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A REVIEW ON ORGANOGELS: AS A NEW FORMULATION

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ABSTRACT:-

A gel is a semi-solid formulation having an external solvent phase which is either apolar (organogels) or polar (hydrogels) that is immobilized inside the voids contained in a three-dimensional networked structure. Organogels are bi-continuous systems composed of gelators and apolar solvents that may or may not contain water molecules entrapped inside the self-assembled structures of the gelators. When used at a concentration of around 15%, the gelators may undergo physical or chemical interactions, resulting in the formation of self-assembled fibrous structures that become entangled with one another, resulting in the formation of a three-dimensional networked structure. The resulting three-dimensional networked structure blocks the flow of the external apolar phase. Sterol, sorbitan monostearate, lecithin, and cholesteryl anthraquinone derivatives are examples of gelators. The unique characteristics such as thermo-reversibility, viscoelasticity, and versatility impart a longer shelf-life and ease of preparation to organogels. These characteristics can easily be adjusted by simple formulation modifications, resulting in highly-structured architectures. The organogels have ability to entrap both hydrophilic and hydrophobic compounds within its structure have also widened the scope of use of organogels in various delivery systems. These characteristics make these structures excellent matrices with the ability to deliver an efficient drug concentration over a long period of time, thus enhancing the chances for patient compliance. Their hybridization with other materials also allows for customizing their potential as drug delivery systems. Organogels have potential applicability in numerous ways; hence this article discusses the various aspects of it.

Keywords: Organogels, Organogelators, Drug delivery

1. INTRODUCTION:-

Gels have been defined as a semisolid, cross-linked system containing a condensed solid particles interpenetrated by a liquid (1). Gels can be referred to as hydrogels or organogels, which can be distinguished on the basis of polarity comprised by the gel i.e. if the liquid phase in gel is water then it is termed as a hydrogel, whereas if the liquid phase in the gel is an organic solvent, then it is termed as an organogel. Organogels are the carriers used for delivering the medicament at its desired site (2). Organogels are formed by gelators, which are foundational building blocks. Gelators are often certain low-molecular-mass substances (e.g. sorbitan derivatives, lecithin, fatty acid derivatives, bis-urea compounds, etc.) (3–5). The gelators help in the formation of a 3D structure of mesh network due to the entanglement of self-assembled fibrous structures, which is formed due to some physical or chemical interactions of gelators when used in the concentration of < 15 % (approx.) (6,7). Gelators are hence responsible for

immobilizing the apolar solvent phase. The gels formed by the physical interactions are termed as physical gels (held by physical forces such as Vander Waals, Hydrogen bonds) whereas the gels formed by chemical bonding are termed as chemical gels (held by covalent bonds)(7). The gelators elevate the surface tension which predominantly prevents the flow of the solvent phase. Gelators immobilize organic solvents by the establishment of non-covalent intermolecular interactions forces (H-bonds, electrostatic interactions, metal coordination, p-p stacking and London dispersion forces), resulting in the formation of various entangled structures like wrinkles, lamellar and fibres (8–11). The thermo-reversible property, non-irritating nature, and biocompatibility of the organogels have generated much interest in their potential application as a drug delivery system. Wide formulations can be developed for the administration of drugs via various routes using organogels as they can incorporate hydrophilic and hydrophobic bioactive agents within their gel structure. The rate-limiting step in the bioavailability of drugs from organogels is its characteristic features, i.e., high permeability, low aqueous solubility, which affect the rate of drug release from drug delivery systems. They have no confined application as they can be used for topical application or for release of drugs into systemic circulation by cutaneous delivery and percutaneous absorption (7,12).

2. TYPES OF ORGANOGEL:-

Lecithin Organogels (LOs) :-

Since LOs have the desirable physicochemical characteristics ideal for topical formulations, these are employed most frequently for topical application. These are useful for delivery of wide variety of hydrophilic as well as lipophilic drugs through the skin. Lecithin is a constituent of natural origin which can be isolated from various animal and plant sources (except egg yolk) and hence biocompatible, safe and stable (7,13,14). It is a potential vehicle for a number of bioactive agents. Lecithin is chemically a phosphatidyl choline- constituent of the class phospholipids. It has been observed that, the lecithin is unable to form gel if its phosphatidyl content is less than 95% (7,15). The concept of designing organogels with lecithin was first mentioned by Luisi and Scartazzini in the year 1988 (16). Lecithin can only produce gelation if it is used in its pure form (e.g., the hydrogenated form of soya-lecithin failed to induce gelation). The unsaturated fatty-acids present in naturally occurring lecithin are hence important(15).

Pluronic Lecithin Organogels (PLOs):-

High purity lecithin is costly and difficult to procure in significant quantities. Due to the convenience of synthetic polymers such as pluronics, which serve as co-surfactant and stabilizer, were widely studied in combination with lecithin to formulate lecithin micro-emulsion based organogels (17). It was prepared in 1990 in the US by a compounding pharmacist to use it as a topical carrier system (15). The primary benefit of employing PLs in organogels is their capacity to self-assemble into micelles at approximate physiological temperatures (11). Pluronic F-127 is a copolymer which causes gelation when used in the concentration of 15-30% w/v (18). It is formed by adding the Pluronic -F127 to the LOs. Therefore, lecithin is its precursor. The distinguishing factor between the LOs and PLOs is that PLOs contain an extra constituent: Pluronic F-127 It is majorly used for topical and transdermal drug delivery systems and also for oral and mucosal drug delivery systems to some extent. (15). It forms non transparent yellow gel (19). After topical administration, PLOs ruptures the lipid layer of the stratum corneum and delivers the drug into the systemic circulation by minimal irritation to the skin (7,18). Additionally, in order to have a synergistic effect, it has also demonstrated to be a useful transporter for combinations of drugs (20). It works best when combined with the medications whose molecular weight is less than 500 Da (21).

Limonene GP1/PG Organogels:-

Limonene is a terpenoid with magnificent penetration power and is used in transdermal drug delivery systems as it can enhance the bioavailability of drugs (22). This organogel is prepared by mixing suitable amount of GP1 (dibutyllauroylbutamide)- amino acid type of organogelator—with limonene and PG (propylene glycol), followed by its incubation at 120°C. After cooling down to an appropriate

temperature, it forms a gel that appears white in color. It has been observed that the co-existence of limonene with GP1 and PG influences its rheological behavior to some extent, whereas their chemical characteristics are not significantly affected (7,15,19,23). The GP1/PG organogels tend to have increased gel moduli due to the incorporation of limonene, which gives an indication of increased gel physical stability (24). Other terpenoids such as cineole, linalool, etc., have also been successfully mixed with GP1 and PG to obtain an effective organogel with improved penetration power(18).

Micro-emulsion based organogels (MBG) stabilized by Gelatin:-

Micro-emulsions offer good bioavailability of drugs, when introduced via topical or systemic routes of drug delivery system. Micro-emulsions are known to deliver a greater amount of drug than other gel systems (15). The micro-emulsion system can undergo gelation when gelatin is dissolved in the water microphase, and the resultant gel will consist of more than 80% hydrocarbon solvent (25). The basic mechanism involved in the formation of MBG is that, a solution of gelatin in water is added to the parent micro-emulsion after it has been incubated at 50°C in the incubation chamber. In order to obtain an optically transparent single phase gel, the resulting liquid is forcefully mixed and then allowed to cool to ambient temperature (26). Gelatin is a protein which has the ability to form gels. It can undergo gelation when its concentrated solution is heated beyond 45° C and is then cooled down below 35°C and increases thermostability. When gelatin is added to w/o micro-emulsions, a transparent gel of the complete micellar solution is obtained (27)(28) (7,15,19).

Sorbitan organogels derived from fatty-acids:-

Sorbitan monopalmitate (span 40) and Sorbitan monostearate (span 60) are the gelators of this class. They are non-ionic, hydrophobic in nature, and possess surfactant properties. They form a solid-fiber matrix when heated with the apolar solvent and then cooled down to a relatively lower temperature. A gel of toroidal reverse micelle is formed due to a drop in the temperature, which is followed by self-assembly leading to its transformation into rod-shaped tubules. The gel so-obtained is; white, opaque, semisolid, and thermostable at room temperature. These organogels are used as a vehicle for hydrophilic vaccines(29–31).

Polyethylene organogels:-

Low molecular-weight polyethylene is solubilized in mineral oil at a high temperature of more than 130°C, yielding a colorless organogel. This causes intermolecular interaction within the polyethylene, which leads to the precipitation of its molecules, which forms a solid-fiber matrix to form a gel(16). They are generally used as a base for ointment preparations (19). A study conducted in the 1950s concluded that the patches of polyethylene organogel were found to be non-irritating along with low sensitizing properties (15).

Eudragit organogels:-

Eudragit organogels are formed by the mixture of polyhydric alcohols (propylene glycol, glycerol), high concentration (30-40%) of Eudragit (L or S) and liquid PEG To prepare a formulated Eudragit organogel, the drug is first dissolved in the PEG, and this solution is then added to the Eudragit powder. This mixture is further triturated with the help of mortar and pestle for approximately one minute. The concentration of Eudragit and the amount of drug is found to directly influence the consistency of the gel. Gel viscosity is enhanced with high concentration of Eudragit, whereas gets decreased with increasing amount of drug(15). In low concentration of drug, the gel has high rigidity as well as stability (7,15).

Supramolecular organogels:-

These organogels are made of the gelators of low molecular mass. The molecules of different gelators of this class differ immensely in their structural characteristics. Hence, they have offered a scope of interest to develop different gels with technological application. Example gels having sensitivity towards external stimuli such as light. Remarkable thermoreversibility and mechanical capabilities are displayed by supramolecular organogel system with controlled self-assembled structures. These organogels can offer controlled drug delivery. They can be used as carrier for multiple purposes (15,32).

L-alanine derived organogels:-

LAM (N-lauroyl-L-alanine methylester) undergoes gelation with organic solvents such as; triglycerides, soya-bean oil. It is not as extensively used as other organogels. At room temperature, it remains in gel state (7,15,18). In a two-phase mixture of water and an organic solvent, fatty acid derivative of L-alanine is capable of gelling the solvent-specific portion of the mixture without gelling the aqueous portion (33). This characteristic makes it considerably more appealing to use in organogel. It can be used as implant for sustain release system. Currently, it is used as a vehicle for the drugs like leuprolide, rivastigmine (7,18).

3. IMPORTANCE OF ORGANOGELS:-

For the conveyance of medications in the body/ target site, numerous procedures and frameworks have been analyzed. Out of the effective applications accessible, organogels are getting greater fame on account of the simplicity of utilization, better ingestion through the skin layers, etc. Amongst the existing dosage forms, organogels are the easiest to prepare and have also been proven to be cost-effective(7,34,35). They offer an enhanced stability profile than that of other gels. The characteristic features of organogels not only make it easier for the manufacturer to process them, but also have an easy handling and utilization method for the consumers, hence making it of commercial importance. The organogels can deliver the drugs more effectively than other dosage forms. This has been validated through a study which was conducted by I.M. Shaikh et al, where it was observed that the penetration efficiency of organogel (LO) was more than that of hydrogels, when applied over skin (35,36). As it offers controlled drug delivery system, many chronic diseases could be cured if the organogels get loaded with appropriate drugs and then are implanted within the target site. This characteristic also terminates the obligation of frequent dosing. They have an extended application as they lend opportunities to incorporate various constituents having wide-ranging characteristics. Organogels can be used an alternative to UV-treatment methods. Hence, it will eliminate the chances of cancer caused by exposure to UV-rays (37,38). The characteristic features of organogels not only make it easier for the manufacturer to process them, but also have an easy handling and utilization method for the consumers, hence making it of commercial importance. Organogel can reduce/control the dissemination rate of medication, hence making it liable for designing of an appropriate formulation for an appropriate purpose, to deliver the drug as required. Since it comprises of both hydrophobic and hydrophilic parts, both; lipophilic and hydrophilic bioactive agents can be consolidated within it (15,38). Therefore, wide-ranging drugs could be incorporated within them.

4. ADVANTAGES OF ORGANOGELS:-

It is an easy formulation to prepare, along with longer life span. Bioactive agents of distinct characteristics can be incorporated (37,38). Their physical form remains unaffected by the factor of time owing to the structural cohesion. It is cost-effective as it requires a lower number of components (37–39). They have simple handling and usage requirements. It also provides improved patient-compliance (34). It has a wide range of applications for topical drug delivery systems. It has thermal-stability (38). A few chemical modifications can lead to the release of drugs in the desired manner and at the desired place (34). It bypasses first-pass metabolism, ensuring that medicines have the highest possible bioavailability. They are relatively safe as bio-compatible constituents are used. Hence, it can be used as a vehicle for a wide range of drugs. It is non-invasive and is better tolerated by the patients. It is a thermodynamically stable system. As it can be used for an extended period of time, the need for dosing is less frequent. It has both hydrophobic and hydrophilic units. Therefore, bioactive agents of either nature can be incorporated into it. There is no risk of microbial contamination as they are insensitive to moisture (34,38) .

5. LIMITATIONS:-

It accounts for low thermostability. It has a greasy texture (2). For the drugs which are intended to be penetrated through skin, they must possess appropriate partition coefficient. It holds good chances for the occurrence of swelling (uptake of liquid resulting in increase in its volume) or syneresis (natural shrinkage- if allowed to be at rest for a period of time) (15,40). Organogels intended for topical application might irritate the local skin. Topical organogels cannot comprise bioactive agents with molecular weights of more than 500 Dalton since skin can be permeated by drugs with molecular weights under 500 Dalton (18). The purity of the constituents present is important, or else there might be no gel formation. Few organogelators are not available on large-scale, hence cause expense elevation for formulation. E.g.: Lecithin organogelator. The purity of the constituents present is important, or else there might be no gel formation. Precise control of process variables (pH, temperature, etc.) is mandatory. Skin permeation enhancers and non-polar solvents are added in order to achieve deep penetration through skin, which may produce toxicity. Because of the gelator and the necessary solvent used, it is difficult to determine whether the gelation process will be successful.(41)

6. PROPERTIES OF ORGANOGEL:-

A few characteristic attributes that organogels possess includes; non-invasiveness, non-toxicity, etc. But its substantial physico-chemical properties, which frame it as a significant and essential system, are as follows:-

Viscoelasticity:-

The term "viscoelasticity" is related to the materials that possess the two properties, i.e., viscosity and elasticity. The viscoelastic property of organogels has also been authenticated by stress relaxation studies (6,42). They act as solids at lower shear stress (elasticity) and as a flowing fluid at escalated shear stress (15,38). At low shear rates, there is no pressure acting over them; hence they behave like solids with an intact structure, but at higher shear stress, as the pressure increases, the 3D-mesh network within the structure starts rupturing, permitting it to flow. It is observed that the organogels appear to follow the Maxwell model of viscoelasticity. It is observed that they retain plastic-flow behavior. "Organogels" are similar to other gel systems; the gelling agent creates an ongoing, three-dimensional network in the solvent, obstructing the flow of liquid. The rheological behavior of the gelator solution and its interaction with the solvent can greatly influence the flow-property of the organogels (6,15).

Thermostability:-

The nature of the organogels makes them innately thermostable. The capability of the gelators to undergo self-assembly under suitable conditions to produce organogels may be responsible for the stability of the organogels. The overall free energy of the system decreases when the gelators undergo self-assembly, yielding a low-energy thermostable organogel. At elevated temperatures, the molecules within the organogels acquire some kinetic energy to reduce any loss in their structure, and in low temperatures, they resume to their original structure. This innate property of the organogel is responsible for its longer shelf-life, which makes it desirable to be used as a carrier for the delivery of bioactive agents as well as in the cosmetic industry (15,16,19).

Thermoreversibility:-

The matrix structure of the organogel is distorted when it is heated at a temperature that is extended from its critical temperature and hence it starts flowing. This added thermal energy causes interaction amongst the molecules of the organogel, causing disruption in the structure. But as the temperature decelerates, the interaction of the molecules also retards, which results in the reverting back of the organogel to its original configuration. This whole phenomenon is called thermoreversibility property of the organogels. For example, PLOs, when heated above 25° C (critical temperature), lost solid-matrix configuration, and after cooling, and returned to a stable configuration. The fluid matrix systems (Fluid matrix organogels) are thermoreversible (7,16).

Non-Birefringence:-

Birefringence is the optical property of a material that allows propagation of light when polarized light passes through it. The organogels are non-birefringent, i.e., they do not allow the propagation of light when polarized light passes through their matrix. As a result, when the organogels are viewed under polarized light, they appear as a dark matrix. This can be attributed to the isotropic nature of the organogels. Hence, the organogels possess the property of non-birefringence (16,19,29,43).

Optical clarity:-

The transparency or opacity of the organogels will depend on the chemical make-up they possess. For example, sorbitan monostearate organogels and PLOs are opaque, whereas the lecithin organogels are transparent in nature (30,44)

Chirality Effect:-

It has been observed that the stability and growth of the solid-fiber networks are both impacted by the presence of chirality in LMW (Low-Molecular Weight) gelators [2-4]. Additionally, the thermoreversibility of the gels produced as a result of the self-assembled solid-fiber network is also related to chirality [2-4]. A competent solid-fiber gelator has been shown to be generally effective in possessing a chiral center, but fluid-fiber gels are unaffected by chirality. The gelators inclusive of chiral centers aid in the production of a tight molecular packing, which offers kinetic and thermodynamic stability to the system of organogels. The Crown ether phthalocyanine organogel is a good chiral organogel example(7,45).

Biocompatibility:-

Previously, the organogels were formulated by using several non-biocompatible components, which resulted in non-biocompatible organogels [2-4]. Currently, research on organogels involving different biocompatible constituents such as vegetable oil, cocoa butter, etc. has opened up new aspects for their extended use in numerous biomedical applications (15,19,38,40).

7. Organogelators:-

Organogelators are the gelling agents that have the capability to transform a preparation into a semisolid mass, i.e., gel. They are used to impart the desired consistency in organogels. Hence, they are an integral component in the formulation of organogels. The solubility of the organogelator in the solvent generates a few forces, which is the reason for the stability of the thermodynamic and kinetic characteristics of the gel (7). Organogelators have the property of changing their physical state depending upon the temperature. They remain as a solid matrix at room temperature but transform into liquid at relatively lower temperatures. The structure of organogels mainly depends upon the constructing ability of the organogelator(9). The degree of cooperative self-assembly in an organogel is also regulated by the gelator's structure and solubility(46). The most manageable type of organogelators are n-alkanes and is useful in gelling the other proportionally short-chained alkanes (2) .It precipitates out as fibers forms a 3D-structure. It is mainly responsible for the design/structure of organogels. They produce bond formation within the molecules of organogels, leading to their interaction and bonding amongst each other and an increase in the thickness of the preparation. Depending upon the type of bond they form, organogelators can be regarded as-Hydrogen bond forming organogelators, viz., amino acids, amides, carbohydrates, etc., or as Non-hydrogen bond forming organogelators, viz., anthraquinone, steroidal moieties, anthracene, etc. (9,19,38). The ongoing research on organogelators has formed a branch for other novel types of gelators, including sugar-based organogelators and green organogelators, etc.(47,48). These new types of gelators each have their own concepts that should be studied comprehensively for a better understanding of the widespread availability of organogelators from a variety of sources.

Types of organogelators:-

Aryl cyclohexanol derivatives:-

These are 4-Tertiary Butyl-1-aryl cyclohexanols derivatives. Their characteristic features, which they impart in the gel, may differ depending upon the nature of the apolar solvent involved in the organogel. They possess low solubility in apolar solvents and hence they might appear as a turbid or transparent preparation, depending on the nature of apolar solvent involved. Their physical state is solid at room temperature. They can produce gelation only if the phenyl group in their structure lies in the axial configuration. The derivatives possessing phenyl groups in the equatorial configuration are unable to form the gel. They help in obtaining the organogels with the desired property of thermo-reversibility. A few common examples of this class are CCL4, benzene, cyclohexane, etc.

Polymer organogels:-

These are long-chain containing gelling agents. These are the gelators that possess a high capability of inducing gelation. They have molecular size of more than 2 kilo Dalton. They can impart gel-formation even if used in very low concentrations. They can appear in different shapes (straight, branched, etc.). Their efficiency of imparting gelation can be modified if their chemical structure is somewhat altered. They can be further divided into physical or chemical organogelators. If they form chemical bonds within the network of organogel, then they are regarded as physical organogelators which result in a cross-linked network, and if they form non-covalent bonds, then they are regarded as chemical organogelators which result in an entangled chain-linked network. The transition temperature for the transformation of the gel state to a sol state is also very low. They have relatively higher gel-strength than other LMOGs. They mostly include L-lysine derivatives and the other conventional examples are polyethylene, polycarbonate, polymethylmethacrylate, polyester, etc.(18,19,34,38,40).

Gemini organogelator:-

"Gemini" means "twins". This word has been derived from Latin language [4]. The first Gemini organogelator of L-lysine was synthesized by Suzuki et al.(49) It had two chains of L-lysine of different chain lengths, linked together by an amide bond [2, 4]. This chain length is inversely proportional to the gelation ability of the gelator [12]. They possess good gelation properties. They have a high ability to immobilize various kinds of apolar solvents. A good example of this class is Bis(N-lauroyl-L-lysine ethyl ester) oxyl amide which can immobilize solvents like ketones, alcohols, etc.(9,18,19,38)

Boc-Ala(1)-Aib(2)-β-Ala(3)-OMe Organogelators:-

It is a synthetic tripeptide gelator of synthetic origin. It is capable of undergoing self-CB (1, 2-dichlorobenzene), 1-chlorobenzene, etc.

Low-Molecular –Weight Organogelators (LMWOs):-

These are the gelling agents that possess a small molecular weight (≤3000 Dalton) (9,50). Assembly which is the contributor of its gel-formation ability. They form thermoreversible and transparent gels. The apolar solvents, to which they can immobilize include benzene. These are most widely used organogelators. They contain a high capability of immobilizing the aqueous phase, even if used in small concentrations (<2%). The length of the alkyl chain in LMWO directly influences its gelling ability (51). They mostly form solid-fiber matrices or can form fluid-fiber matrices depending on the intermolecular interaction they perform. A solid-fiber matrix can be obtained if the organogelator is cooled down beyond the solubility range of the gelator, which is then followed by a rapid, incomplete precipitation, in the organic solvent, which leads to physical intermolecular interactions. For forming a fluid matrix, a polar solvent should be added to the solution of surfactant, leading to the re-arrangement of molecules to form a clump, hence immobilizing the aqueous phase. This also results in a difference in the kinetic-stability between both the matrices, which can be used as a distinguishing factor. Solid-fiber matrix offers an enhanced mechanical property compared to that of fluid-fiber matrix. This is because a solid-fiber matrix contains a highly arranged molecular structure compared to a fluid-fiber matrix. LMOGs have been further categorized into steroidal organogelators, ALS organogelators, etc., depending on the chemical backbone they possess(7,19,34,38,52).

8. MECHANISM OF ORGANOGELATION:-

Organogelling is generally induced by the incorporation of a polar solvent into the organogel. If lecithin is present in it, then, it itself assembles into reverse spherical micelles at a concentration of ~0.01mM. This is triggered by the addition of small and critical amounts of polar additives which bind to the hydrophilic head portion of the lecithin. This creates linear networks. If the amount of polar additive is further increased, then it results in the formation of flexible, long tubular micelles of 2.0 to 2.5 nm in radius and hundreds to thousands of nanometers in length. After overlapping with each other sufficiently, they entangle themselves and build up a transient 3D network.

In the case of PLOs, the mechanism of gelling and the structural network may be related to the synergistic contribution of both phospholipids and polymeric co-surfactant molecules in their respective hydrated states. In this case, solvent molecules and lecithin phosphate groups can be arranged in such a way that a hydrogen-bonded network will be formed (15,34,52).

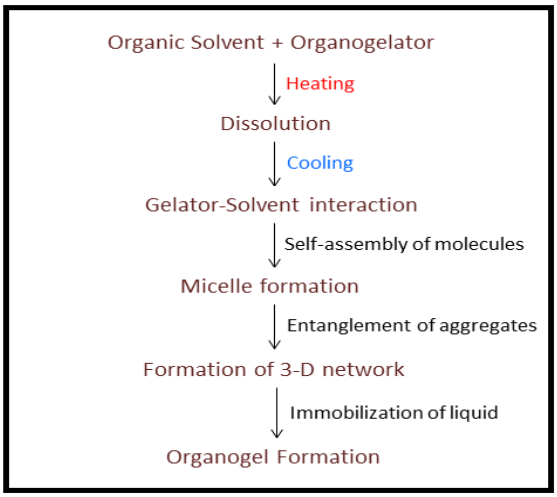

Fig 1: Mechanism of Organogelation.

9. MECHANISM OF GEL PERMEATION INTO SKIN:-

Human skin is made up of different types of tissue layers, but the Stratum Corneum,which is the outermost skin layer, is the rate limiting barrier for the permeation of gel into the skin (35). It was found that lipid based formulation work most efficiently by improving penetration through the skin, but they alter the hydration state of the skin, causing dermatitis. On the other hand, aqueous formulations are able to maintain the bioactive state of the skin but exhibit poor penetration (18). Organogel is the promising vehicle because it consists of both oil and aqueous phase also the lecithin organogel deliver bioactive agents. In the case of Pleuronic Lecithin organogels, penetration and permeation are enhanced due to lecithin, which disorganizes the structure of the skin, transiently opens the pores of the skin. It is believed that this happens due to the interaction between the lecithin's phospholipid and skin lipids. Hence, there occurs the formation of a cylindrical network which results in an increase in the area of the lecithin polar region, and non-polar solvent acts as a penetration enhancer and then penetration occurs by- forming a thin film on the skin surface. Dissolution of drug occur in the carrier system and diffusion to the skin surface. Partitioning of drugs occur through the epidermal layer. Diffusion of drugs through the upper dermal layer. Uptake by blood capillary cells and then circulation of drugs. (16,18,35).

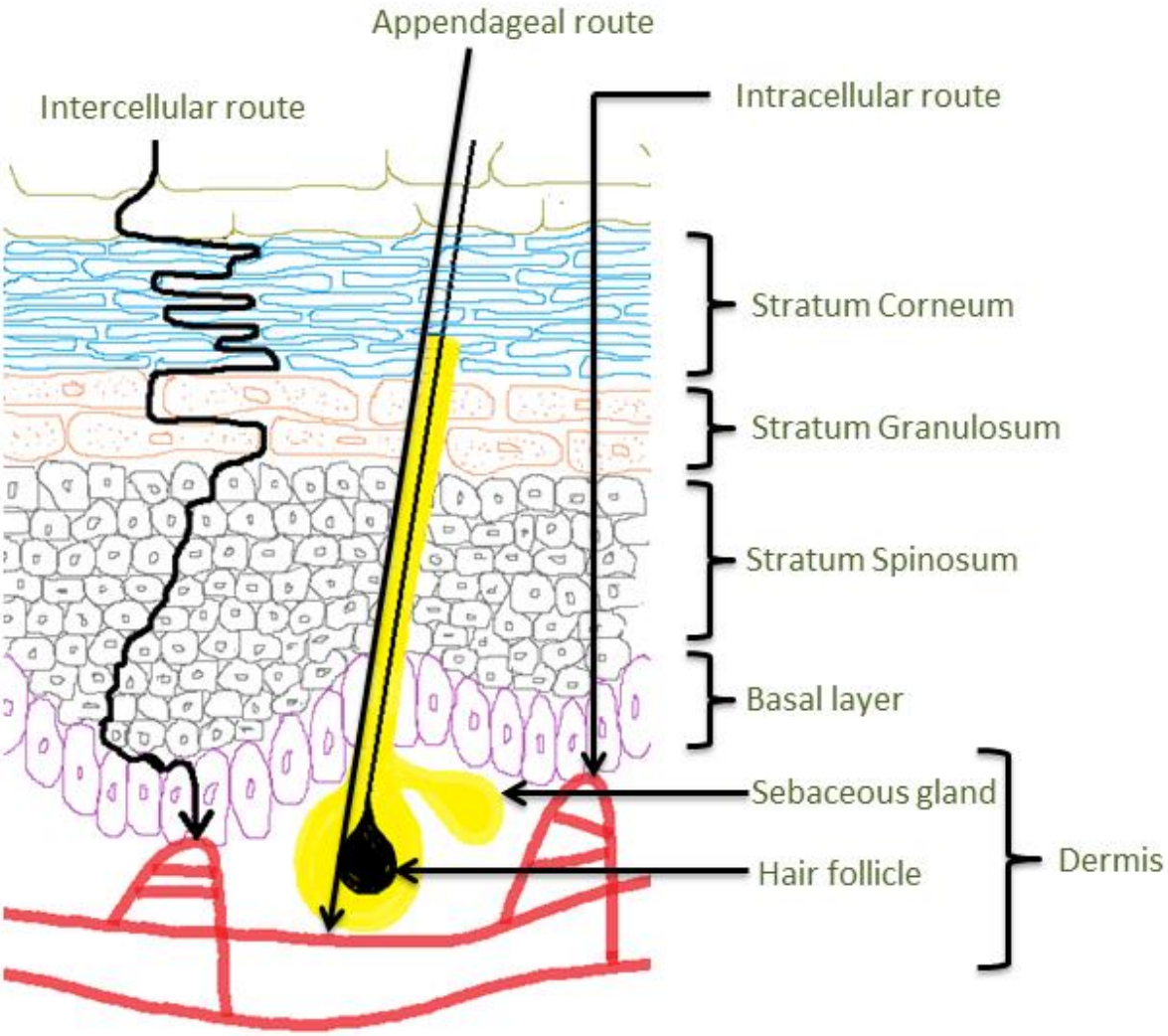

Fig 2: Pathways for permeation of organogel into skin

11.1 Method for preparation of organogels:-

At 60^{o}C, the oil-surfactant mixture is heated to produce a transparent solution that, when cooled, transforms into organogels. Lecithin solutions are made by first dissolving lecithins in organic solvents using a magnetic stirrer, according to the phase diagrams that have been constructed. Organogels are created by adding water with the use of a micropipette syringe. Heat may be used occasionally to completely dissolve drugs. Lecithin and an organic solvent are combined to create the oil phase, which is then let to stand overnight to guarantee full breakdown. When preparing the aqueous (polar) phase, pluronic is added to ice-cold water and stirred to ensure thorough dissolve. The produced PLO is blended with the pluronic's aqueous phase using a high-shear mixing technique by a magnetic stirrer. Fatty-acid gelators can also be used to create organogels by first dissolving them at a higher temperature in a water-in-oil emulsion, then lowering the temperature. The solubility of the gelator decreases as a result of the drop in temperature, which leads to precipitation and self-
assembly of the gelators into a network of tubules that become entangled to create a gelled structure (2,19).

11.2 Formulations of organogels used in drug delivery:-

Sr. No	Types	Administration Route	Study carried out	Model Drugs	Reference
1.	Sorbitan monostearate (SMS)	Nasal Oral Subcutaneous & intramuscular	In vitro release In vitro release In vivo efficacy	-- Propranolol - Cyclosporin A	(53) (54)
2.	Lecithin	Transdermal	Clinical studies -Skin permeation and effectiveness in vivo -Skin permeation in vitro - Skin release in vitro	Metoprolol Aceclofenac, indomethacin& Diclofenac, Bioactive agents	(55) (56)(57)(13)
3.	Eudragit organogels	- Rectal - Buccal	- In vivo efficacy - In vivo efficacy	Salicylic acid BSA	(58)(44)

12. Evaluation of organogels:-

PARAMETERS	DESCRIPTION
Gelation Studies	A straightforward visual test to establish whether gelation has been established and includes: inverting the reaction vessel, pouring with organogel; if the sample does not flow, gelation has occurred (40). (9)
Rheological Behavior	An indication of the structural organization of the organogel is Obtained by its rheological behavior. The viscosity the usually determined with the help of a Brookfield viscometer (59). (1)
Structural features	Utilizing NMR spectroscopy, the molecular design of organogels has It has been evaluated, and FTIR spectroscopy has demonstrated hydrogen bonding. Optical microscopy, freeze fracture electron microscopy, transmission electron microscopy and X-ray diffraction have been used to learn about the molecular packing within the organogel network (29) (38). (2).
Phase transition Temperature	It is the determination of the temperature at which the organogel transforms from gel state to sol state. It provides details on the types of the microstructures that make up the cross-linked gelling network. The presence of uniform microstructures within the gel is indicated by a restricted PTT range (3-5°C). Hot stage microscopy (HST) and high sensitivity DCS are employed to determine it. Basically, the organogels are placed in glass tubes which are subjected to incrementing temperature. The transition is analyzed by inverting the tubes and this temperature is then noted (57).
pH	A digital pH meter is used to assess the pH of the formulation. A suitable amount of organogel is dissolved in a solvent. The pH meter& electrode is submerged in this mixture, which then display the value of pH (42)
Water Content	Evaporation of water can cause viscosity to drop, which can impair the stability of the gel. The use of NIR spectroscopy (NIR, 1800-2200) to measure water content (57)
Stability study	The stability of organogels can be determined at different temperature and relative humidity conditions as per ICH guidelines. 25°C ± 2°C at 75 ± 5% RH 40°C ± 2°C at 75 ± 5% RH
In vitro studies	Through a dialysis membrane, the formulation is subjected to in vitro diffusion. An apparatus designed by Chowdary et al., which is used to

	examine the drug release profile from organogels. (30) A Franz diffusion cell can be employed to determine the drug release (2).
In vivo studies	Various animals, such as rats, are employed as models for several evaluation such as skin irritation tests, compatibility tests, etc.
Physical examination	It is a preliminary assessment in which, the prepared organogel is evaluated for its color, texture, appearance, odour, etc. (29)

13. Factors affecting organogels:-

pH:-

A pH change stimulates the reversible transition of an organogel from a gel state to a sol state (60). Hence, pH can influence the physical state of gels.

Temperature:-

Organogels are often less stable with increasing temperatures, causing disruption of the 3D mesh-network structure. This also aids in causing a fluctuation in the viscosity of the organogels- as the temperature increases, the viscosity decreases [4]. Hence, the temperature range during their storage should be closely controlled(19)(5)(18).

Organogelator:-

The type of organogelator used for the preparation has the capability to influence the mechanical and rheological properties of the organogel(40).

Adjuvants:-

a) Surfactants: Characteristics of gel can be varied depending upon the surfactant.

b) Salts: The addition of salt to the organogel may result in salting-out (formation of more secondary bonds amongst the molecules)(15,38).

c) Organic solvent: The structure of organogel depends upon the nature of solvent (polar/non-polar).

d) Organogelator: The rate of drug release from the organogel is affected by/depends upon the concentration of the gelator used (61).

e) Skin permeation enhancers: These chemical entities might also possess additional characteristics, which may interact and alter the properties of organogel.

E.g.: Terpenes operate as chemical penetration enhancers and also act as rheology modifiers, which may result into any alteration in the flow property and deformation characteristics of an organogel (62).

Moisture:-

Organogels swell when exposed to moisture as they absorb water molecules from it This may aid in the instability of the organogels (38).

Purity:-

The constituents used in organogel should be in its pure form. Any impurity in the components may lead to instability in the network of the matrix. E.g.: Lecithin is unable to induce gelation if not used in its pure form(2,40).

14. Application of organogels:-

Pharmaceutical industry:-

a) Topical drug delivery system: -

This includes the dermal and transdermal systems. The skin, being the largest tissue in the body, provides good bioavailability of drugs, as the drugs meant to enter the systemic circulation via permeation through the skin bypass the first-pass metabolism. Polaxomer lecithin organogels (PLOs) contain isopropyl myristate/isopropyl palmitate as an apolar organic solvent used as a vector for the release of NSAIDs (ketoprofen, flurbiprofen,diclofenac sodium), used as an analgesic. Reverse micellar MBGs possess soya-lecithin/iso-octane/water as a solvent phase for the delivery of propranolol. Organogels can be regarded as a potential matrices for the controlled release of topical antimicrobials. Organogels loaded with

Piroxicam are used for the treatment of rheumatoid arthritis. In-situ forming organogel of L-alanine injectable can be used for the release of labile macromolecular drugs. Various studies on formulation of transdermal organogels, such as development of PLO with mometasone furoate for psoriasis and fluconazole-loaded organogels based on olive oil for fungal infections, have exhibited positive results(63) (42)(9).

b) Oral and trans-mucosal drug delivery system:-

The drugs can be delivered through oral cavity with the help of implantation of bio-adhesive organogels i.e. the drugs will be administered as implants. The drug can be dissolved within the organic solvent and then mixed with the muco-adhesive polymer. An organogel of 12-HSA-soyabean oil was used for the delivery of ibuprofen (15). An in-vivo study conducted in rats depicted that the organogels can be used as a vector for controlled release of lipophilic drugs (38). Sorbitan monoleate based organogel, incorporated with cyclosporine A is given orally. An oral organogel can be prepared by incorporating an NSAID (ibuprofen) to achieve desired therapeutic results(64).

c) Parenteral drug delivery system:-

Parenteral routes are the preferential choice for the administration of drugs, as it avoids first-pass metabolism, provides quicker onset of action, etc. An in-situ forming organogel prepared for sustain delivery of leuprolide (used in prostate cancer) from the L-alanine derivatives in safflower oil and was injected by SC route. It was observed that the gel degraded slowly to release the drug, over a period of 14-25 days (15)(7). Sorbitan monostearate (SMS) organogel preparation given by SC and i.m. route for the release of propranolol/ cyclosporine A/ BSA and HA(7).A study depicted that, safflower oil-based N-methyl pyrrolidone (NMP) injections were introduced into rats subcutaneously, which was well-tolerated by the surrounding tissues over a period of eight weeks(65). The injection of an in-situ organogel forming implant based on SAM (N-stearoyl-L-alanine methyl ester) demonstrated significant promise for safe drug delivery and would be a suitable delivery method for therapeutic medications that require regulated release (66). A successful evaluation was conducted for the purpose of using parenteral organogel in schizophrenia therapy(67).

d) Ophthalmic drug delivery system:-

Ophthalmic solutions are generally used for administering drugs in the eye, but due to its consistency, frequent dosing is required as the drug may not be properly absorbed in the target site. Hence thicker preparations like gels are desired to increase the contact time to facilitate the maximum absorption of drugs from the formulation.

i) Methazolamide is incorporated into carbomer and Polaxomer gels for the treatment of glaucoma which was ineffective when formulated as ophthalmic solution (38).

ii) Organogelators are employed with drugs such as Eudragit L and S for preparing ophthalmic preparation for sustained delivery (50).

B) Vaccines:-

i) The micro-emulsion based organogels can be used as a vehicle for delivery of hydrophilic vaccines.

ii) Niosomes containing organogels have been formulated, in which the vaccines are entrapped. After administration of these gels via i.m. route, a depot effect was observed(15).

Food industry:-

They are primarily employed in food industry, due to their ability to reduce oil mobility in food items, particularly those containing multiple ingredients. Organogels can be used as replacer for Trans and saturated fat in processed foods to install a specific texture. Wax-based organogels provide good oxidative stability, and also influence the firmness and spreadability and thus can be used in spreadable food product(63)(68) (18)

Cosmetics industry:-

Low molecular weight organogelators (LMOGs) such as DBS, 12-HSA, etc. are used for preparation of lipsticks(69). 12-HSA organogelator is used in sunscreens to block UVB rays(41). It is possible to improve the properties of organogels developed for cosmetic applications by using organic solvents like Amazonian oils, which already possess moisturizing and nourishing effects (70). Various dermatological cosmetics such as lip-gels, skin and hair protectants, etc. can be prepared in the form of organogels(38)(18). Other cosmetic preparations such as shampoo, dentifrices, perfumes, etc. are prepared in the form of organogels(15).

CONCLUSION:-

Organogels are a visco-elastic substance primarily made by gelling the organic solvent with a bioactive agent. It has captivated a section of curiosity to explore all the aspects of their application, as these can potentially eliminate or replace many components, techniques as well as limitations being faced normally for different types of formulations, due to unique properties. The organogels have a huge area for application, although possess few drawbacks and limitations. Though these can be administered to the body via various drug delivery routes, the major site is topical route considering ease of application and many more reasons. A stable organogel designed with all the bio-compatible components might attract the commercial market in future as they can potentially become the preferential choice of formulators and consumers.

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