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SELF-EMULSIFYING OILS FOR OCULAR DRUG DELIVERY. II. *IN VITRO* RELEASE OF INDOMETHACIN AND HYDROCORTISONE

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Abstract: The objective of this study was to compare the *in vitro* release of indomethacin and hydrocortisone from self-emulsifying drug delivery systems (SEDDS) and aqueous or oily suspensions. SEDDS carriers were obtained by dissolving Cremophor EL, Tween 20 or Span 80 in Miglyol oil. The release experiment was performed over 6 h using a dialysis cellulose membrane and acceptor fluid imitating composition of a lacrimal fluid. The release data fitted to the Higuchi's equation. Apparent diffusion constant of indomethacin (k_H) was in the range 2.55–3.78 $mgh^{-0.5}$ and was hardly affected by the formulation type. In the case of hydrocortisone k_H value was the highest for aqueous and oily suspensions (2.16–2.33 $mgh^{-0.5}$) and for SEDDS systems was not increased even if solubility of the drug was almost 3 times higher than in water or oil. This observation leads to the conclusion that SEDDS does not enhance diffusion rate and other factors can be responsible for the expected better drug absorption through cornea from SEDDS *in vivo*. Analysis of the release kinetics from suspension type formulations supports the hypothesis that it may be reasonable to propose SEDDS with the small access of the suspended drug as the most promising formulation.

Keywords: hydrocortisone, indomethacin, *in vitro* drug release, self-emulsifying drug delivery systems (SEDDS), surfactants, oils

Ocular drugs are usually formulated as eye drops – solutions or suspensions. The major problem in ocular therapy is small topical absorption of drugs due to relative impermeability of cornea and short residence time of the ocular preparation resulting from precorneal events such as tear turnover, tear dilution, blinking. The drug bioavailability from eye drops is typically less than 5%. On the other hand, recommended frequent dosing at high concentration can result in several side effects and decreased patient's compliance (1–3). The effective barrier to drug absorption is the cornea. The epithelium and the endothelium of cornea are rich in the lipids, while the stroma has a high water content what makes cornea a rate-limiting barrier for both hydrophilic and lipophilic molecules (4–6).

Lipophilic drugs are able to cross the lipophilic cornea relatively easily, but their poor solubility does not allow to obtain solutions at the effective concentration. Since only dissolved fraction is able to cross the barrier, the most effective drug absorption is achieved when solution is applied. The approach for drugs that are poorly soluble in water is to formulate aqueous suspensions. Although suspensions allow for high drug loads and the use of relatively safe excipients, without solubilizing agents, but the drug absorption from these formulations is problematic. To make corneal penetration (diffusion) possible the drug present in suspension has to dissolve at least in a small portion in the aqueous/oil phase or in lacrimal fluid. This process can be ineffective due to washing the drug out of the eye before the total dose has been dissolved. Moreover, precise administration of a dose from suspensions depends upon their homogeneity and dosing mistakes occur because of flocculation, caking or simply not shaking the bottle by a patient before administration. Oily solutions allow to dissolve some drugs that are poorly soluble in water and thus, in contrast to suspensions, provide the drug in a form ready for absorption. However, typical oily solutions cause blurred vision due to difference in

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refractive index between the preparation and the tears, so they are being marketed with an advice for night time applications. Moreover, very frequently lipophilic drugs are still poorly soluble in oils, so the appropriate therapeutical concentration is not achieved (7–9).

Self-emulsifying drug delivery systems (SEDDS) are preparations used to improve the bioavailability of poorly soluble drugs. SEDDS are mixtures of oil and surfactant, where active substance is usually better soluble than in oil alone. Surfactants form reverse micelles in oil and the drug is incorporated in these nanostructures. There is increasing number of studies reporting on successful SEDDS formulation. An example of a commercially available oral SEDDS are Neoral Sandimmun® (cyclosporine A), Norvir® (ritonavir) and Fortovase® (saquinavir) (10, 11).

Until now, SEDDS have not been used as carriers for ocular drug delivery. SEDDS after application to the eye form with lacrimal fluid, upon gentle agitation (blinking), oil-in-water emulsions. As in oral delivery, it is believed that SEDDS may increase drug bioavailability by drug solubilization and increasing membrane permeability (12). In our previous study, the effect of SEDDS composition on solubility of some active substances was investigated. Hydrocortisone dissolves in Miglyol 812 at a concentration of 0.39 mg/mL, whereas indomethacin shows higher solubility in oil (4.18 mg/mL). Except Tween 20, other surfactants (Cremophor EL, Tween 80, Span 80) in SEDDS increased solubility of indomethacin and hydrocortisone in oils. The best solubility of hydrocortisone was noted in SEDDS with 5% Cremophor EL (1.40 mg/mL), whereas the highest indomethacin solubility was in 5% oily solution of Span 80 (7.16 mg/mL) (13).

The surfactants are rarely employed in ocular preparations due to the eye irritation risk. The example of aqueous solutions containing Cremophor EL, Tween 20 or Tween 80 are ophthalmic preparations with dexamethasone, fluorometholone or diclofenac sodium. It is suspected that surfactants in oils are less irritant than in aqueous solutions and our preliminary studies in cell cultures confirm this (14). *In vivo* drug release from the formulations and dissolution in lacrimal fluid is required as the steps preceding drug absorption. The release step can be a rate-limiting factor for drug absorption if the drug is in suspension or is encapsulated in micelles. For oily solutions, the drug is released following oil/water partition events.

Hydrocortisone and indomethacin have poor solubility in water, which does not allow for preparation of eye drops as solutions, but the use of suspensions results in poor bioavailability. The objective of the present part of the study was to compare the *in vitro* release of indomethacin and hydrocortisone from aqueous suspensions, oily suspensions and from self-emulsifying oils (SEDDS). The investigated preparations of indomethacin were solutions (0.6% w/w of the dissolved drug) in three types of SEDDS – containing 1% of either Cremophor EL or Tween 20 or Span 80. For comparison, aqueous or oily suspensions (0.6% or 1.0% of the drug) were also studied. For hydrocortisone the release rate was investigated from solutions or suspensions in SEDDS (1% or 5% Cremophor EL) as well as from aqueous or oily suspensions.

EXPERIMENTAL

Materials

Components of the formulations: benzalkonium chloride, Span 80 – sorbitan monooleate, Tween 20 – polyoxyethylene sorbitan monolaurate (Sigma Aldrich, Steinheim, Germany); Cremophor EL – polyethoxylated castor oil (BASF, Burgbernheim, Germany); hydrocortisone (Amara, Kraków, Poland); indomethacin (Jelfa, Jelenia Góra, Poland); Miglyol 812 – medium-chain triglicerides (Caesar & Loretz, Hilden, Germany); Pharmacoat 615 – hypromellose, viscosity 15 cP (2% aqueous solution, 20°C; Shin-Etsu Chemical, Japan); sodium chloride (Chempur, Piekary Śląskie, Poland).

Dialysis tubing cellulose membrane (25 mm × 16 mm, m.w. cut 12400 Da) (Sigma Aldrich, Steinheim, Germany) was used in the release studies.

Substances to prepare acceptor fluid: calcium chloride anhydrous, di-sodium hydrogen phosphate dodecahydrate, magnesium chloride hexahydrate, sodium chloride, sodium dihydrogen phosphate dihydrate (Chempur, Piekary Śląskie, Poland); potassium chloride (POCh, Gliwice, Poland).

Methods

The compositions of investigated formulations are shown in Tables 1 and 2. For indomethacin, three different SEDDS were prepared by dissolving the drug (0.6% w/w) in the mixture of oil and surfactant. Besides, suspensions (0.6% or 1.0% w/w) in oil or in the aqueous vehicle were prepared (solid particles size was below 20 μm). Hydrocortisone was dissolved in two different SEDDS in concentrations approaching saturation (0.057 and 0.14% w/w) or was suspended to achieve concentration 1.0% w/w. For comparison, suspensions (1.0% w/w) in oil

Table 1. Investigated formulations with indomethacin.

Preparations	Drug concentration (%)	Composition		Amount of indomethacin (mg) in dialysis bag (3 mL)
Aqueous suspension	0.6	* indomethacin * 2% solution of hypromellose * benzalkonium chloride * 1.8% solution of sodium chloride	60.0 mg 5.0 g 1.0 mg to 10.0 g	18.0
Aqueous suspension	1.0	* indomethacin * 2% solution of hypromellose * benzalkonium chloride * 1.8% solution of sodium chloride	100.0 mg 5.0 g 1.0 mg to 10.0 g	30.0
Oily suspension	0.6	* indomethacin * Miglyol 812	60.0 mg to 10.0 g	18.0
Oily suspension	1.0	* indomethacin * Miglyol 812	100.0 mg to 10.0 g	30.0
Solution in SEDDS (1% Span 80)	0.6	* indomethacin * Span * Miglyol 812	60.0 mg 80 0.1 g to 10.0 g	18.0
Solution in SEDDS (1% Cremophor EL)	0.6	* indomethacin * Cremophor EL * Miglyol 812	60.0 mg 0.1 g to 10.0 g	18.0
Solution in SEDDS (1% Tween 20)	0.6	* indomethacin * Tween 20 * Miglyol 812	60.0 mg 0.1 g to 10.0 g	18.0

Table 2. Investigated formulations with hydrocortisone.

Preparations	Drug concentration (%)	Composition		Amount of indomethacin (mg) in dialysis bag (3 mL)
Aqueous suspension	1.0	* hydrocortisone * 2% solution of hypromellose * benzalkonium chloride * 1.8% solution of sodium chloride	100.0 mg 5.0 g 1.0 mg to 10.0 g	30.0
Oily suspension	1.0	* hydrocortisone * Miglyol 812	100.0 mg to 10.0 g	30.0
Solution in SEDDS (1% Cremophor EL)	0.057	* hydrocortisone * Cremophor EL * Miglyol 812	5.7 mg 0.1 g to 10.0 g	1.7
Solution in SEDDS (5% Cremophor EL)	0.14	* hydrocortisone * Cremophor EL * Miglyol 812	14.0 mg 0.5 g to 10.0 g	4.2
Suspension in SEDDS (1% Cremophor EL)	1.0	* hydrocortisone * Cremophor EL * Miglyol 812	100.0 mg 0.1 g to 10.0 g	30.0
Suspension in SEDDS (5% Cremophor EL)	1.0	* hydrocortisone * Cremophor EL * Miglyol 812	100.0 mg 0.5 g to 10.0 g	30.0

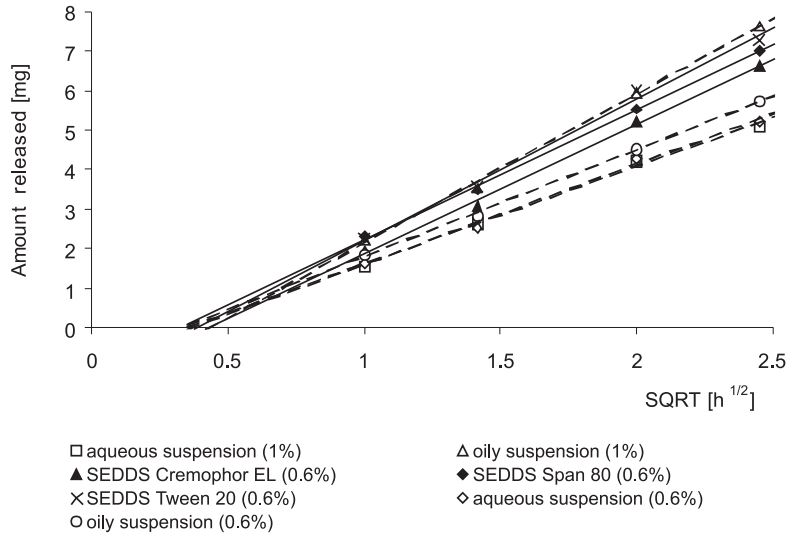

Figure 1. Amount of indomethacin released from suspensions and SEDDS. (Legend: in parenthesis concentration of the drug in the preparations is given; solid lines show release profiles from SEDDS and broken lines – from suspensions)

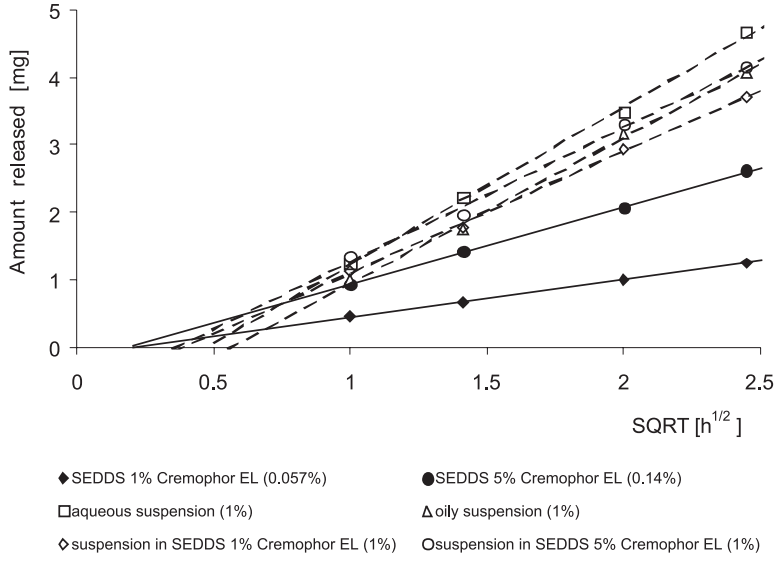

Figure 2. Amount of hydrocortisone released from suspensions and SEDDS. (Legend: in parenthesis concentration of the drug in the preparations is given; solid lines show release profiles from SEDDS and broken lines – from suspensions).

or in the aqueous vehicle were prepared (solid particles size was below 20 μm).

The release experiments were performed using cellulose dialysis membrane. The acceptor fluid was a buffer imitating composition of the lacrimal fluid: sodium chloride (5.4 g), potassium chloride (1.5 g), calcium chloride anhydrous (0.15 g), magnesium chloride hexahydrate (0.2 g), di-sodium hydrogen phosphate dodecahydrate (4.62 g), sodium dihydrogen phosphate dihydrate (1.01 g) and water (to 1000.0 mL). The pH was adjusted to 7.1 and osmotic pressure was 290 mOsm/L.

The dialysis bag was filled with 3.0 mL of the investigated preparation and placed in a beaker containing 70 mL of the acceptor fluid preheated to 37 ± 0.5°C. The total area for diffusion was approxi-

Table 3. Dissolution profiles of indomethacin (results are expressed as the means ± SD, n = 8).

Formulation	Surfactant (concentration)	Drug concentration [mg/mL]		Amount of the drug released [mg] (% of the total dose)				Higuchi's plot		
		Total	Dissolved	Time [h]				Lag time [$h^{1/2}$]	r^2	k_H [$mg/h^{1/2}$]
				1	2	4	6			
Aqueous suspension	–	6.0	0.05	1.64 ± 0.17 (9.1 ± 0.9)	2.52 ± 0.21 (14.0 ± 1.2)	4.28 ± 0.09 (23.8 ± 0.5)	5.22 ± 0.14 (29.0 ± 0.8)	0.37	0.995	2.55
	–	10.0	0.05	1.56 ± 0.10 (5.2 ± 0.3)	2.65 ± 0.23 (9.1 ± 0.6)	4.21 ± 0.21 (14.0 ± 0.7)	5.09 ± 0.11 (16.9 ± 0.4)	0.35	0.996	2.47
Oily suspension	–	6.0	4.18	1.86 ± 0.17 (10.4 ± 1.0)	2.83 ± 0.12 (15.7 ± 0.7)	4.52 ± 0.16 (25.1 ± 0.9)	5.73 ± 0.31 (31.8 ± 1.8)	0.33	0.999	2.70
	–	10.0	4.18	2.23 ± 0.15 (7.4 ± 0.5)	3.54 ± 0.14 (11.8 ± 0.5)	5.92 ± 0.27 (19.7 ± 0.9)	7.64 ± 0.21 (25.5 ± 0.7)	0.44	0.998	3.78
Solution in SEDDS	Cremophor EL* (1%)	6.0	6.0	1.96 ± 0.13 (10.9 ± 0.7)	3.08 ± 0.17 (17.1 ± 1.0)	5.21 ± 0.16 (28.9 ± 0.9)	6.61 ± 0.23 (36.7 ± 1.4)	0.43	0.997	3.27
	Span 80* (1%)	6.0	6.0	2.29 ± 0.17 (12.7 ± 0.9)	3.47 ± 0.34 (19.3 ± 1.8)	5.53 ± 0.21 (30.7 ± 1.1)	7.01 ± 0.55 (38.9 ± 2.9)	0.33	0.999	3.29
	Tween 20* (1%)	6.0	6.0	2.25 ± 0.18 (12.5 ± 0.9)	3.55 ± 0.29 (19.7 ± 1.6)	6.01 ± 0.28 (33.4 ± 1.5)	7.29 ± 0.27 (40.0 ± 1.5)	0.38	0.995	3.58

* saturated solutions

mately 13 cm^2. The beaker with the dialysis bag was shaken (150 rpm) in a water bath. At time intervals (1, 2, 4 and 6 h) 3.0 mL samples were withdrawn from the acceptor medium and analyzed by a spectrophotometric method at the analytical wavelength: 242 nm (hydrocortisone) or 320 nm (indomethacin).

To analyze the mechanism of drug release from the formulations, the release data were fitted to the Higuchi's equation:

$$Q = k_H \sqrt{t}$$

where Q is the amount of drug released (mg) at time t and k_H is the diffusion rate constant (Higuchi's constant) (15, 16). The amount of drug released was plotted against the square root of time (SQRT, $\sqrt{t}$) and the linear regression analysis of the obtained plots was performed. The validity of applying Higuchi's equation was indicated by the correlation coefficient (r^2). The slope of the resulting linear curve was calculated and presented as k_H value.

Statistics

Results are expressed as the means ± SD for 8 experiments. The data were statistically analyzed using Statistica version 8.0 software (StatSoft, USA). The level of significance was accepted with $p < 0.05$.

RESULTS AND DISCUSSION

In this study, *in vitro* release of hydrocortisone and indomethacin from various formulations was investigated. In suspensions only the dissolved, i.e., very small, portion of the drug can diffuse through dialysis membrane into the acceptor media. On the other hand, in SEDDS the drug can be entrapped in micelles which can not diffuse the membrane, thus only free, soluble fraction is able to be released to the acceptor fluid. In both cases, due to the equilibrium in the system, upon release of the dissolved/free drug to the acceptor compartment, a new portion of the drug is dissolved from suspended parti-

Table 4. Dissolution profiles of hydrocortisone (results are expressed as the means ± SD, n = 8).

Formulation	Surfactant (concentration)	Drug concentration [mg/mL]		Amount of the drug released [mg] (% of the total dose)				Higuchi's plot		
		Total	Dissolved	Time [h]				Lag time [$h^{1/2}$]	r^2	k_H [$mg/h^{1/2}$]
				1	2	4	6			
Aqueous suspension	–	10.0	0.32	1.23 ± 0.11 (4.1 ± 0.4)	2.21 ± 0.10 (7.4 ± 0.3)	3.48 ± 0.11 (11.6 ± 0.4)	4.65 ± 0.15 (15.5 ± 0.5)	0.48	0.999	2.33
Oily suspension	–	10.0	0.39	1.00 ± 0.08 (3.3 ± 0.3)	1.74 ± 0.13 (5.8 ± 0.4)	3.17 ± 0.13 (10.6 ± 0.6)	4.06 ± 0.25 (13.5 ± 1.0)	0.56	0.997	2.16
Suspension in SEDDS	Cremophor EL (1%)	10.0	0.57	1.13 ± 0.11 (3.8 ± 0.4)	1.77 ± 0.14 (5.9 ± 0.5)	2.93 ± 0.14 (9.8 ± 0.5)	3.70 ± 0.24 (12.3 ± 0.8)	0.39	0.998	1.80
	Cremophor EL (5%)	10.0	1.40	1.34 ± 0.05 (4.5 ± 0.2)	1.96 ± 0.11 (6.5 ± 0.4)	3.31 ± 0.13 (11.0 ± 0.4)	4.14 ± 0.17 (13.8 ± 0.6)	0.36	0.995	1.99
Solution in SEDDS	Cremophor EL* (1%)	0.57	0.57	0.45 ± 0.04 (26.6 ± 2.2)	0.67 ± 0.06 (39.4 ± 3.4)	1.01 ± 0.06 (59.3 ± 3.7)	1.25 ± 0.08 (72.9 ± 4.6)	0.18	0.997	0.56
	Cremophor EL* (5%)	1.40	1.40	0.93 ± 0.05 (22.1 ± 1.3)	1.43 ± 0.08 (34.1 ± 1.9)	2.06 ± 0.12 (49.0 ± 2.9)	2.61 ± 0.13 (62.2 ± 3.1)	0.18	0.999	1.15

* saturated solution

cles or is liberated from micelles, thus the diffusion across the membrane continues.

The indomethacin and hydrocortisone release process are shown as the absolute mass and percentage of the total dose released from suspensions and SEDDS (Table 3 and 4). Released drug doses, when presented in percentage of the total dose, can be compared only if the initial concentrations in the formulations were the same. More clear demonstration of a drug available for absorption can be done by comparing the profiles presented as the absolute mass released or as diffusion coefficients.

According to Higuchi's equation, the amount of drug released is proportional to $\sqrt{t}$ and it has been pointed out that a lag time exists in the release process due to the time necessary for the drug to be released from the dosage form and to diffuse across the membrane (17). The amount of drug released against the square root of time ($\sqrt{t}$) is shown in Figure 1 and 2. The straight plots with a correlation coefficients (r^2) higher than 0.99 (Tables 3 and 4) indicate that the data, both for hydrocortisone and indomethacin, fit to Higuchi's equation. This also proves that sink conditions and infinite dose conditions were being applied (18).

The straight lines allow for conclusion that the release process during the observation time (6 h) was a simple diffusion of the drugs through a membrane, and the characteristics of this transport was unchanged. The slopes of the Higuchi's plots can be used as an apparent release constant (19).

Concentration of indomethacin in SEDDS was 0.6% (w/w) and these preparations formed practically saturated solution. The concentration of indomethacin in aqueous and oily suspensions was 0.6% or 1.0%. Indomethacin is a lipophilic substance (logP 4.17, the oil-water distribution coefficient is about 80) and its solubility determined in Miglyol 812 and in water (13, 20, 21) is given in Table 3.

Irrespective of the used carriers and the total concentration of the drug in formulation the percentage of indomethacin released was similar – after 6 h 30–40% of the total dose was released from aqueous or oily suspensions and from SEDDS. However, the effect of the carrier should be demonstrated

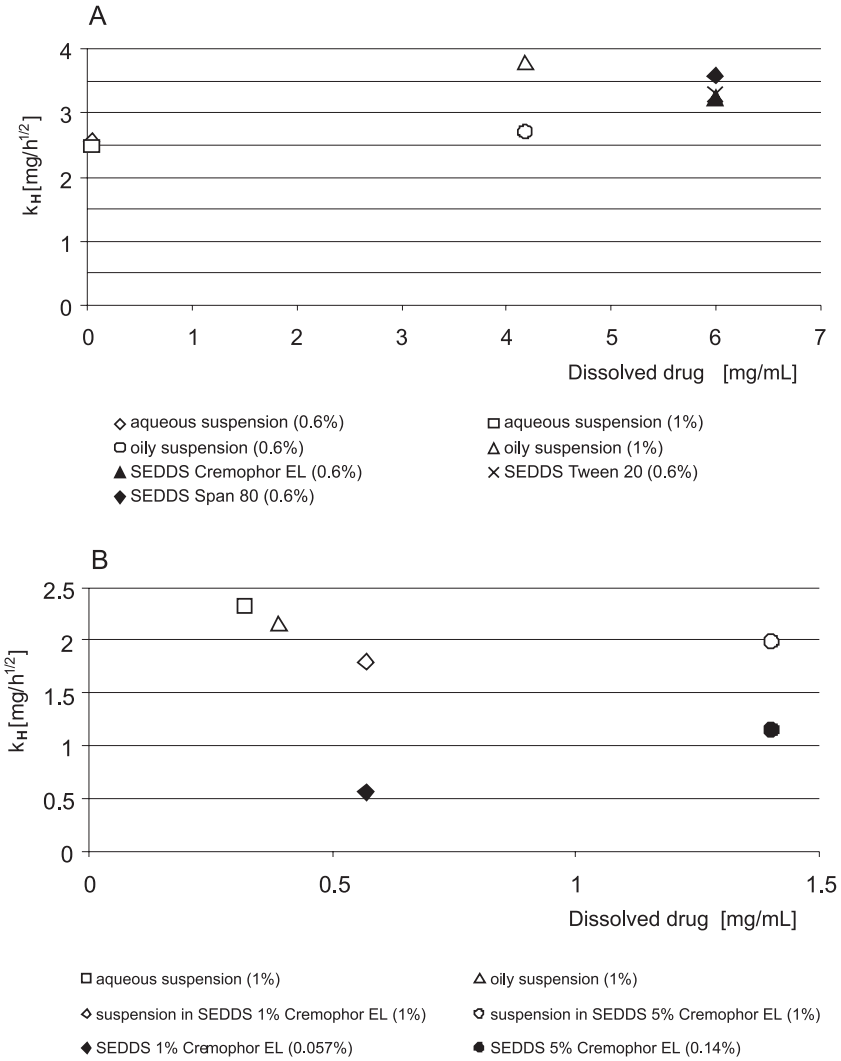

Figure 3. Relationship between k_H (the diffusion rate constant) and concentration of the dissolved drug in aqueous or oily suspensions and SEDDS (C dissolved): A – indomethacin, B – hydrocortisone.

if the mass transport is considered. The absolute mass of indomethacin released from the aqueous suspensions containing either 0.6% or 1.0% of indomethacin was the same, what results from the same concentrations of the dissolved dose in both preparations (Table 3). Slightly lower amount of the drug released was observed from 0.6% than from 1.0% oily suspension. The similar profiles were observed when indomethacin was released from SEDDS (indomethacin concentration 0.6%), particularly when Tween 20% was used as a surfactant. No effect of the carrier was observed on the lag time values which were in a narrow range 0.33–0.44 h.

For comparison of the release kinetics from formulations representing different physical state (solution, suspension) or containing various concentrations of the investigated active substance, the apparent diffusion constants is the most indicative. Figure 3A demonstrates the effect of formulation on the apparent diffusion constant (k_H) of indomethacin as a function of the concentration of dissolved fraction of the drug in the carrier. It can be seen that this kinetic parameter is hardly affected by the formulation type since calculated k_H value for all investigating formulations is found in a narrow range of 2.55–3.78. Thus, the use of SEDDS as a carrier does

not influence diffusion of the free drug. Due to incorporation of indomethacin in the reverse micelles present in SEDDS, the free fraction of the drug, able to cross the membrane is small, resulting in a diffusion rates similar to the observed for oily or aqueous suspensions.

Very effective diffusion of indomethacin from aqueous suspension in spite of the very small solubility of the drug in water indicates that a good equilibrium exists in the system and the released drug is easily replaced by free molecules released from the solid particle surface. The results demonstrate that dissolution rate does not limit the diffusion across the membrane, and thermodynamic activity in the system is constant.

The release of hydrocortisone was examined from the aqueous and oily suspensions (drug concentration 1.0% w/w), suspension in SEDDS (1.0%) and solution in SEDDS. In the latter formulation, hydrocortisone concentration was, depending on the surfactant, 0.057% (1% Cremophor EL) or 0.14% (5% Cremophor EL), what corresponds to hydrocortisone solubility in these carriers. Hydrocortisone is moderately lipophilic (logP 1.61) and its solubility in water and in Miglyol 812 is given in Table 4 (13, 20).

Solubility of hydrocortisone in SEDDS was lower than observed for indomethacin and this was a reason why the release rate was investigated not only from solutions but also from suspensions prepared with SEDDS. When the profiles are presented in a percentage of the total dose released (Table 4), the effect of SEDDS is well pronounced – within 6 h only from SEDDS (solution type) more than 60% of the drug was released. However, this effect resulted only from the low concentration of indomethacin in this system. When the process is presented in an absolute mass transfer, faster release is observed for all suspension-type formulations and the similar profiles were observed irrespective of the carrier (oil, water, SEDDS). In contrast to solutions of hydrocortisone in SEDDS, the drug released from suspensions presented, however, only small percentage of the total dose (below 20%) and the lag time was 2–3 times longer. This indicates that in suspension under *in vivo* conditions a majority of the drug can be lost and topically unavailable, while non-absorbed drug is eliminated to nasolacrimal duct and can evoke the systemic side-effects.

Data presented in Figure 3B support similar conclusions as already discussed for indomethacin. The equilibrium in the suspension type systems is established and due to relatively fast dissolution step the apparent diffusion rate for the systems containing even very small fraction of the drug dissolved is relatively high. In comparison with oily or aqueous suspensions, the k_H value calculated for SEDDS systems is similar or smaller, even if solubility in the presence of 5% (w/w) Cremophor is almost 3 times higher. The results demonstrate that SEDDS does not lead to the increase in thermodynamic activity what can result in higher diffusion constant. Interesting is the observation that higher apparent release constant was achieved when the access of the drug was present in the SEDDS. This can be explained by a hypothesis that an undissolved fraction serves as a drug reservoir, as also demonstrated for aqueous or oily suspensions.

CONCLUSIONS

In the proposed experimental model, SEDDS, despite of the increased drug solubility, does not allow for faster drug release and penetration through the dialysis membrane because the thermodynamic activity of the drug was not improved. This observation leads to the conclusion that the expected enhanced drug absorption through cornea from SEDDS *in vivo* may result only from the effect of the formulation on the barrier permeability or interaction with the tear fluid. The observed release profiles demonstrate that relatively fast dissolution of hydrocortisone and indomethacin in suspensions (aqueous, oily or in SEDDS) is a process responsible for the similar release rates despite of the large difference in the concentration of the dissolved drug fraction in each investigated formulation.

Although in respect to the clinical use, solution type formulations ensure more effective absorption of the drug while majority of the dose in suspension type formulations will be unavailable for topical absorption, our findings support the hypothesis that it may be reasonable to propose SEDDS with the small access of the suspended drug as the most promising formulation.

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