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ORGANOGELS – REVIEW

P. V. Kamala Kumari[*1], Y. Srinivasa Rao[1], G. Ekshitha, V. Harika

Department of Pharmaceutics, Vignan Institute of Pharmaceutical Technology, Beside VSEZ, Duvvada, Visakhapatnam-49

*Corresponding Author E-mail: kamalaparavastu@gmail.com.

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ABSTRACT

Organogels are semi- solid systems, in which an organic liquid phase is immobilized by a three-dimensional network composed of self- assembled inter-wined gelator fibers, platelets, tubules. Despite of the liquid composition, there exist a difference in the morphological appearance of solids and rheological behavior. These organogels have specific molecular requirements like gelation, depending on the physical and fiber interactions. In the last decade, interest in physical organogels has grown rapidly with the discovery and synthesis of a very large number of diverse molecules, in which can gel organic solvents at low concentration. In general, organogels are thermodynamically stable in nature and utilized mainly for drug delivery of bioactive agents in toxicology. This review aims at providing an overview of organogels, its preparation, properties, characteristic parameters and various applications in different industries.

INTRODUCTION

The term gel is a soft, solid like material that has both solid and liquid components. The solid component is present as mesh or network of aggregates, which immobilizes the liquid component. For the last few decades, gels have been presented to the extent of a cliché, as being materials to recognize easily. The gel is said to be a hydrogel or an organogel or oleogel depending on the nature of the liquid component: water in hydrogels and non-dispersion medium like fixed oil, mineral oil, organic solvent in organogels referred to as organogelator [1]. It is now generally accepted that a gel is a semi-solid material composed of low concentrations (less than 15%) of gelator molecules that, in the presence of an appropriate solvent, self - assembled via physical or chemical interactions. Physical gels are held by weaker physical forces of attraction such as van der Waals interactions and hydrogen bonds, whereas chemical gels are held by covalent bonds. The macroscopic phase separation into crystalline and liquid layers is avoided in these systems owing to the balance between gelator aggregating forces and solubilizing solvent-aggregate interactions. The overall thermodynamic and kinetic gel stability results from the interplay of the opposing forces related to the organogelator's partial solubility in the continuous phase [2-5]. Hydrogels have been fabricated in a variety of different shapes such as rods, disks, films, microparticles depending on the intended applications and their administration. In addition to this some thermo responsive gels can be administered parenterally as a liquid, which forms a gel *in situ* at body temperature. The lower molecular weight organogels depends on physical interactions for the formation of aggregates sufficiently long to overlap and induce solvent gelation. Depending on the kinetic properties of aggregates, the lower molecular weight oragnogles are composed of both solid and

liquid fiber networks [6]. Despite the numerous trends in gelling processes as well as the impressive variety of gelators identified [7] it remains difficult to predict the molecular structure. Today still, the discovery of gelators remains serendipitous and is usually followed by investigative screening of different solvent systems potentially compatible with gelation. Prediction of gelation potential of a given molecule might seem possible by investigation of its propensity towards chemical or physical inter-molecular interactions; however no generalizations are so far possible. Many factors such as steric effects, rigidity, and polarity can counter the molecule's aggregating tendency. Control over the gelation process as well as the conception of new gelling molecules remain important challenges to face in the quest of new organogelators.

Organogel types and drug loaded

Organogels can be prepared by using various gelator molecules and they are grouped below with some model drugs loaded in them. From the below tabulations as shown in Table 2 and Table 3 we could observe that compared to other drugs, NSAID has been incorporated numerous numbers in organogel.

Method of preparation of organogels

Generally, organogels are prepared by heating a mixture of a gelator and an organic liquid (or organic solvent) in order to obtain a dispersion mixture, which after cooling at room temperature, leads to the formation of a jelly structure. Organogelator molecule interactions induce a gelator organization into well-defined aggregates, such as tubular rods, fibrils and fibers. Mainly three methods are used for the organogel preparation: fluid-filled fiber mechanism, solid fiber mechanism and mechanical homogenization and micro-irradiation method.

Fluid-filled fiber mechanism

The gelation process takes place with the addition of a trace amount of water into the solution of apolar solvent and surfactant, such as lecithin molecules. Before the addition of water, the surfactant is dispersed in the organic medium. Upon addition of small amount of water, the surfactant molecules assemble themselves together to form micelles and then to short tubular or cylindrical micellar aggregate. The water molecules bind stoichiometrically to the hydrophilic head of the surfactant molecules. The water molecules link two surfactant molecules together which forms linear networks with the hydrogen bonds between polar molecules and phosphate groups of the lecithin molecules. Long, flexible and wormlike tubular micellar structures were formed upon addition of small amount of water. Tubular micro-structures, thus formed, overlap and entangle with each other to form athree-dimensional gel network of fibrils and fibers, which possesses viscoelasticity and thermo-reversibility properties. The organic liquid gets entrapped in the spaces between the entangled reverse micelles [28]. In general firstly surfactants and co-surfactants mixtures were dissolved in a polar solvent that leads to formation of reverse micelles. Elongated tubular reverse micelle is entangled to form a 3- dimensional network.

Solid fiber mechanism

The solid fiber mechanism involves the dispersion of the solid organogelator into the apolar solvent by hot emulsification and formation and a polar liquid mixture of organogelator. After cooling to room temperature, organogelator molecules precipitate out as fibrils which undergo non-covalent physical interactions amongst each other and form a three dimensional fibrillar network structure. The apolar solvent is then immobilized by the gelator fibers and a semi-solid organogel is thus formed [29, 30].

Physico-chemical properties and specific characteristics of organogels [31].

Viscoelasticity

Organogels present both viscous and elastic properties and seem to follow Maxwell model of viscoelasticity. They behave solid-like formulation at lower shear rates and hence show an elastic property. At high shear stress, the physical interacting points between the fiber structures start getting weakened and when the shear stress is high enough to disrupt the interactions amongst the fiber structures, the organogels start to flow.

Non-birefringence

When viewed under polarized light, organogels appear as a dark matrix. This property of not allowing the polarized light to pass through its matrix is regarded as non-birefringent.

Thermo-reversibility

As the organogels are heated up above their characteristic T_{gel}, they lose their solid-like structure and start to flow. This has been attributed to the disruption in the physical interactions between the gelator molecules due to the increase in the thermal energy within the organogel. But as the heated organogels systems are subsequently cooled down, the physical interactions between organogelators prevail and organogels revert back to their initial solid- like consistency.

Thermostability

Organogels are inherently thermostable. As the gelators undergo self-assembly, it results in the decrease in the total free energy of the system and renders organogels as low- energy thermostable system. They thus present a suitable vehicle for bioactive agents and for cosmetic applications where a longer shelf-life is desirable.

Optical clarity

Depending on their composition, organogels may be transparent or opaque. As example, lecithin organogels are transparent in nature while the sorbitan mono-stearate organogels are opaque. The optical clarity depends also on the organogelator concentration. Generally, 5 %w/w is a threshold organogelator concentration from which organogels present a more pronounced opacity.

Biocompatibility

Initially, organogels were developed using various non-biocomaptible organogelators which rendered them unusable for therapeutic applications.

Chirality effect

The presence of chiral centers within the organogelators plays an important role in the formation of a compact molecular packing, which provides a thermodynamic and kinetic stability to the organogel system.

Characterization of organogels

Evaluation and physicochemical characterization are very important steps after organogel formation. Organogels show particular physico-chemical properties and characterization parameters which confirm the purity and the stability, evaluation techniques as shown in Table 4. [29].

APPLICATIONS OF ORGANOGELS

Organogels as vehicles for anti-cellulite ingredients

Cellulite leads to vascular, structural and hypertrophic alterations in adipose tissue. This is due to changes in the conjunctive dermic and subcutaneous tissue. Studies have been conducted to evaluate the properties of a delivery system made from a pluronic lecithin organogel formulation and two physiotherapeutic ingredients, *Aloe Vera* and *Hydrocotyleasiatica*. PLO have been the interest of many studies, and proved to be effective as a dermic, and transdermal vehicle of medication. PLO were formed with Pluronic F127™ (Poloxamer 407), isopropyl palmitate, soy lecithin and water. The advantage of the organogel over hydrogels with the same ingredients is that it facilitates the transdermal penetration to a greater degree. It is important in the treatment of cellulite as the ingredients must be able to reach the deepest layer of the skin to act upon the cells where fat is accumulated in the adipose tissue.

Organogels in antiperspirant gel formulation

A gelator of particular interest for many applications is HSA. Many patents have been filed describing formulations with HSA, cosmetic oil, antiperspirant actives, and sometimes a copolymer [32]. Even when used at relatively low concentration, HSA tends to give rise to rigid gels that have limited capacity to retain fluids. It has been found that HSA organogels modified by incorporating selected copolymers produce a more stable crystalline structure, which improves the oil retention, and thus a better fracture resistance. Better rheological properties also assess a facilitated spreadability over the skin [33]. Moreover, modified HSA organogels allow to overcome the use of higher hydrophilic lipophilic balance (HLB) surfactants, in particular anionic, many of which are potentially harsher on skin than the more lipophilic lower HLB surfactants.

Organogels in make-up products

In care and make up products, it is common to find a structured, namely gelled or rigidified, liquid fatty phase. This is particularly the case in solid compositions such as balms and lipsticks, eye shadows, concealers and foundation. This structuring is generally obtained with the aid of waxes or fillers.

Unfortunately, these adjuvants tend to mattify the composition which is not always wanted for some products. It is necessary to structure the fatty phase, meaning the oil phase, to limit its exudation from solid compositions and its migration after application. It has been found that the use of organogelators combined with particular polymers, allowed to structure oil-based phases. Gels obtained are more or less solid, and have a good mechanical strength, an acceptable rheology and enhanced heat stability [34].

Propolis organogel for treating wounds

Propolis is a hard resinous material derived by bees from plant juices. It contains pollen, waxes, resins and a large amount of flavonoids [35]. It exhibits significant antibacterial, antifungal and sometimes antiviral properties, depending on the chemical composition and the geographic location. It has been widely use in traditional medicine for treatment of wounds and burns. Pluronic lecithin organogels (PLO) containing 4% w/w of propolis extract were developed, evaluated and designed for treating wounds [36]. Various formulations have been developed, depending on the concentration of lecithin and pluronic; the topical formulation containing 3 %w/w of lecithin and 20 %w/w of pluronic has been evaluated as the best one in terms of effectiveness, showing a higher drug release, skin permeation and antimicrobial activity compared to propolis suspension in water. It can offer an alternative therapeutic way to treat wounds and scars.

Pseudopeptidic organogels for cosmetic applications

Simple short peptidic sequences derived from natural amino acids have been studied as organogelators for a variety of solvents. In general, the organogelling behavior is associated with the presence of a central aliphatic spacer. The properties of the pseudopeptides can be modulated through the proper selection of amino acids and spacer. Specific applications for these types of gel in cosmetic formulations include the location where the products are applied as creams or gels, in order to increase contact time and ease their topical application. Gels with high transparency and stability are obtained from low concentrations of organogelators. They have a great biocompatible potential. Amides of stearic acid with ethanolamine or ethylene diamide have been used for the preparation of toilet oil bars that enable the release of oil when wetted water.

Diffusing particles based on organogelling xerogel fibres

In this case, the creation concerns particles in the form of a mass, essentially constituted by a plurality of fibers of organogelator [37] . It is not strictly speaking an organogel but a derivative. The organogelator is preferably DBS. These fusiform particles have interesting optical properties as they have a total light transmittance higher than 0.8, with a diffuse transmittance higher than the specular transmittance. They are prepared by solvent evaporation method or shearing. They bring a *soft-focus* effect, which is an interest property when we tend to obtain an optical amelioration of the skin, in particular to “blur” wrinkles with a make-up product as a cream or foundation

Organogel-based cosmetic tablets and capsules

There is a need in the field of cosmetics to have alternative types of containers, for example regarding travel situation, where there are more and more restrictions concerning liquids containing in canyon baggage and bag weight. Tablets and capsules of cosmetic products as shower gel, soap, perfumes or creams, seems to be a good alternative to classical containers. Hurwitz *et al.* presented the development of cosmetic tables or capsules soluble in water and able to deliver the active ingredient, which is in an inner cavity protected by an outer shell. The outer shell can be an effervescent ingredient (mixture of citric acid and sodium bicarbonate), a gelatin composition to encapsulate the ingredients, a coating agent or an organogel [38]. It is described as non - crystalline non glossy thermoreversible solid materials composed of an organic liquid such as an organic solvent, a mineral or a vegetable oil.

Types of organogels

Organogels in the drug delivery systems include [8- 12] as shown in (Table 1)

S.No	Types	Description
1.	Lecithin organogels.	Lecithin is a phospholipid, extracted from various plants and animal tissues apart from the egg yolk. Lecithin organogels have been used as carriers for hydrophilic and hydrophobic drug molecules.
2.	Sorbitan mono-stearate organogels.	Sorbitan mono-stearate organogels are opaque, thermo reversible, semi-solids whose microstructure consists of surfactant tubules dispersed in the organic continuous phase. Sorbitan mono-stearate (Span 60) and Sorbitan mono-palmitate (Span 40) have been found to gel a number of organic solvents at low concentrations.
3.	Micro/Nanoemulsion based organogels.	Micro-emulsions are dispersions of two immiscible liquids which are thermodynamically unstable systems. The use of a micro emulsion gel as vehicle may enhance transdermal penetration by various mechanism.
4.	Poly (ethylene) organogels.	The polyethylene organogels are colorless in nature. These are extensively used as ointment bases. Poly (ethylene) was also used in the formulation of 5-iodo-2'-De-oxyuridine for the treatment of oral herpes simplex lesions.
5.	Pluronic Lecithin Organogel (PLO)	PLO is a soy lecithin-based organogels. PLO may or may not contain sorbic acid in both the phases, which acts as a preservative. It occurs as yellow colored, odorless and opaque gel which is quickly absorbed from the skin.
6.	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 of Eudragit.
7.	Fatty acid derived sorbitan organogels	These gelators are hydrophobic non-ionic molecules having surface active properties and have the ability to immobilize various solvents like isopropyl myristate and vegetable oils. These gelators form solid-fiber matrix when the heated solution of gelator in a polar solvent is cooled down. The formation of the gel has been attributed to the formation of toroidal reverse micelles as the temperature is lowered.

Table 2: Organogel types and model drugs loaded

S.No	Types of organogel	Ingredients	Model drugs loaded
1.	Lecithin organogels [13].	Egg lecithin or soya lecithin, organic solvents, aqueous phase, sorbic acid	Diclofenac[2].,Indomethacin[21].,Piroxicam [21].,Aceclofenac[22].,Fluriprofen[23]., Propranolol [24].
2.	Pluronic lecithin organogels [14, 15].	Pluronic F 127 (poloxamer) polymer, Soya lecithin, sorbic acid, IPM, potassium sorbate, water	Diclofenac[20].,Ibuprofen[21].,Ketoprofen[24]., Methimazole[26]., Dexamethasone
3.	Limonene derived organogels [16].	Limonene incorporated within Dibutyllaurylglutamide (GPI) in propylene glycol	Diclofenac [2].,Ibuprofen [21].,Ketoprofen [23]., progesterone[21].
4.	Non-ionic surfactant based organogel [17].	Cetyl alcohol, stearyl alcohol, Tween, isopropyl myristate, n-butanol, water	Cyclosporine A, Zidovudine[21]., BSA

5.	Sorbitan monosterate organogel [18].	Span 20, Tween 80, isopropyl myristate, non-polar solvents like eucalyptus oil, n-octanol, propylene glycol, PEG (polyethylene glycol), ethyl alcohol, isopropyl alcohol	Antigens, Sumatriptan[27]., Clobetasol propionate[27].,Doxorubicin
6.	Poly ethylene organogels [19].	Poly ethylene's mineral oils, sorbic acid	Leuprolide[21]., Propranolol hydrochloride[23].
	Surfactant and polymer based organogels.	Oil phase: Gelucire 44/14, plurololeique, lauroglycol 90 Water phase: Sodium alginate, glycerin, water	Acyclovir, Salicylic acid [23].
	Eudragit organogel [19].	Copolymer of ethyl acrylate, methyl acrylate, polyhydric alcohols, ethylene glycol	Salicylic acid[25]., Ketoprofen [22].,BSA

Table 3: Research work done on organogels

S.No	Name of the drug	Route of administration	Type of Organogel	Result/Purpose
1.	DiltiazemHCl[39].	Transdermal	Lecithin-pluronic organogel	Antihypertensive
2.	Triclosan[40].	Topical dermal delivery	Carbopol 974 P NF organogel	Antibacterial, antifungal agent
3.	Caffeine [41].	Topical	HA microparticles in lecithin organogels	Cellulite
4.	Mefenamic acid [42].	Topical delivery	Pluronic lecithin based organogels	Anti-inflammatory
5	Ketoprofen, Dexamethasone [43].	Transdermal	Pluronic lecithin based organogels containing ricinoleic acid	NSAIDS
6.	Sumatriptan[44].	Transdermal	Tubular micelles of pluronic lecithin organogel	Antinociceptive
7.	Lornoxicam[45].	Topical	Lecithin organogels	Arthritis
8.	Bifonazole[46].	Topical	Sorbitan mono- stearate organogel	Antifungal
9	Etodolac[47].	Transdermal	Lecithin organogel	Rheumatoid arthritis
10	Clotrimazole[48].	Topical	Sorbitan mono- stearate organogel	Anti-fungal
11	Etodolac[49].	Topical	Carbopol 934 organogel	Anti-inflammatory
12.	Chlorpheniramine maleate[50].	Transdermal	Span 60/Tween 20 based organogel	Anti-histamine
13.	Fluconazole [51].	Topical	Span 80/Tween 80 based organogel	Antifungal

Table 4. Characterization parameters and evaluation techniques of organogels.

Characterization parameters	Evaluation techniques
Physicochemical properties: The isotopic nature and optical clarity organogel study Establishing the hydrogen bonds as one of the major driving force for the self-assembly of organogelator molecules in organic solvent The knowledge of molecular packing within the organogel network.	Spectroscopy techniques; nuclear magnetic resonance (NMR) and Fourier transform infrared (FTIR) spectroscopy. SEM and TEM Dynamic and static light scattering (DLS, SLS) Small angle neutron scattering (SANS)
Rheological behavior Viscoelasticity and swelling	Viscosimetry, Rheology, FTIR spectroscopy
Phase transition temperature; -Gives an insight into the nature of micro structure that forms gelling fibrilar three dimensional network	-Hot stage microscopy -High sensitivity differential scanning calorimetry (DSC)
Gelation kinetics -T gel and T melt determination -Gelation kinetics	-Rheology,- DSC, Inverse method (IM), Turbidity method (TM)
In vitro drug release	-Franz diffusion cell
Safety and skin compatibility studies	-Human skin irritation study -Histopathological studies
Structural features Molecular architecture of organogels Hydrogen bonding	-Spectroscopy techniques: NMR and FTIR spectroscopy -Determination emulsion type-oil- in- water or water- in- oil (dye test)
Final product -Drug content Proportions Stability	-High performance liquid chromatography (HPLC) -Ultraviolet (UV) spectrophotometry -Homogeneity -Optimization with ternary phase diagram -Stability studies

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 choosen according to their compatibility with intended applications, such as nontoxic solvents for pharmaceutical formulations. The topical/transdermal route, organogels have been investigated for oral, rectal and parenteral applications. Sorbitan mono-stearate organogels and amphiphilogels 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 mono-stearate amphiphilogels to solubilise such drugs to increase bioavailability should be investigated further. The potential of amphiphilogels to enhance the transdermal delivery of small drug molecules has not yet been investigated. Over the last decade, the interest has been increased in development of organogels for various cosmetic applications including make-up, care of skin, nails, hair, lips, antiperspirant, anti-cellulite, etc. Novel systems such as organogel nanospheres, orgalogelator fusiform particles and organogel-

based tablet and capsule have been designed for delivering cosmetic agents and the results obtained are very impressive. Important progress is also observed in the field of organogelators with the arrivals of new generation of LMOGs like pseudopeptidic LMOGs or supramolecular self-assembling POGs, which are potential ingredients for cosmetic and dermocosmetic applications.

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