Drug Development and Industrial Pharmacy, 35:525–547, 2009
Copyright © Informa UK, Ltd.
ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040802448646

informa
healthcare

Microemulsions as a Surrogate Carrier for Dermal Drug Delivery

Adnan Azeem, Zeenat Iqbal Khan, M. Aqil, Farhan Jalees Ahmad, Roop Kishan Khar, and Sushama Talegaonkar

Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard, New Delhi, India

Microemulsions are isotropic, thermodynamically stable transparent (or translucent) systems of oil, water, and surfactant, frequently in combination with a cosurfactant with a droplet size usually in the range of 20–200 nm. Since their discovery, they have attained increasing significance both in basic research and in industry. Due to their distinct advantages such as enhanced drug solubility, thermodynamic stability, facile preparation, and low cost, uses and applications of microemulsions have been numerous. Recently, there is a surge in the exploration of microemulsion for transdermal drug delivery for their ability to incorporate both hydrophilic (5-fluorouracil, apomorphine hydrochloride, diphenhydramine hydrochloride, tetracaine hydrochloride, and methotrexate) and lipophilic drugs (estradiol, finasteride, ketoprofen, meloxicam, felodipine, and triptolide) and enhance their permeation. Very low surface tension in conjunction with enormous increase in the interfacial area due to nanosized droplets of the microemulsion influences the drug permeation across the skin. A large number of oils and surfactants are available, which can be used as components of microemulsion systems for transdermal delivery but their toxicity, irritation potential, and unclear mechanism of action limit their use. Besides surfactants, oils can also act as penetration enhancers (oleic acid, linoleic acid, isopropyl myristate, isopropyl palmitate, etc.). The transdermal drug delivery potential of microemulsions is dependent not only on the applied constituents of the vehicle but also drastically on the composition/internal structure of the phases which may promote or hamper the drug distribution in the vehicles. This article explores microemulsion as transdermal drug delivery vehicles with emphasis on components selection for enhanced drug permeation and skin tolerability of these systems and further future directions.

Keywords microemulsion; transdermal drug delivery; permeation; drug solubilization; skin; surfactants; tolerability

INTRODUCTION

There is a heightened focus on speciality pharmaceuticals that add value and patent protection in major pharmaceutical markets by providing better delivery of drug. Innovations in the area of drug delivery are taking place at a much faster pace as compared to the last two decades. Today, transdermal drug delivery (TDD) is a well-accepted means of delivering many drugs to the systemic circulation, and current transdermal devices are used to treat motion sickness, hypertension, angina, female menopause, severe pain states, nicotine dependence, and male hypogonadism (Benson, 2005; Guy, 1996). Recently, US FDA gave approval to Novartis to market exelon patch (rivastigmine) for the treatment of Alzheimer's disease. Transdermal products for Parkinson's disease, depression, anxiety, attention deficit hyperactivity disorder (ADHD), and postmenopausal bone loss are at various stages of formulation and clinical development. It is expected that many more drugs will be included in the list of successful transdermal drug delivery systems (TDDS) in the near future.

Delivery of drugs via skin has many attractions including increased patient acceptability (noninvasiveness), avoidance of gastrointestinal disturbances (Payne, 1998), first-pass metabolism of the drug (Crook, 1997), and sustained delivery of drugs to provide steady plasma profiles, particularly for drugs with short half-lives and hence reduced systemic side effects (Thomas & Finnin, 2004). However, most of the transdermal candidates have low permeability across the skin (Flynn, 1990). The stratum corneum is responsible for the barrier function of the skin (Scheuplein & Blank, 1971). It consists of keratin-rich corneocytes embedded in an intercellular lipid matrix composed of ceramides, free fatty acids and their esters, and cholesterol and its sulfates that are structured in bilayers (Schurer & Elias, 1991). For most substances, the main barrier resides in the intercellular lipid domains. This has led to considerable activity toward different percutaneous penetration enhancement technologies, including vehicle drug interaction, mechanical disruption (Henry, Mc Allister, Allen, & Prausnitz, 1998; Mitragotri, Edwards, Blankschtein, & Langer, 1995; Prausnitz, 2004), electrical disruption (Denet, Vanbever, & Preat, 2004; Guy, 1998; Kaalia, Naik, Garrison, & Guy, 2004; Weaver, Vaughan, & Chizmadzhev, 1999), chemical modification of the barrier function (Prausnitz et al., 2004; Stoughton &

Address correspondence to Sushama Talegaonkar, Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard, New Delhi 110062, India. E-mail: stalegaonkar@gmail.com

Fritsch, 1964; Walker & Smith, 1996; Williams & Barry, 2004), and vesicular and particulate drug delivery (Barry, 2001; Schreier & Bouwstra, 1994) (Figure 1).

Of late, there has been a surge in the development of vesicular and particulate carriers such as liposomes (Fang, Hwang, Hwang, & Fang, 2006; Maestrelli, Gonzalez-Rodriguez, Rabasco, & Mura, 2006; Manosroi, Kongkaneramit, & Manosroi, 2004), niosomes (Fang, Yu, Wu, Huang, & Tsai, 2001; Kumhar et al., 2003; Uchegbu & Vyas, 1998; Vanhal, Vanrensen, Devringer, Junginger, & Bouwstra, 1996; Vora, Khopade, & Jain, 1998), ethosomes (Choi & Maibach, 2005; Dayan & Touitou, 2000; Elsayed, Abdallah, Naggar, & Khalafallah, 2006; Touitou, Dayan, Bergelson, Godin, & Eliaz, 2000; Touitou et al., 2002), transferosomes (Cevc, 2004; Cevc & Blume, 2001; Choi & Maibach, 2005), solid lipid nanoparticles (Liu et al., 2007; Muller, Radtke, & Wissing, 2002; Souto, Wissing, Barbosa, & Muller, 2004), and microemulsions for topical and transdermal delivery as they show excellent biocompatibility and capability of incorporating drugs of varying solubility. Particularly, recent attention has been focused on microemulsion which in addition to the aforementioned advantages exhibits superior stability. Microemulsions represent pharmaceutically versatile formulations for drug delivery to and through the skin. This novel vehicle has a potential of increasing percutaneous delivery of both hydrophilic and lipophilic drugs compared to conventional formulations (Boltri, Morel, Trotta, & Gasco, 1994; Bonina et al., 1995; Delgado-Charro, Iglesias-Vilas, Blanco-Mendez, Lopez-Quintela, & Guy, 1997; Dreher, Walde, Walther, & Wehrli, 1997; Kreilgaard, Pedersen, & Jaroszewski, 2000; Kriwet & Muller-Goymann, 1995; Trotta, Morel, & Gasco, 1997). The application of microemulsion vehicles for TDD is becoming increasingly popular as the potential of these formulations is realized. Oral (Araaya, Tomitab, & Hayashib, 2005; Kima et al., 2005; Pineyro-Lopez et al., 2007), parenteral (Jumma & Muller, 1998; von Corswant, Thoren, & Engstrom, 1998; Zhao, Chen, Gao, Ding, & Li, 2005), ophthalmic (Fialho & da Silva-Cunha, 2004; Habe & Keipert, 1997; Lv, Li, Zheng, & Tung, 2006), pulmonary (Sommerville, Cain, Johnson, & Hickey, 2000), nasal (Lianly, Nandi, & Kim, 2002; Vyas, Babbar, Sharma, Singh, & Misra, 2005), vaginal (D'Cruz & Uckun, 2001; D'Cruz, Yiv, & Uckun, 2001), and rectal are the other modes of delivery. In addition to drug delivery, other potential applications include food (Bodnar, Floter, Hogervorst, & Van Oosten, 2004), cosmetics (Chung, Tan, Tunhill, & Scharpf, 1994; Linn & York, 1989; Sonneville-Aubrun, Simonnet, & L'Alloret, 2004), agriculture (Herold, Beardmore, & Parrish, 2004; Narayanan & Jon, 2003), enhanced oil recovery (Gilje, Sonerson, Hollberg, Holmberg, & Svennberg, 1992; Shah, 1998), combustion (Gillberg, 1984), metal cutting (Prince, 1977), lubrication (Prince, 1977), enzymatic catalysis, organic and bio-organic reactions (Sjoblom, Lindberg, & Friberg, 1996), chemical synthesis of nanoparticles (Asua, 2002), and so on.

This article considers the current knowledge on microemulsions in relation to their use to alter the penetration rate of the drugs across the skin, mechanism of skin permeation, and dermal tolerability of these vehicles. The influence of microemulsion composition, components, and structure on their drug delivery potential is also discussed.

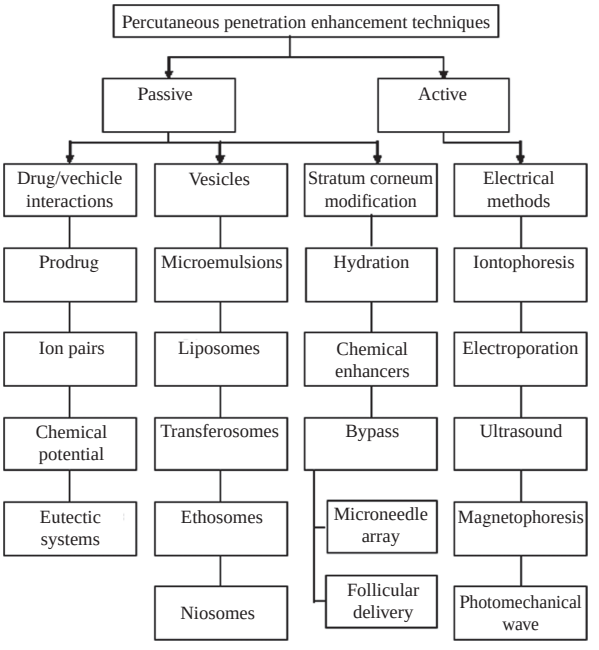

FIGURE 1. Some percutaneous penetration enhancement techniques.

MICROEMULSIONS

In 1959, Schulman, Stoeckenius, and Prince visualized the existence of small emulsion-like structures by electron microscopy and subsequently coined the term "microemulsions." Microemulsions are thermodynamically stable, isotropically clear mixtures of oil, water, and surfactant, frequently in combination with a cosurfactant (Danielsson & Lindman, 1981). These homogeneous systems, which can be prepared over a wide range of surfactant concentration and oil to water ratio, are all fluids of low viscosity.

Microemulsions as drug delivery vehicles show favorable properties such as thermodynamic stability (long shelf life), easy formation (zero interfacial tension and almost spontaneous formation), optical isotropy, ability to be sterilized by filtration, high surface area (high solubilization capacity), and very small droplet size. The small droplets provide better adherence to membranes and transport drug molecules in a controlled fashion.

The key differences between ordinary emulsions (macroemulsions) and microemulsions are that the former are thermodynamically unstable and will eventually lead to phase separation (Shinoda & Lindman, 1987). In addition, the droplet size of the macroemulsion increases with time. Second, emulsions are

cloudy having particles of 1–10 μm in size, whereas microemulsions are clear or translucent in appearance having droplet size usually in the range of 20–200 nm. Because the droplet size is less than 25% of the wavelength of visible light, microemulsions are transparent. Third, macroemulsions require a lot of energy for their preparation (high-shear mixing), whereas microemulsions do not as they are formed spontaneously when their components are brought into contact, that is without substantial energy supply, for example, in the absence of heating or the use of high-shear equipment. The latter point is significant in view of the cost of the commercial production of the system. Also, emulsions are relatively viscous as compared to microemulsions.

The term microemulsion is actually a misnomer. Having a droplet size in the nanometric scale (typically in the range of 10–100 nm) qualifies them to be called as nanoemulsion. This term is recently being increasingly preferred by various authors (Shafiq et al., 2007; Shakeel et al., 2007; Wu, Ramchandaran, Bielinska et al., 2001; Wu, Ramchandaran, Weiner et al., 2001).

Structure

Microemulsions are dynamic systems in which the interface is continuously and spontaneously fluctuating (Lam & Schechter, 1987). Structurally, they are divided into oil-in-water (o/w), water-in-oil (w/o), and bicontinuous microemulsions. In w/o microemulsion, water droplets are dispersed in the continuous oil phase, whereas o/w microemulsion is formed when oil droplets are dispersed in the continuous aqueous phase. In systems where the amounts of water and oil are similar, a bicontinuous microemulsion may result. In all three types of microemulsions, the interface is stabilized by an appropriate combination of surfactants and/or cosurfactants. The mixture of oil, water, and surfactants is able to form a wide variety of structures and phases depending on the proportions of the components. The flexibility of the surfactant film is an important factor in this regard. A flexible surfactant film will enable the existence of several different structures, such as droplet-like shapes, aggregates, and bicontinuous structures, and therefore broaden the range of microemulsion existence. A very rigid surfactant film will not enable existence of bicontinuous structures which will impede the range of existence.

The internal structure of a microemulsion vehicle is very important for the diffusivity of the phases and thereby also for the diffusion of a drug in the respective phases. Researchers have been trying zealously to understand the complicated phase behavior and the various microstructures encountered in the microemulsion systems (Hellweg, 2002).

Components of Microemulsion Formulations

A large number of oils and surfactants are available, which can be used as components of microemulsion systems for transdermal delivery, but their toxicity, irritation potential, and unclear mechanism of action limit their use. One must choose materials that are biocompatible, nontoxic, clinically acceptable, and use emulsifiers in an appropriate concentration range that will result in mild and nonaggressive microemulsions. The emphasis is, therefore, on the use of excipients that are generally regarded as safe (GRAS).

Oil Phase

The oil component influences curvature by its ability to penetrate and hence swell the tail group region of the surfactant monolayer. Short-chain oils penetrate the tail group region to a greater extent than long chain alkanes and hence swell this region to a greater extent, resulting in increased negative curvature (and reduced effective hydrophilic lipophilic balance (HLB)) (Ghosh & Murthy, 2006).

Saturated and unsaturated fatty acids have penetration-enhancing property of their own, and they have been studied since a long time. The mechanism by which fatty acids increase skin permeability appears to involve disruption of the densely packed lipids that fill the extracellular spaces of the stratum corneum (Aungst, 1989). It has been reported that C10–C12 saturated fatty acids possesses an optimal balance between partition coefficient or solubility parameters and affinity to skin (Ogiso & Shintani, 1990). In contrast, for penetration enhancers containing unsaturated alkyl chains, C18 appears near optimum. For such unsaturated compounds, the bent *cis* configuration perturbs the lipid packing more than does the *trans* configuration (Aungst, Rogers, & Shefter, 1986). *Cis*-unsaturated fatty acids (e.g., oleic acid, linoleic acid, and linolenic acid) have been reported to form separate domains within stratum corneum lipids which effectively decrease either diffusional path length or the resistance and in this way may induce highly permeable pathways in the stratum corneum (Ongpipattanakul, Burnette, & Potts, 1991; Tanojo, Bowstra, Junginger, & Bodde, 1997). The presence of double bonds in the structure has been proposed to cause the formation of kinks in the lipid structure to allow water permeation across the skin (Potts & Francoeur, 1990).

Among unsaturated fatty acids, oleic acid (a monounsaturated fatty acid) has been reported to be an effective skin penetration enhancer for polar and nonpolar drugs (Barry, 1987). Several naturally occurring oils, including almond, olive, maize, and sunflower oils, are major sources of linoleic acid (a polyunsaturated fatty acid).

It must be borne in mind that the skin penetration-promoting effects of fatty acids are selective for individual drugs. For example, neither lauric acid nor capric acid had any effect on the permeation of salicylic acid (Cooper, 1984) but both were shown to increase the permeation of naloxone (Aungst et al., 1986). Similarly, oleic acid increased the flux of salicylic acid 28-fold and of 5-fluorouracil 56-fold through human skin in vitro (Goodman & Barry, 1989), but the addition of oleic acid to propylene glycol (PG) did not improve the human skin permeation flux achieved with PG alone of hexyl nicotinate in vivo (Tanojo, Boelsma, Junginger, Ponec, & Bodde, 1999).

Fatty acid esters are also a popular choice. Of these, isopropyl myristate (IPM) is the most popular (Alvarez-Figueroa &

Blanco-Mendez, 2001; Baroli, Lopez-Quintela, Delgado-Charro, Fadda, & Blanco-Mendez, 2000; Carlfors, Blute, & Schmidt, 1991; Dalmora, Dalmora, & Oliveira, 2001; Djordjevic, Primorac, Stupar, & Krajisnik, 2004; Kantaria, Rees, & Lawrence, 1999; Ktistis & Niopas, 1998; Mei, Chen, Weng, Yang, & Yang, 2003; Peira, Scolari, & Gasco, 2001; Peltola, Saarinen-Savolainen, Kiesvaara, Suhonen, & Urtti, 2003; Schmalfuß, Neubert, & Wohlrab, 1997; Trotta, Gasco, & Pattarino, 1990; Trotta, Ugazio, Peira, & Pulitano, 2003; Trotta et al., 1997). But the mechanism of its action is poorly understood. In some cases, IPM does not show a significant effect (Morimoto et al., 1993). Isopropyl palmitate (IPP) (Dreher et al., 1997; Gallarate, Carlotti, Trotta, & Bovo, 1999; Garcia-Celma, Azemar, Pes, & Solans, 1994; Kemken, Ziegler, & Muller, 1991a; Sintov & Shapiro, 2004) has also found application, especially in microemulsion gels. Guo, Liu, Li, Nie, and Pan (2006) studied four drugs ranging from hydrophilic to lipophilic (ribavirin, nimesulide, gliclazide, and oxaprozin) to study the effect of IPP on skin permeability and found significant increase in the flux and permeation of all the four permeants. Ethyl or methyl esters of lauric, myristic, and oleic acid have also been employed as the oil phase.

Medium-chain triglycerides such as Miglyol 812 have been used quite frequently (Paolino, Ventura, Nistico, Puglisi, & Fresta, 2002; Spiclin, Gasperlin, & Kmetec, 2001; Spiclin, Homar, Zupancic-Valant, & Gasperlin, 2003; Valenta & Schultz, 2004; Warisnoicharoen, Lansley, & Lawrence, 2000). Other oils commonly used are triacetin (Rhee, Choi, Park, & Chi, 2001), isostearylic isostearate (Escribano, Calpena, Queralt, Obach, & Domenech, 2003; Kreilgaard et al., 2000), olive oil (Derle, Sagar, & Pimpale, 2006b; Wu, Ramchandaran, Bielinska et al., 2001), and soybean oil (Kantarci, Ozguney, Karasulu, Guneri, & Basdemir, 2005; Madhusudhan, Rambhau, Apte, & Gopinath, 2006).

Recent trend is toward the use of semisynthetic oils that are more stable than their natural counterparts. Novel semisynthetic medium-chain derivatives, which can be defined as amphiphilic compounds with surfactant properties, are being increasingly preferred. Moreover, with stringent quality control, oils with defined specifications can be manufactured with reproducible quality.

Hydrophobic drugs need to have a significant solubility in the dispersed oil phase for an efficient o/w microemulsion system to form. However, it is to be further noted that the oils in which the drug is most soluble do not necessarily form microemulsions with the highest drug solubilization capacity (Malcolmson, Satra, Kantaria, Sidhu, & Lawrence, 1998). Also, increasing the oil content in o/w microemulsions leads to an increase in droplet size.

Surfactants

The surfactant chosen must be able to lower the interfacial tension to a very small value, which facilitates dispersion process during the preparation of the microemulsion and provide a flexible film that can readily deform around the droplets and be of the appropriate lipophilic character to provide the correct curvature at the interfacial region. The HLB of a surfactant can be a useful guide for surfactant selection. It is generally accepted that low HLB surfactants are favored for the formulation of w/o microemulsion, whereas surfactants with high HLB (>12) are preferred for the formation of o/w microemulsion. Surfactants having HLB greater than 20 often require the presence of cosurfactants to reduce their effective HLB to a value within the range required for microemulsion formation.

There is no doubt that skin penetration can be enhanced by surfactants. The magnitude of enhancement is dependent to a large extent on the physicochemical properties of the permeant and the nature of the vehicle used. A high surfactant concentration is needed to stabilize the colloidal phase of microemulsions. Recent research work is, therefore, focused on both diminishing their concentration as well as searching for well-tolerated surfactants. Employing surfactants from native origin such as phospholipids, the natural biofriendly molecules, or alkyl polyglycosides seems to generate mild and nonaggressive microemulsion systems. Besides, polymeric surfactants such as poloxamers that are permitted for parenteral application appear to be useful as well.

Lecithin is a naturally occurring mixture of the diglycerides of stearic, palmitic, and oleic acids, linked to the choline ester of phosphoric acid, commonly called phosphatidylcholine. It is the most widely used phospholipid. It is nontoxic even in high concentrations and does not lead to skin irritation. An excellent and comprehensive report on the safety assessment of lecithin was prepared by Fiume (2001). Numerous studies have been conducted using lecithin-based microemulsions for enhancing the penetration of ascorbic acid (Gallarate et al., 1999), diclofenac (Dreher et al., 1997; Kriwet & Muller-Goymann, 1995), indomethacin (Dreher et al., 1997), ketoprofen (Paolino et al., 2002; Rhee et al., 2001), hematoporphyrin (Trotta, Gasco, Caputo, & Sancin, 1994), methotrexate (Trotta, Pattarino, & Gasco, 1996), and so on. Absorption of phospholipids on skin can increase tissue hydration, consequently increasing drug permeation. Phospholipids can fuse with stratum corneum lipids, perturb its structure, and facilitate drug delivery (Kirjavainen et al., 1999; Williams & Barry, 2004). Different phospholipids have different effects on the partitioning of the drug into the bilayers. Kirjavainen et al. (1999) used stratum corneum lipid liposomes as model for the lipid matrix of stratum corneum. Estradiol, progesterone, and propranolol were studied. They concluded that EPC (L-α-phosphatidylcholine from egg yolk), SPC (L-α-phosphatidylcholine from soybean), and DOPE (dioleylphosphatidyl ethanolamine), which are in a fluid state, may diffuse into the stratum corneum and enhance dermal and transdermal drug penetration, whereas DSPC (distearoyl phosphatidylcholine) which is in gel state is unable to do so.

Sugar surfactants such as alkyl glucosides and alkyl esters have also been investigated recently (Graf et al., 2008; Savic,

Savic, Vesic, Vuleta, & Muller-Goymann, 2006). They have emerged as a novel, important class of natural surfactants with good skin tolerance. Sucrose esters are approved by WHO as food additives owing to their high safety and excellent properties (Akoh, 1992). They are nontoxic and biodegradable and have large emulsifying capacity (Fanun et al., 2001). Contrary to the ionic or ethoxylated nonionic traditional surfactants, they are mild for skin, with large number of hydroxyl groups in the structure, which may provide an additional skin hydration (Stubenrauch, 2001). The interest in sugar surfactants is motivated by the fact that they can be made from renewable material and that they have favorable properties with regard to performance and environmental compatibility (Hill & Rhode, 1999). Sucrose esters do not lose solubility with increasing temperature. This interesting property can be used to prepare temperature-insensitive microemulsions (Baran & Wade, 1995; Pes, Atamaki, Nakamura, & Kuneida, 1993).

Nonionic surfactants can be useful alternatives to naturally occurring surfactants. For example, polyoxyethylene sorbitan n-acyl esters (Tweens) have been reported to have minimal toxicity. Surfactants such as sorbitan fatty acid esters, polysorbates, pegylated fatty alcohols and fatty acids, and poloxamers are frequently used. Furthermore, nonionic microemulsions are more stable and are less affected by minor changes in pH and electrolyte concentration when compared to their ionic counterparts. There is a wide use of nonionic surfactants in topical formulations as solubilizing agents. Among them, polysorbates are very common. Tween 80 was reported to enhance hydrocortisone and lidocaine permeation and Tween 20 improved the permeation of 5-fluorouracil across hairless mouse skin (Sarpotdar & Zatz, 1986). Other examples of nonionic surfactants include polyoxyethylene surfactants such as Brij 35 and sugar esters such as sorbitan monooleate (Span 80). It is to be noted that HLB ratio of nonionic surfactants is an important factor in increasing solubilization (Marszall, 1987). The mixture of two surfactants which have the same alkyl chain length but a quite opposite solubilizing ability toward oil and water may enhance the mutual solubilization of oil and water. As a general guideline, nonionic and zwitterionic surfactants are less toxic than ionic ones.

With an appropriate oil phase, a novel mild surfactant, Labrasol, has been demonstrated to form microemulsions with several nonalcohol cosurfactants, which diminishes the risk of cutaneous toxicological reactions by the application of topical microemulsions and thus increasing the pharmaceutical relevance of the vehicles (Delgado-Charro et al., 1997). Another surfactant, Plurol Isostearique, with better tolerability has recently been introduced into topical microemulsion formulations and has been demonstrated to provide extensive region of existences with various surfactants and oils (Alvarez-Figueroa & Blanco-Mendez, 2001; Delgado-Charro et al., 1997; Kreilgaard et al., 2000). Dioctyl sodium sulfosuccinate has also been studied as surfactant (Osborne, Ward, & O'Neill, 1988, 1991).

Surfactants, which are able to function as enhancers, are believed to penetrate the skin mainly in their monomer form (Schaefer & Redelmeier, 1996), and it is thus not likely that the micellar-like microemulsion structures are able to penetrate the skin intact (Schreier & Bouwstra, 1994). However, as microemulsions are highly dynamic structures (Lam & Schechter, 1987), it is plausible that monomer surfactants can diffuse to the skin surface and act as enhancers, either by disrupting the lipid structure of the stratum corneum, facilitating diffusion through the barrier phase, or by increasing the solubility of drug in the skin, that is increasing the partition coefficient of the drug between the skin and the vehicle.

Cosurfactants

In most cases, single-chain surfactants alone are unable to reduce the o/w interfacial tension sufficiently to enable a microemulsion to form (Attwood, 1994; Bhargava, Narurkar, & Lieb, 1987; Eccleston, 1994a, 1994b; Lawrence, 1994, 1996; Tenjarla, 1999). The presence of cosurfactants allows the interfacial film sufficient flexibility to take up different curvatures required to form microemulsion over a wide range of composition (Aboofazeli, Lawrence, Wicks, & Lawrence, 1994; Ghosh & Murthy, 2006; Lawrence & Rees, 2000; Stilbs, Lindman, & Rapacki, 1983). If a single surfactant film is desired, the lipophilic chains of the surfactant should be sufficiently short or contain fluidizing groups (e.g., unsaturated bonds). To enable integration of the oil with the interfacial film, the size of the oil molecules should not be too large (Lawrence, 1994). Short- to medium-chain-length alcohols (C3–C8) are commonly added as cosurfactants which further reduce the interfacial tension and increase the fluidity of the interface (Attwood, 1994; Eccleston, 1994a, 1994b; Tenjarla, 1999). They also increase the mobility of the hydrocarbon tail and also greater penetration of the oil into this region. Alcohols may also increase the miscibility of the aqueous and oily phases due to its partitioning between these phases. Lamellar liquid crystalline phases rather than microemulsion phase often form with longer chain length cosurfactant or in the absence of cosurfactant due to the rigidity of the interfacial film.

Among the short-chain alkanols, ethanol has been widely used as permeation enhancer. Better flux of mefenamic acid (Heard, Kung, & Thomas, 2006), naloxone (Panchagnula, Salve, Thomas, Jain, & Ramarao, 2001), indomethacin (Okabe, Suzuki, Saitoh, Takayama, & Nagai, 1994), levonorgestrel (Friend, Catz, Heller, Reid, & Baker, 1988), and diclofenac (Obata, Takayama, Maitani, Machida, & Nagai, 1993) was obtained through rat skin when ethanol was added. The effect of ethanol is concentration dependent, and therefore under certain conditions, it can even decrease the permeation (Megrab, Williams, & Barry, 1995; Williams & Barry, 2004). The penetration enhancement activity of ethanol can be due to the increase in the drug solubility in the vehicle (Williams & Barry, 2004) or alteration in the structure of membrane with resultant increase in the permeability of drug (Megrab et al.,

1995; Williams & Barry, 2004). Another plausible mechanism is based on the fact that ethanol is volatilized from the applied formulation and, consequently, increases the drug concentration to a supersaturated state with greater driving force for permeation.

Medium-chain alcohols are also used as penetration enhancers. Among these, 1-butanol was reported to be the most effective enhancer for levonorgestrel traversing rat skin when compared with branched alkanols (Friend et al., 1988). Decanol was found to be an optimum enhancer for melatonin among other saturated fatty alcohols that were investigated (from octanol to myristyl alcohol) (Friend et al., 1988). PG has been found to act as an enhancer by a mechanism similar to that of ethanol (Williams & Barry, 2004) and increased the permeation of 5-fluorouracil (Goodman & Barry, 1989). However, large contents of the agent in a vehicle may substantially reduce the partition coefficient between the skin and the vehicle for the drug, which can counteract the benefits of the increased concentration gradient by reducing the overall activity of the drug in the vehicle and thereby actually decreasing the transdermal flux (Turi, Danielson, & Woltersom, 1979).

Transcutol (diethylene glycol monoethyl ether) is also a mild surfactant (Gattefosse Corporation, 1982) and can be used effectively. It has been recognized as a potential transdermal permeation enhancer due to its nontoxicity, biocompatibility with skin, and excellent solubilizing properties (Godwin, Kim, & Feltan, 2002).

The surfactant and cosurfactant ratio is a key factor influencing the phase properties. Attwood, Mallon, Ktistis, and Taylor (1992) showed how size and location of microemulsion is changed on changing the mass ratio of polysorbate 40/sorbitol from 1:1 to 1:3.5. Similar studies using polysorbate 80 (Ktistis, 1990) and polysorbate 60 (Attwood & Ktistis, 1989) have shown a change in the optimum polysorbate/sorbitol mass ratio (i.e., that producing the largest microemulsion region) from 1:2.5 for polysorbate 80 to 1:2 for polysorbate 60 to 1:1.5 for polysorbate 40. Such effects were attributed to differences in the packing of surfactant and cosurfactant at the o/w interface.

Method of Preparation

Microemulsions are prepared by the spontaneous emulsification method (phase titration method) and can be depicted with the help of phase diagrams. As quaternary phase diagram (four component system) is time consuming and difficult to interpret, pseudoternary phase diagram is often constructed to find the different zones including microemulsion zone, in which each corner of the diagram represents 100% of the particular component. The methodology has been comprehensively discussed by Shafiq-un-Nabi et al. (2007). Figure 2 represents the pseudoternary phase diagram depicting the microemulsion region.

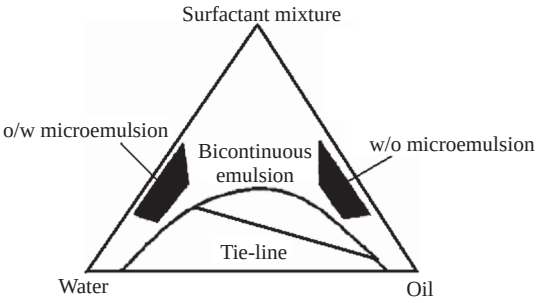

FIGURE 2. Pseudoternary phase diagram depicting microemulsion region.

Characterization

The size distribution of microemulsions gives essential information for a reasonable understanding of the mechanism governing both the stability and the penetration into the skin (Constantinides & Yiv, 1995; Mueller & Mueller, 1984). Due to the possibility of different types of structures, characterization of microemulsions is a very hard task, and this is the reason why many techniques have been developed for this purpose, and often, the combination of more than one of them is required for a reliable characterization (Kogan & Garti, 2006). Many technologies such as dynamic light scattering (DLS) (Kang et al., 2004; Porras et al., 2004), small angle neutron scattering (SANS) (Burnett, Rees, Steytler, & Robinson, 2004; Pedersen, 1999; Silas & Kaler, 2001, 2003), and small angle X-ray scattering (SAXS) (Dungan, 1997; Engstrom & Larsson, 1999; Gasco, 1997; Glatter et al., 2001; Kawakami et al., 2002; Podlogar, Gasperlin, Tomsic, Jamnik, & Bester Rogac, 2004) as well as cryo transmission electron microscopy (Danino, Gupta et al., 2002; Danino, Talmon et al., 2002; Jian, Ganzuo, Zhiqiang, Guowei, & Kejian, 2001; Magdassi, Ben Moshe, Talmon, & Danino, 2003) and pulsed field gradient spin echo (self-diffusion) NMR (Andersson & Lofroth, 2003; Fanun et al., 2001; Koa, Kob, Kim, & Park, 2003; Kreilgaard et al., 2000; Lopez et al., 2004; Myers, 1999) have been in growing use in particle size characterization.

SAXS can be used to get information about shape and dimension of microemulsion droplets, whereas SANS can also provide information about the amphiphilic stratum dividing the oil phase from the water phase without big system perturbations. Light scattering can be subdivided into bulk light scattering and surface light scattering. In bulk light scattering, the intensity of the scattered light is usually measured at different angles and for different droplets concentration in the microemulsion. Surface light scattering, also called photon correlation spectroscopy (PCS), is based on the reflection of a laser beam on the o/w interface. Due to Brownian motions, this surface is not perfectly plane so that the laser beam is reflected in all directions. The intensity variation of the reflected beam provides information about system dynamics. This technique can be used to estimate dispersed phase dimensions. The major

drawback in adopting scattering techniques is the requirement of sample dilution to reduce droplet interactions. Indeed, unfortunately, dilution of the microemulsion can reflect into structure and composition modifications of the various phases.

Other methods—for example, electrokinetic chromatography, conductance, viscosity, electrical birefringence, infrared spectroscopy, and calorimetry—are also employed for investigating the internal physicochemical states of microemulsions (Attwood, 1994; Djordjevic et al., 2004; Kumar & Mittal, 1999; Moulik & Paul, 1998; Mrestani, El-Mokdad, Ruttinger, & Neubert, 1998a; Mrestani, Neubert, & Krause, 1998b). Microcalorimetric studies can be used for the evaluation of the enthalpies associated with the process of microemulsification which can give useful information about the stability of the system. Fourier transform infrared (FTIR) spectroscopy has been used to characterize water environments in microemulsions, especially interfacial-"bound" water close to the surfactant head groups and "bulk-like" water in the droplet core.

Microemulsions characterization by electron microscopy technique poses serious problems. Sample preparation may lead to structure alteration or breakup. However, the freeze fracture electron microscopy allows overcoming this problem as it involves a very rapid microemulsion freezing followed by system fracture. Accordingly, a microscopic analysis of the fractured surface can be performed. The rapid freezing prevents structure modifications, and the real microemulsion structure can be observed.

Viscosity measurement can indicate the presence of rod- or worm-like reverse micelles, whereas conductivity measurement provides a means of determining whether a microemulsion is oil-continuous or water-continuous as well provides a means of monitoring phase inversion phenomena. Dielectric measurements are a powerful means of probing both the structural and the dynamic features of microemulsion systems.

NMR self-diffusion and relaxation constitute selection tools for the determination of microstructural information. Self-diffusion studies, coupled with microscopic analysis, can be used to prove the existence of microemulsion bicontinuous structures. On the other hand, relaxation is one of the most reliable methods for the determination of droplets shape and dimension, especially in concentrated systems as the rotational diffusion of droplets is evaluated. In addition, this technique is useful for the characterization of the surfactant film separating the oil phase from the water phase and can also provide useful information about microemulsions phase diagrams. Simultaneous information regarding water, oil, and surfactant regions can be attained. Moreover, information regarding drug solubility and disposition within the phases can also be obtained.

Understanding the relationship between microstructure and composition of microemulsion is important to prepare and optimize microemulsions for efficient use in drug delivery.

MICROEMULSIONS IN TRANSDERMAL DRUG DELIVERY

The ultimate goal of TDD is to ensure that drugs are delivered, preferably at a specific rate, to the systemic circulation. Penetration of drug into dermal vasculature follows exposure of the skin to a dosage form from which the active constituent must partition, followed by diffusion of the compound through the external strata to the dermis. Partitioning of the drug from the dosage form is highly dependent on the relative solubility of the drug in the components of delivery system and in the stratum corneum. Thus, the formulation of the vehicle may markedly influence the degree of penetration of the drug (Bonina, Carelli, Di Colo, Montenegro, & Nannipieri, 1993). Partitioning is governed to a large extent by the thermodynamic activity of the drug in the vehicle, and this aspect is, therefore, of major importance in controlling the degree of penetration of any one compound (Davis & Hadgraft, 1991). One of the major challenges for topical formulations today is to promote the penetration of drug across the skin barrier without inducing irreversible effect on its properties.

As colloid systems or "swollen micelles," microemulsions have both hydrophilic and lipophilic areas, but unlike macroemulsions, microemulsions are not made up of a continuous or dispersed phase. This may explain why the microemulsions are better at penetrating the stratum corneum and blending into the skin lipids. The incorporation of a lipophilic drug into the internal phase of an o/w microemulsion has recently become an attractive technique for solubilizing the drugs and using microemulsions as topical drug delivery vehicles (Osborne et al., 1991).

However, it is pertinent to note that the TDD potential of microemulsions is dependent not only on the applied constituents of the vehicle but also drastically on the composition/internal structure of the phases which may promote or hamper the drug distribution in the vehicles (Kreilgaard et al., 2000; Osborne et al., 1988, 1991). The latter situation can arise either due to diffusional hindrances of the drug (i.e., encapsulation of the solvent or adsorption to the surfactant film), unfavorable partitioning of the drug from the internal to the external phase, or unfavorable overall partition coefficient between the microemulsion and the skin. This has been demonstrated in a study (Kreilgaard et al., 2000) where the delivery rates of lidocaine were higher from the microemulsions with lower saturation level, due to the structural limitations for free drug diffusion in other vehicles, independently of whether the vehicles contained equal drug loads or near-saturated drug loads.

Role in Skin Permeation

Several plausible mechanisms have been proposed about the role of microemulsion in transdermal delivery of a drug:

1. A large amount of drug can be incorporated in the formulation due to the high solubilizing capacity that might increase thermodynamic activity toward the skin (Hua, Weisan, Jiayu, & Ying, 2004).

2. The permeation rate of the drug from microemulsion may be increased, as the affinity of a drug to the internal phase in microemulsion can be easily modified to favor partitioning into stratum corneum, using different internal phase, changing its portion in microemulsion (Kreilgaard, 2002).
3. The surfactant and cosurfactant in the microemulsions may reduce the diffusional barrier of the stratum corneum by acting as penetration enhancers (Rhee et al., 2001).
4. The percutaneous absorption of drug will also increase due to hydration effect of the stratum corneum if the water content in microemulsion is high enough (Mohammed & Manoj, 2000).

Generally, microemulsions have favorable solvent properties due to the potential incorporation of large fraction of lipophilic and/or hydrophilic phases. Furthermore, investigations have indicated that the unique structural organization of the phases in microemulsions may contribute to additional solubility regions, increasing the load capacity of microemulsions compared to nonstructured solutions containing the same fraction of the constituents (Kreilgaard et al., 2000; Malcolmson & Lawrence, 1990, 1993; Malcolmson et al., 1998).

Owing to the small droplet size and large amount of inner phase in microemulsions, the density of droplets and their surface area are assumed to be high. Therefore, droplets settle down to close contact with the skin providing high concentration gradient and improved drug permeation. Moreover, low surface tension ensures good contact with the skin. Also, the dispersed phase can act as a reservoir making it possible to maintain an almost constant concentration gradient over the skin for a long time (Elena, Paola, & Maria, 2001).

Due to the presence of both hydrophilic and lipophilic domains, it can be suggested that microemulsions are able to interact with both the lipid (nonpolar) and the protein (polar) pathway by entering the stratum corneum via the intercellular route. The drug dissolved in the lipid domain can directly partition into lipids of stratum corneum, or lipid vesicles themselves can intercalate between the lipid chains of the stratum corneum, thereby destabilizing its bilayer structure, leading ultimately to increased permeability of the lipid pathways to the drug. On the other hand, the hydrophilic domain of the microemulsion can hydrate the stratum corneum to a greater extent, which plays an important role in the percutaneous uptake of the drug. As some lipid chains are covalently attached to the corneocytes, hydration of these proteins will also lead to the disorder of the lipid bilayers. The greater drug penetration-enhancing efficacy of the microemulsions as compared to conventional vehicles can be attributed to the combined effect of both the lipophilic and the hydrophilic domains of the microemulsions.

Review of Microemulsions as Transdermal Drug Delivery Vehicles

Many studies have been conducted incorporating different drugs in microemulsions in the recent past. A good indication of the transdermal delivery potential of microemulsions can be obtained from such scientific deliberations. An overview of these studies is summarized in Tables 1 and 2. Researchers have keenly explored their potential applications in various therapeutic conditions that have been illustrated in the following sections.

Delivery of Hormones

Biruss, Kahlig, and Valenta (2007) investigated the permeation and chemical stability of 17-β-estradiol, progesterone, cyproterone acetate, and finasteride incorporated into a microemulsion system consisting of Brij 30, ethanol, and eucalyptus oil. The microemulsions were gelified by polycarbophil and polymeric emulsifier in a final concentration of 2% (wt/wt) and silicon dioxide in a final concentration of 6% (wt/wt). All the microemulsions with polymer increase the transdermal flux, except the microemulsion with polycarbophil where a decrease in flux of cyproterone acetate with respect to pure microemulsion was seen. Best permeation results for 17-β-estradiol, progesterone, and finasteride were obtained with microemulsions with polymeric emulsifiers, polycarbophil, and silicon dioxide, respectively. All the polymers in the microemulsions increased the chemical stability of the used hormones after an observation period of 6 weeks. Addition of polycarbophil increased the chemical stability of progesterone and finasteride. Polymeric emulsifier protected 17-β-estradiol against chemical degradation while silicon dioxide increased the stability of cyproterone acetate. A reason of chemical degradation of the selected drugs in the pure microemulsions might be chemical hydrolysis caused by the freely available water. The polymer binds with water and interacts with droplets of the microemulsions. Additionally, polyacrylic acid derivatives possess antimicrobial activity themselves. The presence of ethanol and eucalyptus oil seems to have a synergistic influence on the chemical and microbial stability.

Peltola and coworkers (2003) prepared a series of eight microemulsions containing estradiol. The oil phase consisted of either Epikuron 200, oleic acid, or IPM, and aqueous phase consisted of phosphate-buffered saline (PBS) pH 7.4, and these were first combined with surfactant (Tween or Span). Cosurfactant (ethanol or isopropanol) was added gradually with magnetic stirring until the system was transparent. One formulation was converted into microemulsion gel by the incorporation of Carbopol 940. The results of the transdermal transport experiments revealed that the steady-state flux of estradiol across human skin from the microemulsions was 200- to 700-fold higher than from the control. Also, the lag times of permeation were shorter (about 1 h) for microemulsions than from the control (10–20 h). Comparison of results from ethanol solution to ethanol-containing microemulsions showed that estradiol solubility and flux improved 130- to 170-fold and 10- to 30-fold, respectively. Similarly, solubility and flux of estradiol from the isopropanol-based microemulsion increased 25- and 18-fold, respectively, compared to isopropanol

TABLE 1
Overview of In Vitro Studies of Transdermal Drug Delivery with Microemulsions

Drug	Microemulsion Components			Membrane/ Skin	References
	Oil Phase	Surfactants/Cosurfactants	Aqueous Phase		
$[^3H]H_2O$	Octanol	Dioctyl sodium sulfosuccinate	Water	Human	Osborne et al. (1988), Osborne et al. (1991)
5-Fluorouracil	IPM	AOT	Water	Mouse	Gupta, Jain, and Varshney (2005)
8-Methoxsalen	IPM	Tween 80, Span 80, 1,2-octanediol	Water	Pig	Baroli et al. (2000)
Aceclofenac	Labrafil M1944CS	Cremophor ELP, ethanol	Water	Rat	Lee, Lee, Kim, Yoon, and Choi (2005)
Apomorphine hydrochloride	IPM, decanol	Epikuron 200, 1,2-propanediol, benzyl alcohol	Water, aerosil 200	Mouse	Peira et al. (2001)
Ascorbic acid	IPM, cetearyl octanoate	Dodecylglucoside cocoamide propylbetaine, phosphatidylcholine, 2-ethyl-1,3-hexanediol	Water	—	Gallarate et al. (1999)
Ascorbyl palmitate	Mygliol 812	Labrasol, Plurol Oleique	Water	—	Spiclin et al. (2001)
Celecoxib	IPM	Caprylic/capric mono-/diglycerides, polysorbate 80	Water	Rat	Subramanian, Ghosal, and Moulik (2005)
Cyclosporin A	IPM	AOT, Tween 85	Water	Rat	Liu et al. (2006)
Cyproterone acetate	Eucalyptus oil	Brij 30, ethanol	Water	Pig	Biruss et al. (2007)
Dehydoepiandrosterone	Labrafil M1944CS, Plurol Oleique	Labrasol, transcutol	Water	Pig	Ceschel et al. (2005)
Desmopressin acetate	IPP	Tagat 02, Span 80	Water	Human	Getei, Wohlrab, and Neubert (2005)
Diclofenac	IPM	Lecithin	Water	Human	Dreher et al. (1997)
Diclofenac	Diclofenac diethlamine	Lecithin	Water	Human	Kriwet and Muller-Goymann (1995)
Diclofenac	IPM	Labrasol, Plurol Oleique	Water	—	Djordjevic et al. (2004)
Diclofenac	IPM	Tween 80, ethanol	Buffer pH 7.4	Guinea pig	Kamal, Iimura, Nabekura, and Kitagawa (2007)
Diclofenac sodium	Soybean oil	Brij 58, Span 80, isopropyl alcohol, propanol	Water	Rabbit	Kantarci et al. (2005)
Diphenhydramine hydrochloride	IPM	Tween 80, Span 20	Water	Human	Schmalfuß et al. (1997)
	IPP	Glycolipid	Water	Human	Neubert, Schmalfuss, Wolf, and Wohlrab (2005)

(*Continued*)

TABLE 1
(*Continued*)

Drug	Microemulsion Components			Membrane/ Skin	References
	Oil Phase	Surfactants/Cosurfactants	Aqueous Phase		
Econazole nitrate	Medium-chain triglyceride, α-tocopherol, stearylamine/D-eoxycholic acid	Lipoid E-80, Poloxamer 188	Water, glycerol	Rat	Peimi, Korner, Benita, and Marty (1999)
Estradiol	Epikuron 200, oleic acid, IPM	Tween 80, Span 20, Span 80/ethanol, isopropanol	Water	Human	Peltola et al. (2003)
	Eucalyptus oil	Brij 30, ethanol	Water	Pig	Biruss et al. (2007)
Finasteride	Eucalyptus oil	Brij 30, ethanol	Water	Pig	Biruss et al. (2007)
Felodipine	IPM, benzyl alcohol	Tween 20, taurodeoxycholate	Water, transcutol, carbopol	Mouse	Trotta et al. (1997)
Fluoxetine	Lauroglycol, butylated hydroxytoluene	Labrasol, transcutol	Water	Human	Parikh and Ghosh (2005)
Flurbiprofen	IPM, ethyl oleate	Aerosol OT, Span 80	Water	Rat	Ambade et al. (2008)
Glucose	Octanol	Dioctyl sodium sulfosuccinate	Water	Human	Osborne et al. (1991)
Hematoporphyrin	IPM, decanol, hexa decanol, oleic acid, monoolein	Lecithin, sodium monohexylphosphate, benzyl alcohol	Water, PG	Mouse	Trotta et al. (1994)
Hydrocortisone	Eucalyptus oil	Tween 80, ethanol, ispropanolol, propylene glycol	Water	Rabbit	ElMaghraby (2008)
Indomethacin	IPM	Lecithin	Water	Human	Dreher et al. (1997)
Inulin	Olive oil	Tween 80, Span 80	Water	Rat, mouse	Wu, Ramchandaran, Bielinska et al. (2001)
Ketoprofen	Mygliol 812	Lecithin, *n*-butanol	Water	Human	Paolino et al. (2002)
Ketoprofen	Triacetin, oleic acid	Labrasol, cremophor RH	Water	Rat	Rhee et al. (2001)
Lidocaine	IPP	Glyceryloleate, polyoxyl 40 fatty acid derivatives, tetraglycol	Water	Mouse	Sintov and Shapiro (2004)
Lidocaine	Isostearylic isostearate	Labrasol, Plurol Isostearique	Water	Rat	Kreilgaard et al. (2000)
Meloxicam	IPM	Tween 85, ethanol	Water	Rat	Yuan et al. (2006)
Methotrexate	Decanol	Lecithin, benzyl alcohol	Water, PG	Mouse	Trotta et al. (1996)
Methotrexate	Ethyl oleate	Labrasol, Plurol Isostearique	Aq. 154 mM NaCl (pH 7.4)	Pig	Alvarez-Figueroa and Blanco-Mendez (2001)
Methotrexate	IPM	Tween 80, Span 80, 1,2-octanediol	Water	Pig	Alvarez-Figueroa and Blanco-Mendez (2001)
Miconazole nitrate	Medium-chain triglyceride, α-tocopherol, stearylamine/ D-eoxycholic acid	Lipoid E-80, poloxamer 188	Water, glycerol	Rat	Peimi et al. (1999)

Nabumetone	Soybean oil	Lecithin, 1-*O*-alkylglycerol, 1-*O*-dodecylglycerol, 1-*O*-tetradecylglycerol	Water	Rat	Madhusudhan et al. (2006)
Nifedipine	Benzyl alcohol	Tween 20, taurodeoxycholate	Water	Mouse	Boltri et al. (1994)
Nifedipine	Oil of ylang yland, cinnamon oil, lavender oil, menthol, menthone, cineole	Ethanol (5, 25, 100%)	—	Rabbit	Thacharochi and Rao (1994)
Niflumic acid	Octyl octanoate	Sucrose monolaurate sucrose dilaurate, medium-chain alcohol	Water	Human	Bolzinger et al. (1998)
Nimesulide	Olive oil	Tween 80, isooctanol	Water	Rat	Derle, Sagar, Kotwal, Ingole, and Chauhan (2006a)
Piroxicam	Oleic acid	Labrasol, ethanol	Water	Rat	Park, Cui, Yun, Ko, and Chi (2005)
Prilocaine hydrochloride	Isostearylic isostearate	Labrasol, Plurol Isostearique	Water	Rat	Kreilgaard et al. (2000)
Progesterone	Eucalyptus oil	Brij 30, ethanol	Water	Pig	Biruss et al. (2007)
Propranolol	IPM	Tween 80	Water	Artificial	Ktistis and Niopas (1998)
Prostaglandin E_1	Oleic acid	Labrasol, Plurol Oleique	Water	Mouse	Ho et al. (1998)
Retinoic acid	IPM	Epikuron 200, Oramix NS10, ethanol, 1,2-hexanediol	Phosphate buffer	Artificial, pig	Trotta et al. (2003)
Sodium ascorbyl phosphate	Mygliol 812	Labrasol, Plurol Oleique	Water	Artificial	Spiclin et al. (2003)
Sodium diclofenac	Isostearylic isostearate, oleic acid, R(+)-limonene tributyrine	Labrasol, Plurol Oleique	Water, buffer pH 7.4	Rat, rabbit	Escribano et al. (2003)
Sodium fluorescein	Mygliol 812, soybean oil	Brij 97	Water	Pig	Valenta and Schultz (2004)
Sodium nonivamide acetate	IPM	Tween 80, Span 20, ethanol	Water	Rat	Huang et al. (2008)
Sodium salicylate	IPM	Tween 21/81/85, bis-2-(ethylhexyl) sulfosuccinate	Water, gelatin	Pig	Kantaria et al. (1999)
Sucrose	Ethyl oleate	Labrasol, Plurol Isostearique	Water, 154 mM NaCl	Mouse	Delgado-Charro et al. (1997)
Tetracaine	IPM	Lecithin, *n*-propanol	Water	Mouse	Changez et al. (2006b)
Triptolide	IPM	Tween 80, 1,2-propylene glycol	Water	Rat	Mei et al. (2003)
Triptolide	IPM	Tween 80, propylene glycol	Water, menthol	Mouse	Chen et al. (2004)
Valdecoxib	Oleic acid	Tween 80, PG	Water	Human	Derle et al. (2006b)
Vinpocetine	Oleic acid	Labrasol, transcutol	Water	Human	Hua et al. (2004)

IPM, isopropyl myristate; IPP, isopropyl palmitate.

TABLE 2
Overview of In Vivo Studies of Transdermal Drug Delivery with Microemulsions

	Microemulsion Components				
Drug	Oil Phase	Surfactants/Cosurfactants	Aqueous Phase	Species	References
Apomorphine hydrochloride	IPM, decanol, ascorbyl palmitate	Epikuron 200, benzyl alcohol, sodium taurocholate	Water, ascorbic acid	Human	Priano et al. (2004)
Bupranolol	IPP	Tween 85	—[a]	Rabbit	Kemken et al. (1991a), Kemken, Ziegler, and Muller (1991b)
	IPP	Targat, glycerol monooleate	—[a]	Rabbit	
	IPP	Tween 85, poloxamer 101	—[a]	Rabbit	
Carazolol	IPP	Tween 85	—[a]	Rabbit	
Diclofenac sodium	Jojoba oil	Brij 96V, hexanol	Water	Rat	Shevachman, Garti, Shani, and Sintov (2008)
Hydrocortisone	IPM	Sucrose laurate, PG	Water	Human	
	IPM	Targat, Plurololeat	Water	Human	Lehmann et al. (2001)
Lidocaine	Isostearylic isostearate	Labrasol, Plurol Isostearique	Water	Rat	Kreilgaard (2001)
	Isostearylic isostearate	Labrasol, Plurol Isostearique	Water	Human	Kreilgaard, Kemme, Burggraaf, Schoemaker, and Cohen (2001)
Lidocaine hydrochloride				Pig	Sintov and Brandys-Sitton (2006)
Methyl nicotinate	IPP	Lecithin	Water	Human	Bonina et al. (1995)
Piroxicam	IPM	Hexadecyltrimethylammonium bromide	Aqueous phoshate buffer (pH 5.5)	Rat	Dalmora et al. (2001)
Prilocaine hydrochloride	Isostearylic isostearate	Labrasol, Plurol Isostearique	Water	Rat	Kreilgaard (2001)
Tetracaine	IPM	Lecithin, *n*-propanol	Water	Rat	Changez, Chander, and Dinda (2006a)
Theophylline	Oleic acid	Labrasol, cremophor RH 40	Water	Rat	Zhao et al. (2006)
Timolol	IPP	Tween 85	—[a]	Rabbit	Kemken et al. (1991b)

[a]Supersaturated vehicle with water uptake during the study.
IPM, isopropyl myristate; IPP, isopropyl palmitate.

solution. The authors concluded that the superior flux was mainly due to the large solubilizing power of the microemulsions, which leads to larger concentration gradients toward the skin. Flux of estradiol in the skin was expected to be at an adequate level for therapeutic effects.

Delivery of Analgesics

The optimum formulation prepared by Yuan, Li, Mo, and Zhong (2006) for transdermal delivery of meloxicam consisted of 0.375% meloxicam, 5% IPM, 50% Tween 85/ethanol (1:1), and water. They found that the content of oil (5–15%) played an important role in microemulsion formulation, and it affected the skin permeation rate directly. The skin permeation of meloxicam was the highest when the percentage concentration of IPM was 5% and was 3.3 times of the control group (25% surfactant and 25% ethanol micelle solution). The results suggested that the microemulsion had better skin penetration ability compared to the micelle solution.

Kantarci et al. (2005) prepared microemulsion formulations for topical delivery of diclofenac sodium without or with PG and dimethyl sulfoxide (DMSO) as enhancers and compared the enhancing effect with commercial formulation C (Voltran Emulgel®, Novartis, Turkey) by Franz diffusion cells fitted with intact excised rabbit skin. First microemulsion formulation (MI)

comprised of soybean oil (32.5%), water (6.3%), Brij 58 (5.1%), Span 80 (45.9%), and isopropyl alcohol (10.2%). The other microemulsion formulation (MP) comprised of soybean oil (27.2%), water (10%), Brij 58 (5.2%), Span 80 (47.1%), and propanol (10.5%). DMSO and PG were added as enhancers (10%, wt/wt) at the last step. All formulations prepared contained 1% (wt/wt) diclofenac sodium. One gram of Voltran Emulgel contained 11.6 mg diclofenac dimethylammonium (equivalent to 10 mg/g diclofenac sodium), isopropyl alcohol, PG, cream 45, and other additives. Without enhancer, microemulsion formulations equated with C formulation for the penetration of diclofenac.

It was found that the effect of enhancer was not similar when incorporated into different formulations. For example, PG showed a better effect than DMSO when incorporated into MI, whereas DMSO was superior to PG when incorporated into MP. As compared to DMSO, PG showed good enhancer effect when incorporated into MI and MP ($p < .05$). The enhancing effect of PG on diclofenac sodium absorption from microemulsions can also be explained by the combination of soybean oil with PG. Soybean oil contains saturated and unsaturated fatty acids. The mixture of fatty acids and PG resulted in optimal effect of fatty acids as permeation enhancers; this mixture may fluidize lipids in the stratum corneum and reduce the resistance of the stratum corneum.

In another study, diclofenac and indomethacin in a microemulsion gel were used as model drugs. The microemulsion gel consisted of soybean phosphatidylcholine (lecithin), IPP, and water. The investigators found a significant increase (3- to 6-fold) in flux through excised human skin for both drugs applied in the microemulsion vehicle compared to the neat oil phase (Dreher et al., 1997).

Three ternary solvent systems and a microemulsion containing 1% (wt/wt) diclofenac sodium were prepared by Escribano et al. (2003) and compared with commercially available semisolid preparation and 1% (wt/wt) diclofenac sodium transcutol/buffer (19:80) solution that served as reference formulations. Ternary solvent systems comprised of enhancers such as oleic acid, lauric acid, transcutol, and D-limonene. All formulations showed higher flux compared to the microemulsion. Drug penetration enhancement in ternary solvent systems may be due to alteration in the structure of stratum corneum caused by the combination of enhancers used. Synergic action was reflected in the values of permeation parameters with respect to the solution and the synergy obtained with transcutol/oleic acid or transcutol/lauric acid. It was found that oleic acid provided more permeation capacity to diclofenac than lauric acid, which can be due to the *cis* double bond at C9 which causes a kink in the alkyl chain and disrupts the skin lipids more efficiently. The highest value of permeability coefficient and flux at 24 h were observed for formulation containing 59.2% transcutol, 14.9% oleic acid, 5% D-limonene, and 19.9% water, which showed greater anti-inflammatory activity, both local and systemic than the semisolid preparation. Despite the expectation that dermally applied microemulsion would penetrate the stratum corneum, it behaved like the solution and its excipients hardly favored the penetration of diclofenac. This may be attributed to the lower percentage of the penetrating agents. Therefore, optimum concentration of the components of the vehicle is also important in addition to the structure of the vehicles.

Rhee et al. (2001) showed that transdermal delivery from the formulations was greatly influenced by the microemulsion components level. The transdermal flux of ketoprofen was dependent on the oil incorporated into a labrasol–cremophor–water microemulsion with 3% drug load. An inverse correlation was observed between surfactant content and transdermal flux.

Bolzinger, Carduner, and Poelman (1998) investigated the influence of a bicontinuous sugar ester-based microemulsion vehicle on the topical bioavailability of niflumic acid. Niflumic acid was incorporated at different concentrations (0.3, 0.6, and 1%) and its anti-inflammatory activity was compared in vivo with Nifluril ointment, a commercially available form. The methyl nicotinate model was used to induce inflammation. The vascular response to methyl nicotinate on the treated areas was monitored by a laser Doppler flowmetry technique. The investigators concluded that the 1% niflumic acid microemulsion was as efficient as the 3% niflumic acid ointment.

Delivery of Immunosuppressive Agents

Triptolide has been reported to be effective in the treatment of patients with a variety of inflammatory and autoimmune diseases, especially rheumatoid arthritis. Chen et al. (2004) investigated the microemulsion-based transdermal delivery of triptolide. High drug concentration cannot be used because of severe skin irritation. Microemulsion systems consisting of oleic acid, Tween 80, PG, and water were prepared and their transdermal ability and skin irritation were also evaluated. Permeation studies were performed from microemulsion formulations and aqueous solution containing 20% PG through mouse skin. A steady increase of triptolide in the receptor chambers during 24 h was observed from microemulsion formulations, whereas permeation flux from the aqueous solution decreased significantly after 10 h, which revealed the inability of the aqueous solution to provide prolonged delivery of triptolide. The permeation profiles of the microemulsions followed zero-order release kinetics. Menthol was found to be a suitable penetration enhancer. It was found that microemulsions containing lower amounts of Tween 80 and PG provided higher permeation flux, which may be attributed to the high thermodynamic activity of the drug in these microemulsions. A microemulsion system containing 0.025% triptolide, 6% oleic acid, 20% Tween 80, 10% PG, 62.975% water, and 1% menthol was found to be most suitable for triptolide delivery. Furthermore, the irritation studies did not show visible irritation after application of microemulsion for 7 days on the skin of rabbits. However, the aqueous solution containing 0.025% triptolide induced significant erythema and edema. This formulation appears to be better than the one previously suggested by

Mei et al. consisting of 40% IPM, 50% Tween 80/PG (5:1), and water, which was a w/o type of microemulsion. In the latter formulation, triptolide is solubilized in the outer oily phase and therefore might directly contact the surface of the skin which may lead to skin irritation on chronic use.

Delivery of Anesthetics

Kreilgaard et al. (2000) prepared seven microemulsion vehicles with varying concentration of labrasol, Plurol Isostearique, isostearylic isostearate, and water to compare transdermal flux of a lipophilic (lidocaine) and a hydrophilic (prilocaine hydrochloride) model drug through excised rat skin with a commercially available o/w emulsion (Xylocain® 5% cream, lidocaine; AstraZeneca, Denmark), a hydrogel (Xylocain® 2% gel, lidocaine hydrochloride; AstraZeneca), and an o/w emulsion based on an eutectic mixture of the drugs (EMLA® 5%, lidocaine and prilocaine; AstraZeneca). The transdermal flux of lidocaine and prilocaine hydrochloride varied substantially according to both the composition of the applied microemulsion vehicle and the incorporated drug concentration relative to the saturation limit of each vehicle. The optimized microemulsions were found to increase the permeation rate of lidocaine up to fourfold compared to the o/w emulsion and approximately 50% compared with EMLA. Similarly, the microemulsion vehicles were found to increase transdermal flux of the hydrophilic model drug up to 30 times compared to the hydrogel.

Changez, Varshney, Chander, and Dinda (2006b) found that the skin flux of tetracaine hydrochloride was dependent on the composition of lecithin–*n*-propanol–IPM–water microemulsions. At lower K_m (surfactant/cosurfactant) ratio (i.e., 0.5:1 and 0.8:1), the rate of permeation of tetracaine was higher when compared to the microemulsion of higher K_m ratio (1:1 and 1.5:1). Image analysis of transmission electron micrograph after 6 h of the application of the lecithin microemulsion showed 3.5-fold ($p < .001$) increase in the intercellular space in the epidermis and 3.8-fold ($p < .001$) enhancement of upper epidermis. Confocal laser scanning microscopy results showed that sweat gland and hair follicles also provided path for permeation through the skin.

Delivery of Antipsoriatic Drugs

Trotta and coworkers (1996) showed that the transdermal delivery of methotrexate, an antipsoriatic drug, could be increased up to 10-fold from a lecithin–water–PG–decanol–benzyl alcohol microemulsion compared to that from the water–PG solution alone, and threefold compared to an oil suspension. Also, mean lag time was considerably decreased with the microemulsion vehicle. Various counterions (monooctyl phosphate, monodecyl phosphate, monodecyl glycerophosphate, taurodeoxycholate, dodecyl sulfate, and dioctyl sulfosuccinate) added to the microemulsion increased the transdermal flux of methotrexate even further and a marked increase in the flux of drug was measured when dodecyl sulfate and dioctyl sulfosuccinate were used.

The use of microemulsions for iontophoretic drug delivery does not appear to provide any advantages compared to aqueous solutions. Alvarez-Figueroa and coworkers reported a decrease in transdermal iontophoretic delivery of methotrexate from a microemulsion vehicle (Alvarez-Figueroa & Blanco-Mendez, 2001) relative to that from an aqueous Hepes buffer even though the microemulsions were superior to the aqueous solution in regard to rate of passive diffusion of the drug. Presumably, microemulsions hamper iontophoretic delivery due to the decreased conductivity when incorporating oil and surfactants into the aqueous phase.

Liu, Li, Wang, Han, and Dong (2006) prepared various microemulsions of cyclosporin A comprising aerosol OT (AOT), Tween 85, IPM, and water. Results of conductance, viscosity, and surface tension measurement showed transition to a bicontinuous structure. The microemulsions increased transdermal delivery of cyclosporin A up to 10 times compared to the suspension. The authors concluded that increased transdermal delivery was mainly due to water concentration and dependent on the structure of the microemulsions.

Baroli, Lopez-Quintela, Delgado-Charro, Fadda, and Blanco-Mendez (2000) prepared six microemulsion formulations of 8-methoxsalen (8-MOP) using water, IPM, Tween 80, and Tween 80 : Span 80 : 1,2-octanediol (3:1:1.2, by wt). The in vitro permeation data showed that the microemulsions increased the 8-MOP total penetration through the skin by order of 1.9–4.5, as compared with IPM. The results suggested that the studied microemulsion systems might be appropriate vehicles for the topical delivery of 8-MOP.

Delivery of Antiasthmatics

Nine microemulsions with varying concentration of oleic acid, cremophor RH 40, labrasol, and water were prepared and the effect of the content of oil (5, 10, and 12%) and surfactant mixture on the skin permeation of theophylline was evaluated (Zhao, Liu, Zhang, & Li, 2006). It was observed that when the content of surfactant mixture decreased from 54 to 30%, the skin permeation rate of theophylline increased 1.28 times. The thermodynamic activity of microemulsion at the lower content of surfactant mixture was a significant driving force for the release and penetration of the drug into skin (Rhee et al., 2001). So the increased concentration of surfactant in the dispersed systems might decrease drug release and its permeation in the skin. Skin permeation rate increased as the content of oil increased. The permeation rate of theophylline was almost linearly improved as a function of loading dose, and the permeation of microemulsion accorded with the Fick's first diffusion law.

Delivery of Antiparkinsonian Drugs

Peira et al. (2001) studied the feasibility of transdermal delivery of apomorphine hydrochloride incorporated into microemulsions on hairless mouse skin. Epikuron 200 was used as surfactant and the mixture of IPM and decanol as oil

phase. Octanoic acid was added as ion-pairing agent, which increased the lipophilicity of apomorphine and hence increased partitioning was observed. The experiments were monitored for 24 h, a pseudo-zero-order kinetics was achieved for the microemulsions. The investigators concluded that even if the flux through intact human skin were different from that through hairless mouse skin, the concentration of apomorphine in the plasma might become sufficient to have a therapeutic effect on increasing the application area.

Delivery of Antihypertensives

Nicardipine hydrochloride is a calcium channel blocker indicated for the treatment of hypertension. Aboofazeli, Zia, and Needham (2002) prepared a microemulsion-based gel composed of soybean lecithin, PG, oleic acid, dimethyl isosorbide, and IPM after a preliminary study of vehicle effects on the percutaneous absorption of nicardipine. A binary mixture of PG and oleic acid and a ternary mixture of PG, oleic acid, and dimethyl isosorbide possessed the maximum flux and minimal lag times as compared with those obtained when pure solvents were applied. In vitro percutaneous penetration studies revealed that the microemulsion gel has skin-enhancing potential and could be a promising matrix for the transdermal delivery of nicardipine.

Delivery of Antifungal Agents

Miconazole nitrate (MCN) is a broad spectrum antifungal agent. Peira, Carlotti, Trotta, Cavalli, and Trotta (2008) formulated positively charged microemulsions of MCN comprising water, 1-decanol/dodecanol (2:1, wt/wt), lecithin and/or decyl polyglucoside at different weight ratios, PG, 1,2-hexanediol and a cationic charge-inducing agent stearylamine, and L-alanine benzyl ester (ALAB) or cetyltrimethylammonium bromide. Skin accumulation of the drug from positively charged microemulsions was found to be nearly twice than from their negatively charged counterparts. The authors ascribed increased accumulation to the interaction between positive microemulsion systems and negatively charged skin sites. The results suggested that positively charged microemulsions could be used to optimize drug targeting without a concomitant increase in systemic absorption.

El Laithy and El Shaboury (2002) evaluated the influence of the vehicle on the release and permeation of fluconazole dissolved in jojoba oil. Series of cutina lipogels (Cutina CPA [cetyl palmitate], CBS [mixture of glyceryl stearate, ctearyl alcohol, cetyl palmitate, and cocoglycerides], MD [glyceryl stearate], and GMS [glyceryl monostearate]) in different concentrations as well as gel microemulsion were prepared. The results of in vitro drug release in Sorensen citrate buffer (pH 5.5) and permeation studies showed highest values from the gel microemulsion. The antifungal activity of fluconazole showed the widest zone of inhibition with the gel microemulsion.

Delivery of Antiaging Agents

Vitamin C acts as an antioxidant by scavenging and destroying aggressive oxidizing agents and free radicals that are involved in the process of skin aging. But it is an extremely unstable compound, and derivatives such as hydrophilic sodium ascorbyl phosphate or lipophilic esters with fatty acids such as ascorbyl palmitate were synthesized to improve stability. Gallarate et al. (1999) studied the stability of ascorbic acid in several o/w microemulsions, o/w and w/o emulsions, and a w/o/w multiple emulsion. IPM and cetearyl octanoate were used as oils, dodecylglucoside and cocoamide propylbetaine were used as surfactants, and 2-ethyl-1,3-hexanediol was used as cosurfactant. Ascorbic acid stability against oxidation was examined in the prepared systems and compared to the aqueous solutions at different pH values. It was found that all examined emulsified systems provided protection against oxidation for ascorbic acid, and degradation rate was slower than in aqueous solutions, and it increased with increasing pH. The highest protection of the ascorbic acid was achieved by solubilizing it in a w/o/w multiple emulsion.

Spiclin et al. (2003) formulated w/o and o/w microemulsions containing sodium ascorbyl phosphate for topical application. Components of the microemulsions were Miglyol 812, labrasol, Plurol Oleique, and water. As thickeners of w/o microemulsions, magnesium stearate, colloidal silica, and cetostearyl alcohol were taken. On the basis of physical stability, colloidal silica was selected. For o/w microemulsions, xanthan gum was selected among the thickening agent, which also included ethylcellulose, sodium alginate, methylcellulose, HPMC K4M, and HPMC E4M. From both thickened and nonthickened w/o systems, less ascorbyl phosphate was released than from o/w systems. The external oil phase is apparently a barrier for the diffusion of a hydrophilic, freely soluble compound. Larger amount of release of sodium ascorbyl phosphate from o/w systems was the consequence of its disposition in the external phase and consequently higher diffusion rate. The addition of xanthan gum decreased the amount of released compound due to the increased viscosity of the system. The addition of colloidal silica led to the opposite effect. The authors assumed that colloidal silica modified the physicochemical characteristics of the external phase and hence the diffusion of highly hydrophilic ascorbyl phosphate from the internal to the external phase of the microemulsion. The release profiles were also evaluated by fitting the experimental data to different order kinetic equations, and it was concluded that the rate determining step for sodium ascorbyl phosphate release from microemulsions is transported within the carrier system.

Treatment of Acne Vulgaris

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, Boonsaner,

Leatwimonlak, and Boonme (2007) developed water–IPP–AOT–1-butanol microemulsions as alternative formulations for the topical delivery of clindamycin phosphate. Effect of AOT : 1-butanol ratios 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.

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) 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, Ahuja, and Khar (2005) 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. The accumulation of tea tree oil in the follicular casts was 0.43 ± 0.01, 0.41 ± 0.009, 0.21 ± 0.006, and 0.16 ± 0.005 percentage by weight (milligram oil/gram of sebum plug) for microemulsion, liposomal dispersion, multiple emulsion, and colloidal bed, respectively. Their work demonstrated that the microemulsion and liposomal formulations were more efficient for the delivery of tea tree oil through the follicular route.

Skin Tolerability Studies of 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.

Escribano and coworkers (2003) 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% D-limonene) 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.

The microemulsions studied by Lehmann, Keipert, and Gloor (2001) showed skin irritation. The water-continuous microemulsion (IPM/sucrose laurate–/PG/water, 4:18:30:48%, by wt) significantly increased transepidermal water loss (TEWL) and produced dehydration compared with an untreated control area when 50 μL was applied to a 3-cm-diameter area thrice daily over a 3-day period. Also, the oil-continuous microemulsion (IPM/Tagat/Plurololeat/water, 65:20:10:5%, by wt) significantly increased TEWL, but the skin hydration state was unchanged.

Paolino et al. (2002) 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.

Delgado-Charro and coworkers (1997) 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. 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.

For the skin irritancy test, a single dose of 10 μL of the optimized microemulsion (4% oleic acid, 20.5% labrasol, 20.5% transcutol, and 55% water) was applied to the left ear of the mouse with the right ear as a control (Hua et al., 2004). The development of erythema was monitored daily for 6 days. The authors concluded that the microemulsion can be considered to be safe for the transdermal delivery of vinpocetine.

Fang et al. (2004) assessed the skin irritation potential of microemulsion. A microemulsion (0.4 mL) containing flurbiprofen was spread on 2.5 × 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.

Microemulsion (0.025% triptolide, 6% oleic acid, 20% Tween 80, 10% PG, 62.975% water, and 1% menthol) and aqueous solution containing 0.025% triptolide were selected as the test formulations for skin irritation studies (Chen et al., 2004) and were applied to shaved skin on the back of New Zealand rabbits. On one side of the back, a control microemulsion and aqueous solution without any drug and on another side microemulsion and aqueous solution containing 0.025% triptolide were applied for each day. The animals were observed and evaluated for any sign of erythema or edema for a period of 7 days. No erythema or edema was observed on the skin of rabbit for microemulsion. Only rubefaction appeared on the skin of some rabbits occasionally on the third or fourth day and disappeared on the sixth or seventh day. However, the aqueous solution containing 0.025% triptolide induced significant erythema and edema.

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% isostearylic isostearate, 35% labrasol, 35% Plurol Isostearique, and 20% water) containing large amount of surfactant (Kreilgaard et al., 2000). 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.

CONCLUSION

The skin evolved to be a protective barrier. It performs this function remarkably well and presents, therefore, a formidable challenge to the drug delivery scientist. The development of sophisticated biophysical techniques to monitor skin permeability has helped in better understanding the mechanisms of absorption and enhancement. Transdermal route of administration is perhaps one of the most successful controlled release technologies available today.

Microemulsions are currently the object of extensive research worldwide. They represent an interesting, promising, and potential TDDS. They can be formed with different aqueous, surfactant, and oil components and can exist over wide composition ranges depending on the properties of the employed components. Their main advantages as TDD vehicle include excellent solubility properties for both lipophilic and hydrophilic drugs, thermodynamic stability, ease of formation, easy scale up, and overall low cost of the formulation preparation, which makes them very promising vehicles for future topical formulations. By careful modulation of drug release, they can also be used for the treatment of dermatological disorders such as acne and photoaging of skin.

Many in vitro and in vivo studies have examined the relevance of microemulsions as TDDS. Nevertheless, more in vivo studies should be conducted to support the in vitro findings. Most of the permeation studies were conducted on animal models that showed higher permeability than that obtained with the same formulations in humans. In many cases, the irritation issue is not considered. Therefore, in addition to the immediate influence of the formulations both in vitro and in vivo, chronic studies need to be performed so as to assess their effect on the skin including skin irritation and histopathological changes. Conventionally, the transdermal preparations are presented in a patch form, which leads to problems of skin

irritation and darkening of skin surface. Microemulsion when applied in the form of gel or liquid shall obviate this issue and will be more acceptable. Concerted research efforts directed toward evaluating their systemic and local toxicity, as well as their mechanism of action, shall further help in ascertaining their efficacy and safety.

It is important to judiciously select the surfactants and their concentration as a large amount of surfactant is required for microemulsion formation. More research work is required for the production of safe, efficient, and more compatible microemulsion constituents which will further enhance the utility of these novel vehicles. A considerable amount of work still needs to be performed to characterize the physicochemical behavior of the microemulsions. It appears that future work will concentrate on the development of new and sophisticated analytical tools for the microemulsion structure. More systematic studies are needed for the evaluation of their full potential as they can be formed over a wide range of composition. It seems that proper selection of the microemulsion components for the formulation is a key factor in the enhancement of TDD. The studies that have been conducted so far demonstrate that the microemulsion system has tremendous potential as a novel TDD tool. Based on this review, it could be assumed that as a result of these developments, new products based on these novel formulations will emerge in the near future.

ACKNOWLEDGMENTS

A. Azeem is highly grateful to the University Grants Commission, Government of India, for providing financial assistance in the form of research fellowship.

REFERENCES

Aboofazeli, R., Lawrence, C. B., Wicks, S. R., & Lawrence, M. J. (1994). Investigations into the formation and characterization of phospholipid microemulsions III. Pseudo-ternary phase diagrams of systems containing water-lecithin-isopropyl myristate and either an alkanoic acid, amine, alkanediol, poly ethylene glycol alkyl ether or alcohol as co-surfactant. *Int. J. Pharm*., *111*, 63–72.

Aboofazeli, R., Zia, H., & Needham, T. E. (2002). Transdermal delivery of nicardipine: An approach to in vitro permeation enhancement. *Drug Deliv*., *9*, 239–247.

Akoh, C. C. (1992). Emulsification properties of polyesters and sucrose ester blends: Carbohydrates and fatty acid polyesters. *J. Am. Oil Chem. Soc*., *69*, 9–19.

Alvarez-Figueroa, M. J., & Blanco-Mendez, J. (2001). Transdermal delivery of methotrexate: Iontophoretic delivery from hydrogels and passive delivery from microemulsions. *Int. J. Pharm*., *215*, 57–65.

Ambade, K. W., Jadhav, S. L., Gambhire, M. N., Kurmi, S. D., Kadam, V. J., & Jadhav, K. R. (2008). Formulation and evaluation of flurbiprofen microemulsion. *Curr. Drug Deliv*., *5*, 32–41.

Andersson, M., & Lofroth, J.-E. (2003). Small particles of a heparin/chitosan complex prepared from a pharmaceutically acceptable microemulsion. *Int. J. Pharm*., *257*, 305–309.

Araaya, H., Tomitab, M., & Hayashib, M. (2005). The novel formulation design of o/w microemulsion for improving the gastrointestinal absorption of poorly water soluble compounds. *Int. J. Pharm*., *305*, 61–74.

Asua, J. M. (2002). Miniemulsion polymerization. *Prog. Polym. Sci*., *27*, 1283–1346.

Attwood, D. (1994). Microemulsions. In J. Kreuter (Ed.), *Colloidal drug delivery systems* (pp. 31–71). New York: Marcel Dekker.

Attwood, D., & Ktistis, G. (1989). A light scattering study on oil-in-water microemulsions. *Int. J. Pharm*., *52*, 165–171.

Attwood, D., Mallon, C., Ktistis, G., & Taylor, C. J. (1992). A study on factors influencing the droplet size in nonionic oil-in-water microemulsions. *Int. J. Pharm*., *88*, 417–422.

Aungst, B. J. (1989). Structure/effect studies of fatty acid isomers as skin penetration enhancers and skin irritants. *Pharm. Res*., *6*, 244–247.

Aungst, B. J., Rogers, N. J., & Shefter, E. (1986). Enhancement of naloxone permeation through human skin in vitro using fatty acids, fatty alcohols, surfactants, sulfoxides and amides. *Int. J. Pharm*., *33*, 225–234.

Baran, R. J., & Wade, W. H. (1995). Temperature insensitive microemulsion phase behavior with non-ionic surfactants. *J. Dispers. Sci. Technol*., *16*, 165.

Baroli, B., Lopez-Quintela, M. A., Delgado-Charro, M. B., Fadda, A. M., & Blanco-Mendez, J. (2000). Microemulsions for topical delivery of 8-methoxsalen. *J. Control. Release*, *69*, 209–218.

Barry, B. W. (1987). Mode of action of penetration enhancers in human skin. *J. Control. Release*, *6*, 85–97.

Barry, B. W. (2001). Is transdermal drug delivery still important today? *Drug Discov. Today*, *6*, 967–971.

Benson, H. A. E. (2005). Transdermal drug delivery: Penetration enhancement techniques. *Curr. Drug Deliv*., *2*, 23–33.

Bhargava, H. N., Narurkar, A., & Lieb, L. M. (1987). Using microemulsions for drug delivery. *Pharm. Tech*., *11*, 46–52.

Biju, S. S., Ahuja, A., & Khar, R. K. (2005). Tea tree oil in follicular cats after topical delivery: Determination by high performance thin layer chromatography using a perfused bovine udder model. *J. Pharm. Sci*., *94*, 240–245.

Biruss, B., Kahlig, H., & Valenta, C. (2007). Evaluation of an eucalyptus oil containing topical drug delivery system for selected steroid hormones. *Int. J. Pharm*., *328*, 142–151.

Bodnar, I., Floter, E., Hogervorst, W., & Van Oosten, C. W. (2004). *Microemulsions*. US Patent No. 6716473.

Boltri, L., Morel, S., Trotta, M., & Gasco, M. R. (1994). In vitro transdermal permeation of nifedipine from thickened microemulsions. *J. Pharm. Belg*., *49*, 315–320.

Bolzinger, M. A., Carduner, T. C., & Poelman, M. C. (1998). Bicontinuous sucrose ester microemulsion: A new vehicle for topical delivery of niflumic acid. *Int. J. Pharm*., *176*, 39–45.

Bonina, F. P., Carelli, V., Di Colo, G., Montenegro, L., & Nannipieri, E. (1993). Vehicle effects on in vitro skin permeation of and stratum corneum affinity for model drugs caffeine and testosterone. *Int. J. Pharm*., *100*, 41–48.

Bonina, F. P., Montenegro, L., Scrofani, N., Esposito, E., Cortesi, R., Menegatti, E., & Nastruzzi, C. (1995). Effects of phospholipid based formulations on in vitro and in vivo percutaneous absorption of methyl nicotinate. *J. Control. Release*, *34*, 53–63.

Burnett, G. R., Rees, G. D., Steytler, D. C., & Robinson, B. H. (2004). Fluorescence correlation spectroscopy of water-in-oil microemulsions: An application in specific characterization of droplets containing biomolecules. *Colloids Surf. A Physicochem. Eng. Asp*., *250*, 171–178.

Carlfors, J., Blute, I., & Schmidt, V. (1991). Lidocaine in microemulsion—a dermal delivery system. *J. Dispers. Sci. Technol*., *12*, 467–482.

Ceschel, G. C., Bergamante, V., Maffei, P., Borgia, S. L., Calabrese, V., & Biserni, S. (2005). Solubility and transdermal permeation properties of dehydoepiandrosterone cyclodextrin complex from hydrophilic and lipophilic vehicles. *Drug Deliv*., *12*, 275–280.

Cevc, G. (2004). Lipid vesicles and other colloids as drug carriers on the skin. *Adv. Drug Deliv. Rev*., *56*, 675–711.

Cevc, G., & Blume, G. (2001). New highly efficient formulation of diclofenac for the topical, transdermal administration in ultradeformable drug carriers, Transfersomes. *Biochim. Biophys. Acta*, *1514*, 191–205.

Changez, M., Chander, J., & Dinda, A. K. (2006a). Transdermal permeation of tetracaine hydrochloride by lecithin microemulsion: In vivo. *Colloids Surf. B Biointerfaces*, *48*, 58–66.

Changez, M., Varshney, M., Chander, J., & Dinda, A. K. (2006b). Effect of the composition of lecithin/n-propanol/isopropylmyristate/water microemulsions on barrier properties of mice skin for transdermal permeation of tetracaine hydrochloride: In vitro. *Colloids Surf. B Biointerfaces*, *50*, 18–25.

Chen, H., Chang, X., Weng, T., Zhao, X., Gao, Z., Yang, Y., Xu, H., & Yang, X. (2004). A study of microemulsion systems for transdermal delivery of triptolide. *J. Control. Release, 98*, 427–436.

Choi, M. J., & Maibach, H. I. (2005). Elastic vesicles as topical/transdermal drug delivery systems. *Int. J. Cosmet. Sci., 27*, 211–221.

Chung, S. L., Tan, C.-T., Tunhill, I. M., & Scharpf, L. G. (1994). *Transparent oil-in-water microemulsion flavor or fragrance concentrate, process for preparing same, mouthwash or perfume composition containing said transparent microemulsion concentrate, and process for preparing same*. US Patent No. 5283056.

Constantinides, P. P., & Yiv, S. H. (1995). Particle size determination of phase-inverted water-in-oil microemulsions under different dilution and storage conditions. *Int. J. Pharm., 115*, 225–234.

Cooper, E. R. (1984). Increased skin permeability for lipophilic molecules. *J. Pharm. Sci., 73*, 1153–1156.

Crook, D. (1997). The metabolic consequences of treating post menopausal women with non-oral hormone replacement therapy. *Br. J. Obstet. Gynaecol., 104*(Suppl. 16), 4–13.

Dalmora, M. E., Dalmora, S. L., & Oliveira, A. G. (2001). Inclusion complex of piroxicam with β-cyclodextrin and incorporation in cationic microemulsion. In vitro drug release and in vivo topical anti-inflammatory effect. *Int. J. Pharm., 222*, 45–55.

Danielsson, I., & Lindman, B. (1981). The definition of microemulsion. *Colloids Surf., 3*, 391–392.

Danino, D., Gupta, R., Satyavolu, J., & Talmon, Y. (2002). Direct Cryogenic-temperature transmission electron microscopy imaging of phospholipids aggregates in soybean oil. *J. Colloid Interface Sci., 249*, 180–186.

Danino, D., Talmon, Y., & Zana, R. (2002). Cryo-TEM of thread like micelles: On the grid microstructural transformations induced during specimen preparation. *Colloids Surf. A Physicochem. Eng. Asp., 169*, 67–73.

Davis, A. F., & Hadgraft, J. (1991). Effect of supersaturation on membrane transport of hydrocortisone acetate. *Int. J. Pharm., 76*, 1–8.

Dayan, N., & Touitou, E. (2000). Carriers for skin delivery of trihexyphenidyl HCl: Ethosomes vs. liposomes. *Biomaterials, 21*, 1879–1885.

D'Cruz, O. J., & Uckun, F. M. (2001). Gel-microemulsions as vaginal spermicides and intravaginal drug delivery vehicles. *Contraception, 64*, 113–123.

D'Cruz, O. J., Yiv, S. H., & Uckun, F. M. (2001). GM-144, a novel lipophilic vaginal contraceptive gel-microemulsion. *AAPS PharmSciTech, 2*, E5.

Delgado-Charro, M. B., Iglesias-Vilas, G., Blanco-Mendez, J., Lopez-Quintela, M. A., & Guy, R. H. (1997). Delivery of a hydrophilic solute through the skin from novel microemulsion systems. *Eur. J. Pharm. Biopharm., 43*, 37–42.

Denet, A.-R., Vanbever, R., & Preat, V. (2004). Skin electroporation for topical and transdermal delivery. *Adv. Drug Deliv. Rev., 56*, 659–674.

Derle, D. V., Sagar, B. S. H., Kotwal, R. S., Ingole, R. D., & Chauhan, S. S. (2006a). A comparative in vitro evaluation of transdermal permeation of valdecoxib and its complex with HP-β-cyclodextrin from microemulsion based gel. *Indian Drugs, 43*, 625–629.

Derle, D. V., Sagar, B. S. H., & Pimpale, R. (2006b, September–October). Microemulsion as a vehicle for transdermal permeation of nimesulide. *Indian J. Pharm. Sci., 68*, 622–625.

Djordjevic, L., Primorac, M., Stupar, M., & Krajisnik, D. (2004). Characterization of caprylocaproyl macrogolglycerides based microemulsion drug delivery vehicles for an amphiphilic drug. *Int. J. Pharm., 271*, 11–19.

Dreher, F., Walde, P., Walther, P., & Wehrli, E. (1997). Interaction of a lecithin microemulsion gel with human stratum corneum and its effect on transdermal transport. *J. Control. Release, 45*, 131–140.

Dungan, S. R. (1997). Microemulsions in foods: Properties and applications. In C. Solans & H. Kuneida (Eds.), *Industrial applications of microemulsions.* (p. 148). New York: Marcel Dekker.

Eccleston, J. (1994a). Microemulsions. In J. Kreuter (Ed.), *Colloidal drug delivery systems* (pp. 31–71). New York: Marcel Dekker.

Eccleston, J. (1994b). Microemulsions. In J. Swarbrick & J. C. Boylan (Eds.), *Encyclopedia of pharmaceutical technology* (pp. 375–421). New York: Marcel Dekker.

El Laithy, H. M., & El Shaboury, K. M. F. (2002). The development of cutina lipogels and gel microemulsion for topical administration of fluconazole. *AAPS PharmSciTech, 3*, 1–9.

Elena, P., Paola, S., & Maria, R. G. (2001). Transdermal permeation of apomorphine through hairless mouse skin from microemulsions. *Int. J. Pharm., 226*, 47–51.

ElMaghraby, G. M. (2008). Transdermal delivery of hydrocortisone from eucalyptus oil microemulsion: Effects of cosurfactants. *Int. J. Pharm., 355*, 285–292.

Elsayed, M. M. A., Abdallah, O. Y., Naggar, V. F., & Khalafallah, N. M. (2006). Deformable liposomes and ethosomes: Mechanism of enhanced skin delivery. *Int. J. Pharm., 322*, 60–66.

Engstrom, S., & Larsson, K. (1999). Microemulsions in foods. In P. Kumar & K. L. Mittal (Eds.), *Handbook of microemulsion science and technology* (p. 789). New York: Marcel Dekker.

Escribano, E., Calpena, A. C., Queralt, J., Obach, R., & Domenech, J. (2003). Assessment of diclofenac permeation with different formulations: Anti-inflammatory study of a selected formula. *Eur. J. Pharm. Sci., 19*, 203–210.

Fang, J.-Y., Hwang, T.-L., Hwang, Y.-L., & Fang, C.-L. (2006). Enhancement of the transdermal delivery of catechins by liposomes incorporating anionic surfactants and ethanol. *Int. J. Pharm., 310*, 131–138.

Fang, J.-Y., Leu, Y.-L., Chang, C.-C. (2004). Lipid nano/submicron emulsions as vehicles for topical flurbiprofen delivery. *Drug Del., 11*, 97–105.

Fang, J.-Y., Yu, S. Y., Wu, P. C., Huang, Y. B., & Tsai, Y. H. (2001). In vitro skin permeation of estradiol from various proniosome formulations. *Int. J. Pharm., 215*, 91–99.

Fanun, M., Wachtel, E., Antalek, B., Aserin, A., Hoffman, R. E., & Garti, N. (2001). A study of the microstructure of four-component sucrose ester microemulsions by SAXS and NMR. *Colloids Surf. A Physicochem. Eng. Asp., 180*, 173–186.

Fialho, S. L., & da Silva-Cunha, A. (2004). New vehicle based on a microemulsion for topical ocular administration of dexamethasone. *Clin. Exp. Ophthalmol., 32*, 626–632.

Fiume, M. Z. (2001). Final report on the safety assessment of lecithin and hydrogenated lecithin. *Int. J. Toxicol., 20*, 21–45.

Flynn, G. L. (1990). Physicochemical determinant of skin absorption. In T. R. Gerrity & C. J. Henry (Eds.), *Principles of route-to-route extrapolation for risk assessment* (pp. 93–127). New York: Elsevier.

Friend, D., Catz, P., Heller, J., Reid, J., & Baker, R. (1988). Transdermal delivery of levonorgestrel. *J. Control. Release, 7*, 243–250.

Gallarate, M., Carlotti, M. E., Trotta, M., & Bovo, S. (1999). On the stability of ascorbic acid in emulsified systems for topical and cosmetic use. *Int. J. Pharm., 188*, 233–241.

Garcia-Celma, M. J., Azemar, N., Pes, M. A., & Solans, C. (1994). Solubilization of antifungal drugs in water/POE(20) sorbitan monooleate/oil systems. *Int. J. Pharm., 105*, 77–81.

Gasco, M. R. (1997). Microemulsions in the pharmaceutical field: Perspectives and applications. In C. Solans & H. Kuneida (Eds.), *Industrial applications of microemulsions* (pp. 98–120). New York: Marcel Dekker.

Gattefosse Corporation. (1982). *Company information material*. New York: Elmsford.

Getei, M., Wohlrab, J., & Neubert, R. H. H. (2005). Dermal delivery of desmopressin acetate using colloidal carrier systems. *J. Pharm. Pharmacol., 57*, 423–427.

Ghosh, P. K., & Murthy, R. S. R. (2006). Microemulsions: A potential drug delivery system. *Curr. Drug Deliv., 3*, 167–180.

Gilje, E., Sonerson, L., Hollberg, P. E., Holmberg, K., & Svennberg, S. (1992). *Norwegian Patent Nos. 170411 and 17097*.

Gillberg, G. (1984). In K. J. Lissant (Ed.), *Emulsions and emulsion technology* (pp. 1–43). New York: Marcel Dekker.

Glatter, O., Orthaber, D., Stradner, A., Scherf, G., Fanun, M., Garti, N., Clement, V., & Leser, M. E. (2001). Sugar-ester nonionic microemulsion: Structural characterization. *J. Colloid Interface Sci., 241*, 215–225.

Godwin, D. A., Kim, N.-H., & Feltan, L. A. (2002). Influence of transcutol® CG on the skin accumulation and transdermal permeation of ultraviolet absorbers. *Eur. J. Pharm. Biopharm., 53*, 23–27.

Goodman, M., & Barry, B. W. (1989). Lipid-protein-partitioning theory of skin enhancer activity: Finite dose technique. *Int. J. Pharm., 57*, 29–40.

Graf, A., Ablinger, E., Peters, S., Zimmerb, A., Hooka, S., & Rades, T. (2008). Microemulsions containing lecithin and sugar-based surfactants: Nanoparticle templates for delivery of proteins and peptides. *Int. J. Pharm., 350*, 351–360.

Guo, H., Liu, Z., Li, J., Nie, S., & Pan, W. (2006). Effect of isopropyl palmitate on the skin permeation of drugs. *Biol. Pharm. Bull., 29*, 2324–2326.

Gupta, R. R., Jain, S. K., & Varshney, M. (2005). AOT water-in-oil microemulsions as a penetration enhancer in transdermal drug delivery of 5-fluorouracil. *Colloids Surf. B Biointerfaces, 41*, 25–32.

Guy, R. H. (1996). Current status and future prospects of transdermal drug delivery. *Pharm Res., 13*, 1765–1769.

Guy, R. H. (1998). Iontophoresis-recent developments. *J. Pharm. Pharmacol., 50*, 371–374.

Habe, A., & Keipert, S. (1997). Development and characterization of microemulsions for ocular application. *Eur. J. Pharm. Biopharm., 43*, 179–183.

Heard, C. M., Kung, D., & Thomas, C. P. (2006). Skin penetration enhancement of mefenamic acid by ethanol and 1,8-cineole can be explained by the 'pull effect'. *Int. J. Pharm., 321*, 167–170.

Hellweg, T. (2002). Phase structure of microemulsions. *Curr. Opin. Colloid Interface Sci., 7*, 50–56.

Henry, S., Mc Allister, D. V., Allen, M. G., & Prausnitz, M. R. (1998). Microfabricated needles: A novel approach to transdermal drug delivery. *J. Pharm. Sci., 87*, 922–925.

Herold, A. E., Beardmore, R. A., & Parrish, S. K. (2004). *Herbicide microemulsion-forming-concentrates, microemulsions, and methods*, US Patent No. 6803345.

Hill, K., & Rhode, O. (1999). Sugar-based surfactants for consumer products and technical applications. *Fett-Lipid, 101*, 25–33.

Ho, H., Chen, L. C., Chiang, H. S., Spur, B. P., Wong, P. Y. K., & Sheu, M. T. (1998, June 21–26). *Proceedings of the 25th International Symposium on Controlled Release of Bioactive Materials*, Las Vegas, p. 579.

Hua, L., Weisan, P., Jiayu, L., & Ying, Z. (2004). Preparation, evaluation and NMR characterization of vinpocetine microemulsion for transdermal delivery. *Drug Dev. Ind. Pharm., 30*, 657–666.

Huang, Y. B., Lin, Y. H., Lu, T. M., Wang, R. J., Tsai, Y. H., & Wu, P. C. (2008). Transdermal delivery of capsaicin derivative-sodium nonivamide acetate using microemulsions as vehicles. *Int. J. Pharm., 349*, 206–211.

Jian, X., Ganzuo, L., Zhiqiang, Z., Guowei, Z., & Kejian, J. (2001). A study of the microstructure of CTAB/1-butanol/octane/water system by PGSE-NMR, conductivity and cryo-TEM. *Colloids Surf. A Physicochem. Eng. Asp., 191*, 269–278.

Jumma, M., & Muller, B. W. (1998). The effect of oil components and homogenization conditions on the physicochemical properties and stability of parenteral fat emulsions. *Int. J. Pharm., 163*, 81–89.

Junyaprasert, V. B., Boonsaner, P., Leatwimonlak, S., & Boonme, P. (2007). Enhancement of the skin permeation of clindamycin phosphate by AerosolOT/1-butanol microemulsions. *Drug Dev. Ind. Pharm., 33*, 874–880.

Kaalia, Y. N., Naik, A., Garrison, J., & Guy, R. H. (2004). Iontophoretic drug delivery. *Adv. Drug Deliv. Rev., 56*, 619–658.

Kamal, M. A. H. M., Iimura, N., Nabekura, T., & Kitagawa, S. (2007). Enhanced skin permeation of diclofenac by ion-pair formation and further enhancement by microemulsion. *Chem. Pharm. Bull., 55*, 368–371.

Kang, B. K., Chon, S. K., Kim, S. H., Jeong, S. Y., Kim, M. S., Cho, S. H., Lee, H. B., & Gilson, K. (2004). Controlled release of paclitaxel from microemulsion containing PLGA and evaluation of anti-tumor activity in vitro and in vivo. *Int. J. Pharm., 286*, 147–156.

Kantarci, G., Ozguney, I., Karasulu, H. Y., Guneri, T., & Basdemir, G. (2005). In vitro permeation of diclofenac sodium from novel microemulsion formulations through rabbit skin. *DDR, 65*, 17–25.

Kantaria, S., Rees, G. D., & Lawrence, M. J. (1999). Gelatin stabilized microemulsion-based organogels: Rheology and application in iontophoretic transdermal drug delivery. *J. Control. Release, 60*, 355–365.

Kawakami, K., Yoshikawa, T., Moroto, Y., Kanaoka, E., Takahashi, K., Nishihara, Y., & Kazuyoshi, M. (2002). Microemulsion formulation for enhanced absorption of poorly soluble drugs: I. Prescription design. *J. Control. Release, 81*, 65–74.

Kemken, J., Ziegler, A., & Muller, B. W. (1991a). Investigations into the pharmacodynamic effects of dermally administered microemulsions containing β-blockers. *J. Pharm. Pharmacol., 43*, 679–684.

Kemken, J., Ziegler, A., & Muller, B. W. (1991b). Pharmacodynamic effects of transdermal bupranolol and timolol in vivo: Comparison of microemulsions and matrix patches as vehicle. *Methods Find. Exp. Clin. Pharmacol., 13*, 361–365.

Kima, S. K., Leea, A. H., Leea, V. S., Leea, Y.-K., Kimb, C.-Y., Moonc, H. T., & Byuma, Y. (2005). A lecithin-based microemulsion of rh-insulin with aprotinin for oral administration: Investigation of hypoglycemic effects in non-diabetic and STZ-induced diabetic rats. *Int. J. Pharm., 298*, 176–185.

Kirjavainen, M., Monkkonen, J., Saukkosaari, M., Valjakka-Koskela, R., Kiesvaara, J., & Urtti, A. (1999). Phospholipids affect stratum corneum lipid bilayer fluidity and drug partitioning into the bilayers. *J. Control. Release, 58*, 207–214.

Koa, C. J., Kob, Y. J., Kim, D. M., & Park, H. J. (2003). Solution properties and PGSE-NMR self-diffusion study of $C_{18:1}$ E_{10}/oil/water system. *Colloids Surf. A Physicochem. Eng. Asp., 216*, 55–63.

Kogan, A., & Garti, N. (2006). Microemulsions as transdermal drug delivery vehicles. *Adv. Colloid Interface Sci., 123–126*, 369–385.

Kreilgaard, M. (2001). Dermal pharmacokinetics of microemulsion formulations determined by in vivo microdialysis. *Pharm Res., 18*, 367–373.

Kreilgaard, M. (2002). Influence of microemulsion on cutaneous drug delivery. *Adv. Drug Deliv. Rev., 54*, S77–S98.

Kreilgaard, M., Kemme, M. J., Burggraaf, J., Schoemaker, R. C., & Cohen, A. F. (2001). Influence of a microemulsion vehicle on cutaneous bioequivalence of a lipophilic model drug assessed by microdialysis and pharmacodynamics. *Pharm Res., 18*, 593–599.

Kreilgaard, M., Pedersen, E. J., & Jaroszewski, J. W. (2000). NMR characterization and transdermal drug delivery potential microemulsion systems. *J. Control. Release, 69*, 421–433.

Kriwet, K., & Muller-Goymann, C. C. (1995). Diclofenac release from phospholipids drug systems and permeation through excised human stratum corneum. *Int. J. Pharm., 125*, 231–242.

Ktistis, G. (1990). A viscosity study on oil-in-water microemulsions. *Int. J. Pharm., 61*, 213–218.

Ktistis, G., & Niopas, I. (1998). A study on the in-vitro percutaneous absorption of propranolol from disperse systems. *J. Pharm. Pharmacol., 50*, 413–418.

Kumar, P., & Mittal, K. L. (1999). *Handbook of microemulsion science and technology*. New York: Marcel Dekker.

Kumhar, S. K., Jain, S. K., Pancholi, S. S., Agrawal, S., Saraf, D. K., & Agrawal, G. P. (2003). Vesicular transdermal drug delivery system of ethinylestradiol and levonorgestrel for contraception and hormone replacement therapy. *Indian J. Pharm. Sci., 65*, 620–627.

Lam, A. C., & Schechter, R. S. (1987). The theory of diffusion in microemulsions. *J. Colloid Interface Sci., 120*, 56–63.

Lawrence, M. J. (1994). Surfactant systems: Microemulsions and vesicles as vehicles for drug delivery. *Eur. J. Drug Metab. Pharmacokinet., 3*, 257–269.

Lawrence, M. J. (1996). Microemulsions as drug delivery vehicles. *Curr. Opin. Colloid Interface Sci., 1*, 826–832.

Lawrence, M. J., & Rees, G. D. (2000). Microemulsion based media as novel drug delivery systems. *Adv. Drug Deliv. Rev., 47*, 89–121.

Lee, J., Lee, Y., Kim, J., Yoon, M., & Choi, Y. W. (2005). Formulation of microemulsion systems for transdermal delivery of aceclofenac. *Arch. Pharm. Res., 28*, 1097–1102.

Lehmann, L., Keipert, S., & Gloor, M. (2001). Effects of microemulsions on the stratum corneum and hydrocortisome penetration. *Eur. J. Pharm. Biopharm., 52*, 129–136.

Lianly, I. L., Nandi, I., & Kim, K. H. (2002). Development of an ethyl laurate based microemulsion for rapid onset of intranasal delivery of diazepam. *Int. J. Pharm., 237*, 77–85.

Linn, E. E., & York, T. O. (1989). *Skin moisturizing microemulsions*, US Patent No. 4797273.

Liu, J., Hu, W., Chen, H., Ni, Q., Xu, H., & Yang, X. (2007). Isotretinoin loaded solid lipid nanoparticles with skin targeting for topical delivery. *Int. J. Pharm., 328*, 191–195.

Liu, H., Li, S., Wang, Y., Han, F., & Dong, Y. (2006). Bicontinuous water-AOT/Tween 85-isopropyl myristate microemulsion: A new vehicle for transdermal delivery of cyclosporine A. *Drug Dev. Ind. Pharm., 32*, 549–557.

Lopez, F., Cinelli, G., Ambrosone, L., Colafemmina, G., Ceglie, A., & Palazzo, G. (2004). Role of the cosurfactant in water-in-oil microemulsion:

Interfacial properties tune the enzymatic activity of lipase. *Colloids Surf. A Physicochem. Eng. Asp., 237*, 49–59.

Lv, F.-F., Li, N., Zheng, L.-Q., & Tung, S.-H. (2006). Studies on the stability of the chloramphenicol in the microemulsion free of alcohols. *Eur. J. Pharm. Biopharm., 62*, 288–294.

Madhusudhan, B., Rambhau, D., Apte, S. S., & Gopinath, D. (2006). Improved in vitropermeation of nabumetone across rat skin from 1-O-alkylglycerol/lecithin stabilized o/w nanoemulsions. *J. Dispers. Sci. Technol., 27*, 921–926.

Maestrelli, F., Gonzalez-Rodriguez, M. L., Rabasco, A. M., & Mura, P. (2006). Effect of preparation technique on the properties of liposomes encapsulating ketoprofen–cyclodextrin complexes aimed for transdermal delivery. *Int. J. Pharm., 312*, 53–60.

Magdassi, S., Ben Moshe, M., Talmon, Y., & Danino, D. (2003). Microemulsion based on anionic Gemini surfactant. *Colloids Surf. A Physicochem. Eng. Asp., 212*, 1–7.

Malcolmson, C., & Lawrence, M. J. (1990). A comparison between nonionic micelles and microemulsions as a means of incorporating the poorly water soluble drug diazepam. *J. Pharm. Pharmacol., 42* (Suppl.), 6.

Malcolmson, C., & Lawrence, M. J. (1993). Comparison of the incorporation of model steroids into non-ionic micellar and microemulsion systems. *J. Pharm. Pharmacol., 45*, 141–143.

Malcolmson, C., Satra, C., Kantaria, S., Sidhu, A., & Lawrence, M. J. (1998). Effect of oil on the level of solubilization of testosterone propionate into non-ionic oil-in-water microemulsions. *J. Pharm. Sci., 87*, 109–116.

Manosroi, A., Kongkaneramit, L., & Manosroi, J. (2004). Stability and transdermal absorption of topical amphotericin B liposome formulations. *Int. J. Pharm., 70*, 279–286.

Marszall, L. (1987). HLB of nonionic surfactants: PIT and EIP methods. In M. J. Schick (Ed.), *Nonionic surfactant: Physical chemistry* (pp. 493–547). New York: Marcel Dekker.

Megrab, N. A., Williams, A. C., & Barry, B. W. (1995). Oestradiol permeation across human skin, silastic and snake skin membranes: The effects of ethanol/water cosolvent systems. *Int. J. Pharm., 116*, 101–112.

Mei, Z., Chen, H., Weng, T., Yang, Y., & Yang, X. (2003). Solid lipid nanoparticle and microemulsion for topical delivery of triptolide. *Eur. J. Pharm. Biopharm., 56*, 189–196.

Mitragotri, S., Edwards, D. A., Blankschtein, D., & Langer, R. (1995). A mechanistic study of ultrasonically enhanced transdermal drug delivery. *J. Pharm. Sci., 84*, 697–706.

Mohammed, C., & Manoj, V. (2000). Aeosol-OT microemulsions as transdermal carriers of tetracaine hydrochloride. *Drug Dev. Ind. Pharm., 26*, 507–512.

Morimoto, Y., Sugibayashi, K., Kobayashi, D., Shoji, H., Yamazaki, J.-I., & Kimura, M. (1993). A new enhancer-coenhancer system to increase skin permeation of morphine hydrochloride in vitro. *Int. J. Pharm., 91*, 9–14.

Moulik, S. P., & Paul, B. K. (1998). Structure, dynamics and transport properties of microemulsions. *Adv. Colloid Interface Sci., 78*, 99–195.

Mrestani, Y., El-Mokdad, N., Ruttinger, H. H., & Neubert, R. H. H. (1998a). Characterization of partitioning behaviour of cephalosporins using microemulsion and micellar electrokinetic chromatography. *Electrophoresis, 19*, 2895–2899.

Mrestani, Y., Neubert, R. H. H., & Krause, A. (1998b). Partition behaviour of drugs in microemulsions measured by electrokinetic chromatography. *Pharm. Res., 15*, 799–801.

Mueller, B. W., & Mueller, R. H. (1984). Particle size distributions and particle size alterations in microemulsions. *J. Pharm. Sci., 73*, 919–922.

Muller, R. H., Radtke, M., & Wissing, S. A. (2002). Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. *Adv. Drug Deliv. Rev., 54*, S131–S155.

Myers, D. (1999). *Surfaces, interfaces and colloids*. New York: Wiley.

Narayanan, K. S., & Jon, D. I. (2003). *Water miscible emulsions of pyrethroid insecticides or triazole fungicides*, US Patent No. 6541516.

Neubert, R. H., Schmalfuss, U., Wolf, R., & Wohlrab, W. A. (2005). Microemulsions as colloidal vehicle systems for dermal drug delivery. Part V: Microemulsions without and with glycolipid as penetration enhancer. *J. Pharm. Sci., 94*, 821–827.

Obata, Y., Takayama, K., Maitani, Y., Machida, Y., & Nagai, T. (1993). Effect of ethanol on skin permeation of nonionized and ionized diclofenac. *Int. J. Pharm., 89*, 191–198.

Ogiso, T., & Shintani, M. (1990). Mechanism for the enhancement effect of fatty acids on the percutaneous absorption of propranolol. *J. Pharm. Sci., 79*, 1065–1071.

Okabe, H., Suzuki, E., Saitoh, T., Takayama, K., & Nagai, T. (1994). Development of novel transdermal system containing d-limonene and ethanol as absorption enhancers. *J. Control. Release, 32*, 243–247.

Ongpipattanakul, B., Burnette, R., & Potts, R. O. (1991). Evidence that oleic acid exists as a separate phase within stratum corneum. *Pharm. Res., 8*, 350–354.

Osborne, D. W., Ward, A. J., & O'Neill, K. J. (1988). Microemulsions as topical drug delivery vehicles: Part 1. Characterization of a model system. *Drug Dev. Ind. Pharm., 14*, 1202–1219.

Osborne, D. W., Ward, A. J., & O'Neill, K. J. (1991). Microemulsions as topical drug delivery vehicles: In vitro transdermal studies of a model hydrophilic drug. *J. Pharm. Pharmacol., 43*, 450–454.

Panchagnula, R., Salve, P. S., Thomas, N. S., Jain, A. K., & Ramarao, P. (2001). Transdermal delivery of naloxone: Effect of water, propylene glycol, ethanol and their binary combinations on permeation through rat skin. *Int. J. Pharm., 219*, 95–105.

Paolino, D., Ventura, C. A., Nistico, S., Puglisi, G., & Fresta, M. (2002). Lecithin microemulsions for the topical administration of ketoprofen: Percutaneous absorption through human skin and in vivo human skin tolerability. *Int. J. Pharm., 244*, 21–31.

Parikh, D. K., & Ghosh, T. K. (2005). Feasibility of transdermal delivery of fluoxetine. *AAPS PharmSciTech, 6*, E144–E149.

Park, E. S., Cui, Y., Yun, B. J., Ko, I. J., & Chi, S. C. (2005). Transdermal delivery of piroxicam using microemulsions. *Arch. Pharm. Res., 28*, 243–248.

Payne, R. (1998). Factors influencing quality of life in cancer patients: The role of transdermal fentanyl in the management of pain. *Semin. Oncol., 25*, 47–53.

Pedersen, J. S. (1999). Analysis of small-angle scattering data from micelles and microemulsions: Free-form approaches and model fitting. *Curr. Opin. Colloid Interface Sci., 4*, 190–196.

Peimi, M. P. Y., Korner, D., Benita, S., & Marty, J.-P. (1999). Positively and negatively charged submicron emulsions for enhanced topical delivery of antifungal drugs. *J. Control. Release, 58*, 177–187.

Peira, E., Carlotti, M. E., Trotta, C., Cavalli, R., & Trotta, M. (2008). Positively charged microemulsions for topical application. *Int. J. Pharm., 346*, 119–123.

Peira, E., Scolari, P., & Gasco, M. R. (2001). Transdermal permeation of apomorphine through hairless mouse skin from microemulsions. *Int. J. Pharm., 226*, 47–51.

Peltola, S., Saarinen-Savolainen, P., Kiesvaara, J., Suhonen, T. M., & Urtti, A. (2003). Microemulsions for topical delivery of estradiol. *Int. J. Pharm., 254*, 99–107.

Pes, M. A., Atamaki, K., Nakamura, N., & Kuneida, H. (1993). Temperature insensitive microemulsions in a sucrose monoalkanoate system. *J. Colloid Interface Sci., 178*, 666.

Pineyro-Lopez, A., Pineyro-Garza, E., Torres-Alanis, O., Reyes-Araiza, R., Gomez-Silva, M., Waksman, N., Salazar-Leal, M. E., & Lujan-Rangel, R. (2007). Evaluation of the bioequivalence of single 100-mg doses of two oral formulations of cyclosporin a microemulsion: A randomized, open-label, two-period crossover study in healthy adult male Mexican volunteers. *Clin. Ther., 29*, 2049–2054.

Podlogar, F., Gasperlin, M., Tomsic, M., Jamnik, A., & Bester Rogac, M. (2004). Structural characterisation of water-Tween 40®/Inwitor 308®-isopropylmyristate microemulsions using different experimental methods. *Int. J. Pharm., 276*, 115–128.

Porras, M., Solans, C., Gonzalez, C., Martinez, A., Guinart, A., & Gutierrez, J. M. (2004). Studies of formation of w/o nanoemulsions. *Colloids Surf. A Physicochem. Eng. Asp., 249*, 115–118.

Potts, R. O., & Francoeur, M. L. (1990). Lipid biophysics of water loss through the skin. *Proc. Natl Acad. Sci. USA, 87*, 3871–3873.

Prausnitz, M. R. (2004). Microneedles for transdermal drug delivery. *Adv. Drug Deliv. Rev., 56*, 581–587.

Prausnitz, M. R., Mitragotri, S., & Langer, R. (2004). Current status and future potential of transdermal drug delivery. *Nat. Rev. Drug Discov., 3*, 115–124.

Priano, L., Albani, G., Brioschi, A., Calderoni, S., Lopiano, L., Rizzone, M., Cavalli, R., Gasco, M. R., Scaglione, F., Fraschini, F., Bergamasco, B., & Mauro, A. (2004). Transdermal apomorphine permeation from microemulsions: A new treatment in Parkinson's disease. *Mov. Disord., 19*, 937–942.

Prince, L. M. (1977). *Microemulsions: Theory and practice*. New York: Academic Press.

Rhee, Y.-S., Choi, J.-G., Park, E.-S., & Chi, S.-C. (2001). Transdermal delivery of ketoprofen using microemulsions. *Int. J. Pharm., 228*, 161–170.

Sarpotdar, P. P., & Zatz, J. L. (1986). Evaluation of penetration enhancement of lidocaine by nonionic surfactants through hairless mouse skin in vitro. *J. Pharm. Sci., 75*, 176–181.

Savic, S. D., Savic, M. M., Vesic, S. A., Vuleta, G. M., & Muller-Goymann, C. C. (2006). Vehicles based on a sugar surfactant: Colloidal structure and its impact on in vitro/in vivo hydrocortisone permeation. *Int. J. Pharm., 320*, 86–95.

Schaefer, H., & Redelmeier, T. E. (1996). *Skin barrier: Principles of percutaneous absorption*. Basel: Karger.

Scheuplein, R. J., & Blank, I. H. (1971). Permeability of the skin. *Physiol. Rev., 51*, 702–747.

Schmalfuß, U., Neubert, R., & Wohlrab, W. (1997). Modification of drug penetration into human skin using microemulsions. *J. Control. Release, 46*, 279–285.

Schreier, H., & Bouwstra, J. (1994). Liposomes and niosomes as topical drug carriers: Dermal and transdermal drug delivery. *J. Control. Release, 30*, 1–15.

Schurer, N. Y., & Elias, P. M. (1991). The biochemistry and function of stratum corneum lipids. *Adv. Lipid Res., 24*, 27–56.

Schulman, J. H., Stoeckenius, W., & Prince, L. M. (1959). Mechanism of formation and structure of microemulsions by electron microscopy. *J. Phys. Chem., 63*, 1677–1680.

Shafiq, S., Faiyaz, S., Sushma, T., Ahmad, F. J., Khar, R. K., & Ali, M. (2007) Development and bioavailability assessment of ramipril nanoemulsion formulation. *Eur. J. Pharm. Biopharm., 66*, 227–243.

Shafiq-un-Nabi, S., Shakeel, F., Talegaonkar, S., Ali, J., Baboota, S., Ahuja, A., Khar, R. K., & Ali, M. (2007). Formulation development and optimization using nanoemulsion technique: A technical note. *AAPS PharmSciTech, 8*(2), E1–E6.

Shah, D. O. (1998). *Micelles, microemulsions and monolayers: Science and technology*. New York: Marcel Dekker.

Shakeel, F., Baboota, S., Ahuja, A., Ali, J., Aqil, M., & Shafiq, S. (2007). Nanoemulsions as vehicles for transdermal delivery of aceclofenac. *AAPS PharmSciTech, 8*(4), E1–E9.

Shevachman, M., Garti, N., Shani, A., & Sintov, A. C. (2008). Enhanced percutaneous permeability of diclofenac using a new U-type dilutable microemulsion. *Drug Dev. Ind. Pharm., 34*, 403–412.

Shinoda, K., & Lindman, B. (1987). Organised surfactant systems: Microemulsions. *Langmuir, 3*, 135–149.

Silas, J. A., & Kaler, E. W. (2001). The phase behavior and microstructure of efficient cationic-nonionic microemulsions. *J. Colloid Interface Sci., 243*, 248–254.

Silas, J. A., & Kaler, E. W. (2003). Effect of multiple scattering on SANS spectra from bicontinuous microemulsions. *J. Colloid Interface Sci., 257*, 291–298.

Sintov, A. C., & Brandys-Sitton, R. (2006). Facilitated skin penetration of lidocaine: Combination of a short-term iontophoresis and microemulsion formulation. *Int. J. Pharm., 316*, 58–67.

Sintov, A. C., & Shapiro, L. (2004). New microemulsion vehicle facilitates percutaneous penetration in vitro and cutaneous drug bioavailability in vivo. *J. Control. Release, 95*, 173–183.

Sjoblom, J., Lindberg, R., & Friberg, S. E. (1996). Microemulsions-phase equilibria characterization, structures, applications and chemical reactions. *Adv. Colloid Interface Sci., 65*, 125–287.

Sommerville, M. L., Cain, J. B., Johnson, C. S., Jr., & Hickey, A. J. (2000). Lecithin inverse microemulsions for the pulmonary delivery of polar compounds utilizing dimethylether and propane as propellants. *Pharm. Dev. Technol., 5*, 219–230.

Sonneville-Aubrun, O., Simonnet, J. T., & L'Alloret, F. (2004). Nanoemulsions: A new vehicle for skin care products. *Adv. Colloid Interface Sci., 108–109*, 145–149.

Souto, E. B., Wissing, S. A., Barbosa, C. M., & Muller, R. H. (2004). Development of a controlled release formulation based on SLN and NLC for topical clotrimazole delivery. *Int. J. Pharm., 278*, 71–77.

Spiclin, P., Gasperlin, M., & Kmetec, V. (2001). Stability of ascorbyl palmitate in topical microemulsions. *Int. J. Pharm., 222*, 271–279.

Spiclin, P., Homar, M., Zupancic-Valant, A., & Gasperlin, M. (2003). Sodium ascorbyl phosphate in topical microemulsions. *Int. J. Pharm., 256*, 65–73.

Stilbs, P., Lindman, B., & Rapacki, K. (1983). Effect of alcohol cosurfactant length on microemulsion structure. *J. Colloid Interface Sci., 95*, 583–585.

Stoughton, R. B., & Fritsch, W. (1964). Influence of dimethyl sulfoxide on human percutaneous absorption. *Arch. Dermatol., 90*, 512–517.

Stubenrauch, C. (2001). Sugar surfactants—aggregation, interfacial, and adsorption phenomena. *Curr. Opin. Colloid Interface Sci., 6*, 160–170.

Subramanian, N., Ghosal, S. K., & Moulik, S. P. (2005). Enhanced in vitro percutaneous absorption and in vivo anti-inflammatory effect of a selective cyclooxygenase inhibitor using microemulsion. *Drug Dev. Ind. Pharm., 31*, 405–416.

Tanojo, H., Boelsma, E., Junginger, H. E., Ponec, M., & Bodde, H. E. (1999). In vivo human skin permeability enhancement by oleic acid: A laser Doppler velocimetry study. *J. Control. Release, 58*, 97–104.

Tanojo, H., Bowstra, J. A., Junginger, H. E., & Bodde, H. E. (1997). In vitro human skin barrier modulation by fatty acids: Skin permeation and thermal analysis studies. *Pharm. Res., 14*, 42–49.

Tenjarla, S. (1999). Microemulsions: An overview and pharmaceutical applications. *Crit. Rev. Ther. Drug Carrier Syst., 16*, 461–521.

Thacharochi, D., & Rao, K. P. (1994). Transdermal absorption of nifedipine from microemulsions of lipophilic penetration enhancers. *Int. J. Pharm., 111*, 235–240.

Thomas, J. B., & Finnin, C. B. (2004). The transdermal revolution. *Drug Discov. Today, 9*, 697–703.

Touitou, E., Dayan, N., Bergelson, L., Godin, B., & Eliaz, M. (2000). Ethosomes-novel vesicular carriers for enhanced delivery: Characterization and skin penetration properties. *J. Control. Release, 65*, 403–418.

Touitou, E., Godin, B., Karl, Y., Bujanover, S., & Becker, Y. (2002). Oleic acid, a skin penetration enhancer, affects Langerhans cells and corneocytes. *J. Control. Release, 80*, 1–7.

Trotta, M., Gasco, M. R., Caputo, O., & Sancin, P. (1994). Transcutaneous diffusion of hematoporphyrin in photodynamic therapy: In vitro release from microemulsions. *STP Pharma. Sci., 4*, 150–154.

Trotta, M., Gasco, M. R., & Pattarino, F. (1990). Diffusion of steroid hormones from o/w microemulsions: Influence of the cosurfactant. *Acta Pharm. Technol., 36*, 226–231.

Trotta, M., Morel, S., & Gasco, M. R. (1997). Effect of oil phase composition on the skin permeation of felodipine from w/o microemulsions. *Pharmazie, 52*, 50–53.

Trotta, M., Pattarino, F., & Gasco, M. R. (1996). Influence of counterions on the skin permeation of methotrexate from w/o microemulsions. *Pharm. Acta Helv., 71*, 135–140.

Trotta, M., Ugazio, E., Peira, E., & Pulitano, C. (2003). Influence of ion pairing on topical delivery of retinoic acid from microemulsions. *J. Control. Release, 86*, 315–321.

Turi, J. S., Danielson, D., & Woltersom, J. W. (1979). Effects of polyoxypropylene 15 stearyl ether and propylene glycol on percutaneous penetration rate of diflorasone diacetate. *J. Pharm. Sci., 68*, 275–280.

Uchegbu, I. F., & Vyas, S. P. (1998). Nonionic surfactant based vesicles (niosomes) in drug delivery. *Int. J. Pharm., 172*, 33–70.

Valenta, C., & Schultz, K. (2004). Influence of carrageenan on the rheology and skin permeation of microemulsion formulations. *J. Control. Release, 95*, 257–265.

Vanhal, D., Vanrensen, A., Devringer, T., Junginger, H., & Bouwstra, J. A. (1996). Diffusion of estradiol from non-ionic surfactant vesicles through human stratum corneum in vitro. *STP Pharma. Sci., 6*, 72–78.

von Corswant, C., Thoren, P., & Engstrom, S. (1998). Triglyceride based microemulsion for intravenous administration of sparingly soluble substances. *J. Pharm. Sci., 87*, 200–208.

Vora, B., Khopade, A. J., & Jain, N. K. (1998). Proniosome based transdermal delivery of levonorgestrel for effective contraception. *J. Control. Release, 54*, 149–165.

Vyas, T. K., Babbar, A. K., Sharma, R. K., Singh, S., & Misra, A. (2005). Intranasal mucoadhesive microemulsions of clonazepam: Preliminary studies on brain targeting. *J. Pharm. Sci., 95*, 570–580.

Walker, R. B., & Smith, E. W. (1996). The role of percutaneous penetration enhancers. *Adv. Drug Deliv. Rev., 18*, 295–301.

Warisnoicharoen, W., Lansley, A. B., & Lawrence, M. J. (2000). Nonionic oil-in-water microemulsions: The effect of oil type on phase behaviour. *Int. J. Pharm., 198*, 7–27.

Weaver, J. C., Vaughan, T. E., & Chizmadzhev, Y. (1999). Theory of electrical creation of aqueous pathways across skin transport barriers. *Adv. Drug Deliv. Rev., 35*, 21–39.

Williams, A. C., & Barry, B. W. (2004). Penetration enhancers. *Adv. Drug Deliv. Rev., 56*, 603–618.

Wu, H., Ramachandaran, C., Bielinska, A. U., Kingzett, K., Sun, R., Weiner, N. D., & Roessler, B. J. (2001). Topical transfection using plasmid DNA in a water-in-oil nanoemulsion. *Int. J. Pharm., 221*, 23–34.

Wu, H., Ramachandaran, C., Weiner, N. D., & Roessler, B. J. (2001). Topical transport of hydrophilic compounds using water-in-oil nanoemulsions. *Int. J. Pharm., 220*, 63–75.

Yuan, Y., Li, S.-M., Mo, F.-K., & Zhong, D.-F. (2006). Investigation of microemulsion system for transdermal delivery of meloxicam. *Int. J. Pharm., 321*, 117–123.

Zhao, X., Chen, D., Gao, P., Ding, P., & Li, K. (2005). Synthesis of Ibuprofen eugenol ester and its microemulsion formulation for parenteral delivery. *Chem. Pharm. Bull., 53*, 1246–1250.

Zhao, X., Liu, J. P., Zhang, X., & Li, Y. (2006). Enhancement of transdermal delivery of theophylline using microemulsion vehicle. *Int. J. Pharm., 327*, 58–64.

Copyright of Drug Development & Industrial Pharmacy is the property of Taylor & Francis Ltd and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.