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Solubilization of tropicamide by poloxamers: physicochemical data and activity data in rabbits and humans *

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Summary

A series of polyoxyethylene–polyoxypropylene (POE/POP) block copolymers (Poloxamers, or Pluronics) were evaluated as solubilizers for tropicamide, a poorly water-soluble mydriatic/cycloplegic drug. The selected Pluronics were L64, P65 and F68 (POP weight 1750, POE weight 1150, 1650 and 6650, respectively), P75 and F77 (POP weight 2050, POE weight 2100 and 4550, respectively), P84, P85, F87 and F88 (POP weight 2250, POE weight 1950, 2350, 5450 and 9150, respectively) and F127 (POP weight 4000, POE weight 8600). The following studies were carried out: solubility of tropicamide in polymer solutions, partition coefficient of the drug between isopropyl myristate and polymer solutions, critical micelle concentration (CMC) of the polymers, viscosity of the polymeric solutions containing tropicamide, mydriatic activity tests on rabbits and humans, cycloplegic activity tests on humans. The solubility isotherms (25 °C) showed that the saturation solubility of the drug increased linearly with increasing surfactants concentration in the 4.0–20.0 w/v concentration range. In the presence of 20% w/v Pluronics the drug solubility increased substantially, ranging from 1.9 times (F88) to ca. 3.0 times (P85) the solubility in water at the same temperature (0.57 g/100 ml). Analysis of the solubility data indicated that the solubility of tropicamide increased as the oxyethylene content of the surfactants increased, and that the amount of drug solubilized per EO unit decreased with increasing hydrophilicity (increasing OE chain length) of surfactants. Calculation of the relative amount of drug bound to the POE and to the POP portions of the surfactant molecules indicated that binding occurs in part to the hydrophilic (POE) outer mantle, and in part to the hydrophobic, (POP) inner core of the micellar aggregates, with POE/POP binding ratios varying from 1.17 to 3.13, depending on the polymer type.

Biological activity tests were carried out with some 15% w/v polymeric solutions (L64, P75, P84, P85 and F87) containing 1.0% w/w tropicamide, and with some 20.0% w/v solutions (P85, F87) containing 1/5% w/w drug. The results indicate that tropicamide bioavailability, both in rabbits and in humans, was not decreased by micellar solubilization, and that some Poloxamers can perform satisfactorily as solubilizing vehicles for tropicamide, producing neutral 1.0% and 1.5% drug solutions which are better tolerated and more effective than the standard aqueous eyedrops.

Introduction

A substantial disadvantage of tropicamide, a synthetic mydriatic and cycloplegic drug widely used for refractive examination, is its relatively poor water solubility (570 mg/100ml at 25 °C).

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The drug solubility may be further reduced by other common ingredients of ophthalmic solutions (buffers, tonicity-adjusting agents, preservatives, etc.). A 1.0% solution in water can be obtained by adjusting the pH of the solution to a relatively low value (about 5.0), and thus increasing the solubility of the drug, which is a weak base, by ionization. The 1.0% tropicamide collyria, however, are irritant and may require several instillations in order to elicit the desired response, on account of the dilution and elimination of the drug resulting from induced lacrimation and reflex linking.

This present study was carried out to evaluate a series of polyoxyethylene–polyoxypropylene (POE-POP) block copolymers (Poloxamers, or Pluronics) as tropicamide solubilizers for the preparation of ophthalmic solutions potentially showing increased eye tolerance and activity.

Although Poloxamers have been widely investigated as topical pharmaceutical vehicles, endowed with solubilizing and/or suspending properties (cf. e.g. Goodhart and Martin, 1962; Saski and Shah, 1965; Newton et al., 1973; Schmolka, 1974; Stoll and Franz, 1978; Chen-Chow and Frank, 1981a and b; Fromming and Heyer, 1981; Geneidi et al., 1981; Hadgraft and Howard, 1982; Lin and Kawashima, 1985; etc.), few applications of these polymers in the ophthalmic field have been reported. A typical property of some Poloxamers, i.e. the capacity of showing a sol–gel transition in the 25–35 °C temperature range, giving the so-called "thermogels", has in particular attracted the attention of some ophthalmic researchers. A gel of this type, based on Poloxamer 407, useful for treatment and prevention of eye disorders (in particular, the sicca syndrome) was patented by Krezanoski (1977). Miller and Donovan (1982) also evaluated this polymer as a vehicle for pilocarpine by testing the miotic response induced in rabbits, while Gurny et al. (1985) compared the miotic activity of the same thermogel with that of some latex preparations, also forming gels in situ. Other ophthalmic applications of Poloxamers have been patented (Ploss et al., 1982).

In the present investigation, the tropicamide-solubilizing properties of a series of Poloxamers (Pluronics L64, P65, F68, P75, F77, P84, P85, F87, F88 and F127), and the in vivo activities (both in rabbits and humans) of some of the resulting solutions are described.

Materials and Methods

Materials

Pluronics L64, P65, F68, P75, F77, P84, P85, F87, F88 and F127 (BASF-Wyandotte) were used as received. Tropicamide (Prodotti Roche SpA), m.p. 96–97 °C, was also used without prior purification. Technical grade isopropyl myristate (IPM, Deltyl, Givaudan S.A.) was purified by distillation under reduced pressure, collecting the fraction boiling at 163–166 °C/3.5 mm Hg.

Solubility tests

Solutions of the polymers (4.0–20.0% w/v) in distilled water (10.0 ml) containing excess tropicamide were shaken 24 h in a thermostated water-bath (25 °C). The solutions, after isothermal filtration and suitable dilution, were analyzed spectrophotometrically (256 nm) for tropicamide, against appropriate blank solutions containing the polymers alone.

Determination of partition coefficients

Partition coefficients of tropicamide between IPM and Poloxamer solutions were determined as follows. To solutions (1.5 ml) of tropicamide (0.4–1.3 g/100 ml) in 15.0% w/v Pluronics (L64, P65, P75, F77, P84, P85 and F87) were added 8.0 ml IPM. The mixtures were shaken 24 h at 25 °C, then the phases were separated by centrifugation, and tropicamide was determined in the aqueous phase as indicated before. The concentration in the organic phase was calculated by difference. In all cases linear partition isotherms were obtained, from whose slopes the partition coefficients were calculated. The IPM/water partition coefficient of tropicamide was also determined.

Determination of the critical micelle concentration (CMC)

The CMCs of the Poloxamer solutions were determined according to the method of Becher (1962), which consists of the measurement of the

spectrophotometric (530 nm) absorption of benzopurpurin 4B in the presence of different concentrations of polymers, using as reference an aqueous solution of the dye.

Viscosity measurements

These were carried out at 30 °C, using a Rheomat 30 viscometer (Contraves A.G.).

Biological tests

Rabbit studies. The tested vehicles (15.0% w/v Pluronics L64, P75, P84, P85 and F87, all containing 1.0% w/w tropicamide) were filtered through 0.8 μm filters (Millipore Millex-AA), then autoclaved at 2 bars for 20 min prior to use. The tests were carried out on male, unanesthetized New Zealand Albino rabbits (2.0–2.5 kg), selected on the basis of their similar response to light intensity, and to the mydriatic activity of tropicamide. The overall procedure and experimental details suggested by Smolen and Schoenwald (1974), and also reported in our previous paper (Saettone et al., 1982) were followed throughout. Each vehicle was tested on groups of at least 6 rabbits; the administered dose was in all cases 10 μl. Commercial 1.0% aqueous tropicamide eyedrops (Visumidriatic 1%, Merck, Sharp & Dohme) were used as a reference vehicle.

Human studies. These tests were carried out using 4 polymeric solutions (Pluronics P85 and F87 15.0% w/v containing 1.0% w/w tropicamide, and the same polymers at the 20.0% w/v concentration, containing 1.5% w/w tropicamide), sterilized as indicated before. Each vehicle was tested, under medical supervision, on groups of at least 10 healthy Caucasian informed male volunteers, aged 18–22 years, free from ocular lesions or disorders. The administered dose was in all cases 50 μl, and the reference vehicle was the same as in the rabbit studies. For the mydriatic activity, the overall testing procedure and data treatment were analogous to those described in a previous paper (Saettone et al., 1984). The cycloplegic activity of tropicamide in the different formulations was evaluated, on the patients also submitted to the mydriatic activity tests, using a special device for near point measurement (Prince Rule, American Optical Co.). After determination of the basal near point of accommodation, the drug was instilled and measurements of the near point were repeated (when necessary, by applying an appropriate refractive correction) at 10 min intervals until full recovery. All measurements were converted to diopters of accommodation, and the results were plotted as D (difference between the basal dioptric value and the observed value) vs time. The average response parameters for each vehicle (peak time, maximal cycloplegic intensity, duration of effect, area under the activity vs time curve) were calculated from these plots.

Results and Discussion

Physicochemical data

Some of the essential characteristics of the polymers selected for this study are listed in Table 1. The compounds belonged to 3 main series, each characterized by a constant molecular weight of the hydrophobic, polyoxypropylene (POP) portion. To a first series (POP weight 1750) belonged Pluronics L64, P65 and F68 (polyoxyethylene, POE, weight 1150, 1650 and 6650, respectively); to a second series Pluronics P75 and F77 (POP weight 2050, POE weight 2100 and 4550, respectively); and to a third series Pluronics P84, P85, F87 and F88 (POP weight 2250, POE weight 1950, 2350, 5450 and 9150, respectively). The last polymer, Pluronic F127 (POP weight 4000, POE weight 8600) was chosen on account of its capacity for forming thermogels of pharmaceutical interest. Table 1 also indicates: (i) the pH values of 15.0 w/v solutions of the surfactants; (ii) the critical micelle concentration (CMC) of the surfactants; (iii) the apparent partition coefficient of tropicamide between IPM and 15% w/v Pluronics solutions; and (iv) the viscosity of the solutions used for the biological tests.

As shown in Table 1, the pH values of the Pluronics solutions were in the range 6.68–7.25, i.e. very close to the ocular physiological range (7.3–7.7). The CMC values, which were obtained by a dye solubilization method, should correspond to the concentration at which polymolecular aggregation of the surfactants occurs (Prasad et al., 1979). Although there is considerable confusion

TABLE 1

Physicochemical properties of the Pluronics used in this study

Pluronic type	Molecular weight	Hydrophobic weight (POP)	Hydrophilic weight (POE)	pH (15.0% w/v)	CMC (% w/v)	K_R [a]	η(mPa · s) [b]
L64	2900	1750	1150	6.81	2.47	0.150	3.34 [c]
P65	3400	1750	1650	7.02	0.32	0.157	–
F68	8400	1750	6650	6.70	0.09	0.144	–
P75	4150	2050	2100	6.96	0.38	0.171	4.26 [c]
F77	6600	2050	4550	6.80	1.20	0.169	–
P84	4200	2250	1950	7.25	0.85	0.138	3.78 [c]
P85	4600	2250	2350	6.85	1.54	0.127	4.36 [c]; 10.05 [d]
F87	7700	2250	5450	6.70	0.60	0.141	8.25 [c]; 28.80 [d]
F88	11400	2250	9150	7.08	0.65	0.170	–
F127	12600	4000	8600	6.68	0.62	0.176	–

[a] Partition coefficient of tropicamide between IPM and 15% w/v Pluronics solutions, at 25 °C. The partition coefficient of tropicamide between IPM and water, K_{IPM/H_2O}, was 0.33 at the same temperature.
[b] Viscosity (Newtonian) of the solutions used for the biological tests (30 °C).
[c] 15.0% w/v solutions.
[d] 20.0% w/v solutions.

on the subject of solution behaviour of Pluronics, whose association pattern with increasing concentration appears extremely complex (Al-Saden et al., 1982), it seems now established that these surfactants may form "monomolecular" micelles, resulting from conformational changes, at low concentrations, and conventional, multimolecular micelles at higher concentrations. The former are detectable by surface tension changes, and the latter by the dye uptake technique, or by other more complex physicochemical methods. The CMC values of the Pluronics under investigation (as determined by the dye uptake method) were in the range 0.09–2.47 g/100 ml: thus all solutions used for the solubility studies (concentration range 4.0–20.0 g/100 ml) were at concentrations well above the CMC.

The apparent partition coefficient values of tropicamide, K_R, between IPM and 15.0% w/v Pluronics solutions were determined in order to evaluate the relative capacity of the drug of distributing, in equilibrium conditions, between an organic phase (potentially representative of the corneal epithelium) and the aqueous, polymeric phase. While the K_R value of tropicamide between IPM and water is 0.33, the partition coefficient values in the presence of 15.0% w/v surfactants showed a marked decrease (average value 0.154, range 0.127–0.176), evidently on account of micellar inclusion and/or complexation of the drug by the polymers.

The saturation solubility values of tropicamide at 25 °C in different concentrations of Pluronics solutions are listed in Table 2. As shown in Table 2, in the presence of 20% w/v surfactants, the drug solubility increased substantially, ranging from 1.9 times (F88) to about 3 times (P85) the solubility in water at the same temperature. The solubility of tropicamide in 20% w/v Pluronic F127 was not determined, on account of the high viscosity of this solution. At the 15% w/v concentration, however, the solubilizing properties of this surfactant were in the same range, or in some cases lower, with respect to those of other members of the series.

The solubility data presented in Table 2 were plotted as mol/l tropicamide solubilized in excess over the water solubility, $S - S_0$, vs the Pluronics concentration, also expressed in mol/l. The resulting solubility isotherms (not reported) showed the saturation solubility of the drug to increase linearly with increasing surfactants concentration in the 4.0–20.0% w/v concentration range. Most of the plots exhibited non-zero intercepts. This might be explained assuming solubilization of tropicamide to begin at concentrations greater than the CMC, thus providing an initially non-linear isotherm. Accordingly, the plot corresponding to the

TABLE 2

Solubility of tropicamide at 25 °C, in g/100 ml, in aqueous solutions of Pluronics

Pluronic conc. (% w/v)	Pluronic type									
	L64	P65	F68	P75	F77	P84	P85	F87	F88	F127
20	1.32	1.27	1.30	1.35	1.33	1.61	1.75	1.51	1.09	–
15	1.13	1.14	1.24	1.04	1.02	1.44	1.49	1.35	0.99	1.02
10	0.95	0.91	0.99	0.88	0.86	1.03	1.14	1.01	0.81	0.84
8	0.84	0.75	0.88	0.77	0.83	–	1.05	–	0.71	–
6	0.73	0.70	0.79	0.70	0.65	0.78	0.95	0.83	0.67	0.69
4	0.65	0.62	0.73	0.65	0.61	0.74	0.84	0.75	0.60	0.62

surfactant with the lowest CMC value, F68 (CMC = 0.09 g/100 ml) showed practically a zero intercept. However, two other Pluronics with higher CMC values, P85 and F87, gave solubility isotherms with intercepts very close to the origin, a fact that might be attributed to the mentioned complex association behaviour of these polymers at low (< CMC) concentrations. In any case, the solubilizing behaviour of Pluronics at low concentrations was not further considered, being outside the scope of the present investigation.

The values of the slopes of the solubility isotherms, representing the moles of tropicamide solubilized per mole of each surfactant, were plotted vs the percentage of oxyethylene in each polymer molecule, as shown in Fig. 1. Since each point in this graph corresponds to the moles of tropicamide solubilized per mole of surfactant, its positive slope indicates that tropicamide shows increased solubilization as the oxyethylene content of the Pluronics increases. Collett and Tobin (1979), in a similar study on substituted acetanilides, obtained analogous results with the more hydrophilic drugs, while the more hydrophobic ones showed a decreased solubilization as the POE content of the surfactants increased. The slope of the graph in Fig. 1, i.e. 2.16×10^{-2}, is very close to that (2.74×10^{-2}) reported for 4-methoxyacetanilide, one of the relatively hydrophilic drugs mentioned by Collett and Tobin (1979), and is in agreement with the moderately hydrophilic character of tropicamide. In further analogy with the results of Collett and Tobin (1979), when the solubilization was expressed as the amount of tropicamide solubilized per ethylene oxide group, the solubilizing capacity of the Pluronics decreased with increasing oxyethylene chain length (cf. Fig. 2). Each point in the graph in Fig. 2 represents the slope of a plot of molar solubilization of tropicamide vs equivalents of ethylene oxide in each Pluronic, i.e. it represents the moles of solubilizate taken into the micelle per individual ethylene oxide unit of surfactant. In summary, the graph indicates that the amount of tropicamide solubilized per EO unit of surfactant decreases with increasing hydrophilicity of surfactant. This result is also in line with the findings of Goodhart and Martin (1962) and of Gouda et al. (1970), who investigated the solubilization of benzoic acid derivatives

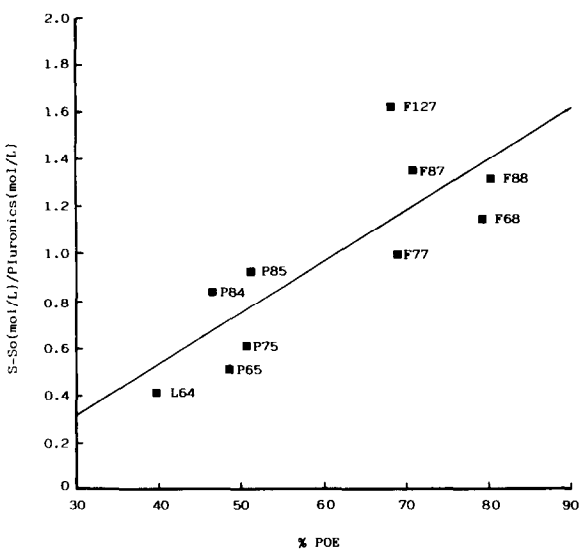

Fig. 1. Moles of tropicamide solubilized per mole of Pluronics vs oxyethylene content of polymers. See text for explanations.

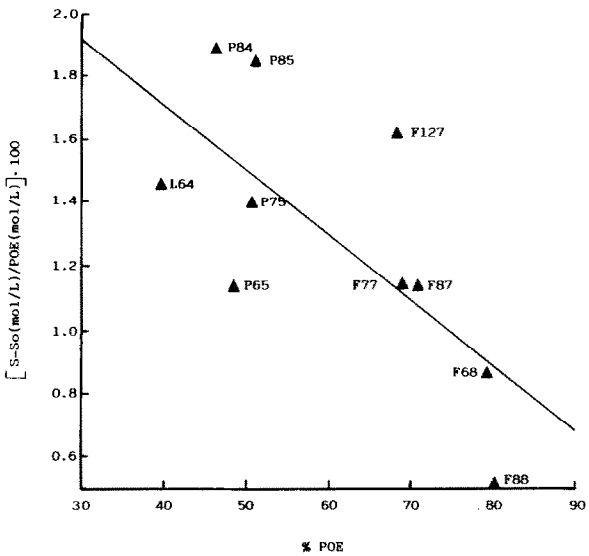

Fig. 2. Moles of tropicamide solubilized per moles of oxyethylene unit of Pluronics vs oxyethylene content of polymers. See text for explanations.

and of barbiturates, respectively, by polyoxyethylene stearates.

The solubilization data were further analyzed according to the method of Mukerjee (1971), in order to obtain information on the relative amount of tropicamide bound to the hydrophilic (POE) and to the hydrophobic (POP) portion of the molecule. This author has shown, in a study on solubilization of benzoic acid derivatives by polyoxyethylene stearate, that a plot of the equivalents of drug solubilized per equivalent of ethylene oxide, $S - S_0/\text{POE}$, versus the stearate/POE mole ratio of the surfactants, gives a linear curve whose intercept, a, represents the solubilization of the drug in the micellar oxyethylene "mantle", and whose slope, b, represents the solubilization in the hydrophobic "core". A plot of this type is shown in Fig. 3. The data of the line, calculated by the least-squares method, are as follows : a (amount of tropicamide bound to the POE portion, in Eq/Eq) $= 8.32 \times 10^{-3}$; b (amount bound to the POP portion, in Eq/Eq) $= 6.15 \times 10^{-3}$; and r (correlation coefficient) $= 0.6272$. The correlation coefficient is rather low, possibly on account of the uncertainties in the reported composition of the Pluronics, which were unpurified commercial samples. The data, however, should be considered indicative of the fact that a substantial portion of the drug is bound to the oxypropylene portion of the molecules, and, if true micelles are present in the polyoxamer solutions, tropicamide should be partly solubilized in the poloxyethylene outer mantle, and partly in the polyoxypropylene inner core of the micellar aggregates. A simple calculation showed the ratio, R, of the moles of tropicamide solubilized by the POE chains to the moles solubilized by the POP chains to be the following (for the polymers used in the subsequent biological study): L64, 1.17; P75, 1.83; P84, 1.54; P85, 1.35; F87, 3.13. Even if the real significance of these figures may be open to question, also on account of the low correlation coefficient of the linear regression illustrated in Fig. 3, the data indicate a substantial binding of tropicamide to the hydrophilic micellar portion. It should be mentioned that Collett and Tobin (1979), in their experiments on solubilization of substituted acetanilides by Pluronics, found that binding by the hydrophobic portion greatly exceeded binding by the hydrophilic portion.

Biological data

The results of the solubilization tests (cf. Table 2) showed that all the polymers under investigation at the 15.0% w/v concentration, with the exception of F88, could take into solution 1.0% w/w tropicamide. For the rabbit experiments a first series of polymers was selected, namely, L64, P75, P84, P85 and F87. The first two were chosen as representative of the "6" and of the "7" series (POP weight 1750 and 2050, respectively). The remaining ones belonged to the "8" series (POP weight 2250), and were chosen on account of their good solubilizing properties: Pluronic F127 was excluded from this first series of tests on account of its particular rheological behaviour. All the solutions tested in rabbits contained 15.0% w/v polymers and 1.0% w/w tropicamide.

The results of the mydriatic activity tests on the experimental animals, summarized in Table 3, indicate that all the polymeric vehicles tested were capable of increasing the bioavailability of 1.0% tropicamide with respect to a standard 1.0% commercial solution of the drug. Two vehicles, L64 and P85, showed a significantly greater AUC value

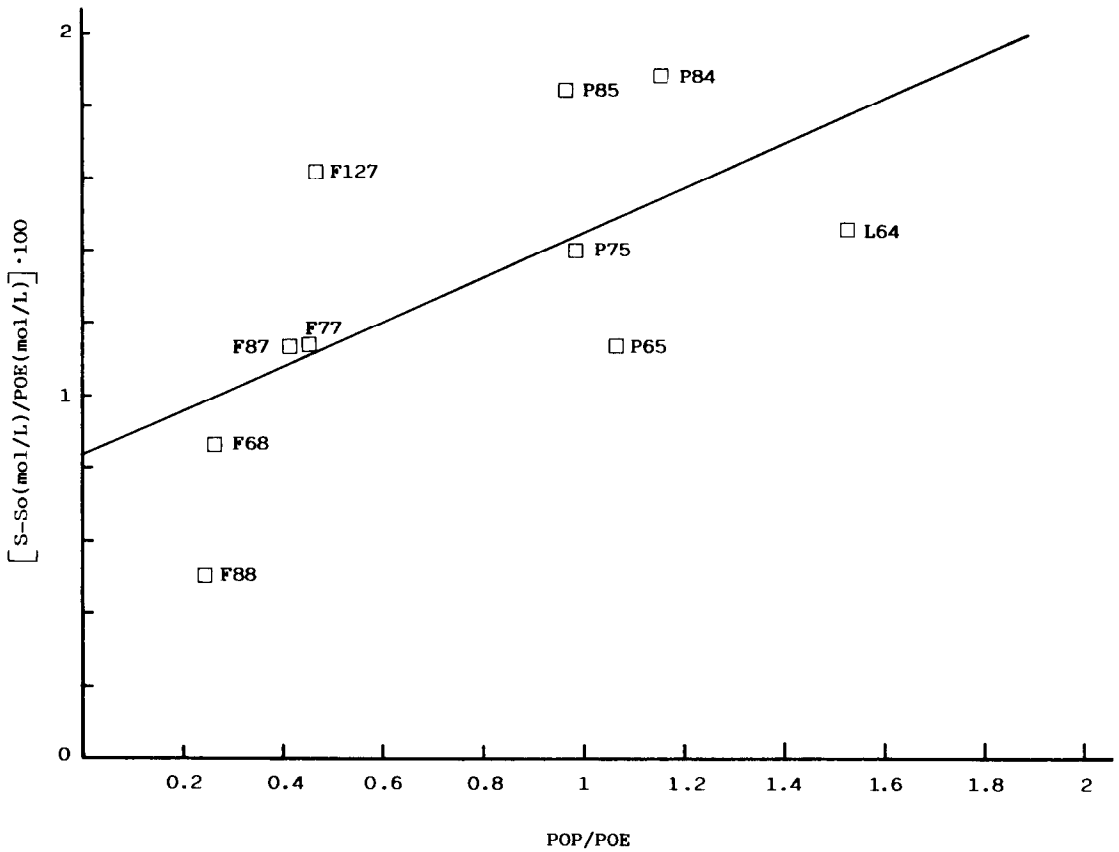

Fig. 3. Moles of tropicamide solubilized per moles of oxyethylene unit of Pluronics vs POP/POE ratio of polymers. See text for explanations.

($P < 0.05$) compared to the reference solution (RS). The bioavailability increases were essentially determined by an increased duration (about 60 min) of the mydriatic effect; the most active vehicle (L64) also increased the I_{max} (maximal mydriatic response), even if not to a statistically significant degree. Also, no statistically significant differences in the AUC values, shown by the different polymeric vehicles, were detectable. All the Pluronic solutions tested, with the exception of L64, reduced slightly the peak time. This was rather unexpected considering the viscosity of the solutions (range 3.34–8.25 mPa · s; cf. Table 1). In fact, an increased vehicle viscosity should prolong the presence of the drug at the absorption site and extend the absorption process, thus producing a delay in the time to peak (Sieg and Robinson, 1977). Actually, the peak time of the most viscous vehicle (F87) was shorter than that of the reference aqueous solution. It might be speculated that tear dilution, caused by the irritant effect of the slightly acidic solution, was responsible for the observed delay in peak time.

The human tests were carried out using 4 polymeric vehicles, namely, 15% w/v P85 and F87 containing 1.0% w/w tropicamide, and the same polymers at the 20% concentration, containing 1.5% w/w drug. Mydriasis and cycloplegia tests were performed together, on the same groups of patients. The overall results are summarized in Table 3. In the mydriasis tests, both 1% polymeric solutions showed a slight decrease of I_{max}, a moderate increase of duration of activity, and only a slight, non-significant increase of bioavailability (AUC) with respect to the reference solution, RS. The 1.5% polymeric solutions showed the same

TABLE 3

Summary of the activity parameters in rabbits and humans of tropicamide in Pluronic solutions

Vehicle	Peak time (min)	I_{max} (mm) (±95% CL)	Duration (min) (±95% CL)	AUC (cm^2) (±95% CL)	AUC_{rel}
Mydriasis, rabbit data					
RS [a]	40	2.66 (0.25)	300 (3)	80 (14)	1.00
L64 15% w/v [b]	40	2.90 (0.22)	360 (28)	130 (14)	1.62
P75 15% w/v [b]	30	2.40 (0.20)	360 (30)	104 (13)	1.30
P84 15% w/v [b]	30	2.33 (0.22)	360 (25)	100 (15)	1.25
P84 15% w/v [b]	20	2.50 (0.27)	360 (41)	107 (12)	1.33
F87 15% w/v [b]	30	2.41 (0.30)	360 (38)	109 (15)	1.36
Mydriasis, human data					
RS [a]	30	4.73 (0.34)	270 (35)	139 (15)	1.00
P85 15% w/v [b]	20	4.59 (0.42)	335 (24)	152 (25)	1.09
F87 15% w/v [b]	20	4.55 (0.59)	335 (25)	143 (37)	1.03
P85 20% w/v [c]	20	4.72 (0.43)	360 (40)	183 (30)	1.32
F87 20% w/v [c]	20	4.72 (0.64)	390 (30)	197 (39)	1.42
Cycloplegia, human data					
RS [a]	10	9.53 (1.52)	180 (52)	126 (39.2)	1.00
P85 15% w/v [b]	20	13.8 (1.61)	240 (41)	216 (105)	1.71
F87 15% w/v [b]	20	10.8 (1.7)	270 (30)	155 (59.1)	1.23
P85 20% w/v [c]	20	11.8 (1.85)	240 (32)	200 (62.3)	1.59
F87 20% w/v [c]	20	13.1 (3.12)	270 (29)	217 (125)	1.72

[a] RS = reference solution: commercial 1.0% tropicamide eyedrops.
[b] 1.0% w/w tropicamide.
[c] 1.5% w/w tropicamide.

I_{max} as the reference solution, but their duration of activity was significantly greater. Both solutions showed an increased bioavailability over RS, but the increase was statistically significant only in the case of the F87 solution. As in the rabbit experiments, the peak time of the mydriatic response was slightly decreased in all cases (20 min vs 30 min for the reference solution).

The results of the cycloplegia tests, conversely, indicate for all vehicles a slight increase of the time to peak, an increase of I_{max} (statistically significant only in the case of P85 15%), and an increased duration of activity, which was significant only for the two F87 vehicles. The cycloplegic AUC was in all cases greater with respect to the reference solution, but in no case was the difference statistically significant, due to a large standard error associated with the measurements. Large inter-subject variations in the cycloplegic response to tropicamide are also evident in the reports of other authors (cf. e.g. Gettes and Belmont, 1961; Pollack et al., 1981). As to any difference with the reference solution, RS, all polymeric vehicles were perfectly tolerated and did not induce a stinging sensation.

Conclusions

The present results indicate that some Poloxamers can perform satisfactorily as solubilizing vehicles for tropicamide, producing neutral 1.0% and 1.5% w/w solutions which are better tolerated and sometimes more effective than the standard aqueous 1% tropicamide collyria.

Previous reports on attempts to increase the efficacy and bioavailability of tropicamide by the use of polymeric additives are contradictory. In rabbit studies, Smolen and Schoenwald (1974) failed to find significant effects attributable to the presence of some polymers, while Minja Lee and Hammarlund (1974) reported that two polymers (hydroxypropylcellulose and guar gum) significantly increased the mydriatic activity of the drug

in the same animals. Mattila et al. (1968), in human studies, reported that the cycloplegic effect of the drug was more influenced than the mydriatic effect by the presence of some adjuvants (methylcellulose and/or a cationic surfactant). Previous work from this laboratory (cf. e.g. Saettone et al., 1982, 1984) has shown, on the contrary, a significant effect of some polymeric additives on the mydriatic response to 0.2% tropicamide both of rabbits and humans. It should be pointed out, however, that high concentrations of the drug must be instilled in order to provide sufficient accommodative inhibition for a cycloplegic refraction: this justifies the use of the standard 1% "acidic" tropicamide eyedrops, or the present attempt to produce neutral 1.0% or 1.5% solutions by micellar solubilization.

One drop of the present 1.5% polymeric solutions could be used to induce clinically useful mydriatic and cycloplegic effects. The overall bioavailability of the drug in the Poloxamer solubilizates depends on a series of factors, some of which, such as the inclusion of the drug in the micelles and its complexation by the polymer macromolecules, may exert a negative influence, while others – e.g. an increased time of residence resulting from an increased viscosity, and a reduced tear dilution and elimination by blinking, due to the absence of an irritant effect – may favour transcorneal absorption and hence bioavailability. The relatively low bioavailability increases observed in humans (1.4 times for mydriasis, and 1.7 times for cycloplegia, with respect to RS) possibly indicate that drug binding and micellar inclusion by the Poloxamers overwhelms the positive effects resulting from: (a) an increased viscosity; (b) a reduced irritancy; and (c) an increased concentration (in the case of the 1.5% solutions). Binding effects are also evidenced by the low K_{IPM/H_2O} values observed in the presence of the polymers, indicative of a reduced capability of the drug to abandon the aqueous phase for an organic, non-polar phase representative of the corneal epithelium.

It is the contention of the present authors, however, that the advantages presented by the Poloxamer solutions tested in the present study may warrant further investigations on their clinical use for refractive examination, or for the treatment of eye conditions requiring the mydriatic/cycloplegic effect of tropicamide.

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