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Review Article

ORGANOGEL: FACTORS AND ITS IMPORTANCE

Nigar Kadar Mujawar*, Sangramsinh Laxman Ghatage and Veerendra C. Yeligar

Department of pharmaceutics, Ashokrao Mane College of pharmacy, peth-vadgaon, Kolhapur. Maharashtra, India.

INTRODUCTION

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[1].There are various types of gel like hydrogel bigel and xerogel.also organogel is one of the type of gel. Various definitions have followed, sometimes the same author providing descriptions ranging from the most elaborate, stating that a gel, Has a continuous structure of macroscopic dimensions that are permanent over the time-span of an experiment and is solid-like in its rheological behavior, to the more basic descriptions stating that if it looks like "Jell-O", It must be a gel[2].

Number of definition of organogel as follow as:

1. A simple working definition of the term „gel" is a soft, solid or solid-like material, which contains both solid and liquid components, where the solid component (the gelator) is present as a mesh/network of aggregates, which immobilizes the liquid component. The solid network prevents the liquid from flowing, primarily via surface tension. The gel is said to be a hydrogel or an Organogel depending on the nature of the liquid component: water in hydrogel and an organic solvent in organogels[3].
2. Organogel, is a non crystalline, non-glassy thermoreversible (thermoplastic) solid material and viscoelastic system, can be regarded as a semi-solid preparation which has an immobilized external apolar phase. The apolar phase gets immobilized within spaces of the three-dimensional networked structure formed due to the physical interactions amongst the self assembled structures of compounds regarded as gelators. Often, these systems are based on self-assembly of the structurant molecules[4].

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[5].These systems are capable of solubilizing lipophilic, hydrophilic, and amphiphilic guest molecules, including enzymes. Thermodynamic stability, thermo reversibility in nature, insensitivity to moisture, resistant to microbial contamination, spontaneous formation and viscoelastic behavior are some of remarkable features of lecithin organogels. Experimental design and statistical analysis have been widely used to develop formulation as well as in process optimization and validation[6]. So organogel ac as potential candidates for controlled release formulations of not only lipophilic drugs, but also hydrophilic drugs[7].

❖ ADVANTAGES

- Ease of preparation.
- More stable than other types of gel.
- Enhanced the drug penetration through the skin.
- Avoid first pass metabolism.

- Organogels are moisture insensitive.
- Cost reduction due to less number of ingredients.
- Thermodynamically stable.
- Short half life drug used
- Controlled release of drug, longer shelf life and for prolonged action used.
- Reduces frequency of drug dosing.
- They are less greasy and can be easily removed from the skin[8].
- Organogel can diminish the diffusion rate of drug because the drug is dissolved in polymer & transported between chains[4].
- Since it consists of both hydrophobic and hydrophilic components, both Liphophilic and hydrophilic drugs can be incorporated[8].

❖ **DISADVANTAGES**

- Drugs with reasonable partition coefficient otherwise drug may not permiable through skin .
- The route is not suitable for drugs that irritate or sensitize the skin.
- In Organogel, lecithin should be in pure form otherwise no gelling will occur.
- Lecithin is most costly and it is not available in large scale.
- If impurity present then no gelling will occur.
- Require proper storage condition.[8]
- When the gel is taken up of liquid with an increasing volume known as swelling .
- When a gel stands for some time, it often shrinks naturally, & some of its liquid is pressed out, known as syneresis[4].

❖ **CLASSIFICATION OF ORGANOGEL**

Fig. 1 presents a flowchart compiling various accepted classifications of gels based on the nature of solvents, gelators, and intermolecular interactions.

Organogels, the focus of this review, can be distinguished from hydrogels by their predominantly organic continuous phase and can then be further subdivided based on the nature of the gelling molecule: polymeric or low molecular weight (LMW) organogelators. Polymers immobilize the organic solvent by forming a network of either crosslinked or entangled chains for chemical and physical gels, respectively. The latter is possibly further stabilized by weak inter-chain interactions such as hydrogen bonding, vander waals forces, and π-stacking. Likewise, the self-assembly of LMW organogelators depends on physical interactions for the formation of aggregates sufficiently long to overlap and induce solvent gelation. Depending on the kinetic properties of aggregates, an important distinction amongst LMW organogels is made between those composed of solid (or strong) versus fluid (or weak) fiber networks. Despite the numerous trends in gelling processes as well as the impressive variety of gelators identified , it remains difficult to predict the molecular structure of a potential gelator,as well as one cannot readily foresee preferentially-gelled solvents.Today still, the discovery of gelators remains serendipitous and is usually number of scientistor investigator involved in the screening of different solvent systems potentially compatible with the gelation process.Gelaton might be due to propensity towords chemical or physical inter-molecular interactions, however no generalizations are so far possible.Number of factors affect on the molecule's aggregating tendancy like steric effects, rigidity, and polarity can counter the molecule's aggregating tendency. Control over the gelation process as well as the conception of new gelling molecules remain important challenges to face in the quest of new organogelator[2].

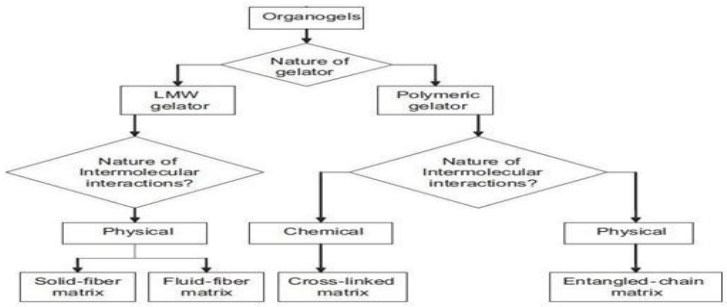

Fig. 1: Classification of organogel

❖ **TYPES OF ORGANOGELATORS**

Table 1: Types of Organogelator

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, polyesters,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 [9 10 11.]

❖ **NEED OF ORGANOGEL**

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 vanderwaal forces so as to form crystalline amorphous regions throughout the entire system. The organogels have lower hydrations, the drug dissolving polymer and is transported between the chains. Cross linking increases hydrophilicity of gels & diminishes the diffusion rate of drug [12].

❖ **ORGANOGEL STRUCTURE AND 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. Lecithin, when being dissolved in nonpolar media alone, self-assembles into reverse spherical micelles at a concentration of ~0.01 mM.57. The enormous uniaxial growth of these spherical reverse micelles and subsequent transformation into tubular or cylindrical micellar aggregates (sphere-to-cylinder transformation) is triggered by the addition of small and critical amounts of polar additive as shown in Fig 2. The molecules of polar solvent, on addition, bind in stoichiometric ratios to the hydrophilic head portion of the lecithin molecules in such a way that 2 adjacent lecithin molecules are bridged together by 1 polar molecule. This leads to the formation of linear networks, from hydrogen bonds formed by the polar molecules and phosphate groups of lecithin molecules and, in turn, to the 1-dimensional uniaxial growth of lecithin reverse micelles.Further increase in the amount of polar additive results in the formation of flexible, long tubular micelles of 2.0 to 2.5 nm radius and hundreds to thousands of nanometers in length. After reaching a critical length, these extended micelles begin to overlap, entangle themselves, and build up a transient 3-dimensional network. This marks a crossover to a system characterized by increased viscosity and viscoelastic properties. Instead of a low viscous solution, a jelly-like phase (ie, LO) is obtained. The LO thus obtained contains a considerable amount (~85 weight percentage) of external phase (ie, the organic liquid) entrapped in the spaces between the entangled reverse micelles. The hydrogen bonding network built up by molecules of polar additive and phosphate groups is also accompanied by stiffness of the phospholipid molecule in the region of phosphate group and glycerol residue, which stabilizes the micellar aggregates (Fig.2). In case of PLOs, the mechanism of gelling and the structural network may be related to the synergistic contribution of both phospholipids as well as polymeric cosurfactant molecules, in their respective hydrated states. The contribution of organic solvent as an external phase in the gelling process is also indicated, as it influences the micellization of lecithin monomers. The requirement of the specific organic solvents for the purpose indicates that it provides appropriate environment for the intermolecular and intramolecular interactions in gelator molecules and the organic solvent molecules. In particular, the effects of polar solvent introduced into

spherical lecithin micelles may be associated with an increase in the crosssectional 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[13].

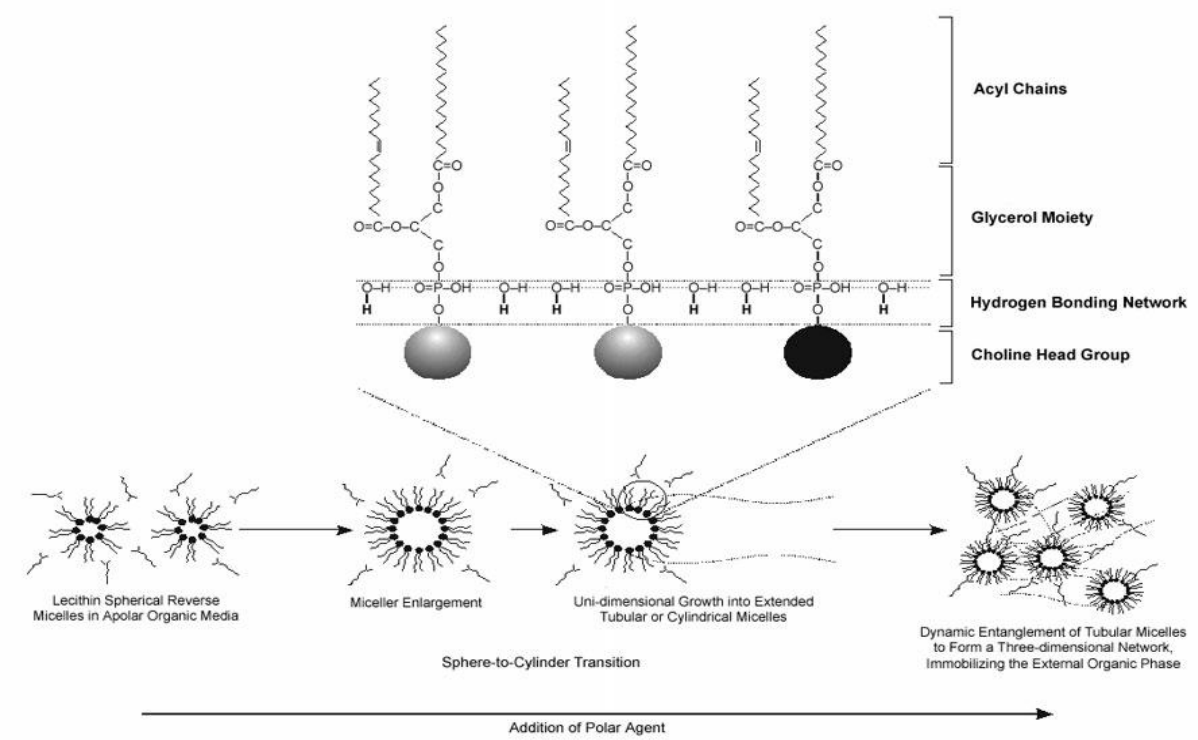

Fig. 2: Formation of a three-dimensional network of reverse cylindrical micelles in lecithin organogel, involving hydrogen bonding between lecithin and polar solvent molecules

❖ **METHOD OF FORMATION OF ORGANOGEL**

1. Fluid-filled fiber mechanism

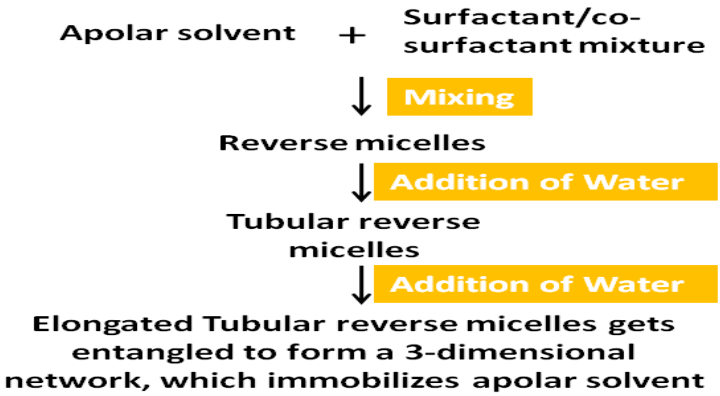

Fig 3: Method of formation of organogels by fluid-filled fiber mechanism[5]

3. Solid fiber mechanism

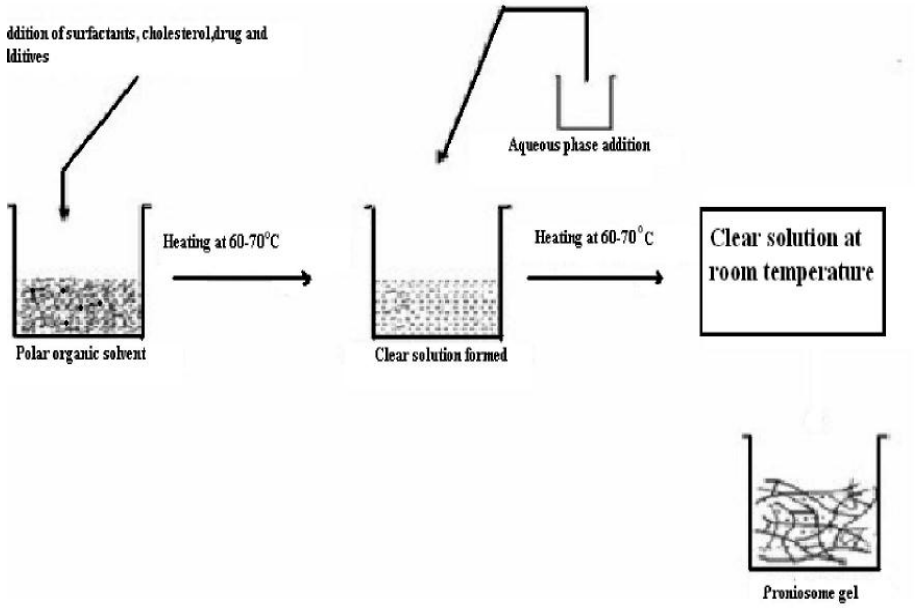

Fig. 4: Method of formation of organogels by solid fiber mechanism[9]

3. Hydration Method

Gel may be prepared by directly hydrating the inorganic 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 [4].

4. Novel method

1. Homogenisation

2. Microirradiation[14]

❖ **PROPERTIES OF ORGANOGEL**

Table 2: Properties of Organogel

S. No.	PROPERTIES	EFFECT
1	Viscoelaticity	Which is associated with the materials having both viscous and elastic properties[4]. The organogels seems to 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 fiber structures start getting weakened until the shear stress is high enough to disrupt the interactions amongst the fiber structures, when the organogels starts flowing. This behaviour may be best explained with the plastic flow behavior[4].
2	Non-birefringence	The organogels when viewed under polarized light appears as a dark matrix. So the isotropic nature of the organogels which does not allow the polarized light to pass through the matrix. This property of the organogels of is regarded as non-birefringent
3	Thermoreversibility	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 configurations

4	Thermostability-	Self assemble nature of organogel important point of view concern with thermostability under suitable condition.As the gelators undergo self-assembly, it results in the decrease in the total free energy of the system and renders the organogels as low-energy thermostable system.So organogel an important vehicle for bioactive agents and for cosmetic applications where a longer shelf-life is desirable.
5	Optical clarity	Depending on the composition of the organogels, the organogels may be transparent or opaque in nature. Example-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 and biocompatible constituents has opened up new dimensions for the use of the same in various biomedical applications[5].

❖ FACTOR AFFECTING ON ORGANOGELS

Table 3: Factor Affecting On Organogels

S. No.	FACTORS AFFECTING	HOW THEY AFFECT
1.	Organic solvent 1.Polar solvent 2.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.
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.
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.
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.
5	Molecular weight	Low molecular weight polymers require a high concentration to build up viscosity and to set to gel possibly.
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.
7	Physicochemical properties 1.Charge 2.Solubility 3.Molecular Weight/spatial configuration	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[12].

❖ **TYPES OF ORGANOGELS**

1. Lecithin organogels

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. The transfer into jelly-like state has been demonstrated only for nonaqueous solutions of naturally occurring unsaturated lecithins . The latter are mainly separated from soy bean and egg yolk.

Lecithin is a trivial name for 1, 2-diacyl-sn-3-phosphocholine. It belongs to a biologically essential class of substances termed phosphoglycerides or phospholipids. The Lecithin organogel play a key role in the lipid matrix of biological membranes, in the cellular metabolism ,used as carriers for hydrophilic and hydrophobic drug molecules.Hydrophobic drugs are dissolved in the oil phase (lecithin + organic solvent) whereas hydrophilic molecules are dissolved in water, which is then added to an organic solution of lecithin to induce gelation. As a biocompatible surfactant so having wide applications in human and animal food, medicine, cosmetics, and manifold industrial applications. Synthetic lecithins containing residues of saturated fatty acids failed to form organogel.The gelling formation was also not observed with hydrogenated soybean lecithin. These studies indicate the importance of lecithin in the naturally occurring form, is important due to which contains unsaturated fatty acids.

2. Sorbitan monosterate organogels

Made up of combination of Sorbitan monostearate (Span 60) and sorbitan monopalmitate (Span 40) have been found to gel a number of organic solvents at low concentrations. 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. Cooling results in reduced affinities between the solvent and the gelator molecules, which self-assemble into tubules. X-ray diffraction and freeze-fracture studies indicate that sorbitan monostearate molecules are arranged in inverted bilayers within the tubules.Sorbitan monostearate organogels are opaque, thermoreversible semi-solids whose microstructure consists of surfactant tubules dispersed in the organic continuous phase. Inverse toroidal vesicles are the precursors of the surfactant tubules. The gelation process was observed as an isotropic sol phase of sorbitan monostearate in isopropyl myristate was cooled using hot-stage light microscopy. At the gelation temperature, inverse toroidal vesicular structures were seen to grow in the organic phase. These toroids are thought to be analogous to other well-known vesicles, liposomes and niosomes, except for their toroidal (rather than spherical).shape and their inverse nature. They are rather short-lived structures: on further cooling of the sol phase, tubules form in the organic medium: it is speculated rod-shaped segments.

3. Micro/Nano-emulsion based organogels

Microemulsions is defined as thermodynamically stable transparent, single optically isotropic liquid system of water, oil and surfactants frequently in combination with suitable cosurfactants. Microemulsions are known to enhance the bioavailability of drugs via topical and systemic routes.Microemulsion appears to have the ability of deliver larger amount of topically applied agents into the mucosa than the traditional gel & creams. The use of a microemulsion gel as vehicle may enhance transdermal penetration by various mechanism, many molecules or solubilised in microemulsion in addition microemulsion induce a change in the thermodynamic activity of the drug they contain, modifying their partition coefficient and thus favour penetration of the stratum corneum. Furthermore, their component surfactant reduces the functional barrier of stratum corneum. Nanoemulsions are thermodynamically stable transparent (translucent) dispersions of oil and water stabilized by an interfacial film of surfactant and cosurfactant molecules having a droplet size of less than 100 nm.

4. Organogels based on other low molecular weight gelators

Scientists have investigated the transdermal delivery of piroxicam from organogels composed of glyceryl fatty acid ester gelators in pharmaceutical oils. The in vivo skin penetration of the drug, evaluated by measuring the anti-inflammatory inhibition of oedema after

treatment, was found to be superior for glyceryl fatty acid ester organogels as compared to traditional topical formulations such as liquid paraffin.Use of a long-chain glutamate based gelator has demonstrated by scientists (N-lauroyl-Lglutamic acid di-nbutylamide) at concentrations of 2–10% to gel isostearyl alcohol and propylene glycol, yielding translucent and opaque gels, respectively. In vitro permeation studies on human skin using haloperidol, an antipsychotic drug, showed facilitated permeation upon incorporation of 5% limonene, a known permeation enhancer.

5. Poly (ethylene) organogels

The only two such systems have been widely tested for drug delivery applications are poly (ethylene) and P (MAAco- MMA) organogels. In a study dating back to the 1950s and involving 300 patients, Poly (ethylene) organogel (PO) patches were shown to be non-irritating and have low sensitizing properties. In a related investigation, 326 patients were treated with spectrocin-containing PO and compared with patients treated with spectrocin in petrolatum base alone.Both antibiotic ointments cleared pyoderma and secondarily infected eruptions in 3–5 days, but it was found that the PO provided a faster, more efficient release. Poly (ethylene) was also used in the formulation of 5-iodo-2'-deoxyuridine for the treatment of oral herpes simplex lesions. A 10% drug-loaded formulation showed a resolution of herpetic lesions in 3-days after treatment initiation, compared to 1–2 weeks in untreated control patients.

6. Supramolecular organogels

In the recent past, molecules of a great structural diversity, for instance from the simplest alkanes to the complex phthalocyanines, have been discovered to be gelators. Recently immense interest has been generated in studying gels derived from low molecular mass gelators (supramolecular or simply molecular gels).The motivation for this is not only to understand the fundamental aggregate structures in the gels at different length scales, but also to explore their potential for futuristic technological applications. Gels have been made sensitive to external stimuli like light and chemical entities by incorporating a spectroscopically active or a receptor unit as part of the gelator molecule. This makes them suitable for applications such as sensing and actuating. The diversity of gel structural architectures has allowed them to be utilized as templates to prepare novel inorganic superstructures for possible applications in catalysis and separation. Gels derived from liquid crystals (anisotropy gels) that can act as dynamically functional materials have been prepared, for example, for (rewritable) information recording.Supramolecular gels can be important in controlled release applications, in oil recovery, for gelling cryogenic fuels etc. They can also serve as media for a range of applications. This tutorial review highlights some of the instructive work done by various groups to develop smart and functional gels, and covers a wide spectrum of scientific interest ranging from medicine to materials science. e.g.: cyanochalcone[15].

7. Eudragit organogels

Eudragit organogels are really mixtures of Eudragit (L or S) and polyhydric alcohols, such as glycerol, propylene glycol and liquid polyethylene glycol, containing high concentrations (30 or 40% w/w) of Eudragit. Drug-containing gels were prepared by dissolving the drug (salicylic acid, sodium salicylate, procain or ketoprofen) in propylene glycol, pouring the resulting solution into Eudragit powder (contained in a mortar), and immediately mixing with a pestle for 1min . Gel consistency and spreading is described using a penetrometer and a spreadmeter.Gel viscosities were found to increase with increasing concentrations of Eudragit and to decrease with increasing drug content. Example the release of model drugs salicylic acid, sodium salicylate and ketoprofen from Eudragit L and S organogels was investigated in vitro by the rotation disk method.Interestingly, the mechanism of salicylic acid release from Eudragit L and S organogels into a phosphate buffer were totally different. Release was due to surface erosion of the Eudragit L organogel but to diffusion through the Eudragit S gel matrix.The authors suggested that drug content in Eudragit organogels be kept low (e.g., 1.25% w/w) to maintain gel rigidity and stability.

8. In situ forming organogel of L-alanine derivative

Nlauroyl- 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. However, the addition of ethanol to a gelator/solvent solution inhibits gelation because the ethanol disrupts the formation of hydrogen bonds (essential for gelator self-assembly into aggregates) between the

gelator molecules. This means that a solution of LAM in an organic solvent can remain in the sol phase at room temperature when some ethanol is added to the mixture. When such a sol phase (20% LAM + 14% ethanol in soybean oil) was placed in phosphate buffered saline at 37°C it turned into a opaque gel within 2 min as the hydrophilic ethanol diffused away into the aqueous buffer, and as gelator–gelator hydrogen bonds were formed. Thus, theoretically, such a LAM/ethanol/soybean oil solution could form gels in situ following its subcutaneous injection, due to ethanol diffusion away from the formulation, into the surrounding tissues; in situ gel formation in rats was indeed investigated. The main advantage of in situ forming gels is their injectability at room temperature. Once a drug-containing gel is formed in situ, it could act as a sustained-release implant.

9. Pluronic lecithin organogels (PLO)

PLO was developed by a compounding pharmacist in the US in the early 1990s as a topical vehicle. Pluronic lecithin organogels are opaque, yellow gel, PLO is 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. Thus, PLO is not really an organogel but it may be thought of as an 'organogel' due to its name.. Pluronic F127 was added to the original lecithin organogel in order to stabilize the gel formulation.Example- 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[16].

10. Premium lecithin organogels (PrLO)

The PrLO is a second general lecithin organogel.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. The penetration of the bioactive agents. This gel do not have pluronic derivative.This gel has been successfully used to accommodate various bioactive avoidance of the skin-irritation and thereby local skin-intolerance agents, *viz.* diclofenac, ibuprofen, ketoprofen and rogesterone, and has reactions been regarded as vehicle of choice for intradermal drug delivery.

11. Limonene GP1/PG organogel

The GP1 (dibutyllauroylglutamide) / PG (propylene glycol) Limonene, a terpene, has been found to be an excellent penetration organogels can be prepared by mixing the appropriate amounts of enhancer and hence has been incorporated within various transdermal GP1, limonene and PG with the subsequent incubation of the formulations for the improving 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. bioactive agent within the dermal tissue. It was found that the presence of limonene within the GP1/PG.Apart from limonene, various other terpene-based penetration enhancers organogels resulted in the alteration of the rheological properties (e.g. linalool, farnesol and cineole) have also been incorporated of the organogels though there was no significant change in the successfully in GP1/PG organogels.So penetration enhancer improve the rate of permeation of bioactive agent.[4]

❖ **CHARACTERIZATION OF ORGANOGELS**

1. Physiochemical properties

Physiochemical properties of the organ gel are due to its structural features. An efficient characterization methodology for any organ gel system begins with its structural elucidation. The isotopic nature and optical clarity organ gel study is feasible by various spectroscopic techniques, namely NMR and FTIR spectroscopy. FTIR spectroscopy has been found to be successful in establishing the hydrogen bonding as one of the major driving force for the self assembly of organogelator molecules in organic solvent. The knowledge of molecular packing within the organogel network has been obtained using scanning and transmission electron microscopies, dynamic and static light scattering (elastic or quasielastic light scattering technique.) small angle neutron scattering {SANS}.

2. Rheological behaviour

The critical parameter such as spreadability, adhesiveness, cohesiveness and gel consistency need to be modified.

3. Viscoelasticity

Organogels have been studied extensively for their rheological attributes and have been determined to be viscoelastic in nature. Scartazzini and Luisi performed the dynamic shear viscosity prepared using different types of organ gel solvent (eg. linear and cyclic alkenes, amines). The higher values obtained using linear alkenes were related to the higher state of structural organization organogels. Similarly, Schurtenberger E T found that increasing the gelator concentration leads to an increase in the viscosity and in turn the gel strength.

4. Swelling

Gels can swell by absorbing liquid with an increase in volumes. Solvent penetrates the gel matrix,so that gel-gel interaction are replaced by gel solvent interaction. Limited swelling is usually the result of some degree of cross linking gel matrix that prevents total dissolution. sol-to-gel, TSG, or gel-to-sol, TGS) gives an insight into the nature of microstructures that form the gelling crosslinked network. The phase transition temperatures also help in optimizing the organogel composition[8].

5. Water content

Water content of organ gel system is critical, as the water loss by evaporation can lead to consequent decrease in viscosity thus affecting the gel stability. Near infra red spectroscopy studies on lecithin/IPP/water organogel system by measuring the water absorption in the NIR region (1800-2200nm). In this region, water shows a strong absorption peaks at 918nm due to H-O-H stretching overtones, which are easily detectable and quantifiable.

6. Phase transition temperature

The phase behavior of organogel varies on changing temperature condition. The phase transition temperature (PTT) (i.e. sol to gel or gel to sol) gives an insight into the nature of micro structure that form gelling cross linked network. For the determination, hot stage microscopy and high sensitivity differential scanning calorimetry have been reported to be useful as accurate and sensitive techniques. PTT also reveals the micro structural homogeneity of the prepared organogel system. For example, a narrow PTT range (i.e. 3) is indicative of homogenous microstructures within the gel[12].

7. Gelation kinetics

Determined by using method like inverse method and turbidimetry method [4]

8. Viscoelaticity

Viscoelasticity is associated with the materials having both viscous and elastic properties. The organogels seems to follow Maxwell model of viscoelasticity. Organogels are the three-dimensional structures which are formed due to the physical interactions amongst the gelator molecules. The organogels behaves like a solid at lower shear rates and hence shows an elastic property. As the shear stress is increased, the physical interacting points amongst the fiber structures start getting weakened until the shear stress is high enough to disrupt the interactions amongst the fiber structures, when the organogels starts flowing. This behavior may be best explained with the plastic flow behavior.

9. Optical Clarity

Depending on the composition of the organogels, the organogels may be transparent or opaque in nature. The lecithin organogels are transparent in naturewhile the sorbitan monostearate organogels are opaque in nature.

10. Thermo Reversibility

Organogels are heated up above a critical temperature, they 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 on cooling, the physical interaction amongst the organogelators prevails and the organogels revert back to the more stable configuration.

11. In Vitro Drug Release

The permeation apparatus designed as described by Chowder et.al.was employed to study the relese profile of druge from semisolid formulation. The media used as receptor fluid. The relese of drug from gel through various membranes was determined using Franz diffusion cell[9].

12. Safety and Skin Compatibility Study

Organogel systems i.e., gels are composed of pharmaceutically approved (non-immunogenic and biocompatible) excipients. However, the level of surfactant and organic solvents in organogels is fairly high. Therefore, it is important to consider the safety and irritancy of the formulation on

prolonged use. The irritation potential of organogels has been assessed by Dreher et al, by carrying out human skin irritation study. Results indicated a very low cumulative skin irritation potential of organogels that supports the suitability of organogels as a topical vehicle for long-term applications[14].

❖ **USES OF ORGANOGELS**

1. For Rheumatoid Arthritis

Rheumatoid arthritis is a chronic disorder for which there is no known cure.Fortunately in the last few years, a shift in strategy toward the earlier institution of disease modifying drugs and the availability of new classes of medications have greatly improved the outcomes that can be expected by most patients.

2. For Osteoarthritis

Eighty percent of individuals older than 65 have radiographic signs of osteoarthritis (OA), and a large percentage have symptoms. Given the chronic nature of the disease and the high incidence of medication side effects in the elderly, an understanding of the risks and benefits of NSAIDs in treating OA is crucial.

3. Inflammatory arthropathies.(e.g.ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome)

4. Dysmenorrhoea (menstrual pain),

5. Postoperative pain, Metastatic bone pain.

6. It are also given to neonate infants whose ductus arteriosus is not closed within 24 hours of birth Headache and migraine

7. Mild-to-moderate pain due to inflammation and tissue injury

8. For Acute gout treatment

9. For Pyraxia: Antipyretics (pertaining to fever) are drugs or herbs that reduce fever.

10. For Muscle injuries

11. Clinicians faced many problems with conventional dosage form for local delivery of drug so to avoid the risk with topical preprations.

12. Topical preparations are made for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membrane with low concentrations of potent active drugs in the bloodstream likewise minimize side effects.

13. Helps in achievement of more constant blood levels with lower dosage of drug by continuous drug input. It is very commonly used dosage form and avoided various side effects which may be shown in other dosage form.

14. The main advantage of topical delivery is to bypass first pass metabolism and Avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time, reduces frequency of drug dosing are other advantage of topicalpreparations[8].

15. In the treatment of skin aging

Skin aging is an unavoidable aspect of human life. Premature skin aging can result from poor care, environmental pollutants, and ultraviolet radiation exposure. Some indicators of skin aging like wrinkles, lines, spots,uneven skin tone, and pigmentation. One cannot avoid aging but cosmetics and pharmaceutical approachesplay an imporatn role in that. Lecithin organogel (LO) is an effective vehicle for topical delivery of many bioactive agents used in aging treatment. Lecithin is cell component isolated from soya beans or eggs and purified to show excellent gelation in non-polar solvents when combined with water. LO can form a heat-stable, resistant to microbial growth, visco-elastic in nature, optically transparent, and non-birefringent, micellar system. Lecithin organogel act as a penetration enhancer.so its ability to dissolve in hydrophilic as well as in lipophilic drugs makes it a dynamic vehicle, which can be explored as a carrier for anti-aging agents[17].

❖ **APPLICATION OF ORGANOGEL**

1. Topical drug delivery

a) Cosmetic

Gels have been employed in a variety of products including shampoo, fragrance products, dentifrices andskin and hair care preparation.

b) Ophthalmic

Drug product like normal lachrymal turnover causes rapid clearance of solution and suspension dosage forms.Most ocular treatments call for the topical administration of drugs in the tissues around the ocular cavity. Various types of dosage forms have been developed for ocular drug delivery of drugs, which include drops, suspensions, ointments and ocusserts and more recently eyelid skin delivery systems ". Eye drops are the most widely used and most popular but sufers from the drawback that a majority of the medication is immediately diluted by tears and is rap-idly drained out by the constant tear flow. Therefore, only a fraction of the administered drug is absorbed to target tissue and thus, repeated administration of eye drops becomes essential, leading to poor patient com-pliance and also undesirable side effects. Suspensions have the disadvantage that the rate of drug release is dependent on the rate of dissolution of drug particles which vary due to constant change in

com-position and outflow of lachrymal fluid. In order to increase the therapeutic eficacy, one of the methods suggested is to increase the viscosity so as to prolong the contact period. But, the addition of vis-cosity builders like CMC did not improve the situation much and in the case of water insoluble ointments, immediate vision was affected. Lecithin-based organogels offer a potential ophthalmic drug delivery system, which may overcome the above mentioned difficulties. These gels present a unique fea-ture of being able to incorporate lipophillic, hydrophilic as well as amphoteric bioactive compounds. They are transparent and hence even their long-term presence in the ophthalmic cavity does not afect vision. The drug is released at a steady rate because of the three-dimensional network of the gel. Also, because of its high viscosity and organic solvent as a continuous phase, they are difficult to wash off. The macroviscosity is high due to the formation of giant micelles containing water which have long tails. Three formulations of organogels have been prepared by Fresta et al.34 using lecithin as gelator and organic solvents used are paraffin, isopropyl palmitate and cyclooctane. Cyclooctane gels have been found to be toxic and parafin-based gels, the safest, whereas iso-propyl palmitate gels cause mild morphological changes.

c) Ointments

It is of various advantages like good tolerability, formation of a protective film over the cornea, protection from conjuctival adhesion. Methazolamide ineffective as an ophthalmic solution has been incorporated into carbomer and poloxamer gels for treatment of glaucoma [4 18].

2. Oral delivery

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

3. Parenteral depot formulations

Anhydrous and water containing organogels were formulated for depot formulations using sorbitan monostereate (SMS) and different gelation modifiers (polysorbates 20 and 80) in various organic solvents and oils. These gels were shown to potentially serve as systems for the controlled release of drugs and antigens. SMS organogels containing vesicle-in-water-in-oil emulsions were investigated in vivo s delivery vehicles for vaccines using albumin (BSA) and haemagglutin (HA) as model antigens. Intramuscular administration of the vesicle-in-water-in-oil gel yielded the longest-lasting depot effect. This can be readily explained by the combined barriers to diffusion present in this formulation (miosomes and gel matrix). Nevertheless, the release is relatively short-lived. This is due to the percolation of interstitial fluid into the gel, causing fragmentation and emulsification of the latter. Based on the observed phenomena, the release mechanism for hydrophilic antigens was assumed to be driven by gel disintegration. The studies also showed that both w/o and v/w/o gels possessed immunoadjuvant properties and enhanced the total primary and secondary antibody titers to the HA antigen in mice. Subcutaneously-injected in situ-forming organogels prepared from L-alanine derivatives in safflower oil were used in the long term delivery of leuprolide, a luteinizing releasing hormone agonist used in prostate cancer. The gels were shown to slowly degrade and release the therapeutic peptide for a period of 14 to 25 days. The efficacy of the system was demonstrated by the sustained induced chemical castration (inhibition of testosterone secretion), lasting up to 50 days. More recently, the same systems, using the N-stearoyl 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. Following subcutaneous injection, the oleo gels provided a 5-fold lower burst effect than control oil formulations, followed by sustained release of the drug for up to 11 days. Histology studies showed these organogels to have a good biocompatibility profile over an 8 week evaluation period. Overall they represent a promising platform for long term sustained drug delivery.

4. In rectal drug delivery systems

Organogels containing Eudragit L and S have been designed for rectal delivery of drugs. The drugs used are Salicylates, Procaine and Ketoprofen 35.

Further, invitro evaluation of the drug (using rotation disc method- JP XI) has shown that after a initial burst of drug release, the drug follows apparent first order kinetics. The burst effect has suggested to be due to rapid release of drug existing on the gel surface at the moment of insertion into the dissolution media. The drug release has found to be dependent on the concentration of Eudragit L or S. While in the case of Eudragit L, the release mechanism has been found to be a erosion dependent process, in the case of Eudragit S, the release has found to confirm to the diffusional model 24. In-vivo evaluation of these systems using rabbits has shown sustained plasma drug levels. Further on the ad-dition of 1 0% linoleic acid or oleic acid as absorption enhancer, bioavailability has been found to be increase to 1 .55-1 .75 -fold and 1 .46-1 .85- fold3s. Thus, Eudragit L based organogels containing linoleic acid or oleic acid hold potential for use as rectal sustained release preparations.

5. In vaccines

The microemulsion-based organogels can be used as a vehicle for delivery of hydrophilic vaccines 23. Accord-ing to Florence et ai., these systems offer various advan-tages like the slow release of antigen from the organogel system produces a depot effect. This has been proved by measuring the clearance rate of radio labeled bovine se-rum albumin administered in wlo gel to mice. The clear-ance rates when compared to those from w/o emulsion and aqueous solution prove that maximum depot effect is obtained from w/o gels. But, this depot effect is compromised by the access of water to the system by perco-lation. The percolation of interstitial fluid into the three-dimensional network of gel leads to its breakdown into smaller fragments and thus leads to the release of the antigen. This is basically useful where a short depot ef-fect is effective, e.g. immunoadjuvants, where a short depot action is thought to be effective in enhancing the immune response to antigens. Further, organogel have been formulated to contain niosomes. The vaccine has been found to be trapped in these niosomes which themselves are located within the surfactant network in the organic medium. A depot ef-fect has been observed after i.m. administration of these gels. The gels could be prepared by the addition of a hot (600 C) aqueous niosome suspension containing the anigen (bovine serum albumin) to the organic solution of the gelator; a vesicle in water in oil (v/w/o) emulsion is formed. This on further cooling gives an opaque and thermoreversible geP7. Thus, organogel-based formula-tions hold a good potential as carriers for vaccines [4, 18].

6. Bioadhesive

Bioadhesive of pharmaceutical interest are mucoadhesives this implies that the substrate for adhesion is the mucus itself. Many of the alternate routes of administration (buccal, ophthalmic, nasal, vaginal, etc) lend themselves bioadhesives because of the presence of mucosal tissue[4].

7. In suppositories

They are used in the formulation of some suppositories Example- Glycerin suppositories BP 1968, Ketorolac tromethamine suppositories (30 mg) and ketoprofen suppositories (50mg)[19].

8. Gelatins gels

They are employed in the preparation of hard and soft capsules that may be used to mask the unpleasant tastes of solids and liquids.

9. Microbiological media

Agar and gelatin gels are used as a solid media for the culture of microorganisms. The diffusion of antibiotics, antiseptics, vitamins and enzymes through the culture media is used in the microbiological assays of these materials. Such diffusion produces zones of either retarded or enhanced growth on seeded agar plates depending on the activity of the diffusing substance[4].

SOME FORMULATION OF ORGANOGEL IN WHICH SUCCESFULLY BIOACTIVE AGENT INCARPORATED

Some types of organogel in transdermal drug delivery

S. No.	Therapeutic Category	Therapeutic Agent	Drug Delivery
1	Antihypertensive	Nicorandil[20],Diltiazem[21]and Propranolol[6,22]	Transdermal Oral and Nasal
2	Migrane	Sumtriptan[23]	Transdermal
3	Antifungal	Fluconazole[24], and biofonazole[25,26]	Transdermal and topical.
4	Anticancer	CyclosporinsA[27]. Tamoxifen[28]	Transdermal
5.	NSAIDs	Lornoxicam[29],ketorolac triethanolamine[30],acetaminophen[31],Diclofenac sodium[14],piroxicam [32,33] ibuprofen[7] Aceclofenac[34.] and Flurbiprofen[35]	Transdermal, topical and oral
6.	Antibiotics	ciprofloxacin[36]	Transdermal
7.	corticosteroid	Clobetasol Propionate[37]	Topical
8.	AntiHIV	Zidovudine[38]	Transdermal

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