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ORGANOSEL: TOPICAL AND TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT

Organogel a 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. In general, organogels are thermodynamically stable in nature and have been explored as matrices for the delivery of bioactive agents. In the current manuscript, attempts have been made to understand the properties of organogels, various types of organogelators and some applications of the organogels in controlled delivery. These are simple to prepare and are more advantageous than other approaches. It has the advantage of delivery by various routes, including oral, parenteral, topical routes. The present article reviews the current methods used to prepare organogel and their application in drug delivery.

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Key Words

Organogel, Gel, Gelator, Drug
delivery, Biocompatibility.

INTRODUCTION

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 networked structure.¹

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 microemulsions and polymeric gels.

In a recent development, phospholipids in conjunction with some other additives have been shown to provide a very promising topical drug delivery vehicle known as lecithin organogels (LOs).^{2,3}

ADVANTAGES OF ORGANOGELS

- i. **Template vehicle:** Lecithin organogels provide opportunities for incorporation of wide range of substances with diverse physicochemical characters viz., chemical nature, solubility, molecular weight, and size etc.
- ii. **Process Benefits:** Self-assembled supramolecular arrangement of surfactant molecules makes the process very simple and easy to handle.
- iii. **Structural/ Physical Stability:** Structural integrity of organogels is maintained for longer time periods.
- iv. **Chemical Stability:** organogels are moisture insensitive and being organic in character also resist microbial contamination.
- v. **Topical Delivery Potential:** They enhance the skin penetration and transport of the molecules.

- vi. **Safety:** Use of biocompatible, biodegradable and non-immunogenic materials makes them safe for long-term applications.^{4,5,6}

LIMITATIONS OF ORGANOGELS

- i. In the lecithin organogels, the lecithin should be pure otherwise no gelling will occur.
- ii. Lecithin is most costly.
- iii. Lecithin is not available on large scale.
- iv. It should be stored in a proper condition.
- v. The organogel has greasy property.
- vi. The organogel is less stable to temperature⁷.

ORGANOGELEATORS

- i. n-alkanes such as hexadecane & organic liquids.
- ii. Non ionic surfactant- sorbitan monostearate^{8,9}
- iii. Steroids & their derivatives Anthranlyl derivatives.
- iv. Macrocyclic gelators (calixarenes)^{10, 11, 12}.

PROPERTIES ORGANOGELS

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

- a. **Viscoelasticity:** The organogels behaves like a solid at lower shear rates and hence shows an elastic property.¹³ 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.^{14,15,16}
- b. **Non-birefringence:** Organogel of not allowing the polarized light to pass through its matrix is regarded as non-birefringent.^{17, 18, 19}
- c. **Thermoreversibility:** As the organogels are heated up above a critical temperature, the organogels loses its solid matrix like structure and starts flowing.²⁰⁻²³
- d. **Thermostability:** The organogels are inherently thermostable in nature.²⁴
- e. **Optical clarity:** Organogels may be transparent or opaque in nature.²⁵
- f. **Biocompatibility**

TYPES OF ORGANOGELS

Lecithin organogels

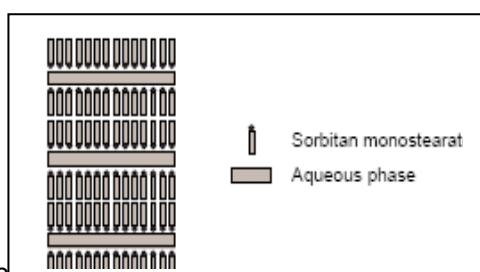
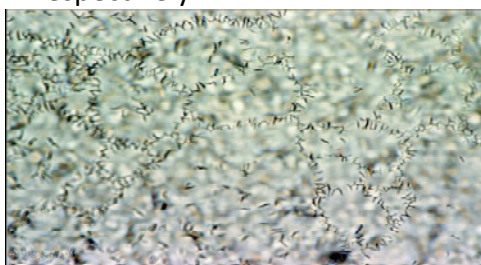
Lecithin is a phospholipid extracted from various plants and animal tissues apart from the egg yolk. The lecithin procured from natural sources is able to form the gelled structures.

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 ($w_0 = [H_2O]/[lecithin]$) is typically 2:10. Excess water leads to destabilization of the gel and phase separation²⁷.

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 as shown in figure no.1 and figure no.2 respectively.²⁸



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.

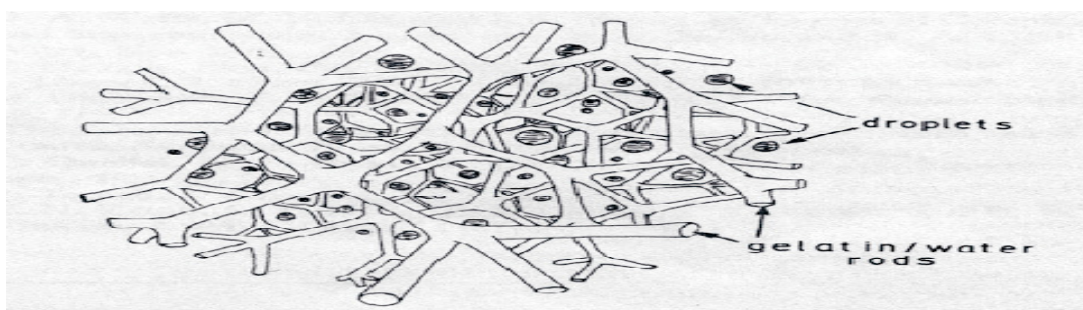
Eudragit organogels

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 isoctane) 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.²⁹



ORGANOGELE FORMULATIONS USED IN DRUG DELIVERY

Sr 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 monostearate (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

METHOD OF PREPARATION

The oil-surfactant mixture was heated at 60°C to obtain a clear solution which on cooling forms

organogels. Based on the phase diagrams constructed, lecithin solutions were prepared by first dissolving lecithins in an organic solvents with the aid of magnetic

stirrer. Formation of organogels takes place on addition of water with the help of micropipette syringe. Sometime heat is applied for complete solubilization of drug.³⁰

The oil phase is prepared by mixing lecithin and organic solvent, the mixture is allowed to stand overnight to

ensure complete dissolution. The aqueous (polar) phase is prepared by adding pluronic to ice cold water, the mixture is agitated to ensure complete dissolution. The prepare PLO, the oil phase is mixed with aqueous phase of pluronic using a high shear mixing method by magnetic stirrer.³¹

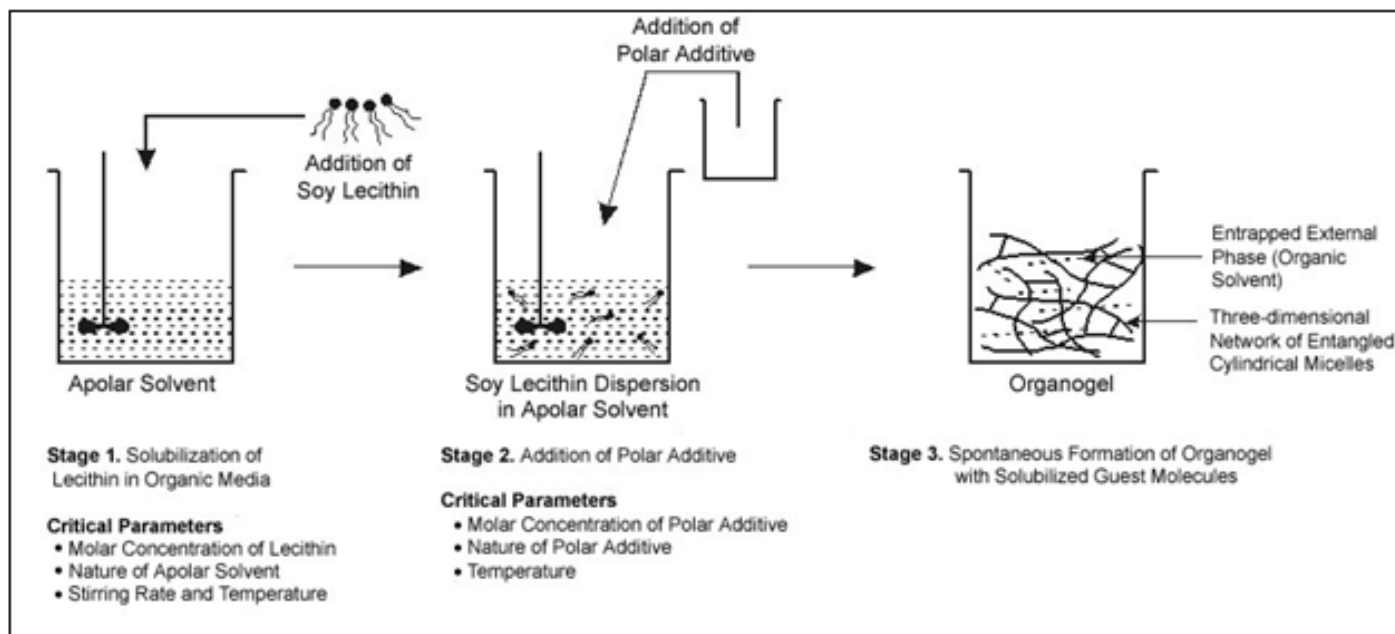


Figure 1. Schematic diagram of the preparation of lecithin organogels.

Lipophilic drugs are solubilized in the organic phase (stage 1), whereas hydrophilic compounds can be solubilized in the polar phase (stage 2). For the preparation of pluronic lecithin organogel (PLO gel), the co-surfactant pluronic is taken along with polar phase (stage 2).³²

CHARACTERIZATION OF ORGANOGEL

Different characterization studies are extremely useful it has been reported as follows:

Rheological behavior

For any vehicle to be used for topical drug delivery applications, it is essential to study its rheological behavior. The latter is important for its efficacy in delivering the molecules onto or across the skin site. The critical parameters like spreadibility, adhesiveness, cohesiveness and consistency need to be modified in a favorable manner. Lecithin organogels (LOs) have been studied extensively for their rheological attributes and determined to be viscoelastic in nature.^{33, 34}

Determination of gelation temperature

Formulations were enclosed in glass tubes (2 mm inside diameter) and observed over a temperature range of 4-5°C. The change from solution to gel of vice-versa was determined by inverting the tube. The temperature was changed at a rate of 5°C h⁻¹ and the temperature at which the physical state of the formulation was changed was regarded as the gelation temperature. In all cases the gelation temperature was reproducible to within 0.1°C. The gel melted completely within a 0.2 – 0.3 °C range.³⁵

Gelation Kinetics

The gelation properties of organogels were investigated in the presence of various solvents. Gel-sol and sol-gel transitions were evaluated by the inverse method and gelation kinetics were determined by turbidimetry.³⁶

In vitro drug release

The permeation apparatus designed as described by Chowdary et al was employed to study the release

profile of drugs from the semisolid formulations. Phosphate buffer 6.4 used as receptor fluid. The release/ permeation of drugs from lecithin gels through various membranes was determined using Franz diffusion cell.³⁷

Safety and skin compatability studies

It is important to consider the safety and irritancy of the formulation on prolong use. No significant alterations in the skin were apparent after three days and stratum corneum was still intact. The irritation potential of Los has been assessed by Dreher et al by carrying out human skin irritation study.³⁸

Structural features

Molecular architecture of organogels has been evaluated using NMR spectroscopy, hydrogen bonding has been established by FTIR spectroscopy. scanning & transmission electron microscopy.

FUTURE PROSPECTS

In the field of topical drug delivery organogel have emerged as one of the most potential carrier systems. In contrast to other lipid-based system such as vesicular system (liposomes and niosomes). Lecithin-organogel systems may prove to have an edge in term of efficacy, stability and most importantly the technological feasibility. Moreover, the topical drug delivery of new biotech generated proteinaceous molecules in the protective non-polar microenvironment of these systems may help protect these sensitive macromolecules from and degradation, while their transport to the desired site. Thus, amidst the increasing opportunities and challenges, the LOs may prove to be highly promising system in realizing the drug delivery objectives while scientists are desperately trying for more viable alternative viz-a-viz existing carrier system.

APPLICATIONS OF ORGANOGELS IN DRUG DELIVERY

The interest on the organogels based products has exponentially grown in the last decade. The use of the organogels as a drug delivery vehicle was quite limited even in the recent past as most organogels were prepared using components which are regarded as non-biocompatible.

In the current section, attempts will be made to have an insight on the application of organogels in drug delivery system via different routes of administration.

Table 1: Bioactive agents successfully incorporated within various organogels

Type of Organogels	Bioactive incorporated agents
Lecithin organogels	Broxaterol, scopolamine, Nicardipine
PLO organogels	Methimazole, dexamethasone
Premium lecithin organogels	Methimazole
MBG organogels	Propranolol HCL, Ketorolac tromethamine
Sorbitan organogels	Antigens, sumatriptan, Doxorubicin
Poly (ethylene) organogels	Leuprolide

Parenteral delivery

In general, sorbitan monostearate organogels have a very short half-life at the injection site. This may be attributed to the diffusion of water molecules within the gelled structure which results in the subsequent disruption of the networked structure due to the emulsification of the gel surface. The same group has also reported the development of a sorbitan monostearate based organogels which has shown sustained delivery of a model antigen and radiolabelled bovine serum albumin after intra-muscular administration of the same in mice. The results indicated the probable use of the formulation as depot. L-alanine based injectable in situ forming organogels may be used for the delivery of labile macromolecular bioactive agents. These in situ forming organogels may be used for sustained delivery of bioactive agents after the same is being administered within the body³⁵.

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 monoleate based 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 and non-steroidal anti-inflammatory drug was incorporated within the gelled structure. In vivo studies in rats showed that the organogels may be used as a controlled delivery vehicle for oral delivery of lipophilic compounds³⁹.

Topical/transdermal delivery

Lecithin-based organogels have long been tried as a matrix for transdermal delivery systems because of its ability to improve the transport rate of the bioactive agents (e.g. aromatic tetraamidines, amino acids and peptides) apart from its proven long-term

biocompatibility and low irritability potential. The transdermal administrations of aromatic tetra-amidines loaded lecithin organogels were able to reduce the tumor cell growth in nude mice xenografted with the highly tumorigenic cell line FH06T1-1. The methyl nicotinate incorporated within lecithin gel showed almost complete percutaneous absorption in experimental human models in a short period of time, characterized by the induction of erythema. The percutaneous delivery of the bioactive agents may further be improved upon by using compounds known as permeation enhancers. The iontophoretic delivery system which uses MBGs, loaded with bioactive agents causes release in the bioactive agent at higher rates when compared to passive diffusion.⁴⁰

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