PLURONIC LECITHIN ORGANOGELS: AN EFFECTIVE TOPICAL AND TRANSDERMAL DRUG DELIVERY SYSTEM

Sourodip Saha, Raahulan Shivarajakumar and Veera Venkata Satyanarayana Reddy Karri *

Department of Pharmaceutics, JSS College of Pharmacy, Ootacamund, JSS Academy of Higher Education and Research, Mysuru - 643001, Tamil Nadu, India.

Keywords: Pluronic lecithin organogel, Topical, Transdermal, Permeability, Clinical trial

ABSTRACT: Pluronic lecithin organogels (PLOs) are thermodynamically stable, biocompatible, viscoelastic with improve drug permeation and localised action. PLOs have gained much popularity compared with other traditional topical and transdermal drug delivery system owing to their lower cost, flexibility of dose and longer contact time. PLOs enhances the permeability of drugs because of desired drug partitioning, modification of skin barrier system by its components and biphasic drug solubility that is it enhanced solubility of poorly soluble drugs and increased penetrability of hydrophilic drugs. In this review we discuss the insights of PLOs as topical and transdermal drug delivery system.

INTRODUCTION: The transdermal and topical delivery of drug has drawn much attention than any other conventional drug delivery systems in the past decade. The reason is due to skin is the largest human organ with more surface area. This route by passes the first pass metabolism and also decrease the limitation of other traditional drug delivery system. Skin has three different layers i.e. epidermis, dermis and subcutaneous. The main barrier in TDDS is the stratum corneum (SC) which is the outer most part among the five layers of epidermis. The composition of SC and the morphology is quite unique in nature due to the tight junctions of corneocytes and with no blood vessels so that permeability of drugs through this layer of the skin is less. Due to this permeability problem various types of formulation has been rejected in the field of TDDS. However lecithin organogels shows a very promising results in transdermal drug delivery. The LOs are viscoelastic, biocompatible, thermodynamically stable in nature. They can be effective for the delivery of hydrophilic, hydrophobic and amphoteric drugs transdermally 1.

LOs are composed of three components lecithin (organogellator), a polar solvent and an organic solvent 2. In LOs reverse cylindrical micelles forms which are the entangled form of three- dimensional (3D) network 3. After solubilizing the lecithin in organic liquids such as isopropyl myristate (IPM), isopropyl palmitate (IPP) and others which are nonpolar the lecithin spherical reverse micelles are formed 1. Due to the broaden tubular micelles formation it leads to hydration of these spherical reverse micelles. These all then entrap in the solution to form a 3D network 2. Finally to produce a gel from the nonviscous solution the external organic phase needs to be immobilize, keeping the

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transparent and optical isotropic nature same like the original one. Pluronic Lecithin Organogels (PLOs) is a type of LOs. The main component in PLOs is pluronic F-127 or poloxamer 407, it is a type of triblock copolymer which contains 70% of the polyoxyethylene and the molecular weight is 12500 Da \(^4, 5\). In the early 1990s, an American compounding pharmacist Marty Jones and his workmate Lawson Kloesel developes PLOs as a vehicle for transdermal and topical delivery of drug from original lecithin organogels \(^6, 7\). There are so many studies that claims PLOs have unique nature that can penetrate the barrier layers of the skin and it will give more therapeutic effect. In PLOs mainly NSAIDs, antifungal, antipsychotic, antiemetics, opioids and hormonal drugs has been used widely \(^8\). PLOs absorbs quickly and not create any kind of irritation in the skin. Hence based on literature we can say that PLOs is a promising vehicle in the TDDS. According to the CompoundingToday.com, a product of the International Journal of Pharmaceutical Compounding (IJP) currently there 85 PLOs formulation are available. Now a days marketed PLO gelkits such as Transderma®, Phlojel® and PLO transdermal cream have become very popular. Depending on patient requirements these marketed PLOs creams and gels are loaded with drugs \(^9\).

**Mechanism of Action of PLOs through Skin:**

Stratum corneum (SC) is the main barrier for the permeation of drug through skin. Hence, to overcome this limitation chemical penetration enhancer’s are widely used in TDDS. However the use of chemical penetration enhancer’s for long term creates skin irritation and sensitization. Because chemical penetration enhancer’s disrupt the lipid layers of the skin. In PLOs the permeation enhanced due to the Lecithin and organic solvent used for its preparation. Lecithin is disorganize the structure of the skin, transiently it opens the pores of the skin and increase the penetration of drugs Fig. 1 \(^10\). But the exact mechanism how lecithin alters the skin is not yet understood clearly. It is anticipated that it may be due to the interaction between the lecithin’s phospholipid and the skin lipids. Organic solvent such as IPM, IPP, ethyl laureate etc. are used in the preparation of PLOs. These organic solvent contains fatty acid esters that gives better feel to the skin compares to the hydrocarbon containing organic solvents \(^11, 12\).

The mechanism by which the fatty acid esters will help in enhancing the penetration is not yet elucidated. However, it is believed that the enhance penetration is due to the solubilisation of SC by fatty acid esters \(^13, 14, 15\).

**Types of Organogels:**

**Lecithin Organogels (LOs):** Lecithin is generally extracted from animal tissues apart from the plant tissues and egg yolk. It is a phospholipid. In designing of organogels lecithin is used for the first time was described by Scartazzini and Luisi in 1988 \(^6\). The lecithin-based organogels are thermoreversible (solto-gel transition temperature at 40 °C), stable thermodynamically, viscoelastic, transparent, biocompatible in nature and non-irritant \(^16\).

**Pluronic Lecithin Organogels (PLOs):** PLOs are a soya lecithin based yellow-coloured, odourless and non-transparent gel which absorbed rapidly by the skin. It comprises of pluronic F127 (also known as poloxamer 407), water, isopropyl myristate or isopropyl palmitate and sorbic acid \(^17\). PLOs are viscoelastic thermostable and biocompatible in nature. It also creates less skin irritation. PLOs are suitable as a vehicle for delivering both hydrophilic and hydrophobic molecules for transdermal and topical uses \(^8\).

**Premium Lecithin Organogels (PrLOs):** The PrLO is a second generation lecithin organogel which is highly thermostable. It provides a good cosmetically acceptability due to its non-tacky and non-greasy nature. The irritation of skin and local intolerance of skin are very negligible cause it does not have any pluronic derivative. PrLOs improves the penetration of bioactive agents, so the bioavailability in tissues also improves.
Due to good bioavailability they used as a vehicle for topical and transdermal drug delivery. PrLOs are used to successfully incorporate various bioactive agents, such as diclofenac, ketoprofen, ibuprofen and progesterone

Limone dibutyllauroylglutamid (GPI) / Propylene Glycol (PG) Organogels: Limonene, is a terpene, it works as an excellent penetration enhancer. For improving the bioactive agent’s penetration and the bioavailability beyond the transdermal layer it used in various transdermal formulation. Limonene generally incorporated in GPI in PG. GPI is an organogelator, which is an amino-acid-type gelator. For improving the penetration rate of bioactive agents except limonene, some other penetration enhancers like farnesol, cineole and linalool can also be used to incorporate in GPI organogels.

Microemulsion based Gelatin stabilized Organogels (MGB): Gelatin is a protein and also a structuring agent extensively used in dirrrent type of food preparations. When the temperature is more than 40 ºC and then reduce below 35 ºC gelatine forms a gelled structure. Adding of gelatin in w/o microemulsion helps in the process of gellation of total solution that is micellar and the formed gel is clear in nature. For the development of organogels which are stabilized in gelatin, w/o microemulsions are used due to its thermostability and ease of preparation. isopropyl myristate (ipm), tween-85, AOT and water contains a typical pharmaceutical- grade w/o microemulsion preferably used in the preparation of MGB. The MBGs are vehicle used for the topical and transdermal controlled delivery of hydrophobic bioactive agents.

Fatty Acid Derived Sorbitan Organogels: In the formation of this type of organogels, sorbitan monostearate and sorbitan monopalmitate gelators are used. These hydrophobic gelators have the ability of solvent immobilization for solvents like isopropyl myristate (IPM) and vegetable oil. After heating the gelator solution in an apolar solvent when the temperature is reduced at lower-level then these gelators forms a solid fibre matrix. At lower-level temperature the toroidal reverse micelles are formed. These reverse micelles rearrange themselves to formed a three-dimensional network structure by rod-shaped tubules. At room temperature the developed gel prepared by these gelators are non-transparent, thermostable and thermoreversible for weeks.

Poly Ethylene Organogels: These organogels are generally uncoloured in nature, for the preparation this type of organogels polyethylene with low molecular weight needs to be dissolve in mineral oil. The temperature should not be more than 130ºC and afterwards shock-cooling is required. As a ointment base this organogels are used.

Physio Chemical Properties of PLOs: Viscoelasticity: In PLO gels both viscous and elastic properties are present. These viscous and elastic nature of PLOs are seems to follows the Maxwell model of viscoelasticity. When the shear rate is low the PLOs act likes solid and they also showed elastic property but with increasing the shear rate the fiber structures start to weaken and when the shear stress is at high level they distort the interactions between the structures of fibers. This behaviour is known as plastic flow behaviour.

Thermoreversibility: In PLOs when the poloxamer concentration is ranging between 20-30% and if they heated above their critical temperature of 20 - 25 ºC then they lose their solid-matrix structure and started to flow. Again with increasing the temperature or after cooling the PLOs they return back to their more stable configuration.

Thermostability: In PLOs the gelator molecule is lecithin, after addition of water it can be self-assembled under suitable condition to form organogels. With increasing in the temperature of PLOs, lecithin molecules absorb the kinetic energy to minimize the loss of the structure of organogels. But when the temperature is low the molecules reassemble and revert back to their previous structure. For this inherent thermostability they are valuable as a vehicle where longer shelf life is required like bioactive agent and cosmetic application.

Non - Birefringence: PLOs are isotropic in nature and it appears as a one phase. So it looks like dark matrix when they viewed under polarized light.
Due to this property the polarized light won’t be able to pass through the matrix 24, 26, 33.

**Hydrophilic Lipophilic Balance:** PLOs are composed of oil and water and they are well balanced with hydrophilicity and hydrophobicity. Hydrophilic and lipophilic drugs will respectively dissolve in polar and non-polar solvent. Due to the amphiphilic nature lecithin molecules are possess polar head groups, they attract the polar drugs and non-polar tails, which solubilize non polar drugs 6.

**Microbial Resistance:** In PLOs the external phase is non-aqueous and the internal phase is aqueous. In aqueous environment micro-organism grow well. But in PLOs presence of non aqueous phase hampered micro-organism’s growth. So the PLOs molecules will be well protected for a longer period of time 34.

**Optical Clarity:** The optical clarity of organogels depends on their composition, they may be transparent or opaque in nature. Lecithin organogels (LOs) are transparent in nature where as PLOs are yellow-colored and opaque in nature.

**Components of PLOs:**

**Pluronic F-127:** Pluronic F-127 or poloxamer 407 is an ABA type block copolymer. It is an odourless, tasteless, waxy and white colour free flowing granules. Pluronic F-127 is generally used as solubilising, emulsifying and wetting agent 8. It has a long chain polymer for that it is solid at room temperature and liquid at cold temperature 4, 5. And when it comes contact with skin it became gel.

**Soya Lecithin:** It is a naturally found mixture of diglycerides of stearic, palmitic and oleic acids linked with the choline ester of phosphoric acid, which is commonly known as phosphatidycholine 2-12. Lecithin is known for its capability of enhancing permeation, it also increase the fluidity of the epidermis of SC. It is also used as dispersing, stabilizing and emulsifying agent 8.

**Water:** Water is mainly used to solubilise the pluronic F-127 and polar drugs. In PLO formation it works as a stabilizing and structure-forming agent 5, 16.

**Isopropyl Palmitate (IPP) / Isopropyl Myristate (IPM):** It acts as a non oleaginous emollient. It is a colorless, clear, odorless liquid which became solid at low temperature. Mainly, it is used to solubilise the lecithin 4, 8.

**Sorbic Acid / Potassium Sorbate:** They are mainly used as a preservative to increase the product shelf life.

**Preparation of the PLOs:** Pluronic lecithin organogels is mainly comprised of three ingredients, they are lecithin pluronic gel and isopropyl palmitate (IPP) / isopropyl myristate (IPM) 4, 18. Generally in PLOs there are two phase, first one is aqueous phase (pluronic gel) and second one is oil phase (lecithin phase), in cold temperatures PLO gels are liquid solution and with increasing the temperature they changed their phase and became gel Fig. 2. For the preparation of PLOs pluronic F127 was used upto 20 - 30% w/w.

**Lecithin Phase (Oil Phase):** For the preparation of lecithin phase first specific amount of soya lecithin is dissolve in isopropyl palmitate (IPP) / isopropyl myristate (IPM) which is used as dispersing, emulsifying, and stabilizing agent and then the mixture needs to keep overnight for lecithin’s complete dissolution 12. Sorbic acid (0.2 - 0.3% w/w) was added in the mixture as a preservative 35.

**Pluronic Gel (Aqueous Phase):** A weighed amount of Pluronic F-127 and potassium sorbate (0.2% w/w) was dispersed in cold water to prepare pluronic gel. For the complete dissolution of pluronic F-127 the mixture needs to keep overnight at 2 - 4 °C in a refrigerator. At last, in final stage 70% of aqueous phase needs to added slowly drop by drop in 30% of oil phase with continuous stirring at 400 rpm by using a mechanical stirrer 36.

**FIG. 2: SCHEMATIC DIAGRAM OF THE PREPARATION OF PLURONIC LECITHIN ORGANOGEL**
Properties of Drug to Incorporate in PLOs:

**Molecular Weight:** Drugs less than 500 Da molecular weight are the good candidate for transdermal and topical application. They showed good permeability across the skin barriers. 38

**pH:** The pH of human skin is 4.2-5.6. Drugs with this pH range are the good candidate for transdermal and topical application. Because drugs within this pH range used to avoid any kind of skin damage.

**Biological Half Life:** Drugs with shorter half-life are the suitable candidate for topical and transdermal route of administration.

**Skin Toxicity:** For the topical and transdermal application of the drug it should be nontoxic, non-irritating and non-sensitizing to the skin. 18

**Therapeutic Index:** Transdermal and topical drug delivery is worthy only for those drugs, which should be used in daily dose basis of few milligrams. So a potent drug, which have the ability of altering the plasma drug concentration with a small amount can either lead’s to toxicity or less effect, is the perfect candidate for formulated in PLO. 5, 18

**Solubility Nature:** The drug should be high lipid soluble and reasonable water soluble in nature so that it can be used in PLOs. 18

**Partition Coefficient:** Drugs with a partition coefficient of 1-3 (stratum corneum / vehicle) show’s good permeability in transdermal drug delivery.

**Characterization of PLOs:** Self-associated supramolecules of PLOs due to their interior structural design makes the characterization complicated. Microstructures are formed as the result of polar and non-polar interaction. Due to their high sensitivity some difficulties arise in the time of investigative studies.

A number of studies claim that the physicochemical properties of PLOs such as rheology, physical and mechanical stability, and release behaviour of the drug depend’s on the molecular arrangement within the PLOs to provide specific structural network. 17, 38

**Structural Features of the PLOs:** The hydrogen bonding is the major driving forces for the self-assembling of the molecule of organogelator in organic solvents. For establishing this hydrogen bonding, FTIR spectroscopy has been found to be successful. 39 By scanning and transmission electron microscopy (SEM and TEM) the molecular packing of organogelator molecules present in the organogel network was studied. Dynamic and static light scattering (elastic or quasielastic light scattering (QLS techniques), Small-Angle Neutron Scattering (SANS), Small-Angle X-ray Scattering (SAXS), and Atomic Force Microscopy (AFM) are some of the techniques that used to study the features of organogels at 1 - 1,000 nm scale. Recently, for the study of molecular arrangement of LOs, SAXS and AFM are used 38, 39, 40, 41, 42, 43

**pH of the PLOs:** For the determination of the pH of PLO gels a Metler Toledo pH meter (Mettler-Toledo Ingold Inc., Billerica, MA) can be used. Before each use the pH meter need to be calibrate with standard buffer solutions of pH 4, 7, and 10. This study was performed in triplicate, and average pH values needs to be recorded. 44

**Drug Content:** In 25 ml volumetric flask totally 0.5 g PLO and 15 ml methanol were added, and then treated by ultrasonic for 30 min (ultrasonic power 200W, frequency 40 kHz). The final volume was adjusted upto 25 ml with methanol. Then 0.22 micron membrane (Millipore_, Billerica, MA) used for filtration, by using the HPLC method the drug concentration of sample was determined. Drug content is expressed in percent, the amount of drug measured in PLO and the actual amount of drug added into the PLO.

**Gel Transition Temperature:** A 10 ml transparent vial containing a magnetic bar is used to determined the gel transition temperature where the PLO was placed in a water bath at 4 °C. The vials which contains the formulation was heated at a slow and constant rate with continuous stirring at 60 rpm. Due to gelation the magnetic bar will stopped, than the temperature of the gelation was measured. 45

**Viscosity:** To determine the viscosity of the PLO gel a Brookfield RVDV-I Prime digital viscometer
(Brookfield Engineering Laboratories, Middleboro, MA) was used with SC4-29 Spindle. At room temperature (25 °C) the tests were performed. At varying speeds of 5, 10, 20, and 50 RPM, the viscosities for the prepared PLO gels were evaluated.

**Physical Examination:** Physical examinations of the prepared PLOs for their colour, appearance, odour, texture and phase separation were carried out by visual inspection.

**Spreadability:** To determine the spreadability of the prepared PLO gel modified wooden block and glass slide apparatus were used. For the determination of spreadability a calculated amount of gel was was used on fixed glass slide, a pan was joined with the movable glass slide and kept above the fixed glass slide. The gel placed in between of the two slides for 5 min. Then slowly the weight removed from the slides. Spreadability was determined by the following formula:

\[ S = \frac{M}{T} \]

Where \( S \) = spreadability in g/s, \( T \) = times in second and \( M \) = mass in grams.

**Differential Scanning Calorimetry:** To determine the changing rate of absorbed heat by drug after dissolve in PLO gels, DSC analysis was performed for drug and PLO gels after drug loading. In aluminium crucibles the samples (5 - 10 mg) needs to be sealed and placed in the Mettler MT 5 microbalance. By using a DSC 822e Mettler Toledo instrument (Mettler Toledo GmbH, Schwerzenbach, Switzerland) fit with a TSO801RO sample robot and a TSO800GCI Gas control fixed with nitrogen gas cylinder, DSC studies were done at a heating rate of 10 °C/min over a broad range (10 - 300 °C). For collecting the scan, Star e software V8.10 was used. Nitrogen gas was clear out at a speed of 10 ml/min.

**Stability Study:** Glass vials were used to store samples of drug loaded PLO gel formulations at various temperature *i.e.* 25 °C, 35 °C, and 45 °C. PLO gels were analyzed for drug content after a regular time interval of 0, 7, 14, 21, 28, and 35 days. In 1 ml of methanol specific amount of drug-loaded PLO gel was dissolved and diluted more for analysis. The stability study of the PLO gel was done in triplicate.

**Water Content:** Due to the water evaporation the viscosity of the PLOs decrease drastically so it is very important to maintain the water content, otherwise it affect the gel stability. For determining the water content in PLOs the simple, fast, and non-destructive technique was Near-infrared (NIR) spectroscopy.

**In-vitro Drug Release Study:** Franz-diffusion cells contains a cellulose membrane (Spectra pore, MWCO 1000 Da) and a Smart membrane to conducted the *in-vitro* release study of drug loaded PLO gels. In diffusion cell the cellophane membrane was fixed in between the donar and receptor chamber. Freshly prepared phosphate-buffer (pH 7.4) solution was used to fill the receptor chamber and stirred by using a magnetic stirrer at 300 rpm. Samples (300 ml) were collected after specific time intervals and replaced with same quantity of freshly prepared buffer. The sample was analyzed to determine the drug content by HPLC at 254 nm. The release kinetics of the formulations were calculated, and release patterns for those formulation were analyzed using three mathematical models: – (a) zero order kinetics– released amount per unit area (mg/cm²) against the time (h), (b) Higuchi kinetics – released amount per unit area (mg/cm²) against the square root of time (h) and (c) first order kinetics – log of released amount per unit area (mg/cm²) against the time (h).

**Preclinical Studies on PLOs:** Various types of systematic studies was performed by clinicians and veterinarians to determine the efficiency of PLOs as a topical and transdermal delivery system has been carried out. In healthy cats after applying a single topical application of a drug (Methimazole, Fluoxetine, Dexamethasone, Buspirone & Amitriptyline) in PLOs to the inner pinna, they didn’t found any significant absorption of drug in the systemic circulation. The drug concentration in plasma are either low or undetectable. However in cats suffering from hyperthyroidism they found that repeated application of drug in PLOs for a couple of weeks resolve many symptoms and they also reduce the total thyroxine levels.

In Table 1, the preclinical study details on PLOs are summarized.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Experiment subjects and no. of subject</th>
<th>Method of Trial</th>
<th>Major Outcomes</th>
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<tbody>
<tr>
<td>Methimazole</td>
<td>13 cats diagnosed with hyperthyroidism</td>
<td>The cats were diagnosed with hyperthyroidism and treated transdermally with methimazole in PLOs base. The dose range was 2.5 mg/cat q 24 h to 10.0 mg/cat q 12 h for the topical application of the drug to the inner pinna of the ear. Blood samples were collected to determine the serum methimazole in high performance liquid chromatography (HPLC) after dosing at 0, 5, 15, 30, 60 min, and 2, 4, 6, 12, 24 h.</td>
<td>Clinical improvement and significant decreases in the concentration of thyroxine has been reported after few days observation compared to pre-treatment concentration. No adverse effects was found after the transdermal application of methimazole during the study period of several months. Bioavailability was found low to undetectable of methimazole in PLOs which was given transdermally as a single dose to the healthy cats. Among those 6 cats, 1 cat achieved nearly 100% bioavailability after transdermal application compare to the oral route.</td>
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<tr>
<td>Methimazole</td>
<td>6 healthy cats</td>
<td>A randomized triple crossover study was conducted of methimazole loaded PLOs, administered by the IV, transdermal and oral routes. Blood samples were collected to determine the serum methimazole in PLOs compared to the methimazole given orally for the control of hyperthyroidism in cats. For this study 47 cats divided into 2 groups with newly diagnosed hyperthyroidism was used.</td>
<td>After 2 weeks of drug administered in orally and transdermally they found that in most no. of cases the serum T₄ concentration was in reference range incase of oral methimazole compared to the transdermally applied methimazole. The gastrointestinal (GI) adverse effects was found more in oral methimazole compared to the transdermally applied methimazole. So at 2 weeks of treatment they found that the overall efficacy of oral methimazole is much higher than the transdermally applied methimazole. In results it was found that lower Peak fluoxetine concentration (Cmax) and longer Cₘₐxₜ time for transdermal compare to oral administration. Sufficient evidence was found that the absorption of fluoxetine through the cats skin into the systemic circulation required 15% w/v PLO formulation. And at last the relative bioavailability of transdermally applied fluoxetine hydrochloride in PLOs is only 10% approximately compare to the oral administration.</td>
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<tr>
<td>Methimazole</td>
<td>47 cats newly diagnosed with hyperthyroidism</td>
<td>A study was conducted to determine the safety and efficacy after transdermal application of methimazole in PLOs compared to the methimazole given orally for the control of hyperthyroidism in cats. For this study 47 cats divided into 2 groups with newly diagnosed hyperthyroidism was used.</td>
<td>After 2 weeks of drug administered in orally and transdermally they found that in most no. of cases the serum T₄ concentration was in reference range incase of oral methimazole compared to the transdermally applied methimazole. The gastrointestinal (GI) adverse effects was found more in oral methimazole compared to the transdermally applied methimazole. So at 2 weeks of treatment they found that the overall efficacy of oral methimazole is much higher than the transdermally applied methimazole. In results it was found that lower Peak fluoxetine concentration (Cmax) and longer Cₘₐxₜ time for transdermal compare to oral administration. Sufficient evidence was found that the absorption of fluoxetine through the cats skin into the systemic circulation required 15% w/v PLO formulation. And at last the relative bioavailability of transdermally applied fluoxetine hydrochloride in PLOs is only 10% approximately compare to the oral administration.</td>
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<tr>
<td>Fluoxetine Hydrochloride</td>
<td>12 healthy cats</td>
<td>The study was conducted to determine the comparative bioavailability and pharmacokinetics for the transdermally (TD) and orally administered fluoxetine hydrochloride in PLO gels. For the study drug was applied to the pinna of cats at two dosage (5 &amp; 10 mg/kg)</td>
<td>After 2 weeks of drug administered in orally and transdermally they found that in most no. of cases the serum T₄ concentration was in reference range incase of oral methimazole compared to the transdermally applied methimazole. The gastrointestinal (GI) adverse effects was found more in oral methimazole compared to the transdermally applied methimazole. So at 2 weeks of treatment they found that the overall efficacy of oral methimazole is much higher than the transdermally applied methimazole. In results it was found that lower Peak fluoxetine concentration (Cmax) and longer Cₘₐxₜ time for transdermal compare to oral administration. Sufficient evidence was found that the absorption of fluoxetine through the cats skin into the systemic circulation required 15% w/v PLO formulation. And at last the relative bioavailability of transdermally applied fluoxetine hydrochloride in PLOs is only 10% approximately compare to the oral administration.</td>
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<td>Dexamethasone</td>
<td>6 healthy cats</td>
<td>A crossover study design was conducted to compared the concentrations of dexamethasone in serum after transdermal and oral administration using PLOs as a base in healthy cats assigned in two groups. The drug was applied either orally or transdermal on the inner pinna of the cats as a single dose (0.05 mg/ kg)</td>
<td>In results they found in case of a single dose of transdermally applied dexamethasone, the serum concentration was below the detection limits after 24 hours whereas the maximum serum concentrations for orally administered dexamethasone range was from 3.8 to 84.4 µg/ml.</td>
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<tr>
<td>Buspirone &amp; Amitriptyline</td>
<td>6 healthy cats</td>
<td>A cross-over study was conducted for the comparison of the availability of these drugs after administered orally and transdermally in adult cats. PLOs are used as a base for the preparation of the transdermal gel. Amitriptyline (5 mg) and buspirone (2.5 mg) single dose was given orally and transdermally among the two groups of cat for the determination of plasma drug concentration.</td>
<td>After analysing the blood sample using commercial Enzyme Linked Immune Sorbent Assay (ELISA) tests they found that the transdermally administered amitriptyline and buspirone has very low systemic absorption compared to the oral route of administration.</td>
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Clinical Studies on PLOs: In clinical studies Diclofenac loaded PLOs was used for the treatment of osteoarthritis of the knee. Patients experienced less pain after using that drug loaded PLOs. In case of ondansetron after a single topical application they found significant analgesic effects.

In another study silymarin loaded PLOs was used for atopic dermatitis where they found good result along with high penetration and hydration effect.

In Table 2, the clinical study details on PLOs are summarized.

<table>
<thead>
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<tr>
<td>Diclofenac</td>
<td>14 patients suffering from lateral epicondylitis</td>
<td>A randomized double blind crossover study was conducted. The PLOs applied thrice a day for 1 week in the lateral elbow and after washout period of 1 week diclofenac loaded PLOs applied on that same part for 1 week</td>
<td>It was found that the pain was significantly less after using diclofenac loaded PLOs. It was also found that the wrist extension strength was more after using the diclofenac loaded PLOs (8.4 Kg) than it was before treatment (5.9 Kg). So topical 2% diclofenac in PLOs shows more effect in pain reduction and it also reduce the wrist extensor weakness in lateral epicondylitis.</td>
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<tr>
<td>Diclofenac</td>
<td>70 patients suffering from osteoarthritis (OA) pain in the knee</td>
<td>A double blind randomized, placebo controlled and parallel group design study was conducted for two weeks. From the WOMAC (VA3.0) osteoarthritis health status measure they determined the responses of the patients</td>
<td>The improvement after using topical diclofenac is greater compare to the placebo group. The 2% diclofenac topical formulation in PLOs have good therapeutic value in patients suffering from OA of the knee. After collecting all the data from patients great improvement was found in case of BAK-PLO over placebo in both of the sensory (p=0.053) and motor subscales (p=0.021). For symptoms like tingling, cramping, and burning pain in the hands they found that the improvement was good. And the authors didn’t found any undesirable toxicities for the BAK-PLO as well as any systemic toxicity. So BAK-PLO used for topical treatment in CIPN improves some of the symptoms.</td>
</tr>
<tr>
<td>Baclofen, Amitriptyline HCl and Ketamine</td>
<td>208 patients</td>
<td>A double blind placebo controlled trial was conducted for the treatment of Chemotherapy-induced peripheral neuropathy (CIPN). Baclofen 10 mg, amitriptyline HCl 40 mg and ketamine 20 mg in PLOs (BAK-PLO) versus placebo (PLO) was used to find out its effect on pain</td>
<td>It was found that 100 µg and 250 µg dose of ondansetron significantly produce dose-dependent analgesic effects. The same amount of dose is also sufficient to reduced the mechanical hyperalgesia produced by capsaicin. For diminishing the capsaicin-induced inflammatory flare 250 µg dose of ondansetron is required.</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>12 human volunteer</td>
<td>A study was conducted where topically 5-HT3 receptor antagonist ondansetron was delivered by using PLOs as vehicle to produce attenuation of nociceptive and inflammatory effects of capsaicin (10 µg/10 µl) in humans after injected intradermally</td>
<td>It was found that 100 µg and 250 µg dose of ondansetron significantly produce dose-dependent analgesic effects. The same amount of dose is also sufficient to reduced the mechanical hyperalgesia produced by capsaicin. For diminishing the capsaicin-induced inflammatory flare 250 µg dose of ondansetron is required.</td>
</tr>
<tr>
<td>Silymarin</td>
<td>15 patients suffering from atopic dermatitis</td>
<td>In a study formulated and clinically evaluated silymarin loaded PLOs was used in the treatment of atopic dermatitis</td>
<td>It was found among the 15 patients 11 patients treated completely and the base showed high penetration and hydration effect. So silymarin loaded PLO may be used as a novel topical formulation for atopic dermatitis in future.</td>
</tr>
</tbody>
</table>

CONCLUSION: PLOs have emerged as a better alternative for traditional topical and transdermal drug delivery systems. PLOs enhances the permeability of drugs because of desired drug
partitioning, modification of skin barrier system by its components and biphasic drug solubility that is it enhanced solubility of poorly soluble drugs and increased penetrability of hydrophilic drugs. Many preclinical and clinical studies mentioned above have explored the potential use of PLOs in treating various diseases. However, very few products of PLOs are available in the market and many are being in various stages of clinical trials. Based on these studies discussed above we can anticipate that more products will be available in the market in near future.

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