CHAPTER 3

LITERATURE SURVEY ON WORK DONE
CHAPTER 3

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3. LITERATURE SURVEY ON WORK DONE

3.1 Solubility Properties of Microemulsions:

Only the dissolved fraction of a drug in a vehicle can enter the skin, making solubility properties one of the initial objectives for a novel pharmaceutical formulation. Generally, microemulsions have favourable solvent properties due to the potential incorporation of large fraction of lipophilic and/or hydrophilic phases. In microemulsion systems consisting of water, 2% (w/w) soybean oil and various volume fractions of nonionic surfactant (Brij 96), Malcolmson and Lawrence (1993) (1) found an increased solubility of three lipophilic model steroids (log P=3.9-4.8) in the microemulsion systems, compared to similar micellar systems in the absence of the oil phase. Even though structural examinations of the microemulsions were not performed, the microemulsion systems were assumed to form ‘o/w’ droplet structures due to the low oil volume fraction. However, two other examined lipophilic steroids (log P=3.4 and 4.3) did not display significantly increased solubility in the microemulsion systems, compared the micellar systems. The authors suggested the main site of solubilisation was in the lipophilic moiety of the micellar surfactant film, and that the solubility of the model drugs was only increased in the microemulsion vehicles, when the drug was additionally soluble in the neat soybean oil. This was confirmed in a later study Malcolmson and Lawrence (1998) (2), where the solubility of testosterone propionate in similar microemulsion and micellar systems, was examined with regards to different oil constituents. This study furthermore demonstrated that an increased solubility of the oil in the lipophilic moiety of the surfactant film, could lead to a competitive situation between the oil and the drug for the solubilisation sites and thereby lead to a decrease in overall drug solubility in the microemulsion vehicles, compared to that of the pure micelles.
Another investigation Kreilgaard et al. (2000) (3) has demonstrated an increase in solubility of both a lipophilic (22-58%) and a hydrophilic (20-36%) model drug in the studied microemulsion vehicles, compared to solubility calculated from the additive solubility of the drugs in the respective neat constituents and their weight fractions in the microemulsion vehicles. The increased solubility of the model drugs was suggested to be attributable to the additional solubilisation sites of the respective hydrophilic and lipophilic moiety of the formed surfactant interface film in the microemulsions.

3.2 Treatment of Acne Vulgaris

Topical delivery of retinoic acid (RA) is a well-accepted treatment in the management of acne vulgaris and an emerging application is its use to reduce photoaging of the skin. The objective of Trotta et al. (2003) (4) was to prepare microemulsions for dermal delivery to prevent its systemic absorption due to the teratogenic adverse effect of the drug. Both o/w and w/o microemulsions were prepared by using phosphate buffer (pH 6.4) (aqueous phase), IPM (oil phase), Epikuron 200 and Oramix NS10 (surfactant phases), and ethanol or 1,2-hexanediol (cosurfactant phase), and the effect of ion pairing was examined. Phenylalanine methyl ester, phenylalanine ethyl ester, and histidine methyl ester were used as counterions. The study revealed that the permeability of the RA from the ethanol (pH 6.4) buffer mixture through polydimethylsiloxane (PDMS) membrane was significantly increased in the presence of the counterions and was confirmed by permeation through pig skin. However, in the presence of counterions, the permeability of RA from microemulsion using PDMS membrane and pig skin was decreased. Water-in-oil microemulsions exhibited the lowest accumulation of the drug in the skin, whereas o/w microemulsions containing counterions (amino esters) showed four to five times higher drug accumulation than the
corresponding drug counterion-free microemulsions. The depth of RA accumulation after 24 h of the application of microemulsions containing ion pair was found to be less than 100 μm, which is the thickness of the corneum and epidermal layers of the pig skin, and this was consistent with the undetectable fluxes from these vehicles. As the components are the same, the change in the relative percentages of water, oil, and surfactant and thus the change in the microstructure of the systems allow vehicles to be formulated, which can provide different drug permeation and different drug accumulation. The investigators concluded that the enhanced skin accumulation of RA could significantly optimize drug targeting without a concomitant increase in systemic side effects and proposed the development of these systems for the topical treatments of skin diseases.

Tea tree oil has been suggested for the treatment of acne vulgaris. Biju et al. (2005) (5) prepared different tea tree oil formulations (colloidal bed, microemulsion, multiple emulsion, and liposomal dispersion containing 5% [wt/wt] tea tree oil) and applied to bovine udder skin. Their work demonstrated that the microemulsion and liposomal formulations were more efficient for the delivery of tea tree oil through the follicular route.

Clindamycin phosphate is one of the commonly used antibiotics for the treatment of acne. It is commercially available in 50% isopropanol solution which may cause skin irritation due to high concentration of alcohol. Junyaprasert et al. (2007) (6) developed water–IPP–AOT–1-butanol microemulsions at alternative formulations for the topical delivery of clindamycin phosphate. Effect of AOT: A 1-butanol ratio on microemulsion region was investigated. The 2:1 AOT: 1-butanol provided the largest microemulsion region. Five microemulsions of 1% (wt/wt) clindamycin phosphate were prepared and the permeation through human epidermis was compared with the 70% isopropanol solution. The
drug permeation from all microemulsions was found to be significantly
greater than that from the solution. Within the same microemulsion type,
the drug permeation increased with increasing amount of AOT/1-butanol.
The drug permeation from o/w microemulsions was relatively higher than
that from w/o microemulsions.

3.3 In vitro Investigations

The vast majority of drug delivery investigations with topical
microemulsions have been performed in vitro, using the classical Franz-
type diffusion cells with various membranes. Although this method
actually determines percutaneous, rather than cutaneous drug delivery, a
good indication of the cutaneous drug delivery potential of
microemulsions can be obtained from these studies.

Cutaneous penetration into defined tissue layers has been investigated by
incubation of a finite dose microemulsion on excised human skin,
followed by biopsy punctures and quantification of the active compound
in stratum corneum–viable epidermis– the dermis skin layers by
Schmalfuss et al. (1997) (7). The three investigated microemulsion
vehicles consisted of (1) a basic composition of Tween 80–Span 20–
IPM–water (7:13:74:5%, w/w) with 1% of a hydrophilic model drug
(diphenhydramine hydrochloride), (2) the basic microemulsion with 2%
cholesterol added and (3) the basic microemulsion with 5% oleic acid
added. Incorporation of cholesterol into the microemulsion significantly
enhanced the dermal delivery of the drug into all skin layers, and
particularly into the stratum corneum layer. Interestingly, the addition of
oleic acid, which is generally acknowledged as a penetration enhancer,
into microemulsion 3, did not increase dermal delivery of drug in any
layers of the skin. The authors suggested the finding was due to the
means of enhancement of the two additives. Cholesterol is believed to
increase the hydrophilic domains in the stratum corneum, facilitating the
passage of hydrophilic substances, while oleic acid is believed to alter the viscosity of the skin lipids, facilitating diffusion of lipophilic substances. A study by Ozguney et al. (2006) (8) has been performed, which had the aim of improving the transdermal permeation of diclofenac sodium. Transdermal permeation studies were carried out using rat skin. Three topical formulations of diclofenac sodium (1%, w/w) were prepared: a gel, an emulsion and a microemulsion. Furthermore, the effect of dimethyl sulfoxide (DMSO), added as an enhancer into the microemulsion system, on the penetration rate of diclofenac sodium was examined. The commercial formulation of diclofenac sodium was examined. The commercial formulation of diclofenac sodium was also tested as a reference. It was found that the flux from the emulsion was $6.5 \times 10^{-2} \, \mu g/cm^2/h$, which was 2.4-times greater than that observed from the commercial dosage form ($2.7 \times 10^{-2} \, \mu g/cm^2/h$). The flux values of the microemulsion and the microemulsion containing DMSO as an enhancer were 1.8- and 2.0-times greater than the commercial dosage form, respectively. In a previous study, it was explained that the interaction of DMSO with the stratum corneum lipid alkyl chains resulted in decreased diffusion resistance of the barrier, with an observed drug partition increase into the skin. One reason for this effect is that the microemulsion had a very low interfacial tension, which allowed for excellent contact with the skin surface, allowing the vehicle to fill even microscopic gaps. This should enhance the vehicle skin drug transfer. The second possible mechanism is related to the high drug loading capacity of the microemulsion; and the third possibility is the penetration-enhancing effect of the microemulsion components. This mechanism can add to the explanation of the effect of cosurfactants, as they are known to act as skin penetration enhancers. Finally, the supersaturation process
may be responsible, as it increases the thermodynamic activity and driving force for transdermal drug transfer.

The potential application of microemulsions as a dermal drug delivery loading penciclovir was evaluated by Zhu et al. (2008) (9). The pseudo-ternary phase diagrams were developed for various microemulsion formulations composed of oleic acid (oil phase), Cremorphor EL (surfactant) and ethanol (cosurfactant). Composition of microemulsion systems was optimized using simplex lattice mixture design including the concentrations of surfactant, cosurfactant and water (independent variables) and the solubility and the cumulative amount of penciclovir permeated through excised mouse skins per unit area (response variables). The physicochemical properties of the optimized microemulsion and the permeating ability of penciclovir from microemulsions were also investigated. The results showed that the optimized microemulsion formulation was composed of oleic acid (5%, w/w), Cremorphor EL (20%, w/w), ethanol (30%, w/w) and water (45%, w/w). The mean particle diameter was 36.5nm and solubility of penciclovir in the emulsion was 7.41 mg/g. The cumulative amount of penciclovir permeated through excised mouse skins from microemulsion was about 3.5 times that of the commercial cream. The permeating ability of penciclovir was significantly increased from the microemulsion formulation compared with commercial cream.

3.4 Skin Tolerability Studies of Topically applied Microemulsions

A microemulsion typically comprises of large amounts of surfactant and oil and it is therefore important to consider the skin irritation and toxicological reactions by topical application of these formulations. Although the risk of tissue irritation is there, few in vivo studies have looked at this issue.
Delgado-Charro and coworkers (1997) (10) tested skin acceptability of unloaded five microemulsions (comprising of ethyl oleate, labrasol, Plurol Isostearique, and water) and three controls (water, PG, and 5% oleic acid in PG) by separately applying for 3 h to the ventral forearm of human volunteers. Transepidermal water loss (TEWL) and relative skin blood flow (SBF) were measured immediately after removing the formulations and repeatedly over a further 3-h period. SBF increased significantly only after the application of the oleic acid/PG-positive control. For all other treatments, SBF remained at the pretreatment value. Immediately after removing all the formulations, TEWL was elevated. However, these values quickly recovered to the pretreatment control except in the case of oleic acid/PG. The in vivo measurements of TEWL and SBF indicated that the microemulsions were well tolerated.

The skin irritation potential of microemulsions has also been investigated by a 20-h pretreatment of excised rat skin with an unloaded microemulsion (1 mL) (10% isostearic isostearate, 35% labrasol, 35% Plurol Isostearique, and 20% water) containing large amount of surfactant by Kreilgaard et al. (2001) (11). Compared to no pretreatment and 20-h pretreatment with neat water, no significant difference was observed in the permeation rate of prilocaine hydrochloride from a subsequently applied microemulsion formulation. The results from a human in vivo study, using a microemulsion vehicle based on the same surfactant system (Labrasol-Plurol Isostearique), indicated that skin barrier function, evaluated by TEWL, was not affected by a 3-h application period.

Paolino et al. (2002) (12) prepared soybean lecithin microemulsion (Mygliol 812N, soybean lecithin, and water) and oleic acid microemulsion (Mygliol 812N, soybean lecithin, oleic acid, and water) containing ketoprofen and tested skin acceptability of these formulations along with conventional w/o and o/w emulsions and hydrophilic gel on
human volunteers. An occlusive patch bearing the formulation was applied to the upper outer arm for 23 h. One hour after removal, skin sites were assessed for signs of skin irritation. After assessment, an identical fresh patch was applied to the same skin area for a further 23 h. One hour after patch removal, skin sites were again assessed. The values of scoring assigned were as follows: vesicles, 5; edema, 4; erythema, 3; flakiness, 2; dryness, 1; wrinkling, 1; and glazing, 1. Microemulsion formulations showed the highest skin tolerability. Wrinkling (2) and glazing (2) were observed with soybean lecithin microemulsion, whereas flakiness (1), dryness (1), wrinkling (2), and glazing (1) were observed with soybean lecithin microemulsion. No edema or erythema was seen. The authors concluded that these microemulsions made up of biocompatible constituents (high percutaneous effect and low human skin irritation) prompt their use as topical delivery systems both in pharmaceutical and cosmetic fields.

Escribano and coworkers (2003) (13) studied skin irritancy of commercially available semisolid preparation of diclofenac and formulated microemulsion (1% diclofenac sodium, 14.9% oleic acid, 59.2% transcutol, 19.9% water, and 5% Dlimonene) by Draize’s method in male albino rabbits. Three squares were drawn on both sides of the back of each rabbit, and the skin of three of them was scarred with a lancet. Then 0.5 mL of each product was applied on each square. After exposure for 24 h, the test substance was removed and the exposed skin was examined for erythema. The mean skin irritation caused by microemulsion was greater than that caused by the semisolid preparation. Thus, the formulation that gave greater diclofenac bioavailability also induced greater erythema. Authors concluded that neither formulation could be considered an irritant and less irritation could be expected in humans as rabbit skin is more sensitive than human skin.
Fang et al. (2004) (14) assessed the skin irritation potential of microemulsion. A microemulsion (0.4 mL) containing flurbiprofen was spread on 2.5 x 2.5 cm shaved back area of the rat skin. TEWL was determined over 3 days after 24 h of application of the vehicles. The results indicated that flurbiprofen itself caused no irritation. The irritant profiles of microemulsions on the skin showed that the formulations composed of IPM produced greater irritation than did soybean oil. The addition of the oleic acid to the emulsions also caused greater disruption of the stratum corneum layers. Almost all irritation recovered within 3 days after 24 h exposure to the vehicles.

3.5 Microemulsion Based Gels for Topical Delivery

One of the problems associated with the use of microemulsions for topical drug delivery is the difficulty of using these vehicles on the skin, because of their fluidity. Gasco et al. (1991) (15) have addressed this problem with the development of a microemulsion for the topical administration of azelaic acid, which has showed therapeutic effects on some pageantry disorders and on acne vulgaris. The viscosity of the o/w microemulsions used in this study was increased with Carbopol ® 934 (Lubrizol) to make them suitable for topical administration.

El laithy and El-shaboury (2002) (16) compared Cutina lipogels and microemulsion gels as possible vehicles for the topical use of the antifungal drug fluconazole. Although they focused the different Cutina based lipogels, it turned out that the microemulsion based gel showed the highest in vitro drug release and the best in vitro percutaneous absorption on mice skin.

Microemulsion gels containing rofecoxib and rofecoxib solid dispersion with polyethylene glycol (PEG) 4000 were prepared by Kashappa Goud H. Desai (2004) (17) for the study of rapid percutaneous absorption. The solubility of rofecoxib in oil phase of microemulsion, e.g., isopropyl
myristate, was increased by the addition of dimethyl formamide and ethanol. Topical microemulsion gels (MEGs) were prepared by using neat rofecoxib as well as its solid dispersion to compare the efficacy of individual MEG with conventional gel (CG). MEGs showed better spreadability than CG and also showed increased globular size with increasing concentration of the oil phase. The release of rofecoxib through dialysis membrane and excised rat abdominal skin was affected by the size of the oil globule in MEGs. Rofecoxib release was higher for MEGs when compared to CG. MEGs containing rofecoxib-PEG 4000 solid dispersion exhibited higher cumulative drug permeation when compared to MEG containing neat rofecoxib. MEGs containing rofecoxib-PEG 4000 solid dispersion exhibited faster anti-inflammatory activity than CG.

Chen et al. (2006) (18) prepared microemulsion-base hydrogel formulation for topical delivery of ibuprofen. Ethyl oleate (EO) was screened as the oil phase of microemulsions, due to a good solubilizing capacity of the microemulsion systems and excellent skin permeation rate of ibuprofen. The pseudo-ternary phase diagrams for microemulsion regions were constructed using ethyl oleate as the oil, Tween 80 as the surfactant, propylene glycol as the cosurfactant. Various microemulsion formulations were prepared and the abilities of various microemulsions to deliver ibuprofen through the skin were evaluated in vitro using Franz diffusion cells fitted with procine skins. The in vitro permeation data showed that microemulsions increased the permeation rate of ibuprofen 5.72–30.0 times over the saturated solution. The optimum formulation consisted of 3% ibuprofen, 6% EO, 30% Tween 80/PG (2:1) and water, showed a high permeation rate of 38.06 μg cm⁻² h⁻¹. Xanthan gum as a gel matrix was used to construct the microemulsion-based hydrogel for improving the viscosity of microemulsion for topical administration. The
studied microemulsion-based hydrogel showed a good stability. The results indicated that the studied microemulsion-based hydrogel might be a promising vehicle for topical delivery of ibuprofen.

Chen et al. (2007) (19) formulated a hydrogel-thickened microemulsion (HTM) for delivering an extremely low concentration of Triptolide. The pseudo-ternary phase diagrams were constructed using isopropyl myristate (IPM), Tween 80, propylene glycol and water. The various HTM were prepared and characterized. The stability tests showed that HTM had good stability. The influence of the addition of hydrogel into microemulsions on the viscosity and permeation ability is investigated. The abilities of HTM to deliver an extremely low concentration of triptolide as a model drug were evaluated using the in vitro permeation studies. The permeation rates of triptolide from various HTM were 2.2–3.6 times over that from the control hydrogel. The addition of 2% menthol into HTM consisting of 3% IPM, 30% Tween 80, 15% propylene glycol, 0.75% carbomer 940 resulted in the highest permeation rate of $0.105\pm0.006\,\text{g cm}^{-2}\,\text{h}^{-1}$, which was 5.8 times over control gel. The powerful permeation enhancing ability of HTM with a suitable viscosity makes it promising alternative carrier for transdermal administration of drug molecule at an extremely low concentration.

Bachhav et al. (2009) (20) developed microemulsion based gel for the vaginal delivery of fluconazole (FLZ). The solubility of FLZ in oils and surfactants was evaluated to identify components of the microemulsion. The ternary diagram was plotted to identify the area of microemulsion existence. Various gelling agents were evaluated for their potential to gel the FLZ microemulsion without affecting its structure. The bioadhesive potential and anti-fungal activity of the FLZ microemulsion based gel (FLZ-MBG) was determined in comparison to the marketed clotrimazole gel (Candid V® gel) by in vitro methods. The vaginal irritation potential
of the FLZ-MBG was evaluated in rabbits. The clinical efficacy of the FLZ-MBG and Candid V® gel was evaluated in females suffering from vaginal candidiasis. The FLZ microemulsion exhibited globule size of 24nm and polydispersity index of 0.98. Carbopol® ETD 2020 could successfully gel the FLZ microemulsion without disturbing the structure. The FLZ-MBG showed significantly higher \( P < 0.05 \) in vitro bioadhesion and anti-fungal activity as compared to that of Candid V® gel. The FLZ-MBG did not show any signs of vaginal irritation in the rabbits. The small-scale clinical studies indicated that the FLZ-MBG shows faster onset of action than Candid V® gel although no difference was observed in the clinical efficacy.

3.6 Recent Patents on Microemulsions as Carriers for Therapeutic Molecules:

Microemulsion systems are now being investigated zealously for topical delivery which is evident from the numerous inventions disclosed in patents on microemulsion used as drug delivery vehicles coming up every year.

The liquid, transparent, multicomponent systems according to the invention of Muller et al. (1988) (21) contained the active agents in a solution of an oily and optionally an aqueous component in the presence of surfactants and cosurfactants. Under certain conditions, the cosurfactants can serve as oil components or vice-versa. The efficacy of the active agents applied in the form of the multicomponent systems according to the invention was much better than that of active agents applied in the form of known multicomponent systems. The multicomponent systems could be used in pharmaceutical products for cutaneous, peroral, vaginal and parenteral administration of pharmaceutical active agents.
The invention of Protopapa et al. (2001) (22) referred to depilatory preparations containing proteolytic enzymes solubilized in microemulsions, formed with lecithin, aliphatic hydrocarbon, alipathic alcohol and buffer solution (pH 7-9) to be applied for permanent enzymic depilation. The invention introduced the use of microemulsions as a medium for the facilitated penetration of the enzymic activity in the epithelial cells of the skin. In addition, their invention referred to a depilation method that applied the preparations of microemulsion containing the enzyme alpha-chymotrypsin, or the enzyme trypsin, for the depilation of any type of skin (fatty-resistant or dry-sensitive). The application of these preparations provided more permanent depilation than the one resulting from other depilatory methods.

From the formulation point of view, microemulsion based topical drug delivery systems involve safety issues since many surfactants are irritating to skin when used in high concentrations. Therefore, appropriate selection of ingredients i.e. surfactants, cosurfactants, oils are the key factors in the formulation of a microemulsion based topical drug delivery system. Neem oil microemulsion was reported in the patent granted to Parmar et al. (2004) (23) that did not use a cosurfactant or alcohol. This oil in water microemulsion included nonyl phenol ethoxylate as the nonionic surfactant and Neem oil that could be mixed to obtain microemulsion for topical applications. The invention, besides being cost effective, helped to overcome the problems of non-uniform distribution associated with the direct use of Neem oil and also reduced the fire and toxicity hazards associated with the use of organic solvents.

Topical drug delivery system has many advantages among which one is the direct delivery and targetability of the drug to affected areas of skin. Warner and Zhang (2005) (24) have presented an invention related to gelled emulsion and microemulsion formulations for dermal drug
delivery, including transdermal drug delivery. In one of the embodiment, the oleyl alcohol (oil phase) with saturated amount of alprazolam has been added to a fixed amount of a 50% ethanol in water solution, followed by the drop wise addition of Tween 80 until a microemulsion is formed. This microemulsion is then incorporated into 20% PVA in water solution. The discontinuous oil phase can be dispersed in the continuous aqueous phase, and the drug-containing microemulsion can be present in a dermal reservoir patch delivery system.

Gel-microemulsion formulation that could be used as a spermicide was reported by Yiv et al. (2006) (25). The formulation comprised of an oil-in-water microemulsion and a polymeric hydrogel. The pharmaceutical composition could also be used as a formulation base for additional therapeutic agents like anti-microbial agents. The microemulsion consisted of a lipid, pharmaceutically acceptable surfactant(s), non-ionic surfactant(s), pharmaceutically acceptable humectant(s) and water. The surfactant involved a block copolymer of ethylene oxide and propylene oxide. The composition had a particle size in the range of 30 to 80 nm. The invention also disclosed a process for preparing the composition by combining surfactants, hydrophilic components and lipids in a container, which were then mildly heated and mixed until a clear and homogeneous microemulsion was formed. The resulting microemulsion was allowed to cool to room temperature. Thereafter, two parts of polymeric hydrogel were added to each part of microemulsion and mixed to form the composition.
### 3.7 Drug profile

**Table 3. Brief profile of drugs (26-30)**

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<td>a group of natural metabolites of Vitamin A related synthetic analogs</td>
<td>a group of natural metabolites of Vitamin A related synthetic analogs</td>
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<td>Chemical Name</td>
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<td>Physical Data</td>
<td>Pharmacological Data</td>
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<tr>
<td>-----------------</td>
<td>------------------------------------</td>
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</tr>
<tr>
<td>351.46 g/mol</td>
<td>White to yellow crystalline solid powder</td>
<td>Negligible solubility in water</td>
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<tr>
<td>300.44 g/mol</td>
<td>Yellow or light orange, crystalline solid powder</td>
<td>It is practically insoluble in water; sparingly soluble to slightly soluble in alcohol; sparingly soluble in ether and isopropyl alcohol; soluble in chloroform and dichloromethane.</td>
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- **Physical Data**
  - **Appearance**: White to yellow crystalline solid powder
  - **Solubility**: Negligible solubility in water

- **Melting Point**: 97-98° C
- **pKa**: 5.6
- **Log P**: 2.8, (octanol/water)
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**Category, indication, available route of administration, and marketed preparations**

<table>
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<tr>
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<th>Retinoids, Dermatologic Agents</th>
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<td>Plaque psoriasis, acne vulgaris and photoaging</td>
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3.8 References


