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Formulation And Evaluation of Timolol Maleate Loaded Ophthalmic Liposomal Gel

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Abstract

Deploying Ocular drug is one of the most difficult tasks difficult tasks in many existing delivery systems. Liposomes have also been shown to improve drug solubility and distribution control, as well as their ability to modify the surface for targeting, retention, and release. This research is devoted to formulation and evaluation of Timolol Maleate loaded Ophthalmic Liposomal Gel for ocular drug delivery. The formulation was evaluated for evaluation tests and results are mentioned in section 4. *Keywords: Anti-Glaucoma , Liposomal gel compositions, Percent Drug Content , Cumulative Drug Release, Stability Study .

1.INTRODUCTION:[1]

Liposomes have been studied as parenteral drug carriers for many years, but have only been considered for drug delivery, including ophthalmic and dermatological treatments, for about a decade. Based on the above, the Anti-Glaucoma drug incorporated into liposomes meets all the requirements for ophthalmic drug use and drug delivery. Chemically, timolol is (S)-1-(tert-butylamino)-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]Propan-2-ol. Timolol Maleate (Figure 1) is an anti-inflammatory drug with the molecular formula C13H24N4O3S and a molecular weight of 316.42 g/mol (pKa 9.21). Timolol (TML) is a β-adrenergic antagonist with an active L-isomer.

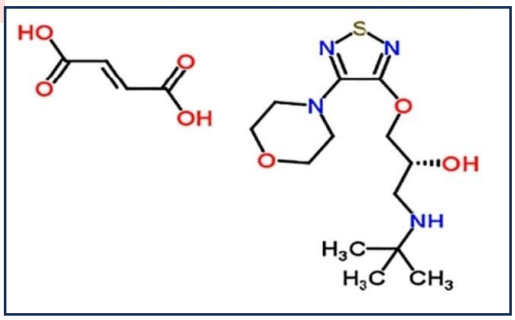


Fig 1: Structure of Timolol Maleate

The Timolol Maleate (TM) Is BCS-1 Class drug so it can used in various novel drug delivery system. TM can be incorporated into, liposomes, niosomes and cubosomes; and found to stable in the incorporation with liposomes and other carriers. The TM is used in treatment of glaucoma as first line treatment to reduce intro ocular pressure in the ocular chamber. It is given in dosage of 0.5 % for eye drops and 10 mg oral a day or twice a day as per disease conditions

2.MATERIALS AND METHODS :

2.1 Materials :

Phospholipid, Cholesterol, Methanol, Chloroform, HPMC K4M, Methyl Paraben, Propyl Paraben, Triethanolamine (TEA), Sterile Water, Dialysis Membrane 5000 Da.

2.2 Instruments :

Rotary Vacuum Evaporator, Digital pH Meter, Lab Stirrer, Franz Diffusion Cell Apparatus, Brookfield Viscometer, UV Spectrophotometer, Magnetic Stirrer.

2.3 Methods :

2,3.1 Standard Calibration Curve of TM :

1 mg of Timolol Maleate was accurately weighed and transferred to 10 ml clean and dry volumetric flask and phosphate buffer pH 7.4 was added in volumetric flask volume was adjusted to 10 ml to give the concentration of 1000µg/ml. from this 1 ml was pipetted out and transferred to another 10 ml clean and dry volumetric flask and volume was adjusted to 10 ml with phosphate buffer pH 7.4 to give the concentration of 100 µg/ml. from this stock solution 1 ml, 2 ml, 3 ml and 4 ml, 5ml ,6ml solution was pipetted out to give the concentration of 10,20,30,40,50, and 60ug/ml. the absorbance was measured at 294 nm and the calibration curve was plot.

2.3.2 Preparation of 0.5 % TM Solution For Liposome Film Hydration :

0.5 % of Timolol Maleate solution was prepared by dissolving 5mg of drug in10 ml of Phosphate buffer prepared from sterile water.

2.3.3 Preparation of Liposome by rotary Vacuum Evaporator Method :

Phospholipid:Cholesterol in 3:2 weight ratios were dissolved in 10 ml of Methanol: Chloroform (1:1) ratio used as solvent. The extract solution was taken in a 500 ml round bottom flask. The flask was rotated in rotary flash evaporator at 150 rpm for 60 min in thermostatically controlled water bath at 40 ^{0}C under vacuum 240 mmHg. The solvent was slowly removed by this process and very thin film of dry liposomes was formed on the flask. The dry lipid film was slowly hydrated with 10 ml of Saline Phosphate Buffer pH 7.4 containing TM. The flask was once again rotated for 2 minutes on Vortex shaker.[8]

2.3.4 Preparation of Ophthalmic Liposomal Gel: [1]

The appropriate amount of HPMC K4M was dissolved in 50 ml of water with help of Lab Stirrer by adding TEA in drop by drop till the transparent gel formed. The 10 ml of gel was taken and homogenised with liposomal suspension by adding few drops of TEA.

Table No.1 Formulation of Ophthalmic Liposomal Gel (OLG)

Sr.No	Components	F1Batch	F2 Batch	F3 Batch
1	Liposomal Suspension (0.5 % TM)	10 ml	10 ml	10 ml
2	HPMC K4M	0.5 %	1 %	1.5 %
3	TEA	Q.S	Q.S	Q.S
4	Methyl Paraben	Q.S	Q.S	Q.S
5	Propyl Paraben	Q.S	Q.S	Q.S
6	Sterile Water	10 ml	10 ml	10 ml

3.Evaluation of Prepared OLG : [9]

3.1 Physical evaluation

The formulations Liposomal gel was evaluated for organoleptic characteristics, occlusiveness.

3.2 Measurement of pH

The pH of the formulated gels was determined using a digital pH meter. The electrode was immersed in the gel and readings were recorded from pH meter.

3.3 Viscosity study

Viscosity measurements were done on Brookfield viscometer by selecting suitable spindle number and rpm. 30 gm of gel preparation was kept in 50 ml beaker, which was set till spindle groove was dipped and rpm was set and reading was measured after five minutes. Viscosity was calculated by using factor. The procedure was repeated three times and observations are recorded as mean.

3.4 Percentage Drug content

Weighed 1 ml of each gel formulation were transferred in 10 ml of the volumetric flask containing 10 ml of Methanol and stirred for 30 min. 0.1 ml of the above solution diluted to 10 ml with alcohol and again, 1 ml of the solution was further diluted to 10 ml with alcohol. absorbance of the solution measured spectrophotometrically at 294 nm.

% Drug Content = Absorbance of Test / Absorbance Standard x 100

3.5 In vitro diffusion studies

The drug release from the formulations was determined by using the Franz diffusion apparatus.1 ml of gel equivalent to 10 mg was spread uniformly on the surface of the dialysis membrane (previously soaked in the medium for 24 h) and was fixed between donor and receptor compartment. The whole assembly was fixed in such a way that the lower end of tube containing gel was just touches (1-2 mm deep) the surface of diffusion medium. 100 ml of pH 7.4 saline phosphate buffer contained in 100 ml beaker is replaced by fresh sample each time when sample withdrawn from receptor chamber, The assembly was placed on thermostatic hot plate with magnetic stirrer and maintained at temperature 37±2 ^{0}C the contents were stirred using magnetic bar at 100 RPM for a period of 3Hr, 1 ml of samples were withdrawn at different time intervals and replace with 1 ml of fresh buffer and after suitable dilution, the sample was analysed at 294 nm.

3.6 Stability study

Stability studies of liposomal suspension and gel were done for 4 weeks under conditions required. Accelerated stability studies were performed by keeping the temperature 40 ±2 ^{0}C and ± 75 % RH. The stability was evaluated by comparing the physical examination, pH measurement, drug content and In vitro diffusion studies.

4.RESULTS AND DISCUSSION

4.1 Physical Evaluation

The prepared Liposomal gel formulation was inspected visually for their colour and appearance. The developed formulations F1, F2, and F3. Were Translucent. All the formulations were free from turbidity.

Table No.2 : Evaluation Of Ophthalmic Liposomal Gel

Sr.No	Batch	Physical Evaluation	pH (SD)	Viscosity(CP)	% Drug Content
1	F1	Good	6.99 ± 0.5	64±0.79	92.05 ±0.84
2	F2	Good	7.03 ± 0.2	74±0.92	95.58± 0.24
3	F3	Good	7.05± 0.9	78 ±0.13	92.22± 0.25

N=3, SD ±

4.2 Measurement of pH

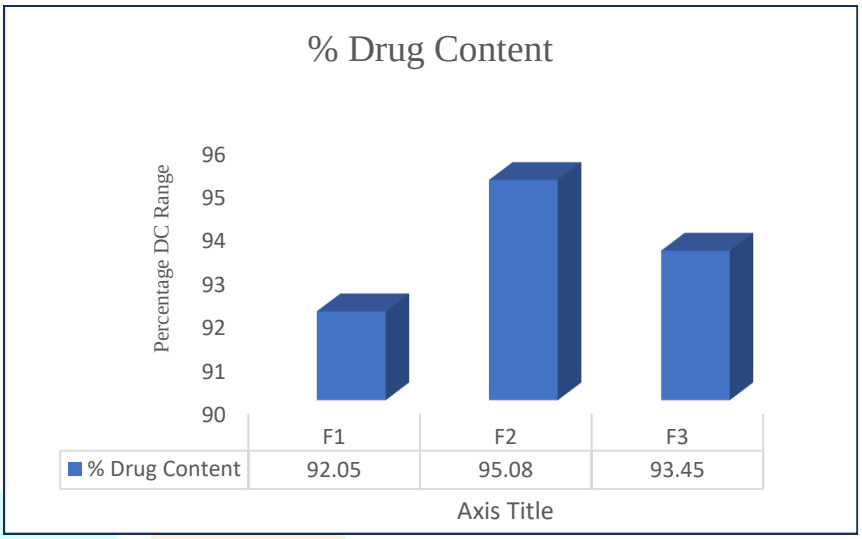
The pH of the formulated gels was determined using a digital pH meter. The electrode was immersed in the gel and readings were recorded from pH meter. The evaluation was triplicate and results were calculated. Results Shown in table No 2.

4.3 Viscosity study

Viscosity measurements were done on Brookfield viscometer by selecting LV1 spindle number and RPM. The evaluation was triplicate and results were calculated. Results Shown in table No 2.

4.4 Percent Drug Content

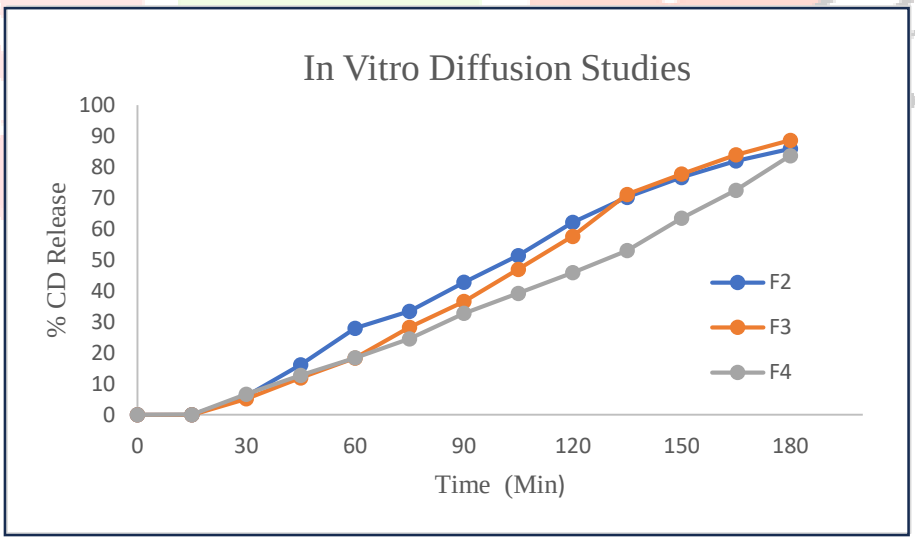
The results for percentage drug contents shown in **Table No.2** and **Graph No1.**



Graph No.1: Percentage Drug Content of Ophthalmic Liposomal Gel Batches

4.5 In vitro diffusion studies

The Ophthalmic Liposomal Gel Formulation **F1, F2** and **F3** shown Cumulative Drug Release **85.93 % , 88.70 % and 83.72%** respectively up to **3 Hr .**



Graph No.2 : In Vitro Diffusion Studies of OLG

4.6 Stability study

Stability studies of liposomal suspension and OLG were done for 4 Weeks under the conditions mentioned in ICH Guidelines. The stability was evaluated by comparing the physical examination, pH measurement, drug content and In vitro diffusion studies. There is no change obtained during the stability study. The Stability study was performed as per section **3.6 .**

5.CONCLUSION

Various formulation (**F1, F2 and F3)** were developed by using a HPMC K4M . Developed formulations of Ophthalmic Liposomal Gel containing **0.5 % Timolol Maleate** evaluated for the physiochemical parameters such as drug content, pH, viscosity, in vitro drug diffusion. Viscosity studies of various formulations revealed that formulation **F2** was better to compare to others. The all the developed formulation, F2 shows **better drug diffusion**, did good Results. pH of the F2 formulation was **compatible with ocular surface**. Thus, Ophthalmic Liposomal Gels can be successfully prepared using **HPMC K4M** as gelling agents suitable for topical application. Hence formulation F2 should be further developed for scale-up to industrial production.

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