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AVAILABILITY OF PHENYLEPHRINE HYDROCHLORIDE FROM OPHTHALMIC MULTIPLE EMULSIONS

A.A.Mohamed, S.Ismail, F.S. habib. and M.A. Attia
Faculty of Pharmacy, Assiut University, Assiut, Egypt

ABSTRACT

Phenylephrine hydrochloride was formulated in different emulsion systems with and without viscolizers (methylcellulose and tylose). The diffusion coefficient of phenylephrine hydrochloride in different formulations has been determined. Results indicated that the diffusion coefficient of phenylephrine hydrochloride from different systems decreased with increasing viscolizer concentration. The mydriatic and intraocular pressure, IOP, responses were followed after the application of the tested formulations to the rabbit's eye. Four parameters have been utilized to assess the performance of the drug formulations. These are, the area under the curve AUC; the maximum response, MR; the time of maximum response. TMR; and the duration of drug action. DA. It was found that the most effective emulsion system appeared to be the multiple w/o/w emulsion containing 1 % w/v methylcellulose followed by that containing 0.5 % w/v tylose.

INTRODUCTION

Topical aqueous ophthalmic drug solutions exhibit low bioavailability due to various loss processes such as drainage, tear turnover, non productive absorption and protein binding [1-3]. The main disadvantages of eye drops are : the short duration of action, ocular irritation, systemic side effects and the susceptibility for bacterial and/or fungal contamination.

In recent years, interest is growing progressively to develop new drug-delivery systems for ophthalmic applications [4,5]. There has been interest in the use of emulsions as delivery systems. A water-in-oil (w/o) or an oil-in-water (o/w) emulsion can be further emulsified to produce multiple emulsion systems (w/o/w or o/w/o).

The basic rational for the use of w/o/w multiple emulsions as a means for controlled delivery of drug, is that, the drug contained in the intermost phase is enforced to partition itself through several phases prior to release into the body fluid of the patient [4]. Pilocarpine delivery from multiple emulsion was studied and it was found that the onset of the intraocular pressure (IOP) peak was delayed and a slow drug release has been performed [5]. The in vitro release of lidocaine from o/w emulsions was studied [6,7].

One of the tools resorted to, in the last few decades for the minimization of drug loss in the precorneal area is the addition of viscolizers to liquid ophthalmic preparations [8,9]. Nyavist et al [6] reported that the incorporation of carbomer 934, a gelling agent, into an o/w emulsion system resulted in a retardation in the release rate of lidocaine.

Phenylephrine hydrochloride was chosen in the present study since it is commonly used in ophthalmology as mydriatic, and it has been recently reported to inhibit, rapidly, the elevation of the IOP in the rabbit eye [10,11].

The aim of the present study was :

a- to formulate phenylephrine hydrochloride in multiple emulsion forms to over come some of the above mentioned shortcoming associated with ophthalmic solutions.

b- to study the release-profile of mentioned drug from different multiple emulsion systems.

c- to investigate the in vivo performane of the drug in the healthy eye of the rabbit .

d- to find-out a correlation between the in vitro and the in vivo studies.

EXPERIMENTAL

1-MATERIALS AND METHODS

1-Materials :

Phenylephrine hydrochloride (Siegfried), Tween 80 (Polysorbate 80), Span 65 (Atlas Chem. Ind., Wilmington, USA). Liquid paraffin(USP grade) Methylcellulose 450 (BDH). Methylhydroxyethylcellulose (Tylose 4000, Hoechst). The other chemicals used were of analytical grades.

2- Equipment ;

Homogenizer (Braun), Shaking water bath (selects, Uniform 320) Spectrophotometer (Shimadzu. Japan). Semipermeable Fisher cellulose membrane 30/32 (Fisher Scientific. Lonodn , U.K.).

3- Preparation of emulsions :

3.1. Simple oil-in-water (o/w) emulsion :

The hydrophilic surfactant used, Tween 80, was dissolved in isotonic phosphate buffer solution (pH 6.8) in a concentration of 5% w/v. The oily phase was added to the aqueous one and homogenized for 15 minutes at 5000 rpm. 3.2. w/o/w multiple emulsions.

The w/o/w emulsions were prepared by re-emulsification of the primary w/o emulsion. A two stage procedure was adopted. The first stage involved the preparation of w/o primary emulsion by mixing the lipophilic surfactant 3.7% viz, Span 65 with liquid paraffin, followed by the addition of the aqueous phase. The blend was homogenized as in the case of simple emulsion. In the second stage, the primary w/o

emulsion was further emulsified in isotonic (or viscous) phosphate buffer solution (pH 6.8) containing a hydrophilic surfactant. In all formulations tested, the drug (2.5% w/v) was dissolved in the internal aqueous phase of the primary emulsion. The concentration ranges of the viscolizers were 0.25 -1 % and 0.125-0.5 % w/v for methylcellulose (MC) and methylhydroxyethylcellulose (Ty), respectively. The constituents of the prepared simple and multiple emulsions are shown in table 1.

4- Tests preformed on emulsions

4-1- In vitro procedure :

The release of the drug from ophthalmic emulsions was carried out using the dialysis method [12]. Two grams of the tested formula was placed in the donor. The cell was placed into a constant temperature water bath shaker previously adjusted at 37° and 50 rpm. Samples of the dialysate were measured spectrophotometrically at 273 nm after appropriate dilution, against a blank similarly treated. A compensation of the liquid by using equal volume of the release medium was carried out.

4-2- Mydriasis and IOP time profile

Albino rabbits of 1.5 -2 kg receiving green fodder and drinking water. Isotonic xylocaine solution (1 % w/v) was dropped into the rabbit's eye to anaesthetize the cornea. It was proved experimentally that , xylocaine had no effect on pupil diameter or IOP of the eye. In all cases, topical doses each of 50 µl of emulsion was used in each experiment and placed in the lower conjunctival sac. Non medicated formulation was applied to the opposite eye which served as control. Six rabbits were used for each. A standardized illumination was kept allover the experiment. The assigned formulation was applied to the right eye, while,the control was applied in the left one. Before and after application of both test and control formulations. The pupil diameter (in mm) and the IOP (in mm Hg) of both eyes were measured using Haab's pupillometer and Maclocof tonometer, respectively, every hour. The parameters

of activity of the drug are: area under curve (AUC), maximum response (MR), time of maximum response (TMR) and duration of drug action (DA).

RESULTS AND DISCUSSION

1- In Vitro

The diffusion coefficient of phenylephrine hydrochloride has been determined in an isotonic solution (PH 6.8), in simple o/w emulsion, non-viscous w/o/w emulsion and viscous w/o/w emulsion systems. The results of these experiments are summarized in table 1. The diffusion coefficient of phenylephrine hydrochloride (2.5 % w/v) formulated in the different systems was determined according to Higuchi model [13].

As can be seen from the values presented in table 1, the addition of viscolizers, either (MC) or (Ty), to the aqueous phase decreased the diffusion coefficient of the drug. This can be attributed mostly to the increase in the viscosity of the aqueous phase. On the other hand, the diffusion coefficient of the drug in the aqueous solution without surfactant was higher than that in the external phase of multiple emulsion. This conclusion can be supported by the notation of BRODIN et al [4], that no significant mixing of the two aqueous phases occurs during the preparation of this multiple system, or that the diffusion in the external aqueous phase of the emulsion is rate-determining. ATTIA and HABIB[5] further support this present conclusion and proved that the diffusion coefficient of pilocarpine hydrochloride from aqueous solution without any surfactant, was higher than that in the external phase of multiple emulsion. From the same table it can be observed that as the lag time increased, the diffusion coefficient decreased.

2- In-vivo

The pharmacokinetic parameters of the change in the mydriatic and intraocular pressure responses induced by phenylephrine hydrochloride were calculated separately for each experiment, and the mean values ± SD of these separated parameters are presented in table 1. Figure 1 and 2 represent the mean IOP response for each time. The area under the IOP curve was smaller in case of isotonic buffer solution and increased in case of the o/w emulsion followed by w/o/w emulsion without viscolizers and then w/o/w emulsion containing methylcellulose. The same sequence concerning the increase in the AUC was observed, but in a less extent with respect to w/o/w emulsion containing different tylose concentrations. The AUC generally increased as the concentration of viscolizer increased, but it is more pronounced in case of MC (table 2).

Thus it can be concluded that the administration of phenylephrine hydrochloride in different emulsion systems increased the AUC of the IOP responce compared with the aqueous solution of the drug. The same observation regarding the AUC can be also stated with respect to the mydriatic effect of the drug (figure 3 and table 2).

The results are also supported by the calculated MR and TMR. Multiple w/o/w emulsion containing 1% MC produced the highest maximum responses for both IOP (7.25 mn Hg) and mydriatic effect (3.31 mm) in a TMR of 3.75 and 1.75 h respectively, while w/o/w emulsion containing 0.5% w/v tylose can be considered as the second system of choice where it gave a maximum IOP response of 4.88 mm Hg in a TMR of 1.5 h, and a mydriatic response of 4.5 mm in 1 h.

Availability of Phenylephrine Hydrochloride from Ophthalmic Multiple Emulsions

When phenylephrine hydrochloride was instilled from the different tested formulations, the response parameter time curve (Figures 1-3) led to plateau, consequently, the figures gave presentation of the approximate strong point of the peak response. The onset of IOP and mydriatic response after application of the drug ocularly in different systems was as fast as after aqueous solution administration. The application of phenylephrine hydrochloride in different systems increased the mean duration of action to reach to 5 h (experimental time) in most formulations with responses of 1.2-6.7 mm Hg and 0.5-1.6 mm for IOP or mydriatic effect respectively.

The obtained results can be attributed to the long contact time of the emulsion (specially those contained higher viscolizer concentration) with the corneal surface leading to sedimentation in the multiple system occurring during the long period of experimentation in which a breakdown of the multiple emulsion may take place which in turn, may be due to blinking of the eye.

With respect to the correlation between the in-vitro and the in-vivo results, from the tables and figures, it is obvious that the in-vitro performance of the tested formulations does not reflect their in-vivo one.

There is actually a reverse relationship between the in-vitro diffusion coefficient of the drug from the tested systems and the in-vivo performance. A decrease in the diffusion coefficient of the drug brings about an increase in the AUC, MR and duration of drug action. This reverse relationship between the in-vitro diffusion coefficient of a drug and its bioavailability was reported for other drugs and ophthalmic drug delivery systems[14]. Turnover of lacrimal fluid, the

low holding capacity of the eye towards fluids, physiology of blinking and reflex tearing are factors contribute to the lose of the drug reservoir in the open system represented by the cul-de-sac, consequently the increasing in the diffusion coefficient of the drug enhances the depletion of drug reservoir and this lead to reduction in prolonged drug effect with lower corneal availability.

Table I: Mathematical treatement of the release data according to diffusion mechanisms and the diffusion coefficients of phenylephrine hydrochloride in different systems

System	r	Lag time (h)	$Dx10^{-2}$ (Cm^2/ h)
Isotonic buffer solution	0.966	0.0163	9.719
o/w	0.999	0.0193	2.098
w/o/w	0.999	0.0261	1.816
w/o/w in 0.25 % MC	0.996	0.0314	1.034
w/o/w in 0.5 % MC	0.998	0.0675	0.983
w/o/w in 1.01 % MC	0.999	0.0801	0.907
w/o/w in 0.125% Ty	0.997	0.0265	1.423
w/o/w in 0.25 % Ty	0.999	0.0328	1.244
w/o/w in 0.5 % Ty	0.998	0.0946	0.594

Table 2 . Pharmacokinetic parameters of the change in the IOP and pupil diameter induced by phenylephrine hydrochloride in rabbit eyes, AUC = area under curve, MR = maximum response, DA = duration of drug action and TMR = time of maximum response, (the values in parentheses represent the standard error of the mean)

System	IOP				Pupil Djameter			
	AUC (mm Hg. h)	MR (mm Hg)	DA (h)	TMR (h)	AUC (mm,h)	MR (mm)	DR (h)	TMR (h)
Isotonic buffer solution	5.130(0.55)	3.25(0.33)	3 (0.13)	1.75(0.18)	4.25(0.18)	1.0 (0.18)	2.5 (0.20)	1.0 (0.01)
o/w	9.87 (0.33)	3.75(0.18)	4.75(0.18)	2.25(0.66)	4.75(0.77)	1.75(0.33)	3.5 (0.45)	1.25(0.18)
w/o/w	10.0 (1.34)	3.75(0.45)	5 (0.11)	3.75(0.33)	5.25(0.88)	2.0 (0.29)	3.25(0.33)	1.0 (0.12)
w/o/w in 0.25% MC	13.69(1.92)	3.88(0.59	4.75(0.18)	1.25(0.18)	7.38(0.26)	2.0 (0.19)	4.25(0.18)	1.25(0.18)
w/o/w in 0.5 % MC	16.13(1.50)	4.25(0.55)	4.5 (0.20)	2.75(0.60)	8.69(1.06)	3.125(0.08)	4.5 (0.20)	1.0 (0.11)
w/o/w in 1.0 % MC	25.33(0.99)	7.25(0.23)	5 (0.12)	3.75(0.18)	10.48(0.53)	3.31(0.19)	5 (0.0)	1.75(0.19)
w/o/w in 0.125% Ty	10.31(1.22)	3.88(0.43)	5 (0.13)	3.0 (0.85)	5.88 (0.22)	2. (0.13)	4.25(0.18)	1.0 (0.13)
w/o/w in 0.25 % Ty	14.56(1.26)	4.38(0.33)	5 (0.18)	1.5 (0.20)	7.0 (0.15)	2.0 (0.11)	4.0 (0.16)	1.0 (0.11)
w/o/w in 0.5 % Ty	19.06(1.43)	4.88(0.36)	5 (0.13)	1.5 (0.20)	9.0 (0.55)	2.5 (0.2)	4.5 (0.2)	1.0 (0.10)

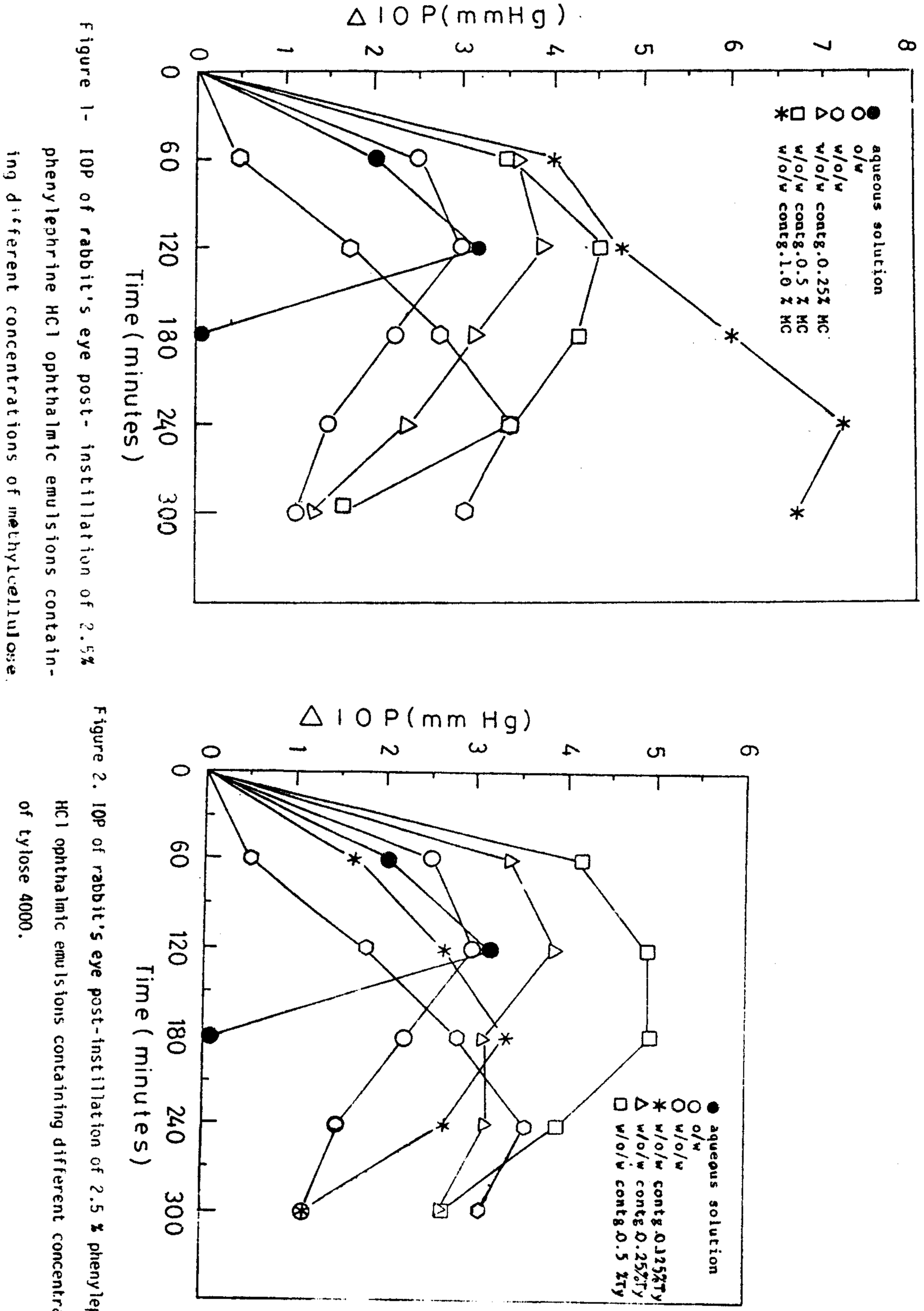

Figure 1- IOP of rabbit's eye post- instillation of 2.5% phenylephrine HCl ophthalmic emulsions containing different concentrations of methylcellulose.

Figure 2. IOP of rabbit's eye post-instillation of 2.5 % phenylephrine HCl ophthalmic emulsions containing different concentrations of tylose 4000.

Availability of Phenylephrine Hydrochloride from Ophthalmic Multiple Emulsions

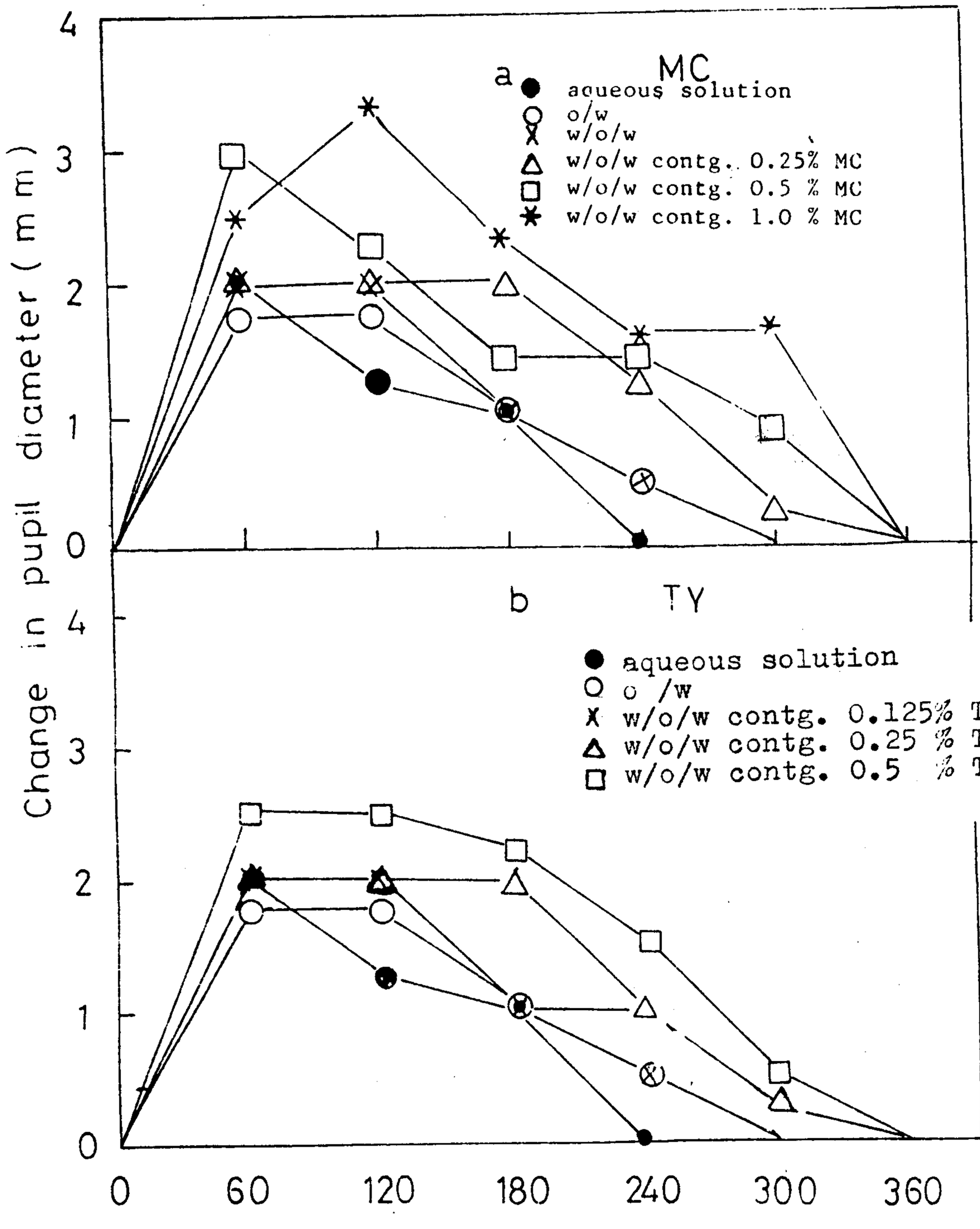

Figure 3. Change in pupil diameter of rabbit's eye post-instillation of 2.5% phenylephrine HCl ophthalmic emulsions containing different concentrations of (a) methylcellulose and (b)tylose

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انطلاق هيدروكلوريد الفنيل افرين من مستحلبات متعددة الطبقات

عبدالرزاق عبدالمجيد محمد ـ سيد اسماعيل محمد ـ فوزية سيد أحمد حبيب ومحمد على عطية .

قسم الصيدلانيات ـ كلية الصيدلة ـ جامعة أسيوط

تم تركيب مستحلبات مختلفه لهيدروكلوريد الفينيل افرين مع أوبدون مركبات زيادة اللزوجة و (سيليولوز الميثيل والتيلوز) وقد تم تقنين معامل الانتشار لهذة المستحضرات معمليا . وأوضحت النتائج أن معامل الانتشار لهيدروكلوريد الفنيل افرين يقل بزيادة تركيزات المواد اللزجه . وقد اجريت تجارب لدراسة تأثير مستحلبات هدا العقار على عيون الارانب وأوضحت الدراسة أن للعقار تأثيرا واضح على توسيع حدقة العين وتقليل الضغط الداخلى لها وذلك من خلال حسابات للمساحة تحت المنحنى وأعلى استجابة ـ ووقت استمرار تأثير الدواء فى العين . وقد وجد أن المستحلب المتعدد الطبقات والذى يحتوى على ١ ٪ من سيليولوز الميثيل له أحسن تأثير يليه الذى يحتوى على ٥ر ٪ من التيلوز .

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