

**Review Article****A Review on organogel for skin aging**

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Skin Aging**ABSTRACT**

Skin aging is one of the prominent problems associated with skin as each part of body ages with the time, skin is the external organ where the sign and symptoms of aging are readily evident. However cosmetics as well as pharmaceutical approaches delayed skin aging. Gel are best fitted in all these essential criteria because of their excellent appearance, smoothness, desired consistency, fast drug release, ease of manufacturing and quality assessment and admirable stability. Recently gel formulation have been modified to yield an advance drug delivery system known as "organogels". Gel define as a semi-solid preparation having an external solvent phase, apolar [organogel] or polar [hydrogel] immobilized within the space available of a three dimensional network structure. Lecithin is a natural surfactant isolated from eggs or soya bean, when it combined with water and non-polar solvent, it form gels. PLO gels have gained importance in recent years as transdermal drug delivery system. It is a thermodynamically stable, visco-elastic system, which is non-irritating, odorless and biodegradable. Pluronic F127 or poloxamer is a copolymer of polyoxyethylene and polyoxypropylene which forms a thermoreversible gel in concentrations between 15-30%w/v. Water plays the role of a structure-forming agent and stabilizes the process of gel formation as it solubilizes the pluronic and other hydrophilic drugs. PLO gel system facilitates the delivery of hydrophilic as well as lipophilic drugs owing to the presence of both oil and aqueous phases within the gel system.

Introduction**Skin**

Largest organ of the body is skin, which form the outer most surrounding layers, protect the body from external environment, its function is essential for survival, as it is a complex organ, which interacts with most other in both physiological +pathological ways.[1]

3 components to skin:

Epidermis: It have five regions:

- Stratum germinativum
- Stratum spinosum
- Stratum granulosom
- Stratum lucidum
- Stratum corneum .Upper most stratum corneum latter consists of:
 - Keratinized
 - Dehydrated
 - Highly cornified cells[2]

Epidermis is most superficial layer of the skin and approximately 100µm thick. Its having keratinized stratified squamous epithelium and its main function is to protect the

body from external environment and diminish fluid loss.[3] Dermis forms the structural foundation of the skin supporting its superficial + deep layers.[1] Its layer of connective tissue to which epidermis is attached and thickness of 1-2mm approx. The main function of it is thermoregulation and supports the vascular network to supply the epidermis with nutrients. Subdivided into two zones:

- Papillary dermis
- Reticular layer

It contains mostly fibroblasts which are responsible for secreting collagen, elastin, glycosaminoglycans, proteoglycans, fibronectin and other extracellular matrix proteins that give the support and elasticity of the skin.[3] Sub dermis a deep subcutaneous adipose layer; acts as a fat + heat store.[1]

Skin aging

Skin aging is one of the prominent problems associated with skin as each part of body ages with the time, skin is the external organ where the sign and symptoms of aging are readily evident. However cosmetics as well as pharmaceutical approaches delayed skin aging. Two different types of aging.

Intrinsic aging : it occurs inevitably as a natural consequence of physiological changes over time at variable get inalterable genetically determined rates.

Extrinsic aging: it caused by environmental factors as repetitive facial expressions, gravity, sleeping positions, smoking and expose to the sunlight. Sun exposure often act simultaneously with the normal aging process and cause earlier skin aging.

Topical formulation

Skin aging can be cure or delayed by applied of topical formulation in skin. But skin act as barrier for anti skin aging agent. Therefore major challenge for topical formulation is to provide a sufficient increase in drug penetration into skin without causing irreversible alteration to the barrier function and drug cross skin barrier by two mechanisms: Transcellular and paracellular transport.

Transcellular path follows by lipophilic drugs where as paracellular follows by hydrophilic agent. Various creams, ointments, lotions available in market for skin aging treatment. But research seek to development vehicles that are natural, biocompatible, non-immunogenic, non-allergic and effective for the patients and also include ease of manufacture, long term stability and ready quality control. [4]

Gel

Gel are best fitted in all these essential criteria because of their excellent appearance, smoothness, desired consistency, fast drug release, ease of manufacturing and quality assessment and admirable stability. Recently gel formulation have been modified to yield an advance drug delivery system known as “organogels”. [4] It was found that lipid based formulation work most efficiently by improving penetration through the skin but drawback with such formulation is that they alter the hydration state to skin, cause dermatitis. On the other hand, water based formulation able to maintain bioactive state of skin but exhibit poor penetration. Therefore a new type of gel called organogel a promising vehicle is developed to deliver wide variety of agent through skin because of presence of both phase oil and aqueous phase and lecithin organogel deliver a bioactive agent in treatment of skin aging. Gels can also be classified according to the bonds present in the gelator network: 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. [5] Depending upon the nature of the liquid component, Gels are basically classified into two types, as either organogels or hydrogels [Fig.1-1]

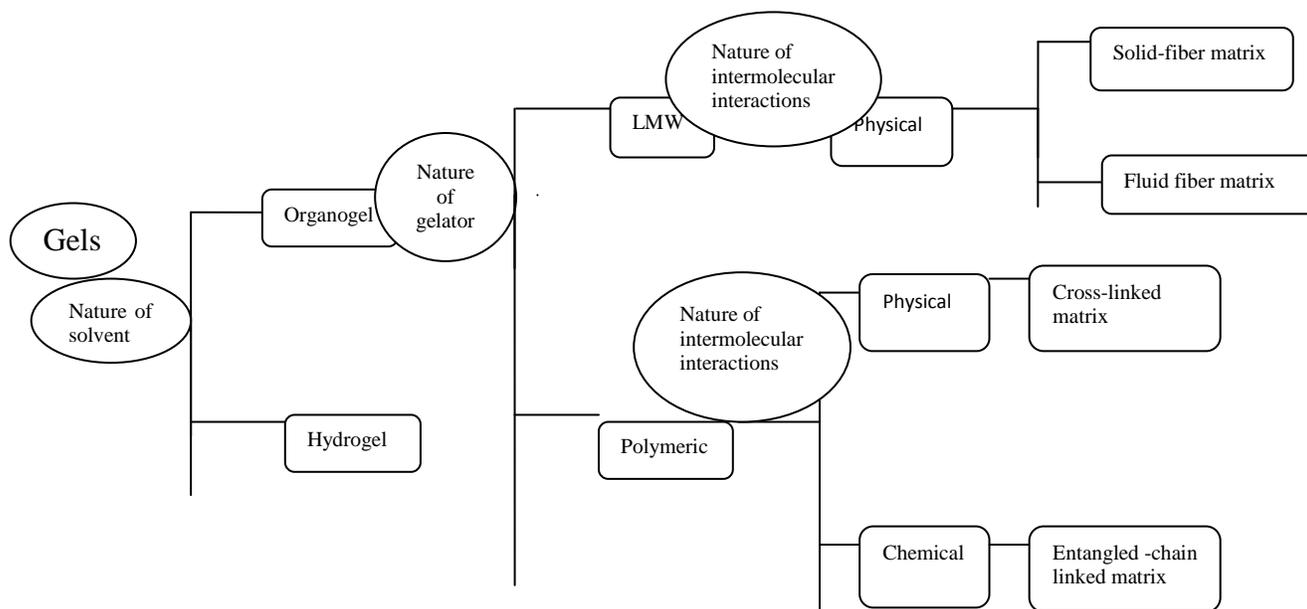


Figure 1-1: Classification of organogels.[1]

Hydrogels

Hydrogels are hydrophilic in nature and capable of absorbing large quantities of water or biological fluids, they are three-dimensional polymeric networks.[6,7] Networks form by Insoluble homopolymers or copolymers, which are insoluble owing to the presence of cross-links. Chemical cross links seems to be entanglement or crystallites while the Physical cross-links include tie-points and junctions which contribute to the network formation and physical integrity.[6-12] As the

hydrogels having the thermodynamic compatibility when they exhibit with water, so they swell in the presence of an aqueous environment.[6,7,12-14]. Their properties show a resemblance to natural living tissues in terms of their water content and soft texture,[7] while the high water content contributes to their biocompatibility. As a result, hydrogels are widely used as contact lenses, membranes for biosensors, linings for artificial hearts, materials for artificial skin, and as drug delivery devices.[15-19]

Xerogel

Xerogel are the solid gels with low solvent concentration. These are produced by evaporation of solvent or freeze drying, leaving the gel framework behind on contact with fresh fluid, they swells and can be reconstituted. E.g. Tragacanth ribbons, acacia tear β -cyclodextrin, dry cellulose and polystyrene. [20]

Organogel

Organogels are thermodynamically stable, visco-elastic bi-phasic systems comprising of a gelator [any substance capable of forming gel] and a nonpolar phase, with or without the presence of water molecules within the network formed by the gelator system. When compared with hydrogel they have a lower degree of hydration. Because of their non-irritating property and biocompatibility they gained importance in the delivery of drugs over the past few years. Although organogel comprised of large amount of liquid systems but it exhibit morphological and rheological properties similar to solids. The thermodynamic and kinetic stability of these systems can be attributed to the opposing forces which are operating and are associated with the organogelator's partial solubility in the continuous phase. The Gelling matrix governs by the resulting interaction and physicochemical properties of gel components. Gels can be classified on the basis of the properties of gelators, solvents and the intermolecular interactions which converted into gels. Organogelators are mostly small molecules, while gelators in a hydrogel are polymeric in nature [Fig.1-1]. Hence, the organogelators are well known by the name Low Molecular Weight [LMW] Organogelators. Depending upon the route of administration, organogel required the change in its formula to Administered the drugs.[21] Solvent system in organogels are non-aqueous liquids, which is a useful topical deliveries for lipophilic drug and aqueous liquids, which is useful for hydrophilic drug mentioned in various pharmacopoeias as well as for hydration of skin. Through percutaneous absorption Organogel achieved the local as well as systemic effect by the presence of a penetration enhancers: their lipophilic nature and occlusive effect are potentiated.[22]

Structure of Organogels

Gels are an intermediate state of the matter, containing both solid and liquid components. The solid component comprises a three dimensional network of interconnected molecules which immobilizes the liquid continuous phase. Hydrogels have an aqueous continuous phase, and organogels have an organic solvent as the liquid continuous medium. Organogels exhibit interesting properties such as the ability to solubilize guest molecules, uses for purification and separation purposes and as transdermal delivery vehicles.[23]

Molecular Model of Organogels

Initially lecithin forms the spherical reverse micelles which are in a nonpolar organic solution, converted into cylindrical from once the water has been added. In 1990 Luisi and Schurtenberger established this with the help of light scattering and small angle neutron scattering techniques. This

one-dimensional growth of micelles is caused by the formation of hydrogen bonds between water molecules and phosphate groups of lecithin molecules so that two adjacent lecithin molecules are bridged together by one water molecule. IR and NMR spectroscopies showed that water molecules could interact simultaneously with phosphate groups of neighbouring lipid molecules via hydrogen bonding, acting as a bridge between them. The hydrogen bond arrange in such a way that it formed a network between solvent molecules and lecithin phosphate groups.[27] Long tubular and flexible micelles formed with increase of water amount. These so-called polymer-like, wormlike or spaghetti-like micelles can be entangled and therefore build up a transient three-dimensional network that is responsible for the viscoelastic properties of the lecithin organogels.[24] The network shrinks and the phase separation occurs, at the critical concentration of water. At still higher concentrations of water, a transformation to a solid, non-transparent precipitate can be observed. This diluted solution is composed of rod-like micelles which their length is not enough to overlap and form a three-dimensional network. It was shown by IR spectroscopic studies that following addition of water to the lecithin solution about three first water molecules are attached to a phosphate group through hydrogen bonds. [25] At this molar ratio, water molecules begin coming to the carbonyl groups. They interact with each other, also forming hydrogen bonds. With increasing further the solvent amount, water molecules are found adjacent to a choline group. At this point the solvent molecules do not interact strongly with lecithin ester groups. A series of polar solvents have been studied to determine how their nature influences the formation of jelly-like hydrogen binding network in lecithin solutions. It has been established [27] that glycerol, formamide and ethylene glycol, in addition to water, have the ability to induce organogel formation in the following order: glycerol > water > formamide > ethylene glycol. These polar solvents tend to be located in the most polar moiety of lecithin near the phosphate group. It has been inferred from the results that the organogel formation is sensitive to the structure of polar solvents, and in turn it should be sensitive to their physicochemical properties. [27]

Drug Release from Organogel

The exact mechanism of drug release varies with the organogel system used. However, in case of a majority of organogel system, drug release occurs by simple diffusion. This diffusion is controlled by the presence of three-dimension network of gelator molecules. The extent of cross-linking determines the rate of drug release. More the crosslinking [higher concentration of gelator], slower is the rate of drug release. However, in case of Eudragit-L based organogel [surface erosion] and in case of Eudragit-S based organogel [diffusion process]. In the case of transdermal and ophthalmic delivery of drug through organogels, attempts have been made to enhance the permeation of drug rather than controlling the release of drug which occurs by diffusion. when organogel are used as carrier for delivery of vaccines the percolation of interstitial fluid into three-dimensional

network of the gel leads to its breakdown into smaller fragments. Which leads to release the drug.[28] The release rate of drug from organogel systems depends on the drug partition coefficient, drug solubility in the oil and aqueous phases, dispersed droplet size, phase volume ratio, viscosity and specific drug-excipient interaction. Small droplet size speeds up the drug release and has superior shelf stability.[29,30] Delivery of a drug from an organogel is also directly proportional to the concentration of the drug. The intensity of drug partitioning into stratum corneum depends mainly on the lipophilicity of the drug used. Usually, the drug from the external phase is released on the surface of the membrane. Following this, drug from the internal phase partitions into the external phase to maintain the equilibrium. Therefore, there are different partitioning processes occurring: between the internal and external phases of the organogel, and between either the internal or the external phase of the organogel and the skin. Drug transport may be controlled by any of these processes, and the thermodynamic driving force for release will reflect the relative activities of the drug in the different phases.[31]

Types of organogels

Lecithin organogels: Lecithin is a phospholipids extracted from various plants and animal tissues apart from egg yolk. Lecithin procured from natural source able to form the gelled structure.[32] The use of lecithin for designing the organogels was first described by Scartazzini and Luisi during the year 1988.[33] Lecithin Organogels [LOs] are composed of phospholipids [lecithin] appropriate organic solvent and a polar solvent. LOs are jelly-like phases consist of a 3-dimensional network of entangled reverse cylindrical [polymer-like] micelles which immobilizes the continuous or macroscopic external organic phase, thus turning a liquid into a gel. 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 nonaqueous solution of lecithin. The molar ratio of water to lecithin [w/o = [H₂O]/[lecithin]] is typically 2:10. Excess water leads to destabilization of the gel and phase separation.[32] 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°C], transparent, viscoelastic, biocompatible and non-irritant.[34,35] The organogels prepared using lecithin has been found to have an isotropic structure. The formation of the organogel in the presence of lecithin may be attributed to the entanglement of fluid-fiber reverse micellar tubular structure.[34] 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].

Sorbitan monostearate organogel: It include the gelators Sorbitan monostearate [Span 60] and sorbitan monopalmitate [Span 40] [hydrophobic non-ionic molecules with surface active properties and have ability to immobilize various solvent viz isopropyl myristate [IPM] and vegetable oil][22] at low concentration can be converted into gel with organic solvent. They 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.[32] and cooling also attributed to the formation of toroidal reverse micelles.

In-situ forming organogels of L-alanine derivative: In situ L-alanine derivative organogel is prepared from N-lauroyl-L-alanine methyl ester [LAM] which gels in the pharmaceutically acceptable organic solvents such as soybean oil and medium-chain triglycerides. Normally, the system exists in the gel state at room temperature but on the addition of ethanol to a gelator/solvent solution it inhibits gelation because the ethanol disrupts the formation of hydrogen bonds [essential for gelator self-assembly into aggregates] between the gelator molecules. Once a drug-containing gel is formed in situ it could act as a sustained-release implant.[38] A fatty acid derivative of L-alanine was capable of achieving solvent-specific gelation from a two-phase mixture of water and organic solvent without gelling the aqueous phase. At relatively high temperatures, the system was in the sol state whereas at low temperature, the organic solution solidified into a gel-like structure. The hydrogen-bonding at amide sites and to dimer formation between the free carboxylic contribute in self-assemble process. The system required the liquid state to incorporate the active compound and inject the solution which is achieved by heating which count as the limitation to the potential clinical use of such gel. This problem could, be overcome by addition of small amount of a water-soluble organic solvent [ethanol], which would interrupt the hydrogen bonds between the organogelator molecules and thus inhibit gelation at RT. Another method would rely on the hysteretic behaviour of some organogelators. This method consists of injecting a system that is liquid at RT and then locally decreasing the temperature below the gelation temperature to solidify the implant. As the temperature at the injection site reverts to body temperature, the system would stay in gel form. In this study, the gelation properties of two L-alanine derivatives [ester and acid forms], dissolved in pharmaceutically acceptable organic solvents, were evaluated. [36]

Poly [ethylene] organogels: The polyethylene organogels are formed when the low molecular weight polyethylene is dissolved in mineral oil at a temperature >130°C which is colourless in nature and subsequently shocked cooled. These organogels have been widely used as ointment bases. The physical interaction of the solid-fibers formed the gelled structure, which formed due to the precipitation of the polyethylene molecules.[37]

Eudragit organogels: This organogel is the mixtures of Eudragit [L or S] and polyhydric alcohols, such as glycerol,

propylene glycol and liquid polyethylene glycol containing high concentrations [30 or 40% w/w] of Eudragit. Drug-containing gels were prepared by dissolving the drug in propylene glycol and pouring the resulting solution along with immediate mixing for 1min [with pestle] into Eudragit powder [contained in a mortar]. As the amount of Eudragit increases viscosity of gel was found to be increased and drug release was decreased and increased the drug release when the amount of Eudragit will decrease. Therefore drug content in Eudragit organogels should be kept low [e.g., 1.25% w/w] to maintain gel rigidity and stability.[38] The addition of the drug procaine was also found to reduce gel rigidity, which was thought to be due to the influence of the drug molecules on the intermolecular forces [e.g., hydrogen bonds] between Eudragit and propylene glycol. The release from Eudragit L and S organogels was investigated *in vitro* by the rotation disk method of the model drugs salicylic acid, sodium salicylate and ketoprofen. Interestingly, the mechanism of salicylic acid release from Eudragit L and S organogels into a phosphate buffer were totally different. Eudragit L organogel release was due to surface erosion of the Eudragit L organogel but to diffusion through the Eudragit S gel matrix. Drug release from Eudragit S organogel thus increased with increasing temperature and agitation rate of the release medium.[39]

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], which occur as yellow colour, odourless and opaque gel which is quickly absorbed from skin and it is also thermostable, viscoelastic and biocompatible in nature. Pluronic F127 or poloxamer is a copolymer of polyoxyethylene and polyoxypropylene which forms a thermoreversible gel in concentrations between 15-30% w/v. Poloxamer exists in a liquid state at refrigerated conditions [4°C] and forms a gel at room or body temperature. Water plays the role of a structure-forming agent and stabilizes the process of gel formation as it solubilizes the pluronic and other hydrophilic drugs. PLO may or may not contain sorbic acid in both the phases, which acts as a preservative. PLO consists of entangled tubular reverse-micelle structures which form temporal three-dimensional structures, like as lecithin organogel. The apolar phase in the PLO constitutes 22 % [v/v] and hence is often regarded as micro-emulsion-based gel. 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.[40] PLO disrupts the lipid layers of the stratum corneum without damaging them. PLO allows the medication to slip through the stratum corneum into the systemic circulation via the dermal-epidermal blood flow so that it is more likely to be absorbed.[41]

In the topical delivery of drugs pluronic and lecithin become very popular. When other route of administration are not feasible to particular medications such as non steroidal anti-inflammatory drugs [NSAID], hormones, antiemetics, opioids, antipsychotic drugs, Calcium channel blockers and Local anesthetics to a specific site, in this case the unique capacity of

pluronic lecithin organogel helps to deliver the drug through the skin. This system was being first developed by a compounding pharmacist in the US in the early 1990s by Jones and Kloesel as a topical vehicle. It is not, however, actually an organogel [a gel where the liquid component is organic rather than aqueous]. Instead, it has an oil phase and an aqueous phase. It is, therefore, more commonly referred to as a cream, or simply a base. Based on the greater aqueous component of the gel one could say that PLO is a hydrogel' suggested by Dr. Sudaxshina Murdan. PLO is nonirritating to the skin, absorbs quickly, and is practically odorless. It consists of reversed polymer-like micelles, which are generated from the initial spherical ones by dissolving trace amounts of water in a non-aqueous solution; the micellar aggregates entangle, forming a temporal three-dimensional network in the bulk phase. It is best used with drugs with molecular weight less than 500 Dalton and these type of gel having two-phase system consisting of an oil [dissolved lipophilic drug] phase and a water [dissolved hydrophilic drug] phase. One phase is injected into the other, back and forth until a smooth homogeneous gel is formed. [42]

Gelatin stabilized micro emulsion based organogel [MBG]: Microemulsion-based gels were initially prepared by dissolving solid gelatin in a hot w/o microemulsion [which was composed of water, AOT and iso-octane] followed by cooling. In microemulsion-based gels the gelatin would dissolve in the water droplets of the w/o microemulsion and that cooling of the system would result in gelation of the water droplets which would lead to clouding of the system and possibly phase separation. Thus microemulsion gelled to a transparent semisolid with a high viscosity and a high electro-conductivity.[9] The number of drugs, proteins and cells have trapped in hydrogels matrices. However, this method is not very useful for hydrophobic drugs [as limited solubility in hydrogels]. Another possible disadvantage of directly dissolving the drug molecules in the polymerization mixture is the possibility that drug molecules may become involved in the polymerization reaction and lose their functionality. These disadvantages can be overcome by Gelatin-stabilised micro-emulsion based gels [MBGs]. The preparation of MBGs was first reported in 1986. The model, suggested by Atkinson *et al.* was based principally on neutron scattering and conductivity data. The MBGs were proposed to consist of an extensive, rigid, interconnected network of gelation /water rods stabilised by a monolayer of surfactant, in coexistence with a population of 'conventional' w/o microemulsion droplets .[43]

Premium lecithin Organogel [PrLO]: The PrLO is a second generation lecithin organogel. This gel do not have pluronic derivative, which results in the avoidance of the skin-irritation and thereby local skin-intolerance reaction.[44] The use of PrLO as a carrier for drug delivery has indicated that the gel higher thermostability apart from its non-greasy and non-tacky help in achieving improved bioavailability in the tissues by improving nature, which provides a cosmetically pleasing acceptability.[45]

Limonene GP1/PG Organogel : The GP1 [dibutyl lauroyl glutamide] / PG [propylene glycol] Limonene, a terpene,

has been found to be an excellent penetration, which is prepared by mixing the appropriate amount of enhancer and various transdermal GPI, limonene and PG with the subsequent incubation of the formulation for enhancing the penetration of the bioactive agent same at 120 °C. When the mixture is cooled down, it forms a across the transdermal layer, thereby improving the bioavailability of the white gel.[45]

Fatty acid derived sorbitan Organogel: The formulation of the gel has been attributed to the formulation of toroidal micelles as cooled down and it reorganize themselves to form rod-shaped tubules which subsequently undergo physical interaction amongst each other thereby forming a three-

dimensional networked structure. These gelators are hydrophobic non-ionic molecules having surface active properties and have the ability to immobilized various solvent viz. Isopropyl myristate and vegetable oil and it form solid-fiber matrix when cooled the solution of gelator and apolar solvent.[32] organogel using fatty acid as gelators may also prepared by dissolving fatty acid in a water-oil emulsion at a higher temperature followed by cooling the emulsion. The decrease solubility of fatty acid decrease with decrease in temperature followed by precipitation and self-assembly of the gelators into network of tubules, which get entangled so as to form a gelled structure.[44]

| S.No | Types of Organogel | Advantages & Application of Organogel | Reference |
|------|---|---|--------------|
| 1 | Lecithin organogels | The lecithin-based organogels have been found to be thermodynamically stable, thermoreversible [sol-to-gel transition temperature at 40°C] viscoelastic, non-irritant and biocompatible. Within its structure these organogels help either in the solubilisation or accommodation of various guest molecules. These properties of the lecithin organogel used as the controlled delivery vehicle. | [37] [44] |
| 2 | Sorbitan monostearate organogel | They are used for delivery of hydrophilic vaccines and sorbitan monostearate. | [37,44] |
| 3 | In-situ forming organogels of L-alanine derivative | It could act as a sustained release implant. Used for delivery of rivastigmine and leuprolide drugs. | [37,44] |
| 4 | Poly [ethylene] organogels | These organogel have been extensively used as ointment bases. The formation of gelled structure may be attributed to the physical interactions of the solid fibers, which formed due to the precipitation of the polyethylene molecules | [37] |
| 5 | Eudragit organogels | The show high gel rigidity and stability when drug concentration was low. | [37] |
| 6 | Pluronic lecithin organogel [PLO] | PLO is the 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 lipophilic and hydrophilic molecules for topical and transdermal applications. | [37] |
| 7 | Gelatin stabilized micro emulsion based organogel [MBG] | Gelatin organogel are thermostable nature and ease of preparation The MBGs have been used to device topical and/or transdermal controlled delivery vehicle for hydrophobic bioactive agents. Gelatin is protein which is used in structuring agent in various food preparation having excess of liquid phase. | [44] |
| 8 | Premium lecithin Organogel [PrLO] | The use of PrLO as a carrier for drug delivery has indicated that the gel help in achieving improve bioavailability in the tissue by improving the penetration of the bioactive agents. This gel has been successfully used for most the bioactive agents, like diclofenac, and ibuprofen has been consider as vehicle of choice for intradermal drug delivery. | [37] |
| 9 | Fatty acid derived sorbitan Organogel | Gels prepared by these gelators are thermostable, thermoreversible and opaque at RT for weeks. | [44] |
| 10 | Limonene GPI/PG Organogel : | Limonene, a terpene, has been found to be an excellent penetration, which is prepared by mixing the appropriate amount of enhancer within the various transdermal formulation, which improves the bioavailability by increasing the penetration of the bio-active agent across the transdermal layer. Apart from limonene, other penetration enhancers which are terpene-based [like linalool, farnesol and cineole] incorporated successfully in GPI/PG organogel. | [44] |

Advantages of organogel

Template vehicle: The wide range of substances can be incorporated in organogel with diverse physicochemical characters viz: chemical nature, solubility, molecular weight, and size etc.[38,46]

Process benefits: The process is very simple and easy to handle because of organogels formulation by virtue of self-assembled super molecular arrangement of surfactant molecules makes the process very simple and easy to handle. [47]

Structural/ physical stability: The organogel do not form semisolids on standing as an organogel consists of

macromolecules existing as twisted matted strands. The units having the strong Vanderwaal forces so as to form crystalline amorphous regions throughout the entire system[39] and it maintained for longer periods of time as it is thermodynamically stable, the structural integrity of organogel.[34]

Chemical stability: Organogel is organic in character also resist microbial contamination and are moisture insensitive.[46]

Topical delivery potential: Since having both hydrophilic and lipophilic character, they can efficiently partition with the skin and therefore enhance the skin penetration and transport of the molecules. Drug delivery into the skin layers [cutaneous

or dermal delivery] and beyond [percutaneous or transdermal delivery] is advantageous because it provides a non-invasive, convenient mode of administration, avoid the first pass metabolism of the active ingredient, an important aspect for highly hepatic metabolized molecules and for drug with short elimination half-life.[39]

Safety: use of biocompatible, biodegradable and non-immunogenic materials makes them safe for long term application.[34]

- ❖ Drug elimination is independent of gastric emptying.
- ❖ Suitable for drugs with short biological half-life and narrow therapeutic window.
- ❖ Increased therapeutic efficacy and decreased fluctuations.
- ❖ Decreased dosing frequency and increased patient compliance.
- ❖ Painless when compared to parenteral therapy.
- ❖ Provides suitability of self-medication.
- ❖ Cost reduction due to less number of ingredients.
- ❖ Organogel can diminish the diffusion rate of drug because the drug is dissolved in polymer and transported between chain.[47]
- ❖ The drug would penetrate to the subjacent tissues attaining high concentrations in the affected muscles / joints, while maintaining low blood levels in PLO.[48]
- ❖ Poorly water soluble drug can be easily formulated using PLO.[48]

Disadvantage

- ❖ When a gel stands for some time, it often shrinks naturally, & some of its liquid is pressed out, known as syneresis,[37] therefore stored in a proper condition.[40]
- ❖ When the gel is taken up of liquid with an increasing volume known as swelling.[37]
- ❖ In most cases the effect is slow and sustained.
- ❖ Chances of irritation to the skin from the penetration enhancers
- ❖ Only drugs small enough to penetrate the skin can be effectively delivered with less than 500 Dalton
- ❖ Less stable to temperature
- ❖ If contamination present then no gelling will occur.
- ❖ Raw material like lecithin is not available on large scale.[40] therefore expensive in production.[44]
- ❖ Permeability of drug through skin depends on the partition coefficient of drug therefore required reasonable partition coefficient.
- ❖ The route is not suitable for the drugs which cause irritation to the skin or sensitive to skin. [45]

Application

Pharmaceutical:

Organogels as Matrix for Transdermal Transport of Drugs: Organogels have been investigated successfully as dermal pharmaceuticals. Example- Aceclofenac [for osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis] cause gastric irritation when administered orally which is avoided by topical transdermal delivery by Ethyl oleate-based lecithin organogel [EO/Lecithin] of aceclofenac can be avoided by topical transdermal drug delivery [effective than

conventional hydrogel]. Topical Microemulsion of Aceclofenac also formed but having disadvantages as needed a large amount of surfactant and co-surfactants for stabilization of nano-droplets, poor viscosity and spreadability. Whereas lecithin organogels not requires such kind of surfactant or penetration enhancer, as itself having the both properties. Organogels are having better spreadability and viscosity than microemulsion. Soyabean lecithin organogels are better than conventional patches of scopolamine and broxaterol as shows a faster rate of transdermal drug delivery. Skin penetration of Diclofenac and Indomethacin found to be increase when used with isopropyl palmitate. [49]

Organogels as Iontophoretic Transdermal Drug Delivery

system: the rate of drug delivery extensively enhance by Intophoresis [mainly topical delivery of large hydrophilic species as proteins, peptides etc. having poor penetration during passive condition].But, problem arises in case during use of solution. This problem overcome by drug loaded gels[facilitates drug handling] and hydrogels have been used as drug reservoir for iontophoresis but major drawback is the microbial contamination of such aqueous systems. Which leads to breakdown of gel structure, redox reaction and pH change.This problem can be avoided by use of organogels as the existence of organic solvent as the continuous phase therefore inhibit the microbial growth.

Organogel as Ophthalmic Drug Delivery Systems:

Eye drops are mostly use for the ophthalmic drug delivery but having drawback that majority of drug is not absorbed to targeted tissue because of immediate dilution by tear flow therefore needed repetitive dosing. Leading to undesirable side effect and poor patient compliance. Suspension can't help in this condition as drug release from it depend on the rate of dissolution of drug particles which vary due to continues change in composition and outflow of lachrymal fluid. Therapeutic efficacy can be increase by prolonging the contact period of medicament which can be done by increasing the viscosity but addition of viscosity builder like CMC not able to improve the situation and in the case of water insoluble ointments immediate vision was affected. These difficulties can be overcome by the organogel. High viscosity and organic solvent as a continuous phase, make them difficult to wash. Due to three-dimensional network of the gel drug release at steady rate.[28]

Organogels in cosmetics: Skin care products are mainly emulsion-based [contain water and an oil phase respectively lipid]. Some products are also there with only an oil phase. Oils but also organogels belong to this group. They are primarily recommended for skins problem, therefore used in the dermatological cosmetics. Individuals with skin barrier disorders depend in high dosage of physiological lipids due to specific group in the organogel this problem is solved and it gain more importance. In this case, lip gels are recommended. In contrast to the liquid-oils they have consistency similar as cream emulsion [gel-like and semi-solid]. This consistency build- up a sponge like structure which is achieved by

additives, thus enabling them to incorporate large amounts of lipids. In case of emulsion hydration is provided by internal processes of the skin as there is no external supply of water. The lipids of the oleogels support this process by reducing the trans-epidermal water loss [TEWL]. In addition to that, urea [natural water-retaining substances] also having antipruritic effects, can be integrated in oleogels and having no problem of long-term stability Unlike water-containing emulsion. Products with high lipid content causes an optimal reduction of any skin roughness. Hence, oleogels are recommended for general skin protection purposes, hand care products, care of lips and also for eye preparation. In perianal skin disorder and diabetic skin recommended as the supportive care. Decubitus oleogels also applied as sun protection and as in massages cause of semisolid property. Products for decorative cosmetics like makeup, mascara, and eye shadows can also possible to prepare by including pigments.[49]

Nutraceutical applications

Scientists modified the physical properties of oils and find it as an alternative to trans and saturated fats, therefore can be

use in the many food products required a specific texture and rheology without causing significant change in the final product quality. This approach can be fulfilled by incorporation of specific molecules [polymers, amphiphiles, waxes] into oils to form oleogels. Polymer like Ethylcellulose [used as base for the topical preparation and more chemically stable than lubricant greases] forming the oleogels by binding oil at levels of 10% with wide varying properties. Sorbitan and glyceryl monostearates olegogel with different types of vegetable oils[which are biodegradable alternatives of traditional lubricating greases]. Oils such as rapeseed and soybean oils [with low-viscosity] yields gels with significantly higher values of the linear viscoelastic functions.[49]

Organogelators [40,44, 47]

Based on capability of forming the hydrogen bond Organogelators may be categorized into two groups. Capable of forming hydrogen bonding eg. Aminoacids, amide and urea moieties and carbohydrates. Which do not form hydrogen bonding eg. Anthracene, anthraquinone and steroid based molecules.

| S. No | Type of organogelators | Properties of Organogelators | Properties of Organogel Synthesized | Examples |
|-------|---|---|--|--|
| 1 | 4-tertbutyl-1-aryl cyclohexanols derivatives | Solid at room temperature; low solubility in apolar solvent | Transparent or turbid depending on the type of apolar solvent [carbon tetrachloride, benzene and cyclohexane]. Categorized under arylocyclohexanol derivatives, helps in designing thermo-reversible organogels. | |
| 2 | Polymeric | Low sol-gel processing temperature and compare with LMW organogel having higher gel strength. | Organogelation even at low concentration and by modifying the chemical structure of these gelators gelling capability can be tailored. They have the lower gel-sol transition temperature. | e.g. poly[ethylene glycol], polycarbonate, polyesters, and poly[alkylene] |
| 3 | Gemini gelators | High ability of immobilizing apolar solvents. | | e.g. N-lauroyl-L-lysine ethyl ester |
| 4 | Boc-Ala[1]-Aib[2]-β-Ala[3]-OMe [synthetic tripeptide] | Capable of self-assembling | Thermoreversible, transparent gels in the presence of various apolar solvent [1,2-dichlorobenzene[DCB], monochlorobenzene and benzene] | |
| 5 | Low molecular weight gelators | High ability of immobilizing apolar solvents at small concentration [< 2%] | Improved mechanical properties. | e.g. derivative & metallic salts of fatty acids, steroids, amino acid type molecules, carbohydrate amphiphiles, anthryl derivatives & organometallic compound. |

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