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LECITHIN-MICROEMULSION BASED ORGANOGELS AS TOPICAL DRUG DELIVERY SYSTEM (TDDS)

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ABSTRACT

Most of the chemical entities that are being discovered are lipophilic in nature and have poor aqueous solubility, there by posing problems in their formulation into delivery systems. Because of their low aqueous solubility and high permeability, dissolution and/or release rate from the delivery system forms the rate-limiting step in their absorption and systemic availability. This frequently results in potentially important products not reaching the market or not achieving their full potential. Transdermal drug delivery provides the promising delivery system for those drugs. It provides better patient compliance by avoiding invasiveness, prolonging plasma drug level, bypass first pass effect, reduced side effects and easy termination of therapy. Interest in organogels has increased in a wide variety of fields including chemistry, biotechnology and pharmaceutics. It is more reasonable to look for a carrier that interacts with the skin such that it allows various molecules to pass into the skin. In this paper, which follows a review on investigation of lecithin organogels as carriers for the transdermal transport of drugs having problems mentioned above. The general properties of lecithin organogels, method of preparation and its characterization have been discussed. The potential use of lecithin organogels for the transdermal transport of many therapeutic agents have also been discussed in the present review.

Keywords: Transdermal Drug delivery; Lecithin organogels; Release rate; Microemulsion-based gels; Rheology

INTRODUCTION

The skin is an exceptionally effective barrier to most drugs for therapeutic treatment. Very few drugs in therapeutic amount are permeated through skin such as nitroglycerine, scopolamine, nicotine, clonidine, fentanyl, estradiol, testosterone, Lidocaine, and oxybutinin [1]. Therefore, the systems that make the skin more permeable and thereby enhance transdermal delivery are of great formulation interest. The strategies to deliver the medicament into the skin and for systemic circulation have been evolved. The extensive research has been reported on lipids as skin penetration enhancers [2-5]. Lipids in the form of vesicles such as liposomes, niosomes [6-8], ethosomes [9] and transfersomes [10] have been

evaluated. The lipid-based formulations have been in use since decades.

The importance of lipids has especially increased after realizing the utility of natural phospholipids. Lecithin, the natural biofriendly molecules are ubiquitous phospholipids that accounts for more than 50% of the lipid matrix of biological membranes. Soybean lecithin is an apolar organic solvent, on addition of water, forms an entangled dynamic network of long and flexible worm like multi-molecular aggregates termed as 'organogels' [11]. These are characterized by high viscosity and complete optical transparency. Lecithin organogels are emerging as carriers for drug molecules with diverse physicochemical properties including macromolecules [12]. Transdermal transport rates of scopolamine and broxaterol from lecithin organogels were faster than commercial patches [12].

With the advent of high throughput screening techniques, the discovery of biologically active molecules is taking place at a pace never seen before. Most of the chemical entities that are being discovered are lipophilic in nature and have poor aqueous solubility, there by posing problems in their formulation into delivery systems. Because of their low aqueous solubility and high permeability, dissolution and/or release rate from the delivery system forms the rate-limiting step in their absorption and systemic availability. More than 60% of potential drug products suffer from poor water solubility. This frequently results in potentially important products not reaching the market or not achieving their full potential. Pharmaceutical industry is quick in realizing the importance of solubility and dissolution rate in bioavailability and good deal of research has been done in this area. Currently a number of technologies are available to address the poor solubility, dissolution rate and bioavailability of insoluble drugs [13]

Conventional Technologies

Conventionally used techniques [14] based on Noyes-Whitney equation [15] for enhancing solubility, dissolution rate and thereby bioavailability of insoluble drugs include buffered tablets, use of salts, solvates and hydrates, polymorphic forms, complexation, prodrugs, micronisation, solid dispersions and solvent deposited systems.

Newer Technologies

Newer and novel drug delivery technologies developed in recent years for bioavailability enhancement of insoluble drugs are described below.

Lipid Based Delivery Systems

Lipid emulsion technology [16], Self-emulsifying drug delivery system [17], Micro emulsion media as novel drug delivery system [18]

Microemulsion System

Microemulsions are four component mixtures composing of an oil phase, a water phase surfactant/s and a co-surfactant. The tendency towards formation of w/o or o/w microemulsions is dependent on the properties of the oil and the surfactant, the water-to-oil-ratio and the temperature. When a mixture of surfactant and co-surfactant is added to a biphasic oil-water system, a thermodynamically stable, optically transparent or translucent, low viscosity and isotropic mixture spontaneously forms. The transparency of these systems arises from their small droplets diameter (10-100 nm). Such small droplets produce only weak scattering of visible light when compared with that from the coarse droplets (0.5-100 μm) of traditional or standard macroemulsions such as emollient liquids, cream, lotions,

etc., Structurally, microemulsions have normal micellar solutions, reverse micelles, cores or droplets of water or oil, and, for some systems, even bicontinuous structures could solubilize large amounts of both oil and water soluble drugs within microemulsions.

There is rather confusing situation in the medical literatures, where the term "microemulsion" is indifferently used to indicate systems of presumably unlike structure ("true" microemulsions and miniemulsions). Some studies have compared the performance of different emulsified systems (macroemulsions, microemulsion, multiple emulsion and gel-emulsions) prepared with similar oils and surfactants for applications such as controlled drug release or drug protection.

The surfactants used to stabilize such systems may be (i) Non-ionic (ii) Zwitterionic (iii) Cationic (iv) Anionic surfactants. Combinations of these, particularly ionic and non-ionic, can be very effective at increasing the extent of the microemulsion region [18,19].

Rational Approach to Drug Delivery To & Via Skin

There are three main ways to solve the problem of formulating a successful topical dosage formulation [20].

1. We can manipulate the barrier function of the skin e.g., topical antibiotics and antibacterials help a damaged barrier to ward-off infection, sunscreen agents and the horny layer protect the viable tissue from ultraviolet radiation and emollient preparations restore palatability to a desiccated horny layer.
2. We can direct drug to the viable skin tissue without using oral, systemic or other route of therapy.
3. The third approach uses skin delivery for systemic treatment. For example, topical drug delivery systems provide systemic therapy for conditions such as motion sickness, angina and pain.

Dermatologists aim at five main target region–skin surface, horny layers, viable epidermis and upper dermis, skin glands and systemic circulation.

Emulsion-Gels as Topical Formulations

Transdermal and topical formulations are becoming increasingly important and their use in therapy is becoming more widespread. But the skin acts as a barrier to topically administered drugs. Attempts have been made to circumvent the skin barrier by several means, emulsion-gels being one such promising technique [21].

Organogels

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.

In search of a vehicle to deliver the medicament into the skin layer (cutaneous delivery) or through the skin and into systemic circulation (percutaneous absorption) and to target the skin, varied kind of formulation systems and strategies have been evolved. Amongst the many, the lipid-based formulations have been in use since decades. Pharmaceutically, lipid emulsions may allow the sustained release of drugs by sink mechanism [19].

The importance of lipids has especially increased after realizing the utility of phospholipids. The natural bio-friendly molecules which in collaboration with water can form diverse type of polymolecular/super molecular structure with retardant release in sustained release formulation [22].

The topical delivery has been attempted and made successful using a number of lipid based systems viz., vesicular systems [23], lipid microsphere, lipid nanoparticles [13], lipid emulsion [16], polymeric gels [24]. In a recent development, phospholipids in conjunction with some other additives have been shown to provide a very promising topical drug delivery vehicle i.e., lecithin organogel. Lecithin organogels (LOs) are thermodynamically stable, clear, viscoelastic, biocompatible and isotropic gels composed of phospholipids (lecithin), appropriate organic solvent and a polar solvent [25]. Lecithin organogel, the jelly like phase consists of three dimensional network of entangled reverse cylindrical (polymer like) micelle, which immobilize the continuous or macroscopic external organic phase, thus turning liquid into a gel [22].

The formation of three-dimensional network in the organogel is the result of transition at the micellar level in a low viscous network liquid consisting of lecithin cause micelles in non-polar organic liquid [26]. This spherical reverse micellar state of lipid aggregates, twins on to form elongated tubular micelles with the addition of water, and subsequently entangle to form a temporal three dimensional network in the solution bulk. The latter serves to immobilize the external organic phase, thus producing a gel form or the jelly like state of the initial non-viscous solution. However, the transparency and optical isotropy of the organogel remain as before. For this reason, these systems are often called as polymer like micelles and are also termed as living or equilibrium polymer, worm like or thread like micelles [22].

Advantages of Organogels as Topical Delivery Potential [27,28]

- Being well balanced in hydrophilic and lipophilic character, they can efficiently partition with the skin and therefore enhance the skin penetration and transport of the molecules.
- Lecithin organogels also provide the desired hydration of skin in a lipid-enriched environment so as to maintain the bioactive state of skin.
- Lecithin might influence the structure of the skin by disorganizing the lipid layer in the stratum.

Limitations of Organogels

- In the lecithin organogels, the lecithin should be pure otherwise no gelling will occur.
- Lecithin is most costly.
- Lecithin is not available on large scale.
- Should be stored in a proper condition.
- The organogel has greasy property.
- Less stable to temperature.

Organogelling Composition

The organogel matrix chiefly consists of surfactant (lecithin) as gelation molecules, a non-polar organic solvent as external or continuous phase and polar agent, usually water. Lecithin is a trivial name for 1,2-diacyl-Sn-3-phosphocholine. It belongs to a biological essential class of substance termed phosphoglycerides or phospholipids. The latter form the lipid matrix of biological membrane and also play a key role in the cellular metabolism.

As a biocompatible surfactant, it is widely used in everyday life including human and animal food, medicine, cosmetics and manifold industrial applications [29]. Synthetic lecithin containing residues of saturated fatty acids failed to form organogel [27,30]. However, it has been established that unsaturation in

phospholipid molecules is a desired property for the formation of lecithin organogels. Besides lecithin as gelation molecules, the role of organic solvent in providing the desired solvent action into the gelatin molecules is much emphasized. A large variety of organic solvent are able to form gel in the presence of lecithin. Among them are linear, branched and cyclic alkenes, ethers and esters, fatty acids and amines. Specific examples includes ethyl laurates, ethyl myristate, isopropyl myristate (IPM), isopropyl palmitate (IPP), cyclopentane, cycloclane, n-pentane, n-hexane, n-hexadecane and tripropylamine [25].

Amongst the above, the fatty acid esters i.e., application of lecithin organogels. This has been attributed to their skin penetration enhancing property besides their biocompatible and biodegradable nature [29,31].

The third component of polar agent acts as a structure forming and stabilizing agent and has a very crucial role to play in the process of gelling. Water is the most commonly employed polar agent although some other polar solvents such as glycerol, ethylene glycol and form amide have also been found to possess the capability of transferring an initial non-viscous lecithin solution into jelly like state on organogel [22].

As described earlier, the major limitation in formation of lecithin organogels is the requirement of high purity lecithin, the high purity grade lecithin is not only expensive but also difficult to obtain in large quantities. However, recent reports indicates the incorporation of synthetic polymers i.e., pluoronic in lecithin organogels, for their usefulness as co-surfactant and stabilizer [32]. It has been shown that the inclusion of pluronic as cosurfactant makes the organogelling feasible with lecithin of relatively lesser purity [33]. The term "pluronic" refers to series of non-ionic closely related block copolymers of ethylene oxide and propylene oxide [29]. These are primarily used in pharmaceutical formulations as co-surfactants, emulsifier, solubilizers, suspending agents and stabilizers. These pluronic containing lecithin organogels have been termed as pluronic lecithin organogels, poloxamer organogels, pluronic organogels, PLO gel or simply PLOs.

Method of Preparation

The oil-surfactant mixture is heated at 60ºC to obtain a clear solution which on cooling forms organogels [34]. Based on the phase diagrams constructed, lecithin solutions are 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 micropiopette syringe. Sometime heat is applied for complete solubilization of drug [26].

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 prepared PLO, the oil phase is mixed with aqueous phase of pluronic using a high shear mixing method by magnetic stirrer [32].

Characterization of Organogels

In contrast to the ease of preparation, characterization of LOs is relatively complicated on account of their interior structural design build up on the self-associated supramolecules. These microstructures, the resultant of varied polar non polar interactions, are highly sensitive and pose difficulties in the investigative studies. However, different

characterization studies are extremely useful while investigating the potential applications of organogel systems as a topical vehicle. For instance, it has been reported that many of the physicochemical properties of Los viz. Rheological behavior, physical and mechanical stability, and drug release behavior are dependent upon how do molecules arrange themselves to provide the specific structural network within the organogel system [22, 35].

Phase-behavior of organogels

For any vehicle to be used for topical drug delivery applications, it is essential to study its rheological behavior. The latter is important for it efficacy in delivering the molecules onto or across the skin site. The critical parameters like spreadibility, adhesiveness (property related to bioadhesion on skin site), cohesiveness (which indicates structural reformation following application of shear stress, 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 [22].

At higher lecithin concentrations, there is more extensive entanglement of long cylindrical micelles with each other, forming a network-like structure with a very high viscosity. The entrapment of the drug within this network lowers the amount of free drug available for release, causing a decrease in the release across the membrane [26].

Sameles containing different weight ratios (k_m) of lecithin/IPM (20:80) (40:60) (60:40) (80:20) are generally prepared, phase studies are carried out by adding water while stirring. After each addition of 1µ liter of aqueous phase of pure water to the lecithin solutions, the resulting systems are examined for clarity and viscosity. The course of each addition is monitored through cross polaroids in order to determine the boundaries of any organogel and briefringent liquid crystalline domains. The endpoint of the organogel domain at a given k_m is determined when the system became turbid after the addition of a specific amount of water. The phase behavior of the systems is mapped on phase diagrams with the top apex representing the lecithin and the other apices representing IPM and water solution. The transparent, homogeneous, nonbirefringent area enclosed by the line connecting the endpoints are considered as microemulsion based organogel [35].

Organogel structure and mechanism of organogelling

The initially spherical reverse micelles that are formed by lecithin molecules in a nonpolar organic solvent transform into cylindrical micelles, once water is added. This is established with the help of light scattering and small angle neutron scattering techniques. This one dimensional growth of micelles is caused by the formation of hydrogen bonds between water molecules and phosphate groups of lecithin molecules so that two adjacent lecithin molecules are bridged together by one water molecule. IR and NMR spectroscopic methods have revealed that water molecules could interact simultaneously with phosphate groups of neighboring lipid molecules via hydrogen bonding, acting as a bridge between them. In this case solvent molecules and lecithin phosphate groups can arrange in such a way that a hydrogen-bonded network will be formed. The increase in the amount of water results in the formation of long tubular and flexible micelles. These micelles can be entangled and therefore build up a transient three-dimensional network, that is responsible for the viscoelastic properties of the lecithin

organogels. At a critical concentration of water, network shrinks and phase separation occurs. At still higher contents of water a transformation to a solid, nontransparent precipitate can be observed. This diluted solution is composed of rod-like micelles, which their length is not enough to overlap and form a three-dimensional network. The existence of microdomains of different polarity within the same single-phase solution enables water-soluble and oil-soluble drugs to be incorporated. This could be attributed either to the increase in the number of cylindrical micelles or to the further growth of the cylindrical micelles or both, leading to the increase in the solubilizing capacity [35].

Determination of gelation temperature

Formulations are enclosed in glass tubes (2 mm inside diameter) and observed over a temperature range of 4-5°C. The change from solution to gel or vice-versa are determined by inverting the tube. The temperature is changed at a rate of 5°C h' and the temperature at which the physical state of the formulation changes is regarded as the gelation temperature [36].

Gelation Kinetics

The gelation properties of organogels are investigated in the presence of various solvents. Gel-sol and sol-gel transitions were evaluated by the inverse method and gelation kinetics are determined by turbidimetry [37].

In Vitro Drug Release

The permeation apparatus designed as described by Chowdary *et al*. is employed to study the release profile of drugs from the semisolid formulations. The release/ permeation of drugs from lecithin gels through various membranes is determined using Franz diffusion cell [38].

Application and Future Prospects

In the field of topical drug delivery, LOs 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. PLO is probably due to financial constrains as well as the industry focusing on area such as biotechnology and genomics. However, the great interest in PLO in the US has led to formulation of a second generation lecithin organogel premium, lecithin organogel base by Xenex Labs and Max Pharmaceuticals, USA. Table 1 shows some of the application and major findings of lecithin based organogels. A gel using hydroxy propyl cellulose and ethanol was formulated for transdermal delivery of testosterone. Testosterone loaded in the gel was 21 mg/cm^2 [39]. Similarly, a hydrogel formulation of fentanyl or sufentanil was prepared using polyvinyl alcohol and resin buffer. The formulated gel had a skin contact area of 2 cm^2 and 0.16 cm^2, respectively. The approximate weight of gel was 350 mg. This gel was delivered by electrortransport over 20 min in a dosage of 4 µg-5.5 µg [46]. The composition of

transdermal formulation patented by Murdock et al. (2002) is summarized in Table 2. The workers extended this study to a combination of two active ingredients for the treatment of painful spasticity. Amitryptyline appeared to offer limited pain relief when administered transdermally. The results revealed that the combination of gabapentin with doxepine might offer additional benefit. The addition of guaifenesin to doxepine was proposed to be of particular value in cases of painful spasticity [47].

Table 1: Applications and Major Findings of Lecithin Organogel-Based Systems

Organogel formulation	Application/Major findings	References
Lecithin (200mM) IPP gel of broxaterol and scopolamine	Transdermal delivery of compounds	39
Phosphatidylcholine (PC) gel in isopropyl palmitate (IPP) or cyclooctane	Investigated for transdermal transport of various drugs along with amino acids and peptides	27
IPP-lecithin gel of diclofenac and indomethacin	Enhanced efficacy of NSAIDs administered through topical route	40
Phytosphingosine or sphingosine lecithin organogel comprising soy PC, IPP, ethanol and water	Treatment of scars	41
Soya lecithin-isopropyl myristate (IPM) organogel containing ketamine hydrochloride and amitryptiline hydrochloride	Enhance skin penetration and partitioning of the drugs into the skin layers	42
Nicardipine lecithin-IPM organogel	Enhanced skin permeation across guinea pig and human skin	43
Methimazole in LO gel	Significant percutaneous absorption of methimazole	28
LO gel of cardiac glycoside digoxin	Topical administration of the compound in LO gel was found to be effective for the treatment of muscle spasm	44
Cyclobenzaprin in lecithin organogel (Lecithin 10-30%, IPM 10-30%, water 30-60%)	Topical formulation for bauxism.	45
Ketoprofen PLO gel	Administration of ketoprofen in PLO gel offered convenience, produced less side effects and alleviated pain in a specific location	27
PLO gel of Diclofenac, Ibuprofen, Ketamine	Randomized, placebo controlled study on lateral epicondylites employing diclofenac in PLO gel reduced pain and increased functional status	45
Lecithin organgel in combination of Pluronic F-127 (poloxamer 407) solution/ Cyclobenzaprin	Effective formulation for topical treatment of carpal tunnel syndrome	33
Lecithin (20-40% v/v) in isopropyl palmitate or isopropyl myristate containing suitable amount of pluronic and water with or without short chain alcohol	The components of PLO gel provide desired hydration state to the skin, thus effective in the treatment of eczema or psoriasis	41

Table 2: Transcutaneous Absorption of Various Drugs Formulated into Lecithin-Organogel Systems [41]

Active ingredient (mg/ml)	Ingredients*	Dose/day (mg)	Time when blood was withdrawn (days)	Blood serum level (ng/ml)	Reference level (ng/ml)	Remarks
Paroxetine HCl (20)	Etoxydiglycol	40	210	0	49 + 0.26	Poor absorption/ lab error.
Sertraline (15)		100	19	5	30 + 200 mg/ml	Limited absorption/ lab error
Fluoxetine HCl (10)	Ethyl alcohol, Isopropyl myristate	20	7	45	-	Patient benefit
Carbamazepine (150)	Etoxydiglycol	400	120	4.6	4-10µg/ml	Good absorption, No GI side effects and clinical improvement
Carbamazepine (150)	Etoxydiglycol	200	60	10.8	4-10µg/ml	Excellent absorption, No GI side effects and clinical improvement
Buproprion (15)	Water	100	44	>0.5	10-30	Poor absorption, lab error, patient non compliance

* Pluronic F-127 gel and soya lecithin were present in different amounts in all formulations.

CONCLUSION

Lecithin, a biocompatible material has recently gained wide popularity for development of better drug delivery system. Interest in organogels has increased in a wide variety of fields including chemistry, biotechnology and pharmaceutics. Lecithin based delivery systems appear to be unique and industrially feasible approach to overcome the problem of low bioavailability associated with the lipophillic drugs. Lecithin based organogels as transdermal drug delivery provides the promising delivery system for lipophilic drugs. It provides better patient compliance by avoiding invasiveness, prolonging plasma drug level, bypass first pass effect, reduced side effects and easy termination of therapy.

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