A review of pluronic lecithin organogel as a topical and transdermal drug delivery system

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Pluronic lecithin organogel (PLO) is a new transdermal drug delivery system into which drugs can be incorporated. This article reviews PLO and the studies that have been performed

Pluronic lecithin organogel (PLO), a base in which drugs can be incorporated, is currently generating great interest in the US as a topical and transdermal drug delivery vehicle. Compounding pharmacists are advertising the vehicle, as well as their compounding services, and a large number of drugs have already been incorporated within PLO for human and animal use.

There is a need to develop new topical and transdermal drug delivery vehicles,[1] as well as formulate certain drugs into such preparations, for example, for use in neonates who would otherwise be subjected to multiple injections. There is also a need to produce vehicles with good organoleptic properties and which do not contain excipients such as parabens, which may irritate or sensitise the skin.[1] However, although PLO is commercially available from at least three manufacturers, PLO-based drug containing formulations have not yet been marketed commercially. This may be because the evidence, to date, for its efficacy as a transdermal delivery vehicle is mainly anecdotal. Systematic scientific evidence is limited and little is known about its physicochemical properties as a result of the vehicle not having been studied in detail in research laboratories.

It is also not yet known whether using PLO as a drug delivery system has advantages over other existing topical preparations, or whether PLO will replace any of these, because comparative studies have not been carried out. However, it is likely that PLO will replace some of the existing topical vehicles if more hospital formulation pharmacists and specials manufacturers start considering and researching PLO as an alternative vehicle to those currently used, especially for skin conditions that are currently poorly served by existing preparations. This article gives a brief history of PLO and assesses the available literature on its use as a topical and transdermal drug delivery vehicle.

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A brief history

In the early 1990s, PLO was developed as a topical and transdermal drug delivery vehicle from the original lecithin organogel[2] by Marty Jones, an American compounding pharmacist, and his colleague, Lawson Kloesel.[3] They prepared the original lecithin organogel by adding small amounts of water to an organic solution of lecithin. PLO was then produced when they added an aqueous solution of Pluronic F127 (a tri-block copolymer, composed of a polypropylene oxide, sandwiched between two polyethylene oxide units) to the original gel in an attempt to stabilise it.

Collaborations between local physicians, their patients and the two pharmacists, Jones and Kloesel, led to the incorporation of a number of drugs into PLO and anecdotal evidence of its efficacy as a transdermal drug delivery vehicle.[3] Since then, interest in PLO for use in man and animals, especially cats, has increased dramatically and a range of drugs have been incorporated within PLO. As well as its use as a transdermal delivery system, PLO has been investigated and suggested as a vehicle for drug application to the oral cavity.[4–6]

What is PLO?

So what exactly is PLO? It is an opaque, yellow preparation, composed of isopropyl palmitate (or, less commonly, isopropyl myristate), soy lecithin, water and Pluronic F127. It is not an organogel, a gel where the liquid component is organic rather than aqueous, as its name suggests, but consists of an oil phase (lecithin dissolved in isopropyl palmitate in a 1:1 ratio) and an aqueous phase (aqueous solution of 20–30 per cent Pluronic F127). Typically, the oil phase is present at 22 per cent v/v in PLO.[3] PLO is described by Marty Jones as an emulsion which looks and feels like a gel.[3] It has also been described as a cream[7] or, more commonly, simply referred to as a base in which drugs can be incorporated for topical application. Based on the greater aqueous component of the gel one could say that PLO is a hydrogel, though it is only rarely referred to as such.[7] The gel has not been thoroughly characterised and little is known about its physicochemical properties, such as its structure, rheology, stability, effect of drug incorporation on the gel, drug dissolution, solubility in the gel and the extent of drug permeation into and through the skin following topical application.

Method of preparation and drug incorporation

Preparing PLO The oil phase is prepared by mixing lecithin and isopropyl palmitate and allowing the mixture to stand overnight to ensure complete dissolution. The aqueous phase is prepared by adding Pluronic F127 to ice cold water, placing the mixture in a refrigerator and agitating periodically to ensure complete dissolution.[8] Sorbic acid at 0.2 per cent w/w is often added to the two phases as a preservative.[9] To prepare PLO, the oil phase is then mixed with the aqueous phase using a high-shear mixing method — for example, using two syringes, connected by a luer lock for small volumes or by using an electronic pestle and mortar.[3] It is important that the aqueous phase is cold before mixing because an aqueous solution of Pluronic F127 is in the liquid state at a low temperature and gels at a higher temperature.

Incorporating a drug in PLO Drugs may be incorporated within PLO either by dispersing the appropriate quantity of drug into preprepared PLO[10] or, more commonly, by dispersing the drug in either the oil phase or the aqueous phase, depending on

drug solubility, before mixing the two phases.[11,12] Dispersion of the drug in the aqueous phase or oil phase may be conducted by first dissolving the drug in a small quantity of water for a hydrophilic drug,[12] or by mixing the drug with propylene glycol for lipophilic drugs to form a paste,[8,9] which is then mixed with the appropriate aqueous or oil phase.

Drugs used with PLO

A wide range of drugs have been incorporated within PLO for transdermal delivery, examples of which are listed in Panel 1. The skin is, however, a good barrier to drug permeation and drug flux is known to be low. In fact, drug absorption following application to the skin is so low that only a few drugs have been formulated for transdermal delivery. An ideal drug for transdermal delivery is:[16]

- A potent chemical with a daily dose of a few milligrams (in man)
- A small molecule
- One that has a high lipid solubility and reasonable water solubility
- Non-irritating and non-sensitising to the skin

Some of the drugs listed in Panel 1 do not fulfil all the criteria for transdermal delivery. Obvious examples are the large molecular weight insulin, progesterone, which has a minimum daily dose of 200mg when used for premenstrual syndrome, and diltiazem, which has a total daily dose of 180mg. Some of the anecdotal evidence for the efficacy of PLO as a transdermal delivery vehicle with these drugs could therefore have been due to the placebo effect.

Clinical evidence for use

Only a handful of systematic studies have been conducted by clinicians and veterinarians to probe the efficacy of PLO as a transdermal delivery vehicle (see Table 1, p269). In some of these studies, the clinical effects of the drug were measured,[21] while in others, the plasma drug concentration was measured.[18–21] In addition, the efficacy of PLO was assessed following a single application in some studies[18–21] and after repeated applications in others.[17,22,23]

In cats The studies in healthy cats showed that following a single topical application of a drug (methimazole, fluoxetine, dexamethasone, amitriptyline or buspirone) 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.[18–21] On the other hand, the retrospective study in cats suffering from hyperthyroidism showed that repeated application of methimazole in PLO, over a period of weeks and months, led to the resolution of many clinical symptoms and to a reduction in total thyroxine levels.[17] It is possible that the latter results may be due to repeated application of the gel to the same skin site (pet owners were not advised to apply the gel to the same ear or to change sides), which could have resulted in irritation of the skin and enhanced drug absorption through the breached skin barrier. Substantial skin irritation after application of PLO for several days has also been reported.[19] It is also possible that the clinical effects observed were due to oral ingestion of the PLO during grooming.

In man The *in vivo* studies in man, where PLO was applied repeatedly, suggest that PLO may be beneficial as a delivery vehicle for local action.[22,23] In these studies, diclofenac in PLO was applied over a number of weeks for the treatment of osteoarthritis of the knee or for lateral epicondylitis. Following application of PLO, patients experienced less pain[22,23] and increased wrist extension strength.[23] However, drug levels in the blood were not measured and drug absorption into the systemic circulation cannot be assumed.

Panel 1: Drugs incorporated within PLO

Examples of drugs and combinations of drugs that have been incorporated within PLO include:

- Hormones such as estriol and estradiol, dehydroepiandrosterone, progesterone (for premenstrual dysphoric disorder[13–15]), testosterone
- Non-steroidal anti-inflammatory drugs such as ketoprofen, piroxicam, diclofenac
- Selective seretonin reuptake inhibitors such as fluoxetine, paroxetine
- Antipsychotic drugs, such as haloperidol, prochlorperazine
- Secretin
- Selegiline hydrochloride
- Levodopa
- Morphine
- Dexamethasone
- Calcium channel blockers such as diltiazem, nifedipine
- Humulin N insulin
- Clonidine with gabapentin and ketamine hydrochloride
- Cyclopenzaprine with lidocaine
- Methimazole (not available in UK)

This list is not exhaustive

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Table 1: Systematic studies of the efficacy of pluronic lecithin organogel

Drug	Experimental subjects	Study details	Results
Methimazole[21]	Cats suffering from hyperthyroidism; n=13	Retrospective evaluation of cats suffering from hyperthyroidism repeatedly treated with methimazole in PLO	All cats showed improvement, according to owners. Veterinarians reported resolution of clinical signs, eg, weight loss, inappetence (lack of desire), mental changes, vomiting, dry hair coat Significant decrease in total thyroxine between pre-treatment and during treatment values.
Methimazole[22]	Healthy cats; n=6	Triple crossover study to determine bioavailability of topically applied methimazole in PLO to cat pinna compared with intravenous and oral administrations, after a single dose	Generally, there was low to undetectable bioavailability of drug following topical application in PLO. One cat achieved nearly 100 per cent transdermal bioavailability compared with the oral route.
Fluoxetine[23]	Healthy cats; n=4	Parallel study involving three groups of four cats to determine bioavailability, pharmacokinetics and safety of transdermal delivery of fluoxetine (5mg/kg and 10mg/kg) in PLO, and oral fluoxetine following a single dose	Fluoxetine in PLO was absorbed to some extent following topical application. However, bioavailability of transdermal route was 10 per cent of that of oral route.
Dexamethasone[24]	Healthy cats; n=5	Cross-over study to compare serum concentrations of dexamethasone after a single oral or topical application in PLO to cat pinna	No clinically significant absorption of dexamethasone was observed following topical application. All values were below the detection limit of the assay.
Amitriptyline and buspirone[25]	Healthy cats; n=3	Cross-over study to compare absorption of amitriptyline and buspirone after a single oral or topical application in PLO to cat pinna	Plasma concentrations of amitriptyline were below the limit of quantification but above the limit of detection. Plasma concentratios of buspirone were below the limit of detection.
Diclofenac[26]	Patients suffering from osteoarthritis of the knee; n=74	Double-blind, randomised, placebo controlled, parallel-group design, two-week clinical trial to assess the efficacy and safety of topically applied diclofenac in PLO, three times daily for two weeks, to treat pain associated with mild to moderate arthritis of the knee	Patients experienced significantly less pain and stiffness when using diclofenac in PLO.
Diclofenac[27]	Patients suffering from lateral epicondylitis; n=14	Randomised, double-blind, cross-over study to determine effectiveness of diclofenac in PLO, applied three times daily for one week, as a treatment for lateral epicondylitis	Subjects experienced significantly less pain when using diclofenac in PLO. Average wrist extension strength was also significantly greater than before treatment.
Ondansetron[28]	Healthy men; n=12	To determine efficacy of PLO as a transdermal delivery vehicle for ondansetron. Capsaicin intradermally injected; 1 minute later ondansetron in PLO, single application, to the skin surrounding the injection. Pain, hyperalgesia and inflammatory flare were assessed four minutes later.	Application of PLO reduced pain, mechanical hyperalgesia and inflammatory flare induced by intradermally injected capsaicin in a dose-dependent manner.

In a third study, the efficacy of PLO as a transdermal delivery vehicle for ondansetron, following a single application, was evaluated in 12 healthy human volunteers.[24] Although the gel was reported to be a good vehicle for ondansetron, it is difficult to evaluate the benefits of PLO from this study as the preparation of PLO was not described and instead an inappropriate reference[25] was used to indicate the method of preparation. This same reference (which has results pertaining to the original lecithin organogel rather than to PLO) was again used inappropriately as a source which "proved" PLO gels to be efficient vehicles and which afforded local bioavailability.

Second generation lecithin organogels

In addition to the limited amount of systematic evidence for using PLO as a drug delivery vehicle, the lack of interest by pharmaceutical companies to market existing drugs within PLO is probably due to financial constraints as well as the industry focusing on areas such as biotechnology and genomics. However, the great interest in PLO in the US has led to the formulation of a second generation lecithin organogel, Premium lecithin organogel base, by Xenex Laboratories.[26] The advantages of the premium lecithin organogel compared to the original PLO are that it is claimed by Xenex to:

- Be non-greasy
- Be non-tacky
- Have improved stability to temperature

The pluronic component has also been removed, which is interesting because pluronic was initially added to the original lecithin organogel in order to stabilise it.

Like PLO, the new lecithin gel has not been investigated in depth by independent researchers. However, its development is an indication of the need for more efficacious, "off-the-shelf" bases that can be used to incorporate drugs for topical delivery.

Conclusion

The need for further research into PLO as a topical and transdermal drug delivery vehicle is starting to be met. PLO is currently being investigated by the author of this article, and by other researchers. There are a number of possible reasons for the gaps in our knowledge about PLO. They include:

- A lack of communication between pharmacy practitioners and academics
- An assumption by academics that PLO must have been studied already if it is available commercially and if practitioners are using it
- The fact that few academics are engaged in research on topical and transdermal formulations. Academics who are working on the skin as a route of administration are researching novel ways of breaching the skin barrier for systemic absorption of topically applied drugs rather than conventional formulations such as creams and rather than for topical drug delivery

To summarise, PLO characterisation is still needed. The few *in vivo* studies conducted have shown that a single topical application in cats did not lead to significant absorption of the drug into the systemic circulation, but repeated applications to the same skin site in man led to clinical effects. In practice, patients are normally advised to rotate skin sites when transdermal vehicles are applied to reduce the possibility of skin irritation. Thus further systematic *in vivo* studies where PLO is applied repeatedly to both the same and different skin sites are still needed as well as research to assess drug concentrations in the blood, disease progression and regression, and skin irritation.

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