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DESIGN AND *IN-VITRO* EVALUATIONS OF SUBLINGUAL TABLETS OF TIMOLOL MALEATE

Pawar Poonam P*[1] and Kalkotwar Ramesh S[1]

[1*]Department of Quality Assurance Techniques, SND College of Pharmacy, Yeola, Nasik (MH), India.

ABSTRACT

The aim of present research was to formulate fast disintegrating sublingual tablets of Timolol maleate for the emergency treatment of hypertension and also to avoid the first-pass metabolism and to improve its bioavailability. The tablets were prepared by direct compression method by utilizing 3^2 factorial design by incorporation of two super-disintegrants croscarmellose sodium and carboxymethyl cellulose sodium. FTIR studies showed compatibility between drug and excipients. The formulations were evaluated for Pre compression and post compression parameters (hardness, thickness, weight variation, wetting time, water absorption ratio, friability, content uniformity, disintegration time, *In-vitro* dissolution and stability studies). Formulation F4 showed disintegration time of 20 seconds and 97.42 % drug release in 12 minutes with super case II transport mechanism and all parameters with significant results. F4 showed stability even after 90 days time period, so it is considered as the best formulation. We successfully developed the sublingual tablets of Timolol male ate.

KEYWORDS

Sublingual, Compatibility, Croscarmellose sodium, Carboxymethyl cellulose sodium, Disintegration time and Drug release.

Author for Correspondence:

Poonam P. Pawar,

Department of Quality Assurance Techniques,

SND College of Pharmacy, Yeola,

Nasik, Maharashtra, India.

Email: poonampawar151@gmail.com

INTRODUCTION

Sublingual drug delivery is alternative approach to the enteral drug delivery. It avoids first pass metabolism in liver and gastric acid hydrolysis of drugs therefore it shows increase in oral bioavailability of drugs. The systemic drug delivery provide immediate onset of pharmacological effects through the sublingual route. Dysphasia (Difficulty in swallowing) is common problem of all age groups or on reduced liquid intake have difficulties in swallowing the solid dosage forms. Sublingual administration of the drug means placement of drug *i.e.* dosage form under the tongue and drug reaches

directly into the systemic circulation[1]. When a chemical comes in contact with mucous membrane beneath the tongue, it diffuse through it because of connective tissue beneath the epithelium contains a profusion of capillaries; the substance then diffuses into them and enters the venous circulation. Drug solutes are rapidly absorbed into reticulated vein which is lies underneath the oral mucosa and transported through the facial veins, internal jugular vein and brachiocephalic vein and then enter in systemic circulation[2,3].

Blood pressure is the force of blood pushing against blood vessel walls. The heart pumps blood into the arteries (blood vessels), which carry the blood throughout the body. High blood pressure, also called hypertension, is dangerous because it makes the heart work harder to pump blood to the body and it contributes to hardening of the arteries or atherosclerosis and the development of heart failure. Hypertension, also referred to as high BP, is a medical condition in which the blood pressure is chronically elevated. There are several categories of blood pressure are -

- Normal: 120/80 mm of Hg.
- Pre-hypertension: 120-139/80-89 mm of Hg.
- Stage 1 hypertension: 140-159/90-99 mm of Hg.
- Stage 2 hypertension: 160 and above/100 and above[4,5].

The drug Timolol maleate (TM) is a non-selective beta-blocker; therefore, it belongs to BCS Class-I (High solubility and High Permeability). It is used in treatment of various heart related disorders like Hypertension and Myocardial infarction. TM is available for both systemic and ophthalmic use. It slows the heart rate and reduces hypertension and prevents the recurrence of myocardial infarction. TM is absorbed about 90% from gastrointestinal track after oral administration and shows 60 % bioavailability. Half-life of TM is 2.5 to 5 hours. Metabolism is primarily hepatic (80%) via the cytochrome P450 2D6 isoenzyme. Shows extensive first pass effect in liver. Timolol and its metabolites are excreted in urine[6,7]. To avoid the first pass effect we developed sublingual tablets.

Sublingual tablets of TM were developed by using super-disintegrats like croscarmellose sodium (CCS), carboxymethyl cellulose sodium (CMCS) and microcrystalline cellulose in combination. The above mentioned disintegrants showed a rapid swelling which is responsible for disintegration[8,9]. We have used three disintegrants in combination because we required a synergistic effect which is not produced by using single disintegrant. Microcrystalline Cellulose (MCC) is also an important ingredient in the development of sublingual tablet because MCC plays important function in the disintegration of tablet. It has good absorbing and wicking properties. It provides passage for disintegrating the fluid into the tablet, leading to the rapid swelling of disintegrant which results in rapid disintegration of a tablet[10].

MATERIAL AND METHODS

Materials

Timolol maleate (TM) was obtained from FDC Ltd., Aurangabad, India. Croscarmellose Sodium (CCS), Carboxymethyl cellulose sodium (CMCS), Microcrystalline Cellulose (MCC) and Mannitol were purchased from Research Lab Fine Chem. Industries, Mumbai, India. Sodium Saccharine and Magnesium stearate were purchased from Vishal Chem., Mumbai, India. Acacia was purchased from Merck Ltd., Mumbai, India. All other chemicals and reagents used were of Analytical grade.

Method

Pre-formulation studies

Organoleptic properties

The sample of Timolol maleate was studied for organoleptic characters such as color, odor and appearance.

Melting point

Melting point of TM was determined by capillary method. TM was dried and introduced into a small dry capillary tube, which was then sealed at one end so as to form a compact column. The capillary was then tied to a thermometer and introduced in the thiele's tube. Heating was then started at the rate of increase in temperature of 3°C per minute. Heating was continued until the substance was melted. At this stage, the thermometer reading was noted[11].

Quantification of Timolol maleate by UV Spectroscopy

Preparation of phosphate buffer pH 6.8

The 28.80 gm of disodium hydrogen phosphate and 11.45 gm of potassium dihydrogen phosphate was dissolved in distilled water in 1000 ml volumetric flask and it is sonicated (Ultrasonic) for 5 min. and the volume was made up to mark[7].

Preparation of standard stock solution

The standard stock solution of 100µg/mL was prepared. For this 10 mg of TM was weighed accurately and is transferred to 100 mL volumetric flask and phosphate buffer pH 6.8 was added to it. TM was dissolved in it by vigorous shaking followed by ultrasonication (Ultrasonic) for about 5 minutes. The volume was made up with the same solvent up to the mark[12].

Preparation of calibration curve for Timolol maleate

For the calibration curve the suitable dilutions was made from the above stock solution of ranges 5, 10, 15, 20, 25 µg/mL and the absorbance of these solutions was taken in photometric mode of Shimadzu UV-1800 at the obtained λ max. The calibration curve of absorbance vs. concentration was plotted.

Fourier transform infrared spectroscopic (FTIR) study of Timolol maleate

The FTIR spectra of TM were recorded using a Fourier Transform Infrared spectrophotometer (Agilent Technologies, carry 630). The dry sample of TM was mixed with IR grade KBr and from this mixture the pellets was prepared in hydraulic press. The spectrum was scanned over a frequency range 4000–650 cm^{-1}. The peaks obtained in the spectra were compared with corresponding functional groups in the structures of TM[13].

Drug-excipients compatibility studies

Interaction of TM with the excipients, which was present in the formulations, was monitored with the help of FTIR (Agilent Technologies, carry 630). The FTIR spectrums of physical mixture of TM: CCS: CMCS: MCC: Acacia powder: Sodium Saccharine: Mannitol: Magnesium stearate in 1:1 proportion respectively was scanned and this obtained spectrum was compared to standard spectra of TM for any possible drug-excipients interaction[13].

Preparation of sublingual tablets of TM

The three disintegrants CCS, CMCS and MCC were used to prepare tablet by direct compression method. A 3^2 factorial design was utilized to analyze effects of the two independent variables (CCS and CMCS) on the disintegration time, in *in-vitro* drug release. All the ingredients were correctly weighed and transferred through a mesh # 80 sieve. Firstly TM, CCS, CMCS, MCC and acacia powder were mixed properly on a butter paper by spatula to make uniformity in powder blend. Afterwards, mannitol and sodium saccharine were mixed geometrically in a mortar and pestle. Finally, Magnesium stearate was added and mixed. The blend was directly compressed to a final tablet weight of 100 mg by using 6 mm flat punch in rotary tablet press (Labpress)[2]. Compositions of various formulations are shown in Table No.1.

Pre-compression evaluations

Bulk density

The weighed amount of powder was transferred to the graduated cylinder with a funnel to calculate bulk density. The bulk density was measured by proportion of the sample weight to the volume occupied and calculated by following formula[14],

Bulk density = Weight of powder ÷ Volume occupied.

Tapped density

The measured quantity of powder was transferred to graduated cylinder. This cylinder was equipped to tap density apparatus (Electrolab, ETD-1020). The cylinder was tapped for 100 times. The tapped density was concluded as the ratio of sample weight to tapped volume measured from cylinder and tap density values was calculated by following formula[14],

Tapped density = Weight of powder ÷ Tapped volume.

Carr's index

The compressibility index determines free flow of powder blend (Carr index) and was calculated by measuring the tap density and bulk density values of powder by following formula[15,16],

Compressibility index = [(Tapped density - Bulk density) ÷ Tapped density] × 100

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[15,16]. It is calculated by formula,

Hausner's ratio = Tapped density ÷ Bulk density

Angle of repose

The angle of repose (Θ) was determined by using funnel method. The blend was poured through funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of heap (r) was measured and angle of repose was calculated using the formula,

$\text{Tan } \Theta = h/r$

i.e. $\Theta = \tan^{-1} (h/r)$

Where, 'Θ' is the angle of repose, 'h' is the height of pile and 'r' is radius of the pile[15,17].

Post-compression evaluations

Hardness test

Tablets require a certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. Tablet hardness was measured by using hardness tester (Veego). It is expressed in Kg/cm^2. From each batch three tablets were measured for the hardness and average of three values was noted along with standard deviations[18,19]. The minimum hardness required was 1.12 Kg/cm^2 for satisfactory sublingual tablet production[13].

Thickness test

Thickness of the tablet is important for uniformity of tablet size. The thickness of tablets was determined by using Varnier caliper (Zoom Classic) for that three tablets from every formulation were used and the results were averaged[20].

Weight variation test

The weight variation test was performed as per Indian Pharmacopoeia. Indian Pharmacopoeia given the limit of weight variation is of 7.5 % for the tablets of 100 mg total weght[7]. Weight variation test was done through a random selection of 20 tablets from each formulation. They were weighed individually by utilizing electronic digital weighing balance (Wensar, PGB 200). The average weight of tablets and their standard deviation were calculated[20].

Wetting time

The tablet was placed at the centre of two layers of tissue paper placed into a petri-dish. After the paper was thoroughly wetted with distilled water, excess water was completely drained out of the dish. The time required for the water to diffuse from the wetted tissue paper throughout the entire tablet was then recorded using a stopwatch[17].

Water absorption ratio

A piece of tissue paper folded twice was placed in a small petri-dish containing 6 ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighed. Water absorption ratio, R was determined using following equation[17],

$R = 100 \times Wa - Wb/Wa$

Where, Wa = Weight of tablet after water absorption; Wb = Weight of tablet before water absorption.

Friability

The friability (*F*) of tablets using 20 tablets as a sample was measured using a Roche Friabilator (Electrolab, EF-1W). Previously weighed tablets were rotated at 25 rpm for 4 minutes. The tablets were taken out, dedusted and reweighted[21]. The percentage friability was calculated from the loss in weight as given in equation below[15]. The weight loss should not more than 1% W/W[17].

$F = 100 \times [1-W_0/W]$

Where, W_0 = Final weight; W = Initial weight

Content uniformity

Five randomly selected tablets from each formulation were crushed into the fine powder. From this powder mixture accurately weighed powder equivalent to 10 mg of TM was added to 100 ml of phosphate solution pH 6.8. From this solution, 1 ml was withdrawn and diluted up to 10 ml in a volumetric flask, and the samples were analyzed UV spectrophotometer (Shimadzu, UV-1800) at wavelength 295.40 nm. The drug concentration was determined from the calibration curve of timolol maleate[22,23].

Disintegration time

Randomly selected six tablets from each formulation were placed individually in each tube of the basket. This basket was positioned to the disintegration test apparatus (Electrolab, ED-2 AL) and the discs were placed on tablets to avoid floating of the tablets. The phosphate buffer pH 6.8 was used as disintegration media and is maintained at a temperature of 37°± 2°C and time taken for the entire tablet to disintegrate completely was taken as disintegration time[17]. For sublingual tablets disintegration time should be less than 3 minutes[24].

***In vitro* drug release/ Dissolution studies**

The *in vitro* drug release study of sublingual tablets was carried out by using United States of Pharmacopoeia (USP) type II dissolution apparatus (Labindia, DS-8000^{+}). Phosphate buffer pH 6.8 of about 900 ml was used as dissolution medium and the release was achieved at 37˚ C ± 0.5˚ C, by maintaining rotation speed of paddle 50 rpm. The 10 ml Samples were withdrawn at predetermined time intervals (3, 6, 9, 12, 15, 18 and 21 minutes) and the volumes were replaced with the fresh dissolution medium. The samples were analyzed by UV spectrophotometer (Shimadzu, UV-1800) at 295.40 nm. The experiment for different formulations (F1-F9) was conducted and cumulative percentage drug release was calculated[25].

Kinetic data analysis

To determine the drug release pattern from the device, the dissolution data were analyzed with different kinetic models like Zero-order kinetic, First order kinetic, Higuchi equation, Hixson-Crowell equation, and Korsmeyer-Peppas equation. The release mechanism was observed by the value of diffusional exponent form Korsmeyer- Peppas model[26,27] (Table No.2).

Stability testing

For the stability testing of Timolol maleate tablets, the stability chamber (Remi, CHM 6S) was used. The Timolol maleate tablets were stored at well closed, light resistant container at 25˚ C ± 2˚ C at 60 ± 5 % RH for 90 days[28,29]. The tablets were tested periodically for appearance, hardness, thickness, disintegration time and dissolution test.

RESULTS AND DISCUSSION

Pre-formulation study

Organoleptic properties

Timolol maleate was found to be white, crystalline, odorless powder.

Melting point

The melting point of Timolol maleate was found to be 198-202˚C. The reported melting point is 202 ± 0.5˚C.

Quantification of Timolol maleate by UV Spectroscopy

The spectrum of TM was taken in phosphate buffer pH 6.8. It shows the maximum absorbance at 295.40 nm. So 295.40 nm was taken as λ max for TM. The graph of absorbance vs. concentration for TM was found to be linear with R^2 0.999. It follows Beer's law (Figure No.1). The results are given in Table No.3.

Fourier transform infrared spectroscopic (FTIR) study of Timolol maleate

The FTIR spectra of pure TM (Figure No.2) showed the peaks at wave numbers (cm-1), corresponding to the functional groups present in the structure of the TM (Table No.4). The FTIR spectrum of TM exhibited characteristic signals. The presence of absorption bands corresponding to the functional groups present in the structure of TM, and the absence of any well-defined unaccountable peak showed a confirmation of the purity of the drug sample.

Drug-excipients compatibility studies

The stability of Timolol maleate in the presence of excipients used in the formulations was observed. The FTIR spectrum of the Timolol maleate was compared with FTIR spectrum of the physical mixture of TM and excipients which did not show any shifting of the functional group of TM (Figure No.3), therefore, there was no possible drug-excipients interaction.

Pre-compression evaluations

Bulk density

The bulk density of all formulations was found in rang of 0.58 to 0.63 g/mL (Table No.5).

Tapped density

The tapped density was found to be in range of 0.62 to 0.69 g/mL (Table No.5).

Carr's index

The Carr's index was found to be in range of 6.34 to 10.09 (Table No.5) and it indicates that the formulation blends have excellent flowing property.

Hausner's ratio

The Hausner's ratio was found to be in range of 1.06 to 1.1 (Table No.5) and it indicates that the formulation blends have excellent flowing property.

Angle of repose

The angle of repose for all nine formulations was determined and it was in range of 28.5 to 30.16˚ (Table No.5). Formulation F1 showed angle of repose 30.16˚ it is indicative of passable flowing property. Remaining formulations showed the good flowing property.

Post-compression evaluations

Hardness test

The hardness of tablets was found to be in the range of 1.86 Kg/cm^2 to 3.06 Kg/cm^2 (Table No.6). The minimum hardness required was 1.12 Kg/cm^2 for satisfactory sublingual tablet production. All formulation batches showed the hardness within the specified limit.

Thickness test

Thickness was determined for all nine formulations separately in triplicates for each formulation. The thickness was found to be in range of 2.52 mm to 2.8 mm (Table No.6).

Weight variation test

Weight variation was found in the range of -0.98 %W/W to 5.71 %W/W (Table No.6). Weight variation was within the limit as per I.P.

Wetting time

Wetting time was found to be in the range of 25 seconds to 37.53 seconds (Table No.6).

Water absorption ratio

Water absorption ratio was found to be in the range of 44.47 % to 69.44 % (Table No.6).

Friability test

The friability was found in the range of 0.54 % W/W to 0.9 % W/W (Table No.6). It was within the specified limit.

Content uniformity

The content uniformity for all the tablet formulations was found in between 97.83 % to 100.83 % of the Timolol maleate (Table No.7).

Disintegration time

Disintegration time was found to be in between 19 seconds to 125 seconds (Table No.7). It was within the specified limit for sublingual tablets.

Dissolution studies

Dissolution studies of all formulations showed the maximum percentage drug release for F4-97.42%, and F7- 95.95% in 12 minutes, F2-95.84%, F3-95.51% and F9-95.51% in 15 minutes, F1-93.34%, and F5- 96.99, F6- 97.20% and F8- 96.68% in 18 minutes time period (Figure No.4). All formulations showed the extended drug release and F8 showed the highest drug release when compared to other formulations. F4 showed maximum drug dissolution within short time period as compared to remaining eight batches.

Kinetic data analysis

The criteria to choose the best model to describe the drug release from the tablet, was the coefficient of determination (R^2). Formulation F2 and F5 followed the zero order kinetic. All remaining formulations showed zero order kinetic. The formulations showed higher R^2 for Higuchi model *i.e.* 0.949 to 0.996 which was indicative of the formulations having diffusion mechanism. The Hixson-Crowell model showed R^2 values in range of 0.898 to 0.979 means the formulations have the property of change in diameter or surface area.

The release mechanism of drug from the tablet depends on the values of "n" in the Korsmeyer-Peppas equation, "n'' is the diffusional exponent. All formulations showed values of "n'' in the range between 1.394-1.769 (Table No.8). This means that\ these formulations followed super case II transport for release of drug[26]. The disintegrants like CCS and CMCS both have the swelling properties, so drug release occurs by diffusion and Swelling with super case II transport mechanism.

Stability studies

The hardness, thickness, disintegration time and dissolution time of the tablets showed no variation in results after 90 days time period, so it is consider as stable (Figure No.5 to 8).

Table No.1: Formulation composition of sublingual tablets of Timolol maleate

S.No	Ingredients (Mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Timolol maleate	10	10	10	10	10	10	10	10	10
2	Croscarmellose sodium	5	5	5	4	4	4	3	3	3
3	Carboxymethyl cellulose sodium	5	4	3	5	4	3	5	4	3
4	Microcrystalline cellulose	10	10	10	10	10	10	10	10	10
5	Magnesium stearate	2	2	2	2	2	2	2	2	2
6	Acacia powder	6	6	6	6	6	6	6	6	6
7	Sodium saccharine	5	5	5	5	5	5	5	5	5
8	Mannitol	57	58	59	58	59	60	59	60	61
9	Total weight	100	100	100	100	100	100	100	100	100

Table No.2: Diffusion exponent and drug release mechanism for cylindrical shape

S.No	Release exponent (n)	Drug transport mechanism
1	0.45	Fickian diffusion
2	>0.45 - < 0.89	Anomalous transport (Non -Fickian transport)
3	0.89	Case II transport
4	> 0.89	Super case II transport

Table No.3: Spectroscopic data for calibration curve of TM

S.No	Concentration (PPM)	Absorbance (at 295.40 nm)
1	0	0
2	5	0.2200
3	10	0.4201
4	15	0.6602
5	20	0.8503
6	25	1.0671

Table No.4: Interpretation of FTIR spectrum of TM

S.No	Wave number (cm^{-1})	Functional groups
1	~3100	O-H stretch
2	2969	N-H stretch
3	2855	C-H stretch
4	1704	C=O stretch
5	1620	N-H bend
6	1588	C=C bend aromatic
7	1493	C=N stretch
8	1452	C-N stretch
9	1231, 1121, 1058	C-O stretch

Table No.5: Pre-compression evaluations

S.No	Batch Code	Bulk density (g/mL)	Tapped density (g/mL)	Carr's index	Hausner's ratio	Angle of repose (˚)
1	F1	0.63±0.0081	0.68±0.005	7.8±0.88	1.07±0.011	30.16±0.51
2	F2	0.62±0.0081	0.69±0.026	10.09±2.08	1.1±0.028	28.63±0.52
3	F3	0.61±0.0057	0.66±0.015	7.47±0.33	1.07±0.015	28.94±1.53
4	F4	0.61±0.0081	0.67±0.026	8.89±2.18	1.08±0.03	29.09±0.24
5	F5	0.59±0.005	0.64±0.01	7.28±0.81	1.07±0.011	28.5±0.92
6	F6	0.59±0	0.63±0.005	7.32±0.84	1.07±0.011	29.95±1.07
7	F7	0.61±0.005	0.66±0.015	9.97±1.58	1.08±0.025	29.53±0.66
8	F8	0.59±0	0.63±0.005	6.34±0	1.06±0.011	29.08±1.54
9	F9	0.58±0.005	0.62±0.015	6.35±1.45	1.06±0.015	29.96±0.99

Table No.6: Results of quality control tests designed for sublingual tablets of TM

S.No	Batch code	Hardness (Kg/cm^2)	Thickness (mm)	Weight variation (%W/W)	Wetting time (Sec.)	Water absorption ratio (%)	Friability (%W/W)
1	F1	1.86±0.115	2.52±0.028	1.33±0.577	25.66±1.154	63.06±6.138	0.54±0.02
2	F2	1.93±0.230	2.53±0.060	5.31±0.185	28.66±1.527	69.44±1.902	0.7±0.028
3	F3	2.13±0.305	2.57±0.023	4±2.6	33.66±3.214	58.1±1.8471	0.85±0.04
4	F4	2.46±0.230	2.64±0.144	5.23±1.350	25±1	62.66±2.516	0.9±0.01
5	F5	2.6±0.2	2.64±0.046	-0.98±3.47	26.66±0.577	59.33±1.154	0.69±0.02
6	F6	2.26±0.115	2.8±0.0115	4.8±0.894	32.33±2.081	49.68±2.490	0.76±0.04
7	F7	2.4±0.2	2.74±0.110	5.71±0.900	33.66±2.081	66.66±1.154	0.8±0.034
8	F8	2.66±0.115	2.8±0.0115	4.2±1.9078	35±1	61.8±3.2993	0.83±0.05
9	F9	3.06±0.230	2.75±0.052	-1.53±3.00	37.53±0.577	44.47±2.832	0.89±0.02

Mean (± S.D.) of three determinants

Table No.7: Results of sublingual tablets of TM

S.No	Batch code	Content uniformity (%)	Disintegration time (Sec.)
1	F1	98.83±0.2886	21±0.5773
2	F2	100.83±0.2081	57±1
3	F3	99.73±1.1503	27±0.5773
4	F4	99.53±0.5507	20±0.5773
5	F5	97.83±0.7371	125±1.1547
6	F6	98.83±0.4041	80±1
7	F7	98.06±0.7505	19±0.5773
8	F8	97.93±0.5507	54±1
9	F9	100.6±0.1732	30±0.5773

Mean (± S.D.) of three determinants

Table No.8: Dissolution kinetics for formulations

S.No	Batch code	Zero order		First order		Higuchi model		Korsmeyer-Peppas model		Hixson-Crowell model	
		R^2	K0	R^2	K1	R^2	KM	R^2	n	R^2	KH
1	F1	0.806	4.764	0.974	-0.064	0.960	23.15	0.805	1.444	0.931	0.149
2	F2	0.972	6.16	0.905	-0.085	0.975	24.66	0.862	1.577	0.970	0.193
3	F3	0.709	5.321	0.958	-0.081	0.925	24.30	0.750	1.542	0.898	0.178
4	F4	0.774	5.791	0.962	-0.124	0.983	28.27	0.803	1.769	0.979	0.257
5	F5	0.931	4.991	0.900	-0.081	0.996	23.00	0.831	1.438	0.931	0.164
6	F6	0.755	4.400	0.947	-0.074	0.949	21.97	0.743	1.394	0.945	0.156
7	F7	0.837	7.309	0.969	-0.110	0.959	24.14	0.802	1.760	0.969	0.240
8	F8	0.823	4.876	0.986	-0.083	0.976	23.64	0.785	1.433	0.977	0.191
9	F9	0.805	5.605	0.978	-0.082	0.974	24.64	0.780	1.555	0.959	0.184

R^2: Correlation coefficient of different models.
K0: Zero-order release rate constant.
K1: First order release rate constant.
KM: Higuchi release rate constant.
KH: Hixson–Crowell release rate constant.
N: Drug release exponents.

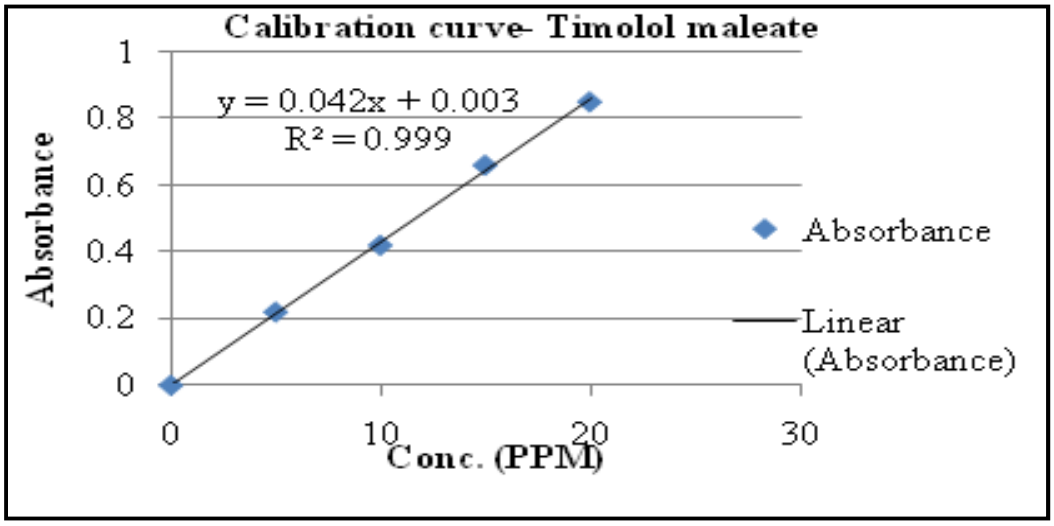

Figure No.1: Calibration curve for Timolol maleate

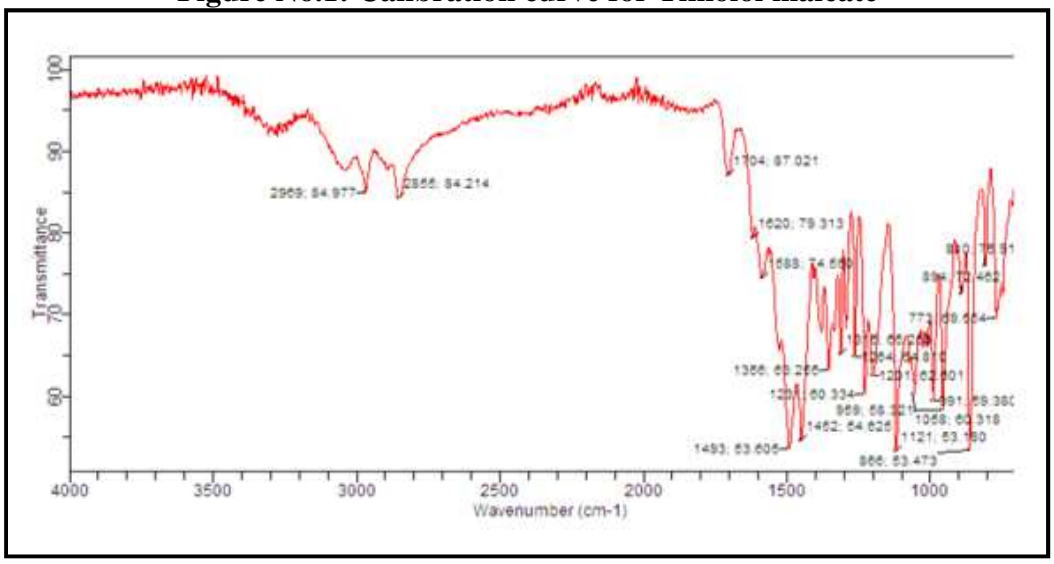

Figure No.2: FTIR spectrum of Timolol maleate

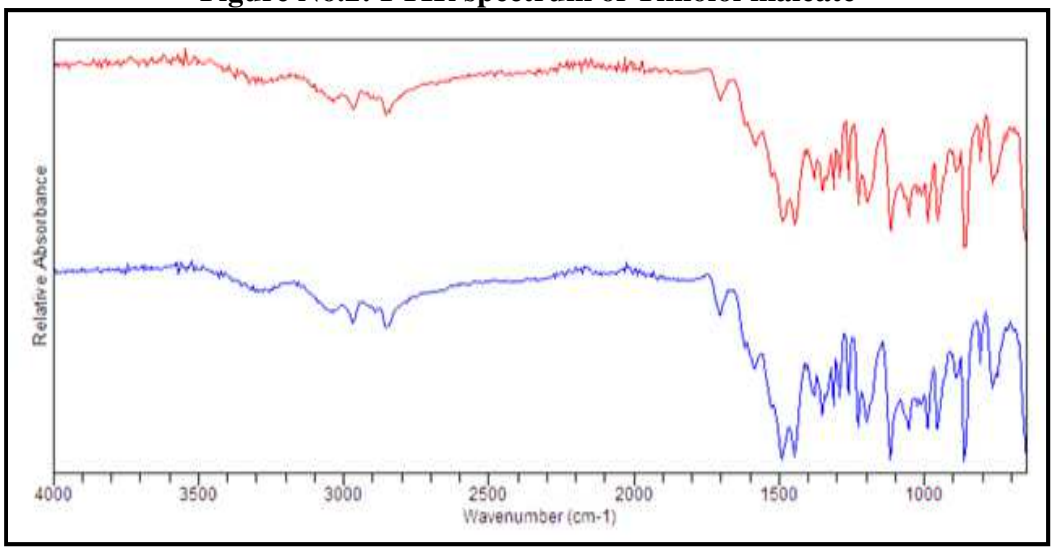

Figure No.3: Compatibility studies of drug with excipients

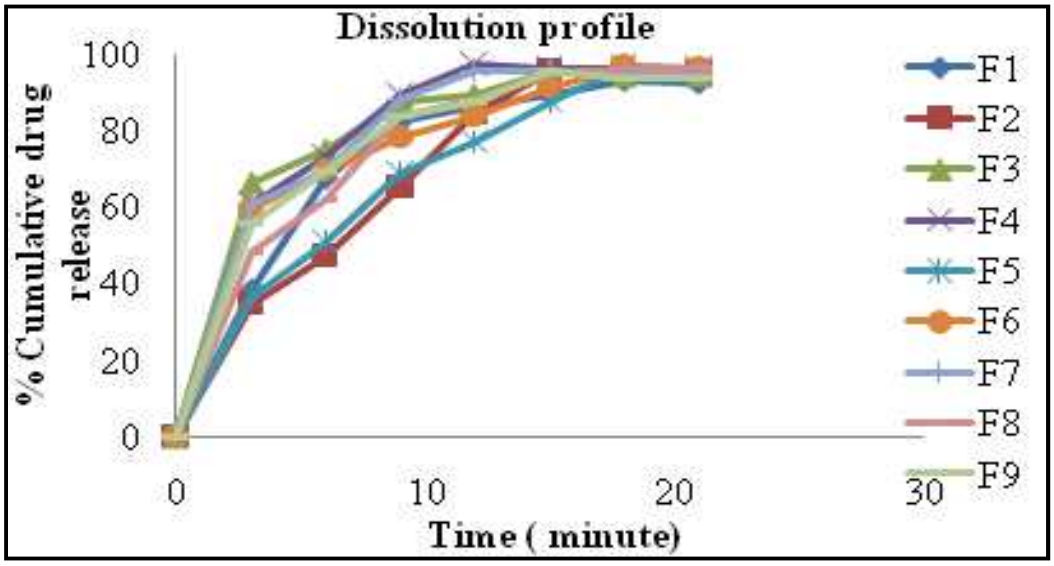

Figure No.4: Dissolution profile for sublingual tablets of TM

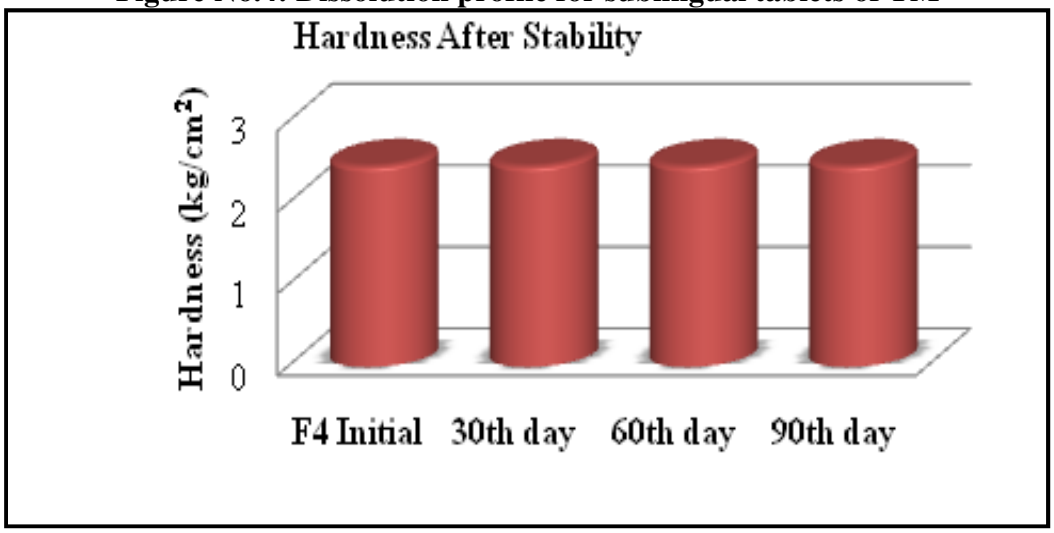

Figure No.5: Comparative hardness of tablets before and after stability test

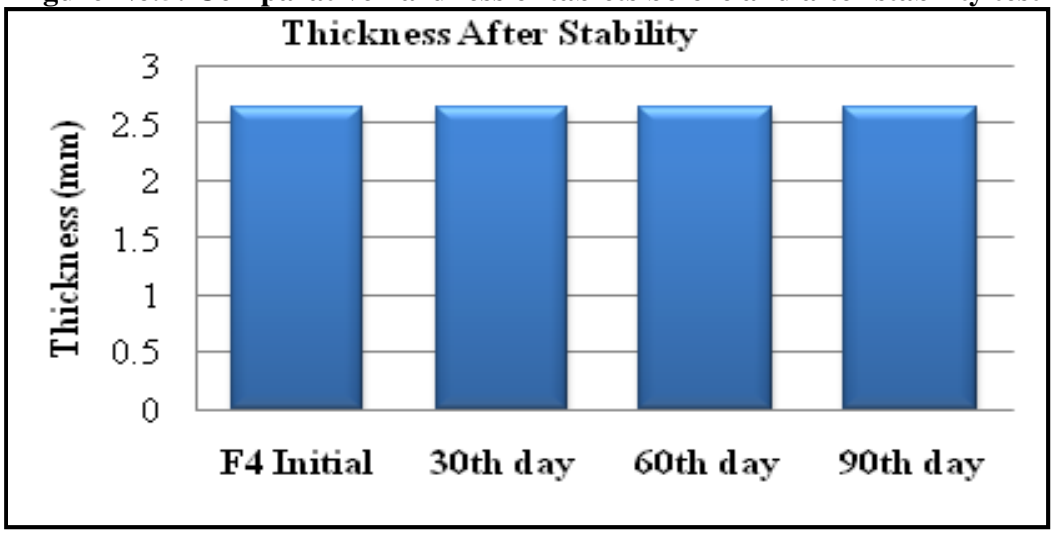

Figure No.6: Comparative thickness of tablets before and after stability test

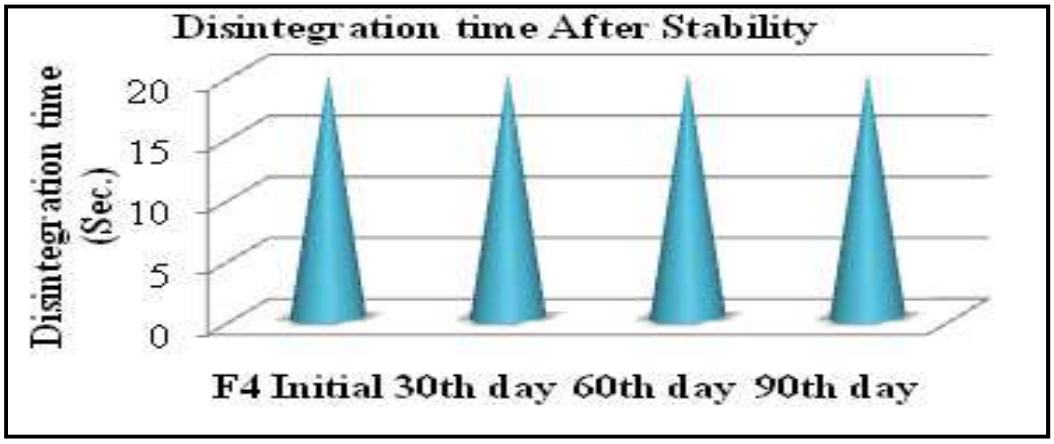

Figure No.7: Comparative disintegration time of tablets before and after stability test

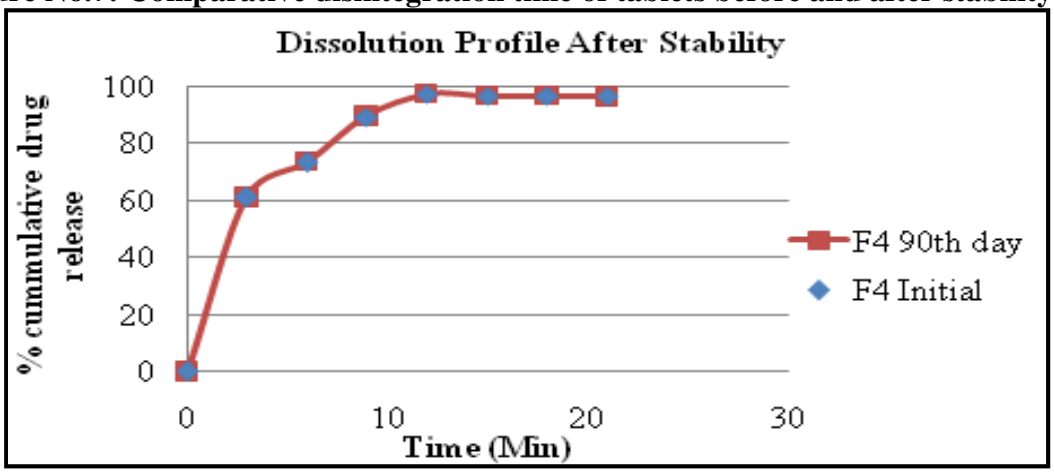

Figure No.8: Comparative dissolution profile of tablets before and after stability test

CONCLUSION

All the tablet formulations showed acceptable pharmacopoeial limit specifications for all parameters. FTIR study revealed drug-excipients compatibility. When formulation of F4 was compared with the remaining formulations for disintegration time, wetting time, % drug release, and content uniformity, it was found to be superior to others because it was disintegrated within 20 seconds and percentage drug release was 97.42 % within 12 minutes. The disintegration time of F7 is 19 seconds which was less than F4 formulation by only one second; but F4 showed drug release of 97.42 % in 12 minutes while in the same time period F7 showed only 95.95 % of drug release. Disintegration time and dissolution rate seems to be the most important parameters for successful sublingual tablet, it was concluded that F4 was the best formulation batch amongst the all formulations.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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