Review article Available online www.ijsrr.org ISSN: 2279–0543

International Journal of Scientific Research and Reviews

A Review on Organogels and Fluid Filled Method

Gupta Rakesh*, Gupta Mukesh K. and Sharma Hemant K.

[1]Department of Pharmaceutics, Alwar Pharmacy College, MIA, Alwar-301001, Rajasthan, India.

ABSTRACT:-

Organogels are generally formed by immobilization of various liquids within 3-dimensional network, formed by self assembly, formed of molecules called as gelators. Organogels shows longer shelf-life, no need of sophisticated instruments, less chances of batch to batch variations, ease of preparation and thermo-reversible nature of the organogels-based formulations. Organogels was observed that addition of span caused an abrupt rise in the viscosity, producing a transition of the initial non-viscous solution into gel of jelly like taste. Mechanism by fluid filled, formulate by vortexing or mixing method.

Keywords:- Organogel, Classification of gels, Properties & advantages of organogels, Types of organogels and fluid-filled mechanism.

Corresponding Author:

Gupta Rakesh
Department of Pharmaceutics,
Alwar Pharmacy College, MIA, Alwar-301001, Rajasthan, India.
E Mail - rakeshapcpharma@gmail.com Mob. No. - +91-9785193954

INTRODUCTION

Topical preparations are formulate which are applied directly to an external body surface by spreading, rubbing, spraying or instillation**.** Fungal infection of skin is now-a-days one of the common dermatological problem. The physicians have a wide choice for treatment from solid dosage to semisolid dosage form and to liquid dosage formulation. The topical route of administration has been utilized either to produce local effect for treating skin disorder or to produce systemic drug effects. Within the major group of semisolid preparations, the use of topical gels has expanded both in cosmetics and in pharmaceutical preparations.

Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal, and skin as topical routes. Skin is one of the most accessible organ of human body for topical administration and main route of topical drug delivery system. Number of medicated products is applied to the skin or mucous membrane that either enhances or restores a fundamental function of a skin or pharmacologically alters an action in the underlined tissues. Such products are referred as topical or dermatological products. [1]

1. Topical Drug Delivery System

A topical delivery system defined as the substance that carries a specific drug into contact with and through the skin. The challenge to topical drug delivery is the transport across the skin barrier.

Topical delivery includes two basic types of product:

- External topical that are spread, sprayed, or otherwise dispersed on to cutaneous tissues to cover the affected area.
- Internal topical that are applied to the mucous membrane orally, vaginally or on anorectal tissues for local activity.

For the most part topical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes. Although some unintended drug absorption may occur, it is sub therapeutics quantities and generally of minor concern.

1.1. Advantages of topical drug delivery systems:

- Avoidance of first pass metabolism.
- Convenient and easy to apply.
- 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 etc.

- Achievement of efficacy with lower total daily dosage of drug by continuous drug input.
- Avoids fluctuation in drug levels, inter- and intrapatient variations.
- Ability to easily terminate the medications, when needed.
- A relatively large area of application in comparison with buccal or nasal cavity.
- Ability to deliver drug more selectively to a specific site.
- Avoidance of gastro-intestinal incompatibility.
- Providing utilization of drugs with short biological half-life, narrow therapeutic window.
- Improving physiological and pharmacological response.
- Improve patient compliance.
- Provide suitability for self-medication. [2]

2. *Mechanism of gel permeation into skin*

There are two possible mechanisms for gel permeation into skin has been proposed.

1. Gel permeation into the skin occurs by diffusion through lipid intercellular matrix in stratum corneum.

2. Gel provides a slight disorganization of the skin allowing the permeation of the gel and the active drug through the stratum corneum.[3]

3. *Introduction to gels*

Gels are the semisolid viscoelastic systems. They are said to be the systems easy to identify then to define. We use many gels in our day to day life, such as soaps, shampoo, toothpaste, hair gel and cosmetics, as well as contact lenses and gel pens etc. Gel can either be natural gel or artificial or synthetic gel [4]. They may be considered as the intermediate between solid and liquid state of matter. Gels are considered to be at the interface between “complex fluids” and phase-separated states of matter [5]. Despite higher concentration of liquids in the composition of gels, they exhibit the properties of solids. Gels may also be considered as dispersions in which solid is a continuous phase and liquid is a discrete or discontinuous phase.

The gels can be dried and obtained in solid form. Depending upon the method of drying gels may be classified as either aerogel (formed by replacing the liquid phase with air), cryogel (obtained by freeze drying), and xerogel (obtained by using conventional drying method).[4]

There are 2 major types of gels, i) Hydrogels and ii) Organogels. The classification is based on nature of liquid, that the gel immobilizes. Hydrogels contains high amount of water in there composition. Whereas gels in which, the immobilized liquid is organic solvent are termed as organogels (figure 1).

Organogels are generally formed by immobilization of various liquids within 3-dimensional network, formed by self assembly of fibers, formed of molecules called as gelators.[5] The network stops the flow of liquid by altering the surface tension of the liquid. It is the network of the gelators which gives gel a structure and stickiness. Interaction between gelators molecule to form aggregate and hence the fibers might be either covalent (chemical) or simply physical. Chemical gels are thermally irreversible whereas gels formed by weak non-covalent interactions (physical gels) are reversible [4]. Due to involvement of complex mechanism behind bonding interactions and formation of network, it's difficult to predict the ability of any molecule to gel the specific solvent. Hence research in the field of gels is largely based on serendipitous discoveries of gelators through blind screening. Many of the aspects of organogels are still poorly understood.[5, 6]

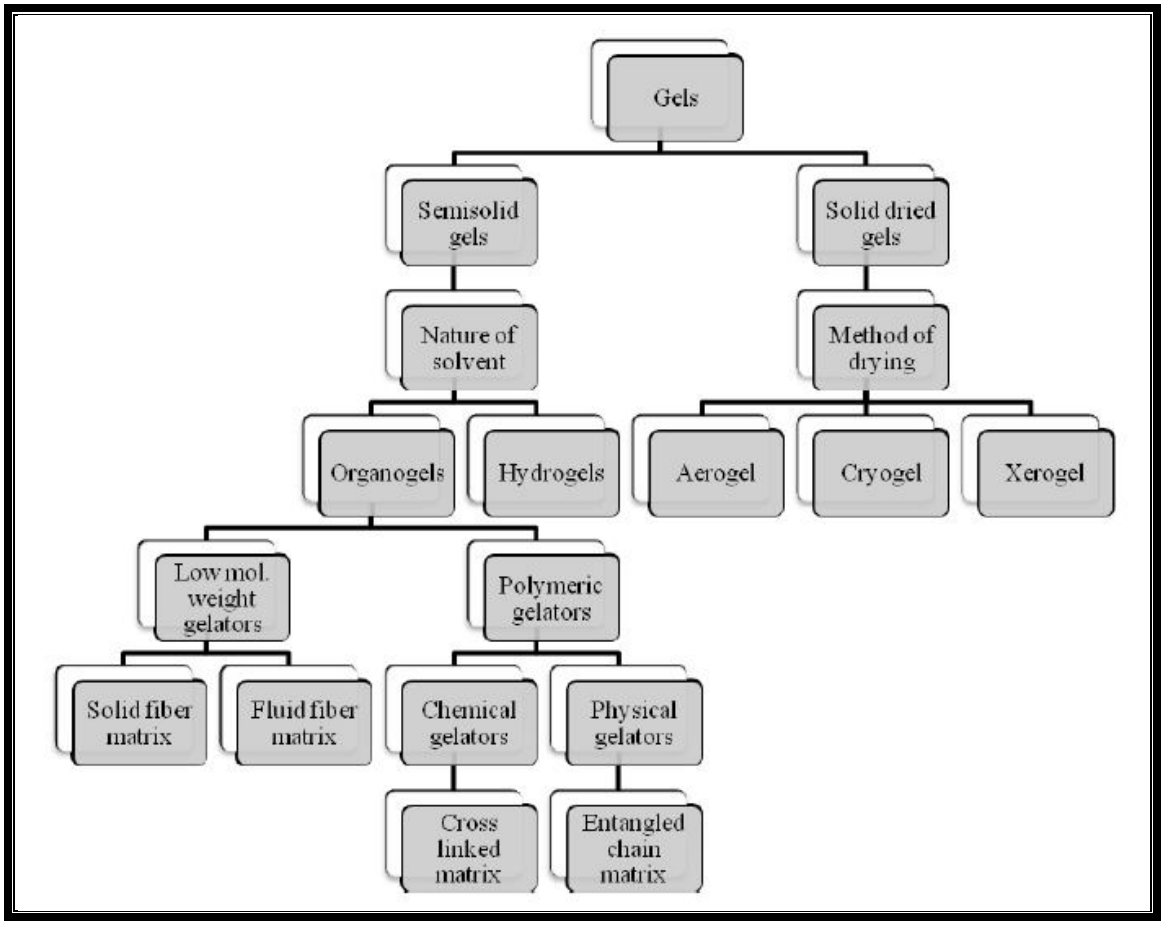


Figure 1: Classification of gels

A minimum concentration of gelator required to gel the solvent is known as Critical gelation concentration (CGC). Below CGC concentration the resulting system exhibits flow properties and behaves as a liquid.

Stability of organogels depends on concentration of gelator, presence of aqueous phase, storage temperature, and properties of solvent. Organogels shows thermo-reversible behaviour. As temperature increases the interaction between gelator molecules decreases and organogels forms a liquid state, but as the temperature decreases the interactions between gelator molecules are restored and organogels obtain their original form.[7]

Organogels are reported to have many applications in Pharmaceuticals, nutraceuticals, food, cosmetics, and preservation of arts etc.

Organogels do have some advantages over conventional drug delivery system, which includes longer shelf-life, no need of sophisticated instruments, less chances of batch to batch variations, ease of preparation and thermo-reversible nature of the organogels-based formulations. The ability of the organogels to accommodate both hydrophilic and hydrophobic compounds within its structure has also widened the scope of use of organogels in various delivery systems. The research on biocompatible and edible organogels has added a new dimension in the food and pharmaceutical industries because of the easy preparation of the organogels.[8] The ability of the organogels to tailor the release of the solute molecules incorporated within its structure is keeping the researchers keen to develop new controlled drug delivery systems. Edible oil organogels have unique physical, functional and nutritional properties.[9]

Most of the organogels developed till-date consists of toxic solvents (like cyclohexanes, n-octane, kerosene etc) hence their human applications may create serious problems. Unfortunately, scarce toxicological information about many commonly used organogelators also restricts the use of organogels in drug delivery.[8] Hence more stress is being given on the development of biocompatible organogels which are based on generally regarded as safe (GRAS) materials. Edible oils can serve as better organic solvents for human use.

4. Organogels

A gel may be defined as a semi-solid formulation having an external solvent phase apolar (Organogels) or polar (hydrogel) immobilized within the spaces available of a three dimensional net-worked structure. The topical administration of drugs, in order to achieve optimal cutaneous and percutaneous drug delivery has recently gained an importance because of various advantages such as ease of administration non-invasive, better tolerated and compliance, local enhanced transdermal

delivery, avoidance of local gastrointestinal toxicity, avoidance of first pass metabolism and delivery benefits.

In search of a vehicle to deliver the medicament into the skin layers (cutaneous delivery) or through the skin and into the systemic circulation varied kinds of formulation systems and strategies have been evolved. The topical delivery has been attempted and made successful using several lipid-based systems viz vesicular systems, lipid microspheres, lipid nanoparticles, lipid micro-emulsions and polymeric gels.[10]

Organogels was observed that addition of span caused an abrupt rise in the viscosity (10-104), producing a transition of the initial non-viscous solution into gel of jelly like taste. The amount of water required to produce the gel was found to be critical but now, organogels have been studied extensively in many laboratories worldwide with regard to their varied aspects such as formulation component, formation and gelling mechanism, physico-chemical properties etc and have been proposed as a matrix for topical drug delivery.

❖ **Properties of Organogels :-**

In the present section, attempts will be made to discuss about the various physicochemical properties of the Organogels.

- **Viscoelaticity**: 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.
- **Non-birefringence**: Organogel of not allowing the polarized light to pass through its matrix is regarded as non-birefringent.
- **Thermoreversibility**: As the organogels are heated up above a critical temperature, the organogels loses its solid matrix like structure and starts flowing.
- **Thermostability:** The organogels are inherently thermostable in nature.
- **Optical clarity:** Organogels may be transparent or opaque in nature.
- **Biocompatibility**: Initially, organogels were developed using various non-biocompatible organogels which rendered the organogels non-biocompatible of late, research on organogels using various biocompatible constituents has opened up new dimensions for the use of the same in various biomedical applications.[11]

❖ **Advantages of Organogels :-**

- **Template vehicle:** Span 80 and Tween 80 based Organogels provide opportunities for incorporation of wide range of substances with diverse physicochemical characters viz., chemical nature, solubility, molecular weight, and size etc.
- **Process Benefits:** Self-assembled supramolecular arrangement of surfactant molecules makes the process very simple and easy to handle.
- **Structural/ Physical Stability**: Structural integrity of organogels is maintained for longer time periods.
- **Chemical Stability:** organogels are moisture insensitive and being organic in character also resists microbial contamination.
- **Topical Delivery Potential:** They enhance the skin penetration and transport of the molecules.
- **Safety:** Use of biocompatible, biodegradable and non-immunogenic materials makes them safe for long-term applications.[10]

4.1. Types of Organogels:-

❖ **Lecithin Organogels:-**Lecithin is a phospholipids extracted from various plants and animal tissues apart from the egg yolk. The lecithin procured from natural sources is able to form the gelled structures. Lecithin Organogels (Los) are thermodynamically stable, clear, viscoelastic, biocompatible and isotropic gels 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.

❖ **Sorbitan Monostearate Organogels:-**Sorbitan monostearate (Span 60) and sorbitan monopalmitate (Span 40) have been found to gel a number of organic solvents at low concentrations. 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.

Delivery vehicles for hydrophilic vaccines and sorbitan monostearate molecules are arranged in inverted bilayers within the tubules.

- **Sorbitan Monooleate Organogels:-** Span 80 and Tween 80 have been found to gel a number of organic solvents at low concentrations.

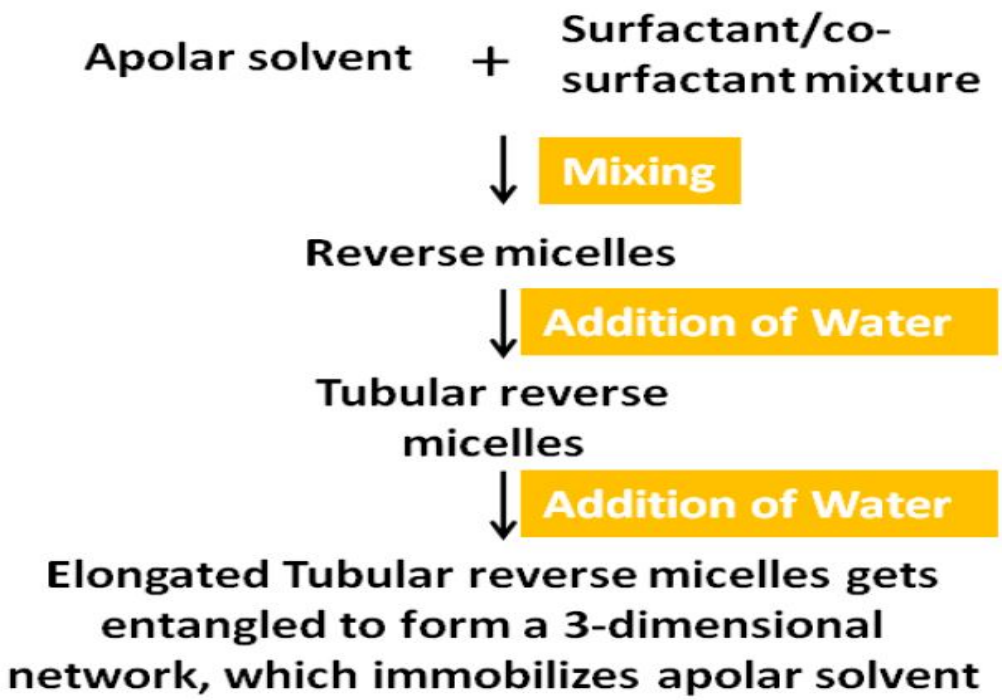


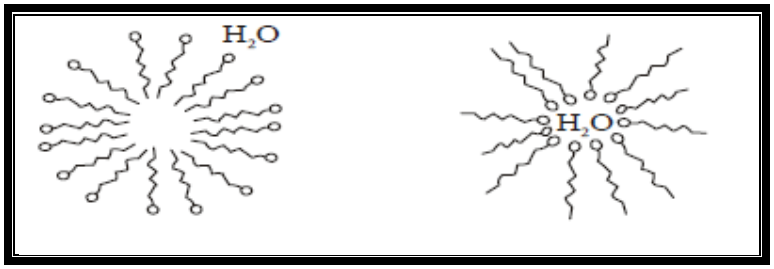
Figure 2: Method of formation of organogels by fluid-filled mechanism

- **In situ formation of an organogel 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.

- **Eudragit Organogels:-**Eudragit organogels are different from the organogels they are 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 (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 1 min. Gel viscosity was found to increase with increasing concentrations of Eudragit and to decrease with increasing drug content. The drug content in Eudragit organogels should be kept low (e.g., 1.25% w/w) to maintain gel rigidity and stability.

- **Microemulsion-based gels:**-Microemulsion-based gels were initially prepared by dissolving solid gelatin in a hot w/o microemulsion (which was composed of water, AOT and isooctane) 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[10].



Micelle Reverse Micelle

Figure 3: Schematic Representation of a Reverse Micelle

REVERSE MICELLES

In an organic nonpolar solvent, surfactants can also form aggregates in which the nonpolar tail region of the surfactants are oriented toward, and in contact with bulk nonpolar solvent while the polar moieties are located in the interior of the aggregate where they are shielded from the bulk nonpolar solvent. These aggregates are termed reverse micelles or inverted micelles (Figure 3) since they are inverted (or reversed) compared to the normal aqueous micelle. If prepared in the presence of trace amounts of water, the reverse micelles can contain a water pool in the interior of the micelle. These inner water molecules are shielded from the bulk organic solvent. Depending on the amount of water present, such systems are also referred to as water-in-oil micro emulsions (w/o μE). When the system contains just enough or less water to hydrate the hydrophilic groups of the surfactant, it is considered a true reverse micelle. W/O μE's contain more water than necessary for surfactant

head group hydration and have an increased micelle diameter and larger aggregation numbers. This distinction between reverse micelles and w/o μE's is characterized by the water to surfactant ratio, which is typically designated as wo or Ro and is equal to the concentration of water present divided by the concentration of the reverse micelle forming surfactant. For convenience, the term reverse micelle will be typically used although the system may actually be considered a w/o μE.

SELECTED APPLICATIONS-

- Solubilization - One of the most basic and important applications of reverse micelles is their ability to increase the solubility of compounds that would otherwise be insoluble or sparingly soluble in a nonpolar solvent. Reverse micelles can solubilize alcohols, amines, alkynes and aqueous solutions of acids, bases, and buffers.[12]

Reverse micelles can also solubilize, with retention of activity, a number of hydrophilic biomolecules, which is of particular importance in biochemistry, biotechnology and medicine.[13, 14] Proteins and enzymes can be selectively solubilized in reverse micelles for extractive separation purposes with subsequent recovery achieved by various techniques.[15, 16] In most cases, binding is thought to occur due to electrostatic interactions between the charged surface of the biomolecules and the reverse micelle surfactant charged head group.[17] Therefore, a particular protein or enzyme can be selectively extracted from an aqueous solution mixture to the water pool of the reverse micelle if the biomolecules have different isoelectric points.[12] For example, Vinogradov et al. have selectively extracted two different enzymes from inclusion bodies grown in E.coli and shown that they both refolded to their native active conformations in a reverse micelle system. These inclusion bodies contain mainly misfolded and inactive products that are otherwise difficult to extract and activate by conventional techniques.[18] Therefore the use of reverse micelles is advantageous in this regard. The primary disadvantage of this technique is in the recovery process where it is often difficult to recover pure protein void of any water or surfactant. However, a new recovery technique has been investigated using pressurized CO_2 with increased purity of precipitated protein.[17] Numerous other examples of the utilization of reverse micelles for solubilizaton and extractive separations have been reporte.[16, 17, 18]

GENERAL PROPERTIES AND APPLICATIONS

Although based on limited data, it appears that Organogels exhibit many of the same General basic properties as reverse micelle solutions and thus can be utilized for similar

Purposes and applications. The difference between Organogels and reverse micelles is that Organogels are in a "Semi-solid" form because of gelation and can be used in situations that would otherwise be difficult with a liquid, i.e. the reversed micelle solution. This "Semi-solid" form allows for easier handling and reuse. Also, they are stable in many different types of solvents which are useful in analyte (or product) recovery schemes where a product can be extracted without the loss of physical properties or formation of emulsion systems that results when reverse micelles in solution are utilized.

Table 1:- Organogel formulations used in drug delivery [10]

S. No.	Types	Route of Administration	Study Conducted	Model drugs
1.	Lecithin	Transdermal	Clinical trials. In vivo skin permeation & efficacy. In vitro skin Permeation	Diclofenac, Piroxicam, tetrabenzamidin, Scopolamine, Propranolol, Aceclofenac, Indomethacin, Diclofenac.
2.	Sorbitan Monosteara T(SMS)	Nasal, Oral Subcutaneous Intramuscular	In vitro release In vitro release In vivo efficacy	Propranolol Cyclosporin A BSA and HA
3.	PLOs	Transdermal	Clinical trials. In vivo skin permeation & efficacy. In vitro release.	Promethazine, Ondansetron, Diclofenac Methimazole, Fluoxetine,Dexamethaz one, Amitriptyline, Methadone, Morphine, Buspirone Scopolamine, Metoclopramide.
4.	L-alanine Derivative	Subcutaneous	In vitro/in vivo In vitro/in vivo	Rivastigmine Leuprolide
5.	Eudragit Organoges	Rectal. Buccal	In vivo efficacy In vivo efficacy	Salicylic acid BSA

These features have led to their application in transdermal drug delivery, as fluorescent sensor platforms and as a catalytic medium for synthetic reactions, particularly for enzyme

mediated reactions and production of pure chiralmolecules. [19, 20]

When dermatological preparations are used in order to obtain local topical effect (rubefacient, astringent, antikeratoid, antiparasite, topical antibacterial, -viral, -microbial, etc.), the active agent must remain on the skin surface such long-lasting as possible.

4.2. Mechanism of Organogels Formation:-

A gel can be divided into primary, secondary, and tertiary structure like a protein to understand the mechanism of gel formation. Primary structure (Aº to nm scale) is composed of unidirectional aggregation of gelator molecules. The secondary structure (nm to µm scale) is nothing but the morphology of the aggregates like micelles, vesicles, fibers, ribbons or sheets.[21,22] Whereas tertiary structure of a gel (µm to mm scale) involves the interaction of individual aggregates to form gel network.[4]

As stated earlier, organogels are formed by 3-dimensional network of intertwined fibers.[11] Fibers may be either fluid filled or solid. The mechanism of formation of both is illustrated in figure 4 and figure 5 respectively.

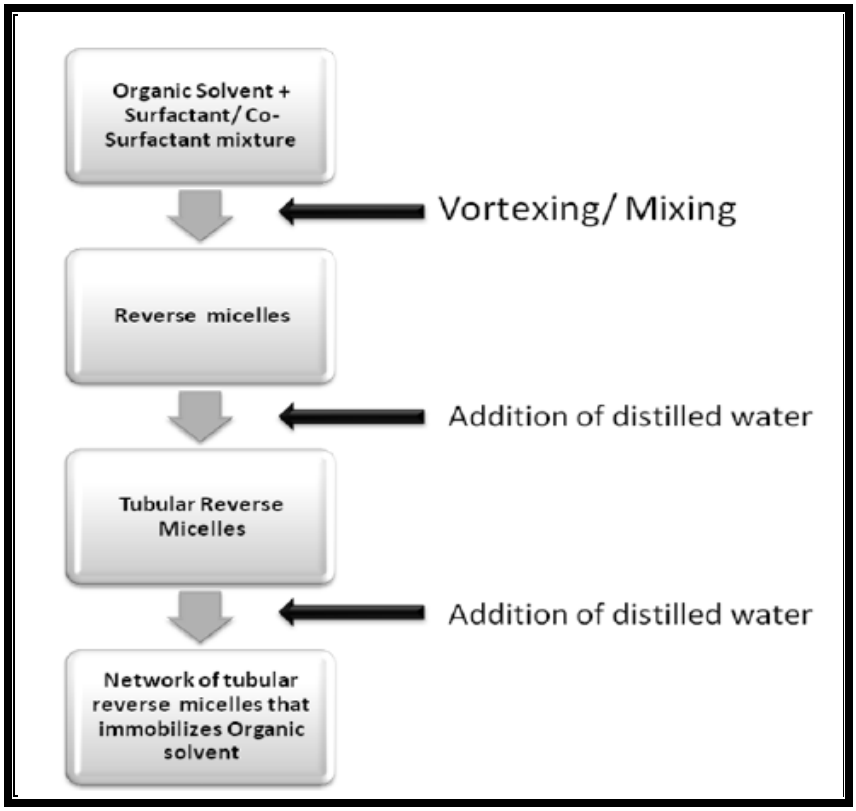


Figure 4: Method of formation of organogels by fluid-filled mechanism. [8, 23]

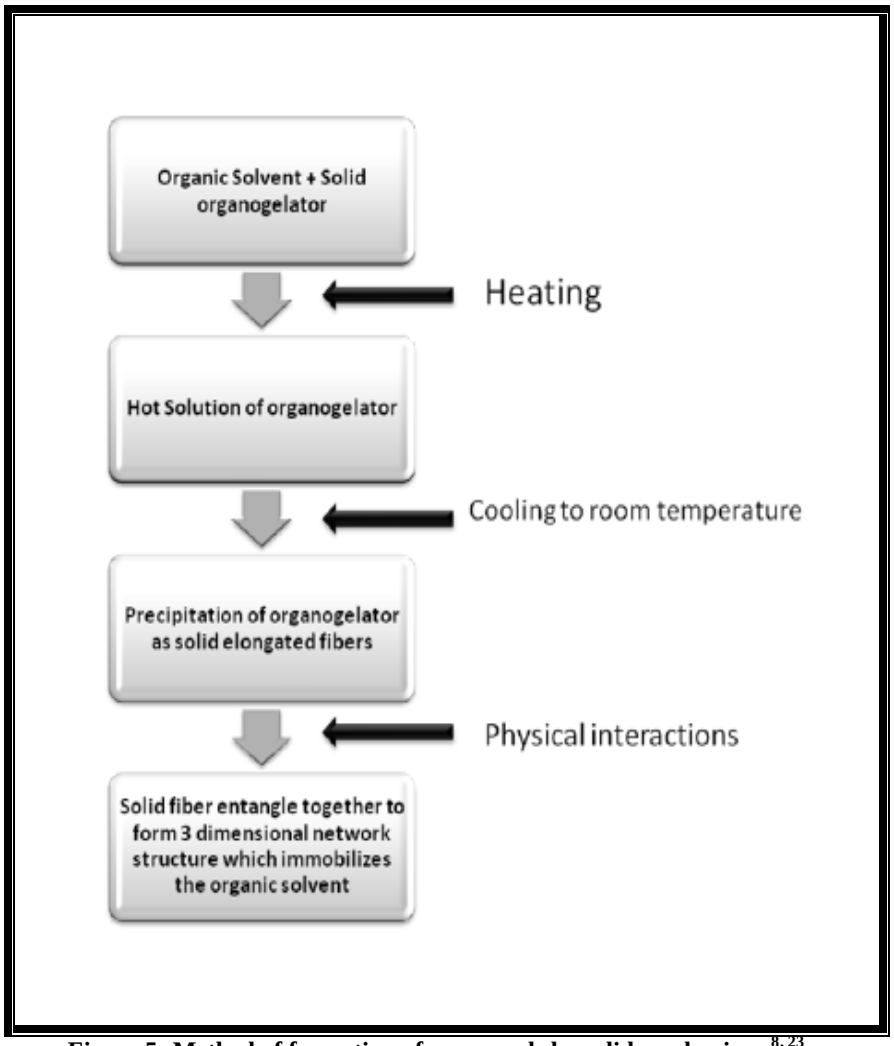


Figure 5: Method of formation of organogels by solid mechanism. [8, 23]

4.3. Organogels Picture's:-

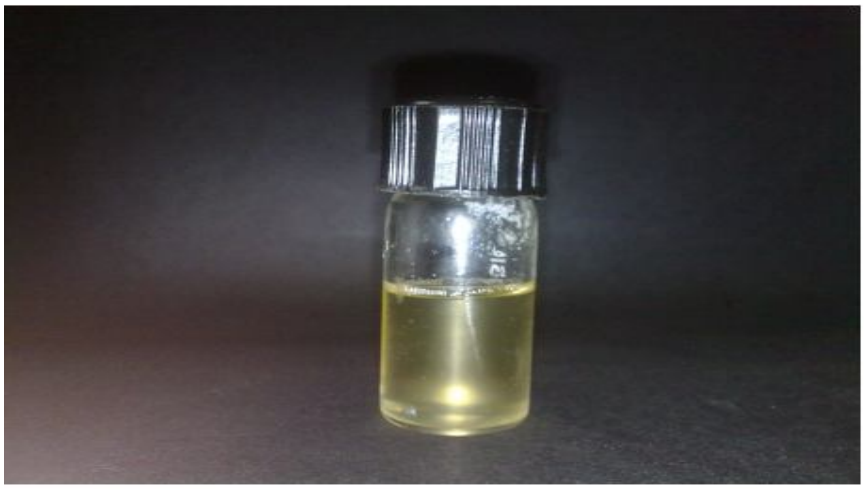


Figure 6: Organogel on heating

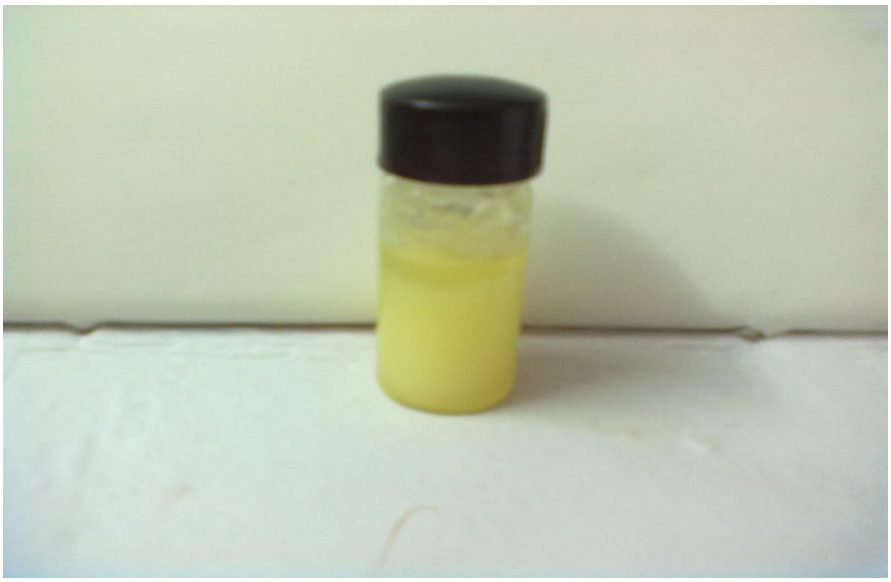


Figure 7: Organogel on cooling

REFERENCES:-

1. Niyaz BB, Prakasam K, Goli D. Formulation and evaluation of Gel containing Fluconazole-Antifungal Agent, International Journal of Drug Development & Research, Oct-Dec 2011;3(4):109-128.
2. Reddy GSC, Anilreddy Dr.B, Jotish M, Pranitha CN, Suryadevara H. International Journal Of Pharmacy & Technology, Dec-2010; 2(4):584- 602.
3. Maity GC. Low Molecular Mass Gelators of Organic Liquids. Journal of Physical Sciences, 2007;11: 156-171.
4. Terech P and Weiss RG. Low Molecular Mass Gelators of Organic Liquids and the Properties of their Gels, Chemical Reviews, 1997; 97(8):3133-3160.
5. Dastidar P. Structure–Property Correlation of a New Family of Organogelators Based on Organic Salts and Their Selective Gelation of Oil from Oil/Water Mixtures, Chem. European Journal, 2004;10:5311-5322.
6. Rogers MA, Wright AJ, and Marangoni AG. Crystalline stability of self-assembled fibrillar networks of 12-hydroxystearic acid in edible oils. Food Research International, 2008;41(10):1026-1034.
7. Vintiloiu A and Leroux JC. Organogels and their use in drug delivery - A review. Journal of Controlled Release, 2008;125(3):179-192.
8. Hughes NE. Potential food applications of edible oil organogels. Trends in Food Science & Technology, 2009;20(10):470-480.

9. Patil KD, Bakliwal SR, Pawar SP. organogel: Topical and transdermal drug delivery system, International Journal of Pharmaceutical and development, 2011;3(6):58-66.
10. Pal K, Sahoo S, Kumar N, Bhattacharya C, Sagiri SS, Jain K, Ray SS and Nayak B. Organogels: Properties and Applications in drug delivery, Designed Monomers and Polymers 2011;14:95–108.
11. Hinze WL. Organized Assemblies in Chemical Analysis. ed.; JAI Press Inc. Greenwich, 1994;1:186.
12. Luisi PL, Giomini M, Pileni MP, Robinson BH. Reverse Micelles as Hosts for Proteins and Small Molecules, Biochim, Biophy, Acta, 1988;947:209-246.
13. Orlich B, Scchomacker R. Enzyme Catalysis in Reverse Micelles, Advances in Biochemical Engineering & Biotechnology, 2002;75:185-208.
14. Bohidar HB, Behboudnia M. Characterization of reverse micelles by dynamic light scattering, Colloids and Surfaces A: Physicochemical and Engineering Aspects, 2001;178:313-323.
15. Krishna SH, Srinivas ND, Raghavarao MS, Karanth NG. Reverse Micellar Extraction for Downstream Processing of Proteins/Enzymes, book title: History and Trends in Bioprocessing and Biotransformation which is part of the series Advances in Biochemical Engineering/Biotechnology, 2002;75:119-183.
16. Zhang H, Lu J, Han B. Precipitation of Lysozyme Solubilized in Reverse Micelles by Dissolved CO_2. Journal of Supercritical Fluids, 2001;20:65-71.
17. Vinogradov AA, Kudryashova E V, Levashov AV, Dogen VW. Solubilization and Refolding of Inclusion Body Proteins in Reverse Micelles, Analytical Biochemistry, 2003;320:234-238.
18. Kantaria SR, Rees GD, Lawrence MJ. Gelatin-Stabilised Microemulsion-Based Organogels: Rheology and Application in Iontophoretic Transdermal Drug Delivery, Journal of Controlled Release, 1999;60:355-365.
19. Velasco GN, Valencia GMJ, Garcia DME. Fluorescent Organofilms for Oxygen Sensing in Organic Solvents Using a Fiber Optic System Analyst, 1997;122:1405-1409.
20. Wang X. Reversible organogels triggered by dynamic K+ binding and release, Journal of Colloid and Interface Science, 2011;353(2):412-419.
21. Terech P. Structural variations in a family of orthodialkoxyarenes organogelators, Journal of Colloid and Interface Science, 2006;302(2):633-642.
22. Murdan S, Gregoriadis G and Florence AT. Novel sorbitan monostearate organogels, Journal of pharmaceutical sciences, 1999;88(6):608-614.