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TECHNOLOGY AND BIOPHARMACEUTICAL AVAILABILITY OF SOLID OCULAR INSERTS CONTAINING SULFADICRAMIDE AND SOME PROMOTERS

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Abstract: Technology for obtaining solid ocular inserts made of poly(vinyl alcohol), containing sulfadicramide and some sorption promoters, was worked out. The rate of drug release was studied by assuming the pseudo–first order kinetics to hold true. An isolated animal cornea was used to measure the coefficients of permeability and the efficiency of sulfadicramide penetration through these corneas.

Keywords: sulfadicramide, biopharmaceutical promoters, polymer ocular inserts, permeability coefficients.

Increased attention has been given in recent years to the development of new systems for the delivery of ophthalmic drugs. Some ocular delivery systems extend the duration of drug action by enhancement of corneal adsorption; these include soluble gels and emulsions, ointments, ocular inserts, ion–pair associations, pro–drugs and liposomes. Other delivery systems provide for a controlled release of drugs, thus avoiding the pulse–entry with which side–effects are associated. These systems can be based on any of several different mechanisms, and include both soluble and nonsoluble matrices.

Studies on the biopharmaceutical availability of the ocular ointments containing sulfadicramide (SDC) have indicated that the release of that active substance also follows to the zero–order kinetics, yet the released SDC does not show the ability to penetrate into an animal cornea *in vitro* (1). Addition of selected sorption promoters to these ointments enabled SDC to penetrate through animal cornea *in vitro* (2).

The earlier described polymer solid ocular inserts produced on the basis of poly(vinyl alcohol) were proved to inhibit a penetration of the active substance released from them through the cornea (3). The aim of the study reported in this paper is to work out a technology of obtaining solid ocular inserts made of PVA containing, in addition to SDC, some sorption promoters, as their addition substantially affects the solubility of the active substance in lacrimal fluid and enables it to diffuse through the cornea (2) and to evaluate their biopharmaceutical performance.

EXPERIMENTAL

Reagents

Sulfadicramide („Polfa'' Poznań, Poland); glutathione oxidized (Roanal, Hungary); polyoxyethylene–9 lauryl ether, L–α–lysophosphatidylcholine and deoxycholic acid sodium salt were purchased from Sigma Aldrich Chemicals Co (Poland); water was double distilled from silica glass. All other reagents and solvents were of reagent grade.

Apparatus

Perfusion apparatus for the determination of the permeability rate of drugs constructed according to the literature (4); UV/Vis spectrophotometer Specord M–40 (Carl Zeiss, Germany); pH–meter (EKO, Wrocław).

Preparation of a solid ocular insert containing sulfadicramide and some promoters

The ocular inserts made of PVA and containing SDC were prepared on the basis of the earlier obtained PVA membranes modified under earlier established thermal conditions, *i.e.* kept for 2 hours at 150°C (3). SDC was subjected to triple micronisation with absolute ethanol by grinding in a mortar until the solvent evaporated completely. The size of SDC molecules was determined in a projection microscope MP–3 at a 500 x magnification. A small amount of the micronized SDC was deposited on the object glass and covered with a microscopic cover glass. Five measurements were made, each time the sizes of 50 particles in the view field were measured and assigned to

Table 1. Distribution (%) of particle sizes of micronized SDC

Sample number / SDC particle size [μm]	1	2	3	4	5	SDC mean Particle size distribution [%]
1-3	16	18	12	6	28	16.0
4-6	72	56	52	46	62	57.6
7-9	8	20	16	22	6	14.4
>10	4	6	20	26	4	12.0

particular size classes, and the percentual contribution of each class of particles was estimated (Table 1).

Carefully weighed portions of 1.25 and 1.50 mg of a mixture containing micronized SDC and 1% addition of a given promoter (sodium deoxycholate, lauryl ether of polyoxyethylene–9 and L–α–lysophosphatidylocholine) were placed between two squares of 2x2 cm of thermally modified PVA membranes. The mixture was deposited centrally in the form of a uniformly distributed layer of powder film. The sides of the membrane squares were sealed with a 5% water solution of PVA. After drying, the round inserts were cut out in the form of circles of about 1.5 cm^2 in area (5) and in this form they were used for further experiments.

Conditions of kinetic studies

The rate of SDC release from the ocular inserts prepared and containing sorption promoters, was measured under earlier described conditions (3) by using a Ringer solution of pH 7.25.

The coefficients of SDC permeability through the animal cornea *in vitro* were determined by using pretreated pig eyeballs. The corneas used in this work were obtained from pigs, aged 7–8 months. The eyes were rapidly excised at the slaughterhouse and transported to the laboratory packed in ice. Eyes with no visually observed epithelial defects were used within 1 hour of the death of the animal. To facilitate dissection, the whole eye was placed in a holder. The cornea with a 2 mm ring of the sclera were carefully removed with a pair of scissors and mounted in a perfusion apparatus. During these preparatory manipulations, the epithelium was frequently moistened with the Ringer solution and great care was taken to avoid damage of the cornea. Before and during the experiment, the fluid was gassed with a mixture of 95% O_2–5% CO_2. The functionality of the cornea used in the studies was verified by a slit–lamp following the application of 0.05 ml of 5% aqueous solution of fluorescein according to the method of Yokoi *et al.* (6). To measure the rate of SDC permeability through the animal cornea, 1 ml of the glutathione Ringer solution of the concentration 0.09 g/l was added to the donor compartment prior to the insert containing SDC.

RESULTS

Changes of SDC concentrations in the presence of sorption promoters, upon its release from

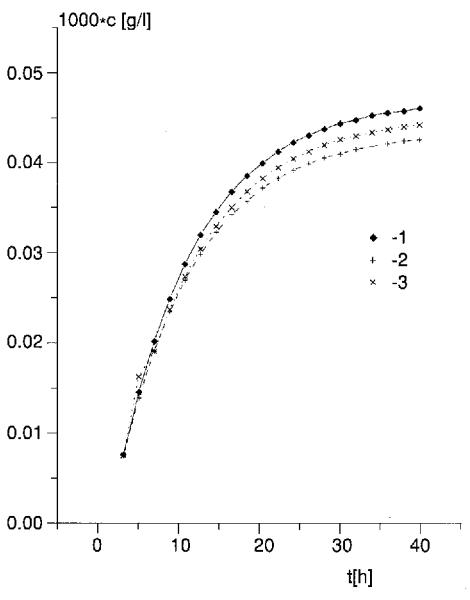

Figure 1. Time *vs.* concentration of SDC released from ocular inserts produced from PVA membranes containing 1.25 mg SDC and some promoters (1 – sodium deoxycholate, 2 – lauryl ether polyoxyethylene–9, 3 – L–α–lysophosphatidylcholine).

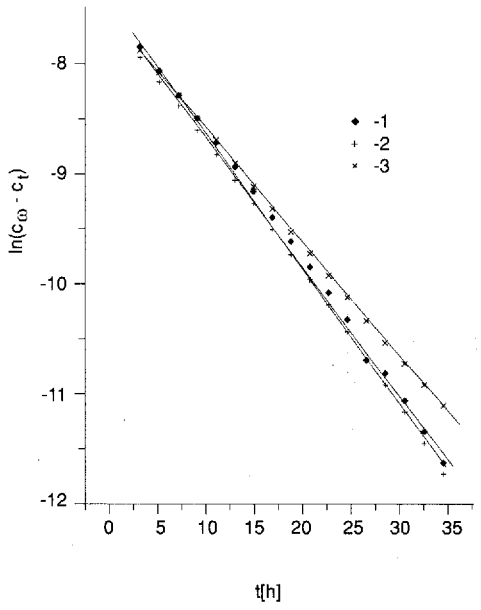

Figure 2. Logarithm of concentration (c∞ – c) as a function of time for SDC released from ocular inserts produced from PVA membranes containing 1.25 SDC and some promoters (1 – sodium deoxycholate, 2 – lauryl ether polyoxyethylene–9, 3 – L–α–lysophosphatidylcholine)

particular inserts, (Figures 1–2) were interpreted in terms of the pseudo–first order kinetics.

The results of SDC dialysis and statistical evaluation are presented in Table 2.

The permeability of SDC, released from a proper insert, through an isolated live cornea of a pig eye was studied for 4 hours because it has been established that the prepared animal eyeball, when placed in Ringer's solution containing glutathione, maintains its basic life functions for this period of time (7). Changes of SDC concentrations upon its release from solid ocular inserts (Figure 3), were interpreted according to the zero–order equation.

Results of SDC dialysis through the pig cornea in the presence of sorption promoters are provided in Table 3.

DISCUSSION

One of the main problems in ocular therapy is to ensure that a proper dose of a drug is provided and that its concentration at receptor sites is therapeutically available within a recommended time period. As the eye is equipped with a number of barriers protecting it from external factors, including the externally applied drugs, many of the drugs cannot enter the inside of the eyeball as they

Table 2. Results of studies on the kinetics of SDC release from PVA ocular inserts and their statystical evaluation

Contents of SDC in inserts [mg]	Promoter	a	10^5 k [s^{-1}]	r	Y
1.25	Sodium deoxycholate	0.0958±0.0031	2.661±0.086	0.9988	85.7
	polyoxyethylene-9 lauryl ether	0.0920±0.0018	2.556±0.049	0.9996	74.8
	L-α-lyso-phosphatidylcholine	0.1059±0.013	2.803±0.037	0.9998	83.4
2.50	Sodium deoxycholate	0.1059±0.0023	2.942±0.065	0.9992	94.9
	polyoxyethylene-9 lauryl ether	0.1056±0.0019	2.933±0.053	0.9994	87.9
	L-α-lyso-phosphatidylcholine	0.0916±0.0004	2.544±0.012	0.9999	92.8

a – slope of a semilogarithmic plot for (X∞ – X) = f(t) for SDC released
k – pseudo first-order rate constants
r – correlation coefficient
Y – yield (%) of SDC release

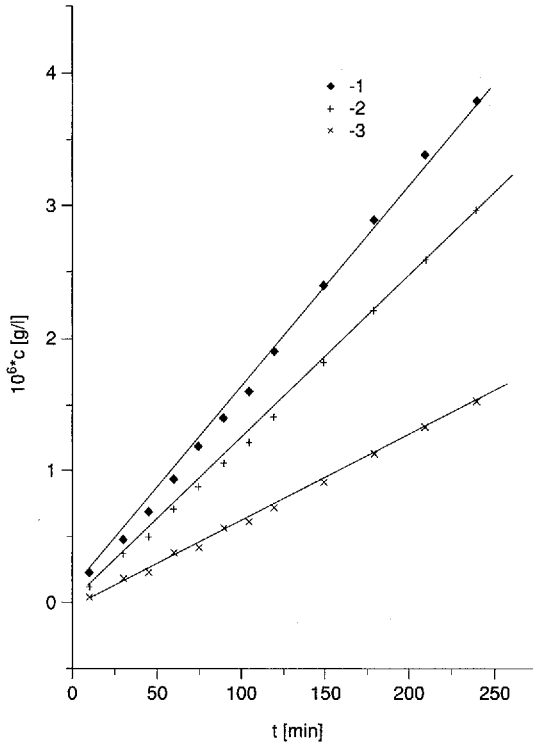

Figure 3. SDC transport through the cornea, released from the ocular inserts containing 2.50 mg SDC and some promoters (1 – sodium deoxycholate, 2 – lauryl ether polyoxyethylene–9, 3 – L–α–lysoposphatidylcholine) as a function of time.

are removed with lacrimal fluid (8). One possible solution is to introduce new forms of ocular drugs ensuring the sustained release of the drug, *e.g.* polymer ocular inserts containing an active substance (9–11).

Construction of polymer ocular inserts containing SDC is based on the use of thermally modified PVA membranes. From earlier studies it is known that annealing of such membranes for 2 hours at 150°C enhances crystallization of the polymer molecules whereby their solubility in lacrimal fluid is reduced and the time of release of the active substance from inserts is protracted (3). The polymer inserts containing SDC were obtained by the envelope technique (3, 12), by preparing circular envelopes of the size similar to that of contact lenses (5). Their, diameter a bit greater, was determined by the size of the opening between the compartments in the perfusion dialyzer used in the studies (3, 4) and by the fact that we tried to avoid the contact between the lacrimal liquid substitute, *i.e.*, Ringer solution, with the margin of the polymer insert closed by water solution of PVA.

In view of the low efficiency of the drug release from the inserts containing about 5 mg of SDC (3), we used only the doses of 1.50 and 2.50 mg SDC (Table 2).

The three promoters were chosen on the basis of the literature reporting their beneficial effect enhancing the mechanisms of absorption of drugs applied to the eyeball, through the intra–nasal path and through the skin (2, 13–18).

The studies of the rate of SDC release from the inserts (Figures 1, 2, Table 2), performed *in vitro*, showed that the yield of this process considerably increased in the presence of all promoters considered, in particular for the insert containing 2.50 mg of SDC and reached up to 88–95% of the initial dose. This should guarantee a sufficiently high level of therapeutic concentration of this sulfonamide in the eye for a period of 8–9 days and this is the time needed for total dissolution of this form of drug in lacrimal fluid without the necessity of removing it from the conjunctival sac (2). The rate constants of SDC release from the inserts as well as the coefficients of linear correlation of the

Table 3. Results of SDC transport through cornea in presence of sorption promoters

Promoter	10^7 P_c	r	Y
Sodium deoxycholate	1.1324±0.1690	0.998	9.9
polyoxyethylene–9 lauryl ether	0.8768±0.0742	0.996	6.1
L–α–lysophosphatidylcholine	0.4352±0.0284	0.995	3.2

P_c – permeability coefficient [cm s^{-1}]
r – correlation coefficient
Y – yeld (%) of SDC dialysis through the cornea *in vitro*

drug concentration as a function of time (Figure 2) prove that these are pseudo–first order processes (Table 2).

The rate of SDC penetration through the pig eye cornea was established with the aid of the earlier described dialysis apparatus (3–5). Changes in the concentration of SDC diffusing through the cornea as a function of time (Figure 3) were interpreted according to the zero–order kinetics. Coefficients of permeability Pc were calculated (Table 3). Similarly as when studying biopharmaceutical availability of ocular ointments containing SDC and the same sorption promoters (2), the best promoting effect in this work was obtained for sodium deoxycholate (Tables 2, 3).

The mechanism of promoter activity significantly depends on promoter polarity. Lipophilic compounds affect only intracellular structures. Molecules of these compounds take positions among hydrophobic lipid chains thus loosening the structure of the cornea lipid layer. Small polar promoter molecules, when used at low concentrations, can interact with intracellular proteins whereas, when applied at higher concentrations they can accumulate in intercellular spaces and interact with the polar groups of lipids. Owing to the formed solvation eyelets, new spaces appear favoring penetration substances lipophilic in nature. Consequently, diffusion of lipophilic compounds is easier. The mechanism of the promoting activity of sodium deoxycholate which also shows mucolytic properties, most probably involves favoring diffusion of small SDC molecules by inducing temporary changes in the structure of cornea and its permeability, without penetration of the aqueous humor. The former was proved in the earlier studies of biopharmaceutical availability of ocular ointments containing SDC performed on pig eyeballs (2). The same yield of SDC release from PVA inserts containing L–α–lysophosphatidylocholine (Table 2) and the lowest yield of its permeability through the cornea (Table 3) suggest that the presence of this promoter may lead to the formation of channels enabling the drug to penetrate in the lacrimal fluid environment; however, it does not affect significantly the biological availability of SDC.

By far, the lowest yield of SDC release from the ocular inserts containing 2.50 mg SDC was observed when using lauryl ether of polyoxyethylene–9, although its promoting effect was significant. Most probably, this promoter may wash out proteins from biological membranes thus enhancing biological availability of SDC (Table 3).

A significant increase in SDC release from PVA in the presence of promoters is also due to the fact that even when added at about 1%, the promoters essentially improve the solubility of SDC which is hardly soluble in the Ringer solution (at 25^0 C, SDC solubility in Ringer solution is 1.00 g/l) (3).

It is expected that further studies with other derivatives of cholic acids, *e.g.*, sodium taurocholate, sodium deoxytaurocholate or sodium glycolate will enhance the biological availability of SDC released from ocular PVA inserts.

CONCLUSION

The sorption promoters such as polyoxyethylene–9 lauryl ether, L–(–lysophosphatidylocholine and deoxycholic acid sodium salt increase the penetration of the drug through animal cornea *in vitro*. The results obtained in this work represent a significant progress relative to those of the earlier works when no diffusion of the SDC released from the inserts without sorption promoters through animal eye cornea was found possible.

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