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Review Article

A Review on Organogel and Its Application in Drug Delivery

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ABSTRACT

Organogels, a three-dimensional network containing self-assembled gelator fibers. Unique property of this organogels is their solid-like characteristics despite their liquid formulation. This character has been developed due to the locking of organic liquid by the self-assembled gelator fiber thus making them a convincing drug delivery system. To formulate organogels various assembly methods, including gelation have been practiced. Nowadays, organogels have been efficiently used in transdermal, oral and parenteral routes. Recent researches boost them as a matrices for achieving the efficient controlled drug release. Encapsulating sensitive and potent APIs or ingredients has also done using organogels thus making it a big step in encapsulation technology. Also, advancement in technology leads to the use of organogels in tissue engineering, providing scaffold for cell growth and regeneration. In this review, we touched the base of the organogels, their techniques, applications and recent updates on their therapeutic applications in controlled drug delivery system.

INTRODUCTION

Gel, a semi-solid material composed of a liquid phase entrapped within a 3D cross-linked structure. By changing the solvent polarity, they are classified into hydrogels (water) and organogels (organic solvent). [1] In this, organogels have better properties such as non-crystalline, self-assembling and thermo-reversible systems. Organogelators play an important role in the self-assembling property. They are often a low molecular weight compound or polymers. Improved drug permeation, bypassing the first-pass metabolism and patient compliance are the important factors on choosing organogels. They are suitable for transdermal drug delivery and sustained release formulation because of their ability to structure oil. Apart from pharmaceuticals, organogels had found ways to the other fields such as food technology, material science, etc. [2, 3]

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MERITS OF ORGANOGELS

- **Simplified procedure –** requires less efforts to prepare.
- **Optimized stability –** low sensitivity to moisture-induced degradation, high shelf-life.
- **Controlled release –** Drug deposits in local tissues thus enables zero-order kinetics thus reducing the administration frequency.
- **Improved permeation –** Increased permeation through Stratum Corneum (top-layer of skin).
- **Biocompatibility –** No significant changes in cytochrome activity.
- **High bio-availability –** Enhanced permeation and avoiding first-pass metabolism results in increased bio-availability.
- **Cost and Production –** Low cost and simple formulating procedures makes organogels an economically better.
- **Patient compliance –** Since, no invasive delivery route involved, results in good patient compliance [4, 5]

DEMERITS OF ORGANOGELS

- Low choice of drugs – Drug should have a good equilibrium distribution ratio for cutaneous penetration. [6]
- Lecithin dependency – High grade and purest lecithin should be employed for gelation to occur.
- Physical instability – Time dependent hygroscopic expansion and thermodynamic instability are important constraints. [7]
- Scalability constraints – Some ingredients (like lecithin) have stringent regulatory compliance and economic viability. [8]

TYPES OF ORGANOGELS

Lecithin Organogels

In 1988, Scartazzini and Luisi discovered the mechanism of formation on lecithin organogels (LOs), cylindrical reverse micelles stabilized by hydrogen bonding between lecithin's phosphate group and polar molecules. [9] Lecithin, a natural phospholipid dissolved on organic solvents is mixed with polar solvents (water or glycerol). LOs requires high-pure lecithin (>95%) only from natural sources. Advantages includes enhanced skin permeation, solubilize both hydrophilic & lipophilic compounds and thermos-sensitive gelation (~40 °C). [3, 6]

Pluronic Lecithin Ogranogels

Pluronic Lecithin Organogels (PLOs) composed of soy lecithin, Pluronic F-127 (a thermos-sensitive polymer), isopropyl palmitate and water. [7] Unlike LOs, PLOs completely depends on the Pluronic F-127 for the stability and drug solubility. Pluronic F-127 strengthens the gel matrix, increase skin permeation and allows customizable drug loading. Apart from transdermal drug delivery, recently PLOs have been used in oral mucosal delivery, hormone replacement and pain management. [10, 11]

Sorbitan Monosterate Organogels

Sorbitan Monosterate (Span 60), a non-ionic surfactant, forms a well-structured gels in the presence of an organic solvent. These thermo-sensitive systems is used in topical formulations becacuse they can act as a drug reservoir and a penetration enhancer, especially for hydrophilic drugs. Optical opacity and cooling rates sensitivity

are the key parameters to be considered while formulating. [12-14]

Limonene GP1/PG Organogels

PG (propylene glycol)/GP1 (dibuty-lauroylglutamide) limonene is a terpenoid that has a high penetration rate. Significant amounts of enhancer and different transdermal GP1 were combined to create limonene organo-gel, which was then incubated in limonene and propylene glycol. [15] Prepared at 120°C to increase the biologically active chemicals' penetration. The blend mixture expanded the rate and extent of the white gel by forming a translucent layer on top as it cooled. Chemicals in dermal tissues that are biologically active. The limonene's presence within the GP1/PG was determined. Many different terpene-based chemicals (such as linalool, farnesol, and cineole) were also added to the organo-gels because of limonene, which resulted in different rheological properties. However, the GP1/PG organo-gels did not change appropriately. [16, 17]

Eudragit Organogels

Eudragit organogels are prepared from a mixture of polyalcohols (propylene glycol, glycerol, liquid PEG), adding high amount of Eudragit (L or S) (30-40% w/w). Drug is dissolved in PEG then it is added to the Eudragit powder. This mixture is triturated for one minute, results in gel like consistency. Gel viscosity is adjusted using the Eudragit concentration. [3, 6]

Properties Of Organogels

Viscoelasticity

Typically organogels exhibit Maxwell viscoelasticity framework. If the shear stress tends to above the critical point the fiber formation will erode and the gel flows like a liquid. [18, 19]

Non-birefringence

The organogels when observed beneath polarised light detectable as a shadow matrix. So the homogenous identity of the organogels that prohibits authorize the polarised light to transit the matrix. This attribute contained in the organogel is considered as non-birefringence. [20, 21]

Optical clarity

Most of the organogels will be in non-opaque and some will be non-transparent. For example, lecithin organogels are non-opaque at the same time Sorbitan monosterate organogels are non-transparent. [13]

Biocompatibility

At first, organogels were formulated using many non-biocompatible materials but now usage of biocompatible ingredients has opened a new gate for application of the organogel in biomedical purposes. [3, 22]

Thermo-stability

As the gel-forming agent undergoes non-covalent assembly, it results in the attenuation in the Gibbs free energy of the network and transforms into the organogel, a thermodynamically stable network. So, the organogel is an essential vehicle for drugs and for cosmetics where a prolonged shelf-life is needed. [20, 21]

Thermo-reversibility

If the temperature is raised beyond a threshold temperature, the organogels dissipate its solid-matrix-like formation and began flowing. This has been correlated with the breakdown in the mechanical interactions within the gelator molecules due to the expansion in the organogels. For example, in the case of pluronic lecithin

organogels, if we raise the temperature beyond 25˚C threshold temperature, it attenuates solid matrix conformation and after annealed reverts to an equilibrium conformation. [3, 9]

ORGANO-GELATORS

Organo-gelators are self-assembling molecules that convert non-aqueous media into gels by establishing a 3D structure. Their solvation behaviour modulates the gel's thermodynamic and dynamic stability. Demonstrating thermos-reversiblity, the aggregation elastic network at ambient temperature undergoes solvation upon thermal activation. The gel's structure is governed by the gelator's molecular structure and loading efficiency for collective supramolecular crystallization. Organo-gelators are classified as hydrogen bonding (e.g., amino acids, amines) or non-hydrogen bonding (e.g., anthraquinones, steroids). [23]

Types of organo-gelators

(a) Aryl cyclohexanol derivatives

These are 4-tertiary butyl-1-aryl cyclohexanols derivates. They exhibits heterogeneity due to the non-polar medium. Minimal dissolvability in a non-polar medium thus results in opaque formulations. They assist in acquiring organo-gels with optimal attributes of thermo-reversibility. Some illustrative cases of this group are carbon tetrachloride, benzene, cyclohexane, etc. [5]

(b) Gemini organo-gelators

The word Gemini in Latin means “twins”. In the domain of organo-gelators, the initial Gemini-types analog based on the L-isomer of lysine was synthesized by Suzuki *et. al*., comprising two l-isomer of lysine chains of differing lengths produced via a CONH linkage. These gelators manifest outperforming gelation functionalities facilitating the validated entrapment of heterogeneous non-polar solvation medium. [9, 24]

(c) High molecular weight organo-gelators

High molecular weight organo-gelators (HMOGs) are demonstrated by the molecular weights surpassing 2kDa and exhibit exceptional gel-forming ability, generating stable gels at low concentrations. These gelators can exhibit various molecular architectures, involving linear and branched structures. Their gel formation performance is customizable through structural alterations. HMOGs are grouped as mechanical organo-gelators, self-assembling gels via reversible non-covalent interactions (e.g. hydrogen bonding, van der Waals). [24]

(e) Low molecular weight organo-gelators

Low molecular weight organo-gelators (LMWOs) characterized by a molecular mass ≥ 3000 Da are the predominantly employed group of gelators due to their effective gel-forming functionality. They aggregate via supramolecular interactions to exhibit thermo-reversible and non-opaque gels that effectively trap various apolar solvation mediums, encompassing benzene. Low molecular weight organo-gelators assemble two core matrix types solid-fiber and fluid-fiber systems. [25, 26]

Mechanism Of Gel Permeation into Skin

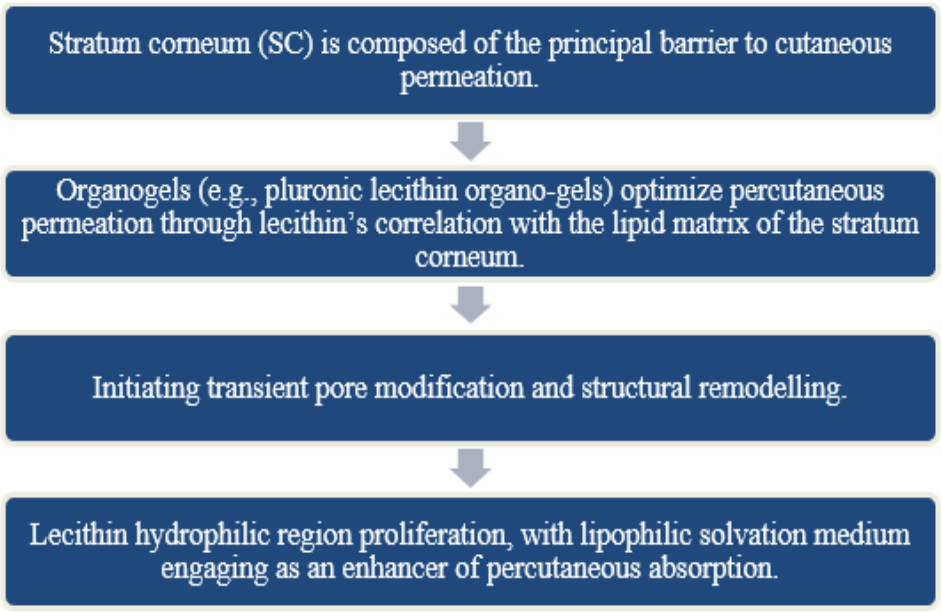

Figure 1: Mechanism of gel permeation into skin [5]

Application Of Organogels

Organogels have an unparalleled advantage in drug delivery due to their biocompatibility and bioactivity especially the inherent networked nano/microstructures served as a base for therapeutic compounds. Organogels allows entrapping a vast variety of therapeutic compounds which makes them useful as drug delivery tool.

Topical Drug Delivery System

The skin being the largest organ in the body, provides high bioavailability of drugs, as the drugs directly enters the systemic circulation via permeation through the skin bypassing the first pass metabolism. Lecithin organogels contain isopropyl myristate as a polar organic solvent used as a vector for the release of NSAIDs. Organogels can be regarded as a potential tool for the controlled release of topical antimicrobials.

Oral and Trans-Mucosal Drug Delivery System

The drugs can be delivered through oral cavity with the help of bio-adhesive organogels. The drugs can be dissolved in the organic solvent and then mixed with the muco-adhesive polymer. An organogel of 12-hydroxystearic acid-soyabean oil was used for the delivery of ibuprofen. An *in vivo* study conducted depicted that the organogels can be used as delivering agent for controlled release of lipophilic drugs.

Ophthalmic drug delivery systems

Ophthalmic solution are generally used for administering drugs in the eye, but due to its consistency, frequent dosing is required as the drug may not be properly absorbed in the target site. Thicker preparation like gels are desired to increase the contact time to facilitate the maximum absorption of drugs. Methazolamide is incorporated into carbomer and poloxamer gels for the treatment of glaucoma which was ineffective when formulated as ophthalmic solution.

Parenteral Drug Delivery System

Parenteral routes are the preferential choice for the administration of drugs, as it avoids first pass metabolism, provides quicker onset of action. An *in situ* forming organogel prepared for sustain delivery of leuprolide from the L-alanine derivatives in safflower oil and was injected by subcutaneous route. It was observed that the gels degraded slowly to release the drug. A study depicted that sunflower oil-based N-methyl pyrrolidone (NMP) injections were introduced into rats subcutaneously, which was well-tolerated by the surrounding tissues over a period of eight weeks. L-alanine methyl ester organogelators in safflower oil, were used in the sustained delivery of rivastigmine, a cholinesterase inhibitor used in the treatment of Alzheimer's disease.

FACTORS AFFECTING ORGANOGEL

Table 1: Factors affecting organogel

Factor	Effect of factor	Reference
Solvent type	Solvent plays a key role in organic gel formation and determines the properties of the gel	[18]
Purity	Ingredients should be in their pure form (≥95%); No gelation if purity is unmet.	[24]
Temperature	Depends on type of polymer and its formation mechanism	[27]
Surfactants	Gel property is varied by ratio and concentration	[18]
Organogelator	Affects rheological and mechanical properties	[24]
Moisture	Organogels tends to absorb moisture and swell results in instability	[18]
pH	Gel to Sol transition is influenced under pH change	[28]
Molecular Weight	Low molecular weight is highly preferred	[29]
Phase Transition Temperature	Optimal PTT can results in homogenous microstructure formation	[30]

EVALUATION OF ORGANOGEL

Table 2: Evaluation parameters for organogels [31]

Parameter	Description
Physical examination	The preliminary assessment of organogel; Colour, odour, texture, appearance etc.
pH	Sufficient amount of organogel is diluted in a solvent then pH is measured using the a pH meter
Water Content	NIR Spectroscopy is used to measure the water content (NIR, 1800-2000)
Phase transition Temperature	Temperature at which gel to sol state transition happens. DSC and hot stage microscopy is used to determine it.
Viscosity	Brookfield Viscometer is used to determine the visocity
Stability study	As per ICH guidelines. 25°C ± 2°C at 75 ± 5% RH 40°C ± 2°C at 75 ± 5% RH
Gelation Studies	Inverted test tube method is followed. If organogel does not flow gelation has occurred.
in vitro studies	Franz Diffusion cell apparatus is used to determine the diffusion rate and drug release

CONCLUSION

In this review we covered the basics of organogels, types of organo-gelators, factors affecting them. Application of organogels is vast, it cannot confined only to pharmaceutical industry. It also has been used in food industry, cosmetic, etc. Tailoring of organogels is very easy task thus making them a good potential for drug delivery.

Both hydrophilic and hydrophobic drugs can be incorporated by changing the organo-gelators based on their needs. Recent developments paved way for studying the thermodynamic stability and thermo-sensitivity of the organogels leads to formulation of barrier breaking organogels. Despite all this growth, there is a need in substantial growth of organagel based formulation in market. In the future organogels are expected to explore fully for their various unique properties and their applications.

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