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Review

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Nanoemulsion as potential vehicles for transdermal delivery of pure phytopharmaceuticals and poorly soluble drug

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Abstract

Nanoemulsion (NE) is defined as an O/W or W/O emulsion producing a transparent product that has a droplet size from 20-200nm and does not have the tendency to coalesce. It is promising for transdermal delivery of drugs as an efficient route of drug administration. Several mechanisms have been proposed to explain the advantages of nanoemulsions for the transdermal delivery of drugs. In transdermal delivery, the goal of dosage design is to maximize the flux through the skin into systemic circulation. A useful strategy for improving percutaneous flux is to improve the concentration of drug or choose an appropriate vehicle for the transdermal delivery. The nanoemulsions system should be a promising vehicle due to powerful ability to deliver drug through skins. With these approaches, **t**he aim of this present study is to review the potential of nanoemulsion formulation for transdermal delivery of pure phytopharmaceuticals and poorly soluble drugs. Some nanoemulsions have however exhibited sufficiently high level of stability for them to be proposed as vehicle for drug delivery. Using the transdermal route eliminates the side effects, increases patient compliance, avoids first-pass metabolism, enhance bioavailability and maintains the plasma drug level for a longer period of time.

Key words: Transdernmal, poorly soluble drug, phytopharmaceuticals, nanoemulsion.

Introduction

The confusion as to what differentiates a microemulsion [1] and an emulsion has been further complicated by the emergence in the literature of another oil and water dispersion, known as a nanoemulsion, although the terms mini or sub micron emulsion have also been used. The distinction between a microemulsion and a nanoemulsion is even blurred because the description of a nanoemulsion is very similar to that of a microemulsion in that they are both oil-in-water dispersion of small droplet diameter (for nanoemulsion a range of 20-200nm [1, 2] is typically quoted) and of narrow droplet size distribution. Although the physical appearance of a nanoemulsion resembles that of a microemulsion, in that both systems are transparent (or translucent) and of low viscosity, there is an essential difference between the two systems, namely that a nanoemulsion (i.e. an emulsion) is, as at best, kinetically stable, while microemulsion is thermodynamically stable [3]. As a consequence, many of the nanoemulsion reported in the literature do not posses long term stability. Some nanoemulsions have however exhibited sufficiently high level of stability for them to be proposed as vehicle for drug delivery [4]. It is worth commenting that, while the distinction between a nanoemulsion and emulsion, in terms of their size, rather arbitrary,

nanoemulsion because of their small droplet size, posses a higher stability against sedimentation or creaming that an emulsion [5, 6].

One supposed advantage of a nanoemulsion over a microemulsion is that it requires a lower surfactant concentration for its formation. For example, nanoemulsion droplets of radius 60-70 nm and containing 20wt% isohexadecane; were using only 4wt% of a mixture polyoxyethylene 4-dodecyl ether and polyoxyethylene 6-dodecyl ether surfactants [7].

When comparing this surfactant concentration with the 20wt% surfactant typically needed to prepare a microemulsion containing a comparable amount of oil, one should realize that the droplet size of microemulsion thus produced would typically be 10nm. Consequently [8], in order to produce nanoemulsion droplet of the comparable size, the amount of surfactant required would increase (the surfactant of droplet varies with that of the squares of the droplet radius) to a compatible value. The pertinent question (in terms of drug delivery) is what is most beneficial or the optimal size of the droplets. Recent results suggest that small may not always be better, especially because of the need for large amount of surfactant which, under certain circumstances, actually hinders drug absorption [9].

Nanoemulsion, as consequences of their relative high kinetic stability, low viscosity, and transperancy/transluency, are very attractive for range of industrial applications, including the pharmaceutical field where they have been explored as drug delivery systems [9-11]. It is worth nothing however that the most stable nanoemulsion are generally, although not exclusively, prepared using expensive, high energy input method such as microfluidization, ultrasonication, which makes their production expensive [3,12].

Objectives: Improving the following parameters:-

- Effectiveness and bioavailability
- Ease of development
- Breadth of application
- Stability
- Reduce side effect and toxicity
- Drug loading
- Uniformity
- Costs
- Ease of formulation & manufacture
- Drug properties
- Therapeutic considerations

Nanoemulsions, swollen micelles, micelles

There is much debate in the literature as to what exactly differentiates a nanoemulsion from a micelle at low volume fractions of disperse phase. Some investigators have perceived a difference between nanoemulsions and micellar systems containing solubilized oil or water, and have used the terms “swollen” micellar solution or solubilized micellar solutions to describe such systems [13]. These investigators argue that the term nanoemulsion should be restricted to system in which the droplets are the large enough size such that the physical properties of the dispersed oil or water phase are indistinguishable from those of the corresponding oil or water phase, thereby theoretically making it possible to distinguish between oil-in-water (or water-in-oil) nanoemulsion and micellar solutions containing small amounts of solubilized oil (water) [14]. However, in most cases, the transformation between micelles progressively swollen with oil (water) and a nanoemulsion containing an isotropic core of oil (water) appears to be gradual with no obvious transition point. As a consequence, there is no simple method available for determining the oil (water) content at which the core of the swollen micelles becomes identical to that of bulk phase. Many researchers therefore use the terms nanoemulsion to include swollen micelles, but not micelles containing no oil (or water).

Nanoemulsions and cosolvent systems

The above broad definition does not require a nanoemulsion to contain any microstructure. In other words, it includes systems that are co-solvents, i.e. systems in which the constituent components are molecularly dispersed. Most researchers in the field agree, however, that for nanoemulsion to be formed, it is important that the system contains some definite structure. In other words, there is definite boundary between oil and water phases, and at which the amphiphilic molecules are located and that a co-solvent is not a type of nanoemulsion. The only way to distinguish a nanoemulsion from a co-solvent unambiguously is to perform either scattering study (light, X-ray or neutrons) or PFG-NMR measurements. Region of co-solvent formation generally appear at low concentrations of oil or water [14, 15].

Nanoemulsion as Drug Delivery Systems

It is clear from its description that nanoemulsion posses a number of properties that make their use as drug delivery vehicles particularly attractive. Indeed, nanoemulsions (or microemulsion) were first studied with the view of using them as potential vehicles for poorly-water soluble drugs, in the mid 1970s by Elworthy and Attwood [16]. However, it was not until the mid to late 1980s that they were widely investigated as drug delivery systems; this interest being largely the result of the arrival on the market of the cyclosporine A microemulsion pre concentrate, Neoral.

Among the physical properties that make nanoemulsions attractive as drug delivery vehicles is their transparent nature, which means that the product is not only aesthetically pleasing, but allows easy visualization of any contamination. The small size of the domains present means that a nanoemulsion can be sterilized by terminal filtration. Furthermore, depending on the composition of the nanoemulsion, it may be possible to heat sterilize the nanoemulsions. Since the oil-in-water nanoemulsions are able to incorporate lipophilic components, they can be used to facilitate the administration of water-insoluble drugs [17]. Significantly, the small droplet size provides a large interfacial area for rapid drug release, and so the drug should exhibit an enhanced bioavailability, enabling a reduction in dose, more consistent temporal profiles of drug absorption, and the protection of drugs from the hostile environment of the body. In addition to increasing the rate of drug release, nanoemulsion can also be used as a reservoir and actually slow the release of drug and prolong its effect, thereby avoiding high concentrations in the blood. Whether a drug is rapidly or slowly released from nanoemulsion depends very much on the affinity of the drug for the nanoemulsion. Since nanoemulsions contain surfactants (co-surfactants) and other excipients, they may serve to increase the membrane permeation of drug [18, 19].

Drug delivery routes across human skin

Drug molecules in contact with the skin surface can penetrate by three potential pathways: through the sweat ducts, *via* the hair follicles and sebaceous glands (collectively called the shunt or appendageal route), or directly across the stratum corneum (Fig. 1).

The relative importance of the shunt or appendageal route versus transport across the stratum corneum has been debated by scientists over the years [20-22] and is further complicated by the lack of a suitable experimental model to permit separation of the three pathways. In vitro experiments tend to involve the use of hydrated skin or epidermal membranes so that appendages are closed by the swelling associated with hydration. Scheuplein and colleagues [23, 24] proposed that a follicular shunt route was responsible for the pre steady-state permeation of polar molecules and flux of large polar molecules or ions that have difficulty diffusing across the intact stratum corneum.

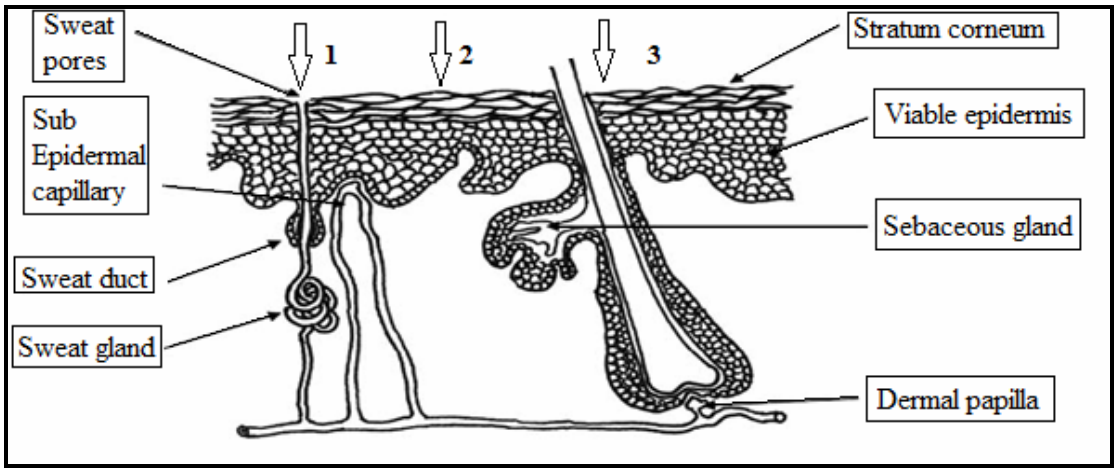

Fig.1. Simplified representation of skin showing routes of penetration: 1. through the sweat ducts; 2. directly across the stratum corneum; 3. via the hair follicles.

Water is an essential component of the stratum corneum, which acts as a plasticizer to prevent cracking of the stratum corneum and is also involved in the generation of natural moisturizing factor (NMF), which helps to maintain suppleness. Traditionally it was thought that hydrophilic chemicals diffuse within the aqueous regions near the outer surface of intracellular keratin filaments (intracellular or transcellular route) whilst lipophilic chemicals diffuse through the lipid matrix between the filaments (intercellular route) [24] (see Fig. 2).

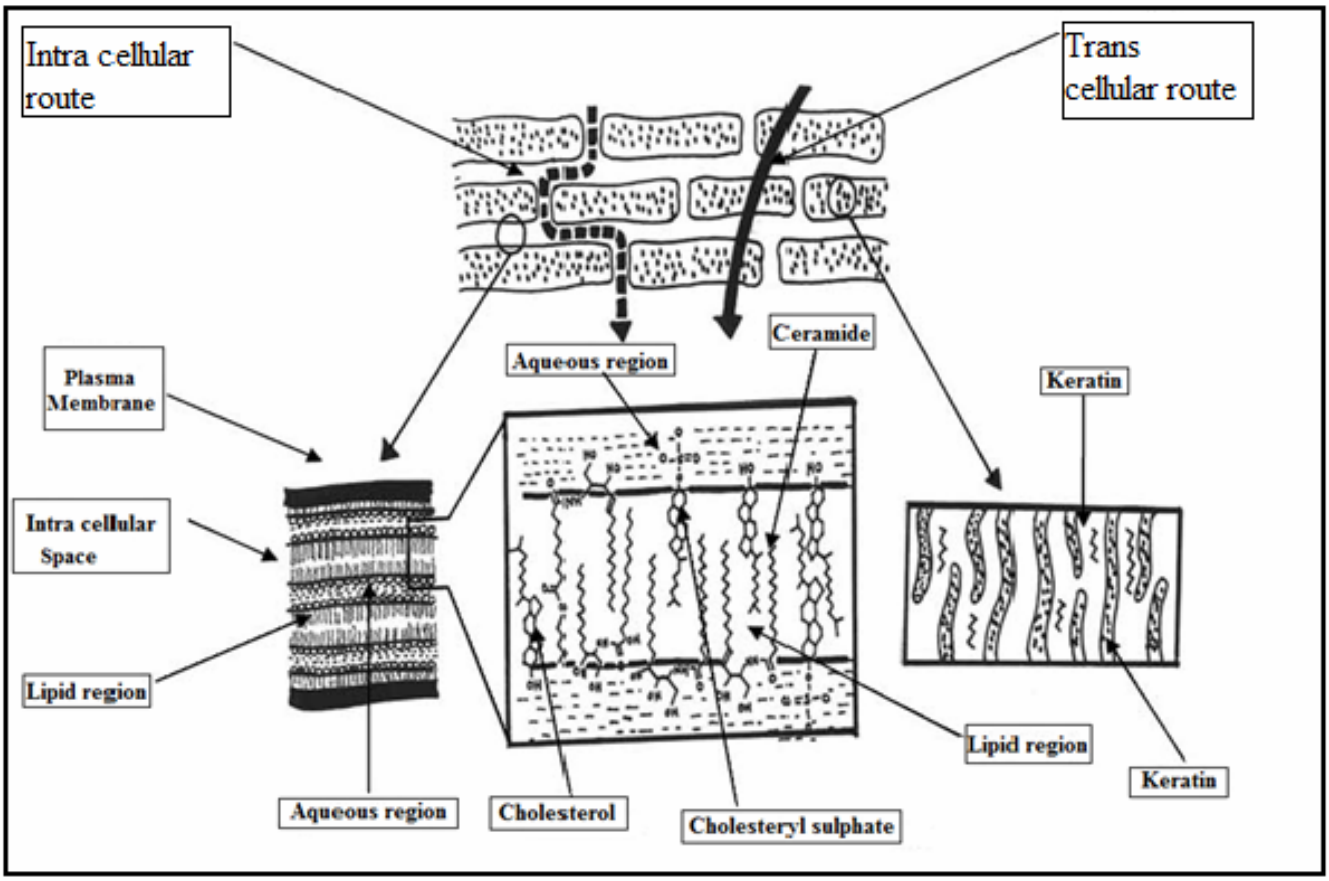

Fig.2. Diagrammatic representation of the stratum corneum and the intercellular and transcellular routes of penetration.

A molecule traversing via the transcellular route must partition into and diffuse through the keratinocyte, but in order to move to the next keratinocyte, the molecule must partition into and diffuse through the estimated lipid lamellae between each keratinocyte. This series of partitioning into and diffusing across multiple hydrophilic and hydrophobic domains is unfavourable for most drugs. Consequently, based on more recent data the intercellular route is now considered to be the major pathway for permeation of most drugs across the stratum corneum [25-29]. Drug permeation across the stratum corneum obeys Fick's first law (equation 1) where steady-state flux (J) is related to the diffusion coefficient (D) of the drug in the stratum corneum over a diffusional path length or membrane thickness (h), the partition coefficient (P) between the stratum corneum and the vehicle, and the applied drug concentration (C_0) which is assumed to be constant:

$$\frac{dm}{dt} = J = \frac{DC_0P}{h} \quad \ldots\ldots\ldots\ldots (1)$$

Equation (1) aids in identifying the ideal parameters for drug diffusion across the skin. The influence of solubility and partition coefficient of a drug on diffusion across the stratum corneum has been extensively studied and an excellent review of the work was published by Katz and Poulsen [30]. Molecules showing intermediate partition coefficients (log P octanol/water of 1-3) have adequate solubility within the lipid domains of the stratum corneum to permit diffusion through this domain whilst still having sufficient hydrophilic nature to allow partitioning into the viable tissues of the epidermis [31]. Optimal permeability has been shown to be related to low molecular size [22] (ideally less than 500 Da [32]) as this affects diffusion coefficient, and low melting point which is related to solubility.

Penetration enhancement by stratum corneum modification

There is extensive literature, including many excellent reviews [33-36] describing chemicals and methods to reduce the barrier capability of the stratum corneum in order to promote skin penetration. The enhancer activity of many classes of chemicals has been tested including water, surfactants, essential oils and terpenes, alcohols, dimethyl sulfoxide (DMSO), Azone analogues. In addition some chemicals have been identified as penetration retarders. The activity of penetration enhancers may be expressed in terms of an enhancement ratio (ER):

$$ER = \frac{\text{Drug permeability coefficient after enhancer treatment}}{\text{Drug permeability coefficient before enhancer treatment}}$$

Barry and coworkers [37-39] devised the lipid-protein partitioning (LPP) theory to describe the mechanisms by which enhancer's effect skin permeability:

- Disruption of the intercellular bilayer lipid structure
- Interaction with the intracellular proteins of the stratum corneum
- Improvement of partitioning of a drug, coenhancer, or cosolvent into the stratum corneum.

Hydration

Water is the most widely used and safest method to increase skin penetration of both hydrophilic [40] and lipophilic permeants [41]. The water content of the stratum corneum is around 15 to 20% of the dry weight but can vary according to humidity of the external environment.

Lipid Disruption/Fluidization by Chemical Penetration Enhancers

Many enhancers, such as Azone, DMSO, alcohols, fatty acids and terpenes, have been shown to increase permeability by disordering or 'fluidizing' the lipid structure of the stratum corneum [42, 43].

Interaction with Keratin

In addition to their effect on stratum corneum lipids, chemicals such as DMSO, decylmethylsulphoxide, urea and surfactants also interact with keratin in the corneocytes [44].

Increased Partitioning and Solubility in Stratum Corneum

A number of solvents (such as ethanol, propylene glycol, TranscutolÒ and N-methyl pyrrolidone) increase permeant partitioning into and solubility within the stratum corneum, hence increasing P in Fick's equation (Eqn. 1). Indeed, ethanol was the first penetration enhancer-cosolvent incorporated into transdermal systems [45].

Combined Mechanisms

Fick's law (Eqn. 1) shows that a combination of enhancement effects on diffusivity (D) and partitioning (K) will result in a multiplicative effect. Synergistic effects have been demonstrated for many combinations, such as Azone and propylene glycol [46], Azone and Transcutol [47], oleic acid and propylene glycol, terpenes and propylene glycol [48], various combinations and alcohols e.g. N-methylpyrrolidone and propylene glycol, urea analogues and propylene glycol [49], supersaturation and oleic acid [50].

Skin Irritancy and Toxicity Due to Chemical Penetration Enhancers

Chemical penetration enhancers increase skin permeability by reversibly damaging or altering the physicochemical nature of the stratum corneum to reduce its diffusional resistance. One of the problems associated with many chemical penetration enhancers is that they cause irritancy in the skin [51].

Other Physical and Electrical Methods

These include iontophoresis (driving charged molecules into the skin by a small direct current – approximately 0.5 mA/cm2), phonophoresis (cavitation caused by low frequency ultrasound energy increases lipid fluidity), electroporation (application of short micro- to milli-second electrical pulses of approximately 100-1000 V/cm to create transient aqueous pores in lipid bilayers) and photomechanical waves (laser-generated stress waves reported to cause a possible transient permeabilisation of the stratum corneum [52-54]).

An overview of current techniques

Shinoda K *et al* reported that the microemulsions are thermodynamically stable isotropic system in which two immiscible liquids (i.e., water and oil) are mixed to form a single phase by means of an appropriate surfactant or its mixture. These are homogeneous systems of low viscosity that can be prepared over wide range of surfactant concentrations and oil-to-water ratios. Hoar and Schulman introduced the word microemulsion (ME), which they defined as a transparent obtained by titrating a normal coarse emulsion with medium-chain alcohols1.The short to medium chain alcohols are generally considered as co surfactant in the ME system.

Kriwet K *et al* studied that the nanoemulsions have improved transdermal permeation of many drugs over the conventional topical formulations such as emulsions and gels. This article describes the potential of nanoemulsion systems in transdermal delivery of aceclofenac using nonirritating, pharmaceutically acceptable ingredients without using additional permeation enhancers, because excipients of nanoemulsions themselves act as permeation enhancers.

Faiyaz *et al* reported that the aim of the present study was to investigate the potential of a nanoemulsion formulation for transdermal delivery of aceclofenac. Various oil-in-water nanoemulsions were pre- pared by the spontaneous emulsification method. The nano-emulsion area was identified by constructing pseudo ternary phase diagrams. The prepared nanoemulsions were subjected to different thermodynamic stability tests. The nanoemulsion formulations that passed thermodynamic stability tests were characterized for viscosity, droplet size, transmission electron microscopy, and

refractive index. Transdermal permeation of aceclofenac through rat abdominal skin was determined by Franz diffusion cell. The in vitro skin permeation profile of optimized formulations was compared with that of aceclofenac conventional gel and nanoemulsion gel.

Benson *et al* reported the transdermal drug delivery: penetration enhancement techniques. Transdermal delivery of drugs through the skin to the systemic circulation provides a convenient route of administration for a variety of clinical indications. Transdermal delivery systems are currently available containing scopolamine (hyoscine) for motion sickness, clonidine and nitroglycerin for cardiovascular disease, fentanyl for chronic pain, nicotine to aid smoking cessation, etc.

Wu H *et al* investigated that the A variety of water-in-oil nanoemulsions were prepared using sorbitan monooleate (Span®80), polyoxyethylene 20 sorbitan monooleate (Tween®80), olive oil and water. The nanoemulsions were tested for their ability to facilitate transport of a model hydrophilic solute, inulin, across hairless and hairy mouse skin and hairy rat skin following topical in vitro application. The transport of inulin incorporated in water-in-oil nanoemulsions was found to be significantly higher (5- to 15-fold) than that obtained with micellar dispersions or aqueous controls. The rate and extent of inulin transport across hairy mouse skin was found to be highly dependent on the hydrophile–lipophile balance (HLB) of the surfactant mixture in the nanoemulsion.

Xu J. *et al* investigated that the preparation of neem oil microemulsion and its acaricidal activity in vitro was developed in this study. In these systems, the mixture of Tween-80 and the sodium dodecyl benzene sulfonate (SDBS) (4:1, by weight) was used as compound surfactant; the mixture of compound surfactant and hexyl alcohol (4:1, by weight) was used as emulsifier system; the mixture of neem oil, emulsifier system and water (1:3.5:5.5, by weight) was used as neem oil microemulsion. All the mixtures were stired in 800 rpm for 15min at 40 8C. The acaricidal activity was measured by the speed of kill. The whole lethal time value of 10% neem oil microemulsion was 192.50 min against Sarcoptes scabiei var. cuniculi larvae in vitro.

Mei Z *et al* investigated that the Triptolide (TP) has been shown to have anti-inflammatory, immunosuppressive, anti-fertility and antineoplastic activities. However, its clinical use is restricted to some content due to its poor water solubility and some toxic effects. In order to find innovative ways for administering TP and alleviating its disadvantages, the controlled release delivery systems such as solid lipid nanoparticle (SLN) and microemulsion have been developed. In the present paper we describe the preparation and some characterization of specialized delivery systems for TP. The transdermal delivery capacity and anti-inflammatory activity were also evaluated. The results indicated that these SLN dispersions and microemulsions could serve as efficient promoters for the TP penetrating into skin.

Teichmann A *et al* investigated that the Comparison of stratum corneum penetration and localization of a lipophilic model drug applied in an o/w microemulsion and an amphiphilic cream. In the present study, the lipophilic dye curcumin incorporated in an oil-in-water microemulsion and in an amphiphilic cream was applied onto the skin of human volunteers.

Cui J *et al* reported that the Curcumin is a poorly water-soluble drug and its oral bioavailability is very low. A new selfmicroemulsifying drug delivery system (SMEDDS) has been successfully developed to improve the solubility and oral absorption of curcumin. Suitable compositions of SMEDDS formulation were screened via solubility studies of curcumin and compatibility tests. The formulation of curcumin-loaded SMEDDS was optimized by a simplex

lattice experiment design. The optimal formulation of SMEDDS was comprised of 57.5% surfactant (emulsifier OP: Cremorphor EL = 1:1), 30.0% co-surfactant (PEG 400) and 12.5% oil (ethyl oleate).

Tsai Y *et al* investigated that the hesperetin is one of the flavonoids and possess anti-inflammatory, UV- protecting and antioxidant effects. Permeation issues for topical delivery systems of such effects are occasionally problematic, and in view of the fact that microemulsions are potential carriers for transdermal delivery system, the objective of this study was to design an optimal microemulsion formulation by in vitro permeation study for hesperetin topical dosage form and determine its topical photoprotective effect and skin irritation by in vivo study. The hesperetin-loaded microemulsion showed an enhanced in vitro permeation compared to the aqueous and isopropyl myristate (IPM) suspension dosage form of hesperetin.

Lin C *et al* reported that the ternary phase diagram of a curcumin-encapsulated O/W microemulsion system using food-acceptable components, lecithin and Tween 80 as the surfactants and ethyl oleate as the oil phase, was constructed. The stability and characterisation of curcumin in microemulsion were investigated. The results indicated that a composition of curcumin microemulsion (DI water: surfactants (the mole ratio of lecithin/Tween 80 was 0.3): EO = 10:1.7:0.4 in wt ratio) was stable for 2 months with an average diameter of 71.8 ± 2.45 nm, as detected by UV–Vis spectra and diameter distributions. The microemulsion possesses an ability to be diluted with aqueous buffer without destroying its structure for 48 h.

Conclusion

Recent review focused on the development of nanoemulsions, which seem to be an interesting alternative for transdermal drug delivery. The nanoemulsions system should be a promising vehicle due to powerful ability to deliver drug through skins. With these approaches, **t**he aim of this present study is to review the potential of nanoemulsion formulation for transdermal delivery of pure phytopharmaceuticals and poorly soluble drugs.

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