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# PREPARATION AND EVALUATION OF TIMOLOL MALEATE MATRIX TABLET USING HYDROGEL FORMING POLYSACCHARIDES

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## ABSTRACT

Matrix tablets of timolol maleate were prepared using hydrogel forming natural polysaccharides like sodium alginate, xanthan gum and guar gum alone and with hydrophobic polymers like ethyl cellulose and hydroxyethyl cellulose by direct compression method. The Fourier-transform infrared spectroscopy of drug-polymer and polymer-polymer was studied and revealed the compatibility of drug and polymer. All the precompression parameters like angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio for drug polymer mixture were found within limits of pharmacopeial specification. The tablets were studied for post compression parameters like hardness, thickness, weight variation and drug content were in acceptable range of pharmacopeial specification. The tablets were studied for *invitro* swelling index, *invitro* drug release study. The effect of hydrophobic polymers like ethyl cellulose and hydroxy ethyl cellulose were also studied on *invitro* swelling and drug release. The scanning electron micrography was done for selected swellable matrix tablets revealed that the tablets containing guar gum and hydroxy ethyl cellulose (F9) showed compact structure with fewer cracks. All the matrix tablet showed good swelling up to 12 h maintaining integrity of formulation in rank order of xanthan gum> guar gum> sodium alginate. The *invitro* release of timolol maleate from matrix tablet was 80-90% and extended up to 10 to 12 h for xanthan gum, guar gum, sodium alginate alone and in combination with ethyl cellulose and hydroxy ethyl cellulose. The addition of hydrophobic polymer hydroxy ethyl cellulose showed good swelling with prolonged release as compare to ethyl cellulose. The results of *invitro* swelling correlated with *invitro* release. The *invitro* release followed the rank order of xanthan gum> guar gum> sodium alginate. The *invitro* release obeyed first order kinetic with mechanism of release was diffusion control. The similarity factor calculated for selected formulations F9, F8 and F7 containing guar gum, xanthan gum and sodium alginate along with hydroxy ethyl cellulose showed good similarity with theoretical extended release profile. Hence these combinations could be used to prepare extended release timolol maleate matrix tablets having prolonged therapeutic effect.

**INTRODUCTION:** High patient compliance and flexibility in designing dosage forms attracted the oral drug delivery systems to be the most convenient mode of drug administration when compared to other dosage forms. Of these, matrix systems have gained widespread importance in controlled drug delivery due to cost-effective manufacturing technology [1]. The swellable matrices for oral administration are commonly prepared as tablets by compression of hydrophilic micro particulate polymers.

Many natural polysaccharides like chitosan [2], alginate [3], and gums/mucilage like Xanthan [4], gaur gum [5] more sustain the release of drug from matrix system than widely used synthetic materials like methylcellulose, hydroxypropyl methyl cellulose and sodium carboxymethyl cellulose. These natural or synthetic polysaccharides form hydrogel in aqueous media[6]. Over the past few decades, advances in hydrogel technologies have spurred development in many biomedical applications including controlled drug delivery [7].

Hydrogels are very versatile materials and have attracted significant attention recently as drug delivery system. The hydrogels are entangled polymer networks that trap a large amount of water without dissolving. Hydrogels are comprised of cross-linked polymer networks that have a high number of hydrophilic group or domains. These networks have a high affinity for water, but are prevented from dissolving due to the chemical or physical bonds formed between the polymer chains and water penetrates these networks causing swelling, giving the hydrogel its form. The development of hydrogels from a variety of synthetic and natural material has provided a great deal of flexibility in fabricating of modified release system [8].

Biocompatible & biodegradable hydrogels have been designed using natural polymers and various gums due to low toxicity and susceptible to enzymatic degradation or using synthetic polymers that possess hydrolysable moieties [9]. The hydrogels from these natural polymers have been prepared with a variety of different shapes and formulations that include liquid gel, powders, beads, films, tablets, capsules, microspheres and sponge [10].

Timolol Maleate is a non-selective beta-adrenergic receptor blocking agent. It is used as antihypertensive, antiarrhythmic, antiangina, antiglaucoma agent and as anti-migraine. Its biological half life is 2.5-5 h, commercially it is available as tablets in three strengths of 5 mg, 10 mg or 20 mg. Timolol maleate is soluble in water and ethanol [11]. Timolol maleate was reported as matrix tablets [12, 13] using HPMC (hydroxy propylmethyl cellulose) along with EC (ethyl cellulose) and showed that the release prolonged up to 12 h.

In the resent work, matrix tablets of timolol maleate will be prepared by using combination of hydrogel forming polysaccharide of natural and synthetic origin for better management of cardiovascular problems.

**MATERIALS AND METHODS:** The drug timolol maleate was obtained as gift sample and used as supplied by Indiana Ophthalmic, Surendrangar. All other polymers and chemicals obtained were used as supplied by the standard manufacturers.

**Dose calculations and theoretical extended release profile calculation:** The total dose of timolol maleate for twice-daily SR formulation was calculated by Robinson Eriksen equation using available pharmacokinetic data [14].

The zero-order drug release rate constant (K0) was calculated using following equation

$$K0 = DI \times Ke$$

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

$$Ke = 0.693 / t_{1/2}$$

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

Therefore Ke = 0.693 / 4 = 0.1732 mg/h.

Availability rate R = Ke x DI = 0.1732 x 10 = 1.732 mg/h.

Loading dose (DL) = DI – R x $t_{max}$

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

Therefore; DL = 10 - (1.732 x 2) = 6.54 mg

Maintenance dose DM = R x H

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

DM = 1.732 x 11 = 19.05 mg

Total dose required DT = DL + DM = 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 h thereafter and its theoretical release profile was given in Table.

Theoretical release profile of timolol maleate matrix tablets;

| Time (h) | Cumulative % Release |
|---|---|
| 1 | 26.16 |
| 2 | 33.08 |
| 4 | 46.92 |
| 6 | 60.76 |
| 8 | 74.60 |
| 10 | 88.44 |
| 12 | >90 |

**Method of preparation of matrix tablet:** Direct compression method was employed to prepare matrix tablets of timolol maleate using PVP K30 (polyvinyl pyrolidone) as binder. All the ingredients including drug, polymer and excipients were weighed accurately according to the batch formula (**Table 1**). The drug and all the ingredients except lubricants were taken and the ingredients were mixed in the order of ascending weights and blended for 10 min in an inflated polyethylene pouch. After uniform mixing of ingredients, lubricant was added and again mixed for 2 min. The prepared blend of each formulation was pre-compressed by using punch ( 7.1 mm) according to their weight on a single stroke tablet punching machine (Rimek Press Minipress II MT, Ahmedabad) at a pressure of 0.5 ton and turret speed of 2 rpm to form a matrix tablet.

**TABLE 1: FORMULATION OF TIMOLOL MALEATE MATRIX TABLET**

| Ingredients (mg) | Formulation code | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | SA | XAN | GG | SA | XAN | GG | SA | XAN | GG |
| | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** |
| Timolol maleate | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| Sodium alginate | 75 | -- | -- | 56.25 | -- | -- | 56.25 | -- | -- |
| Xanthan | -- | 75 | -- | -- | 56.25 | -- | -- | 56.25 | -- |
| Gaur gum | -- | -- | 75 | -- | -- | 56.25 | -- | -- | 56.25 |
| PVP K30 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Ethyl cellulose | -- | -- | -- | 18.75 | 18.75 | 18.75 | -- | -- | -- |
| HEC | -- | -- | -- | -- | -- | -- | 18.75 | 18.75 | 18.75 |
| MCC (Q.S.) | 34.25 | 34.25 | 34.25 | 34.25 | 34.25 | 34.25 | 34.25 | 34.25 | 34.25 |
| Magnesium stearate | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Talc | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 |
| TOTAL | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 |
| | DRUG:X =1:3 | | | DRUG:EC:X = 1:(1:3) | | | DRUG:HEC:X = 1:(1:3) | | |

Where SA=Sodium alginate, XAN=Xanthan, GG=Gaur gum, EC= Ethyl Cellulose, HEC= Hydroxyethyl Cellulose; X= either SA or XAN or GG

**Polymer drug interaction by FTIR study:** The drug-polymer and polymer-polymer interaction was studied by FTIR spectrometer using Perkin-Elmer (spectrum-100) Japan. Two percent (w/w) of the sample with respect to a potassium bromide disc was mixed with dry potassium bromide. The mixture was ground into a fine powder and then compressed into a disc in hydraulic press. Each disc was scanned 16 times at 2 mm/ sec at a resolution of 4 $cm^{-1}$ using cosine apodization.

**Evaluation of powder blends for recompression parameters (Angle of repose, Carr's index, Hausner's ratio):** The angle of repose of granules was determined by the funnel-method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a manner that the tip of

the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone measured and angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

Where, h and r are the height and radius of the powder cone, θ is the angle of repose. Angle of repose values more than 40 indicates excellent, good poor flow properties. An accurately weighed quantity of the granules/ powder (W) was carefully poured into the graduated cylinder and volume (V0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP model). The density apparatus was set for 100 tabs and after that the volume (Vf) was measured and continued operation till the two consecutive readings were equal. The bulk density and the tapped density were calculated using the following formula.

$$\text{Bulk density} = W/V0$$

$$\text{Tapped density} = W/Vf$$

Where, W = weight of the powder; V0 = initial volume; Vf = final volume

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is.

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

Where, TD is the tapped density and BD is the bulk density. Hausner's ratio is the ratio of tapped density and bulk density. Hausner found that this ratio was related to inter particle friction and as such could be used to predict powder flow properties. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index.

**Evaluation of tablets for post compression parameter (Hardness, Thickness and weight variation):** Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in $Kg/cm^2$. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated. The thickness of three randomly selected tablets from each formulation was determined in mm using a Screw gauge. The weight variation test was performed as per procedure of IP. The weight (mg) of each of 20 individual tablets, selected randomly from each formulation was determined by dusting each tablet off and placing it in an electronic balance. The weight data from the tablets were analyzed for sample mean and percent deviation.

**Drug content [13]:** The drug content of the matrix tablets was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 90% to 110% of the standard amount. Three tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to about 25 mg of TM was transferred to a 50 ml volumetric flask containing 20 ml of 0.1N HCl. It was shaken by mechanical means for 1h.Then it was filtered through a Whatman filter paper (No.1) and diluted to 50 ml with 0.1N HCl. From this resulted solution 1 ml was taken, diluted to 100 ml with 0.1N HCl and absorbance was measured against blank at 295 nm.

***In-vitro* Swelling study:** The swelling index of the matrix tablet was evaluated in 0.1 N HCL for first 2 h and then in phosphate buffer pH 6.8 for 3 to 12 h. The initial weight of the tablet was determined and then tablet was placed in 20 ml 0.1 N HCL in a petridish and then from hour 3 in phosphate buffer 6.8pH was incubated at $37\pm1^oC$. The tablet was removed at different time intervals (1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0 and 12.0 h) blotted with filter paper and reweighed ($W_2$). The swelling index is calculated by the formula:

$$\text{Swelling index} = 100 (W_2-W_1) / W_1$$

Where, $W_1$ = Initial weight of the tablet, $W_2$ = Final weight of tablet.

**Scanning Electron Microscopy:** Electron micrographs of timolol maleate matrix tablets were obtained using a scanning electron microscope (model JSM T200, Joel Ltd., Tokyo, Japan). The specimens were coated under vacuum with gold in an argon atmosphere prior to

observation. The scanning electron microscope was operated at an acceleration voltage of 20 kV.

***In-vitro* Drug Release Study:** The study was carried out in USP XXIII tablet dissolution test apparatus-II (Electrolab TDT-06), employing basket stirrer at 50 rpm and 900 ml of 0.1N HCL for first 2 h and then dissolution medium was changed with fresh phosphate buffer pH 6.8 as dissolution medium for 3 to12 h maintained at 37±0.5°C. At different time interval 5 ml of sample was withdrawn and replaced with fresh medium. The samples were filtered through 0.25 µm membrane filter paper and analyzed for timolol maleate after appropriate dilution at 295 nm using Shimadzu-1700 UV-Visible spectrophotometer.

**Similarity Factor Analysis (*f2*):** To determine the similarity factor, *in-vitro* release profile of all the batches of tablets was compared with the theoretical release profile, which was calculated earlier. If f2 > 50, it is considered that two products share similar drug release behaviors. The data were analyzed by the following formula[15].

$$f2 = 50 \log \{[1+ (1/N) \Sigma (Ri – Ti)^2]^{-0.5} \times 100\}$$

Where, N = number of time points, Ri and Ti = dissolution of reference and test products at time i.

**Data analysis** [16]: The ANOVA (Analysis of variance) was performed for all the variables like concentration of guar gum, xanthan gum, sodium alginate; concentration of secondary polymers like EC (ethyl cellulose) and HEC (hydroxyl ethyl cellulose) on different evaluation parameters like swelling behavior and *in-vitro* drug release. Regressional analysis was performed by using INSTAT software on the *in-vitro* release data to best fit into various kinetic models like zero order, first order, Higuchi, Korsemeyer-Peppas, Hixson-Crowell model according to the regression coefficient '$r^2$' values.

**RESULTS AND DISCUSSION:** Matrix tablets of timolol maleate were prepared by direct compression method using sodium alginate, xanthan gum, and guar gum in varying concentration as a primary polymer in combination with different secondary polymers like EC and HEC. The optimized formulations of timolol maleate matrix tablets are presented in Table 1. The total weight obtained for tablets were 150 mg using micro MCC as filler. The drug-polymer interaction was studied using FTIR spectroscopy for selected combination of drug with different polymers used. The FTIR spectra obtained is illustrated in figure 1. Timolol maleate exhibits a broad hump in its IR spectrum from 3350 $cm^{-1}$to 3250$cm^{-1}$ corresponding to 1° –OH group and 2° –NH group. Peaks at 3046 $cm^{-1}$, 2967 $cm^{-1}$, 2852 $cm^{-1}$, 1707 $cm^{-1}$ corresponding to the –C-H of $–CH_3$group, $–CH_2$ group and -C=N group of the molecule and cyclic –C-O-C- is confirmed at 2362 $cm^{-1}$.

When drug was incorporated with the sodium alginate, xanthan gum and guar gum individually their respective peaks are not disturbed in the observed IR concluding that there was no drug polymer interaction. Further more for the confirmation of the polymer-polymer interaction; when EC and HEC was incorporated with the sodium alginate, xanthan gum and guar gum with drug also showed all the characteristic peaks due to respective polymers revealing the fact that there was no polymer-polymer interaction.

The above observations recommended use of polycyclic molecules because during none of the formulation process drug has not under gone any chemical reaction with polysaccharides used with combination to other polymers like EC and HEC.

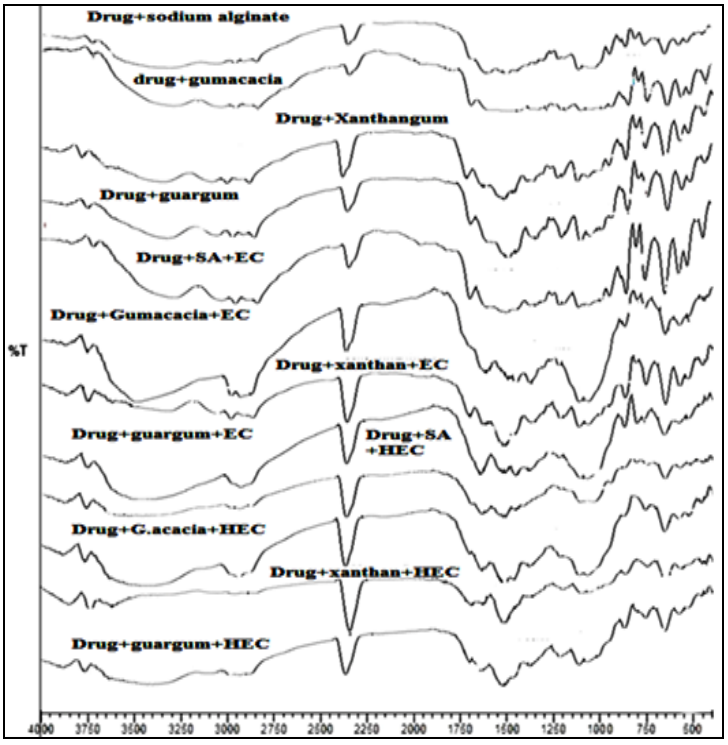


**FIGURE 1: FTIR SPECTRA OF DRUG LOADED MATRIX COMBINATIONS**

Timolol maleate was blended with the polymers and the powder blend was evaluated for pre compression parameter like bulk density, tapped density, Carr's index and Hausner's ratio. The pre compression parameters are depicted in Table 2. All the prepared tablets complies the Indian Pharmacopoeia standard.

**Table 2: Pre compression parameters of timolol maleate loaded powder blend**

| Formulations | Angle of repose | Bulk Density (g/ml) | Tapped Density (g/ml) | Carr's Index (%) | Hausner's ratio |
|---|---|---|---|---|---|
| **F1** | 20.81±0.57 | 0.243±0.12 | 0.285±0.11 | 14.79±0.11 | 1.17±0.03 |
| **F2** | 24.35±0.33 | 0.229±0.19 | 0.298±0.16 | 23.14±0.19 | 1.30±0.07 |
| **F3** | 23.28±0.21 | 0.250±0.21 | 0.288±0.14 | 13.39±0.08 | 1.15±0.09 |
| **F4** | 21.74±0.61 | 0.238±0.21 | 0.297±0.44 | 19.97±0.09 | 1.25±0.03 |
| **F5** | 23.19±0.36 | 0.242±0.11 | 0.296±0.21 | 18.41±0.08 | 1.23±0.08 |
| **F6** | 25.58±0.31 | 0.248±0.09 | 0.298±0.27 | 16.75±0.06 | 1.20±0.04 |
| **F7** | 22.57±0.55 | 0.249±0.15 | 0.288±0.19 | 13.51±0.04 | 1.16±0.05 |
| **F8** | 19.83±0.52 | 0.238±0.32 | 0.294±0.32 | 18.79±0.11 | 1.23±0.02 |
| **F9** | 21.76±0.42 | 0.240±0.17 | 0.286±0.39 | 16.14±0.14 | 1.19±0.06 |

(Mean±SD, n=3)

Timolol maleate powder blend was directly compressed and the obtained tablets were evaluated for post compression parameter like thickness, hardness, friability, weight variation, drug content. The post compression parameters are depicted in Table 3.

**TABLE 3: POST COMPRESSION PARAMETERS OF TIMOLOL MALEATE MATRIX TABLETS**

| Formulation code | Hardness (kg/cm$^2$) (Mean±SD, n=3) | Thickness (mm) (Mean±SD, n=3) | Weight variation (mg) (Mean±SD, n=20) | Drug content (%) (Mean±SD, n=3) |
|---|---|---|---|---|
| **F1** | 5.7±0.06 | 3.41±0.15 | 151.6±0.26 | 101.23±0.10 |
| **F2** | 5.6±0.05 | 3.41±0.13 | 151.8±0.85 | 99.92±0.04 |
| **F3** | 5.9±0.06 | 3.45±0.18 | 151.1±0.04 | 100.45±0.09 |
| **F4** | 5.7±0.05 | 3.42±0.17 | 149.8±0.38 | 101.31±0.11 |
| **F5** | 5.7±0.05 | 3.42±0.15 | 152.0±0.82 | 100.10±0.11 |
| **F6** | 5.7±0.03 | 3.45±0.14 | 150.7±0.43 | 103.40±0.07 |
| **F7** | 5.6±0.03 | 3.48±0.12 | 150.7±0.24 | 100.68±0.06 |
| **F8** | 5.9±0.04 | 3.43±0.15 | 151.1±0.29 | 100.19±0.15 |
| **F9** | 5.8±0.05 | 3.48±0.11 | 151.1±0.14 | 100.03±0.12 |

The hardness of prepared matrix tablets was from 5.7 to 5.9 kg/cm$^2$ and increased due to increasing weight of secondary polymers used. The thickness of the tablets was from 3.41 to 3.48 mm. The drug content was from 99.92 % to 103.40% suggested uniform mixing of drug.

Selected formulations F7, F8 and F9 were characterized by SEM. The surface morphology was shown in **figure 2** from two dimensions as surface (A) and cross section (B). The surface morphology of the F7 showed more intact surface which is having less cracks than F8 and F9 and cross section of the F7 shows more cracks in the SEM analysis than F8 and than F9. Hence here order of the good cross section morphology in terms of cracks in the order of F9 < F8 < F7. Hence, F9 having less crack in cross section leading to less swelling and drug release when compared to F8 and F7.

The swelling study of prepared matrix tablets was performed in 0.1 N HCl for first two h and then from 3 to 12 h in phosphate buffer pH 6.8 and the results are presented as percentage weight change with respect to time in **figure 3 & 4**.

The swelling behaviour of a hydrogel matrix system is an important property for uniform and prolonged release of drug. The swelling behaviour depends upon nature of polymer, concentration of polymer and pH of the medium. The swelling of all the tablets was increased as the time proceeds because the polymer gradually absorbs water due to hydrophilicity of the polymer.

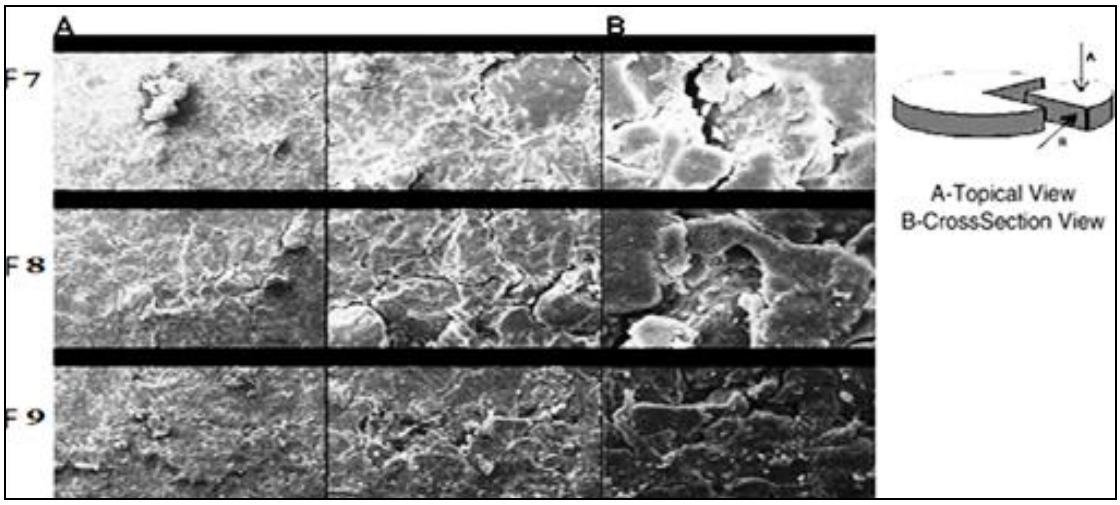


**FIGURE 2: SCANNING ELECTRON MICROGRAPH OF SWELLABLE TIMOLOL MALEATE MATRIX TABLET OF SELECTED FORMULATION F7, F8 AND F9 SHOWING (A) TOPICAL VIEW (B) CROSS SECTION**

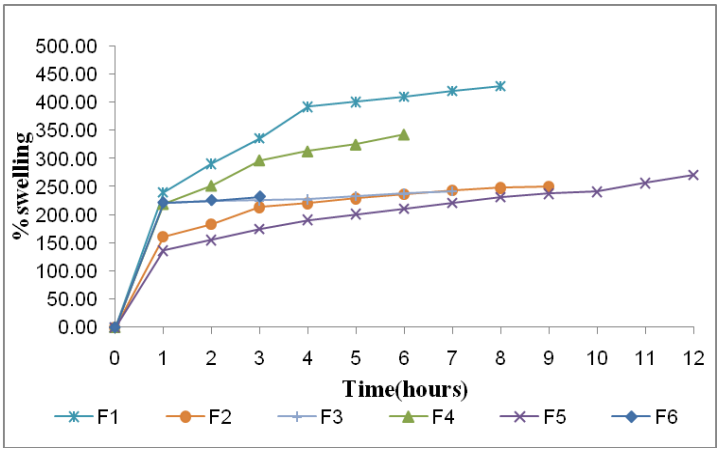


**FIGURE 3: COMPARATIVE *IN-VITRO* SWELLING OF TIMOLOL MALEATE MATRIX TABLETS F1, F2, F3 WITH F4, F5 & F6**

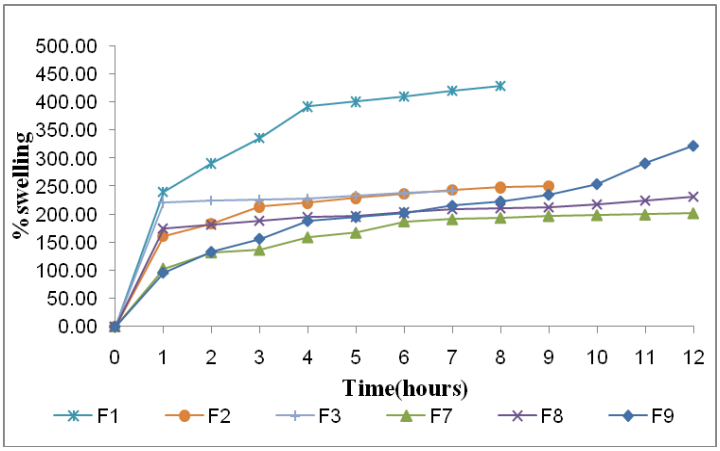


**FIGURE 4: COMPARATIVE *IN-VITRO* SWELLING OF TIMOLOL MALEATE MATRIX TABLETS F1, F2, F3 WITH F7, F8 & F9**

The outermost hydrophilic polymer layer hydrates/swells first and as the hydrated layer progressively dissolves or disperse, the swelling process will continuous towards new expose surfaces thus maintaining the integrity of dosage form. The swelling index was 428.86% for F1 after 8 h which contains sodium alginate with drug in ratio of 1:3. Next polymer used was xanthan gum in combination with the drug in 1:3 ratio in F2 giving 250.74% of swelling up to 9 h which was due to the high swell ability of the xanthan gum. In matrix tablet containing guar gum in F3 as 1:3 ratios showed 242.16% within 8 h. In formulation F4 to F6 combination of primary polymers (like sodium alginate/xanthan/gaur gum) with secondary polymer EC was used.

Here in theses formulations, the water uptake was less giving rapid swelling within 3 to 6 h without maintaining shape of the tablet due to hydrophobic nature of EC which could not take the water. In formulations F7 to F9 the combination of primary polymers with HEC was used. In these formulations the swelling was extended up to 12 h in controlled manner because of water uptake capacity of HEC which give more viscosity along with primary polymer. The overall order of swelling followed the release order according to the hydrophilic polymers as xanthan gum > guar gum > sodium alginate. The addition of HEC results in prolonged swelling as compared to EC.

The *in-vitro* release of timolol maleate was performed in 0.1 N HCL for first two h and then from 3 to 12 h in phosphate buffer pH 6.8. The *in-vitro* release data is illustrated in **figure 5 & 6**. The *in-vitro* release of timolol maleate was mainly affected by drug polymer ratio, nature and amount of polymer and the dissolution medium. The *in-vitro* release of timolol maleate was also depends on swelling behaviour of the polymers used.

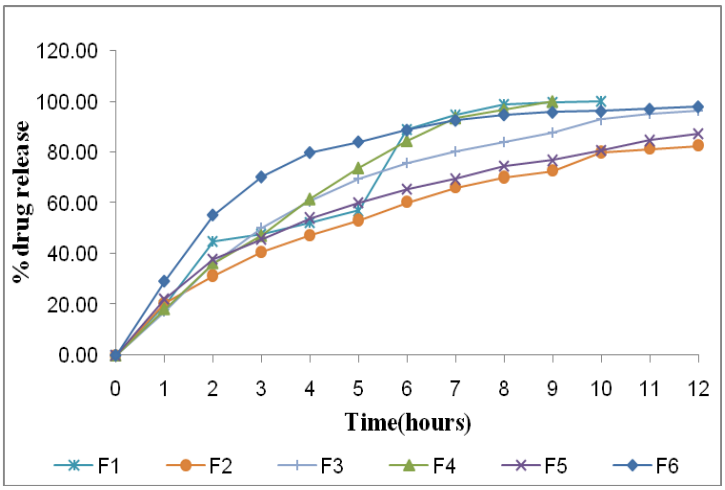


**FIGURE 5: COMPARATIVE *IN-VITRO* RELEASE OF TIMOLOL MALEATE FROM MATRIX TABLETS F1, F2, F3 F4, F5 & F6**

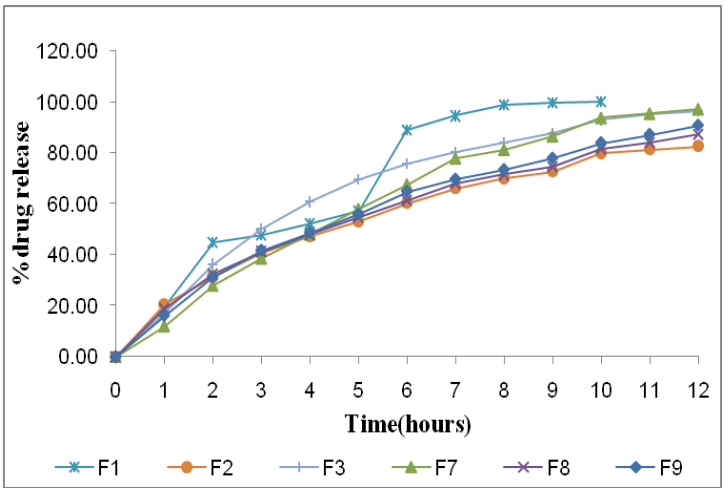


**FIGURE 6: COMPARATIVE *INVITRO* RELEASE OF TIMOLOL MALEATE FROM MATRIX TABLETS F1, F2, F3 F7, F8 & F9**

The matrix tablets containing alone primary polymer as sodium alginate (F1) showed 99.23% release up to 10 h, xanthan gum (F3) showed 82.48% of release up to 12 h and guar gum (F3) showed 96.40% release in 12 h. The natural polymer rapidly hydrated and swelled to form a gel like layer through which water soluble drugs are transported by pore mechanism and also due to formation of soluble erosion matrix [17]. The drug release followed the rank order of using alone polymer as xanthan> guar gum> sodium alginate. The results of *in-vitro* release correlates with the swelling study.

The addition of opposite polymers like EC along with primary polymers in 1:3 ratio (F4 to F6) results in more than 99% of drug release up to 8 h for F4 where as F5 and F6 showed 87.12% and 98.08% release in 12 h. The addition of opposite polymers like HEC along with primary polymers in 1:3 ratio (F7 to F9) prolonged the release of timolol maleate with F7 showed 97.25% release up to 12 h. In F8 containing xanthan gum release was 87.34% and F9 which contains guar gum showed 90.79% up to 12 h. Hence F7, F8 and F9 showed more prolonged the release among the combination of primary polymer with HEC in 3:1 ratio attributed to fact that the presence of HEC prolonged the swelling due to more uptake of water. Hence the addition of HEC resulted in more sustain release as compared to EC.

The *in-vitro* release data was subjected to zero order, first order, Higuchi, Korsemeyer-Peppas and Hixson-Crowell in order to establish the drug release mechanism and kinetics of drug release from the matrix tablets. The Regressional analysis with correlation coefficient '$r^2$' value for different kinetic models is summarized in **Table 4**.

**TABLE 4: REGRESSIONAL ANALYSIS OF THE *IN-VITRO* RELEASE DATA ACCORDING TO VARIOUS RELEASE KINETIC MODELS**

| Formulation code | Zero order | First order | Higuchi | Korsemeyer-Peppas | | Hixson-Crowell | Similarity Factor |
|---|---|---|---|---|---|---|---|
| | $r^2$ | $r^2$ | $r^2$ | $r^2$ | n | $r^2$ | *f2* |
| **F1** | 0.9157 | 0.8745 | 0.9546 | 0.9542 | 0.6859 | 0.9430 | 39.11 |
| **F2** | 0.9281 | 0.9941 | 0.9957 | 0.9962 | 0.5676 | 0.9856 | 55.43 |
| **F3** | 0.8895 | 0.9840 | 0.9800 | 0.9506 | 0.6563 | 0.9930 | 49.93 |
| **F4** | 0.9006 | 0.9453 | 0.9700 | 0.9672 | 0.7072 | 0.9320 | 39.36 |
| **F5** | 0.8960 | 0.9940 | 0.9946 | 0.9839 | 0.5271 | 0.9798 | 58.17 |
| **F6** | 0.7239 | 0.9877 | 0.9168 | 0.8801 | 0.4378 | 0.9280 | 33.35 |
| **F7** | 0.9546 | 0.9527 | 0.9731 | 0.9778 | 0.8221 | 0.9933 | 59.35 |
| **F8** | 0.9375 | 0.9928 | 0.9954 | 0.9936 | 0.5998 | 0.9932 | 60.46 |
| **F9** | 0.9420 | 0.9866 | 0.9909 | 0.9845 | 0.6660 | 0.9959 | 63.93 |

When the data was subjected to zero order and first order kinetic model, a linear relationship was observed with high '$r^2$' value for first order model as compared to zero order model suggested that the release followed first order. Higuchi's model was applied to the *in-vitro* release data, linearity was obtained with high '$r^2$' value suggested that the drug release from tablet followed diffusion mechanism as all the

polymers used were gel based matrix type. When the *in-vitro* release data was subjected to Hixson-Crowell cube root model; good linearity was observed with high '$r^2$' values suggested that the geometrical shape of tablet diminished proportionally over the time due to polymer erosion. In order to define a perfect model which will represent a better fit for the *in-vitro* release data, Korsemeyer-Peppas model was applied which will define exact release mechanism when more than one type of release phenomenon was observed. The value of release exponent 'n' calculated as a slope defines the release mechanism.

Good linearity with high '$r^2$' value was observed with Korsmeyer-Peppas model with value of 'n' obtained was >0.5 and <1.0 suggested that the drug release followed non-Fickian anomalous diffusion due to the higher affinity of hydrophilic polymers towards water. Similarity factor(*f2*) was calculated for all the formulations represented in Table 4 suggested that among 9 formulations; 5 formulations were having similarity factor comparing to theoretical release and found more than 50 value (F2, F5, F7 F8 & F9). For the formulations F3 similarity factor was near to 50 i.e. 49.93, whereas other formulations showed less than 50 value concluding that they do not have similar release as that of theoretical profile.

**CONCLUSION:** Hence, the matrix tablets of timolol maleate can be prepared with hydrogel forming polysaccharides like sodium alginate, xanthan gum, guar gum alone and in combination with HEC to prolonged the release of timolol maleate up to 12 h which showed similar theoretical release profiles may be helpful for the better management of hypertension.

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