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RESEARCH ARTICLE

Development of Fast Dissolving Films of Timolol Maleate : Role of Hydrophillic Polymer

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ABSTRACT

Timolol maleate is a β- adrenoceptor blocker used in the management of raised blood pressure. The purpose of this research work was to formulate the fast dissolving film of Timolol maleate by solvent casting method for the treatment of hypertension, by using the polymers such as HPC, HPMC E5 and HPMC E15 in different concentration. Poly ethylene glycol 400 was used as plasticizer. Films were subjected for physicochemical characterization evaluation such as thickness, weight uniformity, folding endurance, drug content, surface pH study, *in vitro* drug release, and stability study. Films were found to be satisfactory when evaluated for thickness, weight uniformity, in-vitro drug release, folding endurance, drug content and disintegration time. The surface pH of all the films was found to be neutral pH. The in vitro drug release in optimized formulation F1 was found 98 % in 10 min. The optimized formulation F4 also showed satisfactory pH, drug content (99%), effective in vitro drug release (96.7% in 15 min), disintegration time in 30sec and satisfactory stability.

KEYWORDS

Anti-hypertensive; solvent casting technique; hydrophilic polymer; fast dissolving film

INTRODUCTION

Oral Fast dissolving films (FDF) are gaining interest rapidly in the pharmaceutical industry due to their several advantages, the most important being improved patient compliance especially in pediatric and geriatric population because of their ease of administration[1]. Today FDFs are a proven and accepted technology for the systemic delivery of APIs for over the counter medications and are in the early to mid-development stages for prescription drugs. Literature survey shows that till now these films were used for delivery of drugs meant for immediate action[2]. Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability of patients.

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About 60% of all dosage forms available are the oral solid dosage form. But oral drug delivery systems still need some advancement to be made because of their some drawbacks related to particular class of patients which includes geriatric, pediatric and dysphasic patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take solid preparations due to fear of choking. Even with fast dissolving tablets there is a fear of choking due to its tablet type appearance[3].

Now a days, pharmaceutical companies want to formulate the novel oral dosage form which has the higher bioavailability, quick action and most patient compliance. Fast dissolving drug-delivery systems were first developed in the late 1970s as an alternative to conventional dosage

forms for pediatric and geriatric patients who experience difficulties in swallowing traditional solid-dosage forms[4].

The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oro mucosal and intragastric absorption[5].

Timolol maleate is a first generation β adrenoceptor antagonist and a powerful anti-hypertensive drug with comparatively less oral bioavailability of 50-60% due to hepatic first pass metabolism and has a short life of 1-5 hrs. Timolol maleate is soluble in water; thus making it suitable for administration through sublingual route.

MATERIALS AND METHODS

Timolol maleate was provided by Hetero drugs, Hyderabad. HPC, HPMC E5 and HPMC E15 were purchased from SD Fine Chemicals, Mumbai, India. PEG 4000 was purchased from Qualikems fine chemicals, Vadodara, India and all other materials used in this study were of analytical and pharmaceutical grade.

Methods

Preformulation Studies

Drug -Polymer Compatibility Studies

Drug polymer compatibility studies were carried out by using FTIR. The sample was dispersed in KBr powder and analyzed. A spectrum was obtained by powder diffuse reflectance on a FTIR spectrophotometer type FTIR Bruker.

Method of Preparation of Fast Dissolving Films of Timolol Maleate

Fast dissolving films of Timolol maleate were prepared by solvent casting method. The solution for the fast dissolving films of Timolol maleate was prepared by taking 20ml of dichloro methane: methanol solvent in 1:1 ratio. The polymer was added to the solvent solution and stirred continuously until the polymer was dissolved in the solvent and the solvent was kept aside for 1hr to remove all the air bubbles entrapped. To the above solution drug, plasticizer and sweetener in aspartame were added in specific proportions and stirred until the drug was completely dissolved. The mixture of the solution was casted onto a Petri dish and it was dried in oven at 50°C for 24hr. The film was carefully removed from the Petri dish after drying and checked for any imperfections and cut according to the size required for testing the films (1×1 cm^2). The samples were stored in glass container maintained at a temperature of 30±1°C and relative humidity 60±5°C until further analysis[6,10].

Table 1: Composition of Fast Dissolving Films (in mg)

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Timolol Maleate	5	5	5	5	5	5	5	5	5
HPC	15	20	30	-	-	-	-	-	-
HPMC E5	-	-	-	15	20	30	-	-	-
HPMC E15	-	-	-	-	-	-	15	20	30
PEG 4000	2.25	3	3.5	2.25	3	3.5	2.25	3	3.5
Aspartame	1	1	1	1	1	1	1	1	1
DCM:Methanol(1:1)(ml)	20	20	20	20	20	20	20	20	20

Evaluation of Fast Dissolving Films

Weight Variation

All batches were evaluated for its weight variation. Weight variation is evaluated by using electronic balance.1×1 cm^2 of the film was cut at three different places from the casted film. The weight of each film was taken and weight variation was calculated[7-9].

Thickness

The thickness of the patch was measured using digital vernier caliper with a least count 0.01mm at different spots of the film. The thickness was measured at three different spots of the patch and average was taken and standard deviation was calculated. This is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of dose in the strip[7-9].

Folding Endurance

Folding endurance was determined by repeated folding of the film at the same place till the strip breaks. The number of the times the film is folded without breaking was computed as the folding endurance value. This gives an indication of brittleness of the film[9,11].

Tensile Strength

Tensile strength is the maximum stress applied to a point at which the film specimen breaks and can be calculated by dividing maximum load by the original cross sectional area of the specimen. Tensile strength was conducted using Intron universal testing instrument model f-4026. The film was cut into 30x20mm stripes. Tensile test was performed according to ASTM International Test method for thin plastic sheeting. Each test strip was placed in tensile grip on the texture analyzer. Initial grip separation was 20mm and cross head speed was 1 inch/min. The test was concluded when the film breaks. Tensile strength was computed with the help of load required to break the film and cross sectional area to evaluate tensile strength properties of films[9,11].

Tensile strength=force at break (N)/cross sectional area (mm^2).

Percentage Elongation

For the determination of percentage elongation of the film formulations, the tensile strength testing machine was used to fracture the film. Then the percentage elongation of the film was computed with the help of the formula given below:

$$\text{Percentage elongation} = \frac{Df - D0}{D0} \times 100$$

Where, %E=Percentage elongation. D_o=distance between the tensile grips before the fracture of the film. D_f =distance between the tensile grips after the fracture of the film.

Surface pH

The surface pH of fast dissolving films was determined in order to investigate the possibility of any side effect in vivo. As an acidic or alkaline pH may cause irritation of the oral mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined pH electrode was used for this purpose. Oral films were slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the oral film. The procedure was performed in the triplicate and the average with standard deviation was reported[9].

Disintegration of Films

In vitro disintegration time was determined visually in the Petri dish containing 25ml of pH 6.8 phosphate buffer with swirling every 10sec. The disintegration time is the time when the film start to break or disintegrate. Disintegration time provides an indication about the disintegration characteristics and dissolution characteristics of the film. Time taken by film to break and dissolve was measured as in-vitro disintegration time and in vitro dissolution time[11].

Drug Content Estimation

Drug content determination of the film was carried out by dissolving the film of 1cm^2 in 100ml of pH 6.8 phosphate buffer using magnetic stirrer for 1hr. The drug concentration was then evaluated spectrophotometrically at λ

max of 280 nm. The determination was carried out in triplicate for all the formulations and average with standard deviation was recorded[6].

In Vitro Dissolution Study

Dissolution profile of fast dissolving films of Timolol maleate was carried out using USP type I (basket apparatus). The dissolution was carried out in 500ml of pH 6.8 phosphate buffer maintained at 37±0.5°c at 50 rpm. 10 ml of aliquots of samples were taken at various time intervals which were replaced with same volume of fresh pH phosphate buffer maintained at 37±0.5oc. Timolol maleate in the samples were then determined spectrophotometrically at λ max of 280nm. The results were expressed as mean of six determinations. The percent drug released was plotted against time.

Stability Studies

Stability study was carried out at two different storage conditions. One was normal room conditions and the other was 40ºC/75% RH for 4 weeks. Each piece of films of formulation F4 and F5 was packed in butter paper followed by aluminum foil and plastic tape. After 4 weeks the films were evaluated for physical appearance, surface pH, and drug content[11].

RESULTS AND DISCUSSION

Preformulation Studies

Drug –Polymer Compatibility Studies by FTIR

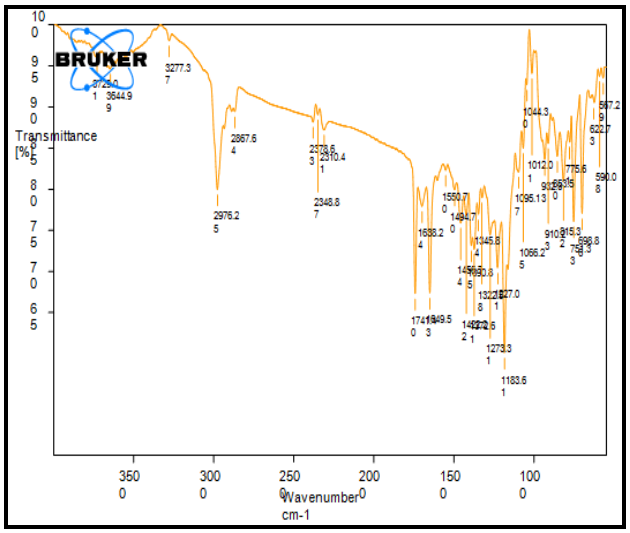

Figure 1: FTIR spectra of pure drug Timolol maleate

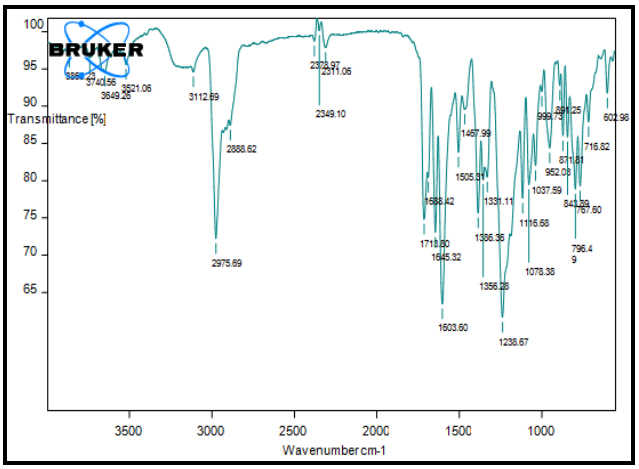

Figure 2: FTIR spectra of the physical mixture of HPMC E5, PEG4000, Timolol maleate and aspartame

Stretching	Normal range Wave number (cm^{-1})	Timolol maleate (pure drug)	Form^{n} with HPMC	Form^{n} F4
C=C	1690-1630	1638	1644	1688
N-H	3500-3300	3339	3341	3421
C-O-C	1300-1000	1251	1297	1116
O-H	3650 & 3400	3615	3668	3649

The IR spectrum of pure Timolol maleate exhibited peaks at 590, 622, 698, 751, 775, 863, 932, 1012, 1066, 1095, 1183, 1273, 1322, 1345, 1422, 1453, 1494, 1550, 1698, 2310, 2348, 2378, 2867, 2976, 3277, 3641, and 3729.

The optimized formulation exhibited peaks at 602, 716, 767, 843, 871, 891, 952, 999, 1037, 1078, 1116, 1238, 1331, 1356, 1386, 1467, 1505, 1603, 1645, 1688, 1713, 2311, 2738, 2888, 2795 and 3112.

From FTIR studies it was observed that the peaks of Timolol maleate were detected and identified in the spectrum of Timolol maleate loaded films confirming that there was no drug excipients interaction.

In Vitro Evaluation of Films

All the fabricated film formulations were smooth and almost transparent with good flexibility. The prepared films were evaluated for all requirements and their results were shown in following tables and figures.

Weight Variation

Three films each of $1cm^2$ were cut at three different places from the casted film and their weight variation was determined. Weight variation varies from 19.00±1.000mg to 36.66±0.577mg. The results for weight variation were shown in table 2.

Thickness

As all the formulations contain different amount of polymers, hence the thickness was gradually increased with the increase in the amount of polymers. All the formulations were found to have thickness in the range of 0.05 mm to 0.18mm.

The results for thickness were given in table 2 and showed gradual increase in the thickness.

Disintegration Time

It was observed that in vitro disintegration time varies from 21 to 46 sec for all the formulations. In vitro disintegration time of FDF's containing HPMC E15 was affected by thickness of the film.

In vitro disintegration time of the films was found to be increased with increase in the amount of polymer. The results were shown in table 2

Surface pH

The surface pH of the films was ranging from6.49 ± 0.021 to 6.81 ± 0.036 shown in the table 2. Since the surface pH of the films was found to be around the neutral pH, there may not be any kind of irritation to the mucosal lining of the oral cavity, therefore more comfortable.

Table 2: Evaluation of physic mechanical parameters of fast dissolving films of Timolol maleate

Formulation Code	Thickness (mm)	Weight Variation (mg)	Surface pH of Film	Disintegration Time (sec)
F1	0.055±0.0047	19.00±1.000	6.49±0.021	21.6±1.527
F2	0.064±0.0041	21.33±0.577	6.58±0.078	23.6±0.577
F3	0.086±0.0047	22.00±1.000	6.63±0.045	26.00±1.000
F4	0.125±0.0045	27.00±1.000	6.81±0.036	30.33±0.577
F5	0.146±0.0057	28.33±0.577	6.77±0.025	31.33±1.527
F6	0.153±0.0057	30.66±0.577	6.74±0.030	34.33±0.577
F7	0.163±0.0047	28.00±1.000	6.72±0.015	36.66±0.577
F8	0.176±0.0055	33.33±0.577	6.79±0.050	40.33±0.577
F9	0.183±0.0057	36.66±0.577	6.73±0.030	46.00±1.000

Each value represents the mean ± SD (n=3)

Table 3: Evaluation of physico- mechanical parameters of fast dissolving films of Timolol maleate

Formulation Code	Tensile Strength (kg/mm^2)	Folding Endurance (No. of Times)	Drug Content (%)
F1	1.43	91.3±5.451	101±0.5%
F2	1.62	92.2±4.453	99±0.5%
F3	1.66	94.5±3.435	100±0.4%
F4	2.95	141.3±6.011	99±0.6%
F5	3.15	145.6±5.372	99±0.5%
F6	3.56	155.5±4.033	100±0.7%
F7	3.61	171.2±2.556	99±0.5%
F8	3.85	177.3±3.589	98±0.6%
F9	4.01	181.2±5.661	99±0.4%

Each value represents the mean ± SD (n=3)

Tensile Strength

A suitable FDF requires moderate tensile strength and folding endurance. Study of the mechanical properties was undertaken for all the formulations. Table 3 shows the comparative mechanical properties of various formulations prepared during the study.

The tensile strength (TS) was found to increase with increase n the concentration of polymer. The tensile strength of formulation F9 was found maximum. The tensile strength testing gives an indication of the strength and elasticity of the film reflected by the parameters, tensile strength (TS) and elongation at break (E/B). A weak and soft polymer is characterized by low TS; as HPC is a soft polymer the formulations containing this polymer exhibited less tensile strength. Hard and brittle polymer shows a moderate TS and low E/B; a soft and tough polymer is characterized by a moderate TS and high E/B whereas a hard and tough polymer shows a high TS and E/B. The tensile strength is the greatest for F9 because of its higher composition of high viscosity polymer. Therefore, such films are tough and strong enough for use.

All the fabricated film formulations prepared were smooth and almost transparent with good flexibility. The results & comparative tensile strength of all formulations were shown in table 3 & Figure 3.

Folding Endurance

The folding endurance of the film increased with the increase in the concentration of the polymers. The number of times the film fold until it broke was given in the table 3. Film formulations from F4 to F9 exhibited good folding endurance, indicating that they are tough and flexible. But formulations F1, F2, F3 containing HPC as polymer showed low folding endurance due to its low viscosity. The results & comparative folding endurance of all formulations were shown in table 3 & Figure 4.

The prepared film formulations were assayed for drug content. It was observed that all the formulations were satisfactory in uniformity of drug as mentioned in table 3 which indicated that there was uniformity of drug content in each film. The drug was present and distributed in each of the assayed film.

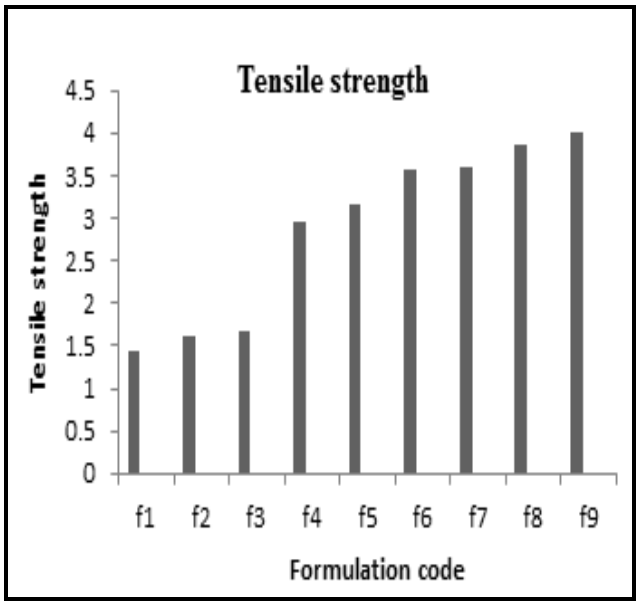

Figure 3: comparative evaluation of tensile strengths of all film formulations

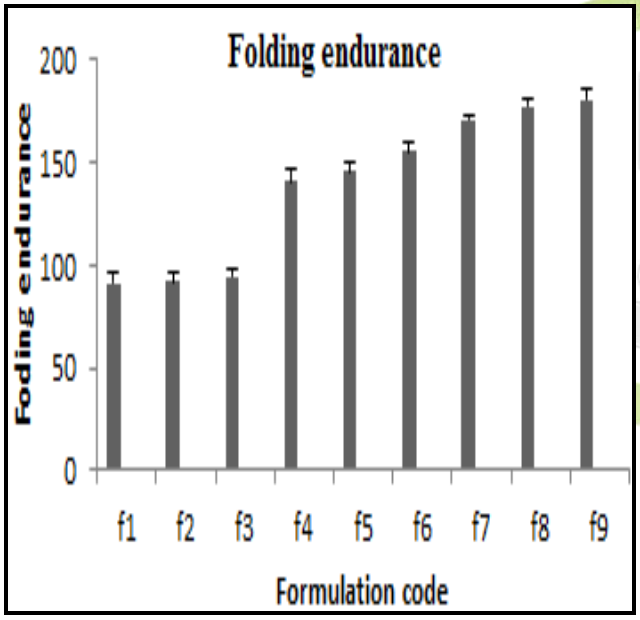

Figure 4: comparative evaluation of folding endurance of all film formulations

In vitro Drug Release Studies

The in vitro drug release profiles of formulations in pH 6.8 phosphate buffer show differences depending on their composition as given in table. A rapid dissolution of all the film preparations was observed by the dissolution test, in which approximately 90% of Timolol maleate was dissolved within 30min. The formulations F1 and F4 showed approximately 90% release within 10min.

Table 4: comparative in vitro dissolution of formulations in pH 6.8 phosphate buffer solution using HPC as polymer. (n=3)

Time (min)	Percent drug release		
	F1	F2	F3
5	66.4±0.893	51.1±0.489	46.2±1.204
10	98.1±1.294	72.9±0.571	60.4±0.030
15	97.7±0.992	97.0±0.623	76.5±0.468
20	97.8±0.537	96.5±0.839	98.9±0.936
30	96.8±0.348	96.7±0.759	96.2±0.773

Each value represents the mean ± SD (n=3)

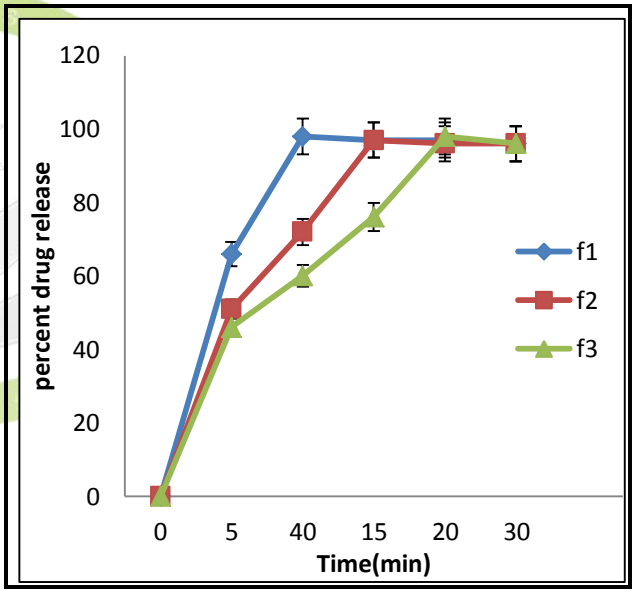

Figure 5: In vitro drug release profile for formulations using HPC as polymer

In vitro drug release studies using the USP Dissolution Test Apparatus Type II revealed that all film formulations with lower polymer concentrations showed more than 80% drug release within 15 minutes with F1 showing maximum release of 98% within 10 minutes. This observation indicates the efficacy of these formulations for rapid drug release. HPC which is a hydrophilic polymer, in contact with the dissolution medium, swell and make a continuous gel layer, erode or undergo

combination of the two. The swelling action of this polymer is controlled by the rate of its hydration in the dissolution medium.

As the film of F1, F2 and F3 formulation possess low physicochemical properties it showed an instant and fast release of the drug at less time. The amount of drug release after 15min decreased gradually because of continuous replacement of the dissolution media with fresh medium at that respective time intervals of sample collection. The results & comparative in vitro drug release of F1-F3 formulations shown in table 4 & Figure 5.

Table 5: comparative in vitro dissolution of formulations in pH 6.8 phosphate buffer solution using HPMC E5 as polymer

Time (min)	Percent drug release		
	F4	F5	F6
5	50.4±0.384	40.8±0.941	40.2±1.054
10	95.6±0.592	69.5±0.553	56.8±0.223
15	98.7±0.837	87.7±0.438	72.0±0.725
20	97.1±1.088	99.9±0.691	94.1±0.269
30	96.6±0.457	97.4±0.285	98.2±0.395

Each value represents the mean ± SD (n=3)

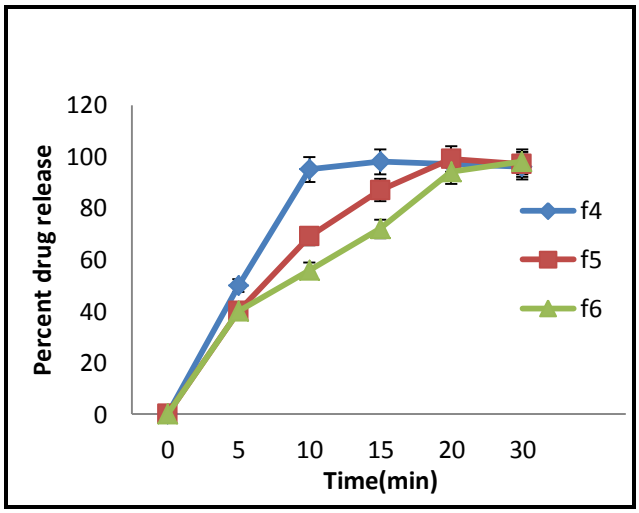

Figure 6: In vitro drug release profile for formulations using HPMC E5 as polymer

HPMC is a hydrophilic polymer frequently used in hydrogel delivery systems. The adjustment of the polymer concentration and the viscosity grade can modify the drug release rate. The drug release mechanism from HPMC polymers which involve water penetration and polymer relaxation to form a viscous rubbery region (gel layer). This gel layer controls drug release by the viscous resistant force to drug diffusion or matrix erosion. Increase in HPMC concentration causes an increase in the viscosity and decreased drug release.

As the viscosity of the polymer increases the rate of drug release from the film decreases. The films of formulations F5 and F6 contain higher concentration of the polymer HPMC E5 the time of drug release from the films was increased gradually from F4 to F5 to F6 formulation. The results & comparative in vitro drug release of F4-F6 formulations shown in table.5& fig.6

Table 6: Comparative in vitro dissolution of formulations in pH 6.8 phosphate buffer solution using HPMC E15 as polymer

Time (min)	Percent drug release		
	F7	F8	F9
5	44.2±1.054	46.6±0.705	40.2±0.847
10	74.8±0.223	56.7±0.552	62.3±1.390
15	88.0±0.725	62.5±0.692	72.9±0.547
20	94.1±0.269	84.3±0.832	78.0±0.684
30	97.2±0.395	97.5±0.480	91.2±2.034

It was also observed that HPMC E15 was able to modulate the Timolol maleate release, as higher amount of HPMC E15 resulted in release of drug at slower rate. The results & comparative in vitro drug release of F4-F6 formulations were shown in Table 6 & Figure 7.

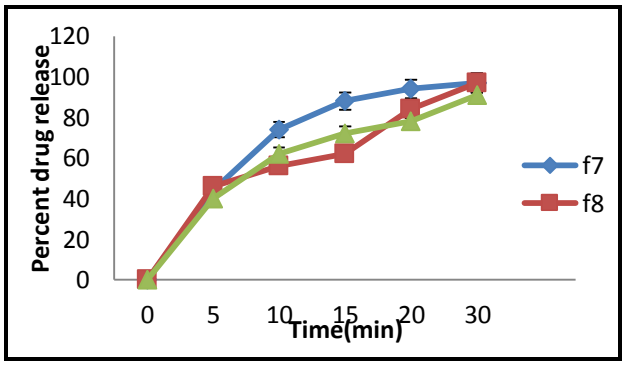

Figure 7: In vitro drug release profile for formulations using HPMC E15 as polymer

Stability Studies

The stability study for formulations F4 and F5 was carried out at normal room conditions and 40^0C/75% RH for a period of one month. The films did not show any change in appearance and flexibility.

The drug content, surface pH, weight and thickness of the films were found almost constant after a period of one month.

The results of F4 & F5 formulations were shown in table 7a & 7b at room temperature and at 40^0C/75 RH respectively.

Table 7a: Stability studies of formulations F4 and F5 at normal room conditions

Parameters	F4		F5	
	Initial	After 4 weeks	Initial	After 4 weeks
Wt. variation	27±1.000	26.66±0.577	28.33±0.577	28.00±1.00
Surface pH	6.81±0.0036	6.8±0.0036	6.77±0.025	6.71±0.057
Thickness	0.125±0.0047	0.125±0.0047	0.146±0.0057	0.146±0.0057
Disinteg. time	30.33±0.577	30.00±1.000	31.33±1.5277	31.2±1.577
Drug content	99±0.6%	98.8±0.57%	99±0.5%	99±0.7%

Table 7b: Stability studies for formulations F4 and F5 at 40^0c/75 RH

Parameters	F4		F5	
	Initial	After 4 weeks	Initial	After 4 weeks
Wt. variation	27±1.000	26.6±0.0577	28.33±0.577	27.00±1.000
Surface pH	6.81±0.0036	6.78±0.0036	6.77±0.025	6.71±0.057
Thickness	0.125±0.0047	0.101±0.0047	0.146±0.0057	0.141±0.0057
Disintig. time	30.33±0.577	29.00±1.000	31.33±1.5277	29.5±1.577
Drug content	99±0.6%	98.88±0.57%	99±0.5%	98.7±0.7%

CONCLUSION

From the results of above study, Timolol maleate oral FDFs, F1, F2 and F3 showed low physico-mechanical properties whereas formulations F4 to F9 were homogenous, slightly opaque and both the sides were found to be smooth and showed acceptable physico-mechanical properties and disintegration time.

From the dissolution data, tensile strength, folding endurance, surface pH study and stability study, it can be concluded that the drug release decreased and slow down with an increase in the concentration of polymers due to the high viscosity of the polymer.. It can therefore be concluded that the most satisfactory formulation F4 met all requirements of an oral FDF dosage form of Timolol maleate.

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