective barrier to both the influx of water and the efflux of the drug in solution.[7-8] As the proportion of the polymer in the formulation increases, the gel formed is more likely to diminish the diffusion of the drug and delay the erosion of the matrix.[9] The dissolution can be either disentanglement or diffusion controlled depending on the molecular weight and thickness of the diffusion boundary layer. The rate of polymer swelling and dissolution as well as the corresponding rate of drug release are found to increase with either higher levels of drug loading or with use of lower viscosity grades of HPMC.[10] However, the use of hydrophilic matrix former alone for sustaining drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved

drug through the hydrophilic gel network. For such drugs it is necessary to include hydrophobic polymers in the matrix system.[11]

Hence, in the present study, an attempt has been made to develop the sustained-release matrix tablets of TM using hydrophilic HPMC K100M CR in combination with hydrophobic ethyl cellulose, and the sustained pattern of Timolol maleate was evaluated by in-vitro drug release for 12 hours. The drug release data were plotted using various kinetic equations (zero-order, first-order, Higuchi's kinetics, Korsmeyer's equation, and Hixson-Crowell cube root law) to evaluate the drug release mechanism and kinetics.

MATERIALS AND METHODS

Materials

Timolol maleate (BP/USP) was a gift sample from Ven Petro-Chem & Pharma (India) Pvt. Ltd., Mumbai. Hydroxypropylmethylcellulose (Methocel K100M CR) viscosity 100,000 mm^2/s, ethyl cellulose (EC-N-20) viscosity 20 mm^2/s, and poly vinyl pyrrolidone (PVP-K90) were kind gifts from Vilin Biomed Pvt. Ltd. (New Delhi, India). Microcrystalline cellulose (Avicel PH-101), magnesium stearate and talc were procured from Loba Chemie (Mumbai, India). Isopropyl alcohol and all the other chemicals used in the study were of analytical grade.

Calculation of theoretical release profile of Timolol maleate from sustained –release formulations

The total dose of Timolol maleate for twice-daily SR formulation was calculated by Robinson Eriksen equation[12] using available pharmacokinetic data.

The zero-order drug release rate constant (K_0) was calculated using following equation

$$K_0 = DI \times K_e \quad (1)$$

Where DI is the initial dose (i.e., conventional dose = 10mg) and K_e is first-order rate constant for overall elimination.

$$K_e = 0.693 / t_{1/2} \quad (2)$$

Where $t_{1/2}$ = Biological half-life of Timolol maleate = 4 hours

Therefore Ke = 0.693 / 4

= 0.1732 mg/h.

Availability rate $R = K_e \times DI$ (3)

= 0.1732 x 10

= 1.732 mg/h.

Loading dose $D_L = DI - R \times t_{max}$ (4)

Where t_{max} = time to reach peak plasma concentration=2 hours

Therefore D_L = 10 - (1.732 x 2)

= 6.54 mg.

Maintenance dose $D_M = R \times H$ (5)

Where H = Number of hours for which sustained action is desired after initial release.

D_M = 1.732 x 11

= 19.05 mg

Total dose required $D_T = D_L + D_M$ (6)

=6.54+19.05

=25.59 mg

≅25 mg

Hence an oral controlled release formulation of Timolol maleate should contain a total dose of 25 mg and should release 6.54 mg in first 1 hour like conventional tablets, and 1.73 mg/h up to 12 hours thereafter.

Preparation of the matrix tablets

Matrix tablets were prepared by wet granulation method. The composition of various formulations is given in Table 1. Drug, Avicel, and polymer(s) were mixed in a polybag, and the mixture was passed through mesh No. 40. Granulation was done using a 5% wt/vol solution of PVP K90 in sufficient isopropyl alcohol. The wet mass was passed through mesh No.18. The wet granules were dried at 55°C ± 5 °C for 1 hour in a hot-air oven (Biotechnics, India) and the dried

Table 1: Composition of sustained release matrix tablets of Timolol maleate

Name of component	Quantity (mg) per tablet[a]					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Timolol maleate	25	25	25	25	25	25
HPMC K 100M CR	24	36	48	12	24	36
Ethylcellulose (EC)	-	-	-	36	24	12
Microcrystalline cellulose	61.4	49.4	37.4	37.4	37.4	37.4
PVP K90	6	6	6	6	6	6
Isopropyl alcohol	Qs	Qs	qs	Qs	Qs	Qs
Magnesium stearate	1.2	1.2	1.2	1.2	1.2	1.2
Talc	2.4	2.4	2.4	2.4	2.4	2.4
Total	120	120	120	120	120	120

Abbreviations: HPMC, hydroxypropylmethylcellulose; qs, quantity sufficient; PVP, polyvinylpyrrolidone.

[a]Formulations: F1, 20% HPMC; F2, 30% HPMC; F3, 40% HPMC; F4, 10% HPMC and 30% EC, F5, 20% HPMC and 20% EC; F6, 30% HPMC and 10% EC. All percentages were calculated with respect to total tablet weight of 120 mg.

granules were sieved through mesh No. 22. These granules were blended with lubrication mixture (1% wt/wt magnesium stearate and 2% wt/wt talc) and compressed using 16 station rotary tableting machine, equipped with flat-faced, round punches of 6-mm diameter (Cadmach Machinery Co, Ahmedabad, India).

Characterization of granules

Prior to compression, granules were evaluated for their characteristic parameters. Angle of repose was determined by funnel method. Bulk density and tapped density were determined by cylinder method, and Carr's index (CI) was calculated using the following equation.[13]

$$CI = (TD - BD) \times 100 / TD \qquad (7)$$

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

The drug content in granules was determined by extracting an accurately weighed amount of powdered granules (100mg) with 0.1 N HCl. The solution was filtered through 0.45-µm membrane and the samples were analyzed using UV/Visible spectrophotometer (Elico Pvt. Ltd., Hyderabad, India) at 295 nm after suitable dilution.

Drug content and physical evaluation of tablets

The prepared tablets were tested as per standard procedure (IP 1996) for weight variation (n=20), hardness (n=6), thickness (n=10), content uniformity (n=3), and friability. The weight variation of the tablets was evaluated using an electronic balance (Shimadzu, AUX 220, Shimadzu Corp, Japan). Hardness of tablet was determined by using a Monsanto tablet hardness tester (Cadmach Machinery Co, Ahmedabad, India). Friability of ten tablets from each formulation was determined using the Roche friabilator (Campbell Electronics, Mumbai, India). Thickness of the tablets was measured by digital Vernier caliper (Mitutoyo Corp, Kawasaki, Japan). Content uniformity was determined by weighing ten tablets individually, and the drug was extracted in 0.1 N HCl. The drug content was determined as described for granules.

In Vitro drug release studies

To study the effects of polymer concentration and nature of the polymer on drug release, the release studies were carried out using USP-24 type II dissolution apparatus (paddle method) at 100 rpm. The dissolution medium consisted of 0.1 N hydrochloric acid for first 2 hours and the phosphate buffer pH 6.8 from 3 to 12 hours (500 mL), maintained at 37 °C ± 0.5 °C. An aliquot (5 mL) 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, Whatman, Maidstone, UK) and drug content in each sample was analyzed using UV/Visible spectrophotometer at 295 nm.

Kinetic Analysis of Dissolution Data

To analyze the in vitro release data various kinetic models were used to describe the release kinetics. The following plots were made: zero order kinetic model (Equation 8) as cumulative amount of drug release vs time, first order kinetic model (Equation 9) as log cumulative of percentage drug remaining vs time, and Higuchi's model (Equation 10) as cumulative of percentage drug release vs square root of time.

$$C = K_0 t \qquad (8)$$

Where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration Vs time would yield a straight line with a slope equal to K_0 intercept the origin of the axes.[14]

$$LogC = LogC_0 - K_1 t / 2.303 \qquad (9)$$

Where, C_0 is the initial concentration of drug and K_1 is first order constant.[15]

$$Q = K_H t^{1/2} \qquad (10)$$

Where, K_H is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.[16] The data were also plotted using the Hixson-Crowell cube root law (Equation 11) as the cube root of initial concentration minus the cube root of percentage of drug remaining in the matrix Vs time.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC\,t} \qquad (11)$$

Where, Q_t is the amount of drug remained in the dosage form at time t, Q_0 is the initial amount of the drug in the dosage form and K_{HC} is the rate constant incorporating the surface volume relation.[17]

Mechanism of drug release

To find out the drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix, first 60% drug release data was fitted in Korsmeyer–Peppas model (Equation 12), which is often used to describe the drug release behavior from polymeric systems when the mechanism is not well-known or when more than one type of release phenomena is involved.[18]

$$Log\,(M_t / M_\infty) = Log\,K_{KP} + n\,Log\,t \qquad (12)$$

Where, M_t is the amount of drug release at time t, M_∞ is the amount of drug release after infinite time, K_{KP} is a release rate constant incorporating structural and geometrical characteristics of the

tablet, and *n* is the release exponent indicative of the mechanism of drug release. The n value is used to characterize different release mechanisms as given in Table 2. For the cylindrical shaped matrices. Case-II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release.[19]

Table 2 Diffusion exponents and solute release mechanism for cylindrical shape

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

Determination of swelling and eroding behavior

Swelling and eroding behavior was determined by a method similar to that reported by Amelia and Vikram.[20] The dissolution jars were marked with the time points of 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours. One tablet was placed in each dissolution jar containing 500 mL of 0.1 N HCl at 37 °C ± 0.5 °C, and the apparatus was run at 100 rpm using paddle. After 2 hours, 0.1 N HCl was replaced with 500 mL of phosphate buffer pH 6.8. The tablets were taken out after completion of the respective stipulated time span as mentioned above and weighed after the excess of water at the surface had been removed with filter paper. The wetted samples were then dried in an oven at 40 °C up to constant weight. The increase of the weight on the tablet reflects the weight of the liquid uptake. It was estimated according to Equation 13.

$$Q = 100(W_w - W_i) / W_i \quad (13)$$

Where Q is the percentage swelling, and Ww and Wi are the masses of the hydrated samples before drying and the initial starting dry weight, respectively.[21]The degree of erosion (expressed as percentage erosion of the polymer content, E) was determined using Equation 14.

$$E = 100(W_i - W_f) / W_i \quad (14)$$

Where W_f is the final mass of the same dried and partially eroded sample.

Similarity factor (f_2) analysis

To determine the similarity factor, *in vitro* release profile of the selected batches of tablets was compared with the theoretical release profile, which was calculated earlier. The data were analyzed by the following formula.[22]

$$f_2 = 50 \log \{[1+ (1/N) \sum (R_i - T_i)^2]^{-0.5} \times 100\} \quad (15)$$

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

Fourier transforms infrared spectroscopy (FTIR)

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

Stability studies

The optimized matrix tablets were subjected to stability studies as per ICH guidelines at 25°C ± 2°C / 60% ± 5% RH and 40°C ± 2°C / 75% ± 5% RH The products were evaluated for their physical characteristics, drug content, and in-vitro drug release profiles over a period of 6 months.[23]

RESULTS AND DISCUSSION

Characterization of granules

The prepared granules were evaluated for their characteristic parameters like angle of repose, bulk density, tapped density, Carr's index, and drug content (Table 3). Angle of repose was less than 30° and Carr's index values were less than 16 for the granules of all the batches indicating good flowability and compressibility. The drug content was more than 97 % for all the granules of different formulations.

Table 3: Characterization of granules of different formulations[a]

Parameters	F1	F2	F3	F4	F5	F6
Angle of repose	26.43(1.22)	26.97(1.65)	28.25(0.68)	23.63(0.85)	25.49(1.45)	25.12(1.06)
Bulk density(g/mL)	0.481(1.05)	0.475(0.87)	0.524(1.42)	0.434(0.68)	0.520(0.74)	0.487(0.85)
Tapped density(g/mL)	0.572(0.88)	0.546(0.93)	0.599(1.27)	0.497(1.36)	0.582(0.69)	0.561(0.53)
Carr's index	15.90(0.75)	13.00(0.84)	12.52(0.64)	12.67(1.12)	10.65(1.04)	13.19(0.94)
Drug content (%)	98.23 2.65)	99.37(1.68)	98.97(3.55)	97.26(1.74)	99.18(1.34)	98.92(0.97)

[a] Data represent mean values and, in parentheses, standard deviations (n=3).

Drug content and physical properties of matrix tablets

The results of the uniformity of weight, hardness, thickness, friability, and drug content of the tablets are given in Table 4. All the tablets of different batches of uniformity of weight as their weights varied between 120.8 and 122.8 mg. The hardness of the tablets ranged from 5.05 to 6.05 kg/cm^2 and the friability values were less than 0.6% indicating that the matrix tablets were compact and hard enough. The thickness of the tablets ranged from 2.96 to 3.13 mm. All the formulations satisfied the content of the drug as they contained 96 to 99.5 % of Timolol maleate and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically within controls.

Table 4: Drug content and physical properties of matrix tablets[a]

Test	F1	F2	F3	F4	F5	F6
Weight (mg), n=20	121.2 (0.83)	122.4 (0.95)	121.8 (0.75)	122.8 (0.58)	120.8 (0.35)	121.6 (0.84)
Hardness (kg/cm^2), n=6	5.05 (0.86)	5.26 (0.37)	5.40 (0.25)	6.05 (0.28)	5.85 (0.36)	5.62 (0.25)
Thickness (mm), n=10	3.11 (0.24)	3.08 (0.53)	2.96 (0.27)	3.03 (0.42)	2.99 (0.33)	3.13 (0.29)
Friability (%)	0.56	0.33	0.49	0.58	0.29	0.38
Drug content (%), n=3	97.25 (1.67)	99.50 (2.55)	96.48 (1.24)	97.48 (1.69)	98.37 (1.35)	99.12 (1.04)

[a] Data represent mean values and, in parentheses, standard deviations.

In Vitro drug release studies

Effect of different concentrations of HPMC K100M (20%, 30%, and 40% wt/wt of total tablet weight) on release rate of TM was shown in Figure 1. The drug release was extended for 5 hours and 6 hours with 20% of HPMC K100M (F1) and 30% HPMC K100M (F2) respectively. However drug release was decreased significantly when 40% HPMC K100M was used in formulation (F3), with a release of 95.7% at 8 hours. In the preliminary studies, further increase in concentration of HPMC did not significantly affect the release rate. On this basis, 40% of HPMC K100M was selected for further studies.

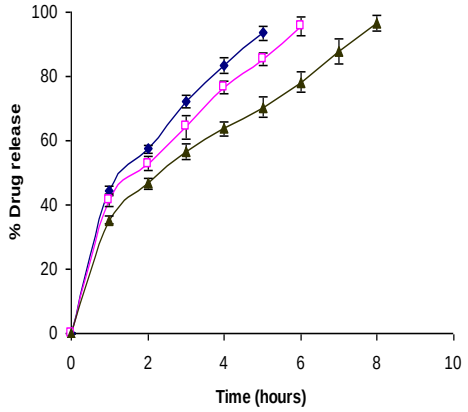

Figure. 1. In vitro release profiles showing the effect of different concentrations of HPMC K100M CR on timolol maleate release from matrix tablets. Data represented as mean ± S.D. (n=6). (♦) F1; (□) F2; (▲) F3.

There was an initial burst release with the HPMC containing formulations. During first hour the release was 44.34%, 41.52%, and 35.23% for batches F1, F2, and F3 respectively. This phenomenon may be attributed to surface erosion or initial disaggregation of the matrix tablet prior to gel layer formation around the tablet core.[24] It is reported in the literature that more than

30% drug release in first hour of dissolution indicates the probability of dose dumping.[25]Therefore to retard the drug release more than 8 hours and to avoid the initial burst release, the tablets (F4, F5, and F6) formulated using combination of hydrophilic HPMC K100M and hydrophobic ethyl cellulose in different ratios.

As indicated in Figure 2, tablets containing both HPMC and EC (F4, F5, and F6) showed less than 30% release (no burst release) in 1 hour, where as more than 30% release (burst release) occurred in batches F1, F2, and F3. Drug release was sustained for 9, 12, and 10 hours for the formulations F4, F5, and F6 respectively. In case of F4 and F5 formulations, the drug release was decreased with an increase in the proportion of EC (94.28% in 9 hours and 97.21% in 12 hours for the formulations F4 and F5 respectively). This is due to the hydrophobic nature of ethyl cellulose seems to have contributed toward reduction in the penetration of the solvent molecules into the matrix. Further in the concentration of HPMC decreases and ethyl cellulose proportion increased, the drug release rate was increased slightly (96.67% in 10 hours) for the formulation F6. This observation can be attributed to poor solubility of EC in the granulating fluid (Isopropyl alcohol) thereby leaving higher proportion of free drug in the formulation that is rapidly released in the initial period of release study. Therefore the formulation F5 (HPMC:EC ratio is 1:1) was optimized as it extended the drug release for 12 hours and exhibited similar drug release pattern as that of theoretical release profile (Figure 3).

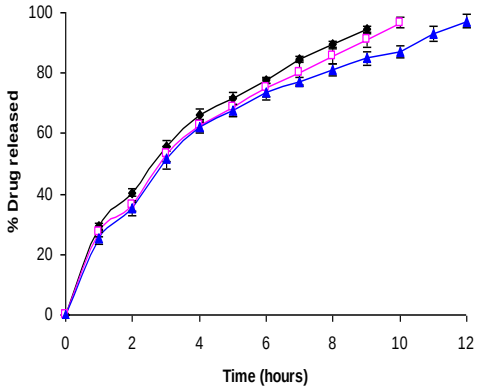

Figure. 2. In vitro drug release profiles showing the effect of Different ratios of combinations of HPMC K100M CR and EC on Timolol maleate release from matrix tablets. Data represented as mean ± S.D. (n=6) (♦) F4; (▲) F5; (□) F6.

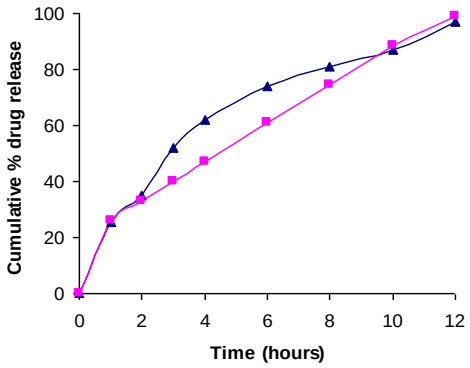

Figure. 3. Comparative in vitro timolol maleate release profile for f_2 test. (■) theoretical release; (▲) F5.

Kinetic analysis of dissolution data

The release rate kinetic data for the optimized formulation is shown in Table 5. Drug release data was best explained by first order equation, as the plots showed the highest linearity (r^2 = 0.9955), followed by Hixson-Crowell (r^2 = 0.9800) and Higuchi's equation (r^2 = 0.9661). As the drug release was best fitted in first order kinetics, indicating that the rate of drug release is concentration dependent. Higuchi's kinetics explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases. The applicability of the formulation to the Hixson –Crowell cube root law indicated a change in surface area and diameter of the tablets with the progressive dissolution of the matrix as a function of time.

Table 5 Drug release kinetics of optimized (F5) matrix tablets[a]

Zero order		First order		Higuchi		Hixson Crowell		Korsmeyer-Peppas		
r^2	K_0 (h^{-1})	r^2	K_1 (h^{-1})	r^2	K_H ($h^{-1/2}$)	r^2	K_{HC} ($h^{-1/3}$)	r^2	n	K_{KP} (h^{-n})
0.8985	5.88	0.9955	0.201	0.9661	27.839	0.9800	0.1997	0.9741	0.66	0.1507

[a] r^2 = Correlation coefficient; K = Kinetic constant; n= Diffusional exponent.

Mechanism of drug release

As shown in Table 5, the corresponding plot (log cumulative percent drug release Vs time) for the Korsemeyer-Peppas equation indicated a good linearity (r^2 = 0.9741). The diffusion exponent n was 0.66, which appears to indicating a coupling of the diffusion and erosion mechanism (Anomalous diffusion) and may indicate that the drug release was controlled by more than one process.

Determination of swelling and eroding behavior

Since the rate of swelling and erosion is related and may affect the mechanism and kinetics of drug release, the penetration of the dissolution medium and the erosion of the hydrated tablets

were determined. The percentage swelling and erosion of optimized tablet was shown in Figures 4 and 5. It can be observed that the matrix tablets underwent both swelling and erosion at the same time. Maximum swelling of tablets was observed in 1 hour, which can be related to the initial release of loading dose. Because of the simultaneous swelling and erosion of matrix tablets, constant release can be obtained from such matrix systems. Constant release in such situations occurs because the increase in diffusional path length due to swelling is compensated by continuous erosion of the matrix.[26]

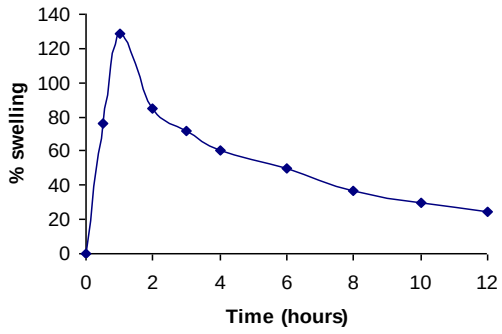

Figure. 4. Swelling behavior of optimized formulation.

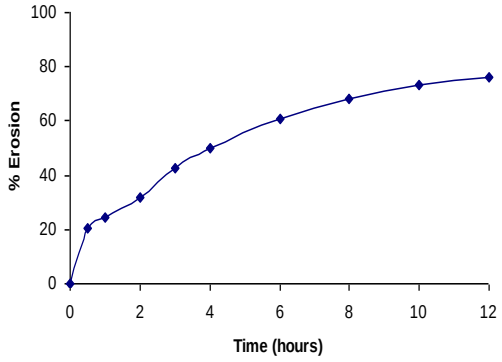

Figure. 5. Eroding behavior of optimized formulation

Similarity factor analysis

Similarity factor analysis between the release profile of optimized tablets and theoretical release showed an f_2 factor (f_2 = 80.18) greater than 50. As shown in Table 6 and Figure 5, the f_2 factor confirms that the release of Timolol maleate from the optimized tablets was similar to that of the theoretical release profile.

Table 6 Similarity factor results

Time (hours)	Average % drug release Reference[a]	Test[b]	f_2 [c] value
0	0.00	0.00	0.00
1	26.16	25.38	99.09
2	33.08	35.09	95.05
3	40.00	51.93	66.77
4	46.92	62.15	61.66
6	60.76	73.88	64.79
8	74.60	81.09	78.84
10	88.44	87.04	97.31
12	99.99	97.21	77.99

[a] Theoretical release.
[b] Optimized formulation (F5).
[c] Average value of f_2 = 80.18.

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of the drug and the optimized formulation were recorded in range of 4000 and 400 cm^{-1} (Figure 6 and 7). 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.

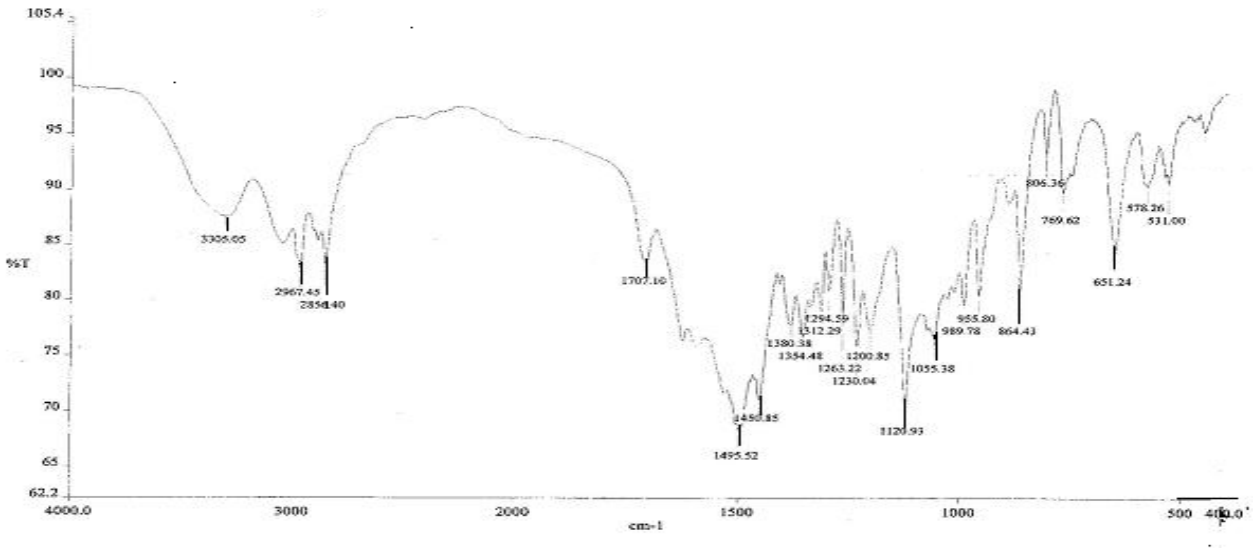

Figure. 6. FTIR spectrum of timolol maleate.

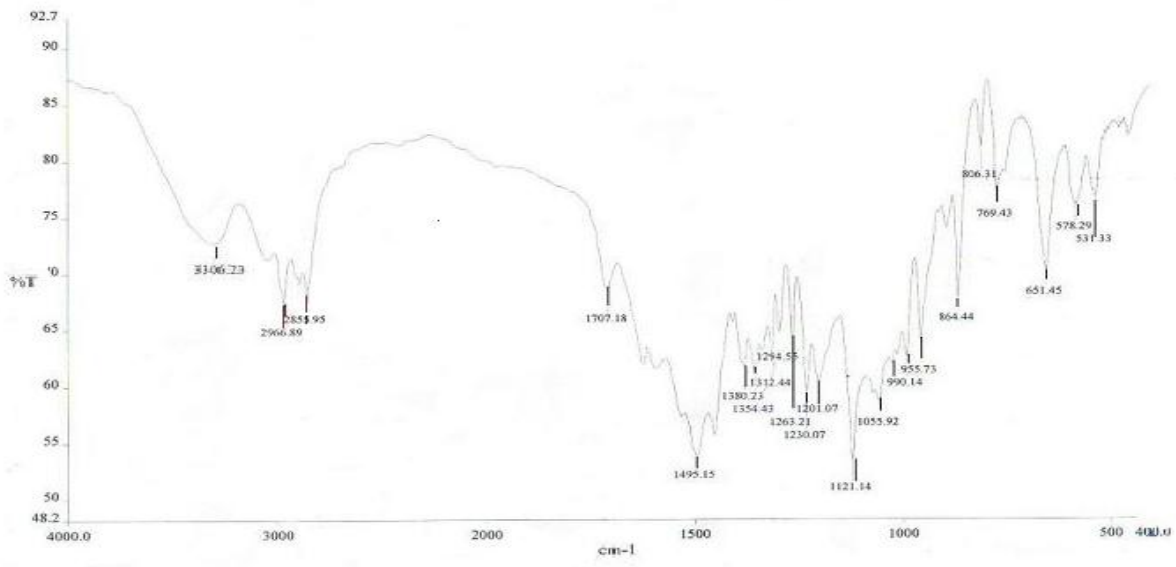

Figure. 7. FTIR spectrum of optimized formulation.

Stability studies

Stability studies of the optimized formulation under accelerated storage conditions as per ICH guidelines did not reveal any degradation of the drug and there was no significant change in the physical properties, drug content, and in vitro release profiles of the optimized formulation after storage for 6 months.

CONCLUSION

Twice daily sustained–release matrix tablet of Timolol maleate was easily prepared using combination of HPMC K100M and EC. Release kinetics indicated that drug release was best explained by first-order equation. The release process involves anomalous diffusion mechanism or diffusion coupled with erosion, as indicated by the n value of 0.66 in Korsmeyer's plot. There was an alteration in the surface area and diameter of the tablets with the progressive dissolution of the matrix as a function of time, as indicated in Hixson-Crowell plot. FTIR and stability studies of the optimized formulation proved the integrity of the developed matrix tablets.

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