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Research Article

# COMPARATIVE ANALYSIS OF OPHTHALMIC GEL FORMING POLYMERS ON THE DRUG RELEASE OF TIMOLOL MALEATE

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**ABSTRACT**

In this research work we have seen the effect of different polymers (Xanthan gum, carbopol, gellan gum) on *in-vitro* release profile of timolol maleate. Ophthalmic drug delivery is the best route of administration for the topical action at the ocular site. The main aim of designing a therapeutic system is to achieve the optimal concentration of a drug entity at the active site for the appropriate duration. Optimum rheological properties of gels increase the contact time by reducing the clearance due to the mucoadhesive property of the polymer used. Mostly gels exhibit pseudoplasticity; they cannot be easily delivered to the eye. The phase transition in the in-situ forming gel preparation can be induced by a pH shift as in case of Xanthan gum and by the presence of the de acetylated gellan gum). From this comparison studies we concluded that xanthan gum in a concentration of 0.4%w/v show the maximum drug release of timolol maleate and other parameters also it shows the best results. Thus, from experimental data, it is clear that the gellan gum and Carbopol can be replaced by xanthan gum polymer in gel forming solution. The viscosity of the formulation is also between the limits and can be tolerable by our eye which is further compared with innovator sample of gellan gum which shows 106cps at 90 RPM.

**Keywords:** Timolol maleate, Gellan gum, Xanthan gum, Benzalkonium Chloride, Carbopol 974P, Mannitol, Glaucoma

## INTRODUCTION

The most common method of the ocular drug delivery is the instillation of drops in to the lower cul-de-sac. Such drops are usually drained quickly, aided by the blinking reflex, the pre corneal region returns to the normal resident volume of around. Glaucoma is the second commonest cause of visual disability in the world. Glaucoma is often called "The sneak thief of sight" because most of the time, it shows no symptoms until there is irreversible vision loss. Glaucoma is a disease with a characteristic of a higher level of intraocular pressure (IOP) which might progressively hurt visibility. The average IOP of population is 15.5 ± 2.57 mmHg. The people, whose intraocular pressure is 20.5 mmHg or more, could be suspected of having glaucoma, and IOP over 24 mmHg were definite case of glaucoma.[1-3]

Glaucoma is characterized by slow progressive degeneration of the retinal ganglion cells (RGCs) and the optic nerve axons, leading to increase in deterioration of the visual field.[3-6] For treatment of glaucoma in this study we use timolol maleate as drug in combination with various different polymers (xanthan gum, gellan gum,carbopol 974P to enhance the bioavailabilty of drug [7-10].Recently, much research has been dedicated to mucoadhesive polymers i.e. macromolecules capable of retaining the medication in the precorneal area not only by viscosity effects, but also by establishing physicochemical interactions with the mucin layer covering the corneal epithelium.

Timolol maleate is non selective β-adrenergic blocker, it competitively blocks stimulation of β -adrenergic receptors in the heart and decreases renin activity which play role in reducing systolic and diastolic blood pressure. Timolol maleate is indicated for treatment of mild to moderate hypertension, reduction of mortality after myocardial infarction (MI), and migraine prophylaxis. β-blocker reduce the production of aqueous humor and reduce the IOP approximately 25%as compared to prostaglandins based on baseline intraocular pressure[11-15].

## MATERIALS AND METHODS

Timolol maleate was obtained as a gift sample from Ven petrochem. Tris buffer (trimethamine), Benzodocenium bromide; Sodium chloride; Mannitol; Xanthan gum Carbopol 974P; Gellan gum; Calcium chloride, potassium chloride, sodium bicarbonate. All the chemicals and reagents required for the present experimental work are of analytical grade.

### Method

Purified water as per solubility parameter of polymer of 60% batch size is taken and polymer is added to dissolve it and kept for stirring (a) and in another beaker (b) 30% water is taken along with timolol maleate and mannitol. After complete dissolution of the drug add tris buffer as pH stabilizing agent. Preservative is added in the preparation after diluting with 2 to 3 ml of purified water. Mix the solution well and make up the final volume of the prepararion. pH of the solution is noted. Sterilization is done by autoclaving for 15 min at 121˚C and then filtered by sartopure 2 PES filter which is combination of 0.2µ and 0.45µ and from using 0.2µ all microorganism of small size cannot filter from it because it is of lowest microorganism size. Eight formulations were prepared with different concentration of different polymers as shown in table 1.

**Table 1: Represents various types of polymers along with its concentration & formulation codes**

| Formulation Code | Polymer type | Polymer Conc.(w/v) |
|---|---|---|
| GF1 | Xanthan gum | 0.4% |
| GF2 | Xanthan gum | 0.5% |
| GF3 | Xanthan gum | 0.6% |
| GF4 | Carbopol | 0.3% |
| GF5 | Carbopol | 0.4% |
| GF6 | Gellan gum | 0.4% |
| GF7 | Gellan gum | 0.5% |
| GF8 | Gellan gum | 0.6% |
| GF9 | Carbopol | 0.5%(Too Viscous) |
| GF10 | Carbopol | 0.6% (Too viscous) |

## EVALUATION PARAMETERS

### *Test for appearance/ clarity*

All the formulations were checked for general appearance i.e. color, clarity, any suspended particulate matter etc. The clarity was checked using wooden board with black and white background. The vials were held horizontally and gently rotated immediately under the lamp and then inverted once or twice to detect foreign particles.

### *pH of the formulation*

The pH of each formulation was recorded using a calibrated digital pH meter. The pH of all formulations was recorded immediately after preparation as well as after 1-2 hours of storage at room temperature [16].

### *Osmolality of the formulations*

Osmolality is the number of osmoles of solute per kilogram of solvent and expressed in terms of osmol/kg or Osmol/kg. It is measured by using osmometer and formulation is first diluted by 2ml to 10 ml and then it is observed by osmometer. It should be in the range of 260-330[17-19].

### *Viscosity of the formulations*

The viscosity determination of prepared formulations was carried out using Brookfield viscometer with spindle S31.Viscosity of samples was measured at different angular velocities (torque). A typical run comprised changing angular velocity from (10-100) rpm with equal rate for each rpm. The rheological parameters of different formulations were studied.[20]

### *Drug content analysis*

20 ppm solutions of different formulation were analyzed using double beam UV spectrophotometer (Shimadzu1800) and drug content was calculated using the formula:

Assay = Absorbance of Sample X concentration of standard / Absorbance of standard X concentration of Sample X 100

### *In vitro release profile study*

In -vitro release of timolol maleate hydrogel formulations was carried out using a glass cylindrical tube (2.5cm in diameter and 6cm in length). The cylindrical tube containing the formulation to be tested was attached to the dissolution apparatus (instead of the basket) and tightly covered with a semi permeable membrane (0.45µm pore size). The cylindrical tube was dipped in a 250 ml simulated tear fluid (pH7.4) and the release study was carried out at 34˚C±0.5, (the temperature of the eye), according to predetermined time regimen, aliquots of 5ml taken and replaced by 5 ml of fresh simulated tear fluid. Timolol maleate concentration was determined spectrophotometrically at $\lambda_{max}$ 295nm.[21-26]

### *Gelling efficiency of selected formulation*

Formulation GF5 gel formation was confirmed by analyzing the difference in the viscosities determined prior and after addition of tears in formulation. For this study, the sample and simulated tear fluid was taken in a ratio of 3:1 (each drop of sample i.e. 30µl-40µl volume of formulation comes to contact with is 10 µl of tear fluid for the study).

**Table 2: Represent various physical parameters of Timolol Maleate Gel**

| Formulation code | Appearance | Initial pH | Osmolality (1%)mosm | Viscosity (CPS) | Drug Amount (Assay) |
|---|---|---|---|---|---|
| GF1 | Clear | 6.95 | 295 | 45.7 | 96.0% |
| GF2 | Clear | 7.01 | 270 | 64.1 | 95.5% |
| GF3 | Clear | 7.01 | 290 | 81.6 | 95.5% |
| GF4 | Clear | 6.99 | 280 | 36.4 | 97.6% |
| GF5 | Clear | 7.02 | 275 | 46.7 | 98.1% |
| GF6 | Clear | 7.01 | 270 | 65.4 | 96.1% |
| GF7 | Clear | 7.00 | 285 | 87.7 | 95.5% |
| GF8 | Clear | 6.99 | 295 | 111.6 | 95.2% |
| GF9 | Not formulated | - | - | - | - |
| GF10 | Not formulated | - | - | - | - |

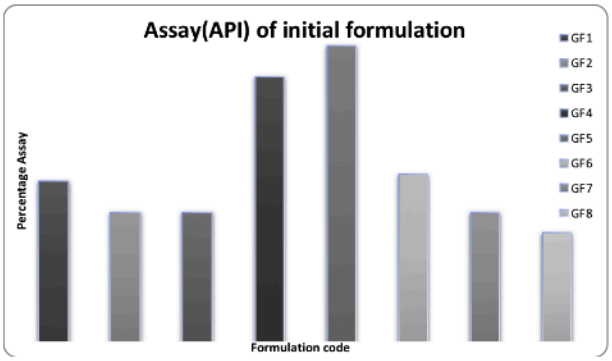


**Figure 1: Percentage purity of all the formulations using various formulation codes**

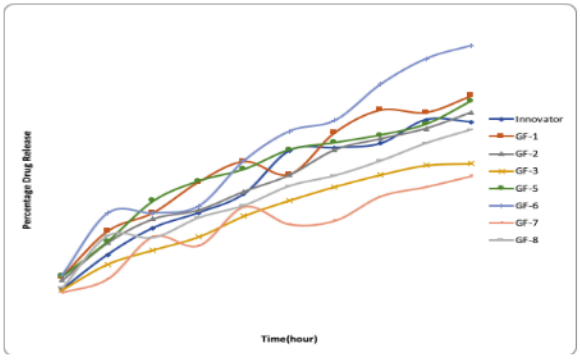


**Figure 2: Comparative percentage drug release of all formulation after 10 hours of study**

## RESULT AND DISCUSSION

### Physical description, pH, Osmolality, viscosity & drug assay

The appearance, pH of preparation after formulation, osmolality viscosity, gelling efficiency and drug content in different formulations was determined and results were given in table 2.

### In vitro release profile study

In-vitro drug release study for all the eight formulations was conducted and drug release profile was prepared (as the formulations using 0.5 %w/v & 0.6% w/v of concentration of Carbopol shows thick lumps which were rejected for further studies). From the in- vitro drug release profile, it was clear that the % drug release decreases as increase in polymers concentration from 0.4%w/v to 0.6%w/v (Gellan gum and Xanthan gum) respectively. The result indicates that by increasing the concentration of polymer, there is increase in viscosity and therefore decreases in percentage drug release. Same result was observed with carbopol in concentration of 0.3%w/v i.e. GF4 and 0.4%w/v i.e. GF5 which showed % drug release 59.3 % and 51.6 % respectively.

As we compare % drug release of formulations GF1, GF5 and GF6 (0.4%w/v of polymers gellan gum, carbopol and Xanthan gum), the release of GF6 shows higher drug release as compare to others. Result obtained clearly showed that the formulation having xanthan gum shows high drug release as compared to other polymers i.e Carbopol & Gellan gum which confirmed using innovator product (Marketed Formulation) was having gellan gum as polymers in same concentration.

### Gelling Efficiency of selected formulation

After performing gelling efficiency test for GF6, we had found that the formulation (having xanthan gum 0.4%w/v) had viscosity 0.6% at 90 RPM initially but it showed enhancement in viscosity i.e. 120.6 at 90 RPM by adding simulated tear fluid. The result of increasing viscosity described good gel formulation which is our target to enhance bioavailability of drug.

## CONCLUSION

From above comparative studies, we concluded that xanthan gum 0.4% w/v concentration shows maximum drug release of timolol maleate. Thus, on this basis GF6 was selected as optimized formulation as all other parameters like pH, viscosity and drug assay (more than 95%) were almost same of all the formulation. Therefore, from the data of all experiment it was concluded that xanthan gum shows the maximum drug release. Hence, we can replace the gellan gum and carbopol by xanthan gum polymer as gel forming solution as its viscosity is also between the limits and having good film forming gel capacity as discussed in the result.

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