Acta Pharmaceutica Sinica B 2012;2(1):8–15

Institute of Materia Medica, Chinese Academy of Medical Sciences
Chinese Pharmaceutical Association

Acta Pharmaceutica Sinica B

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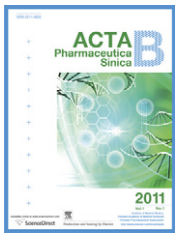

REVIEW

Lecithin organogel: A unique micellar system for the delivery of bioactive agents in the treatment of skin aging

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Received 9 October 2011; revised 15 November 2011; accepted 7 December 2011

KEY WORDS

Skin aging;
Topical;
Lecithin;
Biocompatible;
Organogel

Abstract Skin aging is an unavoidable aspect of human life. Premature skin aging can result from poor care, environmental pollutants, and ultraviolet radiation exposure. Wrinkles, lines, spots, uneven skin tone, and pigmentation are often indicators of skin aging. One cannot avoid aging but cosmetics and pharmaceutical approaches can minimize and delay the damage. Topical applications of biocompatible and biodegradable vehicles have been explored for delivering anti-aging compounds. Lecithin organogel (LO) is an effective vehicle for topical delivery of many bioactive agents used in aging treatment. Lecithin is cell component isolated from soya beans or eggs and purified to show excellent gelation in non-polar solvents when combined with water. LO can form a heat-stable, resistant to microbial growth, visco-elastic, optically transparent, and non-birefringent micellar system. It serves as an organic medium to enhance dermal permeation of poorly permeable drugs by effectively partitioning into the skin. Its ability to dissolve in hydrophilic as well as in lipophilic drugs makes it a dynamic vehicle, which can be explored as a carrier for anti-aging agents.

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Peer review under responsibility of Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association.
doi:10.1016/j.apsb.2011.12.005

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1. Introduction

Skin is one of the most important organs of the human body with important protective functions. One of the most prominent problems associated with skin is aging. Skin aging has been defined as the amassing of skin damage over time[1]. Although each part of the body ages with the time, skin is the external organ where the signs and symptoms of aging are readily evident[2]. However, skin aging can be delayed by cosmetics as well as by pharmaceutical approaches. The permeation of exogenous substances, including agents used in treating skin aging, is prevented by the barrier function of skin. Therefore, the major challenge for topical formulations today is to provide a sufficient increase in drug penetration into skin without causing irreversible alterations to the barrier function[3–5].

Bioactive agents or drugs cross the skin barrier by two mechanisms: transcellular and paracellular transport. Lipophilic agents move across the barrier by a transcellular mechanism whereas hydrophilic agents are likely to follow a paracellular pathway to cross the skin[6]. Various creams, ointments, lotions, as well as gels are available and marketed for skin aging treatment. It was found that lipid-based formulations work most efficiently by improving penetration through the skin, but the drawback associated with such formulations is that they alter the hydration state of the skin, which may result in dermatitis. In contrast, water-based formulations are able to maintain the bioactive state of skin but exhibit poor penetration[7,8].

Lecithin organogels (LO) are promising vehicles to deliver wide variety of agents through the skin because they possess both the properties of oil and aqueous based formulations[9]. In this review we focus on the potential of LO to deliver bioactive agents in the treatment of skin aging.

2. Skin aging and molecular mechanisms

There are two different types of aging: intrinsic aging and extrinsic aging. Intrinsic aging occurs inevitably as a natural consequence of physiological changes over time at variable yet inalterable genetically determined rates. Extrinsic aging is caused by environmental factors such as repetitive facial expressions, gravity, sleeping positions, smoking and exposure to the sunlight. The frequently visible features of intrinsic aging are fine wrinkles, thin and transparent skin, hollowed cheeks and eye sockets, loss of firmness on the hands and neck, sagging, dry skin that may itch, inability to sweat sufficiently, graying hair that eventually turns white, and hair loss. Extrinsic factors, especially sun exposure, often act simultaneously with the normal aging process and cause earlier skin aging. Photoaging is the term principally applied to depict extrinsic aging caused by sun exposure. Photoaging is often indicated by age spots, spider veins on the face, rough and leathery skin, fine wrinkles that disappear when stretched, loose skin, a blotchy complexion, solar elastosis, actinic keratosis, and skin cancer[10,11].

Skin aging is generally accelerated by reactive oxygen species that result from the oxidation of cellular components. Reactive oxygen species include superoxide, hydroxyl radicals, hydrogen peroxide, singlet oxygen, etc. Generation of endogenous reactive oxygen species takes place under mental as well as physical stress[12,13]. The major sources of free radical generation include prostaglandin synthesis, phagocytosis, cytochrome P-450 enzymes, non-enzymatic reactions of oxygen, and ionizing radiation, which damage the molecular structure of DNA, proteins, lipids, and prostaglandins[14,15]. Collagen type I is the most abundant protein of the skin connective tissue present in the dermal extracellular space, where it undergoes enzymatic processing. The formation of collagen bundles is responsible for the strength and resiliency of the skin[16–18]. Smoking increases the production of collagenase, which breaks down the collagen and causes premature wrinkling[19–21]. UV radiation also affects the synthesis of collagen and elastin and changes gene activity by altering signal transduction cascades[22]. Certain hereditary factors and lack of nutrients can also affect skin aging[23,24].

Generally two mechanisms are involved in natural skin defense: the first is enzymatic, including glutathione peroxidase, glutathione reductase, glutathione transferase, catalase, copper-zinc superoxide dismutase, manganese superoxide dismutase, and extracellular superoxide dismutase; the second is nonenzymatic, including low-molecular weight compounds such as ascorbate, glutathione, β-carotene, α-tocopherol, uric acid, and bilirubin, all of which act as free radical scavengers[25–27].

3. Treatment of skin aging

A variety of agents have been tested and are commonly used in the treatment of aging (Table 1). They can help relieve the signs and symptoms of aging through various mechanisms. Broadly, they are delivered as pharmaceuticals, cosmetics, and cosmeceuticals.

4. Concept behind the use of organogel for topical delivery

In order to confront skin aging, all the agents listed above were tested in patients systemically as well as locally. It has been reported that various systemic anti-aging agents required relatively large doses and caused dose-dependent toxicity in many cases. Kockaert et al.[42] discovered that oral administration of vitamin A will result in hypervitaminosis A. Also, some drugs undergo first-pass metabolism, which prevents their delivery to the desired site of action. De la Lastra et al.[43] showed that resveratrol by oral administration undergoes first-pass metabolism. Because of the short half-life, repeated dosing is necessary. Many drugs undergo degradation by gastric acid as well as gut-wall enzymes. Proteins and peptides used in aging treatment can be degraded by the gastric acid and enzymes[44]. Furthermore, many hydrophilic or lipophilic drugs show either poor dissolution or poor absorption on oral administration[45]. Patients are not always in favor of oral as well as parenteral dosage forms. Parenteral delivery causes pain because of invasiveness and a skilled person is needed to deliver the injection. Also, in the case of both oral and parenteral drug delivery, drug effects cannot be stopped once administered. All these shortcomings restrict the use of oral and parenteral dosage forms.

Topical delivery of drugs treating skin aging is most favorably accepted nowadays[46]. Patients usually tend to pay more attention to topical dosage forms because of the convenient administration. No skilled person is required for administration and drugs will not be degraded by acid or enzymes. The effective concentration can be applied at the

Table 1 Various bio-active agents used in the treatment of skin aging.

Bioactive agents	Mechanism
Vitamin C, vitamin E, co-enzyme Q10, ferulic acid, green tea, idebenone, pycnogenol, silymarin	Free radical scavenging and inhibitors of lipid peroxidation[28,29]
Hydroquinone and its derivatives, glycolic acid, malic acid, citric acid, mixed fruit acid, triple fruit acid and sugar cane extract	Inhibit production of melanin[30]
Lactic acid	Hydration of the stratum corneum and prevention of skin damage[31]
Para-aminobenzoic acid derivatives, cinnamates, salicylates, octocrylene, ensulizole, benzophenones, retinoids, butyl methoxydibenzoyl and meradimate	UV filters[32]
Vitamin A	Reduces collagen breakdown by inhibiting the metalloproteinases[33,34]
Vitamin B	Anti-inflammatory effect and anti-acne action[35,36]
N-acetyl glucosamine (NAG) and glucosamine	Build skin structural matrix[37–39]
Metals (zinc, copper, selenium)	Link with proteins superoxide dismutase and metallothionein and act as anti-oxidants[40]
Soyabean derivatives	Inhibit protease activated receptor 2 (PAR-2)[41]

desired site without painful delivery and also avoids first-pass metabolism. In addition, the termination of the topical therapy is easily accomplished. In skin aging treatment, topical dosage forms such as creams, ointments, lotions, linaments and gels are commonly available in the market because of their features including appearance, ease of application, ease of removal, effective at the site of action, and lessened side effects compared to oral and parenteral dosage forms. Many varieties of cosmetic products are available in the market and are commercially advantageous. Nonetheless, cosmetic products even after the various safety tests may cause some undesirable effects including dermatoses[47]. But the use of natural and bio-friendly drug-loaded vehicles can help relieve such problems. Hence, researchers seek to develop novel vehicles that are natural, biocompatible, non-immunogenic, non-allergic, and effective for the patients. For manufacturers, desirable features include ease of manufacture, long-term stability, and ready quality control.

Gels are best fitted in all these essential criteria because of their excellent appearance, smoothness, desired consistency, fast drug release, ease of manufacturing and quality assessment, and admirable stability. The United States Pharmacopoeia (USP) defined gels as semisolids, either suspension of small inorganic particles or large organic molecules interpenetrated with liquid[48]. Gels are transparent or translucent semisolid formulations containing a high ratio of solvent/gelling agent. When dispersed in an appropriate solvent, gelling agents merge or entangle to form a three-dimensional colloidal network structure, which limits fluid flow by entrapment and immobilization of the solvent molecules[49]. Recently, gel formulations have been modified to yield an advanced drug delivery system known as ''organogels'', which is composed of organic as well as aqueous phases possessing various beneficial properties.

5. Lecithin organogels

LOs are gels consisting of an organic medium in liquid phase. LOs are thermodynamically stable, clear, viscoelastic, biocompatible

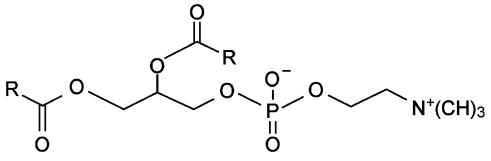

Figure 1 Structure of lecithin.

and isotropic gels which are composed of lecithin (Fig. 1), an organic solvent, and a polar liquid. LO have jelly-like structure that consists of three-dimensional networks of entangled reverse cylindrical micelles, which immobilize the continuous phase and thus convert from liquid to viscous gel[50].

Traditionally, organogel systems are applied topically when the active agent is oil-soluble or penetration into the deeper skin layer is required. Surfactants act as penetration enhancers that alter the membrane bilayer structure and thus reduce the diffusion barrier and enable the drug to penetrate deeply into skin[51]. Since the discovery of simple gelator molecules, organogels have attracted increasing attention. These novel formulations can be used in small quantities without further additives, resulting in more biocompatible products[52]. A wide variety of organogels have been developed by researchers and classified based on the nature of the organogelators, such as LO, gelatin-stabilized organogels, limonene GP1/PG organogel, non-ionic surfactant based organogels and polyethylene organogels[53]. Among these organogels, LOs are a unique micellar system composed of a non-polar oil phase, an aqueous polar phase, and a surfactant phase, which is derived from soy or egg lecithin. Self-assembly of lecithin molecules in nonaqueous media into reversed giant cylindrical micelles occurred when small amounts of water, glycerol, or formamide are added. LO was first introduced by Scartazzini and Luici in 1988[54]. They observed that the addition of small amount of water into nonaqueous solutions of naturally occurring lecithin caused a sudden rise in the viscosity[55]. The chemical name of lecithin is 1,2-diacyl-*sn*-glycero-3-phosphatidylcholine.

Lecithin is a complex mixture of acetone-insoluble phosphatides, which mainly consist of phosphatidyl choline, phosphatidyl

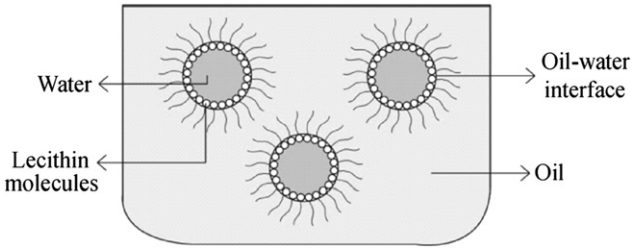

Figure 2 Arrangement of lecithin molecules in micellar systems.

ethanolamine, phosphatidyl serine, and phosphatidyl inositol combined with different amounts of other substances such as triglycerides and fatty acids[56]. The main sources of lecithin are soya beans and egg yolk. Lecithin varies greatly in its physical form, from viscous semi-liquid to powder depending on the content of free fatty acid. It may also vary in color from brown to light yellow depending on whether it is bleached or unbleached[57]. Lecithin is available in various marketed grades like EPIKURON, LIPOID S 100, and CAPCITHIN, which are derived and purified from either soya beans or eggs. Desired gelation in organic solvent occurs only when the lecithin contains more than 95% phosphatidylcholine and is free from fat as well as moisture. Lecithin is a multi-functional surface-active agent. The lecithin molecule can be divided into two portions, the fatty-acid portion, which is attracted to lipophilic drugs, and the phosphoric acid portion, which is attracted to hydrophilic drugs. Because of these two aspects, lecithin molecules arrange themselves at the boundary between immiscible liquids such as oil and water (Fig. 2). This arrangement reduces the interfacial tension between oil and water and makes relatively stable emulsions. Poorly purified lecithin or synthetic lecithins do not exhibit gelation properties[54].

Lecithin is an important component of all living cells and is recognized by Food and Drug Administration as GRAS (Generally Regarded As Safe, 21 CFR 184, 1400). Its unique lipid molecular structure (Fig. 1) performs versatile functions. It has a wide variety of roles in pharmaceuticals, cosmetics and food industries as an emulsifier, viscosity modifier, stabilizer, solubilizer and penetration enhancer[58].

5.1. *Composition of LO*

LO is composed of a biosurfactant (lecithin), which acts as a gelling agent and a non-polar organic media as external or continuous phase and a polar agent (usually water)[59,55]. Lecithin is a biocompatible and biodegradable surfactant as well as a cellular component, which acts as a penetration enhancer[60]. Lecithin contains phospholipid molecules, which are self-assembled to build up the microstructure of organogel. The unsaturated non-polar part of lecithin molecules can affect the critical packing parameter (CPP). It contributes in the development of reverse micellar structures and furthermore converts these micelles to three-dimensional long tubular networks[61]. Organic solvent plays a vital role in organogel by providing the desired solvent action for drug as well as lecithin, and supported its skin penetration enhancing property[9,62,63]. Many organic solvents are available for LO, and include ethyl laureate, ethyl myristate, isopropyl myristate, isopropyl palmitate, cyclopentane, cyclooctane, *trans*-decalin, *trans*-pinane, *n*-pentane, *n*-hexane, *n*-hexadecane, and tripropylamine. It was observed that they are effective in permeation of drug into skin but they exhibit toxicological manifestations[61]. Generally biocompatible and biodegradable organic solvents are preferred because of their safety in use. Natural oils including soyabean oil, sunflower oil, rape seed oil and mustard oil possess desired properties as a solvent in LO[55]. The polar component acts as structural, gel forming and stabilizing agent. The gel-forming ability of the polar solvent depends on its physicochemical properties such as surface tension, dielectric constant and polarity. Water, glycerol, ethylene glycol and formamide have strong gelling potential[64]. Among all these polar solvents, water is a very effective and natural polar agent, which is beneficial for skin hydration and maintains the vitality of the skin. It can hydrate the upper skin layer (stratum corneum), which is a dead, keratinized and compact layer. In addition to the above-mentioned components, some other agents like co-surfactants and anti-oxidants are also incorporated in LO to boost its effectiveness. Co-surfactants such as n-butanol and propylene glycol provide thermodynamic stability as well as flexibility to the micellar system in LO. Co-surfactant lowers the interfacial tension between the nonpolar and polar phase and also enhances skin permeability[65–67]. Oils used in LO may undergo oxidation, which will affect the stability of LO. Hence, antioxidants like ascorbic acid are usually incorporated for stability.

5.2. *Phenomenon of organogelation of lecithin*

The gelation process (Fig. 3) in organogel takes place with the addition of a trace amount of water into the lecithin solution of organic solvent. Initially, the lecithin molecules are randomly dispersed in the organic medium. With the addition of small amount of water, the lecithin molecules will assemble in spherical reverse micellar form. Further addition of water makes the short tubular or cylindrical micellar aggregate.

The water molecules bind stoichiometrically to the hydrophilic head of the lecithin molecules. Thus they act as a bridge between two adjacent lecithin molecules to form the linear networks with the hydrogen bonds between polar molecules and phosphate groups of lecithin molecules. A further increase in a small amount of water results in the formation of long, flexible and worm-like tubular micellar structures (Fig. 4). Thousands of such tubular micro-structures overlap and entangle with each other to form a three-dimensional gel network, which possesses viscoelasticity and thermo-reversibility. The organic liquids get entrapped in the spaces between the entangled reverse micelles[68–70].

5.3. *Beneficial properties of LO*

5.3.1. *Hydrophilic–lipophilic balance*

LOs are well balanced with hydrophilicity and hydrophobicity, as they are composed of oil and water. It can dissolve a wide variety of guest molecules. Hydrophilic drugs dissolve in polar phase and lipophilic drugs dissolve in the non-polar phase. Lecithin molecules are amphiphilic in nature and possess polar headgroups, which attract the polar drugs and non-polar tails, which solubilize nonpolar drugs[44].

5.3.2. *Microbial resistance*

Micro-organisms grow well in aqueous environments but growth is inhibited in non-aqueous environments. With LO, the external phase is non-aqueous and the internal aqueous

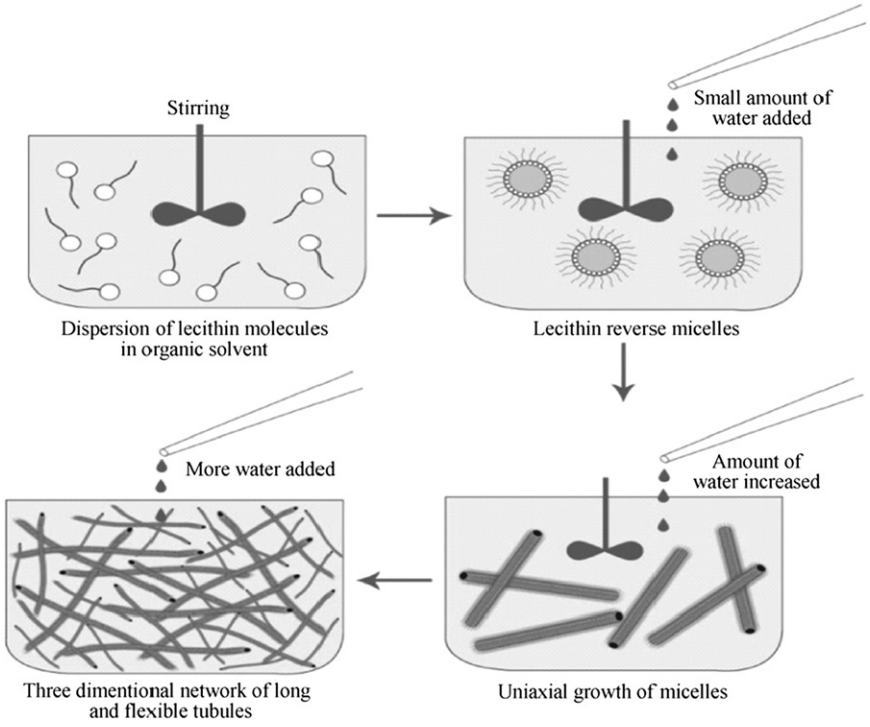

Figure 3 Process of organogelation.

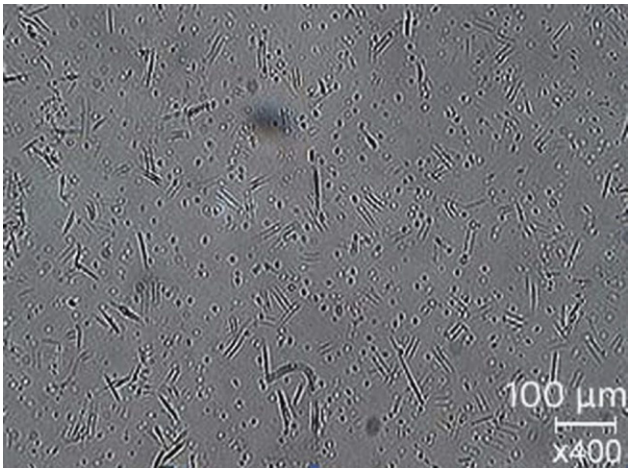

Figure 4 Micro-structure of organogel with long tubular network.

phase and lecithin molecules are well protected from microbial contamination[71].

5.3.3. Non-birefringence and optical transparency

LO is isotropic as it appears as a one-phase system. Optically, it is transparent and provides the benefit of visual inspection so that the presence of any particulate matter can be easily recognized[9,72].

5.3.4. Safety and biocompatibility

LO containing non-polar components such as di-butyl ether, cyclopentane, cyclo-octane, *trans*-decalin, *trans*-pinane, *n*-pentane, *n*-hexane, and *n*-hexadecane may cause some allergic and immunological reactions and chronic dermatoses when applied to the skin for long-term use. However, the use of biocompatible oils such as soyabean oil, sunflower oil, rape seed oil, or mustard oil can minimize such problems. Water as the internal phase can maintain the bioactive state of the skin by hydrating it. Lecithin is biocompatible in nature and is a component of cell membranes. The use of lecithin in organogel is safe. From the results of skin compatibility studies it was revealed that topical use of LO is safe[55,61].

5.3.5. Thermostability

In the organogel lecithin acts as a gelator molecule, which can be self-assembled after addition of water. When the temperature of organogel system increases, lecithin molecules absorb kinetic energy, minimizing the loss of organogel structure. At lower temperatures lecithin molecules reassemble, and therefore LOs are inherently thermostable and valuable for the delivery of bioactive agents and for cosmetic applications[73].

5.3.6. Viscoelasticity

The viscous and elastic nature of LO follows the Maxwell model of viscoelasticity[74]. When the organogels were sheared at low shear rates, they behave like a solid and show an elastic property. With a subsequent increase in shear rate, the tubule structures are weakened. The gelator molecules break the physical interactions from the tubule until the shear stress is high enough to destroy the organogel structure. This behavior is termed as plastic flow behavior[75].

5.4. Phase behavior of LO

A pseudo-ternary diagram (Fig. 5) was constructed for the lecithin–oil–water system. It is constructed by titrating the dispersion of lecithin in oil with water in differing concentration

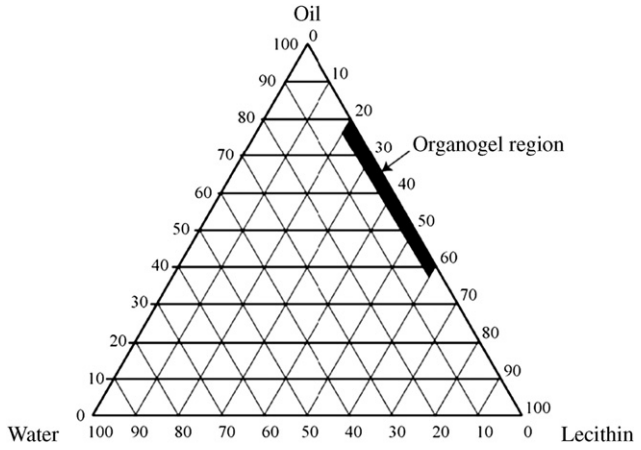

Figure 5 Lecithin–oil–water phase diagram with lecithin–oil ratio of 60:40 (*w*/*w*).

ratios. This explains the phase behavior of the organogels. The phase diagram provides information for the boundaries of the different phases as a function of composition variables and temperatures. Concentrations of lecithin, oil, and water are extremely critical in organogel system. Initially, water in oil micro-emulsion was stabilized by lecithin micelles formed with low concentration of water, which is characterized by optical transparency and low viscosity. As the amount of water increases, the micro-emulsion turned to a viscous gel. Thus, the organogel system is also called a micro-emulsion-based organogel. Phase diagrams for the organogel system also demonstrate the behavior of organogel system such as cloudiness, isotropicity, optical transparency, and viscosity. It was found that an excess amount of water makes the system turbid; hence the concentration of water plays very crucial role in the production of a clear organogel[76].

6. LO in dermal drug delivery

LO meets all the essential criteria for effective drug delivery. Studies of LO have explored its potential as an efficient matrix for dermal administration of many bioactive agents. As the lecithin itself provides skin protection against UV-induced skin aging, it shows additive effects along with incorporated bioactive agents against skin aging. A wide variety of guest molecules such as vitamins A and C, hormones, NSAIDS, peptides, amino acids, local anesthetics and antifungal agents were reported to be effective topically as well as transdermally when delivered by LO (Table 2). Histological evidence indicated that no toxicological manifestations were present even upon the prolonged application on the skin. Drugs are either hydrophilic or lipophilic in nature, but LO can solublize both types of the drugs. LO provides an effective permeation through the skin by fluidizing the membrane lipids as well as by a hydration mechanism. The occlusive nature of LO provides smooth feel on dermal application[9,77,78]. Shaikh et al.[79] reported that LO was found to be more effective and safer for delivery of aceclofenac when compared with hydrogels. Fujii et al.[80] performed experiments on rat skin revealing that the permeation of indomethacin was greater with LO. Zia et al.[72] developed lecithin-stabilized microemulsion-based organogels for topical application of ketorolac tromethamine using soya lecithin as surfactant and isopropyl myristate as oil. It was observed that LO solubilized higher concentrations of ketorolac tromethamine and that its release rate from LO was also enhanced on guinea pig skin. Thus LO was a desirable drug delivery vehicle for water soluble drugs and is capable of providing an appropriate drug release pattern[72]. One of the marketed products of J.A.R. Pharmaceuticals, Ltd. (Edmonton, Alberta, Canada) is Phlojel® Ultra, which is a LO formulated to have cosmetic properties. It is non-greasy and improves skin penetration of incorporated active ingredients. After application to the skin, it is rapidly absorbed without any residue. It has been widely accepted as a superior vehicle for delivering drugs across the skin barrier. By applying the LO formulation, the amount of drug needed to achieve a relatively high local concentration is greatly decreased[81].

Table 2 Dermal delivery of various bioactive agent using LO.

Category	Bioactive agents/drugs
Vitamins	Vitamin A and C[77]
NSAIDS	Diclofenac, ibuprofen, ketoprofen, indomethacin, piroxicam, aceclofenac[9,77,78]
Anti-vitiligo agents	Methoxsalen, triosalen, corticosteroids, calcineurin inhibitors[82]
Anti-scars	Sphingosine, sphinganine, phytosphinosine, *N*-acetylsphingosine, *N*-hexanoylsphingosine, curcumin, apigenin[83]
Skin lightners	Kojic acid, azelaic acid, glycolic acid[84]
Anticholinergic	Scopolamine[78]
β-Adrenergic agonist	Broxaterol[78]
Anti cancer	Aromatic tetra-amidines[85]
Anti-hypertensive	Nicardipine[85]
Psychopharmaceuticals	Fluoxetine, ertraline, paroxetine, amitriptyline, trazadone[86]
Others	Amino acids and peptides[78], botulinium toxins[85]

7. Conclusions

LO provides a new perspective for the topical delivery of anti-aging agents. LO exhibits many desirable physicochemical properties essential for topical vehicles. It can dissolve both hydrophilic and lipophilic drugs and hence acts as effective vehicle to deliver wide variety of drugs across the skin. It is easy to prepare and handle. As LO contains ingredients that are natural, biocompatible, safe and stable, it is likely to play an increasingly important role in cosmetics as well as pharmaceutical agents in treating skin.

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