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Solubility and Transdermal Permeation Properties of a Dehydroepiandrosterone Cyclodextrin Complex from Hydrophilic and Lipophilic Vehicles

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The permeation ability of a compound is due principally to its concentration in the vehicle and to its aptitude to cross the stratum corneum of the skin. In this work *ex-vivo* permeation studies on newly developed formulations containing dehydroepiandrosterone (DHEA) were carried out to investigate vehicles that increase drug permeation through the skin. To enhance the solubility of DHEA, its complex form with α-cyclodextrin was used. In addition, the two forms (pure drug and complex form) were introduced in hydrophilic (water), lipophilic (paraffin oil), and microemulsion vehicles to evaluate the synergic effect of cyclodextrins and microemulsion vehicles on solubility and permeation. From the results, DHEA solubility is notably conditioned by the type of the vehicle used: the highest solubilities (both for pure and complex drug forms) were obtained with microemulsion, followed by paraffin oil and water. Moreover, in all the studied vehicles, the c-DHEA was more soluble than DHEA. Permeation profile fluxes showed very interesting differences. That reflect the varying drug forms (pure drug and complex form), vehicles used, and drug concentrations in the vehicles. The major flux was obtained in complex of DHEA with α-cyclodextrins in the microemulsion vehicle. Therefore, this type of vehicle and drug form would be very useful in the development of a topical formulation containing DHEA.

Keywords α-Cyclodextrin, Dehydroepiandrosterone, Enhancer Effect, Microemulsion, Solubility, Transdermal Permeation

The clinical efficacy of topically administrated therapeutic agents is often suboptimal because of their poor penetration into the skin. Dehydroepiandrosterone (DHEA) is a neutral nonionized compound with poor water solubility. Solubility and partition properties are important parameters affecting transdermal drug permeation. According to Fick's law, the flux of a drug is proportional to the concentration of the drug in the vehicle: high solubility allows a high drug concentration in the donor phase that improves the permeation flux. High solubility usually allows a decrease in the partition coefficient in the stratum corneum of the skin. Thus, drugs with low solubility often show good partition properties and good transdermal transport as in the case of DHEA where low concentrations limit its permeation flux.

The technological strategies used to improve skin permeability generally focus on improving drug solubilities in the vehicle, the diffusion through the vehicle, the partition tendency of the permeant in the rate-limiting lipid phase, and on the use of chemical penetration enhancers. Methods developed to increase solubility of drugs that are not soluble in water are drug complexation, for example with cyclodextrins, and novel vehicle systems, such as liposomail-based delivery systems, supersaturated formulations, and microemulsions (Moser et al. 2001; Guy 1996; Cortesi et al. 1997).

However, once drug concentration is increased above saturation in the supersaturated formulations, the system become thermodynamically unstable. In fact supersaturated formulations are typically subject to recrystallization. Liposomial-based delivery systems show stability problems. This is not the case of with microemulsions that are stable systems. Microemulsions are dispersion of two immiscible components stabilized by a third, amphoteric, component. They are usually four-component mixtures containing a surfactant, a cosurfactant, an oil, and a hydrophilic component. They are thermodynamically stable, self-emulsifying, clear or slightly opalescent, isotropic, and low viscosity mixtures (Acharya, Sanyal, and Moulik 2001; Ceschel et al. 2000). Microemulsions have been investigated as a drug delivery system and also used to dissolve lipophilic drugs in aqueous mediums or hydrophilic drugs in lipophilic mediums (Constantintinides et al. 1996). Microemulsions may enhance transdermal penetration of a drug both by solubilization and

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modification of the partition coefficient, favoring penetration of the stratum corneum. Furthermore, their surfactant components reduce the functional barrier of the stratum corneum acting as chemical enhancers. This latter function may be more or less important, depending on the nature of the surfactant used (Kim, Cho, and Gao 2001; Kawakami et al. 2002; Trotta, Morel, and Gasco 1997).

For transdermal administration, the enhancer action of cyclodextrins (c) on skin permeation of lipophilic drugs is well known. For example, β-cyclodextrin has been shown to improve transdermal absorption of antifungine drugs (Tenjarla et al. 1998). Although cyclodextrins interact with some lipophilic components of the skin (Legendre et al. 1995; Loftsson et al. 1998), only insignificant amounts of cyclodextrins and cyclodextrin complexes are able to penetrate the skin's lipophilic barrier. Cyclodextrins do not act through interaction with stratum corneum components as do chemical enhancers (Loftsson et al. 1998). Cyclodextrins seem to improve drug penetration by solubilizing the lipophilic water insoluble drugs in the aqueous vehicle systems and delivering the drug molecules to the membrane barrier surface (Ceschel et al. 2002; Pattarino et al. 1993; Ukeama et al. 1984; Otagiri et al. 1983).

The interactions of drugs with both cyclodextrins and microemulsions have been described because they can favorably modify the therapeutic activity of different groups of drugs (Pattarino et al. 1993; Otagiri et al. 1983; Ukeama et al. 1983; Frijlink, Schoonen, and Lerk 1989; Lin et al. 1994) For example, it the incorporation of an inclusion complex of piroxicam with β-cyclodextrin in cationic microemulsions increases the stability constant of the complex. Consequently the aqueous solubility of piroxicam was increased via complexation with β-cyclodextrin and association to cationic microemulsions (Dalmora and Oliveira 1999).

Our previous study showed that, from aqueous suspensions, c-DHEA has better solubility, water dissolution and permeation characteristics than DHEA for transcutaneous administration (Ceschel et al. 2002). These results indicate that the increase in permeation can be attributed primarily to the increase in DHEA solubility in the formulation containing c-DHEA. Therefore, it can be excluded that α-cyclodextrin acted as conventional enhancer modifying the permeation coefficient of the drug in the stratum corneum. The study concluded that the high permeation flux demonstrated by c-DHEA must be attributed to a presence of a diffusion layer at the skin surface where the cyclodextrins acts as a carrier, trasporting the drug from the donor phase to the lipophilic part of the skin.

The aim of our present work was to investigate the drug solubility and to promote permeation properties of the complex system c-DHEA from different vehicles constituted by a lipophilic medium and by a microemulsion. We were also interested in finding out if there were synergetic effects in the simultaneous use of a microemulsion vehicle and cyclodextrins. For this purpose suspensions of DHEA and c-DHEA in different vehicles were prepared: two monocomponent solvents (paraffin oil and water) and a microemulsion. The solubility and permeation properties of c-DHEA from these systems, with respect to DHEA, were evaluated.

MATERIALS AND METHODS

DHEA was supplied by Euphar Group S.r.l. (Piacenza, Italy), DHEA/α-cyclodextrin complex (c-DHEA) by Actimex (Trieste, Italy), α-cyclodextrin by Proquina (Milan, Italy), paraffin oil by Polichimica (Bologna, Italy). 2-(2-ethoxyethoxy) ethanol (Transcutol®), caprylocaproil macrogol-8-gliceride (Labrasol®), oleoil macrogol-6- gliceride (Labrafil® M1944 CS), and poligliceril-6-dioleato (Plurol oleique®) were supplied by Gattefosse.

Developed Formulations

DHEA and c-DHEA were dispersed to form suspensions in paraffin oil, a microemulsion and water, respectively, resulting in 6 different formulations. The microemulsion was prepared by mixing distilled water (41.06% w/w) as hydrophilic phase, Labrafil® M1944CS (4.71% w/w) and Plurol oleique® (7.01% w/w) as lipophilic phase, Labrasol® (39.21% w/w) as surfactant, and Transcutol® (8.01% w/w) as cosurfactant.

Since the formation of microemulsion is a spontaneous event, only gentle stirring was required. Previous tests were carried out to calculate DHEA and c-DHEA solubility in the different vehicles so-as to define the dose able to obtain saturated formulations. Formulations were prepared by adding the opportune quantity of DHEA or c-DHEA to the vehicle under moderate stirring.

Solubility Determination

The DHEA equilibrium solubility in various vehicles was measured at 25°C. Suspensions and microemulsion prepared as described were centrifuged at 4000 rpm. The surfactant was recovered, filtered (0.45 μm nylon filter, MSF, Dublin, USA), and assayed for the content in DHEA by HPLC method as previously described (Ceschel et al. 2002).

Tissue Preparation

Porcine skin is used largely for in vitro experiments because it is similar to the human epidermis (Potts et al. 1991). Full-thickness skin with a fair amount of underlying connective tissue was surgically removed from the ears of a freshly killed male pigs (30–50 Kg) obtained, on each study day, from a local slaughter house (CLAI, Imola, Italy) under supervision of a veterinary surgeon. The skin was placed in ice-cold phosphate buffered saline (PBS) pH 7.4. The connective tissue of the skin was carefully removed using fine-point forceps and surgical scissors. The cleaned membrane was then placed in ice-cold

PBS until it was mounted in the diffusion cells (Ceschel and Maffei 1999).

In Vitro Permeation Study

The *in vitro* diffusion studies were carried out in standard Franz diffusion cells having 0,64 cm^2 diffusion area (Frantz 1975; Friend 1992). The receptor compartment has a volume of 48 ml and was maintained at 37°C by means of a water bath, circulator, and a jacket surrounding the cells. The cells were filled with fresh PBS. The solution in the receptor compartments was continuously stirred at 600 rpm using a Teflon coated magnetic stirrer. The porcine skin was clamped between the donor and receiving compartments. Then 1 ml of the tested formulations was placed in the donor compartment.

The amount of drug diffused through porcine skin was determined by removing aliquots of 2 ml from the receptor compartments using a syringe and immediately replacing the same volume of PBS (kept at 37°C). The dilution of the receptor contents during sampling was considered in the calculation of the total permeated amounts. The samples were transferred to volumetric flasks and stored in a refrigerator until they were analyzed. Sampling schedule was 0.5, 1, 2, 4, and 8 hr. All experiments were carried out 6 times.

Permeation through the skin membrane can be considered as a passive diffusion process and can be described by Fick's law:

$$J_s = (dQ_r/dt)(1/A) \quad [1]$$

where J_s is the steady-state flux in mg/cm^2 for tc, dQ_r is the change in quantity of material passing through the membrane into the receptor compartment expressed in μg, A is the active diffusion area in cm^2, and dt is the change in time in hours. The flux of DHEA through the porcine skin was calculated from the amount of drug permeated (dQ_r) over 24 h. The permeability coefficient, K_p, was calculated using the equation:

$$K_p = J_s/C_d \quad [2]$$

where C_d is the donor drug concentration. The Kp value also is:

$$K_p = (D/P)/tc \quad [3]$$

where D is the drug diffusion coefficient into the stratum corneum, P is the drug partition coefficient between stratum corneum and vehicle, and tc is the stratum corneum thickness. The D value was calculated from the lag time with the following equation:

$$\text{Lag time} = h^2/6 \cdot D \quad [4]$$

The P value was calculated with the Equation 3 knowing the D value.

TABLE 1
DHEA solubilities in the vehicles at 25°C

	Paraffin oil	Microemulsion	Distilled water*
DHEA (μg/ml)	$2.01 \cdot 10^2$	$8.97 \cdot 10^2$	6.50
	sd 5.60	sd $2.13 \cdot 10^1$	sd 0.3
c-DHEA (μg/ml of	$3.98 \cdot 10^2$	$9.76 \cdot 10^3$	20.6
DHEA equivalent)	sd $1.13 \cdot 10^1$	sd $1.16 \cdot 10^2$	sd 0.9

*Ref. mean value of three experiments sd.

RESULTS

Solubility Results

Both DHEA and c-DHEA solubilities in the hydrophilic and lipofilic vehicles are reported in Table 1. Solubility results in distilled water are reported as calculated in a previous study (Ceschel et al. 2002). DHEA solubility is remarkably conditioned by the lipophility of the vehicle: DHEA solubility in paraffin is two orders of magnitude higher than in water. In the case of microemulsion, the solubility of DHEA is considerably increased being about 138 times higher than the solubility in water and 4.5 times than the one solubility in paraffin oil.

In all the vehicles, c-DHEA is more soluble than DHEA. The increase in c-DHEA solubility is due to the solubilizing action obtained by the complex c-DHEA. This solubilizing action is less effective in paraffin oil than in water. In water the c-DHEA solubility is about 3.1 times higher than DHEA, whereas in paraffin oil the ratio is 1.9. The highest increase in c-DHEA solubility with respect to the pure drug can be found in the microemulsion in which c-DHEA is about 11 times more soluble than DHEA. This result can be explained by the fact that the microemulsion has a remarkable solubilizing effect versus the complex.

In Vitro Permeation Study

The permeation profiles of prepared formulations are reported in Figure 1, while their fluxes (*Js*) and the other permeation parameters are reported in Table 2. Permeation results in purified water were reported as calculated in a previous work (Ceschel et al. 2002). In all experiments, the permeation profiles showed a curved portion, corresponding to a lag phase, followed by a linear portion that means that an apparent steady-state of DHEA was attained. The fluxes were very different between each other, varying between 7.3 $mg \cdot h^{-1} \cdot cm^{-2}$ obtained with the DHEA water suspension and 43.0 $mg \cdot h^{-1} \cdot cm^{-2}$ of c-DHEA microemulsion. These remarkable differences reflect the high difference in the drug form (pure drug and complex), in the type of vehicle and in the drug concentration into the formulation.

In regard to the permeation parameters reported in Table 2, the diffusional coefficient D is the only parameter that remains constant for all the experiments. This means that the capacity of

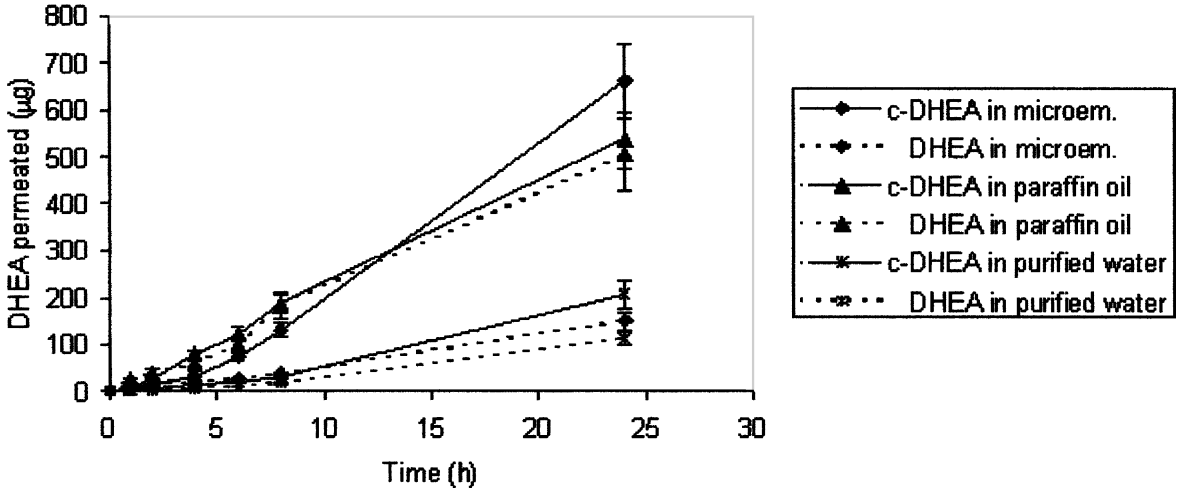

FIG. 1. Permeation profiles of DHEA from the tested suspensions. The continuous lines are the permeation profiles of c-DHEA, the discontinuous are the ones of DHEA.

the drug to diffuse through the stratum corneum is not modifiable and so neither the presence of cyclodextrins nor the vehicle microemulsion act as conventional enhancer, modifying D. It is possible to study the effect of the vehicle on the drug permeation evaluating the permeation parameters of the pure drug from the different vehicles.

As expected, the flux increases with the rise of the DHEA solubility in the vehicle: the highest flux is the one obtained with the paraffin oil while the lowest is the water suspension one in which DHEA is sparingly soluble. The microemulsion flux is intermediate between the other two vehicles, even if it has a solubility action much higher than the paraffin. The microemulsion flux result can be explained considering the partition parameter P: the flux result of the microemulsion is 20 times lower than the one of paraffin oil because the microemulsion has a better drug solubility action. The microemulsion flux was lower than the paraffin even if the drug concentration in the microemulsion is higher. In the case of the aqueous vehicle, the partition parameter P is very high because DHEA is not very soluble in water but the flux remains low because the drug concentration also is low.

Also in c-DHEA the diminishing partition P follows the increase in the solubility action of the vehicle. In the case of c-DHEA, the drug concentration in the vehicle is the prevalent effect on permeation: the highest flux is, in fact, done by the microemulsion that is the vehicle that guarantees the highest c-DHEA solubility. Also an increase in the solubility action of the vehicle is followed by a decrease of drug partition.

TABLE 2
DHEA permeation parameters from the vehicles

	Js (μg/cm^2 h^{-1})	Permeability coefficient (Kp) (cm/h)	Lag time (hr)	Diffusion coefficient (D) (cm^2/h)	Partition parameter (P) skin/vehicle
DHEA in paraffin oil	34.9	$1.74 \cdot 10^{-1}$	2.112	$8.45 \cdot 10^{-4}$	21.73
	sd 2.8	sd $1.41 \cdot 10^{-2}$	sd $6.75 \cdot 10^{-1}$	sd $2.73 \cdot 10^{-4}$	sd 5.35
c-DHEA in paraffin oil	32.8	$8.26 \cdot 10^{-2}$	1.595	$9.07 \cdot 10^{-4}$	5.93
	sd 3.1	sd $7.91 \cdot 10^{-3}$	sd $4.793 \cdot 10^{-1}$	sd $1.21 \cdot 10^{-4}$	sd 2.30
DHEA in microemulsion	9.7	$1.10 \cdot 10^{-2}$	2.617	$6.51 \cdot 10^{-4}$	1.72
	sd 0.3	sd $3.7 \cdot 10^{-4}$	sd $4.96 \cdot 10^{-1}$	sd $1.13 \cdot 10^{-4}$	sd $3.80 \cdot 10^{-1}$
c-DHEA in microemulsion	43.0	$4.32 \cdot 10^{-3}$	3.819	$4.41 \cdot 10^{-4}$	1.01
	sd 9.4	sd $9.5 \cdot 10^{-4}$	sd $4.91 \cdot 10^{-1}$	sd $5.87 \cdot 10^{-5}$	sd $3.49 \cdot 10^{-1}$
DHEA in purified water	7.3	1.12	5.39	$3.13 \cdot 10^{-4}$	358.11
	sd 2.3	sd 0.50	sd 2.15	sd $1.26 \cdot 10^{-4}$	sd 129.7
c-DHEA in purified water	13.66	0.66	5.17	$3.22 \cdot 10^{-4}$	204.92
	sd 3.3	sd 0.19	sd 1.21	sd $7.50 \cdot 10^{-5}$	sd 28.2

*Ref. mean value of 6 experiments sd.

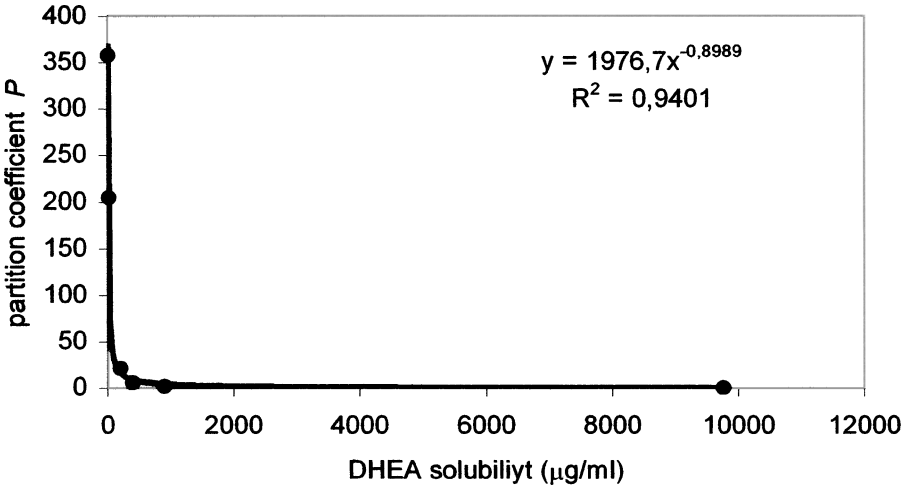

FIG. 2. Correlation between partiton coefficient P as a function of the solubility of the drug in different vehicles (of the complexed and pure forms).

It is possible to study the effect of the presence of the cyclodextrin on the DHEA permeation evaluating the permeation parameters of DHEA in regard to c-DHEA using the same vehicle. At first the partition P and the solubilities of the two drugs in the same vehicle are linked by an inverse correlation. This means that the presence of cyclodextrin acts both increasing the drug solubility and diminishing the drug partition into the stratum corneum.

Concerning the fluxes, the results are not homogeneous and depend on the different vehicles. Both water and microemulsion vehicles present the highest flux when cyclodextrin is present. This means that the effect of the cyclodextrin on the drug solubility prevails on the effect of cyclodextrin on the partition. On the contrary, the flux of the paraffin oil vehicle is higher in the case of DHEA and so the cyclodextrin effect on the partition is prevalent with regard to the effect on the solubility.

DISCUSSION

The c-DHEA demonstrated an improvement in solubility of DHEA in vehicles with very different lipophilic-hydrophilic characteristics. These results suggested better permeation characteristics than DHEA for transcutaneous administration. *In vitro* permeation studies showed that neither the presence of cyclodextrin nor the presence of the surfactants of the microemulsion influenced the diffusion of the drug through the stratum corneum. In fact the flux was influenced primarily by the solubility of the drug (which increases the permeation improving the parameter of the concentration) and by the partition (which decreases the flux diminishing the solubilization of the drug into the stratum corneum). From these results it is possible to hypothesize that when the vehicle or the complex solubilize the drug, the consequence is that the drug itself is retained in the vehicle and the partition into the stratum corneum decreases. This hypothesis is confirmed inserting the partition coefficient P as a function of the solubility of the drug in different vehicles (of the complexed and pure forms) into a graph (Figure 2). The correlation between the two variables was found to be very high: $R^2 = 0.9401$.

CONCLUSION

Since the aim of a topical formulation is the improvement of the permeation of a drug through the stratum corneum, it is important to choose the conditions that best enhance the flux through the skin. In the case of DHEA, the flux is influenced by the partition of the drug but also by the poor solubility of the drug. Therefore, the increased flux is obtained using a microemulsion and the complex c-DHEA. Thus, this type of vehicle would be useful in the development of a topical administration of DHEA.

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