SOLUBILITY OF OCULAR THERAPEUTIC AGENTS IN SELF-EMULSIFYING OILS I. SELF-EMULSIFYING OILS FOR OCULAR DRUG DELIVERY: SOLUBILITY OF INDOMETHACIN, ACICLOVIR AND HYDROCORTISONE

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Abstract: Self-emulsifying drug delivery systems (SEDDS) were prepared by dissolving Cremophor EL, Tween 20, Tween 80 and Span 80 (1% or 5%) in oils (Miglyol 812 or castor oil). Solubilities of three ophthalmic drugs, namely aciclovir, hydrocortisone and indomethacin were determined in these systems. In addition, the effect of a small amount of water (0.5% and 2%) on solubilization properties of the systems was estimated. Of the three substances, indomethacin showed the best solubility in Miglyol while aciclovir was practically insoluble in this oil. The surfactants usually increased drug solubility in the oily phase. Only Tween 20 was found to decrease the solubility of aciclovir and hydrocortisone in Miglyol. Addition of a small amount of water to the oil/surfactant system increased solubility of hydrocortisone, but not of indomethacin. The results of the current study may be utilized to design a suitable composition of SEDDS and allow continuation of research on this type of drug carriers.

Keywords: solubility, self-emulsifying drug delivery systems (SEDDS), nonionic surfactants, Miglyol 812, castor oil

Many therapeutic substances exhibit low solubility in water, which results in their poor bioavailability. Developing novel drug formulations to improve solubility and bioavailability is a challenge facing the pharmaceutical industry. Among ophthalmic preparations, oily solutions, suspensions or ointments can be used as drug delivery options. However, oily solutions and ointments cause vision disorders and should be, therefore, administered before night rest. On the other hand, in the case of suspension, drug absorption by eye structures is limited by the low concentration of the dissolved drug in the dispersing medium. This process can be slow and ineffective as the drug is washed out of the eye before the total dose has been dissolved (1, 2). Among modern formulation strategies, most important are oily preparations such as emulsions, microemulsions, SEDDS, nanoparticles or liposomes.

Self-emulsifying drug delivery systems (SEDDS) are the isotropic mixtures of oils, surfactants and/or co-surfactants. SEDDS can be a useful approach to improve bioavailability of poorly water-soluble drugs by increasing drug dissolution rate or through a potential influence of surfactants on the permeability of corneal barrier. Additionally, surfactants decrease surface tension and may eliminate vision disorders (3-5). Moreover, surfactants in self-emulsifying oils should be less irritating than in the aqueous medium.

Aciclovir, hydrocortisone and indomethacin are ophthalmic drugs poorly soluble or insoluble in water. Aciclovir is an antiviral agent available only as ointment: Cusiviral® (Alcon Cusi), Virolex® (Krka), Viru-POS® (Ursapharm Arzneimittel). It cannot be applied in solutions due to poor solubility in water and oils. Hydrocortisone is an anti-inflammatory drug used to treat inflammatory and allergic conditions and is available as compound ointment Oxycort A® (Jelfa) or prescribed aqueous suspension. Indomethacin is an anti-inflammatory and analgesic agent available as a solution solubilized...
with cyclodextrins – Indocollyre® (Bausch & Lomb) (1, 6). As all the above-mentioned drugs are important agents for the treatment of eye diseases, we made an attempt to determine whether self-emulsifying oils are suitable carriers for these drugs.

In the current study, semisynthetic oil – Miglyol 812 and castor oil were used. Miglyol is a mixture of triglycerides of saturated and unbranched C8 to C12 fatty acids, characterized by high chemical stability and low viscosity. Castor oil is a natural oil with high viscosity. Its main component is a ricinoleic acid glyceride, which thanks to the presence of hydroxyl groups shows higher potential to dissolve certain therapeutic agents. In the study, non-ionic surfactants with various HLB (hydrophilic-lipophilic balance) values were used (7-9).

The study objective was to investigate the solubility of aciclovir, hydrocortisone and indomethacin in Miglyol 812, aciclovir in castor oil and solubility of these drugs in oily surfactant solutions. Additionally, the effect of a small amount of water (0.5% and 2%) on drug solubility in self-emulsifying oils was estimated.

EXPERIMENTAL

Materials
Aciclovir (Uquifa, Barcelona, Spain), Cremophor EL – polyethoxylated castor oil (BASF, Burgbernheim, Germany), hydrocortisone (Amara, Kraków, Poland), indomethacin (Jelfa, Jelenia Góra, Poland), methanol (Chempur, Piekary Śląskie, Poland), Miglyol 812 – fractionated coconut oil (Cesar & Loretz, Hilden, Germany), castor oil (Microfarm, Kraków, Poland), Span 80 – sorbitan monooleate, Tween 20 – polyoxyethylene sorbitan monolaureate, Tween 80 – polyoxyethylene sorbitan monooleate (Sigma Aldrich, Steinheim, Germany).

Methods
Self-emulsifying oils were prepared by dissolving surfactants in the oils at a concentration of 1% or 5% (w/w). The o/w formulations were made by adding 0.5% or 2% (w/w) water.

Drugs were added in excess to conical flasks (25 mL) containing 10 mL of the formulations tested. The prepared mixtures were shaken (250 rpm) at 25 ± 0.5°C for 24 h, in water bath with shaking. Next, the samples were centrifuged (3000 ◊ g, 20 min). Supernatant was collected for analysis.

After proper dilution with methanol, the drug content was determined by the spectrophotometric method at an analytic wavelength: 254 nm (aciclovir), 242 nm (hydrocortisone) and 320 nm (indomethacin). Suitable dilution of methanol was used as a reference solution.

RESULTS AND DISCUSSION

None of the substances tested has water solubility high enough to yield an aqueous solution. In suspension, the dissolved fraction capable of absorption shows a concentration that corresponds to solubility, i.e. 1.3 mg/mL for aciclovir (10), 0.32

![Figure 1. Solubility (mg/mL) of aciclovir in Miglyol 812, castor oil and in oily surfactant solutions. M – Miglyol 812, Cr – Cremophor EL, Tw – Tween , Sp – Span 80](image-url)
mg/mL for hydrocortisone and 0.05 mg/mL for indomethacin. These concentrations, however, do not guarantee high pharmacological activity. Hence, the search for novel drug formulations that would ensure better solubility seems fully justified. For instance, oily solutions can be an alternative delivery mode. In order to enhance solubility and optimize absorption, self-emulsifying oils can be proposed (11, 12).

Determined drug solubility in oils and in oily surfactant solutions is shown in Figures 1-3. The analysis of the results concerning drug solubility should refer to drug lipophilicity, type of oil, surfactant HLB value and surfactant concentration.

The drugs tested vary in lipophilicity, which correlates proportionally with their solubility in oil. The most lipophilic agent, i.e. indomethacin (log $P = 4.17$), shows the highest solubility in Miglyol.
(4.18 mg/mL). According to the pharmacopoeal terminology, indomethacin can be defined as a slightly soluble substance. Hydrocortisone (log P = 1.61) dissolves in Miglyol at a concentration of 0.39 mg/mL, whereas acyclovir, being a hydrophilic compound (log P = -1.56), practically does not dissolve in this oil (8 µg/mL). However, the solubility of acyclovir in the more polar castor oil is even twenty times higher than in Miglyol.

Surfactants were added to oil at a concentration of 1% or 5%, which in different way influenced drug solubility. Tween 20 (HLB = 16.7) did not increase the solubility of aciclovir or hydrocortisone in Miglyol, irrespective of the concentration used. All the surfactants tested, with the exception of Span 80, decreased aciclovir solubility in castor oil. Span 80 did not practically change its solubility.

Span 80, showing the lowest HLB value (4.3), increased solubility in Miglyol of all the drugs tested, having the greatest effect for aciclovir and indomethacin. At a concentration of 1%, it increased aciclovir solubility approximately four times and indomethacin – 1.5 times, whereas hydrocortisone solubility remained practically unchanged. Higher concentration of Span 80 (5%) increased the solubility of hydrophilic aciclovir approximately fifteen times while hydrocortisone solubility was twice as high as when 1% Span 80 was used.

The example of Span 80 shows a correlation between drug lipophilicity and surfactant effect on the increase in solubility in oil. Surfactants had the lowest effect on the solubility of the most lipophilic indomethacin. The maximum effect was obtained with 5% Span 80, although it was only a rise from 4.18 to 7.16 mg/mL. Indomethacin solubility in the presence of 5% surfactants with higher HLB values was 5.22 mg/mL (Tween 20). Thus, in the presence of more hydrophilic surfactants, indomethacin solubility decreased along with the increasing surfactant concentration from 1% to 5%. The solubility of less lipophilic aciclovir and hydrocortisone was higher when the surfactants were used at a concentration of 5%.

The effect on aciclovir solubility in Miglyol was higher, as compared to hydrocortisone, not only for Span 80, but also when Tween 80 and Cremophor EL were used. In order to significantly increase the solubility, surfactants in concentration 5% (w/w) should be applied.

The subsequent stage of the study was to demonstrate whether addition of a small amount of water affects solubilization properties of the oil/surfactant formulation. Surfactant molecules in the oily solvent create a system of reverse micelles, with the hydrophilic inner core and the external layer formed by hydrophobic groups of the surfactant in the oily medium. Upon mild agitation followed by dilution in aqueous medium (lacrimal fluid), the reverse micellar solution undergoes transformation into a liquid crystalline system. The amount of water solubilized by the reverse micelles depends on the type and concentration of surfactant, type of oil, temperature and co-solvent concentration. Drug release from the liquid crystalline system is under control, since drug diffusion from this system is slower. This property can be utilized for ophthalmic, nasal, buccal, rectal, vaginal or even parenteral (subcutaneous) administration (5, 13). With increasing amount of water in this system, w/o type emulsion can be formed. Solubility potentials of more lipophilic drugs, i.e. hydrocortisone and indomethacin, in self-emulsifying oils were assessed in the presence of 0.5% and 2% water.

Addition of water to the systems containing the lipophylic substance, indomethacin, only slightly affected its solubility in oil. As the effect of water on solubilization properties of the systems tested varies a lot, it is difficult to determine the relationship between the type of surfactant and its concentration as well as between the amount of water added and indomethacin solubility in oil. It should be emphasized that in the Span 80/oil systems, addition of 0.5% and 2% water caused a reduction in indomethacin solubility. Indomethacin is a strongly lipophilic substance and has the optimum solubility in solutions containing the lipophilic surfactant Span 80, whereas water may disturb the equilibrium created within the indomethacin/surfactant/oil system.

In the presence of water increased solubilization of the oil/surfactant systems towards moderately lipophilic hydrocortisone can be observed. The most substantial increase in hydrocortisone solubility was noted in a solution with the most hydrophilic surfactant – Tween 20. In the presence of 0.5% water, the solubility increased over 1.7 times (1% Tween 20) and 2.5 times (5% Tween 20). Similar results were obtained for solutions containing 2% water. It was also noted that addition of 2% water increased hydrocortisone solubility less than 0.5%, with the exception of Span 80 solutions, in which higher concentration of the drug was obtained for 2% water content. This indicates a significant effect of the internal structures being formed on thermodynamic activity of the substance.

The results of this study may be utilized for the choice of a suitable solvent in order to design novel forms of the ophthalmic drug (SEDDS) that could improve bioavailability and application comfort.
CONCLUSIONS

In the current study, indomethacin was found to have the best solubility in Miglyol 812. Aciclovir was practically insoluble in Miglyol, showing better solubility, however, in castor oil. Except Tween 20, surfactants in the oily medium (SEDDS) increased the dissolved fraction of indomethacin and hydrocortisone. Solubility of aciclovir in castor oil was decreased by addition of all surfactants.

Addition of 0.5% or 2% water to the SEDDS increased hydrocortisone solubility, except for the preparation containing 5% Cremophor EL and 2% water. Addition of water to indomethacin in SEDDS only slightly changed solubility of this drug.

In comparison with the oil as a simple solvent the most evident increase in solubility of aciclovir and hydrocortisone was offered by SEDDS composed of Miglyol either with Span 80 or Cremophor EL (5%). For indomethacin the effect was small, however SEDDS can offer other advantages: increased bioavailability and elimination of the vision discomfort, what will be the aim of further investigation.

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