AAPS PharmSciTech 2005; 6 (2) Article 40 (http://www.aapspharmscitech.org).

Lecithin Organogels as a Potential Phospholipid-Structured System for Topical Drug Delivery: A Review

Submitted: August 3, 2004; Accepted: April 19, 2005; Published: October 6, 2005

Rajiv Kumar[1] and Om Prakash Katare[1]

[1] University Institute of Pharmaceutical Sciences, Panjab University Campus, Chandigarh-160 014, India

ABSTRACT

The purpose of this review is to give an insight into the considerable potential of lecithin organogels (LOs) in the applications meant for topical drug delivery. LOs are clear, thermodynamically stable, viscoelastic, and biocompatible jelly-like phases, chiefly composed of hydrated phospholipids and appropriate organic liquid. These systems are currently of interest to the pharmaceutical scientist because of their structural and functional benefits. Several therapeutic agents have been formulated as LOs for their facilitated transport through topical route (for dermal or transdermal effect), with some very encouraging results. The improved topical drug delivery has mainly been attributed to the biphasic drug solubility, the desired drug partitioning, and the modification of skin barrier function by the organogel components. Being thermodynamically stable, LOs are prepared by spontaneous emulsification and therefore possess prolonged shelf life. The utility of this novel matrix as a topical vehicle has further increased owing to its very low skin irritancy potential. Varied aspects of LOs viz formation, composition, phase behavior, and characterization have been elaborated, including a general discussion on the developmental background. Besides a comprehensive update on the topical applications of lecithin organogels, the review also includes a detailed account on the mechanistics of organogelling.

KEYWORDS: organogel, lecithin, phospholipids, pluronic, topical delivery.

INTRODUCTION

The topical administration of drugs, in order to achieve optimal cutaneous and percutaneous drug delivery, has recently gained an importance because of various advantages such as ease of administration and delivery benefits. In search of a vehicle to deliver the medicament into the skin layers (cutaneous delivery), or through the skin and into the systemic circulation (percutaneous absorption), varied kinds of formulation systems and strategies have been evolved.[1-6] Among the many, the lipid-based formulations have been in use for decades.[7-11] However, of late, there has been a surge in their number with wide variation and flexibility in the interior designs and structures. The importance of lipids has especially increased after realizing the utility of phospholipids, the natural bio-friendly molecules, which in collaboration with water can form diverse types of supramolecular structures.[12-14] The latter can also be modified sometimes by using some polymeric substances and solvents or by other methods to serve the predestined delivery of the molecules.

Corresponding Author: Om Prakash Katare, University Institute of Pharmaceutical Sciences, Panjab University Campus, Sector-14, Chandigarh, India. Tel: +91-172-2534112; Fax: +91-172-2534112. Email: drkatare@yahoo.com

The topical delivery has been attempted and made successful using several lipid-based systems viz vesicular systems,[15] lipid microspheres,[16] lipid nanoparticles,[17] lipid-microemulsions,[18] and polymeric gels.[19] In a recent development, phospholipids in conjunction with some other additives have been shown to provide a very promising topical drug delivery vehicle known as lecithin organogels (LOs). LOs are thermodynamically stable, clear, viscoelastic, biocompatible, and isotropic gels composed of phospholipids (lecithin), appropriate organic solvent, and a polar solvent.[20,21] LOs, the jelly-like phases, consist of a 3-dimensional network of entangled reverse cylindrical (polymer-like) micelles, which immobilizes the continuous or macroscopic external organic phase, thus turning a liquid into a gel.[22] The formation of a 3-dimensional network in the organogel is the result of transition at the micellar level in a low viscous Newtonian liquid consisting of lecithin reverse micelles in nonpolar organic liquid.[23,24] This spherical reverse micellar state of lipid aggregates turns on to form elongated tubular micelles with the addition of water and subsequently entangles to form a temporal 3-dimensional network in the solution bulk.[22,24-26] The latter serves to immobilize the external organic phase, thus producing a gel form or the jelly-like state of the initial nonviscous solution. However, the transparency and optical isotropy of the organogel remains as before. The supramolecularly associated micellar aggregates in the entangled state bear resemblance with that of uncrossed polymers in semidilute or concentrated solutions.[27,28] For this reason these systems are often called *polymer-like* micelles and are also termed as *living* or *equilibrium* polymers, *wormlike* or *threadlike* micelles.[29-31]

Ease of preparation and scale-up, easier quality monitoring, thermodynamic stability, enhanced topical performance, along with biocompatibility and safety upon applications for prolonged period, make the organogels a vehicle of choice for topical drug delivery. Their skin penetration enhancing ability has also been well recognized. Table 1 illustrates some of the pharmaceutically advantageous properties of LOs.

Lecithin Organogels: An Overview

The first description of LOs was given in an article published by Scartazzini and Luisi in 1988.[20] The authors were investigating the suitable conditions for soy lecithin to form reverse micelles. In these experiments, water was added to various organic solutions of purified soybean lecithin. It was observed that addition of trace amounts of water into nonaqueous solutions of soy lecithin caused an abrupt rise in the viscosity (10^4-10^6 times), producing a transition of the initial nonviscous solution into a gel or jelly-like state. The amount of water required to produce the gel was found to be critical. The phenomenon was observed with various nonpolar media and the list includes more than 50 solvents.[20,21] Thus the organogel formation by the water addition can be considered as a common phenomenon, being inherent in the nonaqueous solutions of lecithin. Subsequent to this observation, further experiments by Scartazzini and Luisi[20] and by Schurtenberger et al[21] involved preliminary investigations on the formation as well as the structural aspects of LOs. Soy or egg lecithin in the concentration range of 50 to 200 mM in different organic solvents, such as linear or cyclic alkanes, esters of fatty acids, and amines, was noted to be effective for gel formation. To date, LOs have been studied extensively in many laboratories worldwide with regard to their varied aspects (eg, formulation components, formation and gelling mechanism, physicochemical properties) and have also been proposed as a matrix for topical drug delivery.

Organogel Composition

The organogel matrix chiefly consists of a surfactant (lecithin) as gelator molecules, a nonpolar organic solvent as external or continuous phase, and a polar agent, usually water. The transfer into jelly-like state has been demonstrated only for nonaqueous solutions of naturally occurring unsaturated lecithins.[23,26] The latter are mainly separated from soy bean and egg yolk. Lecithin is a trivial name for 1, 2-diacyl-*sn*-3-phosphocholine. It belongs to a biologically essential class of substances termed phosphoglycerides or phospholipids. The latter form the lipid matrix of biological membranes and also play a key role in the cellular metabolism.[38] As a biocompatible surfactant, it is widely used in everyday life including in human and animal food, medicine, cosmetics, and manifold industrial applications.[39,40] Synthetic lecithins containing residues of saturated fatty acids failed to form organogel.[22,26,41] The gelling formation was also not observed with hydrogenated soybean lecithin.[26] These studies indicate the importance of lecithin in the naturally occurring form, which contains unsaturated fatty acids.

With reference to the effect of unsaturation in phospholipids on organogelling, no such systematic investigative studies have been conducted to date. However, it has been established that unsaturation in phospholipid molecules is a desired property for the formation of lecithin organogels. This may be attributed to its affect on the nature of self-assembly in which the phospholipid molecules associate and form the microstructures. The unsaturation contributes to the volume factor of the nonpolar region of phospholipid

Table 1. Various Meritorious Features of Lecithin Organogels*

	Salient Features	Reference
Template vehicle	LOs provide opportunities for incorporation of a wide range of substances with diverse physicochemical characters (eg, chemical nature, solubility, molecular weight, size)	20,21,32
Process benefits	Spontaneity of organogel formation, by virtue of self-assembled supramolecular arrangement of surfactant molecules, makes the process very simple and easy to handle.	26
Structural/physical stability	Being thermodynamically stable, the structural integrity of LOs is maintained for longer time periods.	22-24,26
Chemical stability	LOs are moisture insensitive, and being organic in character, they also resist microbial contamination.	20,21,26
Topical delivery potential	• Being well balanced in hydrophilic and lipophilic character, they can efficiently partition with the skin and therefore enhance the skin penetration and transport of the molecules. • LOs also provide the desired hydration of skin in a lipid-enriched environment so as to maintain the bioactive state of skin.	32-34
Safety	Use of biocompatible, biodegradable, and nonimmunogenic materials makes them safe for long-term applications.	35-37

*LOs indicates lecithin organogels.

molecules and may alter the value of critical packing parameter (CPP), favoring the formation of reverse micellar structures. And probably the size of such structures is also one of the crucial factors that play an important role in the gelling process. In addition to the effect on CPP and size of the microstructures, the property of unsaturation can also be interpreted in terms of the degree of hydration of phospholipid molecules that it provides. In contrast to the saturated hydrogenated phospholipids, unsaturation in phospholipid molecules would result in better hydration of the polar head group, thereby increasing the area per lipid polar head group. Consequently, larger area and relatively smaller volume would favorably alter the spontaneous curvature of lipid monomers for the formation of micelles and subsequently their self-assembly to form the micellar network. In addition, the purity of lecithin also plays a critical role in the organogel formation. Poorly purified lecithin does not possess gel-forming properties, and it has been demonstrated that lecithin should contain at least 95% phosphatidylcholine content for the preparation of organogels.[20,21,26]

Besides lecithin as gelator molecules, the role of organic solvent in providing the desired solvent action onto the gelator molecules is much emphasized.[20,26] Many varieties of organic solvents are able to form gel in the presence of lecithin. Among them are linear, branched, and cyclic alkanes; ethers and esters; fatty acids; and amines. Specific examples include ethyl laureate, ethyl myristate, isopropyl myristate (IPM), isopropyl palmitate (IPP), cyclopentane, cyclooctane, *trans*-decalin, *trans*-pinane, n-pentane, n-hexane, n-hexadecane, and tripropylamine.[21] Among these, the fatty acid esters (ie, IPM and IPP) are of particular interest for topical applications of LOs. This has been attributed to their skin penetration enhancing property in addition to their biocompatible and biodegradable nature.[42-45]

The third component, a polar agent, acts as a structure forming and stabilizing agent and has a very crucial role to play in the process of gelling. The gel-forming ability of the polar solvent is governed by its physicochemical properties.[30,46,47] It has been established that gel-forming solvents possess high surface tension, relative permittivity (dielectric constant), solvent polarity (polarity index), and a strong tendency toward hydrogen bonding. Water is the most commonly employed polar agent, although some other polar solvents such as glycerol, ethylene glycol, and formamide have also been found to possess the capability of transferring an initial nonviscous lecithin solution into a jelly-like state or organogel.[30]

As described earlier, the major limitation in the formation of LOs is the requirement of high purity lecithin. The high purity grade lecithin is not only expensive but also difficult to obtain in large quantities. However, recent reports indicate the incorporation of synthetic polymer (ie, pluronics) in LOs, for their usefulness as cosurfactants and stablizers.[48-51] It has been shown that the inclusion of pluronics as cosurfactants makes the organogelling feasible with lecithin of relatively lesser purity.[51] The term pluronic refers to a series of nonionic, closely related block copolymers of ethylene oxide and propylene oxide.[52] Also

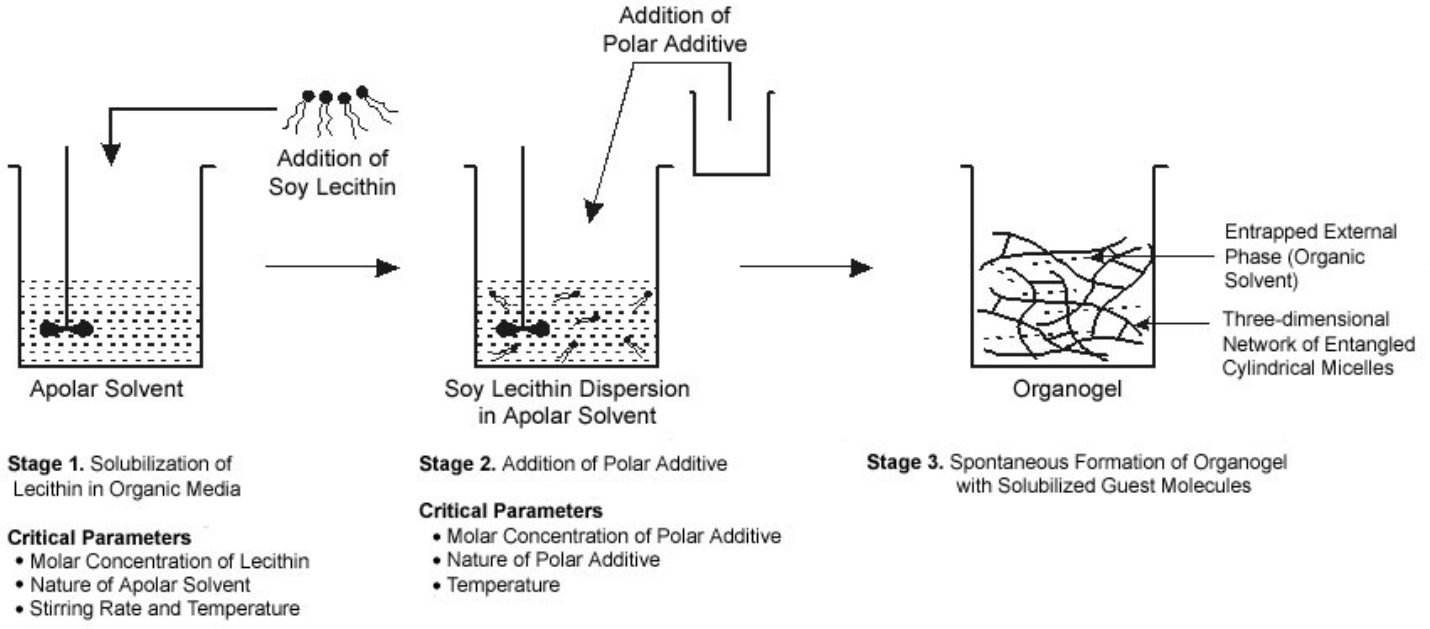

Figure 1. Schematic diagram of the preparation of lecithin organogels. Note: Lipophilic drugs are solubilized in the organic phase (stage 1), whereas hydrophilic compounds can be solubilized in the polar phase (stage 2). For the preparation of pluronic lecithin organogel (PLO gel), the cosurfactant pluronic is taken along with polar phase (stage 2).

known as poloxamers, poloxamer polyols, or lutrols, these copolymers are primarily used in pharmaceutical formulations as cosurfactants, emulsifiers, solubilizers, suspending agents, and stabilizers. These pluronic containing LOs have been termed as pluronic lecithin organogels, poloxamer organogels, pluronic organogels, PLO gel, or simply PLOs. Figure 1 depicts a schematic diagram of the preparation of lecithin organogels.

Phase Behavior of Organogels

The phase behavior of a ternary system of lecithin/organic solvent/polar solvent is mainly governed by the concentration of polar solvent and lecithin.[26,53,54] The same is defined in terms of the parameter, n_w (ie, molar ratio of polar solvent to lecithin; n_w = [polar solvent]/[lecithin]).[20,21] It is noted that the organogel as a homogenous phase exists over a very narrow range of polar solvent concentration.[24,46]

Lately, the phase behavior of lecithin in n-decane employing water as the polar solvent has been discussed.[26] At first, with the addition of water, the thickening effect is observed at a certain specific molar ratio of water to lecithin. After this threshold concentration, further addition of water leads to a sharp increase in the viscosity and the formation of organogel. The organogel state is maintained up to a particular molar ratio of water to lecithin, designated as n_{cr}. At the state where n_w is equal to n_{cr}, the maximum viscosity of organogel is achieved. On continuing the water addition above the n_{cr} (ie, at $n_w > n_{cr}$) the 3-dimensional network collapses and separation of the homogenous organogel takes place in a 2-phase system consisting of low viscous liquid and a compact organogel or jelly-like phase. At still higher concentrations of the polar phase, the transformation of the separated compact organogel into a solid, nontransparent precipitate is observed.

The parameter n_{cr} is considered as a useful, quantitative, and reproducible parameter to characterize various organogels. It is the critical molar ratio of polar solvent to lecithin molecules at which maximum amount of external organic phase is entrapped, and thereafter the phase separation of the organogel accrue.[26,55,56] The n_{cr} values can be easily determined with the help of rheological measurements or visual and optical observations of a ternary system between cross-polarizers. In most of the solvents employed in the preliminary studies on lecithin organogels, the n_{cr} values were found to be in the range of 1 to 12 (as shown in Table 2) employing 80:16:04 weight percentages of lecithin, organic solvent, and water.[20,21]

Further, the phase behavior of the ternary system is also shown to be dependent on lecithin concentrations employed for the formation of organogel system, and the phase separation has been noted to be abolished when the concentration of lecithin exceeds 200 mg/mL.[26,53,54] In one study,[26] using n-decane as the external media and lecithin at concentration smaller than 200 mg/mL, the gel formation was observed at $n_w = 1$, while water was used as a polar additive. With subsequent addition of water (ie, at $n_w = n_{cr}$), the organogel with maximum viscosity was obtained, but the phase separation of organogel occurred at $n_w > n_{cr}$ (ie, at n_w = 3.2–3.4), and a separated semisolid phase was found. However, using lecithin concentration of more than 210 to 220 mg/mL, the phase separation ceased. In this case the transparent and isotropic gel state was maintained even at $n_w \geq 3.2$ to 3.4.

Table 2. n_{cr} Values With Different Organic Solvents Employed in Lecithin Organogel Systems Composed of Soyabean Lecithin/Organic Solvent/Water in 80:16:4 Weight Ratio*

Solvent	n_{cr}
1,7-octadiene	7
Butyl laurate	7
Cyclododecane	12
Cyclooctane	7
Dibutyl ether	6
Ethyl myristate	5
Isooctane	2
Isopropyl myristate	3
Isopropyl palmitate	3
n-hexadecane	1
n-hexane	3
n-octane	2
Trans-decalin	5
Tributylamine	2
Triisobutylamine	3

*Data from Scartazzini R and Luisi PL[20] and Schurtenberger P et al.[21]

Organogel Structure and Mechanism of Organogelling

The organogelling or the gelation of the lecithin solutions in organic solvents is induced as a result of the incorporation of a polar solvent. Lecithin, when being dissolved in nonpolar media alone, self-assembles into reverse spherical micelles at a concentration of ~0.01 mM.[57] The enormous uniaxial growth of these spherical reverse micelles and subsequent transformation into tubular or cylindrical micellar aggregates (sphere-to-cylinder transformation) is triggered by the addition of small and critical amounts of polar additive as shown in Figure 2. The molecules of polar solvent, on addition, bind in stoichiometric ratios to the hydrophilic head portion of the lecithin molecules in such a way that 2 adjacent lecithin molecules are bridged together by 1 polar molecule.[23,30] This leads to the formation of linear networks, from hydrogen bonds formed by the polar molecules and phosphate groups of

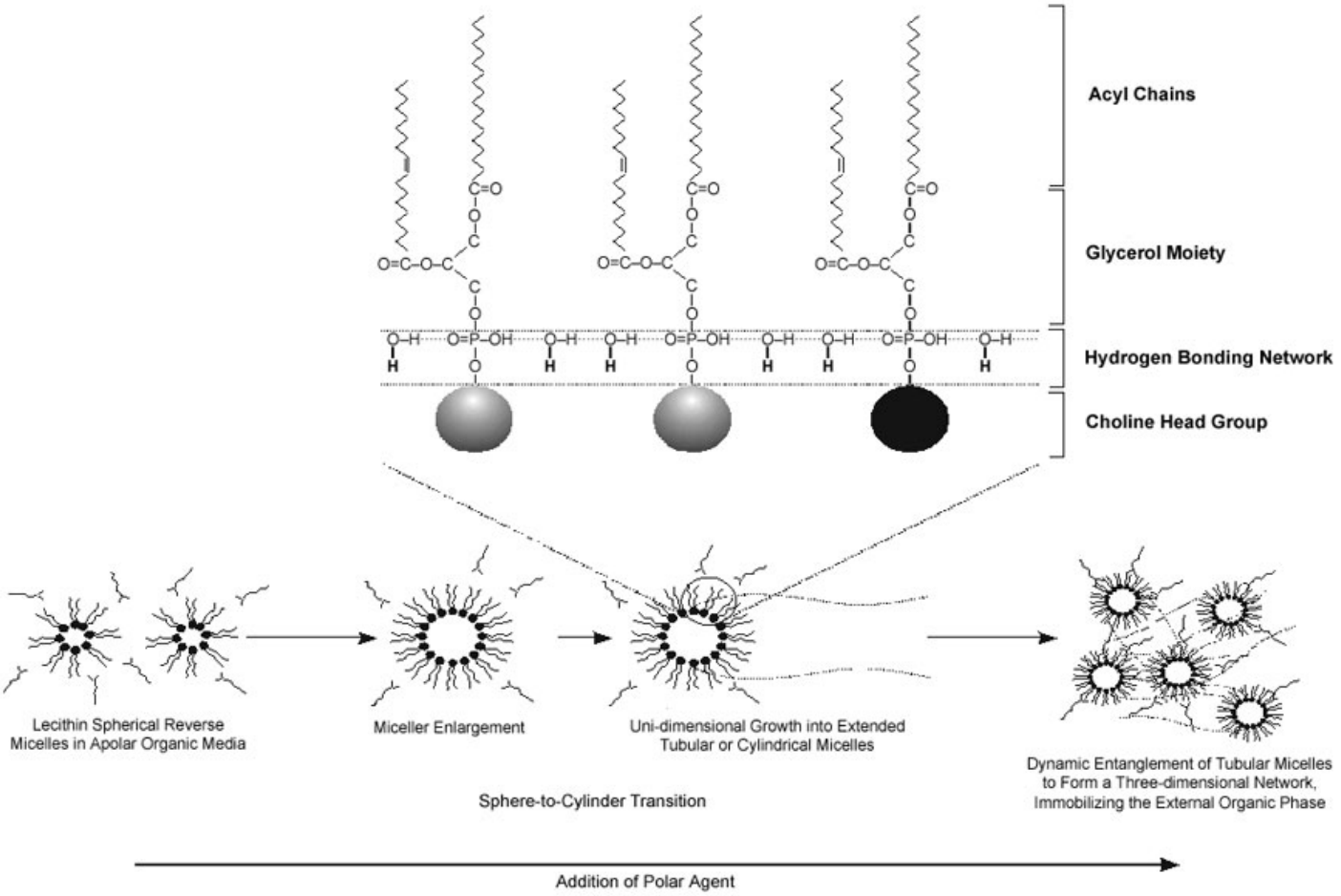

Figure 2. Formation of a three-dimensional network of reverse cylindrical micelles in lecithin organogel, involving hydrogen bonding between lecithin and polar solvent molecules. Data are modified from Shchipunov YA and Shumilina EV30 and Lawrence MJ and Reed GD.81

lecithin molecules and, in turn, to the 1-dimensional uniaxial growth of lecithin reverse micelles. Further increase in the amount of polar additive results in the formation of flexible, long tubular micelles of 2.0 to 2.5 nm radius and hundreds to thousands of nanometers in length.[53,54] After reaching a critical length, these extended micelles begin to overlap, entangle themselves, and build up a transient 3-dimensional network.[24,26,58-62] This marks a crossover to a system characterized by increased viscosity and viscoelastic properties. Instead of a low viscous solution, a jelly-like phase (ie, LO) is obtained. The LO thus obtained contains a considerable amount (~85 weight percentage) of external phase (ie, the organic liquid) entrapped in the spaces between the entangled reverse micelles. The hydrogen bonding network built up by molecules of polar additive and phosphate groups is also accompanied by stiffness of the phospholipid molecule in the region of phosphate group and glycerol residue, which stabilizes the micellar aggregates (Figure 2). In case of PLOs, the mechanism of gelling and the structural network may be related to the synergistic contribution of both phospholipids as well as polymeric cosurfactant molecules, in their respective hydrated states. However, to date no scientific reports have appeared related to the structural details of PLO gels.

The contribution of organic solvent as an external phase in the gelling process is also indicated, as it influences the micellization of lecithin monomers. The requirement of the specific organic solvents for the purpose indicates that it provides appropriate environment for the intermolecular and intramolecular interactions in gelator molecules and the organic solvent molecules. In terms of the molecular-shape approach developed by Israelachvili et al,[63] the aggregate transformations (ie, sphere-to-cylinder transformations) are determined by a change of a curvature for the amphiphile monolayer. In particular, the effects of polar solvent introduced into spherical lecithin micelles may be associated with an increase in the cross-sectional area of the lecithin polar region in which the solvent is arranged. The shape of the hydrated molecules is close to a cylinder.[64] This shape leads to packing

constraints in the spherical micelles that are diminished through the transition into the cylindrical ones with a smaller curvature.

Characterization of Organogels

In contrast to the ease of preparation, characterization of LOs is relatively complicated on account of their interior structural design build-up on the self-associated supramolecules. These microstructures, the result of varied polar-nonpolar interactions, are highly sensitive and pose difficulties in the investigative studies. However, different characterization studies are extremely useful while investigating the potential applications of organogel systems as a topical vehicle. For instance, it has been reported that many of the physicochemical properties of LOs viz rheological behavior, physical and mechanical stability, and drug release behavior are dependent upon how molecules arrange themselves to provide the specific structural network within the organogel system.[20-22]

Structural Features

An efficient characterization methodology for any organogel system begins with its structural elucidation. Molecular architecture of LOs has been evaluated using a wide range of different techniques over the years, but a complimentarity of methods is generally required to fully characterize these systems. The isotropic nature and the optical clarity of LOs makes their study feasible by various spectroscopic techniques, namely, nuclear magnetic resonance (NMR) spectroscopy (ie, ^{2}H NMR, ^{31}P NMR), and Fourier transformed infrared (FTIR) spectroscopy. Luisi et al[20,21] employed ^{2}H NMR and ^{31}P NMR spectroscopy for studying the phase behavior of soybean LOs to establish the absence of birefringence and liquid crystalline phases. Various techniques have been employed to find the nature of binding forces responsible for association of monomers to form self-assembled structures, and FTIR spectroscopy has been found to be successful in establishing the hydrogen bonding as one of the major driving forces for the self-assembly of organogelator molecules in the organic solvents.[24,25,28,30,65] The knowledge of molecular packing within the organogel network has been obtained using scanning and transmission electron microscopies (SEM and TEM),[20] dynamic and static light scattering (elastic or quasielastic light scattering techniques QLS),[21,22,66-68] small-angle neutron scattering (SANS), small-angle X-ray scattering (SAXS), and atomic force microscopy (AFM).[21,22,69-72] These techniques allow many features of organogels to be deciphered at 1 to 1000 nm scale. Recently, SAXS and AFM have become important tools in determining the molecular arrangement of long range structures such as LOs, along with the absolute quantities such as diameter, length, or topology in gels.[72,73] The scattering information (SAXS and SANS measurements) on organogels, which could be obtained even in undiluted samples (ie, without disturbing the originality of the system), combined with mathematical analysis provides such information as static correlation length "ξ," mesh size of the network (or the number density of entanglements 'ν'), diffusion coefficients, and flexibility of the fibrous network, along with the structural features of the cross-sections of LOs.[20,21,70,71,74,75] The direct visualization of the gel in its naïve state is possible using AFM, which allows observing the microstructures of the fibrous network throughout the gel mass. It also provides structural details on the larger length scales (ie, where micellar fibers or chains aggregate into large sized bundles). Thus, multiple instrumental techniques based on microscopy along with spectroscopic and scattering analysis can help reveal the structural details of the lecithin organogel systems.

Rheological Behavior

For any vehicle to be used for topical drug delivery applications, it is essential to study its rheological behavior. The latter is important for its efficacy in delivering the molecules onto or across the skin site. The critical parameters such as spreadibility, adhesiveness (property related to bioadhesion on skin site), cohesiveness (which indicates structural reformation following application of shear stress), and gel consistency need to be modified in a favorable manner. LOs have been studied extensively for their rheological attributes and have been determined to be viscoelastic in nature.[26,29,30,62] These systems, prior to gelling (ie, before the addition of polar phase) exhibit Newtonian behavior but follow Maxwell's rheological (viscoelastic) behavior on addition of the polar phase.[30] It has been reported that the Maxwell rheology model holds good for systems with supramolecular organization, consisting of temporal 3-dimensional network of entangled micelles.[26,30,47,61] Also, the desired viscoelastic property can be managed by modifying the various formulation components (ie, selecting the type of organic solvent, concentration of gelator or cosurfactant, or the type or amount of polar agent), which significantly influence the structural stability and rheological behavior of organogels. For example, Scartazzini and Luisi performed the dynamic shear viscosity (denoted as [ETA*]) determinations of various soy lecithin organogel systems, prepared using different types of organic solvents (eg, linear and cyclic alkanes, amines). The higher values of [ETA*] obtained using linear alkanes were related to the higher state of structural organization in LOs.[21,22] Similarly, Schurtenberger et al[76] found that increasing the gelator concen-

tration leads to an increase in the viscosity and in turn the gel strength of a soy lecithin/IPP organogel matrix.

Phase Transition Temperatures

The phase behavior of organogels varies on changing temperature conditions.[21] The phase transition temperature (PTT) (ie, sol-to-gel, T_{SG}, or gel-to-sol, T_{GS}) gives an insight into the nature of microstructures that form the gelling cross-linked network. The phase transition temperatures also help in optimizing the organogel composition. In one such study, concentration of gelator in a given LO formulation was optimized by monitoring the PTTs of the organogel.[77] PTT also reveals the microstructural homogeneity of the prepared organogel system. For example, a narrow PTT range (ie, 3ºC-5ºC) is indicative of homogenous microstructures within the gel.[77,78] For the determination of PTTs, hot stage microscopy (HSM) and high sensitivity differential scanning calorimetry (HSDSC) have been reported to be useful as accurate and sensitive techniques.[21,23,77] However, the inverse flow method, a simple technique based on visual observations has also been employed.[79]

Water Content

Water content of an organogel system is critical, as the water loss by evaporation can lead to consequent decrease in viscosity thus affecting the gel stability. Nastruzzi and Gambri[80] have proposed near-infrared (NIR) spectroscopy as a simple, rapid, and nondestructive technique for determining the water content in LOs. The researchers performed NIR studies on lecithin/IPP/water organogel system by measuring the water absorption in the NIR region (1800–2200 nm). In this region, water shows a strong absorption peak at 1918 nm due to H-O-H stretching overtones, which are easily detectable and quantifiable. A calibration curve was generated using 1 mL samples of lecithin gel containing different amounts of water (n_w ranging between 0.5 and 3), using as blank a lecithin solution (at same concentration) in IPP without any water addition. Various prepared organogel samples were then analyzed for water content after different lengths of time. Satisfactory results in terms of reproducibility and system precision were obtained. In addition, this technique has also been proposed to be useful to identify phase separation (syneresis) in the prepared organogel formulations.

Topical Drug Delivery Applications of Lecithin Organogel-based Systems

LOs have generated considerable interest over the years as a potential topical drug delivery vehicle.[81] The coexistence of organic and aqueous phase by means of a structurally well-defined micellar network of phospholipids, a large interfacial area, and the possibility to entrap solutes within the gel matrix, along with long-term stability, makes them useful for a variety of applications. The topical applications of various drugs containing LO systems have been demonstrated to significantly enhance the skin permeation and absorption of both lipophilic and hydrophilic substances. The organized microstructural matrix, amphiphilicity, supersolubilizing capacity and interaction of the biolipids with skin tissues are some of the major promoting factors for an enhanced transport of drug molecules into or across the skin. Therapeutic compounds of different chemical and physicochemical background such as muscle relaxants, steroids, hormones, analgesics, antiemetics, cardiovascular agents, antithyroid drugs, and some macromolecules have been incorporated in the LOs with some very encouraging results.

Dermal Drug Delivery

Enhanced skin penetration and site-specific delivery of bioactives into the deeper layers of skin has been achieved employing organogels as a topical vehicle. Topical administration of an LO formulation containing therapeutically effective amount of digoxin has been found to be effective for the treatment of muscle spasm as well as in the management of peripheral or neuropathic pain.[82] Friedman has reported the subcutaneous delivery of cyclobenzaprin, a muscle relaxant, using LO as a topical vehicle.[83] The muscle relaxant administered in lecithin-IPM organogel is shown to provide immediate relief of pain resulting from bruxism (tooth grinding) and tooth clenching. Remarkably high skin penetration of phytosphingosine or sphingosine, a protein kinase C (PKC) inhibitor, incorporated in LO gel, has been reported.[84] The prepared organogel-based formulation was found to effectively inhibit the PKC activity in the skin and mucocutaneous junction, thus useful in the topical treatment of keloids and hypertrophic or burn scars. It was also shown to be effective in psoriasis, psoriatic arthritis, or any other inflammatory condition of the skin that involves PKC. In a similar study, topical application of phytosphingosine (0.1% to 7.5% wt/wt), formulated as PLO employing lecithin, IPP, ethanol, water, and pluronic F-127, is noted to be effective for the treatment of tendons affected by tenosynovitis in carpal tunnel syndrome.[85]

A recent United States patent granted to Crandall (2001), describes the PLO formulation for the effective delivery of antipsoriatic agents and for drugs used in eczema.[51] The patented formulation is composed of lecithin (containing ≥ 95% phosphatidylcholine) dissolved in IPP or IPM to

achieve a final concentration range of 20% to 40% vol/vol, a suitable amount of pluronic, and water with or without short chain alcohol. The composition is also proven to be effective for moisturizing and rejuvenating the keratinous tissue including skin, hair, and fingernails. Padilla et al[86] have also described the efficacy of PLOs for topical use of local anesthetics and nonsteroidal anti-inflammatory drugs (NSAIDs). It is inferred that for those orofacial disorders that are regional, near the surface, and chronic, the LOs are more advantageous over systemic administration of drugs because of the rapid onset of action with low side-effect profile. In one such study, significant improvement in the analgesic action of ketamine hydrochloride and amitryptiline hydrochloride formulated in LO has been reported.[87] The use of these compounds for topical pain relief is otherwise limited owing to their poor skin penetration and partitioning properties. Similarly, a PLO gel containing 3% to 30% extract of Arnica Montana in combination with topical analgesic or systemic opioid is proven to be useful in reducing inflammation and providing relief from both peripheral and central pain.[88] Flores et al[89] have prepared a ketamine PLO gel with an aim to improve the analgesic effect of ketamine. The use of ketamine is otherwise restricted owing to the associated systemic side effects along with extensive first pass metabolism. Developed PLO gel of ketamine, when applied directly to the site of application alleviates the sympathetic or neuropathic pain and also avoids the side effects associated with the drug. Selective delivery of an anti-androgen compound into the pilosebaceous units has also been reported.[90] An organogel-based (LO or PLO) formulation containing extract of saw palmetto (having antiandrogen agent as a principal constituent) along with acyl carnitine and coenzyme Q has been reported as an effective formulation for the topical treatment of androgenic alopecia. LOs have also been found to be an excellent matrix for the delivery of a macromolecule with a molecular weight of 33 000 daltons.[91] PLO gel containing anti-inflammatory macromolecule bromelain (15%) along with capsaicin (0.025%) has been found to be an effective anti-inflammatory composition. Direct application of this PLO gel at the site of inflammation has been found to be useful for treating a variety of inflammatory indications.

Transdermal Drug Delivery

Organogel systems have also been used as a matrix for transdermal transport of different therapeutic compounds. Willimann and Luisi[32] were the first to study LOs as matrix systems for transdermal transport of drugs. The authors investigated the transdermal delivery of scopolamine (an active drug against motion sickness) and broxaterol (a bronchodilatory agent) employing lecithin gel composed of 200 mM of lecithin in a biocompatible solvent IPP, in 2 separate studies. Scopolamine and broxaterol was solubilized in the gel up to a concentration of 40 mg/mL and 75 mg/mL, respectively. Significantly higher transdermal flux of scopolamine in lecithin-IPP gel was observed in comparison to that of drug in aqueous solution. Analogous results were obtained with broxaterol incorporated in lecithin organogels.

Later, Willimann and coworkers[33] investigated these systems for their role in trans-skin permeation of drugs by employing different organic solvents. LOs were prepared employing soybean lecithin with IPP and cyclooctane. The solubility of various drugs such as nifedipine, clonidine, scopolamine, and broxaterol was noted to be increased in lecithin-IPP solution compared with the drug solubility in IPP alone, suggesting the solubility enhancing properties of the organogels. The IPP-based lecithin gel exhibited higher transdermal transport efficiency than that of cyclooctane lecithin gel. This difference in trans-skin delivery rate could be attributed to the penetration enhancing property of the IPP. The authors, in their study, also suggested the transdermal transport of amino acids and peptides using LOs. Bhatnagar and Vyas[34] have investigated the trans-skin permeability of propranolol hydrochloride, a poorly permeable and water-soluble drug incorporated in LOs, across human cadaver skin. Significantly enhanced (~10 times higher) permeability of micellar-borne drug across the human skin was observed when employing drug in 200 mM lecithin/iso-octane/water organogel system in comparison to that of pure drug in solution form or emulsified in the petroleum jelly. Permeation enhancing effect of the lecithin gel was attributed to the vectoring properties of the reverse micelles. It was suggested that the micellar entities being small in size and with hydrocarbon sheath might had been received by the skin barrier as hydrophobic entities, which were allowed for closer interaction with skin barrier leading to enhanced permeation of the drug molecules.

The transdermal delivery and efficacy of various NSAIDs formulated in LOs has also been investigated. In a recent study on indomethacin and diclofenac incorporated in LO gel (IPP, 10 mL; soy lecithin, 1.9 g; water, 135 μL), the transdermal delivery of both the drugs was found to be higher using LO vis-à-vis drug in IPP alone as vehicle.[35] In another report, Grace et al[92] have assessed the efficacy and safety of 2% diclofenac in LO in the treatment of pain associated with mild to moderate osteoarthritis, and this novel topical formulation of diclofenac was found to possess a remarkable therapeutic value. Some reports also indicate the use of LOs for the topical administration of systemic hormones. The transdermal delivery of progesterone, incorporated in LOs, has been studied with an aim to minimize the bioavailability fluctuations associated with its

peroral administration.[93] Also, a transdermal formulation of testosterone has been successfully prepared by incorporating the therapeutically effective amounts of micronized testosterone in a PLO gel.[94]

Ciribassi et al have reported the systemic absorption of fluoxetine hydrochloride through skin using PLO as a topical vehicle.[95] Fluoxetine hydrochloride incorporated in PLO gel was applied to the hairless portion of the pinnae of cats for its transdermal delivery. Plasma samples were obtained and analyzed for drug content. Results of the study showed that fluoxetine in a 15% wt/vol PLO gel absorbed through the skin into the systemic circulation. In another study, Nicardipine, a calcium channel blocker, because of its low dose, short half-life, and extensive first pass metabolism, has been incorporated in a LO system in order to achieve systemic absorption through topical route.[96] Hoffmann et al[97] have investigated the transdermal delivery of methimazole incorporated in LO, in feline patients. Authors assessed the serum thyroxine concentrations and clinical response following topical administration of the drug. Significant reduction in serum thyroxine levels was noted in all the cases with almost 100% reduction in the side effects associated with oral methimazole treatment. The transdermal delivery of aromatic tetra-amidines (compounds with antitumor activity) has also been attempted using soy lecithin organogels.[80] The in vivo efficacy was determined in nude mice carrying xenografted tumor cells and was considered to be very encouraging. In another study on transdermal delivery potential of LOs, Bonina and coworkers[98] have formulated methyl nicotinate-lecithin-IPM organogel and tested in vivo with human subjects. The results showed rapid induction and intense persistence of methyl nicotinate-induced erythema. The solubilization of piroxicam, to increase its transdermal permeation rate, has also been attempted by incorporating the drug in an LO consisting of lecithin/IPM/water.[99] A significant inhibition of carrageenan-induced rat paw edema was observed with organogel formulation of piroxicam vis-à-vis marketed transdermal product after 3 hours. Thus, with the inflow of several research reports on the varied fundamental aspects of LOs, along with some promising results on the front of drug delivery, these systems can be seen as potential tools in the field of topical drug delivery applications (see Tables 3 and 4).

Safety and Skin Compatibility Studies

Lecithin-based organogel systems (ie, LO or PLO gels) are composed of pharmaceutically approved (nonimmunogenic and biocompatible) excipients. However, the level of surfactant and organic solvents in lecithin organogels is fairly high. Therefore, it is important to consider the safety and irritancy of the formulation on prolonged use. In this

Table 3. Topical Delivery of Therapeutic Substances Incorporated in Lecithin Organogels*

Organogel Formulation	Major Findings	Year	Reference
Lecithin (200 mM) IPP gel of broxaterol and scopolamine	Transdermal delivery of compounds	1991	32
Phosphatidylcholine (PC) gel in isopropyl palmitate (IPP) or cyclooctane	Investigated for transdermal transport of various drugs along with amino acids and peptides	1992	33
Propranolol hydrochloride in 200 mM lecithin/iso-octane organogel	Percutaneous delivery of compounds with poor permeability	1994	34
Soybean lecithin/IPP gels containing 10% to 20% short chain esters such as ethyl acetate or propyl acetate	Transdermal delivery of aromatic tetra-amidines for anticancer activity	1994	80
IPP-lecithin gel of diclofenac and indomethacin	Enhanced efficacy of NSAIDs administered through topical route	1999	35
Phytosphingosine or sphingosine lecithin organogel comprising soy PC, IPP, ethanol, and water	Treatment of scars	2001	84
Soy lecithin-isopropyl myristate (IPM) organogel containing ketamine hydrochloride and amitryptiline hydrochloride	Enhance skin penetration and partitioning of the drugs into the skin layers	2002	87
Nicardipine lecithin-IPM organogel	Enhanced skin permeation across guinea pig and human skin	2002	96
Methimazole in LO gel	Significant percutaneous absorption of methimazole	2002	97
LO gel of cardiac glycoside digoxin	Topical administration of the compound in LO gel was found to be effective for the treatment of muscle spasm	2003	82
Cyclobenzaprin in lecithin organogel (lecithin 10%-30%, IPM 10%-30%, water 30%-60%)	Topical formulation for bruxism	2003	83

*IPP indicates isopropyl palmitate; PC, phosphatidylcholine; NSAIDs, nonsteroidal antiinflammatories; IPM, isopropyl myristate; and LO, lecithin organogel.

Table 4. Topical Delivery of Therapeutic Substances in Pluronic Lecithin Organogels (PLO gels)

PLO Gel Formulation	Applications	Reference
Ketoprofen PLO gel	Administration of ketoprofen in PLO gel offered convenience, produced fewer side effects, and alleviated pain in a specific location	48
PLO gel of diclofenac, ibuprofen, ketamine	• Randomized, placebo-controlled study on lateral epicondylites employing diclofenac in PLO gel reduced pain and increased functional status. • Preparation also found to be effective treatment for osteoarthritis	49
PLO gel of ondansetrone	Ondansetrone in PLO gel exhibited dose-dependent attenuation of nociceptive and inflammatory effects of intradermally injected capsaicin in humans	50
Lecithin (20%-40% vol/vol) in isopropyl palmitate or isopropyl myristate containing suitable amount of pluronic and water with or without short chain alcohol	The components of PLO gel provide desired hydration state to the skin, thus effective in the treatment of eczema or psoriasis	51
Lecithin organogel in combination of pluronic F-127 (poloxamer 407) solution/cyclobenzaprin	Effective formulation for topical treatment of carpal tunnel syndrome	85
PLO formulation of local anesthetics and nonsteroidal antiinflammatories (NSAIDs)	Rapid onset of action, associated with low side-effect profile	86
PLO gel containing extract of Arnica Montana in combination with opioid	Effective treatment for pain management	88
Soy lecithin (18%-32% vol/vol) in isopropyl palmitate and pluronic F-127 (10%-40%)/ketamine	PLO gel maximizes the effectiveness of the ketamine, effectively alleviates neuropathic, sympathetic, and myofacial pain	89
Isopropyl palmitate and Poloxamer 407 containing PLO gel of saw palmetto extract	Selective delivery of antiandrogens into the pilosebaceous units for the treatment of androgenic alopecia	90
Bromelain (15%) and capsaicin in PLO gel	Excellent matrix for topical delivery of macromolecule	91
Hormones (eg, progesterone) in PLO gel	Transdermal delivery of hormone	93
Micronized testosterone in PLO gel	Systemic delivery of hormone	94
Fluoxetine hydrochloride incorporated in PLO gel	Systemic delivery of the compound in feline patients	95

context, skin (human skin) compatibility of the gels has been evaluated employing various techniques, before and after application with either IPP alone or with 200 mM lecithin-IPP gel.[33,35] No significant alterations in the skin were apparent after 3 days and stratum corneum was still intact. The irritation potential of LOs has been assessed by Dreher et al, by carrying out human skin irritation study.[36,37] For the same study, acute skin irritation was tested in as many as 151 volunteers in a 48-hour patch test. Results of the study showed very low acute irritation potential of LOs, as only 1% to 2% of the total volunteers showed a very slight erythema. The cumulative irritation test was also performed in order to assess the safety of organogels on long-term application. The parameter IT_{50} was used as an index for the safety level, which is the time of continuous exposure after which 50% of the population reached a cumulative irritation score of ≥ 5. Results indicated a very low cumulative skin irritation potential of LOs. A fairly high IT_{50} value (13 days) supports the suitability of LO-based gels as a topical vehicle for long-term applications. See Table 5 for a list of commercially available pluronic lecithin organogels.

Table 5. Commercially Available Pluronic Lecithin Organogels*

Therapeutic Category	Therapeutic Agents
Antiemetics	Dexamethasone, dimenhydrate, scopolamine
Muscle relaxants	Cyclobenzaprine, baclofen, buspirone
Neuropathy drugs	Clonidine, capsaicin, amitryptiline, gabapentin, phenytoin,
NSAIDs	Diclofenac, ibuprofen, ketoprofen, indomethacin,
Systemic analgesics	Acetaminophen, hydromorphone, morphine sulfate
Systemic hormones	Progesterone, testosterone

*NSAIDs indicates nonsteroidal antiinflammatories. Data from Stafford Pharmacy and Home Healthcare,[101] Maxima Pharmaceuticals Inc,[102] J. A. R. Pharmaceuticals Limited,[103] Drugs-r-us.org,[104] and Reed's RX Compounding Pharmacy.[105]

CONCLUSIONS AND FUTURE PROSPECTS

In the field of topical drug delivery, LOs have emerged as one of the most potential carrier systems. In contrast to other lipid-based systems such as vesicular systems, (liposomes and niosomes), lecithin organogel systems may prove to have an edge in terms of efficacy, stability, and most important, technological feasibility. Moreover, the topical delivery of new biotech- generated proteinaceous molecules in the protective nonpolar microenvironment of these systems may help protect these sensitive macromolecules from degradation during transport to the desired site. The efforts, hitherto made, have been successful in highlighting the prospects of these systems for diverse applications. Now what more is desired are the detailed investigations on the structural and functional aspects of these systems. The influence of the organogel components, such as cosurfactant, organic solvent, or other additives and their concentration, on the kind of microstructures that get generated within the system as well as on the topical drug transport mechanism should be investigated. Development of standards for the raw materials as well as for the processed products also needs effort. Thus, amidst the increasing opportunities and challenges, the LOs may prove to be highly promising systems in realizing the drug delivery objectives while scientists are desperately trying for more viable alternatives vis-à-vis existing carrier systems.

ACKNOWLEDGMENTS

Authors are thankful to the University Grants Commission, New Delhi, India, for providing financial assistance to carry out the research work on lecithin organogels (Grant No UGC. F. N. 7-3/2002[SR-I]).

REFERENCES

1. Barr M. Percutaneous absorption. *J Pharm Sci.* 1962;61:395–409.

2. Hadgraft J, Guy RH. In: *Transdermal Drug Delivery: Development Issues and Research Initiatives*. New York, NY: Marcel Dekker, 1989.

3. Asmussen B. Transdermal therapeutic systems - actual state and future developments. *Methods Find Exp Clin Pharmacol.* 1991;13:343–351.

4. Hadgraft J. Recent developments in topical and transdermal delivery. *Eur J Drug Metab Pharmacokinet.* 1996;21:165–173.

5. Cevc G. Drug delivery across the skin. *Expert Opin Investig Drugs.* 1997;6:1887–1937.

6. Hadgraft J. Passive enhancement strategies in topical and transdermal drug delivery. *Int J Pharm.* 1999;184:1–6.

7. Mitchell DJ, Ninham BW. Micelles, vesicles and microemulsions. *J Chem Soc Faraday Trans II.* 1981;77:601–629.

8. Cevc G, Paltauf E. In: *Phospholipid Characterization, Metabolism and Novel Biological Applications*. Champaign, IL: AOCS Press, 1995.

9. Attwood D, Florence AT. In: *Surfactant Systems: Their Chemistry, Pharmacy and Biology*. London, UK: Chapman and Hall, 1983.

10. Kreuter J. In: *Colloidal Drug Delivery Systems*. New York, NY: Marcel Dekker, 1994.

11. Lawrence MJ. Surfactant systems: microemulsions and vesicles as vehicles for drug delivery. *Eur J Drug Metab Pharmacokinet.* 1994;19:257–269.

12. Schwarz G. Basic kinetics of binding and incorporation with supramolecular aggregates. *Biophys Chem.* 1987;26:163–169.

13. Lehn MJ. Supramolecular chemistry: scope and perspectives (Molecules, Supramolecules and Molecular devices). *Angew Chem Int Ed Engl.* 1988;27:89–112.

14. Zarif L. Elongated supramolecular assemblies in drug delivery. *J Control Release.* 2002;81:7–23.

15. Schmid MH, Korting HC. Liposomes: a drug carrier system for topical treatment in dermatology. *Crit Rev Ther Drug Carrier Syst.* 1994;11:97–118.

16. Abrol S, Trehan A, Katare OP. Formulation, characterization, and in vitro evaluation of silymarin loaded lipid microspheres. *Drug Deliv.* 2004;11:185–191.

17. De Miguel I, Imbertie L, Rieumajou V, Major M, Kravtzoff R, Betbeder D. Proofs of the structure of lipid coated nanoparticles (SMBV) used as drug carriers. *Pharm Res.* 2000;17:817–824.

18. Donatella P, Cinzia AV, Steven N, Giovanni P, Massimo F. Lecithin microemulsions for the topical administration of ketoprofen: percutaneous adsorption through human skin and in vivo human skin tolerability. *Int J Pharm.* 2002;244:21–31.

19. Stamatis H, Xenakis A. Biocatalysts using microemulsion-based polymer gels containing lipase. *J Mol Catal, B Enzym.* 1999;6:399–406.

20. Scartazzini R, Luisi PL. Organogels from lecithins. *J Phys Chem.* 1988;92:829–833.

21. Schurtenberger P, Scartazzini R, Magid LJ, Leser ME, Luisi PL. Structural and dynamic properties of polymer-like reverse micelles. *J Phys Chem.* 1990;94:3695–3701.

22. Capitani D, Segre AL, Dreher F, Walde P, Luisi PL. Multinuclear NMR investigation of phosphatidylcholine organogels. *J Phys Chem.* 1996;100:15211–15217.

23. Walde P, Giuliani AM, Boicelli CA, Luisi PL. Phospholipid-based reverse micelles. *Chem Phys Lipids.* 1990;53:265–288.

24. Shumilina EV, Khromova Y, Shchipunov YA. A study of the structure of lecithin organic gels by Fourier-transform IR spectroscopy. *Zhurnal Fizicheskoi Khimii.* 2000;74:1210–1219.

25. Cirkel P, Koper GJM. The structure of lecithin organogels. *Proceedings of Conference on Colloid Chemistry: Memoriam Aladar Buzagh*; September 23-26, 1996; Budapest, Hungary, Hungarian Chemical Society; 1996;36–39.

26. Shchipunov YA. Lecithin organogel: a micellar system with unique properties. *Colloids Surf A Physicochemical and Engineering Aspects.* 2001;183-185:541–554.

27. Shchipunov YA. Self-organizing structures of lecithin. *Usp Khim.* 1997;66:328–352.

28. Mezzasalma SA, Koper GJM, Shchipunov YA. Lecithin organogel as a binary blend of monodisperse polymer-like micelles. *Langmuir.* 2000;16:10564–10565.

29. Shchipunov YA. Lecithin organogels: rheological properties of polymer-like micelles formed in the presence of water. *Colloid J.* 1995;57:556–560.

30. Shchipunov YA, Shumilina EV. Lecithin bridging by hydrogen bonds in the organogel. In: *Materials Science & Engineering C 3.* 1995;43–50.

31. Shchipunov YA, Duerrschmidt T, Hoffmann H. End-to-end fusion of polymer-like micelles in the lecithin organogel under the action of an electric field. *Langmuir.* 2000;16:297–299.

32. Willimann H, Luisi PL. Lecithin organogels as matrix for transdermal transport of drugs. *Biochem Biophys Res Commun.* 1991;177:897–900.

33. Willimann H, Walde P, Luisi PL, Gazzaniga A, Stroppolo F. Lecithin organogels as matrix for transdermal transport of drugs. *J Pharm Sci.* 1992;81:871–874.

34. Bhatnagar S, Vyas SP. Organogel-based systems for transdermal delivery of propranolol. *J Microencapsul.* 1994;2:431–438.

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

36. Dreher F, Walde P, Luisi PL, Elsner P. Human skin irritation of a soybean lecithin microemulsion gel and of liposomes. In: *Proceedings Int Symp Control Rel Bioact Mater 22 Langmuir.* 1995;640–641.

37. Dreher F, Walde P, Luisi PL, Elsner P. Human skin irritation studies of a lecithin microemulsion gel and of liposomes. *Skin Pharmacol.* 1996;9:124–129.

38. Hanahan DJ. In: *A Guide to Phospholipid Chemistry.* New York, NY: Oxford University Press, 1997.

39. Wendel A. In: *Kirk-Othmer Encyclopedia of Chemical Technology.* New York, NY: John Wiley & Sons, 1995;192–193.

40. Schneider M. Industrial production of phospholipids-lecithin processing. *Lipid Technology.* 1997;9:109–116.

41. Shumilina EV, Khromova Y, Shchipunov YA. Lecithin organogels: the effect of phosphatidylethanolamine additives. *Colloid J.* 1997;59:514–518.

42. Moore J. Final report on the safety assessment of octyl palmitate, cetyl palmitate and isopropyl palmitate. *J Am Coll Toxicol.* 1982;1:13–35.

43. Sato K, Sugibayashi K, Morimoto Y. Effect and mode of action of aliphatic esters on the in-vitro skin permeation of micorandil. *Int J Pharm.* 1988;43:31–40.

44. Arellano A, Santoyo S, Martin C, Ygartua P. Influence of propylene glycol and isopropyl myristate on in vitro percutaneous penetration of diclofenac sodium from carbopol gel. *Eur J Pharm Sci.* 1999;7:129–135.

45. Parsaee S, Sarbolouki MN, Parnianpour M. In vitro release of diclofenac diethylammonium from lipid-based formulations. *Int J Pharm.* 2002;241:185–190.

46. Shchipunov YA, Shumilina EV. Lecithin organogels: role of polar solvent and nature of intermolecular interactions. *Colloid J.* 1996;58:117–125.

47. Shchipunov YA, Hoffmann H. Lecithin organogels with polar additives: rheological studies. *Colloid J.* 1998;60:794–799.

48. Berti JJ, Lipskys JJ. Transcutaneous drug delivery: a practical review. *Mayo Clin Proc.* 1995;70:581–586.

49. Burnham R, Gregg R, Healy P, Steadward R. The effectiveness of topical diclofenac for lateral epicondylitis. *Clin J Sport Med.* 1998;8:78–81.

50. Giordano J, Daleo C, Sacks SM. Topical ondansetron attenuates nociceptive and inflammatory effects of intradermal capsaicin in humans. *Eur J Pharmacol.* 1998;354:R13–R14.

51. Crandall WT, inventor. *Topical moisturizing composition and method*. US Patent 6 316 428. November 13, 2001.

52. Collett JH, Popli H, Kibbe AH, ed. Poloxamer. In: *Handbook of Pharmaceutical Excipients.* 3rd ed. London, UK: Pharmaceutical Press, 2000;386–388.

53. Shchipunov YA, Schmiedel P. Phase behavior of lecithin at the oil/water interface. *Langmuir.* 1996;12:6443–6445.

54. Shchipunov YA, Schmiedel P. Electrorheological phenomena in lecithin-decane-water mixtures. *J Colloid Interface Sci.* 1996;179:201–206.

55. Shchipunov YA, Hoffmann H. Growth, branching and local ordering of lecithin polymer-like micelles. *Langmuir.* 1998;14:6350–6360.

56. Shchipunov YA, Shumilina EV, Ulbricht W, Hoffmann H. The branching of reversed polymer-like micelles of lecithin by sugar-containing surfactants. *J Colloid Interface Sci.* 1999;211:81–88.

57. Shchipunov YA, Durrschmidt T, Hoffmann H. Electrorheological effects in lecithin organogels with water and glycerol. *J Colloid Interface Sci.* 1999;212:390–401.

58. Shchipunov YA, Shumilina EV, Hoffmann H. Lecithin organogels with alkylglucosides. *J Colloid Interface Sci.* 1998;199:218–221.

59. Shchipunov YA, Shumilina EV, Hoffmann H. Lecithin organogels with n-alkyl-D-glucosides and n-alkyl-D-lactobionamide. *Colloid Polym Sci.* 1998;276:368–372.

60. Shchipunov YA, Hoffmann H. Thinning and thickening effects induced by shearing in lecithin solutions of polymer-like micelles. *Rheologica Acta.* 2000;39:542–553.

61. Voit AV, Shchipunov YA. Dynamics of polymer-like lecithin micelles - rheological measurements. *Colloid J.* 2000;62:424–430.

62. Shchipunov YA, Mezzasalma SA, Koper GJM, Hoffmann H. Lecithin organogel with new rheological and scaling behavior. *J Phys Chem B.* 2001;105:10484–10488.

63. Israelachvili JN, Mitchell DJ, Ninham BW. Theory of self assembly of hydrocarbon amphiphiles into micelles and bilayers. *J Chem Soc Faraday Trans II.* 1976;72:1525–1568.

64. Seddon JM. Structure of the inverted hexagonal (H_{11}) phase and non-lamellar phase transitions of lipids. *Biochim Biophys Acta.* 1990;1031:1–69.

65. Suzuki M, Nakajima Y, Yumoto M, Kimura M, Shirai H, Hanabusa K. In situ organogelation at room temperature: direct synthesis of gelators in organic solvents. *Org Biomol Chem.* 2004;2:1155–1159.

66. Schurtenberger P, Peng Q, Leser ME, Luisi PL. Structure and phase behaviour of lecithin-based microemulsions: a study of chain length dependence. *J Colloid Interface Sci.* 1993;156:43–51.

67. Shioi A, Harada M, Tanabe M. Static light scattering from oil-rich microemulsions containing polydispersed cylindrical aggregates in sodium bis(2-ethylhexyl) phosphate system. *J Phys Chem.* 1995;99:4750–4756.

68. Aboofazeli R, Barlow DJ, Lawrence MJ. Particle size analysis of concentrated phospholipid microemulsions. I. Total intensity light scattering. *AAPS PharmSci.* 2000;2:E13.

69. Zemb TN, Barnes IS, Derian PJ, Ninham BW. Scattering as a critical test of microemulsion structural models. *Prog Colloid Polym Sci.* 1990;81:20–29.

70. Terech P, Weiss RG. Low molecular mass gelators of organic liquids and the properties of their gels. *Chem Rev.* 1997;97:3133–3159.

71. Simmons BA, Taylor CE, Landis FA, McPherson GL, Schwartz DK, Moore R. Microstructure determination of AOT + Phenol organogels utilizing small-angle X-ray scattering and atomic force microscopy. *J Am Chem Soc.* 2001;123:2414–2421.

72. Gronwald O, Snip E, Shinkai S. Gelators for organic liquids based on self-assembly: a new facet of supramolecular and combinatorial chemistry. *Curr Opinion Colloid Interface Sci.* 2002;7:148–156.

73. Abdallah DJ, Sirchio SA, Weiss RG. Hexatriacontane organogels. The first determination of the conformation and molecular packing of a low-molecular mass organogelator in its gelled state. *Langmuir.* 2000;16:7558–7561.

74. van Esch JH, Feringa BL. New functional materials based on self-assembling organogels: from serendipity towards design. *Angew Chem Int Ed Engl.* 2000;39:2263–2266.

75. McAllister K, Sazani P, Adam M, et al. Polymeric nanogels produced via inverse microemulsion polymerization as potential gene and antisense delivery agents. *J Am Chem Soc.* 2002;124:15198–15207.

76. Schurtenberger P, Scartazzini R, Luisi PL. Viscoelastic properties of polymerlike reverse micelles. *Rheologica Acta.* 1989;28:372–381.

77. Jibry N, Heenan RK, Murdan S. Amphiphilogels for drug delivery: formulation and characterization. *Pharm Res.* 2004;21:1852–1861.

78. Terech P. Kinetics of aggregation in steroid derivative/cyclohexane gelifying system. *J Colloid Interface Sci.* 1985;107:244–255.

79. Couffin-Hoarau A-C, Motulsky A, Delmas P, Leroux J-C. *In situ*-forming pharmaceutical organogels based on the self-assembly of L-Alanine derivatives. *Pharm Res.* 2004;21:454–457.

80. Nastruzzi C, Gambari R. Antitumor activity of (trans)dermally delivered aromatic tetra-amidines. *J Control Release.* 1994;29:53–62.

81. Lawrence MJ, Rees GD. Microemulsion-based media as novel drug delivery systems. *Adv Drug Deliv Rev.* 2000;45:89–121.

82. Charles L, Matthew D, inventors. *Cardiac glycosides for treating muscle pain and spasm*. US patent appl publ 20030229029. December 11, 2003.

83. Friedman M, inventor. *Treatment of bruxism*. US patent 6 632 843. October 14, 2003.

84. Crandall WT, inventor. *Method for topical treatment of scars with protein kinase C inhibitors*. US patent 6 306 383. October 23, 2001.

85. Crandall WT, inventor. *Method for topical treatment of carpal tunnel syndrome*. US patent appl publ 20020164389. November 7, 2002.

86. Padilla M, Clark GT, Merill RL. Topical medications for orofacial pain: a review. *J Am Dent Assoc.* 2000;131:184–195.

87. Ford PR, inventor. *Topical pain relief composition and carrier*. US patent appl publ 20020028789. March 7, 2002.

88. Archer HK, Pettit MS, inventors. Analgesic and antiphlogistic compositions and therapeutic wrap for topical delivery. PCT Int Appl WO2000045796. February 4, 2000.

89. Flores JA, Crowley KL, inventors. *Process for the preparation of ketamine ointment*. US patent 5 817 699. October 6, 1998.

90. Crandall WT, inventor. *Composition and method for topical treatment of androgenic alopecia*. US patent appl publ 20030049336. March 13, 2003.

91. Crandall WT, inventor. *Transdermal transport of molecules*. PCT Int Appl WO9803641. January 29, 1998.

92. Grace D, Rogers J, Skeith K, Anderson K. Topical diclofenac versus placebo: a double blind, randomized, clinical trial in patients with osteoarthritis of the knee. *J Rheumatol.* 1999;26:2659–2663.

93. Shippen E. Progesterone organogel for premenstrual dysphoric disorder. *J Am Acad Child Adolesc Psychiatry.* 2001;40:262–263.

94. Kryger A, inventor. Topical testosterone formulations. PCT Int Appl WO2002055020. July 18, 2002.

95. Ciribassi JL, Luescher A, Pasloske KS, Robertson-Plouch C, Zimmerman A, Kaloostian-Whittymore L. Comparative bioavailability of fluoxetine after transdermal and oral administration to healthy cats. *Am J Vet Res.* 2003;64:994–998.

96. Aboofazeli RZ, Zia H, Needham TE. Transdermal delivery of nicardipine: an approach to in vitro permeation enhancement. *Drug Deliv.* 2002;9:239–247.

97. Hoffman SB, Yoder AR, Trepanier LA. Bioavailability of transdermal methimazole in a pluronic lecithin organogel (PLO) in healthy cats. *J Vet Pharmacol Ther.* 2002;25:189–193.

98. Bonina FP, Montenegro L, Scrofani N, et al. Effects of phospholipids based formulations on in vitro and in vivo percutaneous absorption of methyl nicotinate. *J Control Release.* 1995;34:53–63.

99. Agrawal GP, Juneja M, Agrawal S, Jain SK, Pancholi SS. Preparation and characterization of reverse micelle based organogels of piroxicam. *Pharmazie.* 2004;59:191–193.

100. Cadden B. Pharmaceutical compounding in pain medicine. *NEPA Newsletter.* 2000. Available at: http://www.ampainsoc.org/societies/nepa/news1_winter00.htm. Accessed: 26 July, 2004

101. Stafford Pharmacy and Home Healthcare. Information on natural hormone replacement therapy. 2003. Available at: http://www.stafford-pharmacy.com/NHRT.htm. Accessed: 26 July, 2004

102. Maxima Pharmaceuticals Inc. DiffusiMax and DiffusiMax Kit [Product Manual]. 2002. Edmonton, Canada: Maxima Pharmaceuticals Inc. Available at: http://www.maximapharmaceuticals.com/maxima1/pdf/WebReady_En_CM_052003.pdf. Accessed: 26 July, 2004

103. J. A. R. Pharmaceuticals Limited. Phlojel and Phlojel Ultra. 2003. Edmonton, Canada: J.A.R. Pharmaceuticals Ltd. Available at: http://www.phlojel.com. Accessed: 26 July, 2004

104. Drugs-r-us.org. Speciality treatments. 2004. Available at: http://www.drugs-r-us.org/treatments.html. Accessed: 26 July, 2004

105. Reed's RX Compounding Pharmacy Web site. Transdermal gels. 2004. Available at: http://www.Reedsrx.com/compounding/gel.htm. Accessed: 26 July, 2004