

ORGANOGELES AS A POTENTIAL TOPICAL DRUG DELIVERY SYSTEM

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REVIEW ARTICLE

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ABSTRACT:

Semisolid preparations for external application to skin have gained much demand, since it is easily absorbed through the skin layers. Many novel topical dosage forms have been discovered, among which organogels appears to play an important role. Interest in organogels has increased in a wide variety of fields including chemistry, biotechnology and pharmaceuticals. Organogels are thermodynamically stable, biocompatible, isotropic gel, which not only give localized effect, but also systemic effect through percutaneous absorption. Organogels are semi-solid systems, in which an organic liquid phase is immobilized by a three-dimensional network composed of self assembled, intertwined gelator fibers. The apolar phase gets immobilized within spaces of the three-dimensional networked structure formed due to the physical interactions amongst the self assembled structures of compounds regarded as gelators. Organogels have been explored as matrices for the delivery of bioactive agents. Compared to conventional topical dosage forms, these novel formulations are found to be more advantageous and efficient. In future, organogels can give way to many promising discoveries in the field of topical dosage forms. The current review aims at giving an idea about organogels, its applications and importance in topical delivery.

Key words: Organogels, Organogelators, Gelation, Properties

Introduction:

Organogels are thermoreversible, viscoelastic materials formed from low-molecular-weight Organogelators. The Organogelators are a class of molecules that can undergo self-organization in particular organic solvents and/or water, often at surprisingly low concentration. [1]. The gel state has been defined in many different ways ; Hermans defined the gel as a colloid disperse system that is solid-like in its mechanical properties and which consists of at least two components that extend themselves continuously throughout the whole system.[2] Later, Flory added that a gel must have a continuous structure, for example, wellordered lamellar structures, disordered physically aggregated polymer networks, covalent polymeric networks, particulate structures. The gel is said to be a hydrogel or an Organogel depending on the nature of the liquid component. If the liquid phase is water, it is hydrogel and as an Organogel if the liquid phase is an organic solvent [3, 4]. In general, Organogels formation is based in the spontaneous self-assembly of individual gelator molecules into three-dimensional networks of

randomly entangled fiber-like structures. This three-dimensional network holds micro domains of the liquid in a non-flowing state mainly through surface tension [5]. Some common examples of gelators include sterol, sorbitan monostearate, lecithin and cholesteryl anthraquinone derivatives. The thermo-reversible property of the Organogels has generated much interest for the potential use of the Organogels as drug delivery system. The thermodynamic stable nature of the Organogels has been attributed to the spontaneous formation of fibrous structure by virtue of which the Organogels reside in a low energy state [6]. The occurrence of the gel-to-sol transition above room-temperature indicates that external energy has to be supplied to the Organogels so as to disrupt the three-dimensional structure and subsequent transformation of the gelled state to the sol state. Apart from the temperature sensitivity, Organogels are also sensitive to the presence of moisture which has also been explored to develop controlled delivery systems [7]. Various Organogel-based formulations have been designed for administration of the bioactive agents by different routes.

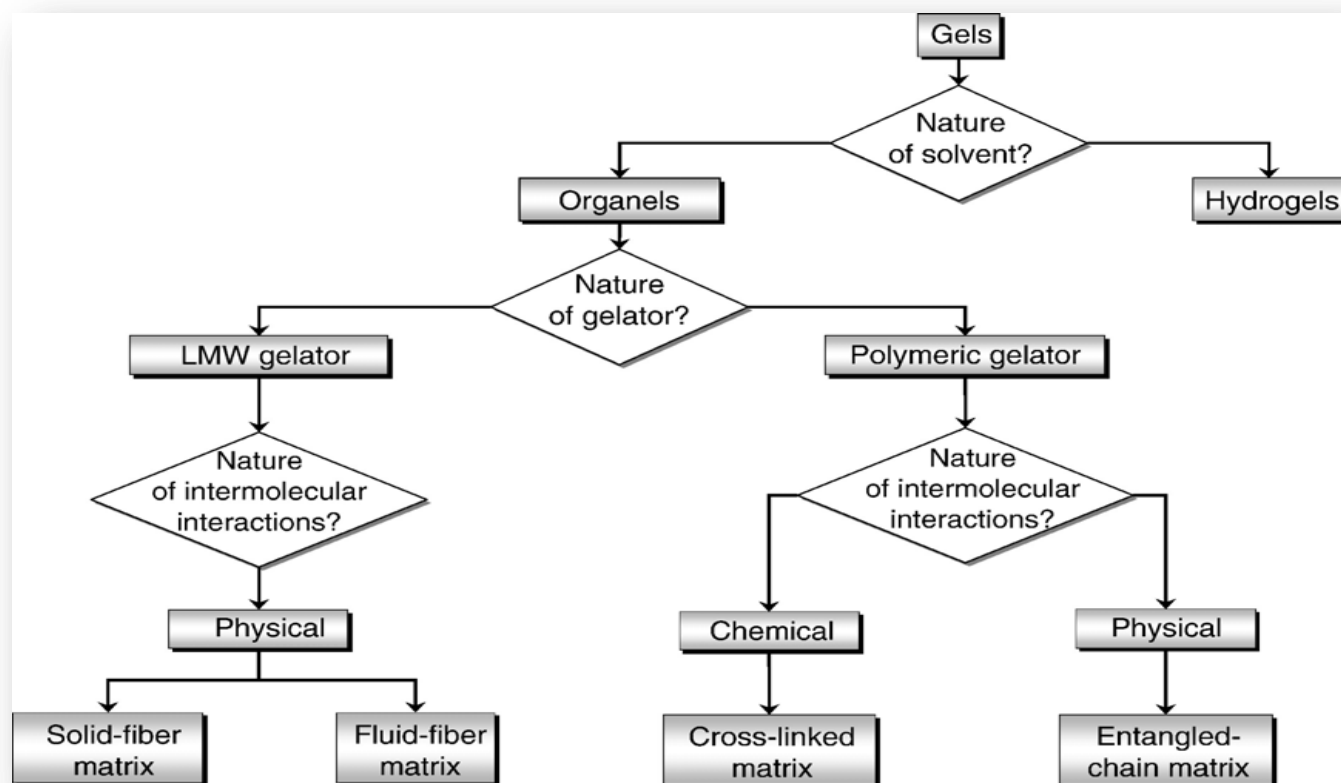


Fig. 1 Organogel Classification

Properties

1. **Viscoelasticity:** The Organogels seems to follow Maxwell model of Viscoelasticity and behave like a solid on low shear rates and starts flowing on high shear rates due to weakening of physical interacting point of fiber matrix [8, 9].

2. **Non-Birefringence:** The Organogels when viewed under polarized light appears as a dark matrix. This can be accounted to the isotropic nature of the Organogels. Organogels do not allow polarized light to pass through its matrix. This property of Organogel is termed as Non-Birefringence [10, 11]

3. **Thermoreversibility:** When Organogels are heated above a critical temperature it lose its solid matrix and start flowing and settel back again on cooling. This has been attributed to the disruption in the physical interactions amongst the gelator molecules due to the thermal energy within the Organogels [12, 13].

4. **Thermostability :** Organogels are thermostable in nature. The stability of the Organogels may be attributed to the ability of the gelators to undergo self-assembly, under suitable conditions, so as to form Organogels.

As the gelators undergo self-assembly, it results in the decrease of the total free energy of the system and renders the Organogels as low-energy thermostable system [14].

5. **Opacity:** Depending on the composition of the Organogels, the Organogels may be transparent or opaque in nature. The lecithin Organogels are transparent in nature while the sorbitan monostearate Organogels are opaque in nature [15, 16].

6. **Chirality effects-** The presence of chirality in the Low Molecular Weight gelators have been found to affect the growth and the stability of the solid-fiber networks. In general, it has been found that a good solid-fiber gelator has a chiral center whereas chirality does not have any effect on fluid-fiber gelators. The presence of chiral centers within the gelators helps in the formation of a compact molecular packing, which provides a thermodynamic and kinetic stability to the Organogels system. Crown ether phthalocyanine Organogels are the excellent example of chiral Organogels [17, 18].

7. **Biocompatibility:** Now a days research on Organogels using various biocompatible constituents has opened up new dimensions for

the use of the same in various biomedical applications. They are found to be biocompatible in nature [19].

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 [20, 21]. 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 [22]. 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 [23, 24]. 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 [25, 26].

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 that the toroids elongate into tubular shapes or split into rod-shaped segments [27-28].

Amphiphilogels for Drug Delivery: The non-ionic surfactants, sorbitan monostearate and sorbitan monopalmitate, were also found to gel other non-ionic surfactants such as liquid sorbitan esters (e.g., sorbitan monooleate and polysorbates). Based on the amphiphilic nature of the liquid component of these gels, the latter were termed 'amphiphilogels'. The amphiphilogels can be hydrophilic when the liquid phase is a hydrophilic polysorbate or hydrophobic when the liquid is a hydrophobic sorbitan ester. These gels are prepared in the same way as sorbitan ester Organogels, have similar microstructures and are stable for ≥ 2 years when kept in sealed containers at room temperature. The amphiphilogels can solubilise certain poorly water-soluble drugs such as cyclosporin, ibuprofen, aspirin and paracetamol.

Drug solubilisation in the gel alters the T_g (it can increase or decrease, depending on the nature of the drug) and the gel microstructure.

Micro/Nano-emulsion based Organogels:

Microemulsions are dispersions of at least two immiscible liquids. They are thermodynamically unstable systems that are stabilized kinetically [29]. 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 [30-32]. 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 [33].

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 [34, 35].

Use of a long-chain glutamate based gelator has demonstrated by scientists (N-lauroyl-L-glutamic acid di-n-butylamide) 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 [36, 37].

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 (MAA-co- 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 [38]. 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 [39].

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 (re-writable) 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 [40, 41].

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 dissolving the 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 [42, 43]. Gel consistency and spreading is described using a penetrometer and a spreadmeter [44]. 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 gel rigidity and stability. The release of model drugs salicylic acid, 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 [45].

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 [46]. 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 [47].

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 [48]. 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 [49]. PLOs are mainly used as a topical or transdermal drug carrier, for example, for hormones [50, 51]. PLOs have also been investigated/proposed as a vehicle to the oral cavity and mucosa [52-54].

Table 1: Organogel formulations and their applications in drug delivery

S. No.	Organogelator used in formulation	Route of administration	Study conducted	Model drugs
1.	Lecithin	Transdermal	Clinical trials In vivo skin permeation and efficacy In vitro skin permeation In vitro release	Diclofenac [55, 56]. Piroxicam [57]. Tetrabenzamidine [58]. Scopolamine and boxaterol [59]. Propranolol [60]. nicardipine [61]. Aceclofenac [62]. Indomethacin and diclofenac [63].
2.	Glyceryl fatty acid esters	Transdermal	In vivo efficacy	Levonorgestrel and ethinyl Estradiol [64].
3.	N-lauroyl-l-glutamic acid di-n-butyl amide	Transdermal	In vitro release	Haloperidol [65, 66].
4.	Poly(ethylene)	Transdermal	In vitro release	Spectrocin [67].
5.	Sorbitan monostearate (SMS) or molaureate	Nasal, Oral, Subcutaneous and Intramuscular	In vitro release In vitro release In vivo efficacy	Propranolol [68]. Cyclosporin A [69]. Bovine serum Albumin and haemagglutinin [70, 71].
6.	N-stearoyl l-alanine methyl or ethyl ester	Subcutaneous	In vitro/in vivo release In vitro/in vivo release and efficacy	Rivastigmine [72]. Leuprolide [73].
7.	Poly (methacrylic acid-co-methylmethacrylate). Poly (methacrylic acid-co-methylmethacrylate). and crosslinked poly(acrylic acid	Buccal, Rectal	In vivo efficacy In vivo efficacy	Salicylic acid Bovine serum Albumin [74].

Advantages

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 [75].

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.

Structural/Physical Stability: The Organogel do not form semisolids on standing because an Organogel consists of macromolecules existing as twisted matted strands. The units are of bound together by strong types of Vanderwaal forces so as to form crystalline amorphous regions throughout the entire system. Being thermodynamically stable, the structural integrity of Organogels is maintained for longer time periods [76].

Chemical Stability: Organogels are moisture sensitive and being organic also resists microbial contamination. Since it consists of both hydrophobic and hydrophilic components, both hydrophobic and hydrophilic drugs can be incorporated [77].

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. Organic solvents could be of natural origin, e.g.: sunflower oil, mustard oil, etc which have been already studied. Drug delivery into the skin layers (cutaneous or dermal delivery) and beyond (percutaneous or transdermal delivery) is advantageous because it provides a non-invasive, convenient mode of administration, allowing the circumvention of first pass degradation of the active ingredient, an important aspect for highly liver-metabolized molecules [78, 79].

Safety: Use of biocompatible, biodegradable and non-immunogenic materials makes them safe for long term applications [45].

Conclusion

Organogels are systems of which the existence is limited to the fine line between uncontrolled gelator aggregation and its complete solubility

in the solvent. Given the strict requirements needed for formation as well as the relatively recent interest granted to these systems, many important questions still remain unanswered. For one, the precise thermodynamic and kinetic factors governing the stability of gelator fibers in the organic solvent need yet to be explored. Such knowledge could be applied to the systematic design of gelators yielding stable Organogel systems. Furthermore, gel components could be chosen according to their compatibility with intended applications, such as nontoxic solvents for pharmaceutical formulations. In the last 10 years there has been an explosive growth in research on Organogels and on publications related to Organogels. Most of the latter report the discovery and/or synthesis of new Organogelators, investigations into the chemical groups necessary for the molecule to be an Organogelator, the properties of their gels including the gel microstructures, and the manner in which the gelator molecules could be arranged in the gelator aggregates. Research into the applications of these gels is still in its infancy despite great excitement about their potential industrial uses. As far as drug delivery is concerned, the absence of an aqueous phase is beneficial as the non-aqueous medium is less likely to support microbial growth. The non-aqueous medium of Organogels also indicates their potential suitability as carriers for oil-soluble drugs, whereas their soft, semisolid consistencies point to their use as vehicles for application to the skin. However, only a few Organogels have been investigated for drug delivery, mainly due to the fact that the components of most Organogels are not pharmaceutically acceptable. Thus, before the Organogels can be studied as a drug carrier, they must be reformulated using pharmaceutically acceptable components. Drug incorporation into the gels is known to alter the gel properties; such as viscosity, and, in some cases, drug incorporation even destroys the gel. Care must be taken, therefore, when drugs are dissolved or suspended in Organogels and the drug-containing formulations must be thoroughly characterized. Currently, literature on the influence of drug incorporation on the physicochemical properties of Organogels is limited.

Lecithin gels have received more attention as transdermal drug delivery vehicles, presumably due to the presence of lecithin: a known skin permeation enhancer. The promise shown by lecithin gels as a transdermal delivery vehicle has resulted in its adoption and adaptation into PLO (which is not an Organogel despite the terminology). PLO is currently the vehicle of choice of US compounding pharmacists and veterinarians for the delivery of drugs by the topical route, despite the lack of any hard, scientific evidence of PLO efficacy as a transdermal drug carrier. Apart from the topical/transdermal route, Organogels have been investigated for oral, rectal and parenteral applications. Sorbitan monostearate Organogels and amphiphilic gels have shown promise as parenteral vaccine adjuvants and as oral vehicles for poorly water-soluble drugs, respectively. Given that many drugs suffer from poor water solubility, which often leads to low bioavailability, the ability of sorbitan monostearate amphiphilic gels to solubilise such drugs to increase bioavailability should be investigated further. The potential of amphiphilic gels to enhance the transdermal delivery of small drug molecules has not yet been investigated.

References

- 1) Grigoriew H, Temeriusz A, Chmielewska D, Gronkowski J, Mirkowska MUSAXS study of influence of gelator polarity on Organogel structure, *J Sol-Gel Sci Technol*, 2007, 44:249–254.
- 2) Terech P, Weiss RG, Low molecular mass gelators of organic liquids and the properties of their gels, *Chem. Rev.* 1997, 97: 3133–3159.
- 3) Vintiloiu A, Leroux JC. Organogels and their use in drug delivery-A review, *Journal of Controlled Release*, 2008, 125:179–192.
- 4) Jibry N, Richard K, Heenan, Murdan S. Amphiphilic gels for Drug Delivery: Formulation and Characterization *Pharmaceutical Research*, 2004, 21(10): 1852-61.
- 5) Abdallah DJ, Weiss RG. n-Alkanes gel n-alkanes (an many other organic liquids). *Langmuir*, 2000, 16: 352–355.
- 6) Wright A, Marangoni A. Formation, structure, and rheological properties of ricinelaidic acid-vegetable oil Organogels, *Journal of the American Oil Chemists' Society*. 2006, 83(6): 497-503.
- 7) Sahoo S, Kumar N, Bhattacharya C, Sagiri SS, Jain K, Pal K, Ray SS, Nayak B. Organogels: Properties and Applications in drug delivery, *Designed Monomers and Polymers*.2011, 14: 95–108.
- 8) Kumar R, Kotare OP. Lecithin Organogel as a potential phospholipid-structured system for topical drug delivery: A Review, *AAPS PharmSciTech*.2005, 6: 298-310.
- 9) Patil KD, Bakliwal SR, Pawar SP. Organogel: topical and transdermal drug delivery system, *International journal of pharmaceutical research and development*.2011, 3(6): 58-66.
- 10) Kamble SR, Udapurkar P, Nakhat PD, Yeole PG, Biyani KR. Development and Evaluation of Sorbitan Monostearate Organogels as a Topical Delivery System for Aceclofenac, *Ind j pharm edu res*. 2011, 45(1): 65-70.
- 11) Toshiyuki S, Daisuke O, Kenji H. Viscoelastic Behavior of Organogels. *Riron Oyo Rikigaku Koenkai Koen Ronbunshu*, 2003, 52: 477-478.
- 12) Dasgupta D. Hybrid thermoreversible gels from covalent polymers and Organogels, *Langmuir*, 2009, 25(15):85-93.
- 13) Guenet JM, *Microfibrillar Networks: Polymer Thermoreversible Gels vs Organogels*, *Macromolecular Symposia*, 2006, 241(1): 45-50.
- 14) Chen Z, A Thermally Stable and Long-Term-Stable Ionic-Liquid-Based Gel Electrolyte for Efficient Dye-Sensitized Solar Cells, *ChemPhysChem*, 2007, 8(9):1293-1297.
- 15) Scartazzini R, Luisi PL, Organogels from lecithins, *J Phys Chem*, 1988; 92: 829-833.
- 16) Murdan S, Gregoriadis G, Florence AT, Novel sorbitan monostearate Organogels, *Journal of Pharmaceutical Sciences*, 1999, 88(6): 608-614.
- 17) Terech P, Weiss RG, Low Molecular Mass Gelators of Organic Liquids and the Properties of Their Gels, *Chemical Reviews*, 1997, 97(8): 3133-3160.
- 18) Engelkamp H, Middelbeek S, Nolte RJM, Self-Assembly of Disk-Shaped Molecules to Coiled-Coil Aggregates with Tunable Helicity, *Science*, 1999, 284(5415): 785-788.
- 19) Motulsky A, Characterization and biocompatibility of Organogels based on lalanine for parenteral drug delivery implants, *Biomaterials*, 2005, 26(31): 6242-6253.
- 20) 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.
- 21) Shchipunov YA, Lecithin Organogel: a micellar system with unique properties, *Colloids Surf A Physicochemical and Engineering Aspects*. 2001, 183-185:541-554.
- 22) Hanahan DJ, In: *A Guide to Phospholipid Chemistry*. New York, NY: Oxford University Press, 1997.
- 23) Wendel A, In: *Kirk-Othmer Encyclopedia of Chemical Technology*, New York, NY: John Wiley & Sons, 1995, 192-193.
- 24) Schneider M, Industrial production of phospholipids-lecithin processing, *Lipid Technology*, 1997, 9:109-116.
- 25) Capitani D, Segre AL, Dreher F, Walde P, Luisi PL, Multinuclear NMR investigation of

- phosphatidylcholine Organogels, *J Phys Chem*, 1996,100:15211-15217.
- 26) Shchipunov YA, Lecithin Organogel: a micellar system with unique Properties, *Colloids Surf A Physicochemical and Engineering Aspects*, 2001, 183(185):541-554.
- 27) Shumilina EV, Khromova Y, Shchipunov YA, Lecithin Organogels: the effect of phosphatidylethanolamine additives, *Colloid J*, 1997, 59:514-518.
- 28) Murdan S, Gregoriadis G, Florence AT, Novel sorbitan monostearate Organogels. *Journal of pharmaceutical sciences*, 1999, 88(6): 608-614.
- 29) Murdan S, Gregoriadis G, Florence AT, Inverse toroidal vesicles: precursors of tubules in sorbitan monostearate Organogels, *International Journal of Pharmaceutics*, 1999, 183(1): 47-49.
- 30) Fernandez P, Andr eb A, Riegera J, Kuhnlea A, Nano-emulsion formation by emulsion phase inversion, *Colloids and Surfaces A: Physicochem, Eng. Aspects*, 2004; 251:53-58.
- 31) Danniellsson I, Lindman B, The definition of microemulsion; *Colloids and Surfaces* 1998, 1(3):391-392.
- 32) El-laithy HM, El-shoboury KMF, The developmental cutina lipogel and gel microemulsion for topical administration of fluconazole, *AAPS Pharm. Sci. Tech*, 2002, 3:35, 1-9.
- 33) Nandi I, Barri M, Joshi H, Study of IPM microemulsion system containing cyclodextrin to improve the solubility of 2 model hydrophobic drug, *AAPS Pharm. Sci. Tech*, 2003, 4: 10, 1-9.
- 34) Shafiq S, Faiyaz S, Sushma T, Ahmad FJ, Khar RK, Ali M, Design and development of oral oil in water ramipril nanoemulsion formulation: in vitro and in vivo evaluation, *J Biomed Nanotech*. 2007, 3: 28-44.
- 35) Penzes T, Csoka I, Eros I, Rheological analysis of the structural properties effecting the percutaneous absorption and stability in pharmaceutical Organogels, *Rheol Acta*, 2004, 43: 457-463.
- 36) Penzes T, Blazso G, Aigner Z, Topical absorption of piroxicam from Organogels — in vitro and in vivo correlations, *Int. J. Pharm*, 2005, 298:47-54.
- 37) Kang L, Liu XY, Sawant PD, SMGA gels for the skin permeation of haloperidol, *J. Control. Release*, 2005, 106: 88-98.
- 38) Lim PF, Liu XY, Kang L, Limonene GP1/PG Organogel as a vehicle in transdermal delivery of haloperidol, *Int. J. Pharm*, 2006, 311: 157-164.
- 39) Robinson RC, Plastibase, a hydrocarbon gel ointment base, *Bull. Sch. Med. Univ. Md*, 1955, 40: 86-89.
- 40) Najjar TA, Sleeper HR, Calabresi P, The use of 5-iodo-2'-deoxyuridine (IUDR) in Orabase and plastibase for treatment of oral herpes simplex, *J. Oral Med*.1969, 24: 53-57.
- 41) Mukhopadhyay S, Maitra U, A notable group of low molecular mass natural products that form gel are some of the bile acids, *Curr. Sci*, 2004; 87: 1666.
- 42) Lipowitz AV, Gelation of an aqueous solution of lithium urate *Chem. Pharm*, 1841, 38: 348.
- 43) Goto S, Kawata M, Suzuki T, Kim NS, Ito C, Preparation and evaluation of Eudragit gels. I. Eudragit Organogels containing drugs as rectal sustained-release preparations, *J. Pharm. Sci*, 1991, 80(10):958-961.
- 44) Kawata M, Suzuki T, Kim NS, Ito T, Kurita A, Miyagoe Y, Goto S, Preparation and evaluation of Eudragit gels: II: in vitro release of salicylic acid, sodium salicylate, and ketoprofen from Eudragit L and S Organogels. *J. Pharm. Sci*.1991, 80(11):1072-1074.
- 45) Goto S, Kawata M, Suzuki T, Kim NS, Ito C, Preparation and evaluation of Eudragit gels. I. Eudragit Organogels containing drugs as rectal sustained-release preparations, *J. Pharm. Sci*, 1991, 80(10):958-961.
- 46) Murdan S, Organogels in drug delivery, *Expert Opin, Drug Deliv*, 2005, 2(3).
- 47) Couffin-hoarau AC, Motulsky A, Delmas P, Leroux JC: In situ forming pharmaceutical Organogels based on the self-assembly of L-alanine derivatives, *Pharm. Res*, 2004, 21(3):454-457.
- 48) Murdan S, Organogels in drug delivery, *Expert Opin, Drug Deliv*, 2005, 2(3).
- 49) The history of Pluronic Lecithin Orgaogel: an interview with Marty Jones, *Int. J.Pharm. Compounding*, 2003, 7(3):180-183.
- 50) <http://www.ijpc.com/editorial/Search> By Keyword.cfm Internatinal Journal of Pharmaceutical Compounding website.
- 51) Schaller JL, Briggs B, Briggs M: Progesterone Organogel for premenstrual dysphoric disorder, *J. Am. Acad. Child Adolesc. Psychiatry*, 2000, 39(5):546.
- 52) Shippen E: Letter to the editor re: progesterone Organogel for premenstrual dysphoric disorder, *J. Am. Acad. Child Adolesc. Psychiatry*, 2001, 40(3):262.
- 53) Charoenbanpachon S, Krasieva T, Ebihara A, Osann K, Wilder SP, Acceleration of ALA induced Pp IX fluorescence development in the oral mucosa. *Lasers Surg. Med*, 2003, 32:185-188.
- 54) Marek CL: Issues and opportunities: compounding for dentistry, *Int. J. Pharm. Compounding* 1999, 3:4-7.
- 55) Padilla M, Clark GT, Merrill RL: Topical medications for orofacial neuropathic pain: a review, *J. Am. Dent. Assoc*, 2000, 131:184-195.
- 56) Grace D, Rogers J, Skeith K, Topical diclofenac versus placebo: a double blind, randomized clinical trial in patients with osteoarthritis of the knee, *J. Rheumatol*, 1999, 26: 2659-2663.
- 57) Mahler P, Mahler F, Duruz H, Double-blind, randomized, controlled study on the efficacy and safety of a novel diclofenac epolamine gel formulated with lecithin for the treatment of sprains, strains and contusions, *Drugs Exp. Clin. Res*, 2003, 29: 45-52.
- 58) Agrawal GP, Juneja M, Agrawal S, Preparation and characterization of reverse micelle based

- Organogels of piroxicam, *Pharmazie*, 2004, 59: 191–193.
- 59) Nastruzzi C, Gambari R, Antitumor activity of (trans) dermally delivered aromatic tetra-amidines, *J. Control. Release*, 1994, 29: 53–62.
- 60) Willmann H, Walde P, Luisi PL, Lecithin Organogel as matrix for transdermal transport of drugs, *J. Pharm. Sci.*, 1992, 81: 871–874.
- 61) Bhatnagar S, Vyas SP, Organogel-based system for transdermal delivery of propranolol, *J. Microencapsul* 1994, 67: 431–438.
- 62) Aboofazeli R, Zia H, Needham TE, Transdermal delivery of nicardipine: an approach to in vitro permeation enhancement, *Drug Deliv.* 2002, 9: 239–247.
- 63) Shaikh IM, Jadhav KR, Gide PS, Topical delivery of aceclofenac from lecithin Organogels: preformulation study, *Curr. Drug Deliv*, 2006, 3: 417–427.
- 64) Dreher F, Walde P, Walter P, Interaction of a lecithin microemulsion gel with human stratum corneum and its effect on transdermal transport, *J. Control. Release*, 1997, 45: 131–140.
- 65) Gao ZH, Crowley WR, Shukla AJ, Controlled release of contraceptive steroids from biodegradable and injectable gel formulations— in vivo evaluation, *Pharm. Res.*, 1995, 12: 864–868.
- 66) Kang L, Liu XY, Sawant PD, SMGA gels for the skin permeation of haloperidol, *J. Control. Release*, 2005, 106: 88–98.
- 67) Lim PF, Liu XY, Kang L, Limonene GP1/PG Organogel as a vehicle in transdermal delivery of haloperidol, *Int. J. Pharm*, 2006, 311: 157–164.
- 68) Robinson RC, Plastibase, a hydrocarbon gel ointment base, *Bull. Sch. Med. Univ. Md*, 1955, 40: 86–89.
- 69) Pisal S, Shelke V, Mahadik K, Effect of Organogel components on in vitro nasal delivery of propranolol hydrochloride, *AAPS PharmSciTech*, 2004, 5: 63.
- 70) Murdan S, Andrysek T, Son D, Novel gels and their dispersions — oral drug delivery systems for ciclosporin, *Int. J. Pharm*, 2005, 300: 113–124.
- 71) Murdan S, Gregoriadis G, Florence AT, Non-ionic surfactant based Organogels incorporating niosomes, *S.T.P. Pharm. Sci.*, 1996, 6: 44–48.
- 72) Murdan S, Bergh VBD, Gregoriadis G, Water-in-sorbitan monostearate Organogels (water-in-oil gels), *J. Pharm. Sci.* 1999, 88: 615–619.
- 73) Vintiloiu A, Lafleur M, Bastiat G, In situ-forming oleogel implant for sustained release of rivastigmine, *Pharm. Res.* (in press), 2008.
- 74) Plourde F, Motulsky A, Couffin-Hoarau AC, First report on the efficacy of L-alanine-based in situ-forming implants for the long-term parenteral delivery of drugs, *J. Control. Release*, 2005, 108: 433–441.
- 75) Murdan S, Gregoriadis G, Florence AT, Sorbitan monostearate/polysorbate 20 Organogels containing niosomes: a delivery vehicle for antigens? *Eur. J. Pharm. Sci.*, 1999, 8: 177–186.
- 76) Aulton ME; *The science of dosage form design*, 2nd Edition, Churchill Livingstone New York, 2002; 89.
- 77) Allen LV, Popovich J, Nicholas G, Ansel HC, *pharmaceutical Dosage form and drug delivery system*, 7th edition, Williams and Wilkins, New York, 375.
- 78) Suzuki M, L-lysine based gemini Organogelators: their Organogelation properties and thermally stable Organogels. *Org Biomol Chem.*, 2003, 1(22): 4124–31.
- 79) Raut SY, Suruse PB, Shivhare UD, Bhusari KP, Development and evaluation of non-ionic surfactant based Organogels for transdermal delivery of zidovudine *Pharmacie Globale (IJCP)* 2010, 1(3):1–7.