Organogels for the controlled delivery of bioactive agents

Preparation Characterization Applications Organogel Based Drug Delivery Systems

Gels are defined as three-dimensional crosslinked network structures with an immobilized, continuous solvent phase. If the immobilized solvent is an apolar liquid, the gels are referred as organogels. Organogels have recently seen an increasing trend as drug delivery vehicles due to greater patient compliance when using this form of treatment and their ability towards tailored release of incorporated bioactive agents. The current review gives an overview on different organogelators, the mechanisms of organogel formation, various characterization techniques and applications of organogels for the controlled delivery of bioactive agents.

Keywords: Organogel, Gel, Gelator, Drug delivery, Biocompatibility.

Introduction

Gels are quite often defined as three-dimensional networked structures, which have the ability to immobilize a liquid phase 1. Gelled systems have been used to develop various products both for daily activities and biomedical importance (e. g., drug delivery systems, toothpastes, shampoos) 2. This has been attributed to the easy handling of these products and the structuring ability of the gels. Gels are basically composed of two components, viz. a liquid phase (either polar or apolar) and a gelling agent (often referred to as a gelator, which undergoes interaction to form a three-dimensional structure) 1. Based on the type of interaction an gelator is undergoing so as to form three-dimensional networks, gels may be categorized either as physical or chemical gels 3. If the interaction amongst

gelator molecules involves covalent bonds then the gelled structure is regarded as a chemical gel whereas the formation of physical gels involve the physical interactions amongst the gelator molecules i. e. no covalent bond formation is involved 4. Often, it has been found that the physical gels are thermoreversible (i. e. it appears as gel below a critical temperature whereas it appears as sol above the critical temperature) and viscoelastic (shows solid-like behavior at lower shear rates whereas it starts to flow at higher shear rates) in nature 3, 5, for example, gelatin gels and sorbitan monooleate organogels. Depending on the polarity of the liquid immobilized within the networked structure, the gels may be regarded either as a hydrogel (polar solvent) or an organogel (apolar solvent) 4, 6. Owing to the solid-like consistency under normal conditions, various gels have been used as structuring agents in food and pharmaceutical industries. In the current review, attempts will be made to discuss about the different organogelators, the probable mechanisms of organogel formation, their characterization methods and applications in the development of the controlled drug delivery systems.

Organogelators

It is now clear that the organogels are semisolid systems that consist of an immobilized apolar solvent as the continuous phase. The components, which have the ability to undergo interaction amongst each other so as to form a networked structure having the capability to immobilize the apolar solvent, are regarded as organogelators. The organogelators, in general, undergo self-assembly under suitable conditions to give rise to organogels. n-alkanes (with carbon numbers of 24, 28, 32 and 36) are the simplest form of

organogelators 6. Some commonly used organogelators include 12-hydroxyoctadecanoic acid 7, sorbitan monostearate, sorbitan derivatives 8, steroids and their derivatives 4, bis-urea compounds and carbohydrate derivatives 9, amino acid derivatives 10. Of these, some commonly used organogelators will be discussed in brief.

Low molecular weight organogelators

Organogelators with a molecular weight < 3000 Da are categorized as low molecular weight organogelators (LMWOs). Many LMWOrs have been found by chance 11. Gel formation occurs due to the interaction of fibrous structures that develop due to the self-assembly of organogelators. Such organogelator fibres may be either solid (formed during the precipitation of the organogelators from the solution of organogelator in an apolar solvent) or fluid-filled (formed due to the entrapment of aqueous phase within the tubular reverse micelles) 12. Immobilization of the apolar solvent within the networked structures has been attributed to the surface tension acting amongst the molecules of organogelators and apolar solvent 4. It has been observed that gel forming solvents posses high surface tension and organogelator interactions with solvents lowers the surface tension and stabilizes the emulsion, eventually gel formation. The solubility profile of LMWOs in the apolar solvent and the presence of chiral centers in the organogelators also play an important role in organogel formation. Organogelators that form solid-fiber structures generally have chiral centers whereas organogelators involved in the formation of fluid-fibre structures usually lacks chiral centers within their chemical structure 13. Hydrogen bonding plays an important role in the development of organogels when

peptides, sugars and bis-urea compounds are used as organogelators, whereas van der Waals interactions play a dominant role when long-chain alkanes are used as organogelators. When cholesterol derivatives are used as organogelators, π-π stacking, vanderwaals interactions and non covalent interactions prevail in the organogels 14 Stability of the gel primarily dependent on the relative strength of intergelator van der waals interactions, hydrogen bonds and strength of solvent gelator interactions which are having linear relationship with the number of methylene units in alkyl chains of length greater than six 15.

Polymeric organogelators

Polymeric organogelators may either undergo chemical reaction or physical interactions so as to form a networked structure. The typical example includes, polyethylene organogels, commonly used in the preparation of colourless ointments which consists of low molecular weight polyethylene in mineral oil and is colorless in nature 4, 12. The other polymeric gelators include ethyl methacrylate and methacrylic acid copolymers 16, which have been used for the development of rectal suppositories 12.

Anthryl and anthraquinone derivative organogelators

These organogelators have an anthracene moiety in their structure, which helps in establishing π-π interactions with apolar solvents (e. g., alcohols, ethers, ketones, cyclohexane, DMSO and halogenated molecules). Common organogelators in this category include 2, 3-didecycloxytetracene (DDOA) and 2, 3-dihexadecycloxytetracene (DHDOT) 8, 17.

Sugar-based organogelators

These organogelators may be identified by the presence of α-glucose and an aromatic moiety in their structure 18-19. The formation of fiber-like structure results from the development of intermolecular hydrogen bonds amongst the sugar moieties with the subsequent exposure of the aromatic moieties to the apolar solvent. These compounds also have the capability to gel polar solvents such as water 18. The gelation mechanism depends on π-π interactions amongst the sugar moieties and the polar solvent. Examples of organogelators in this category include derivatives of methyl glycosides of 4, 6-obenzylidine 20 4″-butoxy-4-hydroxy-p-terphenyl-β-d-glucoside (BHTG)18. Of the different sugar based organogelators, 2, 4-Bis-O-benzylidene-D-sorbitol (DBS) is well known for its versatility of gelling wide range of organic solvents. The nitrogen group containing sorbital derived gelators also retained the property of gelation with less efficiency than their parent compound, DBS 21.

ALS organogelators

ALS organogelators are novel and very broad family of cholesterol based systems. The organogelators in this category have an aromatic moiety (A), which is bound to a steroidal group (S) through a linker group (L). Depending on the nature of A, L and S components of the ALS structure these can gelate a wide range of solvents including polar and apolar solvents, protic and aprotic solvents. The aromatic group of ALS organogelators can be polycyclic aromatic hydrocarbons, azobenzenes, porphyrins. The chemical natures of aromatic group, length and flexibility of linker group have a large impact on

their solubility which ultimately determines the gelation ability and self assembly of cholesterol based LMOGs. The stereochemistry at C-3 position of ALS molecules determines their solubility such as β-epimers are less soluble and form better gels than their counterparts, α-epimers 22. The mechanism of formation of a gelled structure may be attributed to dipole-dipole and van der Waals interactions. Cholesterol derivatives bearing benzylamine or a pyridine moiety are versatile organogelators and benzo-crown ether moiety behave as weak gelators. the other include cholesteryl 4-(2-anthryloxy) butanoate 23 etc., Dimeric cholesterol-based derivatives, A(LS)2 organogelators were reported 22. The aromatic moiety is sandwiched by two L and S groups. Both hydrogen bond formation and van der waals forces play key role in network formation.

Gemini organogelators

The dictionary meaning of the word Gemini is twin. Gemini organogelators essentially consist of two L-Lysine derivatives, which are linked to alkylene chains through amide bonds. A(LS)2 derivatives can be considered as Gemini orgnogelators. The property of organogelation is dependent on the length of the alkylene chains, as it has been found that there is a decrease in organogelation ability with a subsequent increase in alkylene chain length. Bis (N-lauroyl-t-lysine ethyl ester) oxyl amide is a classical gemini organogelator and has the ability to immobilize a large number of apolar solvents including alcohols, ketones, cyclic ethers and acetonitrile. Other examples include hexyl, decyl, dodecyl, 2-ethyl-1-hexyl and 3, 5, 5-trimethylhexyl derivatives of oxalyl amide 24.

Amino-acid based organogelators

Brosse et al. synthesized amino acid-based LMWOs, which were able to immobilize the apolar solvents, even at low concentrations (≤ 0. 2 wt %). The gelled structures developed using these gelators were thermostable. The group further reported that the gelation capability of these gelators varied with the change in amino acid side groups 25. In a recent study, a two-component organogelation system was described. The system employed a mixture of N-epsilon-dodecyl-L-lysine esters and N-dodecyl-L-amino acids (valine, phenylalanine, alanine, glycine, L-lysine), which resulted in an interaction between the amine group of the esters and the acidic group of the amino acids 26. The formation of the gelled structure was attributed to the entanglement of nanofibers formed as a result of the interaction involving the two components. A rigid gel was formed when the phenylalanine derivative of N-dodecyl-L-amino acid was used, whereas a thermostable gel was obtained when lysine derivative of N-dodecyl-L-amino acid was used to gel dodecane. The authors concluded that the properties of the gels may be tailored by varying the composition of the ester and amino acid components 27.

Vegetable oil organogelators

Organic gelators (e. g. 12-hydroxystearic acid, c-oryzanol and β-sitosterol) have been found to be useful in structuring edible oils and to restrict phase separation in food products 28-31. Organogels developed using mixtures of c-oryzanol and β-sitosterol are transparent 29 and are being marketed

Sterol organogelators

Cholesteryl and dicholesteryl compounds with various linking groups have the capability to gel organic phases by forming fibrillar network. The derivatised compounds follow the same fibrillar aggregates formation as they appended with an aromatic ring. Mixtres of sterol molecules with gelation ability got the attention after the success of c-oryzanol and β-sitosterol in triglyceride oils. Individually neither of them can gelate oil. Their mixture forms tubules where oil flows inside and outside the tubules as well 32. These organogelators have been found to be useful in structuring edible oils and to restrict phase separation in food products 28-31. Organogels developed using mixtures of c-oryzanol and β-sitosterol are transparent 29

Mechanisms of organogel formation

Three mechanisms of organogel formation have been proposed till date. These mechanisms discuss about the formation of networked structure by different phenomena. The first mechanism explains the formation of networked structures with fluid-filled fibers while the second mechanism explains about the formation of networked structures with solid fibers and the third mechanism deals with the crosslinking of polymers for creating the networked structures. The process of immobilization of the apolar solvents within these networked structures was attributed to the surface active phenomena present amongst the gelators (forming the networked structures) and the apolar solvent molecules.

As per the first mechanism, organogels are formed by the entanglement of instantaneously-formed fluid-filled fibers. When surfactants are dissolved in an apolar solvent, they result in the formation of reverse micelles. The

instantaneous formation of reverse micelles helps in maintaining a low interfacial tension amongst the polar and apolar phases and attains a thermodynamic equilibrium Subsequent addition of the water to the above reverse micellar solution results in the formation of tubular reverse micelles. Further addition of water causes the elongation in the tubular structure, which gets entangled, thereby forming a three-dimensional network. The most common examples representing this mechanism category include lecithin and pluronic lecithin organogels 8. The mechanism of organogel formation by this method has been shown in Figure 1.

The second mechanism involves the formation of networked structures due to the interaction between solid fibers (Figure 2). This mechanism utilizes the solubility profile of gelators in apolar solvent for the development of organogels. Gelators used for developing the organogels are solubilized in the apolar solvent at higher temperatures. Subsequently, the heated solution of the gelator in the apolar solvent is cooled, resulting in a decrease in the solubility constant of the gelator. The insoluble gelators precipitate out of the solution which then undergoes self-alignment to form solid fibers. The fibers, hence formed undergo physical interaction thereby resulting in the formation of a gelled structure. Common organogels that undergo this process of formation include sorbitan monooleate-based organogels 8.

The third mechanism describes in situ crosslinking of polymeric organogelators in the presence of an apolar solvent, which results in the entrapment of the apolar solvent within the crosslinked polymeric network (Figure 3). Presence of the solvent within the polymeric structure prevents

the structure from collapsing. The method of crosslinking may either be chemical or physical 12.

Characterization of Organogels

Due to the presence of self-assembled structures, the characterization of the organogels is a complex phenomenon. Certain methods have been established to study the structural, thermal and rheological properties of the organogles. Apart from this, biocompatibility studies of the organogels are also necessary to establish it utility as a product for human use. The following section will discuss about the different methods employed for the characterization of organogels.

Ternary Phase Diagrams

Typically an organogel contains a gelator and an apolar solvent. Many organogels are formulated so as to accommodate a polar solvent. The concentration of the gelator, apolar solvent and the polar solvent play an important role in the preparation of an organogel A particular concentration of the gelator is needed before it can induce the gelation of the apolar solvent, this is regarded as the critical gelator concentration. If the concentration of the organogelator is below the critical concentration, the gelator fail to induce the organogelation and occur as a liquid phase. Similarly, there is an upper critical limit of accommodating the aqueous phase into the organogel. If the amount of aqeous phase is above the upper critical limit, gelation may not occur or a bi-phasic system may result, where excess water is not retained within the networked structure. This phenomenon of disrupting the gelled structure with the addition of excess

water is known as gel solvation. It becomes necessary to experimentally find out the different concentrations of all the three components, which have the ability to immobilize the apolar solvent. The experimental data, so obtained, are plotted in a ternary graph (figure 4). The graph divulges a lot of information including the critical gelation temperature and concentration of individual component that forms the gel.

The simplest method to determine the formation of the organogel is to conduct the inverted test-tube method and can be used to determine the compositions of the gelator, apolar solvent and aqueous phase, which can induce organogelation. In this method, the procedure for inducing the organogelation is carried out in a test-tube. After the completion of the procedure, the test-tube is inverted. If the content of the test-tube starts flowing then the system is regarded as sol, indicating that the particular composition has failed to induce organogelation (Figure 5). The system is regarded as an organogel, if the contents of the test-tube do not flow. This is the widely used method to determine the formation of organogels 35.

(A)Organogel

(B)Failed to form organogel

Structural characterization

Structural property characterization of organogels can be carried out through a number of techniques. The simplest method involves simply analyzing organogels under a light microscope. Light microscopy has revealed that sorbitan ester organogels consist of aggregated rod-like tubules within its

structure (figure 6). Depending upon the type of apolar phase, the sorbitan organogels may also contain toroidal vesicle structures as is the case when isopropyl myristate is used as an apolar phase. The presence of polysorbate 20 in the solvent mixture can alter the microstructure of the organogels and results in the formation of star-shaped clusters. The presence of polysorbate 40, 60 and 80 results in the formation of mixed inverse micelles 8.

Rod-like tubule

Addition of co-surfactants increases the stability of gel, but significantly influences the gel microstructure. The presence of polysorbate 20 in the solvent mixture can alter organogel microstructure, resulting in the formation of star-shaped clusters. The presence of polysorbate 40, 60 and 80 results in the formation of mixed inverse micelles8.

Spectroscopic techniques, viz. nuclear magnetic resonance (NMR) and Fourier transform infra-red spectroscopy (FTIR), give information on the various chemical interactions that occur in organogels. The crystalline and non-birefringent nature of lecithin organogels have been determined by NMR spectroscopy 36 where it was found that, FTIR spectroscopy was used to determine the intermolecular interaction amongst the individual components present within lecithin organogels. The NMR measurements are based on protonated hydrogen (1H), deuterated hydrogen (2H), 13C and 31P dynamic parameters and the line width 37 38. The broadening of line width suggested the gelation of soy lecithin and synthetic phosphotidyl cholines in cyclohexane37. The fluidity of hydrocarbon regions in 12-hydroxy stearic acid and decane, decalin, ethyl acetate solvents organogels studied using pulsed field gradient NMR by performing basic translational and rotational

diffusion measurements 38. NMR and FTIR data reveal the functional groups involved and their binding pattern in the strength of organogel. Two carbonyl groups of the sodium bis(2-ethylhexyl)sulfosuccinate (AOT) surfactant are involved in the gel strength whereas only one carbonyl group is involved in gels with phenols39. They found that intermolecular hydrogen bonding plays an important role in the self-assembly of lecithin organogelators40-41.

Information on the molecular arrangement of organogels may also be obtained using scanning electron microscopy, transmission electron microscopy, dynamic and static light scattering, small angle neutron scattering (SANS), small angle X-ray scattering (SAXS) and atomic force microscopy (AFM)42-45. These techniques provide insight into the molecular arrangement. In most cases SEM and TEM observations give insight of the fibrillar aggregates, the network structure reflecting the chirality of the functional groups 46. Light and Polarized light microscopy also can be used for the identification of fibrils and tubules in the organogel network 47. Structural investigation at the nano scale is possible with small angle scattering techniques, SAXS and SANS. These techniques are used to investigate the structural features of aggregates, their junction jones in the network, presence of hydrogen bond and shape of fibres (circular or slightly rectangular) 17. Structures of cholesteryl derivatives also investigated using SAXS technique 17, 48 . In AOT-Penol organogels the SAXS data revealed that the length of AOT-Penol strands is independent of their concentration but dependent on the type of solvent used 49. Tapping mode AFM can be used to vizualize the gel in it’s native state 49and characterize the nano-scale structure of AOT-Phenol organogels. Based on AFM analysis lecithin

organogels consisted of a fibrous network at the organogel surface43. Figure 7 identifies the topography of a novel tween-80 based organogels prepared in our laboratory.

Rheological characterization

Rheology is used to determine the physical properties of the organogels, such as viscosity and viscoelasticity. It has been found that most organogels show plastic rheological properties 50. The deformation of organogels is necessary after the application of sufficient stress for easy spreading and permeation enhancement of drugs after their application over the skin, at lower shear rates, organogels will not flow. As shear rate is increased, the strain within the samples initially increase nonlinearly and progressively grows in linearity at higher shear rates (Figure 8) The shear rate required for the complete deformation of the gel can be known which signifies the strength and maintenance requirements of the gel. The rheology of lecithin organogels has been extensively studied. It has been reported that there is a 104-106-fold increase in viscosity upon addition of trace amounts of water40, compared to the initial lecithin solution. . As a result, the rheological properties of such organogels can be tailored by altering the concentrations of the organogelator and the apolar solvent. In general, with an increase in concentration of the organogelator, there is an increase in organogel viscosity.

Apart from concentration, organogelator chemical composition also plays an important role. For example, it has been found that immobilization of alkanes in lecithin organogels showed an higher apparent viscosity than their native

state. For organogels that incorporate a reverse micellar structure, the amount of added water incorporated will play an important role in altering rheology51-52. With the addition of water to the lecithin-solvent solution, the Newtonian behaviour of the solution changes to Maxwell rheology because of the sphere to rod transformation of reverse micelles and their one-dimensional growth extension 40. Temperature plays a significant role on organogel rheology.. In general, with the increase in the temperature, there is a corresponding decrease in viscosity. This decreasing trend can be attributed to an increase in the kinetic energy amongst the fibers, thereby weakening their interactions. If the temperature is further increased beyond the critical temperature, there is a complete disruption of the network structure and the organogels start flowing freely. Most physical organogels are thermoreversible in nature and are able to attain their high viscous state once cooled below the critical temperature. Lecithin and pluronic lecithin organogel are classical examples of thermoreversible organogels 53-54.

Thermal characterization

As mentioned in the previous section, physical organogels are thermoreversible in nature. The physical organogels are also thermostable in nature and are in a low energy state. Some of them may be stable even for 2 year3, 33, 55-56. The gel-to-sol transition temperature can be studied using a differential scanning calorimeter 57. During heating of an organogel, there is an endothermic peak at the gel-to-sol transition, marked by the initiation and completion of the disruption in networked structure (when the gel starts to flow). Similarly, during cooling, the system undergoes its sol-to-gel transition across a range of temperature. An exothermic peak will result, with

initiation marked by the formation of entangled structures and the thermal signature representing formation of the gelled structure. depending on the composition and the property of the organogel, the gelling temperature and the melting temperature might be same or different 58-59. If the organogel is isotropic in nature, the range of transition temperature should not be more than 3-5oC60. Figure 9 shows the temperature dependence of Tween-80 based organogels developed in our laboratory. The sample showed gel-to-sol transition at 55 oC when subjected to a temperature sweep in a programmable temperature controlled water-bath.

(B) Organogel at 55 oC

Organogel at room-temperature

The thermal characteristics of organogels can also be analyzed with temperature-dependent rheology and hot stage microscopy60. Temperature-dependent rheology deals with subjecting the sample to a temperature sweep with the concomitant application of shear in the linear viscoelastic region. The storage modulus and the loss modulus of the samples are determined, which reveals information on the transition temperatures. The hot stage microscopy employs a controlled heating element attached to the stage of the microscope. The samples, kept in the well-slides, are heated in a controlled manner and are continuously monitored with the microscope.

Biocompatibility test

Most organogels developed to date have consisted of toxic solvents (like cyclohexane, n-octane, kerosene, etc.), rendering them unsuitable for human

applications33. The work dealt with the development of organogels based on generally regarded as safe (GRAS) materials12 got the wide acceptance and are biocompatible. Formulations containing 7. 5% SAM (N-stearoyl L-alanine methyl ester derivatives) in safflower oil when injected into the stratum corneum of rats showed good biocompatibility with surrounding tissues for 8 weeks59. The in vitro nasal delivery of propanolol hydrochloride was investigated by Pisal et al, using an organogel prepared with sorbitan monostearate (SMS), isopropyl myristate and water. The investigation revealed that the surface epithelium lining and granular cellular structure of treated nasal mucosa were intact, supporting the biocompatible nature of these organogels61. Lecithin organogels are considered as the most abundant, biocompatible class for topical drug delivery system62. Various drugs such as scopolamine63 and piroxicam36 have been evaluated for both in vitro and in vivo testing of lecithin organogels. Dreher et al investigated transdermal patch testing of lecithin organogels on human volunteers to find out the irritation potential of lecithin on human skin4, 64.

Organogels in drug delivery

Drug delivery is a process of administration of bioactive agents so as to achieve the therapeutic effect in humans. Research on the development of the various delivery systems is on the rise, which can improve the bioavailability of the bioactive agent. The sustained/ controlled delivery systems help in attaining the same due to its ability to prolong the release of the drug. Of late, the research on the use of organogels as a sustained/ controlled delivery vehicle has seen an exponential rise. This has been made possible because of the use of GRAS materials, having improved

biocompatibility, in the development of organogels. In this section, attempts will be made to discuss some of the applications of organogels in controlled delivery.

Dermal and transdermal drug delivery system

Skin is the largest organ of our body and provides a large surface area, which has been explored for delivering the drugs either locally or systemically. The delivery of the bioactive agents through the skin tissue has received much importance because of its non-invasive administration. Also, there is no need for the hiring a trained person as is required in invasive delivery systems. Apart from this, the bioactive agents meant to enter the systemic circulation does not undergo first pass metabolism thereby increasing the bioavailability of the bioactive agent in the systemic circulation.

The Topical/dermal delivery systems are meant to provide increased drug availability at the site of application, without any significant amount of the drug gaining access to systemic circulation. Various organogels have shown great potential for such use. Pluronic lecithin organogels (PLO) are soy lecithin-based organogels that contains either isopropyl palmitate or isopropyl myristate as an apolar solvent. Additionally, these organogels contain pluronic F127 as one of the major components65. PLOs loaded with non-steroidal anti- inflammatory drugs (NSAIDs) (e. g. ketoprofen and flurbiprofen) for the treatment of heel pain 66. Piroxicam-loaded organogels can be used to treat rheumatoid arthritis 4. PLOs can be used as anaelgesic creams containing lidocaine, ketoprofen and cyclobenzaprine.

Microemulsion-based gelatine organogelss have also been investigated in topical drug delivery. The experimental results with cyclosporine-A indicated maximum concentration of the drug at the skin surface in rat models 67.

Contrary to dermal delivery systems, transdermal delivery systems involve the administration of the bioactive agents to systemic circulation by application of the formulation to the skin surface. Moreover, these systems have been found to be the most patient compliant mode of administration and considered to be one of the safest 36. Permeation of the drug from the skin surface to the systemic circulation is dependent on the permeability of the skin, rate of blood flow to the administration site and the physicochemical properties of the drug68. The use of Permeation enhancers (e. g. terpenes, essential oils, urea, dimethyl sulphoxides and propylene glycol) which are useful additives, aid in transdermal passage of the bioactive agent into the skin69. The thermoreversible nature of the organogels makes them one of the best candidates for the transdermal drug delivery. Most of the organogels are highly viscous and stable at room temperature (25oC), facilitates their storage and becomes less viscous abd gets liquid appearance at body temperature allowing the permeation of drugs.

Lecithin organogels (LOs) have been used in various pharmaceutical formulations because of their biocompatible nature. LOs have the capability to immobilize a wide range of edible oils, organic solvents and various other apolar solvents for pharmaceutical use. The composition of LOs may be tailored so as to increase the permeation of bioactive agents through the skin. Isopropyl palmitate (IPM) immobilized LO are used to increase the

systemic bioavailability of scopolamine and broxaterol, when administered topically 63. The presence of IPM in the LO did not cause any skin irritation 64. IPM-based LOs employed for the post-operative and emergency treatment of pain using the NSAID ketorolac tromethamine 70. Other anti-inflammatory drugs have also been successfully incorporated within IPM-based LOs, including indomethacine, diclofe nac and sodium salicylate 64, 70. Improvement in the s