REVIEW ARTICLE

Pluronic lecithin organogel

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The purpose of this review is to give detail insight of pluronic lecithin organogels (PLOs) as a topical and transdermal drug delivery system. Pluronic lecithin organogel is a microemulsion-based gel that has been effectively used by physicians and pharmacists to deliver hydrophilic and lipophilic drugs topically and transdermally across the stratum corneum. It is thermodynamically stable, viscoelastic, and biocompatible gel composed of phospholipids (lecithin), organic solvent, and polar solvent. Various types of therapeutic agents have been easily incorporated in PLO to improve their topical drug delivery. Pluronic lecithin organogel improves the topical administration of drug mainly because of desired drug partitioning, biphasic drug solubility, and the modification of skin barrier system by organogel components. Beside this, it shows low skin irritation, increases patient compliance, reduces side effects, avoids first pass metabolism, and increases efficiency of drug. In addition, PLO has been shown *in vivo* and *in vitro* to modulate the release and permeation of drugs applied transdermally. Thus, in future, it has wide range of applications and opportunities to experiment with various drugs in this type of drug delivery system.

Key words: *Lecithin, pluronic F-127, pluronic lecithin organogel, systemic study, topical delivery*

INTRODUCTION

The topical and transdermal drug delivery system has gained wide range of application in the field of drug delivery systems. The most common barrier for this type of system is to deliver the drug through the skin via dermal and transdermal route. The skin is composed of three major components: the epidermis, the dermis, and the subcutaneous fat layer (hypodermis)[1-3] [Figure 1].

Of these three layers, the epidermis is the most impermeable one.[3,4] The epidermis is itself a complex multiple layered membrane, yet varies in thickness from approximately 0.06 mm on the eyelids to approximately 0.8 mm on the load-bearing palms and soles of the feet. It contains no blood vessels and hence nutrients and waste products must diffuse across the dermo-epidermal layer in order to maintain tissue integrity. The epidermis contains four histologically distinct layers, which, from the inside to the outside, are *stratum germinativum, stratum spinosum, stratum granulosum* and *stratum corneum*.[1,3] Of these layers, the *stratum corneum* is the most impermeable one. The *stratum corneum* consists of flattened cornified cells similar to bricks, which are embedded in a lipid intercellular matrix similar to mortar. The cornified layer of the *stratum corneum* appears to provide the rate-limiting step to transdermal drug absorption.[3,4] Penetration of the skin depends on diffusion; therefore, the hydration of the skin will affect permeability.[1,3] Thus, the properties of transdermal vehicles must be balanced so that they can deliver hydrophilic as well as hydrophobic drugs through the dermal and epidermal layer.

To deliver a drug through the dermal and transdermal route, various kinds of formulation systems have been evolved, but they have not been able to successfully deliver the drugs through the dermal and epidermal layer. Pluronic and lecithin have become very popular in the topical delivery of drugs. A number of studies have shown that pluronic lecithin organogels (PLOs) have the unique capacity to deliver the drugs through the skin and particular medications such as non steroidal anti-inflammatory drugs (NSAID), hormones, antiemetics, opoids, antipsychotic drugs, Calcium channel blockers and Local anesthetics to a specific site when other routes of administration are not viable.[5-7]

This system was being first developed by a compounding pharmacist in the US in the early 1990s as a topical vehicle[8] and is currently of great interest to the pharmaceutical scientist. It is not, however, really an organogel, a gel where the liquid component is organic rather than aqueous. Instead, it has an oil phase and an aqueous phase. It is, therefore, more commonly referred to as a cream, or simply a base. Dr. Sudaxshina Murdan in Hospital Pharmacist suggests, 'Based on the greater aqueous component of the gel one could say that PLO is a hydrogel'.[5,9]

Pluronic lecithin organogel is nonirritating to the skin,

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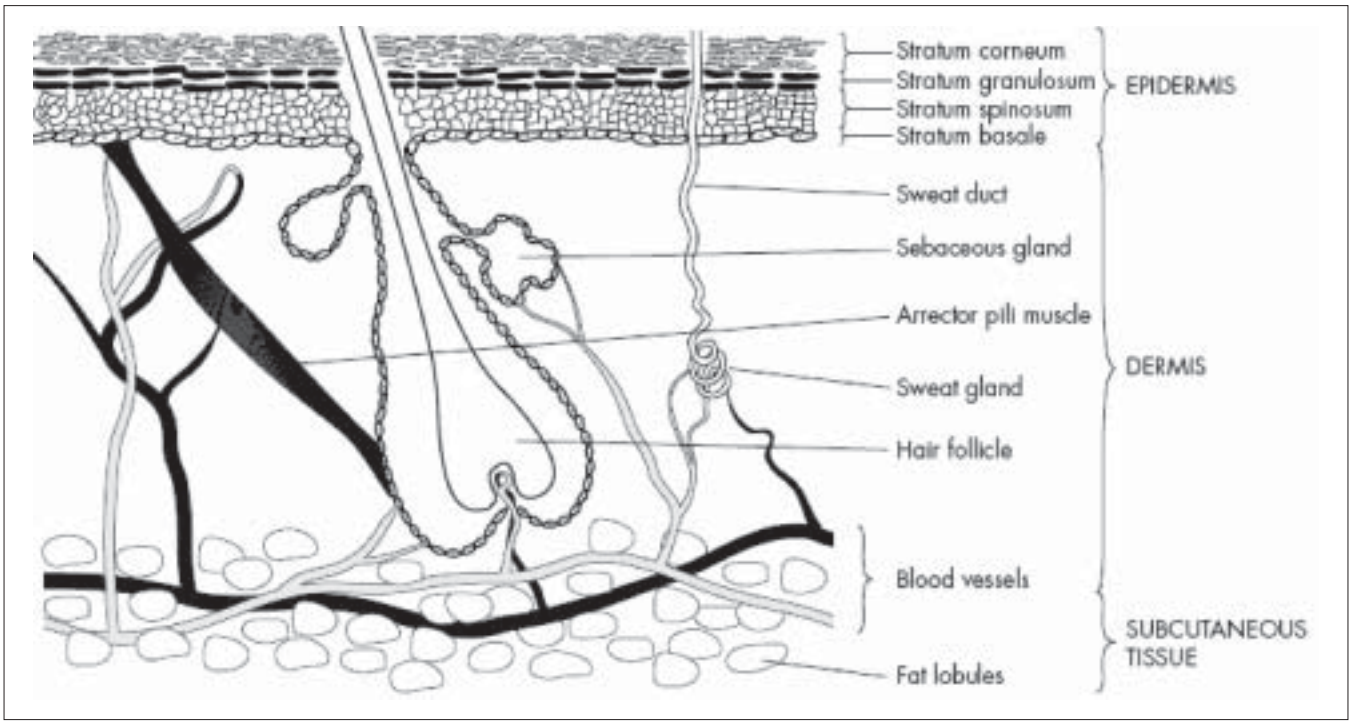

Figure 1: A diagrammatical cross-section through human skin

absorbs quickly, and is practically odorless. It consists of reversed polymer-like micelles. They are generated from the initial spherical ones by dissolving trace amounts of water in a nonaqueous solution; the micellar aggregates entangle, forming a temporal three-dimensional network in the bulk phase.[10-12] It is best used with drugs with molecular weight less than 500 Da. Pluronic lecithin organogel is a two-phase system consisting of an oil (lipophilic) phase and a water (hydrophilic) phase.[6,8] The oil soluble drugs are dissolved in the oil phase and water soluble drugs are dissolved in the water phase. One phase is injected into the other, back and forth until a smooth homogeneous gel is formed.

COMPONENTS OF PLO GEL

Pluronic F-127

Pluronic F-127 or Polaxomer 407 is an ABA type block copolymer, containing 70% of polyoxyethylene fraction[6,13] with a molecular weight of 12,500 Da and a general formula [Figure 2].

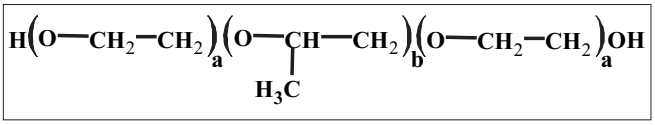

Figure 2: Structural formula of pluronic F-127

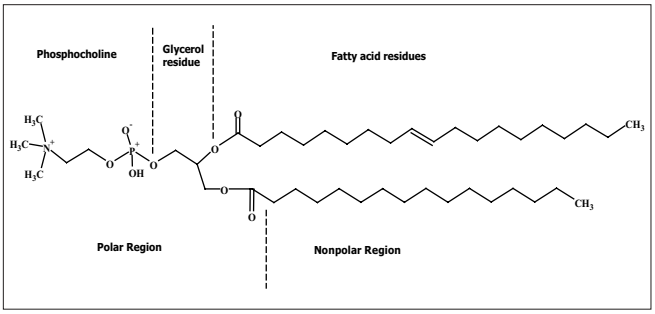

Figure 3: Structural formula of lecithin

It is a white, waxy, free-flowing granules that are practically odorless and tasteless. Used as emulsifying agent, solubilizing agent, and wetting agent[14,15] between 15% and 50% concentration. It is a long chain polymer that has the unique property of being solid at room temperature and liquid at chilled temperature.[6,8,13] Thus, on contacting to skin, it forms gel and facilitate proper inunction and adhesion.

Soya lecithin

Lecithin is a naturally occurring mixture of diglycerides of stearic, palmitic, and oleic acids linked to the choline ester of phosphoric acid, commonly called phosphatidylcholine[10,11] [Figure 3].

Lecithin is thought to be a permeation enhancer as it increases the fluidity of the epidermis, *stratum corneum*. It is used as dispersing, emulsifying, and stabilizing agent.[16]

Water (H_2O)

Water acts as a stabilizing and structure-forming agent in the process of PLO formation. It is also used for solubilizing the Pluronic F-127 and polar drugs.[7,13]

Isopropyl palmitate (IPP)/isopropyl myristate (IPM)
Acts as a non-oleaginous emollient with very good spreading ability and used for solubilizing the lecithin.[6,14] It is a clear, colorless, practically odorless viscous liquid which solidifies at low temperature.

Sorbic acid/potassium sorbate
Used as preservatives to enhance the shelf life of a product.

Therapeutic agents (drugs)
The drugs which have to be incorporated in PLO should posses the following biological and physicochemical parameter.

Biological properties of drug
Therapeutic index: Transdermal drug delivery is suitable only for drugs, for which the daily dose is in the order of few milligrams. So a potent drug, in which the slight increase or decrease in plasma drug concentration can either lead to toxic effect or loss of effect, is being formulated in PLO.[3,5]

Biological half life: The route is suitable for drugs that have short half-life.

Skin toxicity: The drug should be nontoxic, nonirritating and nonsensitizing to skin.

Drug inactivation: The topical route has been effectively used for the hepatic metabolized drug, so while selecting the drug this factor is important. The drug should not be metabolized in the skin itself while permeation through skin.[3]

Physicochemical properties of drug
Molecular weight: Drugs that have molecular weight less than 500 Da show good transdermal permeability.[3,5]

Partition coefficient: Drugs that have a stratum corneum/vehicle partition coefficient of 1-3 show good transdermal permeability.

pH: As the skin has pH of 4.2-5.6, solutions which have this pH range are used to avoid damage to the skin. However, for a number of drugs, there may also be significant transdermal absorption at pH values at which the unionized form of the drug is predominant.

Drug stability: Some drugs are unstable in the gastrointestinal tract environment; such drugs can be conveniently formulated in PLO.

METHOD OF PREPARATION

Pluronic lecithin organogel is mainly composed of Pluronic F-127, soya lecithin, and IPP/IPM. In general, it is made up of two phases, first pluronic phase (aqueous phase) and second lecithin phase (oil phase), i.e., pluronic gel combined with a lecithin based oil. Pluronic lecithin organogel gel looks and feels like a cream but is actually a gel. When the aqueous phase (pluronic gel) is combined with the lecithin oil base creates an emulsion that forms together due to the pluronic gel and the viscosity of that gel at room temperature.[5,8] Chilling of PLO converts the gel in to liquid, which later gets separated in to oil and aqueous phases (usually takes weeks for separation to occur).

Pluronic gel (aqueous phase)
Pluronic gel was prepared by taking specified amount of Pluronic F-127 NF in ice cold water, agitating continuously and placing the mixture overnight for complete dissolution of Pluronic F-127.[6,8] About 0.2% w/w potassium sorbate was added as preservative.

Lecithin phase (oil phase)
Lecithin phase was prepared by taking specified amount of lecithin, IPP/IPM, and 0.2-0.3% w/w sorbic acid as preservative, then keeping the mixture overnight for complete dissolution of lecithin.[6,8]

Lastly, the PLO gel was being prepared by mixing lecithin: IPP liquid phase and the Pluronic phase together well.[15,16] Minimize the incorporation of air.

DRUGS REPORTED IN PLO

Pluronic lecithin organogel, being thermodynamically stable and biocompatible, a various types of therapeutic agents have been incorporated. The drugs which are being incorporated are listed in Table 1.

Table 1: List of drugs incorporated in PLO

Class of drugs incorporated in PLO	Example
Nonsteroidal anti-inflammatory drugs (NSAIDS)	Piroxicam[15], diclofenac[22], ketoprofen[14,16]
Hormones	Dexamethasone[18]
Antiemetics	Promethazine[20], ondansetron[21], scopolamine[6], metoclopramide[23]
Opoids[19]	Methadone, morphine, buprenorphine
Anesthetics[24]	Benzocaine, lidocane
Antipsychotic drugs[8]	Haloperidol, prochlorperazine
Calcium channel blockers	Diltiazem[22]
Miscellaneous	Methimazole[17], ketamine hydrochloride[23], selegiline hydrochloride[24], fluoxetine[23], clonidine[24], carbamazepine[24], baclofen[24], insulin[25]

IN VIVO STUDIES REPORTED FOR PLURONIC LECITHIN ORGANOGEL

Efficiency of PLO as a topical and transdermal delivery system has been studied by carrying out various types of systematic studies conducted by clinicians and veterinarians. While performing these studies, the clinical effects and the plasma drug concentration was measured. In addition, the efficacy of PLO was assessed following a single topical application in some studies and after repeated applications in others.

Hoffman and co-workers[17] performed a study in healthy cats suffering from hyperthyroidism and showed that, following a single topical application of a drug methimazole in PLO to the inner pinna, significant drug absorption into the systemic circulation did not occur and plasma drug concentrations were either low or undetectable. On the contrary, it was observed that absorption of drug (methimazole) may be enhanced after repeated applications of PLO as a result of a decreased penetration barrier due to *stratum corneum* exfoliation and inflammation from the lecithin compound. If this is true, a chronic dosing schedule may result in more significant systemic concentrations of the target drug, but also potentially more topical adverse effects. In addition, the systemic studies performed on various drugs like fluoxetine, dexamethasone, amitriptyline, methadone, morphine, buprenorphine, and buspirone in cats have shown that the single topical application of drugs does not result in significant increase in bioavailability.[9,18,19]

In humans, Glisson *et al*. performed an *in vivo* study to determine the bioavailability of promethazine[20] in a topical pluronic lecithin organogel concluded that the topical promethazine, when applied in a PLO, absorbed systemically having serum concentrations much lower than after parenteral administration, with an absolute bioavailability of 2%. While in second study conducted by James Giordano and co-workers,[21] an ondansetron, a 5-HT receptor antagonist, topically applied in a PLO base vehicle against pain, mechanical hyperalgesia and flare produced by intradermally injected capsaicin has shown good result as a transdermal delivery vehicle, producing significantly greater pain reduction following a single topical application in healthy human volunteers. In addition, PLO has shown good results for locally acting drugs from the class of NSAIDs. In one of the studies, diclofenac-in-PLO was applied to the affected site for the treatment of osteoarthritis of the knee and of lateral epicondilytis results in greater pain reduction and increased wrist extension strength.

Thus, the above studies should be utilized to conduct further research on the value of PLO as a topical and transdermal delivery vehicle.

CONCLUSION

In the field of topical and transdermal drug delivery, PLO is emerged as one of the most novel and effective topical vehicle base for the drugs that have to be taken by injection or by mouth. With the help of PLO, clinicians and veterinarians now have the opportunity to treat their patients through the topical and transdermal route. In addition, PLOs have the advantage of being thermodynamically stable, viscoelastic, and biocompatible gel, and have specific and localized action, increasing the potential analgesic effects at the painful site. Thus, PLO appears to be an effective alternative vehicle for delivering a drug through the topical and transdermal route. In future, it has wide range of application and opportunities for clinicians and veterinarians to experiment with various drugs to study their systemic and local effect.

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Source of Support: Nil, **Conflict of Interest:** None declared.