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ORGANOGELS IN DRUG DELIVERY SYSTEM

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ABSTRACT

In the last decade, interest in physical organogels has grown rapidly with the discovery and synthesis of a very large number of diverse molecules, which can gel organic solvents at low concentrations. Organogels is a viscoelastic carrier system, can be regarded as a semi-solid preparation in which an organic (apolar) liquid phase is immobilized by a three-dimensional network composed of self-assembled, intertwined gelator fibers. An organogel is a non crystalline, non-glassy, thermoreversible (thermoplastic) solid material composed of a liquid organic phase. Organogels are thermodynamically stable, biocompatible, isotropic gel, which not onl give localized effect, but also systemic effect through percutaneous absorption. Organogel can be prepared by solid fiber matrix and fluid fiber matrix method. In the current review aims at giving an idea about the properties of organogels, various types of organogelators and organogels, factors, characterization and applications and importance in drug delivery.

KEYWORDS: Drug delivery, Non-crystalline, Organogel, Self-assembbled, Semi-solid, Thermoreversible, Three-dimentional network, Viscoelastic.

INTRODUCTION

Skin being the largest organ and it is a crucial part of human body. With typical surface area of 1.5 to 2 square meters, the skin holds various blood vessels which make the absorption of drugs easy and simply through topical application.[1] The topical drugs administration achieve most favourable cutaneous and percutaneous drug delivery, has recently gained an importance due to various advantages such as ease of administration and delivery benefits.[2] Organogels make a vehicle of choice for topical drug delivery because of ease of preparation and scale-up, easier quality monitoring, thermodynamic stability, enhanced topical

performance, along with biocompatibility and safety upon applications for prolonged period and skin penetration enhancing ability has also been well recognized.[3]

The United States pharmacopoeia defines gel as "semisolid, being other suspension of small inorganic particle or large inorganic molecules interpenetrated with liquid". This is a true phase system, as an inorganic particle is not soluble but merely dispersed throughout the continuous phase.[3] The gel is said to be a hydrogel or an organogel depending on the nature of the liquid component (solvent). If the liquid phase is water, it is hydrogel and if the liquid phase is an organic solvents it is organogel.[4]

ORGANOGEL

Generally Organogels formation is based on the spontaneous self-assembly of individual gelator molecules into 3-dimensional networks of randomly intertwined fiber-like structures. This 3-dimensional network structure 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 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 resides 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. Various Organogel based formulations have been designed to administer of the bioactive agents by different routes of administration.[6,7]

Classification of Gels[8]

According to USP, gels are classified as

a) Single Phase Gels.

b) Two-Phase Gels.

Based on Nature of Solvent

a) Hydro Gels (water based).

b) Organic Gels (with non aqueous solvent).

c) Xerogels.

Based on Rheological Properties

a) Plastic gels.

b) Pseudo plastic gels.

c) Thixotropic gels.

Based on Physical Nature

a) Elastic Gels

b) Rigid Gel

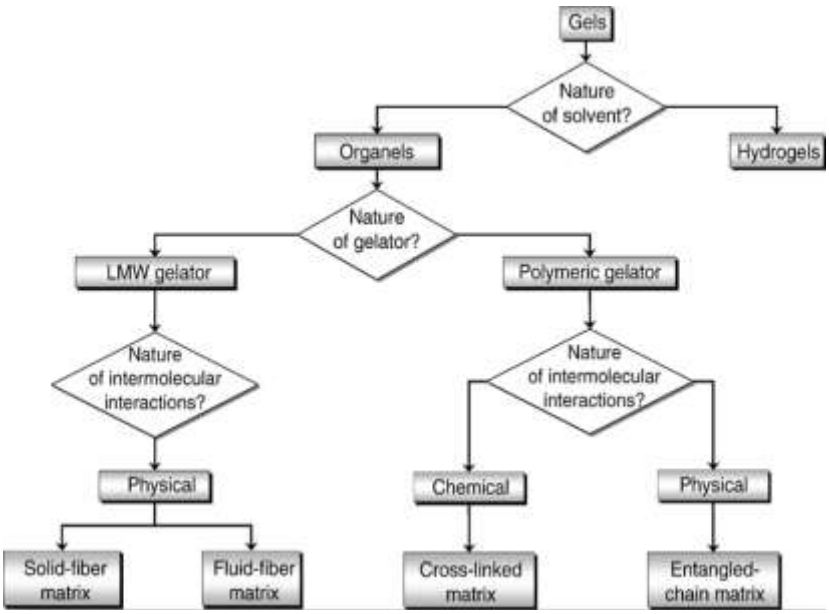

Fig: 1 Classification of Organogel.[4]

ADVANTAGES OF ORGANOGELS[1]

1. Ease of preparation.
2. They are organic in character and also resist microbial contamination.
3. Cost reduction due to less number of ingredients.
4. Longer shelf life.
5. Thermodynamically stable.
6. Both hydrophobic and hydrophilic drugs can be incorporated.
7. Organic solvents could be of natural origin eg: sunflower oil, mustard oil, etc

LIMITATION OF ORGANOGEL[9,10]

1. Less stable to temperature.
2. When a gel stands for some time, it often shrinks naturally and some of its liquid is pressed out known as syneresis.

3. If impurity present then no gelling will occurred.
4. Expensive in production.
5. Raw materials like lecithin are not available on large scale.
6. It should be stored in a proper condition.
7. When the gel is taken up of liquid with an increasing volume known as swelling.
8. The organogel has greasy property.

Need of Organogels

The organogel do not form semisolids on standing. Because an organogel may consists of macromolecules existing as twisted matted strands. The units are of bound together by strong types of Vander Waal forces so as to form crystalline amorphous regions throughout the entire system.[11,12] The organogels have lower hydrations, the drug dissolving polymer and is transported between the chains. Cross linking increases hydrophobicity of gels & diminishes the diffusion rate of drug.[13]

Mechanism of Organogelling

The organogelling or the gelation of the lecithin solutions in organic solvents is induced as a result of the incorporation of a polar solvent. Approaches developed by Israelachvili et al, the aggregate transformation (i.e. sphere-to-cylinder transformations) are determined by a change of a curvature for the amphipmile monolayer. In particular, the effects of polar solvent introduced into spherical lecithin micelles may be associated with an increase in the cross-sectional area of the lecithin polar region in which the solvent is arranged. The shape of the hydrated molecules is close to a cylinder. This shape leads to packing constraints in the spherical micelles that are diminished through the transition into the cylindrical ones with a smaller curvature.[1,14,15]

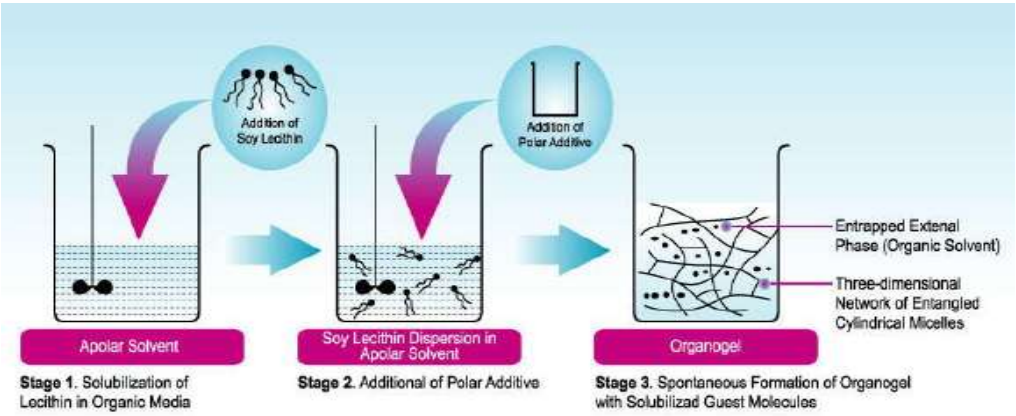

Fig: 2 Mechanism of Preparation of Organogel[1,15]

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. 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.[6,9]

Table No: 1 Types of Organogelators with Their Advantages and Applications[7,14,16]

S.No.	Types of Organogelators	Properties of Organogelators	Properties of Organogel Synthesized
1.	4-tertbutyl-1-aryl cyclohecanols derivatives	Solid at room temperature; low solubility in apolar solvent	Transparent or turbid depending on the type of apolar solvent
2.	Polymeric (e.g. poly(ethylene glycol), polycarbonate, polyester and poly(alkylene))	Low sol-gel processing temperature	Good gel strength
3.	Gemini gelators (e.g. N-lauroyl-L-lysine ethyl ester)	High ability of immobilizing apolar solvents	-
4.	Boc-Ala(1)-Aib(2)-ß-Ala(3)-OMe (synthetic tripeptide)	Capable of self-assembling	Thermoreversible; transparent
5.	Low molecular weight gelators (e.g. fatty acids and n-alkanes	High ability of immobilizing apolar solvents at small concentration (< 2%)	Good mechanical properties[7,9,16]

Method of Preparation of Organogel

Mostly organogels are prepared by heating a mixture of the organogelator and the liquid constituents to form an organic solution/dispersion, followed by cooling of the latter at room temperature, which sets into a gel. Heating allows dissolution of the organogelator into the liquid. Following cooling of resultant solution/dispersion, the solubility of the organogelator in the liquid phase diminishes, and organogelator-solvent interactions are reduced, which results in the gelator molecules 'coming out' of solution. Gelator-gelator interactions lead to gelator self-assemblage (3-dimentional) structure into well-defined aggregates such as tubules, rods and fibres form.[25] The physical organogels, held together by no covalent forces, are thermoreversible: that is, following heating, the gel to the sol phase as the gelator aggregates dissolve in the organic liquid, whereas cooling the hot sol phase results in gelatin. Mainly 3 methods are used for preparation of organogels like-

Fluid-Filled Fiber Mechanism

Solid Fiber Mechanism

Hydration method.[6,17]

Fluid-Filled Fiber Mechanism

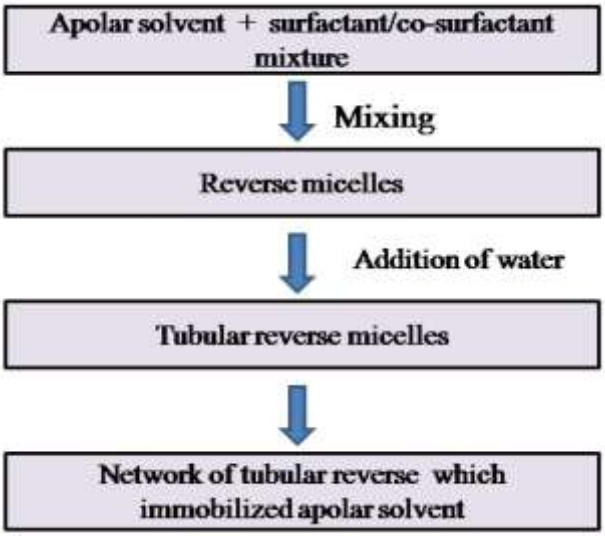

Fig: 3 Method of formation of organogels by fluid-filled fiber mechanism

Solid Fiber Mechanism

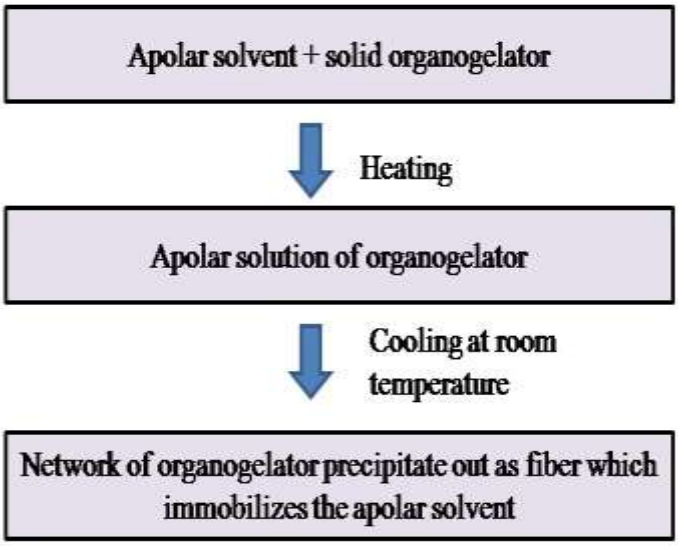

Fig: 4. Method of formation of organogels by solid fiber mechanism

Hydration Method

Gel by prepared by directly hydration the in organic chemical, which produces dispersed phase of the dispersion. In addition of water vehicle, other agents as propylene glycol, propyl gallate and hydroxyl propyl cellulose may be used to enhance gel formation.[18]

TYPES OF ORGANOGELS

1. Lecithin organogels

Lecithin or phosphatidylcholine is the most abundant phospholipid in biological systems and is typically purified from soy beans and egg yolk.[16] 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.[2,5,7] Synthetic lecithins are not used because it contains residues of fatty acids. Unsaturated fatty acid containing lecithin is used for organogel.[15]

2. Pluronic Lecithin Organogels

PLO is a soy lecithin-based, yellow colored, odorless and opaqueorganogel which 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. It is a quickly absorbed from the skin. It has been used for hydrophilic and hydrophobic molecule for topical and transdermal application. Like lecithin organogels, PLO also consists of entangled tubular reverse micelle structures which form temporal three-dimensional structures. 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.[5,6,8,15] PLOs are mainly used as a topical or transdermal drug carrier, for haloperidol, prochlorperazine, secretin and in some hormones. PLOs have also been investigated/proposed as a vehicle to the oral cavity and mucosa.[7]

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. 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. 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.[6-9,14,15,17,18]

4. Limonene GP1/PG organogels

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. 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. 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. 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.[6,7,9,14]

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°C is cooled down to a temperature below 35°C. 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. Microemulsions are preferred for the development of gelatin stabilized organogels because of the thermostable nature and the ease of preparation of the same. The MBGs have been used to device topical and/or transdermal controlled delivery vehicle for hydrophobic bioactive agents.[6,9,14,15]

6. 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.[8,10] 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°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.[6,9,17,18]

7. L-alanine derivative organogel

N-lauroyl-L-alanine methyl ester (LAM) was found to gel the pharmaceutically acceptable organic solvents, soybean oil and medium-chain triglycerides. Normally, the system exists in the gel state at room temperature. It could act as a sustained release implant, used for delivery of rivastigmine and leprolide drug.[2,5,8,14]

8. Eudragit organogels

Eudragit organogels are different from the organogels described in the introduction section as they 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.[6] They show high gel rigidity and stability when concentration was low.[14,18] Drug containing gels were prepared by dissolving the drug (salicylic acid, sodium salicylate, procaine or ketoprofen) in propylene glycol, pouring the resulting solution into Eudragit powder, and immediately mixing with a pestle for 1 min. Gel viscosity was found to increase with increasing concentrations of Eudragit and to decrease with increasing drug content.[16]

9. Sorbitan monostearate organogels

Sorbitan monostearate (Span 60) and sorbitan monopalmitate (Span 40) have been found to gel a number of organic solvents at low concentrations.[6] 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.[19] They are used for delivery of vaccines and sorbitan monostearate.[6]

10. Fatty acid derived sorbitan Organogels

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. Organogels using fatty acid gelators may also be prepared by dissolving the gelators in a waterin- 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.[6,9,14]

Table No. 2: Physicochemical Properties of Organogels[6,8]

S.No	Property	Description
1.	Viscoelasticity	The term viscoelasticity means materials which having both viscous and elastic properties. The organogels follow Maxwell model of viscoelasticity. 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 fibre 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 behaviour may be best explained with the plastic flow behaviour.[14]
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 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.
3.	Thermo reversibility	As the organogels are heated up above a critical temperature, the organogels loses its solid matrix- like structure and starts flowing. 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.
4.	Thermo stability	The organogels are inherently thermo stable 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 thermo stable system.
5.	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
6.	Chirality effects	LMW gelators has been found to affect the growth and the stability of the solid-fiber networks. 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. Example-Crown ether phthalocyanine organogels are the chiral organogels.
7.	Biocompatibility	Initially, organogels were developed using various nonbiocompatible

		organogels which rendered the organogels nonbiocompatible. Of late, research on organogels using various biocompatible constituents has opened up new dimensions for the use of the same in various biomedical applications.

Table No. 3: Various Parameters Affect the Property of Organogels

S. No	Factors affecting parameters	Details about Factors affecting parameters
1.	Organic solvent ❖ Polar solvent ❖ Non-aqueous solvent	The effect of polar solvent introduces into spherical lecithin micelles may be associated with an increase in cross-sectional area of the lecithin polar region, in which the solvent is arranged. A non-aqueous solvent is not particularly limited as long as it replaces water of the bacterial cellulose hydrogel completely without destroying its shape. Example-Polyethylene glycol, Dimethyl ether.[20]
2.	Phase Transition Temperature(PTT)	It gives an insight into nature of microstructures that form the gelling cross linked network. For example – A narrow PTT range is indicative of homogenous microstructures within the gel. For determination of PTT hot stage microscopy and high sensitivity differential scanning calorimetry is accurate and sensitive techniques.[21]
3.	Salt addition	Salt may attract part of water of hydration of the polymer allowing more formation inter molecular secondary bond, this is known as salting out.[22]
4.	Temperature	Depends on the chemistry of the polymer used and its mechanism of interaction with the medium. If the temperature is reduced once the gel is in the solution, degree of hydration is reduced and gelation occurs. Gel resulting from the chemical cross linking often cannot be liquefied by dilution or temperature changes.[17]
5.	Molecular weight	Low molecular weight polymers require a high concentration to build up viscosity and to set to gel possibly.[17]
6.	Surfactants	Gel characteristics can be varied by adjusting the proportion and concentration of the ingredients. Example:Poloxamer 407 is a polyoxyethylene that function as a surfactant.[17]
7.	Physicochemical properties ❖ Charge ❖ Solubility Molecular Weight	The presence of charged groups on a polymer favors mucoadhesion. Polyanions particularly polycarboxylates, are preferred to polycations. Mucoadhesives swell on contact with moisture, increasing the mobility of polymer molecules at the interface and exposing more sites for bond formation. It favors change in entanglement and interaction after the polymer and mucins have interpenetrated.[23]

Table No.4: Organogel Formulations Used as Drug Delivery[1,24-26]

S.No	Formulation	Constituents	Drug Used	Evaluation Techniques
1.	Lecithin Organogel	Soya lecithin, Ethyl Oleate, Water	Aceclofenac	Solubility Analysis of drug, Viscosity Measurement, Dynamic Light Scattering, Invitro efficacy, Histopathological studies
2.	Lecithin organogel	Egg and soya lecithin, Ethanol, triethanolamine, Ethyl oleate, water	Aceclofenac	Physicochemical characterization, photon microscopy, skin irritation,

				Drug content determination, Invitro drug release evaluation
3.	Lecithin microemulsion gel	Soya lecithin, isopropyl palmitate (IPM),water	ndomethacin, Diclofenac	Invitro skin permeation study, FTIR, Dynamic Light Scattering, Scanning Electron microscopy
4.	Lecithin stabilised microemulsion based organogel	Soya lecithin, IPM, water	Ketrolac tromethamine	Invitro efficacy, drug content study, HPLC Analysis
5.	Lecithin stabilised Organogel	Lecithin, IPM, water, glycerol	Clobetasol propionate	Stability studies, Optimisation with Ternary phase diagram, Statistical analysis, Invivo studies.
6.	Pluronic lecithin Organogel	Soya lecithin, sorbic acid, IPM, Pluronic- F-127, potassium sorbate,water	Flurbiprofen	Drug content studies, viscosity determination, Diffusion study
7.	Surfactant and polymer based Organogel	Oil phase: Gelucire 44/14, Plurol oleique, Lauroglycol 90 Water phase: Sodium alginate, Glycerin, water	Acyclovir	Skin permeation studies, HPLC Analysis
8.	Non- ionic surfactant based organogel (microemulsion based)	Tween 80, Span 20, isopropyl myristate,n-butanol,water	Zidovudine	Physicochemical characterization, droplet size determination, determination of type of emulsion(dye test),FTIR, stability studies
9.	Sorbitan monostearate Organogel	Sorbitan monostearate, sorbic acid, tween 20, isopropyl myristate, potassium sorbate, water	Aceclofenac	Psychorheogical charecterization, Drug content studies, Viscosity analysis, Spreadability, Invitro skin permeation, stability studies
10.	Sorbitan monostearate Organogel	Sorbitan monostearate, isopropyl myristate, Different types of non polar solvents like Eucalyptus oil, n-octanol, propylene glycol, PEG (polyethylene glycol), ethyl alcohol, isopropyl alcohol	Oxytetracycline hydrochloride	Psychorheogical charecterization, drug content studies, extrudability, homogeneity, Invitro drug diffusion study, Anti-microbial study
11.	Sorbitan monostearate Organogel	Sorbitan monostearate, Tween, water	Propanolol Hydrochloride	Invitro drug diffusion study, physicochemical charecterisation, stability studies
12.	Surfactant based Organogel	Glyceryl monostearate, Glyceryl distearate, Glyceryl stearate, IPM, fractionated coconut oil, glyceryl caprate	Piroxicam	Invitro and Invivo efficacy studies.

13.	Lecithin nanoemulsion based organogel	Lecithin,n-butanol, isopropyl alcohol, n-propanol, sodium lauryl Sulphate	Metoprolol	Turbidity andpParticle size of nanoemulsions birefringency,rheologic behavior. In vitro drug release.[24]
14.	Pluronic lecithin organogel	Lecithin, IPM, pluronic, F-127, DMSO	Silymarin	FTIR, drug content, viscosity and rheology study, stability study, In vitro release studies, Ex vivo permeability study, clinical evaluation.[25]
15.	Lecithin Organogel	Lecithin, Isopropyl myristate, ethyl oleate and n-octanol	Fluconazole	Viscosity, hygroscopicity studies, drug content and homogeneity, antifungal activity, drug release, stability studies.[26]

EVALUATION OF ORGANOGEL

Physical Appearance

Formulation is inspected visually for their colour, consistency and phase separation.

pH

pH is negative logarithm concentration of the H^+ ion concentration. pH of the formulationdetermines the skin irritability indirectly. pH-was determined by using digital pH meter standardized with standard buffers of pH 4 and pH 7. Then the electrode was inserted into the sample 10 min prior to taking the reading.[8,17,27]

Drug Content

1gm of prepared gel was mixed with 100 ml of suitable solvent. Aliquots of different concentration were prepared by suitable dilution after filtering the stock solution and absorbance was measured. Drug content was calculated using the equation which was obtained by linear regression analysis ofcalibration curve.[8,15,17,28]

Viscosity

The measurement of Viscosity of the Organogel was done with a Brookfield viscosity. The sample rotated at 0.3, 0.5 up to 10 rpm. The sample is allowed to settle for 5 min prior to taking the reading. The value of the viscosity s displayed in the form of cps.[15,17,29]

Spreadability

It indicates the area of organogel readily spreads with uniform application on skin or affected part. Spreadability is determine by time (seconds) taken by two slides to slip off from gel which is placed between the slides under the influence of load. Spreadability expressed in gm.cm2/ second. It is calculated by using the formula.

$$S = M. L / T$$

Where,

M = Wt. tied to upper slide,

L = Length of glass slides and

T = Time taken to separate the slide.[15,17,28]

Extrudability test (tube test)[8]

Extrudability test is based upon the determination of weight required to extrude 0.5 cm ribbon of organogel in 10 sec. from lacquered collapsible aluminum tube. The extrudability value was calculated using following formula.

Extrudability = Weight applied to extrude organogel from tube (gm) / Area (cm^2).

Globule size and its distribution in organogel

Globule size and distribution was determined by Malvern Zetasizer. About 1.0 gm sample was dissolved in double distilled water and agitated to get homogeneous dispersion. Sample was injected to photocell of zetasizer. Mean globule diameter and distribution was obtained.[8,17]

Homogeneity

After the gels have been set in the container, all developed organogel were tested for homogeneity by visual inspection. Appearance and presence of any aggregation also observed by visual inspection.[8,15,17,28]

Gel-sol transition study

Gel-sol transition temperature (Tgs) was found out by incubating the organogels in a water bath, whose temperature was varied from 30-70°C. The temperature, at which the gels started to flow, when the glass vials were inverted was noted as the gel-sol transition temperature.[8,17,27]

Bioadhesive Study

Detachment stress is required force to detach the two surfaces of mucosa when formulation or gel is placed in between them. The detachment stress was measured by using a modified analytical balance. A fresh mice skin wash with saline solution. Fix the membrane on a flat surface of object which was moisture with phosphate buffer (pH 7.4). Another object which is having flat surface at bottom (such as vials) was used for another membrane. The Organogel is placed between two membrane. The height of two objects was adjusted so that membrane surface of both objects can in intimate contact. Then weight was kept rising in the pan until the adjustable object detached. The Bioadhesive strength was measure in formed of adhesion in Newton's Equation. All measurement performed in triplicate. (n=3) (Detachment strews (dyne/cm2) = m×g/A Where m= weight required for detachment of 2 vials (in gm) g= Acceleration due to gravity (980 cm/s2) A= surface area exposed.[15,17,30]

In vitro Diffusion studies

The diffusion studies can be carrying out by in Franz diffusion cell. Gel sample (0.5gm) was taken in cellophane membrane and the diffusion studies were carried out at 37± 1°C using 250 ml of phosphate buffer (pH 7.4) as the dissolution medium. 5 ml of sample was withdrawn periodically at 1, 2, 3, 4, 5, 6, 7 and 8 hr and each sample replaced with equal volume o fresh dissolution medium. Then the samples were analysed percent drug release by using phosphate buffer as blank.[15,17,29]

Skin irritation test

About 0.5 gm test sample was applied to each site (two sites per mice) by introduction under a double gauze layer to an area of skin approximately 1" x 1" (2,54 x 2,54 cm) square. Animals were returned to their cages. After a 24 hour exposure, the organogel is removed. The test sites were wiped with tap water to remove any remaining test sample residue and examined for erythema and oedema.[8,17,31]

Stability studies

The organogel formulations were stored away from light in collapsible tube at 40°C and 75% RH for 3 months. After storage the samples were tested for their physical appearance, pH, % drug release, viscosity and % drug content.[8,17,31]

Application

1. Topical drug delivery.
2. Parenteral drug delivery.
3. Oral drug delivery.
4. Ophthalmic drug delivery.
5. Rectal drug delivery.
6. Delivery system for vaccines.

1) Topical drug delivery

Therapeutic compounds of different chemical and physicochemical background such as muscle relaxants, steroids hormones, analgesics, antiemetic, and cardio vascular agents have been incorporated in the organogel with some encouraging results.[16,18,32]

Cosmetic: Well used in the cosmetic and personal care markets.

Ophthalmic: Drug product like normal lachrymal turnover causes rapid clearance of solution and suspension dosage forms.

Ointments: It is of various advantages like good tolerability, formation of a protective film over the cornea, protection from conjuctival adhesion.

Dermal Drug Delivery

The muscle relaxants administered in lecithin –Isopropyl myristate organogel is shown to provide immediate relief of pain resulting from bruxism (tooth grinding) and tooth clenching. Efective delivery of antipsoriatic agents and for drugs used in eczema. Phospholipids organogel containing anti inflammatory macromolecule bromelain (15%) along with capsaicin (0.025%) has been found to be effective anti inflammatory composition.[18]

Transdermal Drug Delivery

Organogel systems have also been used as a matrix for transdermal transport of different therapeutic compounds. The solubility of various drugs such as nifedipine, clonidine, scopolamine and broxaterol was noted to be increase in lecithin –IPP solution compared with drug solubility in IPP alone, suggesting the solubility enhancing properties of the organogels. Ciribassi et al have reported the systemic absorption of fluoxetine hydrochloride through the skin using phospholipid organogel as a topical vehicle. In another study, Nicardipine, a calcium channel blocker, because of its low dose, short half live and extensive first pass

metabolism, has been incorporated in the system in order to achieve systemic absorption through topical route.[18]

2. Parenteral delivery

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. 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 in mice.[6]

3. Oral delivery

The use of organogels for oral delivery of bioactive agents was reported in the year of 2005. 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 sorbitanmonoleate based organogel formulation. The use of 12-hydroxystearic acid, as organogelator,for the development of organogels with soyabean oil as an apolar phase. Ibuprofen, a NSAID (non-steroidal anti-inflammatory 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.[6,8,17]

4. Ophthalmic drug delivery

For ophthalmic drug delivery lecithin based organogel offer a potential carrier system. This gels able to incorporate lipophilic, hydrophilic as well as amphoteric bioactive compounds. Formulation are transparent and hence even their long-term presence in ophthalmic cavity does not affect vision. Due to three- dimentional network structure of the gel the drug release at the steady rate.[9]

5. Rectal drug delivery

Organogel containing Eudragit R and S has been designed for rectal delivery of drugs. The drugs used are Salicylates, Procaine and ketoprofen. Further, in-vitro evaluation of drug (using rotational disc method – JP XI) Has shown that after a initial burst of drug release, the drug follows apparent first order kinetics. The burst effect suggested tobe due to rapid release

of drug existing on the gel surface at the moment of insertion into the dissolution media. In-vivo evaluation of these system using rabbits has shown sustained plasma drug levels. On the addition of 10% linoleic acid or oleic acid as absorption enhancer, bioavailability has been found to be increase to 1.55 – 1.75 – fold.[7]

6. Delivery system for vaccines

The microemulsion based organogel can be used as a vehicle for delivery of hydrophilic vaccines. According to Florence et al., these system offer various advantages like the slow release of antigen from the organogel system produce a depot effect, further the organogels have been formulated to contained niosomes. The vaccine has been found to trapped in this niosomes located within the surfactant the surfactant network in the organic medium. A depot effect has been observed after i.m. administration of these gels.[7]

SOME FORMULATION OF ORGANOGEL IN WHICH SUCCESFULLY BIOACTIVE AGENT INCARPORATED

S.No	Therapeutic Category	Therapeutic Agent	Drug Delivery
1.	Antibiotics	Ciprofloxacin	Transdermal
2.	Anticancer	Cyclosporins A, Tamoxifen	Transdermal
3.	Antifungal	Fluconazole and Biofonazole	Transdermal and topical
4.	Anti-HIV	Zidovudine	Transdermal
5.	Antihypertensive	Nicorandil, Diltiazem and Propranolol	Transdermal, Oral and Nasal
6.	Corticosteroid	Clobetasol Propionate	Topical
7.	Migrane	Sumtriptan	Transdermal
8.	NSAIDs	Lornoxicam, Ketorolac, Triethanolamine, Acetaminophen, Diclofenac sodium, Piroxicam, Ibuprofen, Aceclofenac and Flurbiprofen	Transdermal, topical and oral[7]

CONCLUSION

Organogels have evolved as one of the potential carrier system for topical delivery. Research into the applications of these gels is still in its infancy despite great excitement about their potential industrial uses. When compared to other lipid based carrier systems, these prove to be better in terms of efficacy, feasibility and shelf life. Since it consists of both hydrophobic and hydrophilic components, both hydrophobic and hydrophilic drugs can be incorporated. In future this carrier system can become a milestone in the field of topical delivery.

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