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Organogels: A Review

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Abstract
Organogels preparations for external application to skin have gained much demand, since it is easily absorbed through the skin layers. In general, organogels are thermodynamically stable in nature and have been explored as matrices for the delivery of bioactive agents. In the last decade, interest in physical organogels has grown rapidly with the discovery and synthesis of a very large number of diverse molecules, which can gel organic solvents at low concentrations. In future, organogels can give way to many promising discoveries in the field of topical dosage forms.
Key words: Drug delivery, organogel, mechanism, types

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.

The topical delivery has been attempted and made successful using several lipid-based systems viz vesicular systems,[15] lipid microspheres,[16] lipid nanoparticles,[17] lipidmicroemulsions,[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.

Advantages of Organogels

1. **Template Vehicle:** Organogels provide opportunities for incorporation of wide range of substances with diverse physicochemical characters viz: chemical nature, solubility, molecular weight, and size etc.
2. **Process Benefits**: Spontaneity of organogel formation by virtue of self-assembled super molecular arrangement of surfactant molecule makes the process very simple and easy to handle.
3. **Structural/Physical Stability:** Being thermodynamically stable, the structural integrity of organogels is maintained for longer time periods.
4. **Chemical Stability:** Organogels are moisture insenstive and being organic also resists microbial contamination.
5. **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.
6. **Safety**: Use of biocompatible, biodegradable and non-immunogenic materials makes them safe for long term applications.

Limitations of Organogels:

1. Should be stored in a proper condition.
2. The organogel has greasy property
3. Less stable to temperature.

Mechanism of Gel Permeation into Skin:

There are two possible mechanisms for gel permeation into skin has been proposed.

1. Gel permeation into the skin occurs by diffusion through lipid intercellular matrix in stratum corneum.
2. Gel provides a slight disorganization of the skin allowing the permeation of the gel and the active drug through the stratum corneum.

Safety and Skin Compatibility Studies

Organogel systems i.e., gels are composed of pharmaceutically approved (non-immunogenic and biocompatible) excipients. However, the level of surfactant and organic solvents in organogels is fairly high. Therefore, it is important to consider the safety and irritancy of the formulation on prolonged use. The irritation potential of organogels has been assessed by Dreher et al, by carrying out human skin irritation study. Results indicated a very low cumulative skin irritation potential of organogels that supports the suitability of organogels as a topical vehicle for long-term applications.

Types of Organogels:

Lecithin organogels: Lecithin organogels have emerged as one of the most potential carrier systems. The organogel matrix mainly consists of a surfactant (lecithin) as gelator molecules, a nonpolar organic solvent as external or continuous phase, and a polar agent, usually water. A lecithin organogel is formed when small amounts of water or other polar substances, such as glycerol, ethylene glycol or formamide, are added to a non-aqueous solution of lecithin. The transfer into jelly-like state has been demonstrated only for nonaqueous solutions of naturally occurring unsaturated lecithins [32, 33]. 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 [34]. Lecithin organogels have been used as carriers for hydrophilic and hydrophobic drug molecules. Hydrophobic drugs are dissolved in the oil phase (lecithin + organic solvent) whereas hydrophilic molecules are dissolved in water, which is then added to an organic solution of lecithin to induce gelation. As a biocompatible surfactant, it is widely used in everyday life including human and animal food, medicine, cosmetics, and manifold industrial applications [35, 36]. Synthetic lecithins containing residues of saturated fatty acids failed to form organogel. The gelling formation was also not observed with hydrogenated soybean lecithin. These studies indicate the importance of lecithin in the naturally occurring form, which contains unsaturated fatty acids [37, 38].

Sorbitan monosterate organogels: Sorbitan monostearate (Span 60) and sorbitan monopalmitate (Span 40) have been found to gel a number of organic solvents at low concentrations. Span 60 gels were found to be more stable than Span 40 gels and were investigated in greater depth. The thermoreversible gels are prepared by heating the gelator/liquid mixture in a water bath at 60°C (which results in dispersion of the gelator in the liquid medium) and cooling of the resulting suspension, following which the latter sets to an opaque, white, semisolid gel. Cooling results in reduced affinities between the solvent and the gelator molecules, which self-assemble into tubules. X-ray diffraction and freeze-fracture studies indicate that sorbitan monostearate molecules are arranged in inverted bilayers within the tubules. Sorbitan monostearate organogels are opaque, thermoreversible semi-solids whose microstructure consists of surfactant tubules dispersed in the organic continuous phase. Inverse toroidal vesicles are the precursors of the surfactant tubules. The gelation process was observed as an isotropic sol phase of sorbitan monostearate in isopropyl myristate was cooled using hot-stage light microscopy. At the gelation temperature, inverse toroidal vesicular structures were seen to grow in the organic phase. These toroids are thought to be analogous to other well-known vesicles, liposomes and niosomes, except for their toroidal (rather than spherical)

shape and their inverse nature. They are rather short-lived structures: on further cooling of the sol phase, tubules form in the organic medium: it is speculated rod-shaped segments. [39-41]

Micro/Nano-emulsion based organogels: Microemulsions are dispersions of at least two immiscible liquids. They are thermodynamically unstable systems that are stabilized kinetically[42]. Microemulsion appears to have the ability of deliver larger amount of topically applied agents into the mucosa than the traditional gel & creams. Microemulsions are defined as thermodynamically stable transparent, single optically isotropic liquid system of water, oil and surfactants frequently in combination with suitable cosurfactants. Microemulsions are known to enhance the bioavailability of drugs via topical and systemic routes. The use of a microemulsion gel as vehicle may enhance transdermal penetration by various mechanism, many molecules or solubilised in microemulsion in addition microemulsion induce a change in the thermodynamic activity of the drug they contain, modifying their partition coefficient and thus favour penetration of the stratum corneum. Furthermore, their component surfactant reduces the functional barrier of stratum corneum[43-45]. Nanoemulsions are thermodynamically stable transparent (translucent) dispersions of oil and water stabilized by an interfacial film of surfactant and cosurfactant molecules having a droplet size of less than 100 nm [46].

Organogels based on other low molecular weight gelators: Scientists have investigated the transdermal delivery of piroxicam from organogels composed of glyceryl fatty acid ester gelators in pharmaceutical oils. The in vivo skin penetration of the drug, evaluated by measuring the anti-inflammatory inhibition of oedema after treatment, was found to be superior for glyceryl fatty acid ester organogels as compared to traditional topical formulations such as liquid paraffin [47, 48]. Use of a long-chain glutamate based gelator has demonstrated by scientists (N-lauroyl-L-glutamic acid di-nbutylamide) at concentrations of 2–10% to gel isostearyl alcohol and propylene glycol, yielding translucent and opaque gels, respectively. In vitro permeation studies on human skin using haloperidol, an anti-psychotic drug, showed facilitated permeation upon incorporation of 5% limonene, a known permeation enhancer[49, 50].

Poly (ethylene) organogels: Very few polymeric organogels have been geared towards pharmaceutical applications. The only two such systems have been widely tested for drug delivery applications are poly (ethylene) and P (MAAco- MMA) organogels. In a study dating back to the 1950s and involving 300 patients, PO patches were shown to be non-irritating and have low sensitizing properties [51]. In a related investigation, 326 patients were treated with spectrocin-containing PO and compared with patients treated with spectrocin in petrolatum base alone. Both antibiotic ointments cleared pyoderma and secondarily infected eruptions in 3–5 days, but it was found that the PO provided a faster, more efficient release. Poly (ethylene) was also used in the formulation of 5-iodo-2'-deoxyuridine for the treatment of oral herpes simplex lesions. A 10% drug-loaded formulation showed a resolution of herpetic lesions in 3-days after treatment initiation, compared to 1–2 weeks in untreated control patients [52].

Supramolecular organogels: Although a low molecular mass gelator was discovered in the early nineteenth century, the supramolecular nature of these materials was poorly understood and they were largely neglected until the late 20th century. In the recent past, molecules of a great structural diversity, for instance from the simplest alkanes to the complex phthalocyanines, have been discovered to be gelators. Recently immense interest has been generated in studying gels derived from low molecular mass gelators (supramolecular, or simply molecular gels). The motivation for this is not only to understand the fundamental aggregate structures in the gels at different length scales, but also to explore their potential for futuristic technological applications. Gels have been made sensitive to external stimuli like light and chemical entities by incorporating a spectroscopically active or a receptor unit as part of the gelator molecule. This makes them suitable for applications such as sensing and actuating. The diversity of gel structural architectures has allowed them to be utilized as templates to prepare novel inorganic superstructures for possible applications in catalysis and separation. Gels derived from liquid crystals (anisotropy gels) that can act as dynamically functional materials have been prepared, for example, for (rewritable) information recording. Supramolecular gels can be important in controlled release applications, in oil recovery, for gelling cryogenic fuels etc. They can also serve as media for a range of applications. This tutorial review highlights some of the instructive work done by various groups to develop smart and functional gels, and covers a wide spectrum of scientific interest ranging from medicine to materials science. [53, 54]

Eudragit organogels: Eudragit organogels are really mixtures of Eudragit (L or S) and polyhydric alcohols, such as glycerol, propylene glycol and liquid polyethylene glycol, containing high concentrations (30 or 40% w/w) of Eudragit. Drug-containing gels were prepared by dissolvingthe drug (salicylic acid, sodium salicylate, procain or ketoprofen) in propylene glycol, pouring the resulting solution into Eudragit powder (contained in a mortar), and immediately mixing with a pestle for 1min [55, 56]. Gel consistency and spreading is described using a penetrometer and a spreadmeter [57]. Gel viscosities were found to increase with increasing concentrations of Eudragit and to

decrease with increasing drug content. The inclusion of the drug procaine was also found to reduce gel rigidity, which was thought to be due to the influence of the drug molecules on the intermolecular forces (e.g., hydrogen bonds) between Eudragit and propylene glycol. The authors suggested that drug content in Eudragit organogels be kept low (e.g., 1.25% w/w) to maintain gelrigidity and stability. The release of model drugs salicylicacid, sodium salicylate and ketoprofen from Eudragit L and S organogels was investigated *in vitro* by the rotation disk method. Interestingly, the mechanism of salicylic acid release from Eudragit L and S organogels into a phosphate buffer were totally different. Release was due to surface erosion of the Eudragit L organogel but to diffusion through the Eudragit S gel matrix. Drug release from Eudragit S organogel thus increased with increasing temperature and agitation rate of the release medium [58].

***In situ* forming organogel of L-alanine derivative:** *N*lauroyl- L-alanine methyl ester (LAM) was found to gel the pharmaceutically acceptable organic solvents, soybean oil and medium-chain triglycerides [59]. Normally the system exists in the gel state at room temperature. However, the addition of ethanol to a gelator/solvent solution inhibits gelation because the ethanol disrupts the formation of hydrogen bonds (essential for gelator self-assembly into aggregates) between the gelator molecules. This means that a solution of LAM in an organic solvent can remain in the sol phase at room temperature when some ethanol is added to the mixture. When such a sol phase (20% LAM + 14% ethanol in soybean oil) was placed in phosphate buffered saline at 37°C it turned into a opaque gel within 2 min as the hydrophilic ethanol diffused away into the aqueous buffer, and as gelator–gelator hydrogen bonds were formed. Thus, theoretically, such a LAM/ethanol/soybean oil solution could form gels *in situ* following its subcutaneous injection, due to ethanol diffusion away from the formulation, into the surrounding tissues; *in situ* gel formation in rats was indeed investigated. The main advantage of *in situ* forming gels is their injectability at room temperature. Once a drug-containing gel is formed *in situ*, it could act as a sustained-release implant [60].

Pluronic lecithin organogels: Pluronic lecithin organogels are opaque, yellow gel, PLO is composed of isopropyl palmitate, soy lecithin, water and the hydrophilic polymer, Pluronic F127. The difference between PLO and its precursor, lecithin gels, is the presence of Pluronic F127 (a hydrophilic polymer that gels water) and the greater amount of water compared with the oil. Thus, PLO is not really an organogel but it may be thought of as an 'organogel' due to its name. PLO was developed by a compounding pharmacist in the US in the early 1990s as a topical vehicle [61]. Pluronic F127 was added to the original lecithin organogel in order to stabilize the gel formulation. The gel's physicochemical properties have not been investigated. However, collaborations between local physicians, their patients and the inventor pharmacist led to the incorporation of many different drugs, such as nonsteroidal anti-inflammatories, haloperidol, prochlorperazine and secretin for patient use and to anecdotal evidence of its efficacy as a transdermal drug delivery vehicle. Many more drugs have since been incorporated within PLO [62]. PLOs are mainly used as a topical or transdermal drug carrier, for example, for hormones [63, 64]. PLOs have also been investigated/proposed as a vehicle to the oral cavity and mucosa [65]

Conclusion

In the last 10 years there has been an explosive growth in research on organogels and on publications related to organogels. Research into the applications of these gels is still in its infancy despite great excitement about their potential industrial uses. When compared to other lipid based carrier systems, these prove to be better in terms of efficacy, feasibility and shelf life.

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