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Pharmaceutical Microemulsion: Formulation, Characterization and Drug deliveries across skin

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Abstract:
Microemulsions have been regarded as more effective topical vehicle than its conventional skin applications like cream and gel. Being transparent and thermodynamically stabile system, microemulsions are formed spontaneously with relative ease of manufacture. Such system has better scale up potential demonstrating their industrial feasibility as well. These nano-structured vehicle exhibited better solubilisation of drug, higher skin permeation of drug in comparison to conventional formulations when applied on skin. Enhanced drug solubilization, increased flux across skin, decrease in diffusion co-efficients are major attributes of microemulsion system owing to internal phase existed in nanosize droplet, ultralow interfacial tension with enhanced surface free energy. Present review focuses on different characterization methods available to establish phase behavior, type of microemulsion, microstructure details, rheological properties etc. Effect of formulation components of microemulsion, trends in selection of new exicipients constituting oil phase, surfactant and co-surfactant has been highlighted herein and future orientations. Microemulsion based system find significant improvement in topical delivery of antifungal, antiviral, anti-inflammatory, antioxidant, local anesthetics, etc.

Keywords: Microemulsion delivery, topical vehicle, permeation enhancement, phase diagram

Review Paper

Introduction

Hoar and Schulman, in 1943 defined microemulsion as the transparent, isotropic system composed of relatively large fraction of surfactant and co-surfactants in comparison water and oil phases. In such systems, dispersed phase droplet does not refract light; hence the dispersed phase globules appeared invisible to naked eye. Globule size was ranged below 200nm and therefore such system became transparent [(1)]. Microemulsion has been shown to possess ultra low interfacial tension (sometime negative) as it can accommodate large fraction of co-surfactant/surfactant mixture at interface thus thermodynamically stable [(2)]. The interface between continuous and internal phase is stabilized by an appropriate combination of surfactants and/or co-surfactant [(3)]. There are detailed theoretical basis which explains stability of microemulsion in terms of surface free energy, interfacial tension, and solubilisation of its components. The theoretical details of microemulsion and its stabilization are given elsewhere in the literature. Micro-structural variations appeared when internal phase are rearranged into several distinctive types [(4)], and it is diagrammatic represented in figure 1.

To describe about the microemulsion types, microstructures and the effectiveness of microemulsion as topical delivery system is increasingly investigated. Three different types of microemulsion are represented in figure-1. Water-in-oil (*o/w*) type consists of oil phase dispersed in continuous water phase. Most of the topical vehicles investigated belong to this type and found to be more effective in drug delivery than w/*o* types[21]. Oil-in-water (*o/w*) microemulsion

comprises of water droplets are internally dispersed into continuous aqueous phase. Though both type of system gained equal importance in topical delivery. Bi-continuous structures are also called lamellar structure where phases remained in micro domains of oil and water and inter dispersed. [5].

To distinguish microemulsion with other biphasic dispersions, microemulsions are nano-sized dispersion comprised of oil phase, aqueous phase, and relatively large proportion of surfactant and co-surfactant mixture in appropriate ratios [6]. Unlike coarse emulsion, microemulsions are spontaneously formed system and possess very low interfacial tension [7]. A process of self-emulsification would be initiated upon addition of large portion of surfactant and co-surfactant mixture to oil and water. As a result, thermodynamically stable microemulsion is formed spontaneously without input of mechanical energy whereas its macro counterparts (coarse emulsions) require large input of mechanical energy for dispersion stability [8]. Dispersed systems are currently employed in percutanous delivery in the form of emulsions, gels and lotions. Coarse emulsions are still being used in topical delivery in the form of *w/o* and *o/w* creams. The major disadvantages of topical formulations are greasiness, poor spreadibility, poor drug transport and availability etc. The major difference between topically applied coarse emulsions and microemulsion [9-12] are given in table-1.

It has been estimated that approximately half of the approved drugs are lipophilic and have poor absorption characteristics when administered from oral route. To meet with such challenge, drug discovery programs searched new alternative route for drug administration with new drug delivery platforms [13]. Formulation scientists have paid special attention to microemulsions as these system are emerged as most effective vehicle for drug delivery across skin either from intradermal or transdermal route [14]. Microemulsions based formulations intended to skin application brings out very promising results as solubility enhancement drug; modify drug permeability in topical microemulsion vehicle and quick penetration of drug in skin [15-18]. Topically administered microemulsion systems have been shown to provide improved drug stabilization in comparison to topical formulation developed conventionally [19].

Table 1: Comparison of topically applied microemulsion and its conventional counterpart

	Microemulsion	Coarse emulsion
Physical		
Droplet size	in *nm*	in *μm*
Viscosity	low	high
Interfacial tension	low	--
Drug solubilization	high	low
Surface activity	high	low
Zeta potential	negative	--
Compositional		
Surfactant (%)	25-75	2-10
Co-surfactant (%)	5-20	not required
Oil phase (%)	0-30	large
Gel base	required	No
Method of preparation		
Spontaneously formed	yes	No
Mechanical stirring	No	Yes
Construction of phase diagram	required	not required
Selection of microemulsion region	required	not required
Transport		
Flux	very high	low
Enhancement ratio	high	low
Diffusion coefficient	low	high
Lag time	very less	high
Mechanism of permeation	skin function, diffusion, surface activity	mainly diffusion
Permeation enhancer	Not required	Required
Stability		
Freeze -thaw	Stable	Not stable
Elevated temperature	Stable	Not stable
Mechanical stability	Stable	Not stable
Drug stabilization	Enhanced	No
Aesthetic		
Appearance	transparent	opaque white
Organoleptic	attractive	Dull
Consistency	fluid	Creamy

METHODS OF CHARACTERIZATION

Microemulsions are the nano-structured vehicles have dynamic structures which prominently affect the performance of topical formulation; hence its structural dynamics need to be completely assessed. In strict sense, pharmaceutical microemulsion should be characterized for ternary components, ternary phase diagram, phase behaviour, selection of specific microemulsion region from phase diagram, identification and characterization of micromulsion region selected for formulation development, dispersed phase droplet size and its distribution and rheological behaviour [6]. Apart from these characteristics, the developed microemulsion formulation needs to be characterized for physical properties such as pH, surface tension and specific gravity [20-22]. Topical formulations developed from microemulsion are greatly influenced by structure of system and its kinetic and dynamic properties.

CONSTRUCTION OF PHASE DIAGRAM

Microemulsion system should possess a definite proportion of three constituents namely: oil, water and mixture of surfactant and co surfactant. The nature and quantity of each component chosen for pharmaceutical microemulsion must be known in order to determine its feasibility of formation, predict its stability and drug delivery potential. To determine the exact proportions of these microemulsion components, a ternary phase diagram need to be constructed [23], [20]. *Pseudo* ternary plot identifies phase boundaries and distinct regions of ternary mixture (oil, water, surfactant/cosurfactant) where it may be existed as biphasic or monophasic, non isotropic, or liquid crystalline in nature and co-existed in a state of dynamic equilibrium. Aqueous titration method is most common method generally used to construct the phase diagram [24-25]. In the absence of aqueous phase, larger proportion of oil and surfactant together formed into reverse micelle which was capable of solubilising least amount of water in its hydrophilic core formed due to orientation of surfactant molecules. On further addition of water into hydrophilic core may result in the formation of *w/o* micro emulsion where water exists as dispersed phase droplets stabilized by interfacial layer of the surfactant /co-surfactant mixture. As water content is increased, the isotropic clear region changes to a more viscous, birefringent one. Upon further addition of water, a liquid crystalline region may be formed, where water is sandwiched between surfactant double layers. Finally, with more amounts of water, this lamellar structure will break down and water will takeover to form a continuous phase containing droplets of oil stabilized by a surfactant /co-surfactant (o/w microemulsions). A representative phase diagram showing different proportions of the three-component existed either in biphasic coarse emulsion while mono phasic form as microemulsion are shown in figure 2.

DETERMINATION OF PHASE BEHAVIOUR

Usually, polarizing and freeze fracture transmission electron microscopy are most common characterization methods used in the study of transparent region. These methods differentiate microemulsion region (isotropic) from liquid crystalline states (mesophases). Clear isotropic one-phase systems are identified as micro emulsions whereas opaque systems showing bifringence characteristics when viewed under cross-polarized light microscope showed

brilliance appearance indicating liquid crystalline state [26-28]. In freeze fracture method, frozen liquid crystalline state when viewed under ultra microscope, well defined cross sections were appeared. No well defined structures were appeared in microemulsion. Badawi et al determined the phase behaviour of a topically applied microemulsion of salicylic acid by cross polarizing microscopy.

SELECTION WITHIN MICROEMULSION REGION

For the development of topical microemulsion formulation, a suitable microemulsion region in ternary phase diagram was carefully located by constructing a phase diagram [29]. Certain factors like drug solubility, the ratio at which surfactant or co-solvent produce permeation enhancement, rheological behaviour of topical formulation and stability issues should be carefully examined from within microemulsion area of the region [30]. A specific ratio of surfactant co-surfactant (S/CoS) may result in high drug solubilization would be selected for topical formulation [31]. This amount of surfactant and co-surfactant along with the percent of oil phase would be added to formulation. This ratio shall be determined from pseudo-ternary phase diagram previously constructed and incorporated in topical formulation. Using optimum oil and water phase ratios with S/CoS, microemulsion can then be prepared at slow rate with gradual stirring until the system become clear. Developed formulation must be allowed to equilibrate so that any chances of instability or phase separation would be ruled out. In a study, microemulsion using oleic acid, propylene glycol, and tween 80 was prepared and it has been shown that amount of water incorporated during preparation of microemulsion system depend upon the co-surfactant/ surfactant ratio and inversely proportional to the percentage amount of the oil phase of system[32]. Further result showed that changes in microemulsion viscosity and conductivity values depend upon the quantity of water dilution.

MICROEMULSION TYPE

When a specific point within microemulsion area was selected for the development of microemulsion formulation but prior to it is obligatory to know the microemulsion type. This characterization method describes which phase of microemulsion is chosen for dispersed phase of microemulsion. It specifically determines whether the microemulsion region was either *w/o* or *o/w* type. There are several methods are available to characterize type of micremulsion but conductivity and dilution methods are largely employed [33]. Oil-in-water (*o/w)* microemulsion type was shown positive conductivity test whereas w/o type of microemulsion did not. In a study, aim to treat recurrence of rosacea infection, a topical microemulsion was prepared using lecithin/butanol/isopropyl myristate. This formulation was found to be *o/w* type as determined by conductivity method [34]. Topical microemulsion containing 5-aminolevulinic acid (5-ALA) was prepared using ethyl oleate and PEG-8 caprylic/capric glycerides:polyglyceryl-6 dioleate (3:1) mixtures. This preparation was found to be o/w type as determined by conductivity measurement [35]. To develop a safe and effective topical delivery of gemcitabine, a microemulsion vehicle was formulated using different surfactant/ cosurfactant ratios and its microemulsion type was determined by conductivity measurement [36]. Rozman et al shown by conductivity method that o/w

microemulsion was most appropriate vehicle in order to determine the effectiveness of microemulsion delivery of vitamins [37].

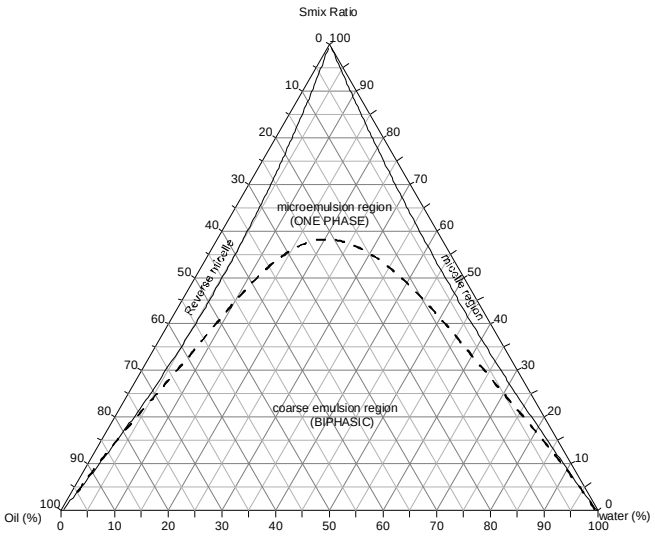
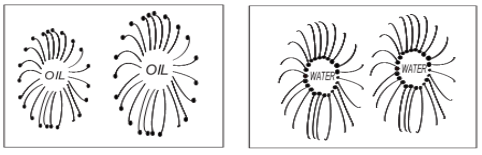


Figure 2: A hypothetical representation of ternary diagram illustrated different phases and regions including microemulsion (area under dotted curve) and coarse emulsion regions (above dotted curve)

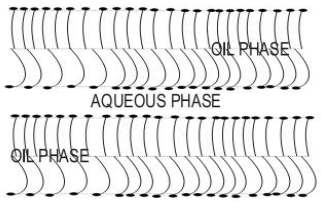
MICROEMULSION STRUCTURE

Small-angle X-ray scattering (SAXS), static as well as Dynamic Light scattering (DLS), Transmission Electron Microscopy (TEM) and NMR spectroscopic method are some of the most revelation techniques to characterize the microstructures of microemulsion[38-39]. Although such techniques are quite simple, easy to interpret experimental data however microemulsions characterized from NMR method require interpretation skills. Although NMR method is very powerful and sophisticated one, diffusion coefficient is directly determined and size of dispersed phase droplets was calculated indirectly. Since other techniques directly focus on droplets size at high resolution and simultaneously reveals any co-existence of laminar structure and microstructural transitions in microemulsions. The droplet-size of microemulsion based topical formulation of capsaicin was determined and differentiated from its true solution by dynamic light scattering method [40]. In an attempt, self diffusion coefficient of topical emulsion was determined by pulsed-field-gradient spin echo NMR spectroscopy confirming its bicontinuous structure [41]. Chen et al examined the combination of o/w microstructure and the three-dimensional gel network of hydrogel in continuous phase within microemulsion using transmission electron microscopy [42]. It has been showed from results that hydrogel thickened microemulsion showed good physical stability of microemulsion. Yet another study confirmed that topical of cyclosporine A had bicontinuous structure in microemulsion by diffusion-ordered NMR spectroscopy [43]. The result of several studies demonstrated by above method of characterization that less droplet size of microemulsion influence the rapid permeation and onset of topical absorption was quick. A good agreement between microstructure and stability of microemulsion was reported by several workers which had been confirmed by these methods of characterization.

Figure 1: Different microstructures arrangement appeared in microemulsions a) in oil-in-water microemulsion b) water-in-oil microemulsion c) bi continuous structures



a) *o/w* type **b)** *w/o* type



c) bi-continuous structure

RHEOLOGICAL BEHAVIOUR

Topical preparations must possess rheological features which facilitate extrudabilty from package and its spreadability when applied to skin during usage. Fluidity of *o/w* microemulsion exhibits its Newtonian behaviour rather than shear thickening. Microemulsions are not exceptionally good enough in providing better rheological properties to formulation. It has been reported that rheology of microemulsion is related to the presence of different microstructures in microemulsion e.g. different types like *o/w* or *w/o* or bicontinous, nature of surfactant, cosurfactant used and its S/CoS ratio [44-45]. Therefore in formulation a gelling agent was incorporated with microemulsion. The incorporation of gelling agent to microemulsion changes the composition of microemulsion altering oil and water phase ratios. It can be observed that changes in drug permeation and stability characteristics were obtained if its composition of phases gets altered. These characteristics of gelled microemulsion or without gelling agent remarkably affect extrudabilty of formulation from package and spreadability over skin. Mostly, a fixed proportion of gelling agent is incorporated in formulation to impart viscous consistency. Chen et *al* developed microemulsion gel using ethyl oleate as an oil phase, Tween 80 as surfactant, propylene glycol as co-surfactant in xanthan gum as gelling agent [46]. The viscous gel used in topical microemulsion improved the consistency without affecting the drug permeation characteristics. Changes in the rheological behaviour help in characterizing the microemulsion region and it has been shown that separation from other related structures like liquid crystals [47]. Bicontinuous structures are dynamic structures with continuous fluctuations in viscosity occurred between the bicontinuous structure, swollen reverse micelle, and swollen micelles [48]. Kantarci et al examined viscosity of topical diclofenac microemulsions prepared from soyabean oil containing Brij® and Span® as surfactants as a function of shear rate and showed that it exhibits Newtonian fluid characteristics [49]. Also the effect of storage temperature on consistency of microemulsion was explored. Koop et al studied the rheology of xanthan-galactomannan (X:G) hydrogels with addition of curcumin in microemulsion (X:GMC) and ethanol (X:GEC). X:GMC hydrogels have gel characteristics and exhibited a significantly higher elastic response than the X:GEC and X:G hydrogels at room temperature, but after heating, an increase in the elastic modulus was observed for the last two systems[50]. Subramanium et al reported increase in microemulsion viscosity due to increase in concentration of medium-chain mono-/di-glyceride in microemulsion[51]. Valenta et al prepared of careegnean gelled microemulsion and reported that the rheologic properties of the formulations can be adjusted with polymer concentration without affecting the permeability of model compound sodium fluorescein [52]. Rozman et al shown that the vitamins release from gel-like microemulsion at skin temperature were comparable to those from o/w microemulsion and were much faster and more complete than from o/w type which was conventionally thickened with carbomer [37].

FORMULATION STRATEGIES

Oil components and its selection

Oil phase constitute a fundamental component of microemulsion and by virtue of its presence it be called as "emulsion" rather it become "true

solution". Oils and essential oils derived from natural sources mainly used as oil phase of microemulsion. These are regarded as safe and biocompatible. However, semi-synthetic derivatives of natural oils are mostly being explored as oil phase. The different oil components of microemulsion derived from different sources in development of microemulsion based topical drug delivery systems are given in table 2.

Table 2: Different oily components evaluated in topical microemulsions

Oil phase	Reference
Natural	
Teatree Oil	63
Soyabean Oil	49
Jojoba Oil	64
Eucalyptus Oil	19, 61
Seasame Oil	65
Babchi Oil	24
Semi-synthetic	
Medium chain triglycerides (cap/cpyl)	61
Isopropyl myristate	60, 66, 67
Ethyl oleate	68
Lauryl alcohol	69
Tocopherol Acetate	70
PEG-40 hydrogenated castor oil	26, 71
Oleic acid	72, 73

Chemically, oils are unsaturated fatty acid derivatives or polyglyceride of fatty acid ester, naturally existed in liquid state. Ideally oil phase selected in topical microemulsion formulaton should be non toxic, non-irritant to skin and less therapeutic activity. Whereas, essential oil are aroma-enriched oily compounds exerts emollient and smoothing effect on skin and therefore incorporated in microemulsion vehicles. Importantly, the criteria by which oil phase component was selected in the topical microemulsion depends on several factors including, enhancement of drug solubility in topical vehicle, increasing the drug permeation rate across skin and mutual miscisibility between surfactant and co-solvents [53-55]. The oil component of microemulsion should be judiciously chosen considering the rheological characteristics of microemulsion [56]. In order to achieve a stable microemulsion, the component of oil phase should be free from rancidity or deteriorate in water phase. It has been observed that component forming the oil phase of microemulsion should be free from trans-estrification, peroxidation or hydrolysis of oil phase during long term storage [57]. It has been shown that inadequately selected oil phase may produce occlusion of skin and might thereby decrease drug fluxes and permeability [58]. Findings from cosmetics science revealed that aesthetic appearance of microemulsion largely due to nature of oil phase incorporated in microemulsions [59].

Isopropyl myristate was mostly employed as oil phase component and it has been shown that its showed excellent mutual miscisibility with other oil components like captex 355/Labrafac in various proportions. Microemulsion was easily prepared from isopropropyl myristate sorbitan mono-oleate as surfactant and can be used as topical delivery of acyclovir [60]. In another study, mono/diglycerides/ triglycerides of capric and caprylic acids was used as oil phase emulsified with Brij-propylene glycol mixture to produce microemulsion vehicle for topical delivery of lycopene. Microemulsion developed using these oil phases were isotropic, fluid and clear could be safe and effective for antioxidant drug [61]. It is very difficult to ascertain the limit of oil phase to be selected in topical microemulsion but various

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reports confirmed that larger proportion of oil phase upto 20% [62].

Co-surfactants

The primary function of surfactant-cosurfactant mixture in microemulsion is to reduce the interfacial tension between two immiscible phases [74]. It has been achieved by incorporating an auxiliary component to surfactant called as co-solvent or sometimes termed as co-surfactant which solubilises surfactant at interface. Ideally, co-surfactant should be non-irritant to skin but in facts it disturbs the normal skin functions and thereby produces more availability of drug across skin[75]. Chemically, these may be simple mono or dihydric alcohols or surfactants mixed with surfactants in microemulsion formulation. The latest advancement in microemulsion technology has brought distinctive co-solvents, but particularly a substituted ether derivative, which reportedly have shown higher solubilisation potential of several lipophilic drugs [76]. These alkanols are simple, low molecular weight compounds, basically volatile in nature. The overview of different co-solvents employed in topical microemulsions was given in table-3. Besides this, it facilitates drug solubilisation capability of overall vehicle [77]. Some recently introduced co-solvents act as drug penetration enhancers in topical formulations [78]. Another important aspect dealt with miscibility of co-solvent with surfactant and oil phase components employed in preparation of a stable formulation. In topical microemulsions, usually it is present in large proportion along with surfactant. It has been reported in literature that a microemulsion consist of cationic or amphoteric surfactant could be incompatibile with wrongly selected cosurfactant [79]. The thermal stability of microemulsion is greatly concerned when appreciable loss of co-solvent took place from microemulsion due to excessive evaporation of co-solvent of microemulsion during storage or may result in phase separation occurred until equilibrium was set up [80].

Table 3: Commonly used co-solvents employed in topical microemulsion

Co-solvent	Reference
Diethylene glycol monoethyl ether	60, 81, 82
Propylene glycol	82, 83
1,2 Octandiol	84
Polyethylene glycol 400	71, 85
n-butanol	15, 86
Ethanol	49, 69, 87
Iso-butanol	88
Tetraglycol	89
1-decanol	90
1,2 hexandiol	91
Polyoxyethylenesorbitan palmitate	67

Surfactants

Surfactants are the multifunctional component present in microemulsion with a prerequisite of large proportion along with co-surfactant in microemulsion. It has been shown that the higher amount of surfactant in microemulsion produce lower droplet size of dispersed phase [92]. Oil is an important component of microemulsion but when it is dispersed in nano droplet its solubilization capacity, drug permeability is significantly changed [93]. Selection of surfactant greatly influences the safety and efficacy of topical microemulsion [94]. There are several theoretical testaments on surfactants available which describes its contribution on interfacial films, solubilzation concepts and thermodynamic background explaining how droplets of dispersed phase get stabilized in microemulsion and become invisible in continuous phase [95]. Surfactant molecule comprises of two distinct

polar region lowering interfacial tension to act on oil water interface. The axiom behind its nano-scale stabilization is the formation of monomolecular layer around dispersed phase droplets and result in formation of several microstructures [96]. Surfactant not only acts on the oil/water interface but facilitates the solublization of drug. The various mechanisms explain the solubilization of drug in microemulsion e.g. by virtue of its localization either on oil/water interface or onto the lipophilic side chain of surfactant molecule, or drug may reside in the core of oil droplets. A list of various surfactants currently being employed in formulation of microemulsion is given in the table 4.

Table 4: Surfactants in topical micro-emulsion delivery

Co-solvent	Reference
Cationic	
hexadecyltrimethylammonium bromide	110
cetyltrimethylammonium bromide	111
Anionic	
Sodium bis 2 ethylhexylsulphosuccinate	112
Non-ionic	
Caprylocaproyl macrogolglyceride	113, 26
Linoleoyl polyoxyl-6 glyceride	114
Tocopheryl polyethylene glycol 1000 succinate	115
Propylene glycol monocaprylate	116
polyoxyethylene(10) oleyl ether	72
polyoxyethylene castor oil	71
Glyceryl monooleate	89
Propylene glycol dicaprylocaprate (2)	51
Polyoxyethylene sorbitan mono oleate	117, 67
polyglyceryl-6 dioleate	35
Ampholytic	
Lecithin	34, 91, 118

However the latest trend of microemulsion research in pharmaceutical formulations, preference is given to non-ionic surfactants over cationic or anionic surfactants [97]. Non-ionic surfactants are glycerides or ester of fatty acid such as lauric, palmitic, stearic or oleic acid specifically are prominently used however especially di or tri glyceride fatty acid esters of capric acid or caprylic acid have been much explored [98]. In topical microemulsions, it has been found that surfactants possess two or three hydrocarbon chain attached with polar group thereby having more solubilising capacity for drugs, are less viscous in comparison to mono glycerides [99]. Since these surfactants are inert in nature, and non irritant to skin and generally regarded as safe (GRAS) [100]. Physical properties such as viscosity, pH, refractive index and specific gravity of the microemulsion formulations are greatly influenced by nature and type of surfactant combined with cosurfactant in formulation. Surfactants used in topical as well as transdermal systems were subjected to skin irritation testing [101]. However it has been shown from the results available that topical surfactants alter the structure of stratum corneum to great extent which causes irritation of skin [102]. It can be said that the surfactant molecules disturb the structures of membrane and hence it also serves a plausible explanation for more permeation of drug across it. A criterion of incorporating minimal surfactant in microemulsion is therefore devised [103]. Another important characteristic where surfactants have great deal of influence is the drug solubilisation in its components. Drug saturated oils were of low drug solubility than the surfactant saturated oils [104]. It has been increasingly reported that topical availability of drug from microemulson formulation is related to enhanced solubilisation capacity of microemulsion and it was a function of emulsifying agent employed in microemulsion [105]. In the presence of surfactant, drug saturated solution of oil develop high concentration

gradient across skin. It resulted in large quantities of drug to transport across skin. However some other factors may be concerned such as droplet size of dispersed phase, surface activity of microemulsion etc. equally responsible for such phenomena [106]. It is very difficult exactly to give a possible explanation regarding how much quantity of surfactant should be present in effective microemulsion vehicle. It has been generalized that excess quantity of surfactant in microemulsion formulation mostly unfavourable for high permeation of drug [107].

A combination of two different surfactants to act synergistically in a microemulsion to produce desirable attributes of solubilization, stability and permeation of drug from formulated microemulsion [108]. Though, no generalized principle on the rationale of taking combination of surfactants in microemulsion has been observed. However some empirically applied features e.g. HLB values and critical packing parameters (CPP) of surfactant were given considerations. [109].

MICROEMULSION IN TOPICAL DELIVERY

Table 5: Microemulsion based topical and transdermal formulations

Category	Drug	Reference
NSAIDS	Piroxicam, Ibuprofen, Salicylic acid, Ketoprofen Diclofenac, Ketrolac	32,46, 22 , 34, 83, 124
ANTIFUNGAL	Fluconazole, voriconazole, miconizole, clindamicin	64, 72, 90, 86
	Amphotericin B, clotrimazole, ketoconazole	21, 15, 58
	Itraconazole Greiseofulvin	125, 126
ANTIVIRAL	Pencyclovir Acyclovir,	30, 60,
ANTIBACTERIAL	Metronidazole	
ANTIOXIDANT	Quercetin, ascorbylpalmitate	117, 119
NATURAL ORIGIN	Hesperitin,	
VITAMINS	Retinoic acid, thyroxine	91, 88
STEROIDAL DRUGS	Estradiol dehydroepiandrosterone	123, 94

Antifungal

Superficial fungal infections like deep skin mycoses are better treated when drug is administered topically than any other route. It minimizes the deleterious effects of drug and produces the local action at the site of application more effectively. Antifungal agents are basically lipophilic in nature easily formulated in topical vehicles. It is advantageous to choice microemulsion as topical vehicle for antifungal agents since ease of preparation due to spontaneous formation, thermodynamic stability, transparent and elegant appearance, increased drug loading, enhanced penetration through the biological membranes, increased bioavailability compared to conventional dosage forms like gel, cream etc. Jadhav et al developed fluconazole topical microemulsion using lecithin and ethyloleate as surfactant and co-solvents respectively [119]. It has been observed that solubility of fluconazole in ethyloleate-lecithin reverse micellar system was almost 3 folds higher than that in ethyloleate. Organogel formed from reverse micelle containing 300 mM of lecithin showed the higher drug release and have better consistency. The histopathological data showed that organogels were safe enough for the topical purpose. El-Hadidy developed topical microemulsion of voriconazole using polyoxyethylene (10) oleyl ether (Brij 97) as surfactant and jojoba oil [64]. Oleic acid and sodium deoxycholate were also incorporated as permeability enhancer in drug loaded microemulsions. It has been concluded that drug loaded microemulsion showed better antifungal activity against *candida albicans* than voriconazole supersaturated solution. Junyaprasert et al developed w/o and o/w novel aerosolized topical formulations of clindamycin

phosphate consisting of isopropyl myristate and 1-butanol microemulsion [72]. The drug permeation from oil-in-water (o/w) microemulsion was relatively higher than that from water-in-oil (w/o) microemulsion. Esposito et al formulated monoglyceride based topical microemulsion of amphotericin B [21]. It has been shown that solubility of amphotericin in formulations was increased up to 20-fold with respect to the single oil and aqueous phases of microemulsion alone. Patel et al reported lauryl alcohol based microemulsions emulsified with labrasol/ ethanol with enhanced solubility of ketoconazole to several folds which may result in high drug permeation across skin [58]. Histopathological investigation of rat skin revealed the safety of microemulsion formulations for topical use. Hashem et al formulated topical clotrimazole microemulsion using two different microemulsion bases made from either lemon oil/Tween 80/n-butanol/water or isopropyl myristate/Tween 80/n-butanol/water [15]. Microemulsion formulations achieved significantly higher skin retention of drug than cream base. The efficacy and tolerability of microemulsion preparations in the treatment of various topical candida *albicans* infections were clinically proved. Chudasma et al studied the permeation of itraconazole from microemulsion based transdermal system [120]. Aggrawal et al studied the topical delivery of griseofulvin from microemulsion base [121].

Antiviral

Zhu et al developed microemulsion based topical hydrogel of penciclovir for the treatment of of herpes *labialis* infection [30]. It has been shown from permeation experimentation in mice that microemulsion alone and in hygrogel form could significantly increase in vitro permeation of penciclovir into both epidermis and dermis. Microstructure changes of skins after administration observed under light microscope and scanning electron microscope (SEM) might result from the interaction of the ingredients of microemulsion with skin, and ascribe for enhanced permeation. Formulations were found to be safe as no erythema or edema, or even slight skin irritation was observed from skin irritation test in rabbit upon single or multiple applications. Shishu et al developed microemulsion formulation of topical delivery of acyclovir for the treatment of cutaneous herpetic infections [60]. The different components used in formulation of microemulsion were isopropyl myristate/Captex 355/Labrafac as an oil phase, nanosized by incorporating polyoxyethylene sorbitol monosterate as surfactant alongwith transcutol, eucalyptus oil, and peppermint oil as permeation enhancers. It has been shown that a single application of microemulsion formulation containing 2.5% transcutol produces 24 h post-injection result in complete suppression of herpetic skin lesions.

Anti-inflammatory

Conventional dosage forms e.g cream, gel or lotion when applied topically has poor drug permeation characteristic across skin. Anti-inflammatory drugs are formulated in these vehicles usually have poor drug absorption. Abd-Allah et al developed a topically applied microemulsion formulation of piroxicam using oleic acid and polyoxythylene sorbitan mono oleate/ propylene glycol as oil phase, surfactant/ co-solvent respectively [32]. It has been reported that microemulsion produced high solubilisation of drug. Results showed that in vitro drug release rate from microemulsion formulation was significantly higher. Dalmora et al also prepared prioxicam microemulsion [122]. Chen et al

developed microemulsion-based hydrogel formulation for topical delivery of ibuprofen [46]. It was formulated using ethyl oleate, polyoxytheylene sorbitan mono oleate, and propylene glycol as oil, surfactant and co-surfactant respectively. The permeation of drug across skin was six fold enhanced when it is formulated in microemulsion vehicle than saturated solution. It was due to more solubilisation capacity of microemulsion vehicle. Topical delivery of ibuprofen through another microemulsion base was investigated by Djekic et al. formulated topical microemulsion of ibuprofen using isopropyl myristate as oil phase, PEG-8 caprylic/capric glycerides as surfactant, octoxynol-12 and polysorbate 20 as co-solvents [123]. Using paddle-over-enhancer cell method, formulations with k_m ratio (40:60) were comparable to hydrogel product. Badawi et al prepared a topical microemulsion of salicylic acid using isopropyl myristate as oil phase, and Tween 80: propylene glycol as surfactant/ cosurfactant in the ratio of 15:1 [22]. The developed formulations were found to be stable evaluated from accelerated stability testing without change in their physical characteristics. Escribano et al investigated topical delivery of diclofenac sodium through microemulsion[73]. Nanosized vehicle formed form transcutol, oleic acid and d-limonene was found to have higher permeability coefficient, flux and amount of drug permeated across human skin. The results were also confirmed by in vivo studies carried out on carrageenan-induced paw edema in rats. Spernath et al prepared microemulsion formulation of diclofenac using tween 80:propylene glycol as surfactant- cosurfactant and phosphatidylcholine as penetration enhancer[83]. Skin penetration from the inverted bicontinuous mesophase and the skin penetration from the o/w-like microstructure were higher than that measured from the w/o-like droplets, especially when the micellar system containing the nonionic surfactant, sugar ester L-1695, and hexaglycerol laurate. Enhancer embedded within the micelle interface significantly increased the penetration flux across the skin compared to micellar systems without the embedded PC at their interface. Paolino et al studied topical microemulsion of ketoprofen using triglycerides as oil phase, a mixture of lecithin and n-butanol as a surfactant/co-surfactant [34]. Ketoprofen-loaded microemulsions showed an enhanced permeation through human skin with respect to conventional formulations. No significant percutaneous enhancer effect was observed for ketoprofen-loaded oleic acid-lecithin microemulsions. The human skin tolerability of various microemulsion formulations was evaluated on human volunteers. Microemulsions showed good human skin tolerability.

Anti acne

Microemulsions as drug delivery system played a pivotal role in improving the agents by enhancing their dermal localization with a concomitant reduction in their side effects. Microemulsions of azelaic acid, a bioactive molecule used in many skin disorders, prepared using the monosodium salt (AZA-Na) has been evaluated as delivery vehicle [124]. Dialysis membrane experiments showed decreasing permeability to AZA-Na, and this was related to its partition at the microemulsion interface. The results suggested that microemulsions containing AZA-Na could be used to optimize drug targeting in acne treatment. Results showed ten-fold increase in the amount of drug released from the

microemulsion when compared to a cream clinically used in treatment of skin disorders.

Antioxidants

Antioxidants have been used in anti-aging and cosmetic products owing to their property of scavenging and destroying aggressive free radicals involved in various skin conditions. Preclinical studies conducted on animal showed that topical application of alpha-tocopherol exert photo-protective effects by reducing the number of sunburnt cells, UV B induced damage and inhibiting photo-carcinogenesis. Rangarajan et al evaluated an *o/w* and *w/o* microemulsion of tocopherol acetate delivered to the epidermis avoiding accumulation in organs other than the skin [70, 73]. The cream or lotion preparations having same amount of vitamin E resulted in excessive accumulation in other organs. Another study showed that combined applications of various antioxidants can increase their potency as compared with a single antioxidant alone. Rozman *et al* have developed a temperature-sensitive microemulsion gel as an effective and safe delivery system suitable for simultaneous topical application of a hydrophilic vitamin C and a lipophilic vitamin E [37]. By changing water content in o/w microemulsion, a gel like microemulsion exhibited temperature sensitive rheological properties. The temperature-driven changes in its microstructure were confirmed by rotational rheometry, viscosity measurements and droplet size determination. The release studies have shown that the vitamin release at skin temperature from gel like microemulsion were comparable to those from o/w microemulsion and were much faster and more complete than from o/w microemulsion conventionally thickened with polymer (carbomer).

Pakpayat et al prepared topical system of ascorbic acid specifically identified bicontinuous structure of microemulsion responsible for stabilization of ascorbic acid [20]. It has been concluded that the major location of ascorbic acid were found in the epidermis where the decomposition of melanin occurred. Therefore this study indicated that microemulsion could be considered as a suitable carrier system for application of ascorbic acid as a whitening agent. Gosenca et al developed topical application for enhancing ascorbyl palmitate stability by addition of newly synthesized co-antioxidant 4-(tridecyloxy)benzaldehyde oxime (TDBO) [125]. It increased ascorbyl palmitate stability in oil-dispersed-in-water (o/w) microemulsions, most presumably due to reduction of ascorbyl palmitate radical back to ascorbyl palmitate, since TDBO free-radical scavenging activity was confirmed. Cytotoxicity experiments demonstrated no significant change in cell viability or morphology in the presence of TDBO-loaded microemulsions regarding unloaded microemulsions, although greater cytotoxicity was observed with increased microemulsion concentrations.

Topical skin protectants

Subramanian *et al* studied the topical delivery of celecoxib using microemulsion as the vehicle for the treatment of UV B induced skin cancer [51]. Various oil to cosurfactant ratios were studied to identify the formulation variables for microemulsion formation. The effect of these variables on skin permeation of celecoxib was evaluated. Topical anti-inflammatory effect of celecoxib was assessed and it showed higher permeation rate and significant anti-inflammatory activity. The studied microemulsion formulations have a prospect for use as a

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potential vehicle for treatment of UV B induced skin cancer.

Baroli et al evaluated alternative formulations for topical administration of 8-Methoxsalen and related furocumarins for the treatment of hyperproliferative skin diseases [84]. Micoremulsion based formulations were consisted of water, isopropyl myristate (IPM) and Tween 80: Span 80: 1,2-Octanediol (3:1:1.2 w/w). Results suggested that in vitro permeation of drug was doubled when compared with saturated solution in IPM and proposed that microemulsion system are promising vehicles for topical delivery.

Conclusion

Pharmaceutical microemulsions have shown a great potential in drug delivery across transdermal or topical applications. These are the nano-structured systems act as biocompatible vehicles for enhanced drug solubilisation, modulating drug permeation characteristics across skin. Microemulsions applied over skin need to be characterized for droplet size, phase diagram, region of phase diagram, conductivity and rheological behaviours. Surfactants and co-surfactants employed in formulation of microemulsion should be selected carefully as these may affect the safety and efficacy of pharmaceutical microemulsion.

References

1) Schulman JH, Stoeckenius W, Prince LM. Mechanism of formation and structure of microemulsions by electron microscopy. J. Phy. Chem. 63 (1959) 1677-1680.

2) Prince LM. (1967) A theory of aqueous emulsion. I. Negative Interfacial tension at oil/water interface, J Colloid & Interfacial Sci. 23; 165- 173.

3) Shinoda K, Kuneida H. Conditions to produce so-called microemulsions. Factors to increase mutual solubility of oil and water by solubilizer. J. Colloid & Interface Sci 1973; 42; 381-387.

4) Shinoda K, Friberg S. Microemulsions. Colloidal aspects. Adv. Colloid & Interface Sci. 1987; 4: 281-300.

5) Boonme P. (2007). Applications of microemulsions in cosmetics. J Cosmet Dermatol 6(4): 223-228.

6) Kreilgaard M. (2002). Influence of microemulsions on cutaneous drug delivery. Adv Drug Deliv Rev 54 Suppl (1): S77-98.

7) Ecclesston GM. Emulsions and microemulsions. Encyclopaedia of pharmaceutical Technology; Vol III ; Informa Healthcare; USA;1548-65.

8) Azeem A, Khan ZI, Aqil M, Ahmad FJ, Khar RK, Talegaonkar S. (2009) Microemulsions as a surrogate carrier for dermal drug delivery. Drug Dev Ind Pharm 35(5): 525-547.

9) Nagarajan R, Molecular theory of microemulsion. Langmuir. 2000; 16; 6400-15.

10) Azeem A, Khan ZI, Aqil M, Ahmad FJ, Khar RK and Talegaonkar S (2009). Microemulsions as a surrogate carrier for dermal drug delivery. Drug Dev Ind Pharm 35(5): 525-547.

11) Lachman.L, Liberman HA, Kanig JL. The Theory and practice of Industrial Pharmacy IIIrd Edn, 1987; pp. 501-32.

12) Schramm LL, Emulsion, foams, and suspension, fundamental and applications.

13) Kumar A, Pathak K, Bali V. (2012). Ultra-adaptable nanovesicular systems: a carrier for systemic delivery of therapeutic agents. Drug Discov Today 17(21-22): 1233-1241.

14) Fini A, Bergamante V, Ceschel GC, Ronchi C, De Moraes CA. Control of transdermal permeation of hydrocortisone acetate from hydrophilic and lipophilic formulations. AAPS PharmSciTech 2008; 9(3): 762-68.

15) Hashem FM, Shaker DS, Ghorab MK, Nasr M, Ismail A. Formulation, characterization, and clinical evaluation of microemulsion containing

clotrimazole for topical delivery. AAPS PharmSciTech 2011; 12 (3); 879-86

16) Sheihet PL, Kohn J, Singer AJ, Michniak-Kohn B. Topical drug delivery by a polymeric nanosphere gel: Formulation optimization and *in vitro* and *in vivo* skin distribution studies. J Control Release 2011; 149 (2): 159-67.

17) Ustundag Okur N, Apaydin S, Karabay Yavasoglu NU, Yavasoglu A, Karasulu HY. Evaluation of skin permeation and anti-inflammatory and analgesic effects of new naproxen microemulsion formulations. Int J Pharm 2011; 416 (1); 136- 44.

18) Escribano E, Obach M, Arevalo MI, Calpena AC, Domenech J. Queralt J. (2005). Rapid human skin permeation and topical anaesthetic activity of a new amethocaine microemulsion. Skin Pharmacol Physiol 18(6): 294-300.

19) 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(2): 142-151.

20) Pakpayat N, Nielloud F, Fortune R, Tourne-Peteilh C, Villarreal AGrillo I. Bataille B. (2009). Formulation of ascorbic acid microemulsions with alkyl polyglycosides. Eur J Pharm Biopharm 72(2): 444-452.

21) Esposito E, Bortolotti F, Menegatti E. Cortesi R. (2003). Amphiphilic association systems for Amphotericin B delivery. Int J Pharm 260(2): 249-260.

22) Badawi AA, Nour SA, Sakran WS, El-Mancy SM. (2009). Preparation and evaluation of microemulsion systems containing salicylic acid. AAPS PharmSciTech 10(4): 1081-1084.

23) Fialho SL, da Silva-Cunha A. (2004). New vehicle based on a microemulsion for topical ocular administration of dexamethasone. Clin Experiment Ophthalmol 32(6): 626-632.

24) Ali J, Akhtar N, Sultana Y, Baboota S, Ahuja A. (2008). Antipsoriatic microemulsion gel formulations for topical drug delivery of babchi oil (Psoralea corylifolia). Methods Find Exp Clin Pharmacol 30(4): 277-285.

25) Sabale V, Vora S. (2012). Formulation and evaluation of microemulsion-based hydrogel for topical delivery. Int J Pharm Investig 2(3): 140-149

26) 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(1-2): 11-19.

27) Burauer S, Belkoura L, Stubenrauch C, Strey R. Bicontinuous microemulsions revisited: a new approach to freeze fracture electron microscopy (FFEM) Colloids & Surfaces A, 228, 1–3, 2003, 159-170

28) Chaiyana W, Rades T, Okonogi S. Characterization and in vitro permeation study of microemulsions and liquid crystalline systems containing the anticholinesterase alkaloidal extract from Tabernaemontana divaricata Int J Pharm, 452, 1–2, 16, 2013, 201-210

29) Patel HK, Barot BS, Parejiya PB, Shelat PK, Shukla A. (2013) Topical delivery of clobetasol propionate loaded microemulsion based gel for effective treatment of vitiligo: ex vivo permeation and skin irritation studies Colloids & Surf. B Biointerface 102: 86-94

30) Zhu W, Guo C, Yu A, Gao Y, Cao F, Zhai G. (2009). Microemulsion-based hydrogel formulation of penciclovir for topical delivery. Int J Pharm 378(1-2): 152-158

31) Zhang YT, Zhao JH, Zhang SJ, Zhong YZ, Wang Z, Liu Y., Shi F, Feng NP (2011). Enhanced transdermal delivery of evodiamine and rutaecarpine using microemulsion. Int J Nanomedicine 6: 2469-2482

32) Abd-Allah FI, Dawaba HM, Ahmed AM. Preparation, characterization, and stability studies of piroxicam-loaded microemulsions in topical formulations. Drug Discov Ther. 2010; 4(4); 267- 75.

33) Kemken J, Ziegler A, Muller BW. (1992). Influence of supersaturation on the pharmacodynamic

effect of bupranolol after dermal administration using microemulsions as vehicle. Pharm Res 9(4): 554-558.

34) Paolino D, Ventura CA, Nistico S, Puglisi G, Fresta M. (2002). Lecithin microemulsions for the topical administration of ketoprofen: percutaneous adsorption through human skin and in vivo human skin tolerability. Int J Pharm 244(1-2): 21-31.

35) Araujo, LM, Thomazine J. A, Lopez RF (2010). Development of microemulsions to topically deliver 5-aminolevulinic acid in photodynamic therapy. Eur J Pharm Biopharm 75(1): 48-55.

36) Tsai, YH, Hsieh YH, Huang YB, Chang JS, Huang CT, Wu PC. (2010). Microemulsions for intravesical delivery of gemcitabine. Chem Pharm Bull (Tokyo) 58(11): 1461-1465.

37) Rozman B, Zvonar A, Falson F, Gasperlin M. (2009). Temperature-sensitive microemulsion gel: an effective topical delivery system for simultaneous delivery of vitamins C and E. AAPS PharmSciTech 10(1): 54-61.

38) Moniruzzaman, M, Tamura M, Tahara Y, Kamiya N, Goto M (2010). Ionic liquid-in-oil microemulsion as a potential carrier of sparingly soluble drug: characterization and cytotoxicity evaluation. Int J Pharm 400(1-2): 243-250.

39) Hathout RM, Nasr M. (2013). Transdermal delivery of betahistine hydrochloride using microemulsions: Physical characterization, biophysical assessment, confocal imaging and permeation studies. Colloids & Surf. B Biointerfaces 110: 254-260

40) Zhang P, Gao W, Zhang L, Chen L. Shen Q, Wang X, Cui Y. (2008). In vitro evaluation of topical microemulsion of capsaicin free of surfactant. Biol Pharm Bull 31(12): 2316-2320.

41) Fanun M., Wachtel E, Antalek B, Aserin A, Garti N. A study of the microstructure of four-component sucrose ester microemulsions by SAXS and NMR Colloids & Surfaces A: Phys7 & Eng Aspects, 180 ,2001, 173-186

42) Chen H, Mou D, Du D, Chang X, Zhu D, Liu J, Xu H, Yang X. (2007). Hydrogel-thickened microemulsion for topical administration of drug molecule at an extremely low concentration. Int J Pharm 341(1-2): 78-84.

43) LiuH, Wang Y, Lang Y, Yao H, Dong Y, Li S. (2009). Bicontinuous cyclosporin a loaded water-AOT/Tween 85-isopropylmyristate microemulsion: structural characterization and dermal pharmacokinetics in vivo. J Pharm Sci 98(3): 1167-1176.

44) Graca M, Bongaerts JHH, Stokes JR, Granick S. Nanotribology, standard friction, and bulk rhelogy properties compared for a Brij microemulsion J Colloid & Interfacial Sci. 333, Issue 2, 15 May 2009, 628-634

45) El-Maghraby GM. (2010). Self-microemulsifying and microemulsion systems for transdermal delivery of indomethacin: effect of phase transition. Colloids Surf B Biointerfaces 75 (2): 595-600.

46) Chen H, Chang X, Du D, Li J, Xu H, Yang X, Microemulsion-based hydrogel formulation of ibuprofen for topical delivery. Int J Pharm; 2006; 315 (1-2);52-58.

47) Fasolin LH, Santana RC, Cunha RL. Microemulsions and liquid crystalline formulated with triacylglycerols: Effect of ethanol and oil unsaturation Colloids & Surfaces A: Physicochemical and Engineering Aspects, 415, 2012, 31-40

48) Schulreich C, Angermann C, Höhn S, Neubauer R, Seibt S, Stehle R, Lapp A, Richardt A, Diekmann A, Hellweg T. Bicontinuous microemulsions with extremely high temperature stability based on skin friendly oil and sugar surfactant. Colloids & Surfaces A: Physicochemical and Engineering Aspects, Volume 418,2013, 39-46

49) Kantarci G, Ozguney I, Karasulu HY, Arzik S, Guneri T. (2007). Comparison of different water/oil microemulsions containing diclofenac sodium: preparation, characterization, release

rate, and skin irritation studies. AAPS PharmSciTech 8(4): E91.

50) Koop HS, Da-Iozzo EJ, de-Freitas RA, Franco CR, Mitchell DA, Silveira JL. (2012). Rheological characterization of a xanthan-galactomannan hydrogel loaded with lipophilic substances. J Pharm Sci 101(7): 2457-2467.

51) Subramanian N, Ghosal SK, Moulik SP. (2005). Enhanced in vitro percutaneous absorption and in vivo anti-inflammatory effect of a selective cyclooxygenase inhibitor using microemulsion. Drug Dev Ind Pharm 31(4-5): 405-416.

52) Valenta C, Schultz K. (2004). Influence of carrageenan on the rheology and skin permeation of microemulsion formulations. J Control Release 95(2): 257-265.

53) Djekic L, Primorac M. (2008). The influence of cosurfactants and oils on the formation of pharmaceutical microemulsions based on PEG-8 caprylic/capric glycerides. Int J Pharm 352(1-2): 231-239

54) Aboofazeli R, Zia H, Needham TE. (2002). Transdermal delivery of nicardipine: an approach to in vitro permeation enhancement. Drug Deliv 9(4): 239-247.

55) Tanojo H, Hans EJ. ginger skin permeation enhancement by fatty acids J Dispersion Sci Tech 20, 1-2; 1999 127-138.

56) Sripriya R, MuthuRaja K, Santhosh G, Chandrasekaran M, Noel M, The effect of structure of oil phase, surfactant and co-surfactant on the physicochemical and electrochemical properties of bicontinuous microemulsion J Colloid & Interface Sci. 314, 2007, 712-717

57) Carlotti ME., Sapino S, Gallarate M, Peira E, Ugazio E. O/W Microemulsions with Vanillin as Vehicles for Antiacne Actives: Preparation, Characterization, and Stability J Dispersion Sci & Tech 29 (7) 2008 991-998.

58) Patel MR, Patel RB, Parikh JR, Solanki AB, Patel BG. (2011). Investigating effect of microemulsion components: In vitro permeation of ketoconazole. Pharm Dev Technol 16(3): 250-258.

59) Kabri T, Arab-Tehrany E, Belhaj N, Linder M. Physico-chemical characterization of nano-emulsions in cosmetic matrix enriched on omega-3. J. Nanobiotech 2011, 9; 11.

60) Shishu S, Rajan, Kamalpreet. (2009). Development of novel microemulsion-based topical formulations of acyclovir for the treatment of cutaneous herpetic infections. AAPS PharmSciTech 10(2): 559-565.

61) Lopes, LB., VanDeWall H, Li HT, Venugopal V, Li HK, Naydin S, Hosmer J, Levendusky M, Zheng H, Bentley MV, Levin R, Hass MA. (2010). Topical delivery of lycopene using microemulsions: enhanced skin penetration and tissue antioxidant activity. J Pharm Sci 99(3): 1346-1357.

62) Cichewicz A, Pacleb C, Connors A, Hass MA, Lopes LB. Cutaneous delivery of a-tocopherol and lipoic acid using microemulsions: influence of composition and charge. J Pharm Pharmacol. 2013; 65(6):817-26.

63) Biju, SS, Ahuja A, Khar RK. (2005). Tea tree oil concentration in follicular casts after topical delivery: determination by high-performance thin layer chromatography using a perfused bovine udder model. J Pharm Sci 94(2): 240-245.

64) El-Laithy HM, El-Shaboury KM. The development of Cutina lipogels and gel microemulsion for topical administration of fluconazole. AAPS PharmSciTech. 2002; 3(4); E35.

65) Ostertag F, Weiss J, McClements DJ. Low-energy formation of edible nanoemulsions: Factors influencing droplet size produced by emulsion phase inversion. J Colloid & Interface Sci, 388, 2012, 95-102.

66) Rangarajan M, Zatz JL. (2003). Effect of formulation on the topical delivery of alpha-tocopherol. J Cosmet Sci 54(2): 161-174.

67) Raza K, Negi P, Takyar S, Shukla A, Amarji B, Katare OP. (2011). Novel dithranol phospholipid microemulsion for topical application: development, characterization and

percutaneous absorption studies. J Microencapsul 28(3): 190-199.

68) Ambade KW, Jadhav SL, Gambhire MN, Kurmi SD, Kadam VJ, Jadhav KR. Formulation and evaluation of flurbiprofen microemulsion. Curr Drug Deliv.2008; 5(1); 32-41.

69) Patel MR, Patel RB, Parikh JR, Solanki AB, Patel BG. (2009). Effect of formulation components on the in vitro permeation of microemulsion drug delivery system of fluconazole. AAPS PharmSciTech 10(3): 917-923.

70) Rangarajan M, Zatz JL (2001). Effect of formulation on the delivery and metabolism of alpha-tocopheryl acetate. J Cosmet Sci 52(4): 225-236.

71) Cao FH, OuYang WQ, Wang YP, Yue PF, Li SP. 2011 A combination of a microemulsion and a phospholipid complex for topical delivery of oxymatrine. Arch Pharm Res 34(4): 551-562.

72) El-Hadidy GN, Ibrahim HK, Mohamed MI, El-Milligi MF. (2012). Microemulsions as vehicles for topical administration of voriconazole: formulation and in vitro evaluation. Drug Dev Ind Pharm 38(1): 64-72.

73) Escribano E, Calpena AC, 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(4): 203-210

74) Rajib K. Mitra, Bidyut K. Paul, Satya P. Moulik Phase behavior, interfacial composition and thermodynamic properties of mixed surfactant (CTAB and Brij-58) derived w/o microemulsion with 1-butanol and 1-pentanol as cosurfactnts and *n*-heptane and *n*-decane as oils J Colloid & Int. Sci. 300, 2006, 755-764

75) Kale NJ, Loyd V, Allen Jr. Studies on microemulsion using Brij 96 as surfactant and glycerin, ethylene glycol and propylene glycol as cosurfactants. Int J Pharm,57;198987-93

76) Djekic L, Primorac M, Jockovic J. Phase behaviour, microstructure and ibuprofen solubilization capacity of pseudo-ternary non-ionic microemulsion J. Mol. Liquids, 160,2011, 81-87.

77) Zhang J, Chai JL, Li GZ, Zhang GY, Xie KC Phase Behaviour of the APG/Alcohol/Alkane/ H2O System. J Dis. Sci &Tech 2025, 2004, 27-34

78) Comelles F. Alternative co-surfactants and co-solvents to prepare microemulsions suitable for practical applications J Dis. Sci &Tech 20, 1-2, 1999, 491-511

79) Comelles F, Leal JS. Butyl lactate: a useful cosurfactant to prepare o/w microemulsions with SDS. J Dis Sci &Tech, 20, 1999, 1777-1788

80) Pepe D, Phelps J, Lewis K, DuJack J, Scarlett K, Jahan S, Bonnier E, Milic-Pasetto T, Hass MA, Lopes LB. Decylglucoside-based microemulsions for cutaneous localization of lycopene and ascorbic acid Int J Pharm 434, 2012; 420-428

81) Ceschel GC, Maffei P, Moretti MD, Demontis S, Peana AT. (2000). In vitro permeation through porcine buccal mucosa of Salvia desoleana Atzei & Picci essential oil from topical formulations. Int J Pharm 195(1-2): 171-177.

82) Salerno C, Carlucci AM, Bregni C. (2010). Study of in vitro drug release and percutaneous absorption of fluconazole from topical dosage forms. AAPS PharmSciTech 11(2): 986-993

83) Spernath A, Aserin A, Sintov AC, Garti N. (2008). Phosphatidylcholine embedded micellar systems: enhanced permeability through rat skin. J Colloid Interface Sci 318(2): 421-429

84) Baroli B, Lopez-Quintela MA, Delgado-Charro MB, Fadda AM, Blanco-Mendez J. (2000). Microemulsions for topical delivery of 8-methoxsalen. J Control Release 69(1): 209-218.

85) Tsai YH, Lee KF, Huang YB, Huang CT, Wu PC. (2010). In vitro permeation and in vivo whitening effect of topical hesperetin microemulsion delivery system. Int J Pharm 388(1-2): 257-262.

86) Junyaprasert VB, Boonsaner P. Enhancement of the skin permeation of clindamycin phosphate by Aerosol OT/1-butanol microemulsions. Drug Dev Ind Pharm 2007; 33(8); 874-80.

87) Kitagawa S, Yoshii K, Morita SY, Teraoka R. (2011). Efficient topical delivery of chlorogenic acid by an oil-in-water microemulsion to protect skin against UV-induced damage. Chem Pharm Bull (Tokyo) 59(6): 793-796.

88) Padula C, Nicoli S, Santi P. (2009). Innovative formulations for the delivery of levothyroxine to the skin. Int J Pharm 372(1-2): 12-16.

89) Sintov AC, Shapiro L. (2004). New microemulsion vehicle facilitates percutaneous penetration in vitro and cutaneous drug bioavailability in vivo. J Control Release 95(2): 173-183.

90) Peira E, Carlotti ME, Trotta C, Cavalli R, Trotta M. (2008). Positively charged microemulsions for topical application. Int J Pharm 346(1-2): 119-123.

91) 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(2-3): 315-321.

92) Malcolmson C, Barlow DJ, Lawrence MJ. Light-scattering studies of testosterone enanthate containing soybean oil/C18:1E10/water oil-in-water microemulsions. J Pharm Sci. 2002 ;91(11):2317-31.

93) Malcolmson C, Satra C, Kantaria S, Sidhu A, Lawrence MJ. Effect of oil on the level of solubilization of testosterone propionate into nonionic oil-in-water microemulsions. J Pharm Sci. 1998; 87(1):109-16.

94) Yang F, Yu XH, Qiao F, Cheng LH, Chen G, Long X, Wang XR, Li XL, Liang RC, Chen YZ. Formulation and characterization of Brucea javanica oil microemulsion for improving safety. Drug Dev Ind Pharm. 2013.

95) Fanun M. Formulation and characterization of microemulsions based on mixed nonionic surfactants and peppermint oil. J Colloid Interface Sci. 2010 Mar 15; 343(2):496-503.

96) Tian Q, Ren F, Xu Z, Xie Y, Zhang S. Preparation of high solubilizable microemulsion of naproxen and its solubilization mechanism. Int J Pharm. 2012;426(1-2):202-10

97) Moniruzzaman M, Kamiya N, Goto M. Ionic liquid based microemulsion with pharmaceutically accepted components: Formulation and potential applications. J Colloid Interface Sci. 2010; 352(1):136-42.

98) Panapisal V, Charoensri S, Tantituvanont A. Formulation of microemulsion systems for dermal delivery of silymarin. AAPS PharmSciTech. 2012;13(2):389-99

99) Yanyu X, Fang L, Qineng P, Hao C. The influence of the structure and the composition of water/AOT-Tween 85/IPM microemulsion system on transdermal delivery of 5-fluorouracil. Drug Dev Ind Pharm. 2012;38(12):1521-9

100) Soliman SM, Abdel Malak NS, El-Gazayerly ON, Abdel Rehim AA. Formulation of microemulsion gel systems for transdermal delivery of celecoxib: In vitro permeation, anti-inflammatory activity and skin irritation tests. Drug Discov Ther. 2010; 4(6):459-71.

101) Fouad SA, Basalious EB, El-Nabarawi MA, Tayel SA. Microemulsion and poloxamer microemulsion-based gel for sustained transdermal delivery of diclofenac epolamine using in-skin drug depot: In vitro/in vivo evaluation. Int J Pharm. 2013 10.1016/j.ijpharm.2013.06.009

102) Hoeller S, Klang V, Valenta C. Skin-compatible lecithin drug delivery systems for fluconazole: effect of phosphatidylethanolamine and oleic acid on skin permeation. J Pharm Pharmacol. 2008; 60(5):587-91.

103) Shalviri A, Sharma AC, Patel D, Sayani A. Low-surfactant microemulsions for enhanced topical delivery of poorly soluble drugs. J Pharm Pharm Sci. 2011; 14(3):315-24.

104) Kogan A, Aserin A, Garti N. Improved solubilization of carbamazepine and structural transitions in nonionic microemulsions upon aqueous phase dilution. J Colloid Interface Sci. 2007;315(2):637-47

105) Tian Q, Ren F, Xu Z, Xie Y, Zhang S. Preparation of high solubilizable microemulsion of naproxen and its solubilization mechanism Int J Pharm. 2012;426(1-2):202-10.

106) Huang YB, Lin YH, Lu TM, Wang RJ, Tsai YH, Wu PC. Transdermal delivery of capsaicin derivative-sodium nonivamide acetate using microemulsions as vehicles. Int J Pharm. 2008; 349(1-2):206-11.

107) Ledet G, Pamujula S, Walker V, Simon S, Graves R, Mandal TK. Development and in vitro evaluation of a nanoemulsion for transcutaneous delivery. Drug Dev Ind Pharm. 2013 doi/abs/10.3109/03639045.2012.763137

108) Idrees M, Rahman N, Ahmad S, Ali M, Ahmad I. Enhance transdermal delivery of flurbiprofen via microemulsions: Effects of different types of surfactants and cosurfactants. Daru. 2011; 19 (6):433-9.

109) Tsai YH, Hsieh YH, Huang YB, Chang JS, Huang CT and Wu PC (2010). Microemulsions for intravesical delivery of gemcitabine. Chem Pharm Bull (Tokyo) 58(11): 1461-1465.

110) Cui Z, Mumper RJ. (2002). Topical immunization using nanoengineered genetic vaccines. J Control Release 81(1-2): 173-184.

111) Correa MA, Scarpa MV, Franzini MC, Oliveira AG. On the incorporation of the non-steroidal anti-inflammatory naproxen into cationic O/W microemulsions. Colloids Surf B Biointerfaces. 2005; 43(2): 108-14.

112) Osborne DW, Ward AJ, O'Neill KJ. Microemulsions as topical drug delivery vehicles: in-vitro transdermal studies of a model hydrophilic drug. J Pharm Pharmacol. 1991; 43(6): 450-4.

113) Djordjevic L, Primorac M, Stupar M. In vitro release of diclofenac diethylamine from caprylocaproyl macrogolglycerides based microemulsions Int J Pharm. 2004;271(1-2):11-9.

114) Zhang Q, Jiang X, Jiang W, Lu W, Su L, Shi Z. Preparation of nimodipine loaded microemulsion for intranasal delivery and evaluation on the targeting efficiency to the brain. Int J Pharm. 2004; 275(1-2): 85-96.

115) Sutthanut K, Lu X, Jay M, Sripanidkulchai B. (2009). Solid lipid nanoparticles for topical administration of Kaempferia parviflora extracts. J Biomed Nanotechnol 5(2): 224-232.

116) Takahashi K, Komai M, Kinoshita N, Nakamura E, Hou XL, Takatani-Nakase T, Kawase M. Application of hydrotropy to transdermal formulations: hydrotropic solubilization of polyol fatty acid monoesters in water and enhancement effect on skin permeation of 5-FU. J Pharm Pharmacol. 2011; 63(8): 1008-14.

117) Alany RG, Rades T, Agatonovic-Kustrin S, Davies NM, Tucker IG. Effects of alcohols and diols on the phase behaviour of quaternary systems. Int J Pharm. 2000; 196(2) :141-5.

118) Schwarz JC, Hoppel M, Kählig H, Valenta C. Application of quantitative 19 F nuclear magnetic resonance spectroscopy in tape-stripping experiments with natural microemulsions. J Pharm Sci. 2013. doi: 10.1002/jps.23646

119) Jadhav KR, Kadam VJ, Pisal SS. (2009). Formulation and evaluation of lecithin organogel for topical delivery of fluconazole. Curr Drug Deliv 6(2): 174-183.

120) Chudasama A, Patel V, Nivsarkar M, Vasu K, Shishoo C. (2011). Investigation of microemulsion system for transdermal delivery of itraconazole. J Adv Pharm Technol Res 2(1): 30-38.

121) Aggarwal N, Goindi S, Khurana R. (2013). Formulation, characterization and evaluation of an optimized microemulsion formulation of griseofulvin for topical application. Colloids Surf B Biointerfaces 105: 158-166.

122) Dalmora, ME, Oliveira AG. (1999). Inclusion complex of piroxicam with beta-cyclodextrin and incorporation in hexadecyltrimethylammonium bromide based microemulsion. Int J Pharm 184(2): 157-164

123) Djekic L, Primorac M, Filipic S, Agbaba D. (2012). Investigation of surfactant/cosurfactant

synergism impact on ibuprofen solubilization capacity and drug release characteristics of nonionic microemulsions. Int J Pharm 433(1-2): 25-33.

124) Pattarino F, Carlotti ME, Gasco MR. (1994). Topical delivery systems for azelaic acid: effect of the suspended drug in microemulsion. Pharmazie 49(1): 72-73.

125) Gosenca, M, Obreza A, Pecar S, Gasperlin M. (2010). A new approach for increasing ascorbyl palmitate stability by addition of non-irritant co-antioxidant. AAPS PharmSciTech 11(3): 1485-1492.

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