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COMMUNICATION

Development of Model Aqueous Ophthalmic Solution of Indomethacin

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ABSTRACT

A new model aqueous solution of indomethacin was developed on the basis of Pluronic™ F68 (15%) and F127 (10%). They showed some practical advantages over the models prepared with polyols and polysorbate 80, which were used for comparison. It was found that both Pluronics acted very similarly and were more effective as solubilizers, created an appropriate viscosity, and formed reversible gels at higher temperatures, ensured the indomethacin chemical stability and prolonged in vitro drug diffusion, and showed high physiological tolerance on rabbit eyes. Moreover, indomethacin stability and solution viscosity in the presence of Pluronics did not change after heat sterilization (i.e., the samples can bear heat sterilization).

INTRODUCTION

Recently, a model 0.5% indomethacin ophthalmic solution was proposed by our laboratory (1). The drug dissolution was achieved by interactions with a surfactant, polysorbate 80, and propyleneglycol. Histological studies have shown that not all additives used cause eye irritation (2). The positive results gave us an impetus to extend the investigations in this field.

The object of the present investigation was to develop new indomethacin model solutions with Pluronics™, as well as to prove their advantages over models with polyols—prototypes of the solution described by us previously in Ref. 1.

The Pluronics were chosen because they are known potent solubilizers; they could increase the solution viscosity when used in appropriate concentrations and are nontoxic (4–7).

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EXPERIMENTAL

Materials

Indomethacin was a gift from Sopharma, Bulgaria; polysorbate 80 (Tween 80™) was supplied by Fluka (Buchs, Switzerland). Poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene) block copolymers (Pluronics™ or Lutrols™) were purchased from BASF (Germany). Sodium dihydrogen phosphate and dicalcium hydrogen phosphate were used as buffer substances (Fluka).

Methods

Preparation of 0.5% indomethacin model solutions (Table 1) were according to methods in Ref. 1. The concentration of the solubilizers used was 20% for the polyols propyleneglycol, polyethyleneglycol, or their 1:1 (w/w) mixture; 10% for Pluronic F127; and 15% for Pluronic F68. All freshly prepared solutions were sterilized at 100°C (water steam) for 30 min.

Viscosity measurements were carried out in triplicate at 20°C using a Rheoviscometer after Hoepler (D.D.R).

For stability studies, 10 ml of each model solution were placed in well closed vials and stored in a hot air oven (Hereus, Germany) at ''stress'' temperatures: 40°C, 50°C, 60°C, 70°C, 80°C, and 90°C. Samples were withdrawn at appropriate intervals of time, and the concentration of the nondegraded drug was spectrophotometrically determined at 320 nm. Another set of samples was stored in the dark at ambient temperature for 10 months and was used as a reference set.

For the in vitro diffusion studies (after Ref. 8), the apparatus was an absorption simulator (Sartorius Co., Germany); 2 ml of each sample were placed in a modified donor phase compartment (1). The acceptor phase was 100.0 ml phosphate buffer at pH 7.5, and the membrane was an artificial intestinal lipid membrane with 2.5 cm^2 surface. The concentration of the diffused indomethacin was determined spectrophotometrically at 320 nm.

In vivo studies of the local tolerance were carried out on the eyes of white male rabbits after a single treatment. Two drops from the solutions were instilled into the right eyes. The left eyes were left as references. The reactions of the folds, the conjunctiva, the cornea, and the iris were observed 30 min after the instillation. The ophthalmic drug preparation Indocid™ suspension and pure solutions of Pluronic 68 (15%) and Pluronic 127 (10%) without indomethacin were used for comparison.

RESULTS AND DISCUSSION

Stability Studies

The comparative stability evaluation at stress temperatures as well as the long-term storage at ''normal'' conditions showed that the indomethacin pseudo-first-order decomposition reaction runs relatively slowly with all model solutions (Fig. 1, Table 2, and Table 3). The activation energy E_a values determined from the Arrhenius plots are in the range 17–20 kcal/mol and are typical of hydrolytic drug degradation.

Assuming that indomethacin hydrolysis runs through a transition state complex formation (3), we also calculated the parameter ΔS^*, representing the difference be-

Table 1

Model 0.5% Indomethacin Aqueous Solutions

	Formulation (w/v), Model Solution Number					
	1	2	3	4	5	6
Indomethacin	0.50	0.50	0.50	0.50	0.50	0.50
Tween 80	1.00	1.00	1.00	—	—	1.00
Propyleneglycol	20.00	—	10.0	—	—	20.00
Polyethyleneglycol 400	—	20.0	10.0	—	—	—
Pluronic F68	—	—	—	15.00	—	—
Pluronic F127	—	—	—	—	10.0	—
High molecular weight polyoxyethylene	—	—	—	—	—	0.40
Stabilizers	0.20	0.20	0.20	0.20	0.20	0.20
Buffer at pH 6.8 ad	100.0	100.0	100.0	100.0	100.0	100.0

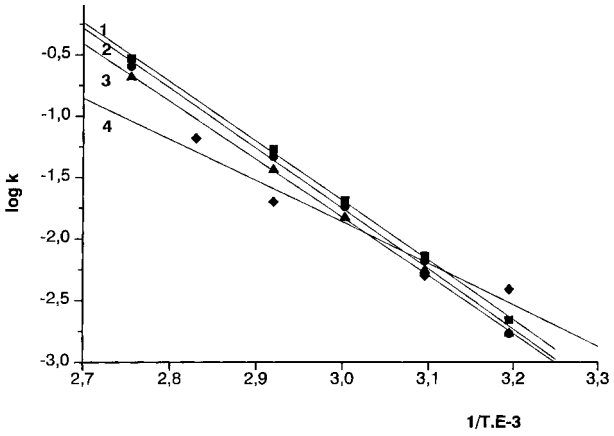

Figure 1. Arrhenius plots: 1, model 1 ($y = 12.83 - 4.84x$; $R = -0.999$); 2, model 2 ($y = 12.95 - 4.90x$; $R = -0.9983$); 3, model 3 ($y = 12.34 - 4.72x$; $R = 0.999$); 4, model 5 ($y = 8.23 - 3.36x$; $R = -0.976$).

tween the standard entropy in the transition state and the entropy in the normal reactant state, by means of Eq. 1 (after Ref. 3):

$$K = (\nu \cdot e^{\Delta S^*/R}) \cdot e^{-\Delta H^*/RT} \quad (1)$$

where $\nu \cdot e^{\Delta S^*/R}$ = Arrhenius factor A, ΔH^* = enthalpy of activation of the transition state; $\Delta H^* \cong E_a$, and ν = frequency of decomposition of the transition state complex.

It is very important to note that all ΔS^* values (Table 3) are negative and can be considered an indication that the assumed activated complex is a less favorable structure (3). Hence, the additives used to formulate model indomethacin solutions influence the drug stability favorably.

However, it is also worthwhile to note that both Pluronics, in comparison to the polyols, act more effectively as solubilizers and stabilizers of the indomethacin and behave very similarly (Fig. 1 and Table 2). Besides, the

Table 2

Rate Constants k_1 *of Indomethacin Decomposition Reaction in Solutions at ''Stress'' Temperatures*

	Samples				
	1	2	3	4	5
40°C					
k_1 (d^{-1})	$2.2 \cdot 10^{-3}$	$1.7 \cdot 10^{-3}$	$1.7 \cdot 10^{-3}$	$3.72 \cdot 10^{-3}$	$3.89 \cdot 10^{-3}$
$t_{50\%}$ (d)	313.6	418.0	418.0	186.3	178.2
$t_{90\%}$ (d)	47.5	63.3	63.3	28.2	27.0
50°C	1	2	3	4	5
k_1 (d^{-1})	$7.19 \cdot 10^{-3}$	$5.53 \cdot 10^{-3}$	$6.63 \cdot 10^{-3}$	$4.47 \cdot 10^{-3}$	$5.01 \cdot 10^{-3}$
$t_{50\%}$ (d)	96.5	125.4	104.5	155.1	138.4
$t_{90\%}$ (d)	14.6	19.0	15.8	23.5	21.0
60°C	1	2	3	4	5
k_1 (d^{-1})	$20.45 \cdot 10^{-3}$	$14.92 \cdot 10^{-3}$	$18.24 \cdot 10^{-3}$	—	—
$t_{50\%}$ (d)	33.9	46.4	38.0	—	—
$t_{90\%}$ (d)	5.1	7.0	5.8	—	—
70°C	1	2	3	4	5
k_1 (d^{-1})	$53.62 \cdot 10^{-3}$	$36.48 \cdot 10^{-3}$	$46.43 \cdot 10^{-3}$	$20.42 \cdot 10^{-3}$	$19.95 \cdot 10^{-3}$
$t_{50\%}$ (d)	12.9	19.0	14.9	33.9	34.7
$t_{90\%}$ (d)	2.0	2.9	2.3	5.1	5.3
80°C	1	2	3	4	5
k_1 (d^{-1})	—	—	—	$67.61 \cdot 10^{-3}$	$66.07 \cdot 10^{-3}$
$t_{50\%}$ (d)	—	—	—	10.2	10.5
$t_{90\%}$ (d)	—	—	—	1.5	1.6
90°C	1	2	3	4	5
k_1 (d^{-1})	$293.5 \cdot 10^{-3}$	$207.3 \cdot 10^{-3}$	$254.25 \cdot 10^{-3}$	—	—
$t_{50\%}$ (d)	2.4	3.3	2.7	—	—
$t_{90\%}$ (d)	0.4	0.5	0.4	—	—

Table 3

Entropy of Activation of the Transition State ΔS Values at Different Temperatures*

		Temperature					
Model	E_a	40°C	50°C	60°C	70°C	80°C	90°C
1	22.1	−71.2	−68.9	−66.9	−65.0	—	−61.7
2	21.7	−71.8	−69.4	−67.5	−65.8	—	−62.4
3	22.5	−71.8	−69.0	−67.1	−65.3	—	−62.0
4	18.4	−70.3	−70.0	—	−67.2	−64.6	—
5	16.9	−70.2	−69.7	—	−67.3	−64.9	—

models with Pluronics remained more stable at higher temperatures. This fact is of great practical advantage since all pharmacopoeias set requirements for eye solution sterility.

For example, the indomethacin decomposition rate constant for the models with Pluronics stored at 70°C are about four times higher than those obtained at 40°C. For the samples with polyols, this increase is about 25-fold. Besides, model 2 with polyethyleneglycol is the most stable when compared to model 1 with propyleneglycol and model 3, which contains a mixture of both polyols. Conversely, at low temperatures, the model solutions with polyols behave very similarly and remain about two times more stable than the samples with Pluronics.

In general, the slower run of the decomposition reaction in the models with Pluronics is probably due to stronger interactions of indomethacin with Pluronic's micelles and, on the other hand, to the gellification that occurs at elevated temperatures.

Viscosity Evaluation

It was found that the apparent viscosity values of the samples with Pluronics were about two times higher than those of the models with polyols and remained unchanged after heat sterilization in the range 10–13 cP. This fact can be considered another practical advantage

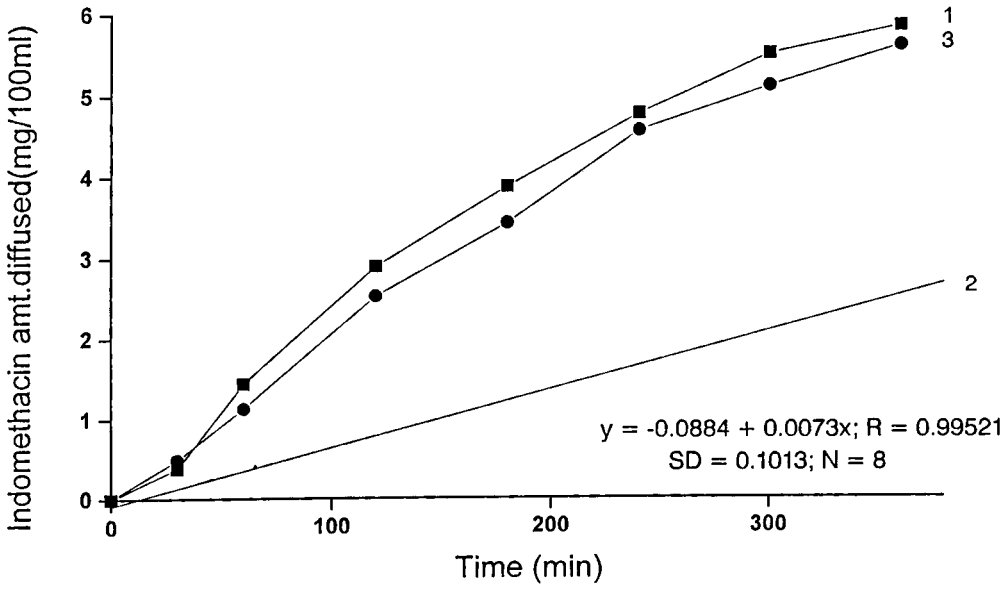

Figure 2. Indomethacin diffusion from model solutions through an artificial barrier: 1, model 1 with $k_d = 2.4\ (cm \cdot min^{-1}) \cdot 10^{-3}$; 2, model 5 with $k_d = 0.9\ (cm \cdot min^{-1}) \cdot 10^{-3}$; 3, model 6 with $k_d = 2.5\ (cm \cdot min^{-1}) \cdot 10^{-3}$.

of the samples with Pluronics over the models with polyols.

In Vitro Diffusion of Indomethacin Through an Artificial Lipid Membrane

The diffusion profiles are depicted in Fig. 2 and clearly show prolonged diffusion, with model 5 containing 10% Pluronics F127 (curve 2). The profile is linear. This phenomenon can be related mainly to the marked ability of Pluronic F127 to increase its viscosity around and above 37°C (9). Hence, it can be expected that Pluronic also will prolong indomethacin activity in vivo.

In Vivo Studies of the Local Tolerance

It was established that the rabbit eye tolerated very well the Pluronics solutions. Moreover, their local tolerance was higher than that for the Indocid suspension and for the model 1 with propyleneglycol.

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