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Organogels: Properties and Applications in drug delivery

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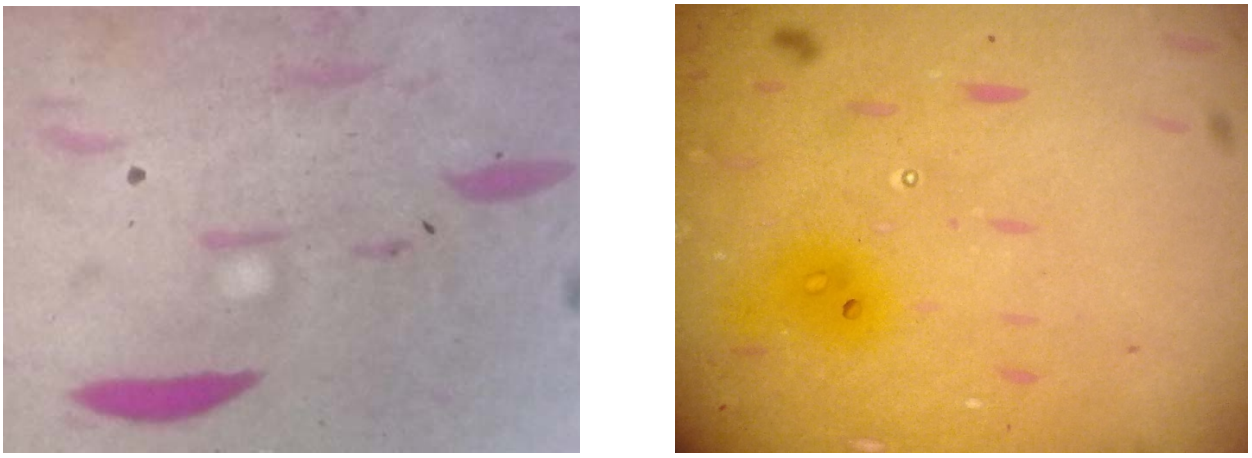
Abstract

Organogel, a viscoelastic system, can be regarded as a semi-solid preparation which has an immobilized external apolar phase. 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. In general, organogels are thermodynamically stable in nature and have been explored as matrices for the delivery of bioactive agents. In the current manuscript, attempts have been made to understand the properties of organogels, various types of organogelators and some applications of the organogels in controlled delivery.

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

1. Introduction

A gel may be defined as a semi-solid formulation having an external solvent phase, apolar (organogels) or polar (hydrogel), immobilized within the spaces available of a three-dimensional networked structure [1-7]. In the current review, attempts will be made to have an insight on the mechanism of formation and applications of the organogels as a delivery system. The organogels may be regarded as bi-continuous systems consisting of gelators and apolar solvent, which may or may not contain water-molecules entrapped within the self-assembled structures of the gelator (Figure 1). The gelators, when used in concentration < 15 % (approx.), may undergo physical or chemical interactions so as to form self-assembled fibrous structures which get entangled with each other resulting in the formation of a three-dimensional networked structure. The three-dimensional networked structure, hence formed, prevents the flow of external apolar phase [1, 8] . Some common examples of gelators include sterol, sorbitan monostearate, lecithin and cholesteryl anthraquinone derivates. 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. 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 [9]. Various organogel-based formulations have been designed to administer of the bioactive agents by different routes administration [1].



(a) **(b)**

Figure 1. Microstructure of lanolin-based organogel (a) polar phase stained with rhodamine dye; (b) apolar phase stained with fluorol yellow 088 and polar phase stained with rhodamine dye

2. Organogelators

The role of organogelators in designing organogels is evident from the above discussion. The organogelators may be categorized into two groups based on their capability to form hydrogen bonding. The examples of organogelators which do not form hydrogen hydrogen bonding include anthracene, anthraquinone and steroid based molecules whereas the hydrogen bond forming organogelators include aminoacids, amide and urea moieties and carbohydrates [10]. It would be wise to have a discussion on the different organogelators, before we discuss about the different types of organogels and their applications in controlled delivery.

1) 4-tertbutyl-1-aryl cyclohexanols derivative organogelators

4-tertbutyl-1-aryl cyclohexanols, categorized under arylcyclohexanol derivatives, helps in designing thermo-reversible organogels. These gelators are solid at room-temperature having low solubility in apolar solvents viz. cyclohexane, benzene and carbon tetrachloride. If the derivatives have the phenyl group in axial configuration, the compounds induce the formation of organogels unlike the derivatives having the phenyl group in equatorial configuration, which fail to induce the formation of organogels. The organogels prepared using these derivatives may be either transparent or turbid and depends on the type of the apolar solvent [11].

2) **Polymer organogelators**

Various polymeric structures have been used as an organogelators. Some common examples of polymeric organogelators include L-lysine derivatives apart from the conventional polymers like poly(ethylene glycol), polycarbonate, polyesters, and poly(alkylene) [12]. The polymer organogelators have been found to induce organogelation even at very low concentrations and their gelling capability of these gelators may be tailored by modifying the chemical structure of the polymer backbone. The gels developed by polymeric organogelators generally have lower gel-sol transition temperature and a comparatively higher gel strength when compared with organogels developed with low-molecular weight organogelators [13].

3) **Gemini organogelators**

The word Gemini is a latin word meaning twins. L-lysine based Gemini organogelators was first synthesized by Suzuki et al. (2003). The authors synthesized the Gemini organogelators which had two L-lysine derivates connected with alkylene spacer chains, of varying chain lengths, by amide bonds. They reported that bis(Nε-lauroyl-L-lysine ethyl ester) oxalyl amide organogelator was able to immobilize a variety of apolar solvents. Apart from this, various other oxalyl amide derivatives containing various alkyl ester groups (e.g. hexyl, decyl, dodecyl, 2-ethyl-1-hexyl and 3,5,5-trimethylhexyl) have also showed relatively good organogelation property [14].

4) **Boc-Ala(1)-Aib(2)-β-Ala(3)-OMe organogelator**

Boc-Ala(1)-Aib(2)-β-Ala(3)-OMe is a synthetic tripeptide which has the capability to undergo self-association so as to form thermoreversible transparent gels in the presence of various apolar solvents viz. 1, 2-dichlorobenzene (DCB), monochlorobenzene and benzene [15-16].

5) **Low Molecular Weight (LMW) organogelators**

As the name suggests, LMW organogelators are low molecular weight compounds, *viz.* fatty acids and n-alkanes, which have the ability to immobilize apolar solvents, even when used in small concentrations (< 2%) [8]. These gelators may produce either solid-fiber matrix or fluid-fiber matrix depending upon the physical intermolecular interactions. Solid-fiber matrix may be formed when a heated mixture of the organogelators in apolar solvent is cooled down below the

solubility limit of the organogelators. This results in the precipitation of the organogelators as fiber-like structures which undergoes physical interaction so as to form a gelled structure. These solid fiber-like structures align themselves into bundles. On the other hand, fluid-fiber matrix is formed by the addition of polar solvent into a solution of amphipaths in apolar solvents. Amphipaths in apolar solvents are present as reverse micelles, which on addition of minute quantity of water forms tubular reverse micellar structures. As more water is added, the tubular reverse micelles get elongated and subsequent get entangled with each other. Increase in the interactions amongst the tubular structures results in the formation of a gelled structure. In general, solid-fiber matrix organogels have improved mechanical properties as compared with the fluid-fiber matrix organogels. This can be attributed to the highly ordered structures present in the solid-fiber matrix organogels as compared to the simple chain entanglements in the fluid-fiber matrix organogels [1].

Apart from the above-mentioned organogels, various amphiphiles having the ability to form self-assembled structures in the presence of apolar solvents have also been tried. These organogelators may be categorized as the derivatives and metallic salts of fatty acids, steroids, amino -acid type molecules, carbohydrate amphiphiles, anthryl derivatives and organometallic compounds [2, 9].

3. Properties organogels

In the present section, attempts will be made to discuss about the various physicochemical properties of the organogels.

a. Viscoelaticity- Viscoelasticity is a term which is associated with the materials having both viscous and elastic properties. The organogels seems to follow Maxwell model of viscoelasticity [17]. As discussed above, organogels are the three-dimensional structures which are formed due to the physical interactions amongst the gelator molecules. The organogels behaves like a solid at lower shear rates and hence shows an elastic property. As the shear stress is increased, the physical interacting points amongst the fiber structures start getting weakened until the shear stress is high enough to disrupt the interactions amongst the fiber structures, when

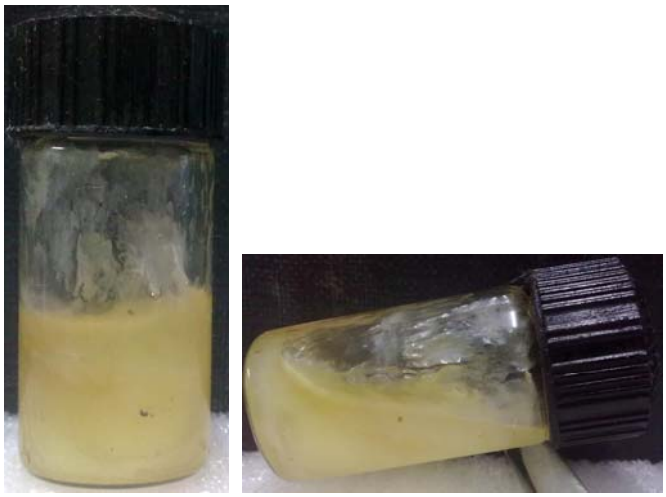
the organogels starts flowing. This behavior may be best explained with the plastic flow behavior [18-19].

The flow property of the organogels can also be understood by monitoring the rheological properties of the gelator solution in apolar solvents during the preparation of the organogels. Let us first take up the case of fluid-fiber containing organogels. It has been observed that, when the trace amounts of water is added to the gelator solution in apolar solvents, there is a subsequent exponential increase in the viscosity which may be attributed to the formation of rigid structure due to the entanglement of the fluid-fiber structures (tubular reverse micelles). A typical example includes the formation of organogels in the presence of lecithin where there is an increase in the viscosity by a factor of 10^4-10^6 (approx.) when water is added to the apolar solution of lecithin [20-21]. In case of solid-fiber containing organogels, the gelators are dissolved in the apolar solvents at a higher temperature. With the subsequent decrease in the temperature there is an increase in the viscosity of the solution which can be attributed to the precipitation of organogelators and subsequent physical interactions amongst the same, resulting in the formation of the organogels.

b. 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 which does not allow the polarized light to pass through the matrix. This property of the organogels of not allowing the polarized light to pass through it's matrix is regarded as non-birefringent [22-24].

c. Thermoreversibility- As the organogels are heated up above a critical temperature, the organogels loses its solid matrix- like structure and starts flowing (Figure 2). This has been attributed to the disruption in the physical interactions amongst the gelator molecules due to the increase in the thermal energy within the organogels. But as the heated organogels systems are subsequently cooled down, the physical interaction amongst the organogelators prevail and the organogels revert back to the more stable configuration [25-27].

d. Thermostability- The organogels are inherently 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 in the total free energy of the system and renders the organogels as low-energy thermostable system. Due to the inherent thermostability of the organogels, they have been proposed as a delivery vehicle for bioactive agents and for cosmetic applications where a longer shelf-life is desirable [28-29].
e. Optical clarity- 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 [21, 30-31].
f. Chirality effects- The presence of chirality in the LMW gelators have been found to affect the growth and the stability of the solid-fiber networks. Thermoreversibility of the gels formed due to the formation of the self-assembled solid-fiber network has also been associated with the chirality. 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 [1, 32-34].
g. Biocompatibility- Initially, organogels were developed using various non-biocompatible organogels which rendered the organogels non-biocompatible. Of late, research on organogels using various biocompatible constituents has opened up new dimensions for the use of the same in various biomedical applications [1, 35].



(a) (b)

Figure 2. Thermal behavior of the organogels (a) semi-solid state of the organogel at room-temperature and (b) sol state of the organogel at 60 ^{o}C

4. Common types of Organogels

4.1. Lecithin organogels

Lecithin is a phospholipid, extracted from various plants and animal tissues apart from the egg yolk. The use of lecithin for designing the organogels was first described by Scartazzini and Luisi during the year 1988 [30]. Since then, a lot of research has been done on lecithin-based organogels. The lecithin procured from natural sources is able to form the gelled structures and has been attributed to the presence of unsaturated chemistry within its structure. The synthetic lecithin and hydrogenated soy lecithin failed to develop organogels. Apart from the chemical structure, the purity of the extracted lecithin also plays an important role in the formation of organogels. Experimental results indicate that the lecithin fails to initiate the process of gellification of the apolar solvent if the lecithin contains < 95% phosphatidyl content. The lecithin-based organogels have been found to be thermodynamically stable, thermoreversible (sol-to-gel transition temperature at 40 ^{o}C), transparent, viscoelastic, biocompatible and non-irritant [21, 36]. The organogels prepared using lecithin has been found to have an isotropic structure. The lecithin organogels help either in the solubilization or accommodation of various guest molecules within its structure. These properties of the lecithin organogels have generated great potential for the use of the same as a controlled delivery vehicle. Typically, in a lecithin organogels the molar ratio of water to lecithin may vary from 1 to 12 [37]. The formation of the

organogel in the presence of lecithin may be attributed to the entanglement of fluid-fiber reverse micellar tubular structures [21]. From the above discussion, it is clear that the lecithin-based organogels have three distinct components *viz.* an apolar phase, a polar phase and a surfactant (lecithin).

4.2. Pluronic Lecithin Organogel (PLO)

PLO is a soy lecithin-based organogels which consists of isopropyl palmitate or isopropyl myristate, water and Pluronic F127 (also known as Poloxamer 407). PLO may or may not contain sorbic acid in both the phases, which acts as a preservative. It occurs as yellow a colored, odorless and opaque gel which is quickly absorbed from the skin. Like lecithin organogels, PLO also consists of entangled tubular reverse-micelle structures which form temporal three-dimensional structures [38]. The apolar phase in the PLO constitutes 22 % (v/v) and hence is often regarded as micro-emulsion-based gel [39]. PLO is thermostable, viscoelastic and biocompatible in nature. PLO has also been found to produce minimal skin irritation. It has been used as a delivery vehicle for both hydrophobic and hydrophilic molecules for topical and transdermal applications [38].

4.3. Premium lecithin organogels (PrLO)

The PrLO is a second general lecithin organogel and has got higher thermostability apart from its non-greasy and non-tacky nature, which provides a cosmetically pleasing acceptability. This gel do not have pluronic derivative, which results in the avoidance of the skin-irritation and thereby local skin-intolerance reactions. PrLO is being marketed as ready-to-use intradermal bases and hence are also sometimes regarded PrLO premixed gels. The use of PrLO as a carrier for drug delivery has indicated that the gel help in achieving improved bioavailability in the tissues by improving the penetration of the bioactive agents [39-41]. This gel has been successfully used to accommodate various bioactive agents, *viz.* diclofenac, ibuprofen, ketoprofen and progesterone, and has been regarded as vehicle of choice for intradermal drug delivery [40-41].

4.4. Limonene GP1/PG organogel

Limonene, a terpene, has been found to be an excellent penetration enhancer and hence has been incorporated within various transdermal formulations for the improving the penetration of the

bioactive agent across the transdermal layer, thereby improving the bioavailability of the bioactive agent within the dermal tissue [42]. Limonene incorporated within dibutyllauroylglutamide (GP1) in propylene glycol (PG) biocompatible organogels has been studied extensively [2, 42] .

GP1 is an organogelator, which can be categorized as amino acid-type gelators. It has been proposed that the GP1 organogelators undergoes extensive intermolecular hydrogen bonding amongst the amide groups present within its structure apart from the hydrophobic interactions amongst the long alkyl chains. Like any other amino acid-type organogelators, GP1 also forms a solid-fiber based matrix. The GP1/PG organogels can be prepared by mixing the appropriate amounts of GP1, limonene and PG with the subsequent incubation of the same at 120 ^{o}C. When the mixture is cooled down, it forms a white gel [2, 43-44] . It was found that the presence of limonene within the GP1/PG organogels resulted in the alteration of the rheological properties of the organogels though there was no significant change in the chemical stability of the organogels. Apart from limonene, various other terpene-based penetration enhancers (e.g. linalool, farnesol and cineole) have also been incorporated successfully in GP1/PG organogels. The presence of penetration enhancers within the organogels results in the improvement of the rate permeation of the bioactive agents [2, 42, 45].

4.5. Gelatin stabilized microemulsion based organogel (MBG)

Gelatin is a protein which has been used as a structuring agent in various food preparations having excess of aqueous phase. It forms a gelled structure when a concentrated heated solution of gelatin having temperature in excess of 40 ^{o}C is cooled down to a temperature below 35 ^{o}C. Based on the above, it is expected that gelatin will only gel the aqueous phase (shielded within the reverse micelles) of the water-in-oil microemulsion, which may be responsible for the phase separation of the aqueous gel and would make the system cloudy in nature. But this does not happen. The addition of gelatin to the water-in-oil microemulsion results in the gellation of the whole micellar solution and the gel formed is transparent in nature [46-47]. Microemulsions are preferred for the development of gelatin stabilized organogels because of the thermostable nature and the ease of preparation of the same [48]. A typical pharmaceutical grade water-in-oil microemulsion used for the preparation of MBG contains isopropyl myristate, AOT, tween 85

and water [22, 47]. The MBGs have been used to device topical and/or transdermal controlled delivery vehicle for hydrophobic bioactive agents [49].

4.6. Fatty acid derived sorbitan Organogels

The gelators categorized under this category include sorbitan monostearate and sorbitan monopalmitate. These gelators are hydrophobic non-ionic molecules having surface active properties and have the ability to immobilize various solvents *viz.* isopropyl myristate, and vegetable oils. These gelators form solid-fiber matrix when the heated solution of gelator in apolar solvent is cooled down. The formation of the gel has been attributed to the formation of toroidal reverse micelles as the temperature is lowered. The toroidal reverse micelles reorganize themselves to form rod-shaped tubules which subsequently undergo physical interaction amongst each other thereby forming a three-dimensional networked structure. The gels developed by using these gelators are opaque, thermoreversible and thermostable at room-temperature for weeks [24, 31].

Organogels using fatty acid gelators may also be prepared by dissolving the gelators in a water-in-oil emulsion at a higher temperature followed by the decrease of the emulsion temperature. The decrease in the temperature results in the decrease in the solubility of the gelator with the subsequent precipitation and self-assembly of the gelators into network of tubules, which gets entangled so as to form a gelled structure [50].

4.7. Poly (ethylene) organogels

The polyethylene organogels are colorless in nature, which are formed when the low molecular weight polyethylene is dissolved in mineral oil at a temperature >130 ^{o}C and subsequently shocked cooled. These organogels have been extensively used as ointment bases. The formation of gelled structure may be attributed to the physical interactions of the solid-fibers formed due to the precipitation of the polyethylene molecules [1].

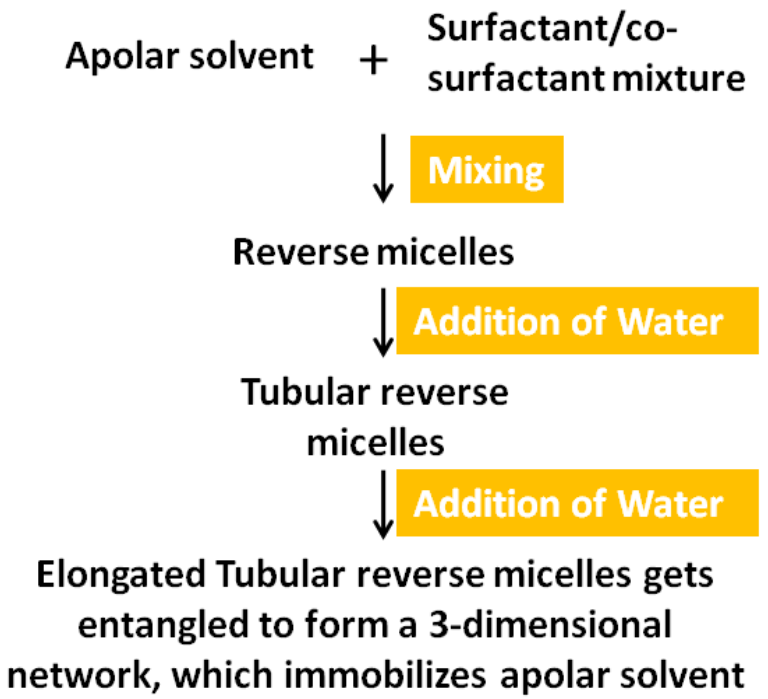


Figure 3. Method of formation of organogels by fluid-filled fiber mechanism

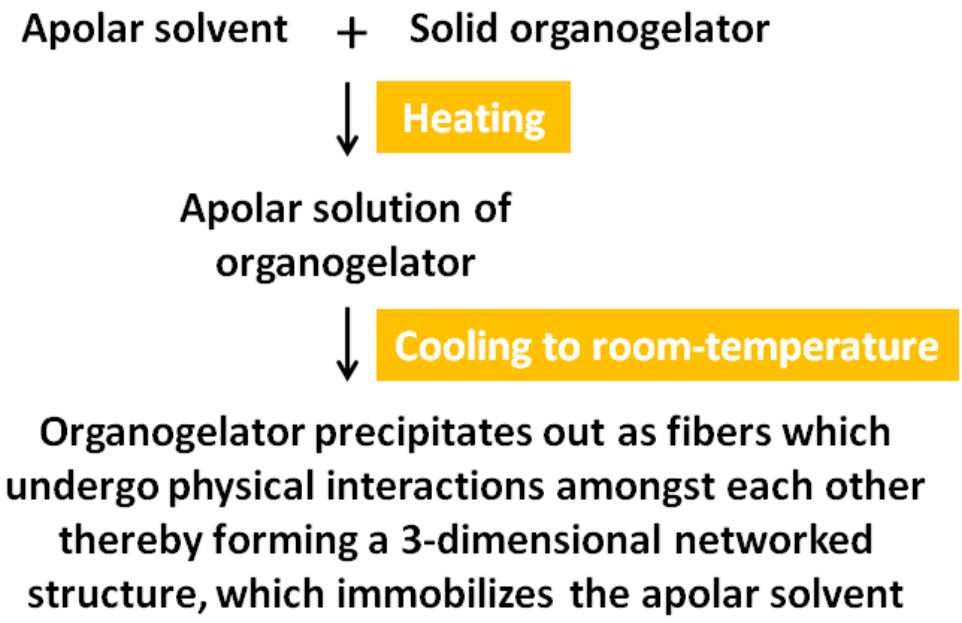


Figure 4. Method of formation of organogels by solid fiber mechanism

5. Applications of organogels in drug delivery

After the report of Scartazzini and Luisi on lecithin organogels, there has been an increased interest in the development of organogels-based products [37]. The interest on the organogels-based products has exponentially grown in the last decade. The use of the organogels as a drug delivery vehicle was quite limited even in the recent past as most organogels were prepared using components which are regarded as non-biocompatible. Of late, this trend has changed and many reports are available on the development of organogels with biocompatible components. But still now only a handful number of organogels are being studied as a drug delivery vehicle. In the current section, attempts will be made to have an insight on the application of organogels in drug delivery system via different routes of administration. Table 1 identifies various bioactive agents which have been incorporated successfully in various organogels.

Table 1: Bioactive agents successfully incorporated within various organogels

Type of Organogels	**Bioactive agents incorporated**	**References**
Lecithin organogels	Broxaterol, scopolamine, Nicardipine	[51-52]
PLO organogels	Methimazole, dexamethasone	[53-54]
Premium lecithin organogels	Methimazole	[55]
MBG organogels	Propranolol hydrochloride, Ketorolac tromethamine	[56-57]
Sorbitan organogels	Antigens, sumatriptan, doxorubicin	[58-61]
Poly (ethylene) organogels	Leuprolide	[62]

5.1. Parenteral delivery

In general, sorbitan monostearate organogels have a very short half-life at the injection site. This may be attributed to the diffusion of water molecules within the gelled structure which results in the subsequent disruption of the networked structure due to the emulsification of the gel surface [63]. The same group has also reported the development of a sorbitan monostearate based organogels which has shown sustained delivery of a model antigen and radiolabelled bovine serum albumin after intra-muscular administration of the same in mice. The results indicated the

probable use of the formulation as depot [50, 64]. L-alanine based injectable in situ forming organogels may be used for the delivery of labile macromolecular bioactive agents. These in situ forming organogels may be used for sustained delivery of bioactive agents after the same is being administered within the body. Various L-alanine derivates, viz. N-stearoyl l-alanine (m)ethyl esters, may be used to immobilize vegetable and synthetic oil in the presence of a hydrophilic solvent. These gels are thermoreversible in nature. The gel-to-sol transition of the l-alanine based organogels was dependent on the concentration of the gelator and the nature of the solvent [10, 35]. Experimental results indicates that the organogels system, when injected subcutaneously in rats releases the bioactive agents (e.g. leuprolide) for a period of 14-25 days with subsequent degradation of the gelled structure [10]. The histopathological examination of injected site indicated biocompatibility of the l-alanine organogels [35].

Tokuyama and Kato synthesized a polymer of stearyl acrylate by free radical polymerization using ethylene glycol dimethacrylate as a crosslinking agent. The crosslinking reaction was carried out in oleyl alcohol, a plant derived oil. The organogel, so developed, were thermo-sensitive in nature which allowed release of the incorporated bioactive agent when the temperature was above 40 ^{o}C while the release was ceased when the temperature fell below 36 ^{o}C [65].

5.2. Oral delivery

To-date, only two references for the oral delivery systems have been reported. The first report on the use of organogels for oral delivery of bioactive agents was reported in the year of 2005 [66]. In the study, the authors reported that cyclosporine A (a potent immunosuppressant) showed improved activity when the same was delivered orally to beagle dogs as sorbitan monoleate-based organogel formulation [66]. The second report deals with the use of 12-hydroxystearic acid, an organogelator, for the development of organogels with soyabean oil as an apolar phase. Ibuprofen, a NSAID (non-steroidal anti-inflammatroy drug), was incorporated within the gelled structure. The release studies indicated that with the increase in the organogelator concentration within the organogel, there was a subsequent decrease in the release rate of the organogels. In vivo studies in rats showed that the organogels may be used a controlled delivery vehicle for oral delivery of lipophilic compounds [67].

5.3. Topical/transdermal delivery

Lecithin-based organogels have long been tried as a matrix for transdermal delivery systems because of its ability to improve the transport rate of the bioactive agents (e.g. aromatic tetra-amidines, amino acids and peptides), apart from its proven long-term biocompatibility and low irritability potential [51, 68-70]. The biocompatibility of these gels has also been confirmed by histological studies [51]. The transdermal administration of aromatic tetra-amidines loaded lecithin organogels were able to reduce the tumor cell growth in nude mice xenografted with the highly tumorigenic cell line FH06T1-1 [71]. The methyl nicotinate incorporated within lecithin gel showed almost complete percutaneous absorption in experimental human models in a short period of time, characterized by the induction of erythema [72]. In a similar experiment, organogels were developed using lecithin and fatty acid esters, which contained indomethacin. The permeation experiments conducted with excised hairless rat skin indicated that the permeation of the indomethacin was higher from the gels which had side chains on both fatty-acid and alcohol moieties [73]. Similar results were obtained with isolated human skin when the gels were loaded with indomethacin and diclofenac [74]. Dreher *et al.* (1997) reported that there is an interaction amongst the isopropyl palmitate (present in lecithin organogels) and the stratum corneum which results in the disruption in the organization of the lipids present in the stratum corneum, isolated from human. This result was quite unexpected as the recent in vivo studies in human have indicated the non-irritant nature of the lecithin gels [64, 74].

Sorbitan monostearate has been exploited extensively for the development of organogels [31, 64, 75]. Sorbitan monostearate has been used along with Tween 20 for immobilizing hexadecane. 17 % (v/v) of aqueous phase may be easily incorporated within these structures and are capable of carrying hydrophilic drugs and vaccines along with hydrophobic compounds [64, 75].

The percutaneous delivery of the bioactive agents may further be improved upon by using compounds known as permeation enhancers. The use of terpenes (e.g. linalool, cineole, limonene, farnesol) as penetration enhancers is very common [2, 42, 45]. The presence of the gelator like GP1in the development of the organogels results in the increased permeation lag-time [45].

The gelatin-containing microemulsion-based organogels (MBGs) are electroactive in nature, unlike most organogels, and may be used in iontophoretic delivery systems [76]. The iontophoretic delivery system which uses MBGs, loaded with bioactive agents, causes release in

the bioactive agent at higher rates when compared to passive diffusion. Apart from this, MBGs results in improved microbial resistance [22].

6. Conclusion

Since 1988, there has been an exponential rise in exploring the possibility of the use of organogels as a drug delivery vehicle. This has been greatly motivated due to the longer shelf-life, ease of preparation and thermo-reversible nature of the organogels-based formulations. Apart from this, the ability of the organogels to accommodate both hydrophilic and hydrophobic compounds within its structure has also widened the scope of use of organogels in various delivery systems. Once the full biocompatibility profile of the organogels is available, these self-assembled structures will take not longer to increase its share-hold within the pharmaceutical and nutraceutical industries by replacing most of the conventional dosing and structuring systems.

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