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A Novel Ocular Delivery System for Phenylephrine Hydrochloride

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The *in vivo* behaviour of phenylephrine hydrochloride in different vehicles like gels of Carbopol 907®, Carbopol 934P® and latex system of cellulose acetate hydrogen phthalate (CAHP) was evaluated by measuring the reduction in intraocular pressure and the mydriatic activity. The parameters that have been utilised to assess the performance of the formulations were the area under the curve (AUC), the maximum mydriasis (I_{max}), the time of maximum response (T_{max}) and the duration of activity (D). The influence of viscosity and mucoadhesion on the bioavailability parameters has also been investigated. Carbopol 934P and CAHP formulations showed prolonged duration of action and greater AUC compared to Carbopol 907 and aqueous solution ($P<0.05$).

Key words : Carbopol®, Cellulose acetate hydrogen phthalate (CAHP), Phenylephrine hydrochloride, Mydriasis, Intraocular pressure (I OP), Rabbit

INTRODUCTION

Conventional ophthalmic formulations show lower bioavailability because of (1) constant lacrimation and (2) nasolacrimal drainage. Thus it becomes necessary to frequently instill concentrated medication to achieve the desired therapeutic effect (Chien *et al.*, 1982). Moreover the systemic absorption of drug drained through the nasolacrimal duct may result in some undesirable side effects (Schoenwald and Smolen, 1971).

The poor bioavailability is due to rapid loss of drug from the precorneal area via drainage, nonproductive conjunctival absorption and vasodilatation due to the drug in conjunction with poor permeability across the corneal membrane. Therefore, a large ophthalmic dose is required to reach the inner eye structure for suitable duration of effect.

Certain synthetic and natural polymers containing carboxyl groups such as polyacrylic acid derivatives and glycosamine glycans have shown capability of good mucoadhesion in the eye (Park and Robinson, 1984; Gurny *et al.*, 1987). It was speculated that mucoadhesive polymer adhered to the precorneal area, could deliver the ionically bound drug to the eye with a controlled rate, the same as sustained release of drug bound to ion exchange resins. This might potentially provide the basis for a liquid controlled/sustained delivery system. Camber and Edmann (1987) also showed that sodium hyaluronate as an ophthalmic carrier resulted in increased retention of the pilocarpine in the tear fluid and 2-fold increased concentration in cornea and aqueous humor. Another approach was to administer drug solution ionically bound via its basic imadazole moiety to a polycarboxylic polymeric carrier (Saettone *et al.*, 1989). In one case pilocarpine ionically bound to alginic acid was administered as a solid state ophthalmic device. In the second case the synthetic polymer carrier (Piloplex), an "emulsion" type of vehicle was given using water-insoluble synthetic polyacrylic acid lauryl methacrylayte. Upon instillation into the eye, the system precipitates in the tear fluid forming a drug depot in the cul-de-sac for extended period of time.

Schoenwald *et al.*, (1978) observed that the duration of miotic activity in albino rabbits was prolonged as a function of the plastic yield value of Carbopol® 907 gels. The controlled release ophthalmic delivery of pilocarpine in Carbopol 934P gel was also investigated by Davies *et al.*, (1988). Pilocarpine nitrate (1%) in Carbopol® 934P gel produced a statistically significant increase ($P< 0.05$) in the bioavailability when compared to equiviscous polyvinyl alcohol solution and nonviscous phosphate buffer saline solution due to mucoadhesion and viscosity. Sodium carboxymethyl cellulose, hydroxymethylcellulose, Carbopol® 940 and Carbopol®

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941 produce excellent hydrogels in aqueous solutions. Carbopol® 907 (M.W. 450,000) the only linear member of the family of Carbopol® resins is used in the applications requiring high carboxylic content without appreciable increase of viscosity. High purity grade Carbopol® 934P is used as thickening, suspending and emulsifying agent and can be also used in tablets to impart sustained release properties. Adrenaline bitartrate in hydrogel base produced greater mydriasis and lower intraocular pressure when compared to aqueous solution (Habib and Attia, 1989).

The aim of the present study was to investigate the influence of Carbopol® 907 (M.W. 450,000), Carbopol® 934P (M.W. 3,000,000) and cellulose acetate hydrogen phthalate (CAHP) latex on the ocular activity of phenylephrine hydrochloride. Phenylephrine hydrochloride (2.5% w/v) was formulated in 4% aqueous Carbopol® 934P,. Carbopol® 907 gel and 10% CAHP latex. *In vitro* mucoadhesion and viscosity of all formulations were also determined.

MATERIALS AND METHODS

Materials

Carbopol® 907 (M.W. 450,000), and 934P (M.W. 3, 000,000) was purchased from BF Goodrich Company Ohio. Cellulose acetate hydrogen phthalate (CAHP) and phenylephrine hydrochloride was obtained from Aldrich Chemical Company Ltd., U.K. All other reagents were of analytical grade.

Preparation of gel

A 4% (w/v) Carbopol® powder was dispersed in aqueous solution of phenylephrine hydrochloride (2. 5% w/v) using high speed stirrer, and neutralised with sodium hydroxide (10 % w/v) for the formation of transparent gel.

The Carbopol® is widely used due to its hydrophilic nature and affinity for water. Carbopol® resin tends to form clumps of particles when haphazardly dispersed in polar solvents. Best mixing is obtained when resins are slowly sprinkled and vortexed the solution. CAHP latex (10% w/v) containing 2.5% phenylephrine hydrochloride was also prepared according to the procedure reported by Gurny (1983).

Viscosity measurement

Viscosities of all three formulations and control were determined using a Brookfield synchro-lectric Viscometer (RVT with helipath assembly) at 5 rpm at 37°C.

In vitro mucoadhesion study

In vitro mucoadhesion of all the three formulations was studied by the method as described earlier (Durrani *et al.*, 1995).

In vivo studies

Measurement of Intraocular Pressure (IOP): Albino rabbits weighing 2.5-3.5 kg were used for the *in vivo* study. Isotonic xylocaine solution (1%) was instilled into the rabbit's eye to anaesthetize the cornea. Xylocaine has been proved to have no effect on the pupil diameter or IOP. Rabbits were kept in restraining boxes and allowed to acclimatize to laboratory conditions for 1 h. Lighting was kept constant throughout the experiment. The formulations (50 µl) was instilled into the rabbit's eye using a micropipette in the lower cul de sac of one eye. The control formulation was administered in the other eye. The Intraocular pressure was determined by tonometer.

Measurement of change in pupil diameter: The pupil diameter was periodically measured with a vernier caliper held at 5 cm from the rabbit eye until it regained its origninal size. The same rabbit was repeatedly used after a washout period of two days.

Statistical Analysis: The statistical analysis of the data was done by the Duncan's new multiple range test for analysis of co-variance. The area under the curve for time vs mydriatic activity was calculated by the trapezoidal rule using Microsoft Excel.

RESULTS AND DISCUSSION

In vitro mucoadhesion

Table I. shows the *in vitro* mucoadhesion force required for the detachment of three different formulations from the mucus. Carbopol® 934P showed statistically significant difference for the force of detachment when compared to Carbopol® 907 and CAHP ($p<0.05$). For water soluble polymers, molecular weight or molecular length appears to be necessary for the adhesion of polymers to a substrate. For example sodium carboxymethyl cellulose having molecular weight over 76,600 have significant bioadhesion (Smart *et al.*, 1984). Chen and Cyr (1970) have shown that mucoadhesion strength was increased as the molecular weight of the water soluble

Table I. *In vitro* Mucoadhesion of test formulations

Test Material	Weight Required for Detachment (gm)	Force, (Newton)(*10)	Force/Area, (Newton/cm^2)
Carbopol® 907	67±3.67	6.7±1.20	2.68±0.30
Carbopol® 934P	87±03.35	8.7±0.33	3.48±0.16[1)]
CAHP	22±08.02	2.2±0.45	0.88±0.23

[1)]statistically significant compared to Carbopol 907 & CAHP ($p<0.05$)

polymer increases above 100,000.

Polyethylene glycol polymer with a highly linear configuration and molecular weight of 20,000 has no adhesion properties. Howevere, as molecular weight is increased upto 4,000,000, the mucoadhesion force is highly increased. The bioadhesion of Carbopol® 907 with linear structure was significantly lower than Carbopol® 934P.

In Vivo studies

Change of pupil diameter and IOP vs time for all formulation are shown in Fig.1. and Fig. 2. In case of mydriatic activity, statistical difference in AUC (area under the curve) for all formulations was also observed with respect to aqueous solution ($P<0.05$) (Table II). Carbopol® 934P formulation reduced the IOP for a long period, significantly resulting in increased AUC compared to Carbopol® 907 and CAHP ($P< 0.005$). Carbopol® 934P formulation showed longer duration of action and maintained the IOP at a normal level over eight hours. In case of aqueous solution of phenylephrine hydrochloride, the activity (IOP and pupil diameter) returned to original state after a short duration due to the rapid clearance of aqueous solution from the *cul de sac*. This effect may resulted from drainage rate of drug from the ocular region (Chrai and Robinson, 1974, Patton and Robinson, 1975). The viscosity of Carbopol® 907 (3% w/v) and Carbopol® 934P (3% w/v) was 18.5×10^4 cp and 20.5×10^4 cp, respectively. The bioavailability of the Carbopol 907 and 934P was not dependent on the viscosity of the formulation, but depend on mucoadhesion forces (Table II). The mucoadhesive polymer and viscolyser may result in increased bioavailability and duration of action of pilocarpine nitrate when compared to PVA

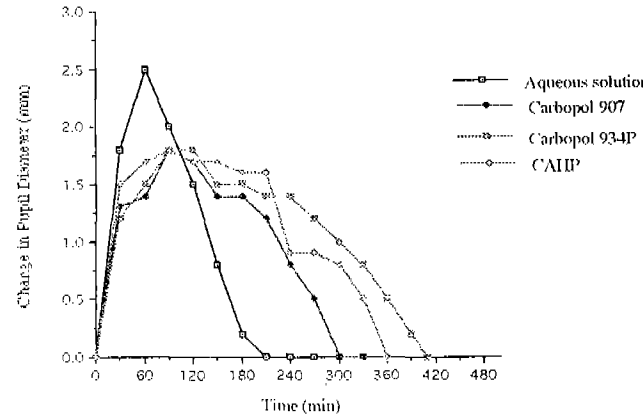

Fig. 1. Changes in pupil diameter (mm) of rabbit's eye after instilation of different formulations of phenylephrine hydrochloride

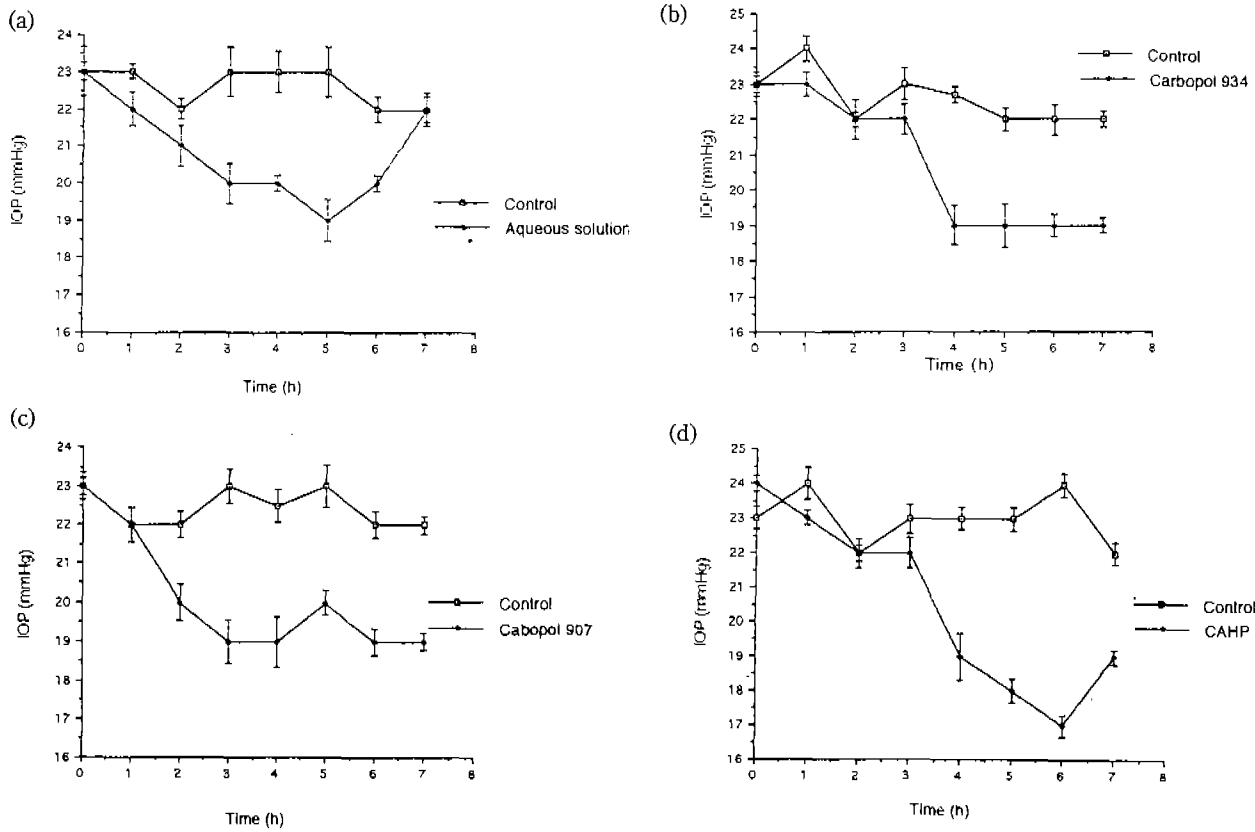

Fig. 2. Changes in intraocular pressure vs time in rabbit's eye after instilation of different formulations of phenylephrine hydrochloride

Table II. Summary of Mydriatic Activity parameters

Formulations	Relative AUC	T_{max} (min)	I_{max} (min)	Duration (min)
Aqueous Solution	1	60	2.5	210
Carbopol® 907	1.7	90	1.55	300
Carbopol® 934P	2.8[1)]	120	1.57	410
CAHP	2.5[1)]	90	1.55	360

[1)]Statistically significant from Carbopol® 907 & aqueous solution ($P<0.05$)

solution with similar viscosity (Davies *et al.*, 1988).

CAHP (10% latex) with a very small viscosity range (190 cps) had the longer duration of action of the latex system compared to aqueous solution. In the lacrimal fluid, the CAHP latex system coalesces and are not cleared rapidly from the ocular surface ($P<0.05$). Although the latex system has low mucoadhesion, it resulted in prolonged duration of action due to the coagulated latex system which reside in the cul de sac for long period. The latex system as described by Gurny *et al.*, (1981) is a highly unstable system which coagulates when there is slight pH change. The present invesigation clearly indicates that Carbopol® 934P can be used as a sustaining vehicle for phenylephrine hydrochloride.

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