Lecithin Microemulsion Based Systems for Dermal Delivery of Drugs: A Review

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ABSTRACT

The purpose of this review is to give an insight into the considerable potential of lecithin based nanocarriers. The lecithin microemulsion and closely related microemulsion based systems are currently of interest to pharmaceutical researchers. Conventional systems for topical delivery of drugs meet many hindrances like reduced permeation and entrapment efficiency. Lecithin nanocarriers with their enhanced bioavailability of drugs present a viable option to address the drawbacks of conventional formulations. Soya and egg lecithin are widely being explored. However, the purity of lecithin plays a significant role in gelation process. The review encompasses lecithin microemulsions, lecithin based microemulsion gels, pluronic lecithin gels and lecithin stabilized microemulsion based hyrogels in improving the topical delivery of drugs. Biocompatible lecithin based systems are known to furnish ways of many promising discoveries in the field of safe and efficacious topical dosage forms.

Keywords:

Microemulsion, Organogel, Pluronic lecithin organogel, lecithin

1. Introduction

Drug delivery via skin is a preferred alternative to overcome the drawbacks of traditional routes of administration. However, skin is a very formidable barrier to entry of both small and large molecules. Drug's physicochemical properties like molecular weight less than 400 - 500 Da, partition coefficient in range of 1 to 3, non ionic nature, a balance between oil and water solubility, melting point less than 200º C facilitates its passive diffusion through skin.

Further it is desirable that the dose of drug is also small [1,2]. This limits the number of drugs that can be used for topical delivery and requires a vehicle that delivers the drug through the skin.

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There has been extensive and concerted research in the area, focused on development of delivery systems to permit adequate transdermal permeation of drugs. Of the different explored vistas, lipid based systems have created a niche for themselves. They are safe and effective drug delivery vehicles, give enhanced skin penetration and accumulation at the targeted site and are clinically efficacious reducing side effects [3, 10].

Phospholipid based nanosized delivery vectors have been exemplary in terms of their utility, versatility and adaptability for topical drug delivery. These natural and biocompatible molecules associate to form nanosized assemblies in aqueous media which can be used as platforms for drug delivery [4]. Being amphiphillic in nature phospholipids can deliver both polar and non-polar drugs and act as bio-friendly permeation enhancers. Phospholipids' similarity to the biomembrane composition renders them

non-allergic. The most widely investigated phospholipid based systems are liposomes and lecithin microemulsions [5].

Lecithin microemulsions as a delivery system, come out to be more advantageous than liposomes because of their ease of preparation, being economically viable alternative, high storage stability including avoidance of organic solvents and intensive sonication, easily scalable, minimal batch to batch variability. Further, their thermodynamic stablilty and spontaneous formation are added benefits [6]. At the same time, lecithin microemulsions are liquid in nature and thus have low contact time with the skin. Transforming them into gel can improve its skin application and addresses its major drawback [7, 8]. This review delves into arena of lecithin microemulsion and lecithin microemulsion based gels in dermal delivery of drugs.

2. Lecithin Based Microemulsion

Microemulsions are thermodynamically stable, isotropic formulations having hydrophilic or lipophillic nanodomains stabilized by the presence of an amphiphillic surfactant at the interface. The ultra low surface tensions observed in microemulsions becomes a possibility by addition of co-surfactants which increase the flexibility of the film and lower the interfacial tension. Microemulsions have been explored for dermal delivery of drugs extensively and well reviewed [9, 10]. It offers advantages like ease of preparation, thermodynamic stability, flexible interfaces promoting rapid drug diffusion [10].

Lecithin being amphiphillic in nature also promotes microemulsion formation alone and in presence of other co-surfactants. The lecithin molecule is composed of various phosphatides such as phosphatidyl choline, phosphatidyl serine, phosphatidyl ethanolamine and phosphatidyl inositol. Further, triglycerides and fatty acids are also a part of the composition. They are mainly obtained from soyabean and egg yolk [11].

The polar and nonpolar groups in lecithin permit solubilisation of both hydrophilic and lipophillic drugs. Lecithin acts as penetration enhancer as it has high affinity to epidermal tissue owing to its similarity to skin lipid components and also it increases hydration of stratum corneum [12, 13]. This leads to enhanced permeation of drugs due to alteration in skin lipid fluidization [14].

Microemulsions improve the transdermal delivery of several drugs over the conventional topical preparations such as emulsions and gels. Mobility of drugs in microemulsions is more facile, as compared to the microemulsion with gel former which will increase its viscosity and further decrease the permeation in the skin. The superior transdermal flux from microemulsions has been shown to be mainly due to their high solubilization potential for lipophilic and hydrophilic drugs [15].

Paolino et al conducted study on lecithin microemulsion of ketoprofen for skin penetration and tolerability. The study showed that ketoprofen loaded microemulsions had enhanced permeation and good human skin tolerability as compared to conventional formulations [16]. Lecithin microemulsion formulations increased estradiol flux 200-700-fold over the control, but permeability coefficients were decreased by 5-18 times. The superiortransdermal flux of estradiol was due to 1500-fold improvement insolubilization of estradiol by microemulsions [15].

Another significant investigation in lecithin microemulsions was on linker based systems by Yuan et al. Alcohol free microemulsion formulation was made possible with the introduction of linker molecules. Linkers are amphiphlic molecules such as sodium octanoate, decaglycerol monocaprylate/caprate and PEG-6-caprylic/capric glycerides, and lipophilic ones such as sorbitan monooleate. They segregate near the oil–water interface but only from one side of the interface [10, 17]. It has been observed that lecithin linker-based microemulsions have an excellent solubilization capacity for a broad

category of oils and increases dermal drug penetration [18, 19]. Lecithin is the major surfactant used in the system and remains unaffected by the formulation conditions like temperature and electrolyte concentration [20]. The higher flux of the active from the system to the skin obtained with linker microemulsions is produced by combination of linkers that increase the mass transfer and reduce the interfacial tension of system. Also this can be attributed to the formation of smaller aggregates (6-10nm) by using hydrophilic linker that can penetrate through the epithelial tissue with ease [20,21]. Moreover, the combination of hydrophilic and lipophilic linkers offers better solubilisation capacity [22, 23]. The linker based systems are less toxic than the alcohol-based lecithin microemulsion systems. This is because of the fact that the hydrophilic linkers concentrates on fluidizing the oil/water interface and probably the interstitial spaces between cells whereas medium chain alcohols fluidizes the membranes of living cells, inducing cell lysis [20, 21]. Linker based lecithin microemulsions can also be employed for extended release systems. The microemulsion imbibed in the skin works as a drug reservoir and was shown to provide extended release for over 24 h. The drug uptake in the skin increases with increase in the drug loading of microemulsion, dosage of microemulsion and the application time. It can be formulated for numerous drugs, is economic and customizable [21].

The most obvious drawback of microemulsion systems is its fluidity or low viscosity which limits its contact time with the physiological membrane. There have been various approaches at increasing the viscosity of lecithin based systems like its transformation to an organogel or using a hydrogel base to increase the viscosity. The further sections delve into viscosity enhanced lecithin systems for dermal delivery of drugs.

3. Lecithin Microemulsion Based Gel or Organogel

Lecithin microemulsion based gels (LMBGs) are thermodynamically stable, clear, viscoelastic, biocompatible, and nonbirefringent gels. They comprise of phospholipids (lecithin), appropriate organic solvent, and a polar solvent. During the investigation of the suitable conditions for soy lecithin to form reverse micelles, gel like structure was observed by Scartazzini and Luisi in 1988 [24]. They observed a sudden increase in the viscosity by the addition of minimal amounts of water into organic solutions of soy lecithin [24]. Since then a lot of research has been done on LMBGs.

LMBGs consist of a 3-dimensional network of entangled reverse cylindrical (polymer-like) micelles (**Figure 1**), which immobilizes the macroscopic external organic phase to a gel like state [25, 26]. The supramolecularly associated micellar aggregates in the entangled state resemble to that of uncrossed polymers insemidilute or concentrated solutions [28,29].These gels-like systems were called microemulsion-based gel or organogel; owing to the presence of organic solvents [10]. The basic three Components in an LMBG are a polar phase, a non-polar phase and a surfactant or lecithin. The amphiphillic lecithin has interfacial activities as well as acts as gelating agent also. The naturally occurring unsaturated lecithin with high degree of purity containing atleast 95% phosphatidyl content have the ability to form gel like structure. The synthetic, hydrogenated and poorly purified lecithin are devoid of gel forming property [24, 29, 30, 31]. A wide array of organic solvents have been used or can be explored for the preparation of lecithin microemulsion gels, of which fatty acid esters (eg., isopropyl myristate, isopropyl palmitate) are of particular interest for pharmacological applications. The formulations so developed exhibit enhanced skin penetration, biocompatibility and biodegradability [32, 33]. Aqueous media constitutes the polar phase in most of the cases. The addition of cosolvents like glycerol, ethylene glycol and formamide in non-aqueous media can also aid to transform a non-viscous lecithin solution into a gel. It is required that the gel forming solvent should be endowed with properties like high surface tension, dielectric constant, polarity index and a strong ability to

form hydrogen bonding [27, 34]. Recently bile salts have been used in the formation of long flexible reverse micellar chains of LMBG that can resemble to the role of water in organogelling [35].The lecithin microemulsion gels are fascinating as delivery vectors for their ability to solubilise lipophilic, hydrophilic, and amphiphilic guest molecules, including enzymes. They are suitable matrix for transdermal as well as topical formulations and are non-irritating. Some of remarkable features of lecithin organogels are thermoreversible nature, insensitivity to moisture, resistant to microbial contamination and spontaneous formation [31, 32, 36].

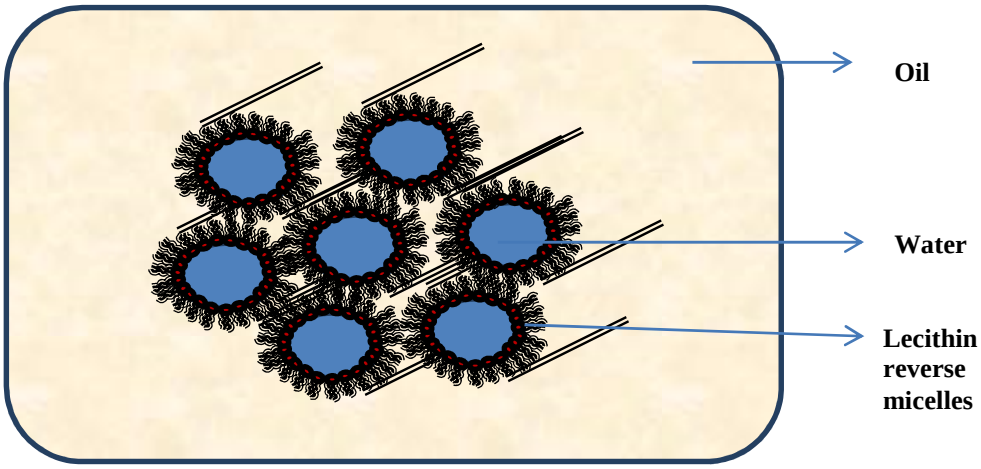

Figure-1 Cylindrical/micellar structure of lecithin in organogel

3.1 Mechanism of skin permeation of microemulsion based gels

Skin is a multilayered barrier comprising three main layers viz. epidermis, dermis and hypodermis. Compromising the barrier is required at times to facilitate drug diffusion. Organogels penetrate through the skin easily due the presence of non-polar solvents which acts as penetration enhancers. On addition of polar solvents gel formation takes place, as a result area of lecithin polar region increases. This additionally increases the thermodynamic activity of the drug driving it into skin. The general mechanism of skin permeation through organogels includes formation of thin film on the skin surface, drug diffusion through the carrier system, followed be partitioning of drug through the epidermal layer and then penetrating to the deeper dermal layers. This results in preferential accumulation in different layers of skin. Numerous researchers have worked on lecithin organogels for topical drug delivery (**Table1 and 2**) [37].

4. Pluronic lecithin microemulsion gel

Pluronic Lecithin Organogels (PLO) have gained importance in recent years as transdermal drug delivery systems as the high purity grade of lecithin is expensive and difficult to obtain in large quantities [10, 52]. Therefore, some researchers tried to incorporate synthetic polymers (e.g., pluronics) in lecithin microemulsion gels, for their feasibility as cosurfactants and stabilizers. Hence, a satisfactory organogel could be obtained with relatively lesser purity of lecithin [53, 54].

Pluronics are block copolymers of ethylene oxide and propylene oxide and are non-ionic, non-irritating and are absorbed quickly and also known commonly as poloxamers. [10, 61]. They are liquid at refrigerated conditions (4^{o}C) and form a thermoreversible gel at body temperature or they can be termed as in-situ gels [56]. The concept of PLO gel was first reported in the 1990s by Jones and Kloesel [52].

Table-1 Topical delivery of various substances using lecithin organogels

Drug class	Name of drugs/agents
NSAIDs	Diclofenac, ibuprofen, indomethacin, ketoprofen, piroxicam, aceclofenac [29-39]
Anti-hypertensive	Nicardipine[40]
Anti-cancer	Aromatic tetra-amidines[40]
Anti-psychotic	Fluoxetine, paroxetine, amitriptyline, trazadone[41]
Anti-vitiligo	Methoxsalen, triosalen, calcineurin inhibitors, corticosteroids[40]
Anti-cholinergic	Scopolamine [39]
Beta-adrenergic agonist	Broxaterol [39]
Vitamins	Vitamin A and C[38]
Others	Proteins and peptides[39], botulinium toxins[40]

Table-2 Organogel formulations and their findings investigated

Organogel Formulation	Findings
Broxaterol and Scopolamine in lecithin-IPP based gel	Potential for transdermal delivery of drugs [42]
Phosphatidylcholine (PC)-IPP based gel	Examined for transdermal transport of amino acids, peptides and various drugs [43]
Soybean lecithin/IPP gels composed of 10% to 20% of esters like ethyl acetate or propyl acetate	Transdermal delivery of aromatic tetra-amidines to assess anticancer activity [44]
Diclofenac and indomethacin in lecithin-IPP gel	Imoroved efficacy though dermal delivery [32]
Phytosphingosine lecithin organogel composed of Soyabean Phosphatidylcholine, IPP, ethanol, and water.	Explored for treatment of scars [47]
Ketamine hydrochloride and Amitryptiline Hydrochloride incorporated in Soy lecithin-isopropyl myristate (IPM) organogel	Enhanced skin penetration Significant partitioning of the drugs into the skin layers [48]
Lecithin-IPM organogel containing Nicardipine	Increased skin permeation [49]
Lecithin Organogel of Methimazole	Significant percutaneous absorption [50]
Digoxin in lecithin organogel	Topical efficacy for the treatment of muscle spasm [45]
Cyclobenzaprin incorporated in lecithin organogel	Useful for bruxism [46]
Lecithin Organogel containing Propranolol hydrochloride	Increase in concentration of lecithin resulted in lower flux of drug [51]

PLO's are biphasic systems comprising an oil phase (e.g. isopropyl myristate or isopropyl palmitate) and an aqueous phase having Pluronic F127 [55]. Water solubilises the pluronics and hydrophilic drugs and thus act as structure forming agent and stabilizes gel formation [56]. PLOs are formed spontaneously and thus have prolonged shelf life. Gel formation can be enhanced by addition of agents other than water such as propylene glycol, propyl gallate and hydroxypropyl cellulose. Depending on the solubility of drug, in PLOs, drug can be incorporated in either oil phase or aqueous phase (**Table 3&4**) [57, 58].

5. Lecithin stabilised microemulsion gels

Lecithin based microemulsions can be incorporated into gel matrices. Hydrogels of these microemulsions were formulated by addition of hydrophilic polymers such as gelatin, carrageenan, and carbopol to enhance the viscosity of the system (**Table 5**). Here the internal microemulsion droplets are not disturbed and continue to be in fluid state with the external water phase being gelled [8, 15, 82-84]

Table-3 Topical delivery of various substances using Pluronic lecithin organogels

Drug class	**Name of the drugs**
Non-Steroidal anti-inflammatory drugs (NSAIDS)	Piroxicam [59], diclofenac [60], Ketoprofen [63] lornoxicam[87]
Hormones	Dexamethasone[61] progesterone[84], testosterone[85], tamoxifen[86]
Antiemetics	Promethazine [62], Ondansetron [63], scopolamine [64], metoclopramide [65]
Opiods	Methadone, morphine, buprenorphine [66]
Anesthetics	Benzocaine, Lidocaine [67]
Antipsychotic drugs	Haloperidol, prochlorperazine [68]
Calcium channel blockers	Diltiazem [60]
Miscellaneous drugs	Methimazole [50], ketamine hydrochloride [65], selegiline hydrochloride [67], fluoxetine [66], clonidine [67], carbamazepine [67], baclofen [67], insulin

Table-4 Pluronic lecithin organogel formulations and their findings

PLO gel formulation	Findings
Pluronic Lecithin Organogel of Ketoprofen	Less pain, Fewer side effects [69]
Diclofenac, Ibuprofen, Ketamine in PLO gel	Reduced pain and increased functionality, potential for effective treatment for Osteoarthritis [70]
Ondansetron in PLO	Dose-dependent decrease of nociceptive and inflammatory effects in response to intradermally injected capsaicin in humans[63]
Lecithin in isopropyl palmitate or isopropyl myristate containing pluronic and water	Efficacious in eczema or psoriasis by increasing skin hydration[71]
PLO of Cyclobenzaprin	Therapeutic management of carpal tunnel syndrome[72]
NSAIDs incorporated in PLO	Rapid onset of action, Less side effects [67]
PLO gel containing extract of Arnica Montana	Used in pain management [73]
PLO of Ketamine	Reduces neuropathic, sympathetic, and myofacial pain by improving ketamine penetration[74]
PLO gel of saw palmetto extract	For the treatment of androgenic alopecia[75]
PLO gel of Bromelain and capsaicin	Excellent for topical delivery of large molecule [76]
PLO gel of hormones (eg, progesterone)	Effective transdermal delivery of hormone [77]
Testosterone (Micronized form) in PLO gel	Achieves effective systemic levels of hormone [78]
Fluoxetine hydrochloride incorporated in PLO gel	Useful for systemic delivery of the compound in feline patients[79]
Tamoxifen PLO gel	Stable, ease of application and biocompatible[80]
Lornoxicam PLO gel	Improved transdermal permeation[81]

Table5 Lecithin stabilized microemulsion formulations and their findings

Formulation	Findings
Lecithin stabilized microemulsion of ketorolac tromethamine	Enhanced skin penetration and drug release[87]
Microemulsion based hydrogel of dexamethasone	Non-irritating, Higher anti-inflammatory potential[83]
Microemulsion based hydrogel of lidocaine and prilocaine	Enhanced skin permeability Skin compliance Safe and efficacious[85]

6. Conclusion

With the ever-increasing promotion of green chemistry and usage of biocompatible ingredients in every aspect of science and technology, drug delivery too does not lag behind. The review tries to summarize and bring together an update on state of art and applications of lecithin based microemulsions in dermal delivery of drugs. Lecithin based delivery systems by virtue of their similarity to biomembranes are nontoxic in nature as well as are efficient modulators of drug permeation. The lecithin being amphiphillic in nature aligns itself along the interface between polar and nonpolar phase. Its structure endows it with a capacity to form lamellar structures and forms reverse micelles in non polar external phase. The introduction of polar media induces growth in the micelles to form long tubular structures which helps in immobilizing the external media. They have shown potential in augmenting dermal deposition of drug which is attributed to its similarity to physiological biomembrane and allows it to blend with the lipid mantle of the membrane. However, the nature of polar phase, non polar phase and physicochemical properties of the drug molecule influences its loading in the system. Although they are excellent delivery vectors, their natural origin warrants strict quality maintenance. Hence, researchers are endeavouring strategies to formulate stable and consistent delivery systems not affected by variations in lecithin origin and quality. Biggest challenge is to commercialize an increasing number of these promising concepts. The trend has picked up with a few products reaching the clinics and it is expected to scale the numbers in future.

DECLARATION

Authors have no conflict of interest to declare.

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