



ORIGINAL ARTICLE

# Formulation and evaluation of new long acting metoprolol tartrate ophthalmic gels



Amal El Sayeh F. Abou el Ela <sup>a,b,\*</sup>, Mona Mohamed El Khatib <sup>a,c,\*</sup>

<sup>a</sup> Department of Pharmaceutics, Faculty of Pharmacy, King Saud University, Female Section, El-Malaz, PO Box 2457, Riyadh 11451, Saudi Arabia

<sup>b</sup> Department of Pharmaceutics, Faculty of Pharmacy, Assiut University, 71526 Assiut, Egypt

<sup>c</sup> Department of Pharmaceutics, Faculty of Pharmacy, Cairo University, Cairo, Egypt

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## KEYWORDS

Metoprolol tartrate;  
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IOP

**Abstract** The rationale of the present work is to formulate and evaluate metoprolol tartrate (MT), which is a beta-1 selective adrenergic blocking agent in a new ocular gel delivery system; this is our way and method to increase its contact to the cornea, giving a longer time of drug contact to the eye and slow possible release from the preparation. Metoprolol tartrate is chosen as a candidate for gel formulation because although it has been available for a few years as ophthalmic solutions, it has not been marketed as an ocular gel yet. Two polymers; Carbopol 934 and Pluronic F127 (PF127) were used in two different concentrations in this study. Metoprolol tartrate was used in two concentrations, 0.5% and 1% (w/w). All formulations were exposed to visual examinations, pH measurement, in vitro release, rheological study and differential scanning calorimetry (DSC). Results showed that all formulations were clear, showed pH within the acceptable range suitable to be administered in the eye, and exhibited pseudoplastic flow behavior. DSC results concluded that, MT was compatible with different polymers used. In vitro release results showed that the release rate of metoprolol tartrate from gel preparations decreased as an inverse function of polymer concentration, and the release rate of the drug increased as the initial concentration increased. Intra-ocular pressure (IOP) measurements of rabbit's eye treated with 1% (w/w) metoprolol tartrate in gel formulations with different concentrations of the polymer were determined. Carbopol 934 gel formulations showed that this polymer extended the duration of pressure reducing effect of MT

\* Corresponding authors at: Department of Pharmaceutics, Faculty of Pharmacy, King Saud University, Female Section, El-Malaz, PO Box 2457, Riyadh 11451, Saudi Arabia. Tel.: +966 561460044; fax: +966 12913735.

E-mail address: [aelsaih@ksu.edu.sa](mailto:aelsaih@ksu.edu.sa) (Amal El Sayeh F. Abou el Ela).

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to more than 5hr when compared with Pluronic F127 gel formulations. The area above the curve (AAC), maximum response, time of maximum response ( $t_{max}$ ), and the duration of the drug action were also calculated.

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## 1. Introduction

It is often assumed that drugs administered topically to the eye are rapidly absorbed and are available at a desired site in the globe of the eye to exert their therapeutic effect. Indeed, this is generally not the case. Were this true we would not see drug products containing as much as 5–10% of such systemically active drugs as atropine, homatropine, and pilocarpine. When a quantity of a topical ophthalmic dosage form is applied to the eye, generally to the lower cul-de-sac, several factors immediately begin to affect the availability of the drug contained in that quantity of the dosage forms (Habib and Attia, 1984).

Although many methods of instilling drugs to the eye have been experimented with the use of drops has emerged and still remains the major method of administration for the topical route. Poor bioavailability of drugs from ocular dosage forms is mainly due to tear production, transient residence time, and impermeability of corneal epithelium (Kaur and Kanwar, 2002). Due to these physiological and anatomical constraints only a small amount of drug, effectively 1% or less of the instilled dose, is absorbed ocularly. So far, many attempts have been made to improve ocular bioavailability by extending drug residence time in the conjunctival sac and improve drug penetration across the cornea, the major pathway of drug entry into the internal eye (Kaur and Kanwar, 2002).

Several ways of prolonging the presence of drugs in precorneal area consist of increasing the viscosity of the dosage form by adding a number of viscosity imparting agents such as water soluble or insoluble, natural, synthetic, and semisynthetic polymers (El-Kamel, 2002). Many studies reported that the aqueous-base gels appear to offer several advantages over the other traditional ophthalmic dosage forms, either in terms of improved ocular bioavailability or enhanced therapeutic response (Zaki et al., 2011). Many of the ophthalmic gels investigated to date have been formulated with either Carbopols or Poloxamers. Poloxamers are a class of gel forming polymers that have been evaluated as semisolid vehicles for the ophthalmic use (Ma et al., 2008; Gratieri et al., 2010).

Poloxamer 407 (Pluronic F127) possesses several properties which appear to make it particularly suitable for use in the formulation of ophthalmic dosage forms, including its low toxicity, mucomimetic properties, and optical clarity (Waring and Harris, 1979). Carbopol is a polyacrylic acid polymer, which shows a sol-to-gel transition in aqueous solution as the pH is raised above its pka of about 5.5 and it is widely used in ophthalmology to enhance precorneal retention to the eye (Deshmukh and Gattani, 2013). Moreover, Carbopol exhibits excellent mucoadhesive properties when compared with other polymers.

Metoprolol tartrate, MT (Fig. 1) is a selective beta-1 blocking agent and because of its ability to lower the elevated intraocular pressure (IOP), it is used clinically to treat patients with ocular hypertension or glaucoma, primarily of the open angle type (Luch, 1983). Treatment with metoprolol tartrate as 0.5%,

1%, 2%, 3%, 4%, 5%, and 8% eye drops was clinically studied. It was found that, the IOP was significantly lowered by the drug in all patients throughout the study but a short-lasting reduction in IOP was obtained with 0.5% eye drops. In addition, the concentrations over 1% were less well tolerated (Alm and Wickström, 1980; Kriegelstein, 1981). The Metoprolol eye drops had no effect on the diameter of the pupil of the eye, blood pressure or resting pulse and moreover, the reduction in intraocular pressure and duration of action showed no diminution (Bucheli et al., 1980).

The aim of this work is the formulation and evaluation of a new gel ocular delivery system of metoprolol tartrate using Carbopol 934 and Pluronic F127. The rheological behavior of the studied formulations was carried out. The formulation variables that could affect the release rate and absorption of the drug in the topical formulations, such as the polymer type, concentration of gelling agent, and the initial drug concentration in the formulations were studied. In addition, the in vivo performance of gel formulations of MT was assessed on the basis of the influence of the drug on the intra-ocular pressure of rabbit's eye, and the duration of the pressure reducing effect. The effect of the drug on the pupil diameter of the eye was also visually examined.

## 2. Materials and methods

### 2.1. Materials

Metoprolol tartrate was kindly donated by (Sid. Co., for Pharmaceutical and Chemical Industry, Egypt). Carbopol 934 (CP 934) was purchased from (Goodrich Chemical Company, OH, USA), Pluronic F127 (PF127) was obtained from (BASF Corp., Wyan-dotte, MI). All other chemicals were of analytical grade.

### 2.2. Methods

#### 2.2.1. Preparation of metoprolol tartrate gels

The gel formulations containing two different concentrations of the drug (0.5% and 1% w/w) were prepared according to the polymer used and the composition is shown in Table 1.

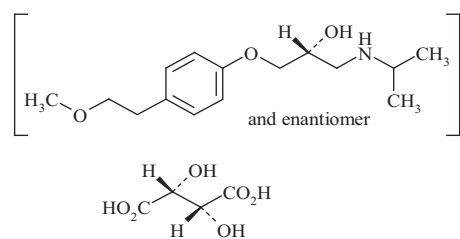


Figure 1 Chemical structure of metoprolol tartrate (Luch, 1983).

**Table 1** Composition of metoprolol tartrate gel formulations % (w/w).

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8
Metoprolol tartrate	0.5	1	0.5	1	0.5	1	0.5	1
Carbopol 934P	1	1	2	2	–	–	–	–
Pluronic F127	–	–	–	–	25	25	30	30
Benzalkonium chloride	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005
Purified water to	100	100	100	100	100	100	100	100

### 2.2.2. Preparation of Pluronic F127 gels

Pluronic F127 gels containing 25% and 30% (w/w) were prepared by the cold method (Schmolka, 1972). The weighed amount of the polymer was slowly added to the water with gentle mixing. The mixture was left in a refrigerator at 4 °C overnight to complete dissolution of the polymer. After the formation of a clear viscous solution, a solution of the drug (0.5% and 1% w/w) in a sterile water was added to the polymer solution and mixed gently using a magnetic stirrer. Drops of a sodium hydroxide solution (0.1 N) were added to adjust the pH of the prepared solutions to 6.8. Benzalkonium chloride (0.005% w/w) as a preservative and sodium chloride to adjust the tonicity were added. The concentration of an isotonicity agent, sodium chloride that rendered the formulations isotonic with the eye fluid was calculated by the sodium chloride equivalent method (Martin, 1993). The solutions were left at room temperature until a clear gel was formed. Gel formulations were prepared one day prior to the use and plain gel was also prepared as a blank for each experiment.

### 2.2.3. Preparation of Carbopol gels

Carbopol 934 gels (1%, 2% w/w) were prepared according to the previously reported method (French et al., 1995). Carbopol was added to the water portion wise with a gentle mixing. After complete addition of the polymer and mixing, the drug solution (0.5% and 1% w/w) was added. Benzalkonium chloride (0.005% w/w) as a preservative and sodium chloride to adjust the tonicity were added. The gel was spontaneously formed by the addition of a triethanolamine.

### 2.2.4. Physical examination

The prepared gel formulations were inspected visually for their appearance (clarity). The pH values of 1% aqueous solutions of the prepared gels were measured by a pH meter (pH mEttler-Toledo GmbH, Switzerland).

### 2.2.5. Differential scanning calorimetry (DSC)

DSC studies were carried out for MT, each of the used polymer and the corresponding physical mixture (1:1) separately in order to determine any incompatibility between the ingredients. Samples of about 5 mg were accurately weighed and encapsulated into flat-bottomed aluminum pans with crimped-on lids (DSC-50, shimadzu Co., Japan). The scanning speed of 10 °C/min from 30 °C to 200 °C was used in the presence of nitrogen at a flow rate of 20 ml/min (Karthikeyan et al., 2010).

### 2.2.6. Rheological studies

The determination of the viscosity of prepared gel formulations was carried out at  $34 \pm 0.5$  °C using a cone and plate viscometer with spindle 52 (Brookfield Engineering Laboratories,

model HADV-II, Middleboro, MA) and connected to a thermostatically controlled circulating water bath (Polyscience, model 9101, Niles, IL). About 0.5 g of the formula to be tested was applied to the plate and left for equilibrium. The shear rate was increased from 100 to 500 s<sup>-1</sup> for Carbopol gels and from 10 to 100 s<sup>-1</sup> for Pluronic F127 gels with 120 s between each 2 successive speeds. The viscosity was determined from the flow curve obtained at different values of the shear rate. All measurements were made in duplicate.

### 2.2.7. In vitro release studies

In vitro release of metoprolol tartrate from different gel formulations was carried out in 100 ml of phosphate buffered solution of pH 6.8 at  $37 \pm 0.5$  °C at 50 rpm using the dialysis method. A semipermeable standard cellophane membrane (molecular cut of 12,000, Sigma Chem. Co., USA) was stretched over the open end of a dialysis cell (2.5 cm diameter and 10 cm in length). One gram of different gel formulations was placed in the dialysis cell, which was suspended so that the membrane was just below the surface of the buffered solution. Samples of 5 ml each were withdrawn from the beaker content at different time intervals, and measured using a UV spectrophotometer (Shimadzu, UV-150-02, Japan) at 275 nm against a blank similarly treated (Ramana et al., 2007). The removed samples were replaced by equal volumes of the phosphate buffered solution. Each of the in vitro release tests was repeated three times.

### 2.2.8. Kinetic analysis of the release data

In vitro release data were analyzed using the equation proposed by Korsmeyer (Abou el Ela et al., 2013):

$$M_t/M_\infty = kt^n$$

where  $M_t/M_\infty$  is the fractional amount of the drug released from the formulation at time  $t$ ,  $k$  is the release rate constant and  $n$  is the diffusion exponent that characterizes the type of the release mechanism during the release process. The values of  $n$  and  $k$  were estimated by the linear regression of  $\log(M_t/M_\infty)$  versus  $\log t$ .

### 2.2.9. In vivo study design and data treatment

Three adult male albino rabbits of weight ranging from 1.5 to 2.0 kg were used in this study. During experiments the test animals were kept in individual cages with free access to food and water. One week at least elapsed between tests in the same rabbit. It was established that this period of time ensured the absence of any carry-over effect or contribution to the observed pharmacological response. Isotonic xylocaine solution (2% v/v) was dropped into rabbits' eyes to anaesthetize the cornea. It was proved experimentally that xylocaine had no effect on the pupil diameter or IOP of the eye. Ophthalmic gel formulations were applied into the right eye, while the left

eye was used as a control. During applications, the rabbit was placed in the supine position, the upper eyelid was slightly raised and the lower eyelid was gently pulled away, thus allowing the drug to be in contact with the eye ball taking care not to exert pressure on the globe with the investigating fingers. In all cases topical doses of 0.1 g each were instilled in the lower conjunctival sac of the eye. The eyelids were held closed for 30–45 s following instillation. After administration of the test formulation, the IOP of both eyes, starting with the right eye, was measured every one hr for 5 h using a Schiøtz tonometer (Riester, Germany). The pupil diameters were also measured visually using Haab's pupillometer. At least three individual successive measurements were made at each time point and the mean was calculated. Four parameters have been utilized to assess the *in vivo* performance of MT, which are the area above the intraocular pressure–time curve (AAC), the maximum response (MR) to the drug in terms of IOP, the time of the maximum response ( $t_{max}$ ) and the duration of the drug action (DA).

#### 2.2.10. Statistical analysis

The results were presented as mean  $\pm$  SD. The *in vivo* data of the effect of MT on the IOP of rabbits' eyes were compared using t-test, and ANOVA test.

### 3. Results and discussion

#### 3.1. Physical examination

The prepared MT gel formulations were clear and the pH values of all the prepared formulations ranged from 6.84 to 6.92,

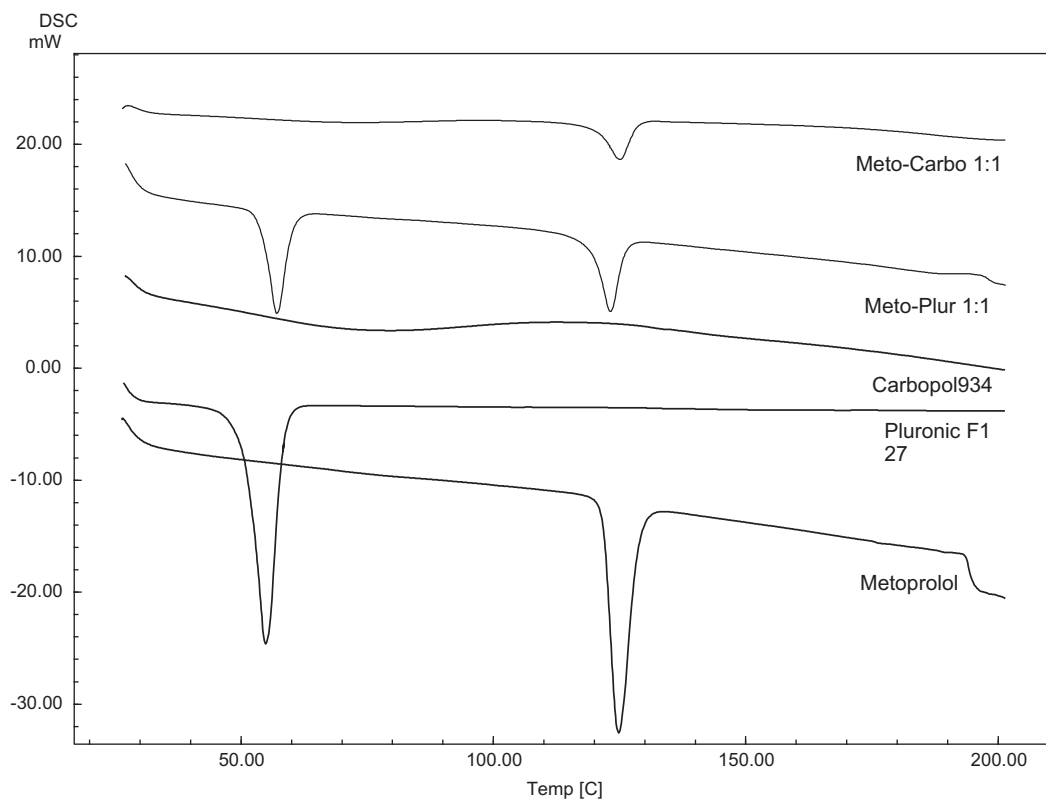
which are considered acceptable to avoid the risk of irritation upon application to the eye.

#### 3.2. Compatibility study between MT and polymers

The compatibility of MT with the different polymers used such as Carbopol 934 and PF127 was studied using DSC. The thermal curves of MT, the polymer, and the MT-polymer physical mixtures (1:1) are shown in Fig. 2. DSC curve showed an endothermic peak at 125.15 °C for metoprolol tartrate and about the same melting endotherm peak was observed for the other drug–polymer mixtures (125.27 °C and 123.42 °C for MT–Carbopol and MT–Pluronic, respectively). Moreover, the enthalpy of the endotherm was also calculated and it was  $-107.34$ ,  $-34.38$  and  $-34.65$  (J/g) for MT, MT–Carbopol and MT–Pluronic, respectively. It is clear that, MT alone has a high enthalpy value while its value decreased after the addition to the molten polymer. There is a non significant change in the thaw melting point after the mixing of MT with the polymers. The thaw melting points were 119.46, 111.1 and 114.88 °C for MT, MT–Carbopol and MT–Pluronic, respectively. This result confirms that there is no mutual interaction between the drug and the polymers.

#### 3.3. Rheological studies

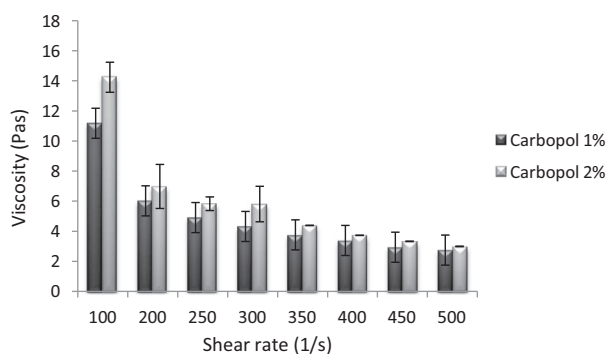
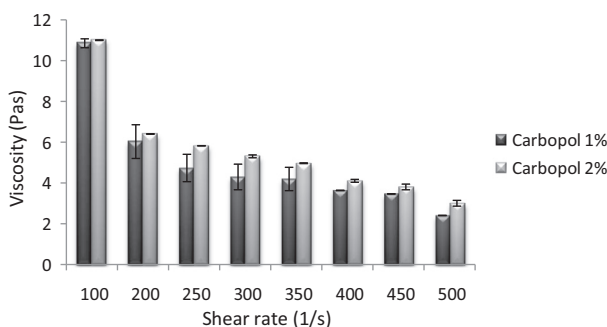
Table 2 and Figs. 3–5 show the flow behavior of all MT gel formulations. It is clear that, all the prepared gel formulations exhibited non Newtonian pseudoplastic flow behavior (shear thinning systems) at  $34 \pm 0.5$  °C. As the shear rate is increased, the normally molecular structure of the gelling material is caused to align its long axes in the direction of a



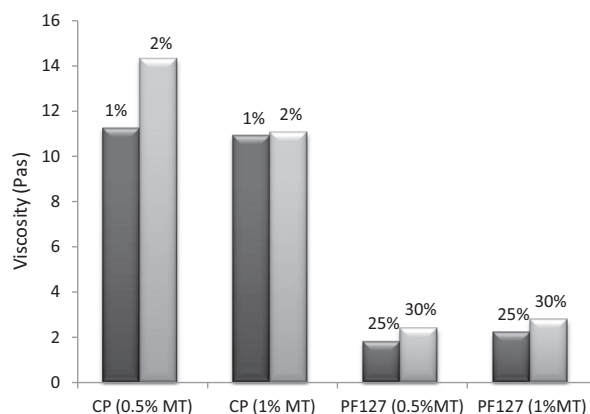
**Figure 2** DSC thermograms showing compatibility of metoprolol tartrate with the used polymers.

**Table 2** Rheological measurements of Pluronic F127 gel formulations containing MT at  $34 \pm 0.5^\circ\text{C}$  ( $n = 2$ , mean  $\pm$  SD).

Viscosity (Pas)				
shear rate (1/s)	25% PF127		30% PF127	
	0.5% MT	1% MT	0.5% MT	1% MT
10	$7.96 \pm 0.16$	$8.72 \pm 0.81$	$12.28 \pm 1.36$	$15.09 \pm 2.40$
20	$4.52 \pm 0.07$	$5.01 \pm 0.58$	$5.80 \pm 0.78$	$7.84 \pm 1.51$
30	$3.09 \pm 0.14$	$3.58 \pm 0.04$	$4.41 \pm 0.57$	$5.56 \pm 0.92$
40	$2.44 \pm 0.26$	$2.99 \pm 0.16$	$4.16 \pm 0.52$	$4.81 \pm 0.41$
50	$2.13 \pm 0.40$	$2.88 \pm 0.30$	$3.97 \pm 0.02$	$4.29 \pm 0.28$
60	$2.01 \pm 0.57$	$2.66 \pm 0.37$	$3.38 \pm 0.08$	$3.79 \pm 0.21$
70	$1.87 \pm 0.64$	$2.42 \pm 0.49$	$3.17 \pm 0.15$	$3.23 \pm 0.18$
100	$1.78 \pm 0.68$	$2.19 \pm 0.16$	$2.37 \pm 0.20$	$2.75 \pm 0.19$

**Figure 3** Viscosity-shear rate bar chart of 0.5% MT gels containing various concentrations of Carbopol ( $n = 2$ , mean  $\pm$  SD).**Figure 4** Viscosity-shear rate bar chart of 1% MT gels containing various concentrations of Carbopol ( $n = 2$ , mean  $\pm$  SD).

flow which in turns reduces the internal resistance of the material and hence decreases its viscosity. Fig. 3 shows the relationship between the viscosity and the shear rate of 1% and 2% Carbopol gels containing the same concentration of MT (0.5% w/w). It is clear that, by increasing the Carbopol concentration, the viscosity value was slightly increased. The same results were observed using higher MT concentration (1% w/w) as shown in Fig. 4. The viscosity of 2% Carbopol gels containing 1% drug is slightly higher than that containing 0.5% drug, this is at all shear rates used with the exception at the shear rate of  $100\text{ s}^{-1}$ , where the viscosity is slightly lower (Fig. 5). Table 2 illustrates the effect of using Pluronic F127 in the two different concentrations (25% and 30% w/w) on the viscosity of gel formulations. A pseudoplastic flow also was

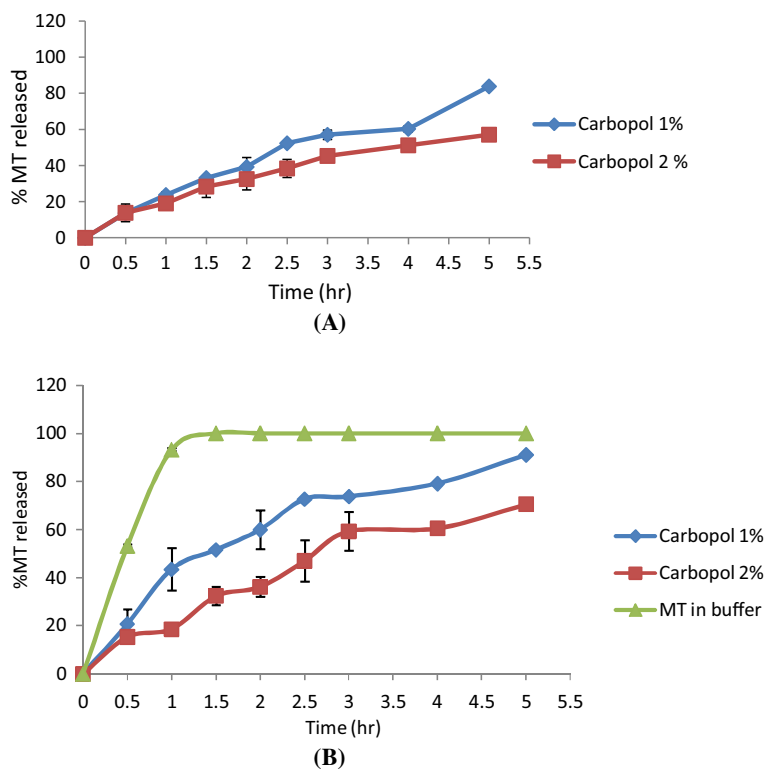
**Figure 5** Effect of concentration and type of polymers on the viscosity of MT gels (shear rate =  $100\text{ s}^{-1}$ ).

obtained and moreover, the gels containing 30% Pluronic F127 exhibited a higher viscosity than that of 25%. This is in agreement with the previous results obtained (El-kamel, 2002). This pseudoplastic behavior of PF127 formulations has also been observed previously (Mansour et al., 2008). It is obvious that by increasing the concentration of PF127 from 25 to 30% w/w for F6, F8 respectively, the viscosity is increased. This is in agreement with the previous results obtained by Jain et al., 1998; Mayol et al., 2008 concluded that a gel is more entangled at higher PF127 concentrations. The recorded viscosity data of the various MT gels at the shear rate of  $100\text{ s}^{-1}$  are presented in Fig. 5, which shows that the Carbopol based gels (F1–F4) exhibited significantly ( $p < 0.05$ ) greater viscosities than Pluronic F127 gels (F5–F8). It was concluded that the increase in the viscosity by increasing the concentrations of both the drug and the polymers used was non-significant. It was reported that the ocular shear rate is a very important parameter and ranges from  $0.03\text{ s}^{-1}$  to  $28,500\text{ s}^{-1}$  so the viscoelastic fluids with a viscosity that is high under low shear rate and low under the high shear rate conditions are often preferred (Zaki et al., 2011).

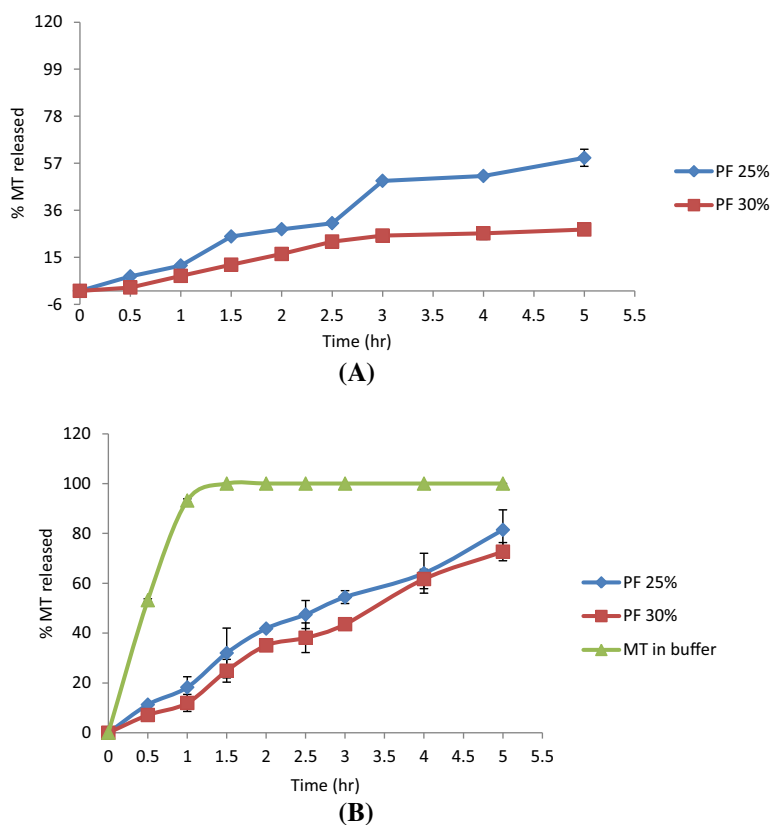
### 3.4. In vitro release of MT from different formulations

#### 3.4.1. Effect of polymer concentration on drug release

In vitro release of MT from different gel formulations using different polymer concentrations (1%, 2% w/w of Carbopol, and 25%, 30% w/w of PF127) was studied as shown in Figs. 6



**Figure 6** In vitro release profiles of MT from gel formulations containing different concentrations of Carbopol. (A) 0.5% (w/w) MT and (B) 1% (w/w) MT ( $n = 3$ , mean  $\pm$  SD).



**Figure 7** In vitro release profiles of MT from gel formulations containing different concentrations of Pluronic F127. (A) 0.5% (w/w) MT and (B) 1% (w/w) MT ( $n = 3$ , mean  $\pm$  SD).

and 7. In general, the release of MT from the isotonic buffer solution (pH 6.8) is significantly higher than that from the all formulated gels. The % release of MT from its buffer solution is  $93.2 \pm 0.655$  after 1 h. The obtained results showed that the release rate of MT from different gel preparations significantly ( $p < 0.05$ ) decreases as an inverse function of the polymer concentration. Fig. 6 shows the % amounts released of MT from the different Carbopol gels. It is observed that at 0.5% w/w MT, the amount of drug released after 5 h is  $83.05 \pm 0.287\%$  and  $57.12 \pm 0.490\%$  for 1 and 2% w/w Carbopol gels, respectively. Moreover, at 1% w/w MT, the % of the drug released is  $90.99 \pm 0.381$  and  $70.47 \pm 0.382$  for 1% and 2% w/w Carbopol gels, respectively. The increase in the viscosity might have contribution to the decreased rate of the drug release from different gel formulations. This may be potentiated by the rheology study that proves a direct proportionality between the polymer concentration and the viscosity value. These findings are in agreement with the other reported results (Ricci et al., 2005). In addition, the % amounts of the drug released using various concentrations of MT (0.5%, 1% w/w) from PF127 gels (25%, 30% w/w) are represented in Fig. 7. The obtained data indicated that at 0.5% w/w MT, the amount of the drug released is  $59.4 \pm 3.818$  and  $27.41 \pm 1.343\%$  using 25 and 30% w/w PF127, respectively while at 1% w/w MT, the amount of the drug released is  $81.43 \pm 3.654$  and  $72.66 \pm 1.624\%$ . For our study the finding that higher polymer concentrations resulted in a lower drug release from the vehicles is in agreement with El-Gendy et al., 2002, who found that the diffusion coefficient of a solute is inversely proportional to the volume fraction occupied by the gel-forming agent (El-Gendy et al., 2002).

#### 3.4.2. Effect of drug loading on in vitro release

The effect of the initial drug concentration on the MT release was also evaluated. Figs. 6 and 7 show the release of MT from various gels using two different concentrations of MT. It is clear from the results that the release of MT from the gel bases increases with an increase of the initial load in the vehicles. It was observed that the % amount released of 0.5 and 1% w/w MT from 1% w/w Carbopol gels is  $83.05 \pm 0.287$  and  $90.99 \pm 0.381$ , respectively, and from 2% Carbopol gels it is  $57.12 \pm 0.460$  and  $70.47 \pm 0.382$ , respectively (Fig. 6). The same finding was observed for the gel formulations containing Pluronic F127 (Fig. 7). These results indicate that as the concentration of the initial drug increases, the release of the drug also increases (Hassan, 2007).

#### 3.4.3. Kinetic analysis of the release data

The release data of MT from its different gel formulations were treated mathematically according to krosmeier equation. The obtained data are illustrated in Table 3. The values of  $n$  (release exponent) lie between 0.5 and 1.0 for all the formulations exhibiting a non-fickian release behavior controlled by a combination of diffusion and chain relation mechanism. Our results are in good agreement with the other reported data (British Pharmacopeia, 2007).

#### 3.4.4. In vivo performance of MT in rabbit's eye

In vivo performance of 1% w/w MT on the intra-ocular pressure (IOP) of rabbit's eye was investigated as a function of the polymer type (Carbopol 934, Pluronic F127) and the polymer

**Table 3** Kinetic constants ( $K$ ), diffusional exponents ( $n$ ) and correlation coefficients ( $r^2$ ) by linear regression of  $\ln(M_t/M_\infty)$  vs  $\ln t$ . The values are mean  $\pm$  SD,  $n = 3$ .

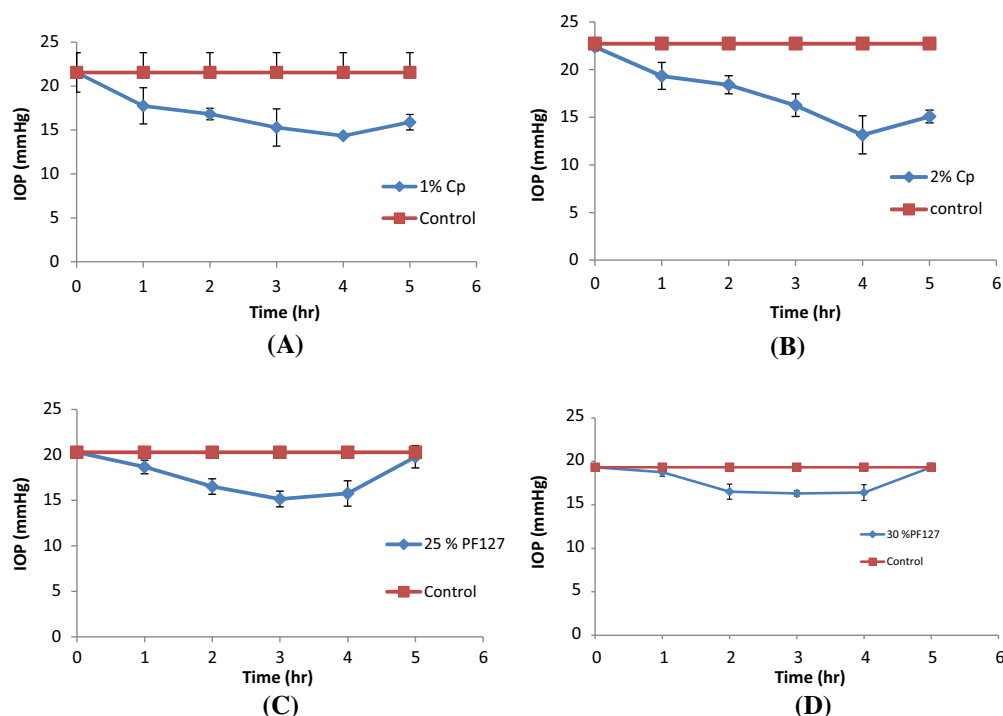
Formula code	$n$	$K$	$r^2$
F1	$0.766 \pm 0.024$	$1.057 \pm 0.585$	0.996
F2	$0.504 \pm 0.014$	$5.250 \pm 0.078$	0.958
F3	$0.627 \pm 0.135$	$1.643 \pm 0.037$	0.990
F4	$0.693 \pm 0.024$	$1.398 \pm 0.198$	0.960
F5	$0.868 \pm 0.025$	$0.442 \pm 0.051$	0.950
F6	$0.805 \pm 0.043$	$0.820 \pm 0.179$	0.990
F7	$0.746 \pm 0.052$	$0.434 \pm 0.108$	0.903
F8	$0.959 \pm 0.063$	$0.317 \pm 0.117$	0.984

concentration (1%, 2% of Carbopol and 25%, 30% of PF127). The beta blocker is known to reduce the IOP when it is applied topically to the eye thus, the IOP was chosen as the parameter of the activity (Plummer et al., 2006). Four parameters were utilized to assess the in vivo activity of the drug. These parameters are the area above the IOP/ time curve (AAC), the maximum response (MR), the time of the maximum response (TMR) and the duration of the drug action (DA). The results of these parameters are collected and reported in Table 4. The time course of the IOP of rabbit's eye following the instillation of 1% MT gels is presented in Fig. 8. It is clear from Fig. 8 and Table 4 that the duration of the drug action (DA) using two different Carbopol concentrations does not terminate by the end of the experimental observation period of 5 h. This indicates that, MT formulated gels have a long duration of the drug action. The difference in the IOP at the end of the experimental time (5 h) from the initial values is 5.78, 7.34 mmHg in the case of 1% and 2% Carbopol gels, respectively. Through the specified experimental time, DA does not show any dependence on the Carbopol concentration ( $p > 0.05$ ). These results could be due to the Carbopol concentrations used. As the concentration of the polymer increases from 1% to 2% w/w, the viscosity does not significantly ( $p > 0.05$ ) increase. The recorded results of the viscosity are  $10.85 \pm 0.219$  and  $11.0 \pm 0.014$  (Pas) at the shear rate of  $100 \text{ s}^{-1}$  for 1% and 2% Carbopol (F2, F4), respectively. With regard to the area above the IOP/time curve (AAC), Table 4 reflects a non dependence ( $p > 0.05$ ) of the AAC on the concentration of Carbopol. The change of the Carbopol concentration from 1% to 2% brings about the same AAC. It is 15.6 and 16.16 mmHg h for 1% and 2% Carbopol gels, respectively. Moreover, the maximum response of the drug (MR) in the relation to the Carbopol concentration was calculated and is summarized in table 4. From this table, it is evident that, the MR is slightly affected by the Carbopol concentration in a way that, 2-fold increase in Carbopol concentration (from 1% to 2% w/w) brings only about 1.3-fold increase in the MR. In addition, the difference between the two prepared Carbopol gels (1% and 2% w/w) is non significant ( $p > 0.05$ ) with regard to the time of the maximum response (TMR) and it gave the same value (4 h). It was noted that there is no correlation between the obtained in vitro release rates of MT from the Carbopol gels and the in vivo pharmacological effect.

On the other hand, Fig. 8 and Table 4 demonstrate that the duration of the drug action (DA) using the PF127 gels in the two different concentrations (25% and 30% w/w) persists

**Table 4** Values of area above the IOP/time curve, maximum response, time of maximum response and duration of action of 1% (w/w) metoprolol tartrate of different gel formulations.

Gel formulations (w/w)	AAC (mmHg h)	Maximum response (mmHg)	$t_{max}$ (h)	Duration of action (h)
<i>Carbopol 934</i>				
1%	15.60	7.39	4	> 5
2%	16.16	9.27	4	> 5
<i>Pluronic F127</i>				
25%	16.05	5.14	3	5
30%	16.26	3.98	3	5

**Figure 8** Intra-ocular pressure (mm Hg) of rabbits' eyes after instillation of 1% (w/w) metoprolol tartrate gels. (A) 1% Carbopol gel, (B) 2% Carbopol gel, (C) 25% Pluronic F127 gel and (D) 30% Pluronic F127 gel ( $n = 3$ , mean  $\pm$  SD).

only for the experimental time and reaches the baseline at 5 h. The differences between the two individual PF127 gels are non significant ( $p > 0.05$ ) with regard to the duration of the drug action. From table 4, it is evident that AAC of 1% w/w MT increases slightly as the concentration of the PF127 increases and it is 16.05, 16.26 mmHg h for 25 and 30% w/w PF127, respectively. The statistical analysis of the recorded data for MR (table 4) depicts that the difference between 25% and 30% w/w PF127 gels is non significant ( $p > 0.05$ ). MR is 5.14, 3.98 mmHg for 25% w/w and 30% w/w PF127 gels, respectively. The same finding was obtained by a comparison between the two individual PF127 gels concerning the time of the maximum response (TMR). TMR is 3 h for both PF127 gel formulations. This may be attributed to the non significant change in the viscosity of PF127 gels which is  $2.19 \pm 0.16$ ,  $2.75 \pm 0.19$  (Pas) for 25% and 30% PF127 gels, respectively as shown in Table 2. From the above mentioned findings, it is observed that, the gel formulations of the drug with the Carbopol polymer produce a greater influence on the duration of the drug action as compared to the PF127 gels.

Furthermore, there is no correlation between the obtained in vitro release rates of MT from the Carbopol and Pluronic F127 gels and the in vivo pharmacological effects. With regard to the pupil diameter of the eyes of the tested rabbits, it is visually observed that, at all time points post-instillation of MT gels, the change in the pupil diameter is non significant for both Carbopol and Pluronic F127 gels as compared to the control eye (no miotic or mediatric effects).

#### 4. Conclusion

The metoprolol tartrate gel formulations were made and examined under different formulation variables. The nature of the polymer and its concentration has influenced the drug release profiles. Higher release rates were observed at lower polymer concentrations. A direct relationship was noted between drug concentration and percent of the drug released. The intra-ocular pressure (IOP) results of rabbits' eyes treated with 1% w/w metoprolol tartrate gel formulations showed that



Carbopol 934 polymer which had higher viscosity values, extended the duration of the pressure-reducing effect of MT to more than 5 h. These results may be due to the prolongation of the ocular contact time, and assistance in drug penetration into the ocular tissue, which increases the duration of the action of the drug and its bioavailability.

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