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High-molecular weight polyoxyethylene as an additive in ophthalmic solutions

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Summary

High-molecular weight polyoxyethylene (POE) was evaluated for potential use as an additive in ophthalmic solutions of indomethacin. The basic drug model was formulated on the basis of hydrotropic and micellar interactions. The influence of POE on the solution viscosity and stability, as well as on in vitro diffusion of indomethacin through an artificial lipid membrane, was comparatively studied with other hydrophilic polymers. It was established that POE shows advantages over hydroxypropylmethylcellulose and polyvinyl alcohol and can be used as a polymeric additive in ophthalmic aqueous solutions of indomethacin.

Introduction

In recent years hydrophilic polymers have been widely used in ophthalmic solutions to improve their therapeutic effectiveness and tolerance. Usually, these polymers increase the corneal contact time of the drug solution, impeding the elimination of the latter by tear turnover. As a result, the drug concentration remains at the therapeutic level over a longer time period so that in some cases a reduction in dose can be made.

The aim of the present investigations was to study high-molecular weight polyoxyethylene (POE) as a viscous additive in ophthalmic solutions of indomethacin. For this purpose, its influence on some characteristic drug solution properties, such as viscosity, stability and in vitro drug diffusion, was evaluated.

There are data in the patent literature concerning dermal preparations with antiseptics as well as ophthalmic solutions for contact lenses, formulated on the basis of POE (German Offen., 1971; US Patent, 1976; Bulgarian Patent, 1983a,b).

The main advantages of this polymer are its low toxicity, good adhesion ability to the mucosae and its high water solubility.

Indomethacin was chosen as a model drug because of its recent use as a potent anti-inflammatory agent in ophthalmic surgery (Searle et al., 1990). Moreover, as a result of previous studies (Bogdanova et al., 1992) an aqueous solution of indomethacin was formulated on the basis of hydrotropic and micellar interactions.

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Materials and Methods

Materials

Indomethacin was a gift from Pharmachim (Bulgaria). High-molecular weight polyoxyethylene (POE) (Mol. Wt 5×10^5–5×10^6) (Badimol®-M) was obtained from the Institute of Polymers (Bulgarian Academy of Sciences).

Hydroxypropylmethylcellulose 80–120 cP (HPMC) was purchased from Aldrich (Milwaukee, WI). Hydroxyethylcellulose (HEC), polyvinyl alcohol 72000 (PVA), sodium ethylmercurithiosalicylate, sodium metabisulfite, propylene glycol, Na_2EDTA, and polyoxyethylene sorbitan monooleate were supplied by Fluka (Buchs, Switzerland).

Methods

0.5% w/v indomethacin aqueous solutions were prepared following the procedure described by Bogdanova et al. (1992).

Viscosity measurements

The viscosity of the indomethacin solutions containing POE, as well as of the pure polymer solutions at the same concentrations (0.15, 0.25 and 0.40% w/v) before and after sterilization, was measured in triplicate at 20°C using a Rheotest (DDR) viscosimeter with S/S1 system of coaxial cylinders.

In vitro indomethacin diffusion

A Sartorius-Absorption simulator (Sartorius GmbH, Germany) with a modified diffusion cell (Ratschev and Dimitrova, 1989) was used. The volume of the test preparation (phase I) was 2 ml. 100 ml of phosphate buffer pH 7.4 served as phase II. The lipid membrane was an intestinal membrane (D1) with a surface area of 2.5 cm^2. The concentration of indomethacin was determined spectrophotometrically at 320 nm in samples withdrawn from phase II. The diffusion constant (k_d) values are calculated according to Stricker (1971).

TABLE 1

Formulation of the basic 0.5% w/v aqueous solution of indomethacin

Composition	Amount (g)
Indomethacin	0.5
Polysorbate 80	0.05– 1.0
Propylene glycol	10.0 –30.0
Hydrophilic polymer	0.15– 3.0
Preservative	0.004
Antioxidants	0.20
Phosphate buffer pH 6.8	ad 100.0 ml

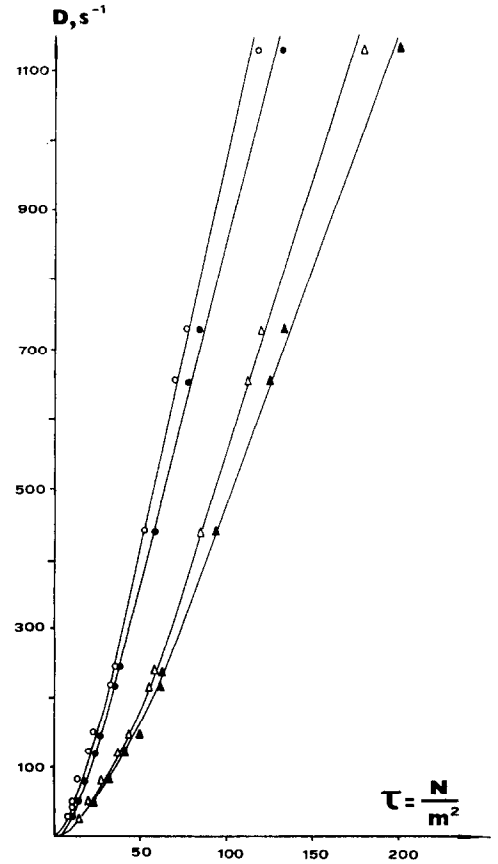

Fig. 1. Rheograms of POE solutions at concentrations (% w/v): 0.4 (▲,△) and 0.25 (●,○). Rheograms depicted with filled symbols correspond to the unsterilized solutions.

Stability studies

Test preparations and storage conditions 10 ml of 0.5% w/v indomethacin solutions formulated with POE were placed in well closed vials and stored at 90°C for 6 h in a hot-air oven (Hereus, Germany).

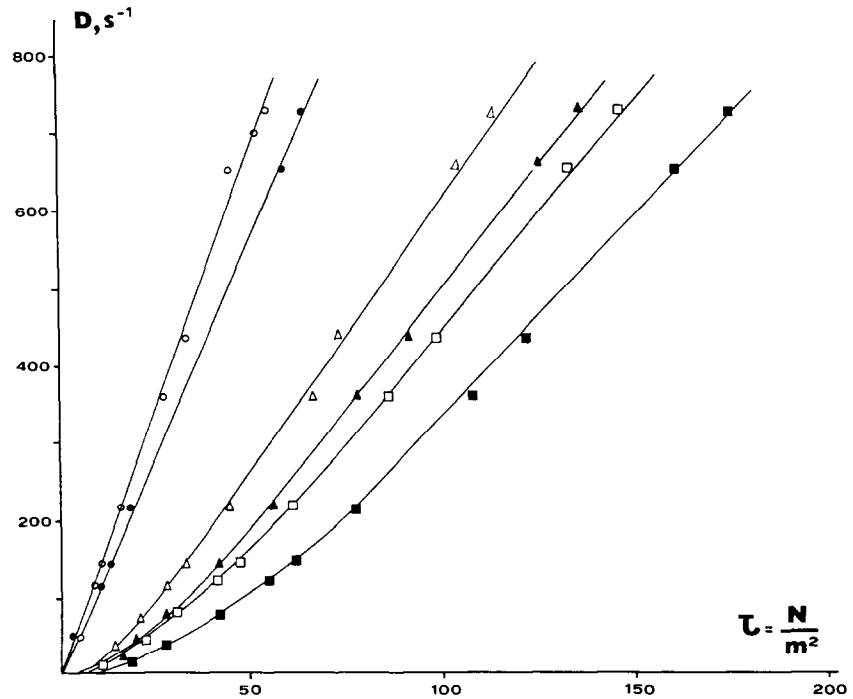

Fig. 2. Rheograms of indomethacin solutions containing POE at concentrations (% w/v): 0.15 (●,○), 0.25 (▲,△) and 0.4 (■,□). Rheograms depicted with filled symbols correspond to the unsterilized solutions.

The amount of undecomposed indomethacin was checked every 60 min up to the 6th hour.

Another set of samples was stored at room temperature in a place protected against light for a 1 year period.

Stability evaluation The stability of the studied solutions was evaluated via the following techniques.

Thin layer chromatography Ready made alufolia of 0.2 mm thickness (DC-Alufolien Kieselgel

TABLE 2

Indomethacin test solutions (0.5% w/v)

Test solution no.	Concentration of polysorbate 80 (% w/v)	Type of polymer	Concentration of the polymer (% w/v)	Diffusion constant (k_d)($\times 10^{-3}$) (cm min^{-1})	Amount of decomposed indomethacin (%)
1	–	–	–	3.64	–
2	1.0	–	–	2.84	12
3	–	POE	0.40	1.90	–
4	0.1	POE	0.40	–	12
5	0.5	POE	0.40	–	11
6	1.0	POE	0.40	2.50	12
7	1.0	POE	0.25	–	13
8	1.0	POE	0.15	–	–
9	–	HPMC	1.0	3.02	18
10	1.0	HPMC	1.0	2.13	11
11	1.0	PVA	3.0	2.13	14
12	1.0	HEC	2.0	1.96	–

60 F254, Fluka, Switzerland) were used. 20 μl methanolic solution of 0.02 mg indomethacin were spotted. The mobile phase consisted of *n*-hexane ethyl acetate (60 : 40 v/v) (Nekrothus and Rechetnyak, 1989). Visualization of the spots was performed under UV light at 254 and 360 nm or with iodine vapor.

High-pressure liquid chromatography The HPLC analyses were performed using a Perkin-Elmer liquid chromatograph (series I/I) provided with a UV detector at a fixed wavelength of $\lambda = 254$ nm, a Rheodyne 7010 injector of 50 μl volume and two Chibar-Lichrosorb RP-18 columns, (250/4 mm, 10 mm and 125/4 mm, 5 mm; Merck, Germany). The mobile phase was 65% methanol/35% water/0.05% acetic acid and the flow rate 1.5 μl/min (Tsai et al., 1986).

UV spectrophotometry The spectral characteristics of indomethacin were checked using a Specord UV-VIS recording spectrophotometer (Germany). The concentration of the undecomposed drug was assayed at 320 nm.

Results and Discussion

The formulation of the ophthalmic solution of indomethacin (Bogdanova et al., 1992) used as a model in our studies is shown in Table 1.

Influence of POE on the solution viscosity

The results are plotted in Figs 1 and 2 and listed in Table 3. All data are compared with those for pure polymer solutions.

As can be seen from Figs 1 and 2, the drug models with POE at concentrations of 0.15, 0.25 and 0.40% w/v, as well as the corresponding solutions of polymer, are pseudoplastic structural systems without thixotropy. Moreover, the viscosity of the drug solutions in comparison to that of pure POE is approx. 1.4-times higher, due mainly to the participation of propylene glycol and not to polysorbate 80.

The curves in Figs 1 and 2, as well as the values in Table 3, also show that the 30 min heat sterilization does not decrease the viscosity significantly. More pronounced differences occur with indomethacin solutions. nevertheless, they are in the range of 4–5 cP which can be considered negligible.

Influence on the in vitro diffusion profile of indomethacin

Figs 3 and 4 depict plots of the amounts of indomethacin diffused through an artificial lipid membrane as a function of time. As can be seen the relationship is linear up to the 3rd hour. This linearity enables the calculation of the diffusion constant (k_d) for the process (Stricker, 1971). The

TABLE 3

Viscosity of pure polymer solutions and corresponding 0.5% w/v indomethacin test solutions

Type of polymer and concentration (% w/v)	Viscosity [a] of polymer solutions (cP)		Test solution no.	Viscosity [a] of indomethacin solution (cP)	
	Unsterilized	Sterilized		Unsterilized	Sterilized
POE (0.4%)	21.3	19.0	6	27.6	22.3
POE (0.25%)	13.1	11.7	7	20.6	16.8
POE (0.15%)	–	–	8	9.1	7.5
HPMC (1.0%) (without polysorbate 80)	18.4	17.9	9	32.3	28.4
HPMC (1.0%)	18.4	17.9	10	36.1	33.0
PVA (3%)	17.7	17.7	11	34.6	34.6
HEC (1%)	–	–	12	28.6	28.0

[a] Viscosity values calculated at $D = 364.5\ s^{-1}$.

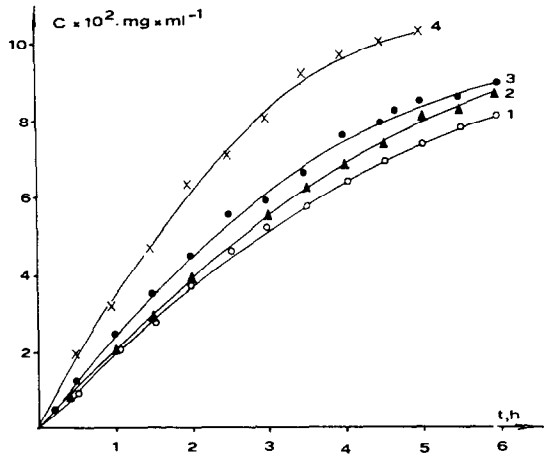

Fig. 3. In vitro diffusion profile of indomethacin from test solutions with: 0.4% w/v POE and 1% w/v polysorbate 80 (○), 0.4% w/v POE with polysorbate 80 (▲), 1% w/v polysorbate 80 without POE (●) and solution formulated without POE and polysorbate 80 (×).

k_d values are listed in Table 3. For comparison, k_d values of indomethacin solutions with HPMC, PVA and HEC are also included.

The results show that POE moderately delays the diffusion of drug, similarly to the other hydrophilic polymers studied (HPMC, PVA and HEC). All values are approx. 1.2–1.9-times lower than that of preparation 2 without a polymer.

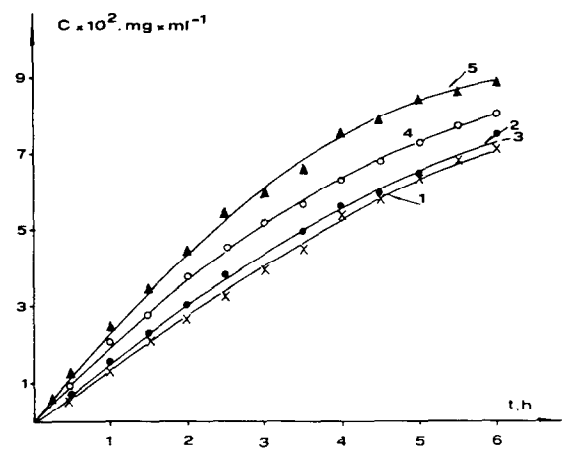

Fig. 4. In vitro diffusion profile of indomethacin from test solutions containing: 2% w/v HEC (×), 1% w/v HPMC (●), 3% w/v PVA (●), 0.4% w/v POE (○) and solution without polymer (▲).

These observations are in agreement with the report of Grass and Robinson (1984) that the diffusion of drugs with low water solubility cannot be significantly delayed when the viscosity of their solutions is in the range 1–90 cP.

Nevertheless, POE in comparison with the other polymers studied exerts a more pronounced effect on the diffusion process. For example, the k_d values of preparation 3 with POE is approx. 1.6-times lower than that of preparation 9 containing HPMC.

In this connection it should also be noted that POE in the presence of polysorbate 80 (preparation 6 increases the rate of diffusion: the k_d value of preparation 6 is about 1.3-times greater than that of preparation 3 which is formulated only with POE. In contrast, HPMC in the presence of polysorbate 80 (preparation 10) delays the diffusion of indomethacin: the k_d value of the model 10 is 1.4-times lower than that of model 9 without polysorbate 80. The different behaviour of the two hydrophilic polymers in the presence of polysorbate 80 suggests that some interactions between tensid micelles and POE can take place. It is clearly evident that similar assumptions need further investigations.

Influence of POE on the stability of indomethacin solutions

The percentages of decomposed indomethacin assayed in different preparations treated under 'stress conditions' are listed in Table 2. The stress conditions – 6 h treatment at 90°C – were chosen on the basis of data reported by Pawelczyk et al. (1979) concerning the hydrolysis of indomethacin in phosphate buffer, pH 7.0 at 90°C.

The results show that POE does not influence the stability of indomethacin in solution. For example, the amount of indomethacin decomposed for model 6 is about 12%, i.e., equal to that of model 2 which is formulated without polymer.

It was also established that the increase in tensid concentration in the range from 0.1 to 1.0% does not increase the stability of indomethacin: the amount of indomethacin decomposed for preparation 4 with 0.1% polysorbate 80 coincides with that of model 6 with a 10-fold higher tensid concentration.

The observations at room temperature confirmed the results obtained from the accelerated stability test. Preparation 6 formulated with 0.4% POE and 1.0% polysorbate 80 shows the stability and can be stored for 1 year.

Conclusions

The results obtained provide sufficient reasons for using POE as an additive in ophthalmic solutions. High-molecular weight polyoxyethylene (POE) in the concentration range from 0.15 to 0.40% w/v does not disrupt the physical and chemical stability of indomethacin aqueous solution. It can delay to some extent in vitro drug diffusion through an artificial lipid membrane and results in optimum viscosity – a prerequisite for prolonged contact with the eye.

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