

Pluronic F-127 and Pluronic Lecithin Organogel (PLO): Main Features and their Applications in Topical and Transdermal Administration of Drugs

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ABSTRACT - Topical drug treatment aims at providing high concentrations of drugs at the site of application so as to avoid adverse systemic effects associated with oral administration. Smart polymers, or stimuli-responsive polymers, are able to respond to a stimulus by showing physical or chemical changes in their behaviour as, for example, the delivery of the drug carried by them. The thermo-responsive nature of Pluronic® F-127 (BASF, Ludwigshafen, Germany) makes it an excellent candidate for the delivery of drugs at various application sites. In recent years, PF-127, and later, Pluronic lecithin organogels (PLO), have attracted particular interest in the design of dermal and transdermal delivery systems with a view to promoting, improving or retarding drug permeation through the skin, bearing in mind that for topical delivery systems, accumulation in the skin with minimal permeation is desired, while for systemic delivery, the opposite behaviour is preferred.

In this review, we discuss the properties and characteristics of PF-127 and Pluronic lecithin organogels (PLO), and present many examples and advantages of the application of these polymeric systems in topical and transdermal administration of drugs.

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INTRODUCTION

Smart polymers, or stimuli-responsive polymers, have been incorporated into the vanguard of drug administration technology as they demonstrate active responses to small changes in the surrounding environment (*physical stimulus* - temperature, ultrasound, light, mechanical stress; *chemical stimulus* - pH and ionic strength; *biological stimulus* - enzymes and biomolecules), which translate into physical or chemical reversible changes in their behaviour as, for example, the delivery of the drug carried by them (1-7).

The main advantages that the addition of smart polymers to drug molecules provide include the ability to administer an efficient concentration of a certain drug at the right time and location, a reduction in adverse systemic reactions, and an increase the patient's adherence to the therapeutic regimen, thereby also allowing a reduction in the drug dose and, consequently, the costs (8).

The development of *in situ* gel systems has received considerable attention over the past few years (9). It is well-known that gels are swollen networks possessing both the cohesive properties of solids, and the diffusive transport characteristics of liquids. Over the last few

decades, gels formed from natural, semisynthetic or synthetic polymers have been confirmed as vehicles for different types of pharmaceutical applications (10).

Generally, hydrogel bases can be easily washed off, but they adhere well to skin or mucous membranes or skin, wet with secreting fluid and thus these systems are usually applied to injured skin and also to eyes (10). The *in situ* gel-forming polymeric formulations offer several advantages such as sustained and prolonged action in comparison to conventional drug delivery systems. From a manufacturing point of view, the production of such devices is less complex and thus lowers the investment and manufacturing costs (9).

Block copolymers are widely used industrially in the solid and rubbery states. They are used as thermoplastic elastomers, with applications in impact modification and pressure sensitive adhesion (11). The use of hydrosoluble vehicles of high viscosity, such as hydrophilic gels, is one of many strategies to obtain a controlled delivery and represents an area very

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important in scientific research (12). Reversible gels refer to those that have the capacity to make, break, and modify the bonds responsible for holding the network together (11,13).

A series of amphiphilic block copolymers have been reported that have temperature-responsive micellisation behaviour and which form hydrogels when above a critical gelation temperature (14).

POLOXAMERS

General characteristics

Poloxamers are non-ionic polymers of polyoxyethylene-polyoxypropylene-polyoxyethylene (PEO_n-PPO_n-PEO_n), which have many pharmaceutical uses (Figure 1) (9,13,15–18). Block copolymers, based on PEO–PPO sequences (ABA-type triblock copolymers composed of PEO (A) and PPO units (B)), are a family of commercially available triblock copolymers which have the following trade names: Pluronics, Poloxamers or Tetronics (18–21).

Poloxamers, like other surfactants, when dispersed in the liquid, at low concentrations, exist individually as monomolecular micelles. But as the concentration of the poloxamer in the system increases, this results in the formation of multimolecular aggregates (22). Polypropylene oxide (PPO) forms central hydrophobic core wherein methyl groups interact via van der Waals forces with substance undergoing solubilisation. However, water solubility is believed to be due to the polyethylene oxide (PEO) block by hydrogen bonding interactions of ether oxygen with water molecules. Due to these interactions, Pluronics are readily soluble in non-polar organic solvents and established themselves in the formulation of dosage forms (23). Pluronics show different aggregate forms depending on the molecular

weight, block sizes, solvent composition, and temperature.

Aqueous solutions of Pluronics in the presence of acids, alkalis, and metal ions are very stable. The Pluronic triblock copolymers are available in various grades differing in molecular weights and physical forms. Depending upon the physical designation the grades are assigned, as F for flakes, P for paste, or L for liquid. The poloxamers normally used are: 188 (F-68), 237 (F-87), 338 (F-108) and 407 (F-127) (9).

These polymers are composed of white granules that are soluble in water and have no odor or taste. They present a sol-gel transition phase below or near the physiological body temperature and a gel-sol transition at around 50 °C in relatively highly concentrations (2,9,13,15,16,24–26).

Pluronics and Tetronics are used as thermoreversible gels with some examples having been approved by the FDA for applications which include as food additives, pharmaceutical ingredients and agricultural products, drug delivery carriers and in injectable systems for tissue engineering processes (19).

PLURONIC F-127

Characteristics and properties

Pluronic® F-127 (BASF, Ludwigshafen, Germany), also known as poloxamer 407 (P407), (copolymer polyoxyethylene₁₀₆-polyoxypropylene₇₀-polyoxyethylene₁₀₆) contains about 70% ethylene oxide, which contributes to its hydrophilicity (25). PF-127 is a copolymer with a weight of 12,000 daltons, a PEO/PPO ratio of 2:1, and is non-toxic, with low viscosity below 4 °C and which forms a semi-solid gel at body temperature (25–29). PF-127 is more soluble in cold water than in hot water due to the increased solvation and hydrogen linkages at low temperatures (2,11).

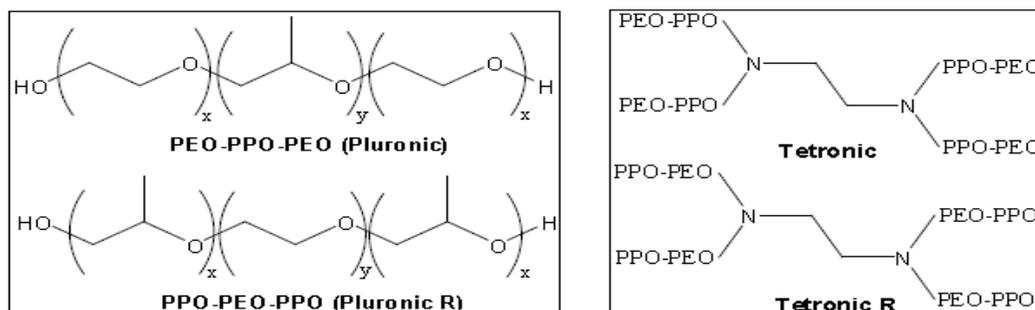


Figure 1. Schematic structure of polymers with amphiphilic balance (19).

The aqueous solutions of PF-127 at concentrations between 20–30% (m/m), reversibly turn into gels at a certain temperatures, i.e. they become more liquid at lower temperatures (4–5 °C) and turn into gels at body temperature (this transformation is reversible and thus solutions return to a liquid state at low temperatures) (11,13,16,25,27,28). This thermogelling results from interactions between the different molecules of Pluronic. The increase in temperature modifies the hydration spheres around the hydrophobic units, which in turn induces higher interactions between these different units (2,30).

In other words, with the increase in temperature of a PF-127 aqueous solution, the PPO block tends to dehydrate and form a core with an outer shell of hydrated PEO chains that aggregate into spherical micelles. The micellar structure of this copolymer in an aqueous environment can be used for incorporation of hydrophilic and hydrophobic drugs, and prolongs drug release (21,29). This characteristic, in addition its low toxicity, biocompatibility with cells and body fluids, and weak immunogenic properties, means PF-127 is a commonly used polymer in drug delivery systems (10,13,15,24,25,29,31).

Rheological characteristics

The gelation temperature of a polymer depends on polymer composition and solution concentration (19,32). Studies have also shown that the drug diffusion coefficient in the gel decreases as PF-127 content increases, coinciding with an increase in gel viscosity. This led the authors to propose that drug release rates are determined by gel viscosity (33). The drug delivery from polymer PF-127 occurs by diffusion and dissolution through the gel that is formed on the area where it was administrated (33). PF-127, at low percentages, has a complete dissolution in water in 4 hours and this feature can be used to prepare pharmaceutical formulas that act in short timespans after administration (short-term therapy). Ricci *et al.* (17) meanwhile showed that the diffusion coefficient of a drug decreases when the concentration of this polymer is increased. A 25–40% aqueous solution of this material will therefore form a gel at body temperature, and drug release from such a gel occurs over a period of up to one week (9). These authors thus also concluded that the time of dissolution increases when drug diffusion through the gel matrix is decreased.

There is therefore a relationship between viscosity and temperature in these gels, with the slope dependent upon PF-127 concentration. This phenomenon was explained on the basis of a previously reported observation that PF-127 micelles in aqueous solution undergo a thermally-induced swelling and desolvation (11).

It was reported by many researchers that various salts, surfactants, polymers, cosolvents and other additives added have marked effects on micellisation, clouding, and solubilisation behaviour of Pluronic solutions. Since almost all pharmaceutical PF-127 gels are formulated with buffer salts, and may contain the salt form of a drug, some authors felt it was important to further investigate the effect of common inorganic salts on these transition temperatures (34). Appropriate salts could potentially be used to tailor the temperatures at which these transitions in PF-127 gels occur, in order to design unique thermoresponsive drug delivery systems. The alteration of these transition temperatures however may also influence the diffusion of the drug in the gel and, hence, release rates (34).

Pandit and Kisaka (34) concluded in their studies that all salts studied (NaCl, Na₂SO₄, Na₃PO₄, CaCl₂, MgSO₄ and Al₂(SO₄)₃) lower the transition temperature. The degree of lowering is proportional to salt concentration, and can be ascribed to salting-out effects. This behaviour parallels the effect of these salts on the temperature-solubility behaviour of aqueous poly(oxyethylene) solutions. The release rate and diffusion coefficient of the drug tested (propranolol) was significantly reduced when NaCl, Na₂SO₄, NaH₂PO₄, MgSO₄ and CaCl₂ were added to the gels (the magnitude of the effect on release rate depends on the nature and concentration of the salt) (35).

With the same objective, Ricci *et al.* (17) showed that the incorporation of organic solvents or salts (sodium chloride or PEG 400 – hydrophilic substances) changes the sol-gel transition temperature of PF-127, increasing also the drug delivery rate (lidocaine hydrochloride). In addition, gel viscosity can be increased by raising the polymer concentration, and hydrophilicity can be increased by adding salts (the presence of NaCl or PEG 400 increases drug release rates). Thus, PF-127 can be used to increase the duration of action of lidocaine, increasing the drug efficiency and decreasing the side effects (17). The viscosity of PF-127 gel in water was slightly lower than in presence of sodium chloride.

The addition of isotonic agents (examples: mannitol, sorbitol and sodium chloride) or

viscosity enhancing agents (examples: hydroxypropylmethyl cellulose, methyl cellulose, carboxymethylcellulose sodium) promotes the increase in viscosity of PF-127 formulations and contributes to the decreased rate of drug release (30).

On the other hand, we know that the gelation temperature of a specific polymeric system is determined by the hydrophilic-hydrophobic balance existing in the polymer (32). This balance can be modulated by incorporating different side chains with hydrophilic or hydrophobic segments. By grafting poly(acrylic acid) (PAA) onto the poloxamer backbone in a one-step reaction via radical polymerisation of acrylic acid (AA) in the presence of poloxamer, the sol-gel transition occurs at a lower concentration than for poloxamer alone as PAA forms physical crosslinking points at low concentrations. The graft copolymer of poloxamers with PAA has several advantages; thermally reversible gelling behaviour over a wide pH range, no phase separation, and bioadhesive properties, all combined in a single molecule (14). In the case of injection of poloxamer into the body, the hydrogel structure of this polymer was eroded from its surface into soluble unimers within one day. More durable and biocompatible block copolymers that undergo micelle aggregation and packing were obtained when the PPO block was replaced with poly(L-lactic acid) and more recently with poly(DL-lactic acid-co-glycolic acid) (PLGA), which contains a biodegradable ester group in its backbone (14).

Anti-inflammatory drugs like indomethacin and naproxen, which are hydrophobic, cause a decrease in micellar size. These drugs also cause decreases in aggregation numbers leading to decreases in the number of micelles (36).

Enhancement of mucosal absorption

There are some drugs, like peptides and proteins, that are very difficult to deliver by conventional methods through the skin because they are polar, charged or have a large molecular weight. In addition, unlike most small drug molecules, some drugs and peptides do not cross the mucosal membrane efficiently. This low mucosal absorption can be attributed to poor membrane permeability due to molecular size, lack of lipophilicity, or enzymatic degradation (9). To overcome these problems, one of the most frequently used approaches is the use of absorption enhancers. These act by one, or a combination, of the following mechanisms: alteration of properties of the mucosal layer,

opening of tight junctions between epithelial cells, reverse micelle formation between membranes, and by increasing the membrane fluidity.

However, the use of enhancing-transport technology, such as iontophoresis, in combination with chemical enhancers provides the opportunity to deliver these kinds of drugs through the skin by increasing permeation (11). Various types of penetration enhancers have been evaluated for organic drugs including surfactants, bile salts, chelators, fatty acid salts, phospholipids, glycyrrhetic acid derivatives, cyclodextrins and glycols (9,37,38).

Morishita *et al.* (39) studied the influence of the addition of the unsaturated fatty acids (such as oleic acid (18:1), eicosapentaenoic acid (20:5) or docosahexaenoic acid (22:6)) on the spreadability and hypoglycemic effect of insulin following buccal administration of the gel formulations in normal rats. All the formulations with unsaturated fatty acids exhibited significantly lower spreadability than the control PF-127 formulation. The increase in the viscosity might have therefore contributed to the decrease in insulin release seen.

Bentley *et al.* (40) concluded in their studies that the presence of lecithin in a poloxamer gel improved the characteristics for topical drug delivery. The addition of lecithin (a permeation enhancer) increased the thixotropy, apparent viscosity and the gelation temperature of the gels. The presence of lecithin in PF-127 gels however decreased the flux of a lipophilic drug through the skin, increasing its skin retention.

Abdel-Mottaleb *et al.* (10) studied the topical administration of fluconazole in PF-127 gels with addition of different additives. The additives used were PEG 400, glycerol, tween 80 and cetrimide. Only the formulations with PEG 400 or glycerol increased the viscosity of the product. Tween 80 and cetrimide, on the other hand, caused a significant decrease in the gel viscosity. All the additives however produced a significant enhancement in the release of fluconazole in comparison with the additive free base, with the highest release being obtained from the formula containing glycerol.

Gonjari *et al.* (41) showed that the addition of penetration enhancers (sodium glycocholate, EDTA or transcutol) in transnasal formulations of PF-127 increased the nasal absorption of sumatriptan succinate. It was also shown that such absorption enhancers increased the gelation temperature of the PF-127 base.

Fitzgerald *et al.* (42) demonstrated that the combination of glycerol and PF-127 produced additive enhancements in naproxen accumulation inside SCC-25 cells (derived from oral mucosa).

Compared with untreated control cells, naproxen content was 74% higher in cells treated with 5% glycerol and 0.05% PF-127. Individually, 5% glycerol and 0.05% PF-127 produced enhancements of approximately 48% and 21%, respectively. PF-127 enhances the solubilisation and cell permeability of lipophilic drugs, and is also capable of altering the properties of the plasma membrane.

These gels however, possess poor bioadhesiveness and high permeability to water, which limited their application as a thermoresponsive matrix. To resolve this problem, Yuan *et al.* (43) developed a thermosensitive and mucoadhesive rectal *in situ* gel of nimesulide (NM) by using mucoadhesive polymers such as sodium alginate (Alg-Na) and HPMC. These gels were prepared by addition of mucoadhesive polymers (0.5%) to the formulations of thermosensitive gelling solution containing PF-127 (18%) and nimesulide (2%). Polyethylene glycol (PEG) was used to modify gelation temperature and drug release properties. Gelation temperature was significantly increased with incorporation of nimesulide (2%) in the poloxamer solution, while the addition of the mucoadhesive polymers played an opposite role on gelation temperature. The addition of PEG polymers increased the gelation temperature and the drug release rate.

Nirmal *et al.* (9) used PF-127 as an *in situ* gel-forming polymer together with mucoadhesive polymers such as Carbopol 934 and hydroxylpropylmethylcellulose to ensure long residence time at the application site. With the same objective, Shin *et al.* (44) used two polymers, Carbopol 934 and PF-127 with different enhancer bile salts, glycols and non-ionic surfactants (examples: sodium cholate, sodium taurodeoxycholate, sodium deoxycholate, tetraethylene glycol, diethylene glycol, polyoxyethylene 2-stearyl ether, polyoxyethylene 23-lauryl ether, polyoxyethylene 2-oleyl ether) to enhance permeation of triamcinolone acetonide through buccal mucosa. Among the enhancers used, sodium deoxycholate showed the best enhancement effects.

Applications of PF-127 gels in pharmaceutical formulations

PF-127 (poloxamer 407) can be used as a carrier for several routes of administration, including

oral, subcutaneous, intranasal, vaginal, rectal, ocular and parenteral (13,45). In the last few years, PF-127 has also had an important role in dermal and transdermal drug delivery systems (13,31).

Some studies have been carried out to test incorporation of PF-127 in short-term therapies such as, for example, fertility control, pain management and infections treatment (46). This kind of polymer has been already tested for external uses (local and sustained delivery) of anticancer and anti-inflammatory drugs (19,31,46). It has been also tested in ophthalmology using pilocarpine (2,11). There have been reported studies related to parenteral formulations (intramuscular and subcutaneous) with interleukin-2 and antibiotics (17). In this same manner, this poloxamer has been successfully tested to carry peptides and proteins (insulin, urease and growth factors), presenting a sustained delivery profile for several hours (26,45).

Topical and dermal applications

Topical drug treatment aims at providing high concentrations of the drug at the site of application so as to avoid adverse systemic effects associated with oral administration of the drug (47). The delivery of drugs onto the skin, for example, is recognised as an effective means of therapy for local dermatologic diseases (10).

In recent years PF-127 has attracted particular interest in the design of dermal and transdermal delivery systems, with a view to promoting, improving or retarding drug permeation through the skin, bearing in mind that for topical delivery systems, accumulation in the skin with minimal permeation is desired, while for systemic delivery, the opposite behaviour is preferred (11,15). In particular, focus has been on the development of topical/dermal formulations containing analgesic or anti-inflammatory drugs due to the fact that the potential for the delivery of these drugs through the skin, for local pain and inflammations at low doses, is attractive. However, in many cases penetration enhancers may also have to be included in the topical/dermal formulations as otherwise only small amounts of drug pass through the skin (11).

Table 1 shows some of the many examples of the use of PF-127 in pharmaceutical systems over time.

Table 1. Examples of the use of Pluronic F-127 (PF-127) in pharmaceutical systems.

Pharmaceutical Formulations	Results	References
Topical administration of anticancer agents (5-fluorouracil and adriamycin) formulated in PF-127 gels.	With increasing concentrations of PF-127 in the vehicle, a corresponding decrease in the apparent release rate of the anticancer agent occurred. The apparent release rate increased with increasing temperature from 30 to 44 °C.	(48)
Percutaneous administration of indomethacin using a rat model.	PF-127 is a good vehicle for percutaneous absorption. The addition of isopropyl myristate or (+) - limonene improved percutaneous absorption (particularly when the gel was applied using an occlusive dressing technique).	(49)
Transdermal gel comprised of ketoprofen; PF-127; and one or more agents selected from: ethyl alcohol, isopropyl alcohol, propylene glycol, polyethylene glycol and glycerin; as well as one or more agents selected from the group of: lauric acid, oleic acid, capric acid, myristic acid, lauryl alcohol and menthol; plus either water or a buffer solution.	The gels possess prolonged anti-inflammatory and analgesic activities, and physicochemical stability, with fewer systemic side effects and gastric irritation, compared to oral administration.	(50)
Percutaneous administration of fentanyl formulated in PF-127 gels (<i>in vitro</i> and <i>in vivo</i> studies).	PF-127 has the potential to increase the therapeutic efficacy of fentanyl citrate or other lipophilic drugs by prolonging percutaneous input into the systemic circulation of rabbits.	(51)
The effects of PF-127 on the permeability of several weak acids and bases through bilayer lipid membranes.	PF-127 facilitated the permeation of comparatively large molecules (such as 2-n-undecylmalonic acid and doxorubicin) across lipid bilayers, while the permeation of small solutes (such as ammonium and acetic acid) remained unaffected. Pluronics also accelerate the translocation of large hydrophobic anions (tetraphenylborate).	(52)
PF-127 hydrogels with piroxicam, and the effects of different non-ionic surfactants as permeation enhancers of the skin (polyoxyethylene-23-lauryl ether, polyoxyethylene-2-oleyl ether and polyoxyethylene-2-stearyl ether).	Poloxamer gels containing piroxicam, and including surfactants as enhancers, are good preparations to promote the percutaneous absorption of drugs. The different non-ionic surfactants give rise to increases in the permeation of the skin. Among the various non-ionic surfactants tested, polyoxyethylene-2-oleyl ether showed the highest enhancement effects.	(53,54)
PF-127 hydrogels with capsaicin and nonivamide (<i>in vitro</i> and <i>in vivo</i> studies).	The incorporation of PF-127 polymer into hydrogels resulted in a retarded release of capsaicin. The <i>in vitro</i> permeation of capsaicin from hydrogels depends on the physicochemical nature and the concentration of the polymer used. The permeation of nonivamide was retarded in later stages of <i>in vitro</i> application.	(55)
<i>In vitro</i> percutaneous absorption of nonivamide from gels of various polymers (PF-127, chitosan and carboxymethylcellulose)	The incorporation of PF-127 polymer into hydrogels resulted in retarded release of nonivamide. Chitosan and carboxymethylcellulose hydrogels produced higher levels of <i>in vitro</i> nonivamide permeation and skin distribution. The <i>in vivo</i> effects of nonivamide on skin perturbation and vasodilation were found to differ depending on dose and duration after topical	(56)

- using Wistar rat as an animal model. application.
- PF-127 gel formulated with ceftiofur. PF-127 (25–35% w/v) was tested alone or with polyvinyl pyrrolidone (PVP), carboxymethylcellulose (CMC), or hydroxypropyl methylcellulose (HPMC) as an additive. The release of ceftiofur is controlled by dissolution of PF-127. An increase in PF-127 content from 25 to 35% resulted in a decrease in the rate of ceftiofur release. PVP, CMC, and HPMC in the gel decreased the rate of release of ceftiofur to some extent. (57)
- PF-127 gel formulated with indomethacin (hexylene glycol (HG) or polyethylene glycol 300 (PEG) as solvents). Tween 80 and PVP were added as excipients. Results indicate that the excipients influence the physical characteristics of the gels. The optimum concentration for gels manifesting as strength of gel was 20% PEG in combination with 1% PVP, which had the highest viscosity and yield value at a low shear rate. Increasing the amount of HG or PEG gave a more viscous gel, with the exception of the 24% w/w HG gels which turned a jelly with or without either Tween or PVP. (58)
- PF-127 gel formulated with insulin (*ex vivo* and *in vivo* skin permeation in rats with chemical enhancer and/or iontophoresis). Linoleic acid and menthone, in combination with iontophoresis, showed a synergistic enhancement of insulin permeation. Iontophoresis, either alone or in combination with linoleic acid, produced a reduction in PGL (plasma glucose levels) to the extent of 36–40%. (59)
- Transdermal timolol delivery from a PF-127 gel. PF-127 gel and an artificial membrane are used to regulate the timolol delivery through pig stratum corneum. At low PF-127 concentrations and for large pore-size membranes (Polyflux, PES-30), the stratum corneum mainly controls timolol delivery. At high PF-127 concentrations and for small pore-size membranes (NF-PES-10), the contribution of the device (gel plus artificial membrane) to the timolol delivery is significant. (60)
- PF-127 and hydroxypropyl methylcellulose (HPMC) formulated with pranoprofen. To increase drug permeation, several types of penetration enhancers such as ethylene glycols, propylene glycols, glycerides, non-ionic surfactants, and fatty acids, were incorporated in the gel formulation. Among the various enhancers used, propylene glycol monolaurate showed the highest enhancement effects. The results of this study suggest that development of a topical gel formulation of pranoprofen with an enhancer is feasible. (61)
- Preparation and evaluation of pranoprofen gel for percutaneous administration. Various penetration enhancers, such as non-ionic surfactants and fatty acids, were incorporated into the gel formulation in an attempt to increase the level of drug permeation. Among the enhancers used, octanoic acid had the strongest enhancement effects. Pranoprofen gel containing octanoic acid as an enhancer, reduced oedema size by approximately 73% compared to that of the control group. (38)
- Transdermal honokiol formulation based on PF-127 copolymer. Honokiol was loaded into PF-127 micelles. This system could have great potential applications for transdermal delivery of hydrophobic drugs such as honokiol. (62)
- In vitro* release of piroxicam in microemulsion formulations from different pharmaceutical topical preparations including. The results showed that incorporation of piroxicam in microemulsion formulas could lead to enhancement of piroxicam release profiles by promoting constant and regular *in vitro* release. Considering the *in vitro* release results, rheological properties and shelf life, a HPMC gel base containing 0.5% piroxicam in a microemulsion (63)

different gel bases such as, methyl cellulose, carboxy methyl cellulose, hydroxypropyl methyl cellulose, Carbopol 934, Carbopol 940, and PF-127 bases.	formula was the optimal preparation among the studied formulations.	
PF-127 gel formulated with terbinafine HCl	PF-127-based thermogelling formulation shows, to some extent, advantages as a vehicle for topical administration of terbinafine.	(31)
Alginate and PF-127 used to design thermogels by either physical blending (A+P) or chemical grafting (AP).	The porosity of the A+P structure was greater compared to that of the AP structure. The results of skin permeation, across porcine skin and nude mouse skin, suggested that these thermogels could produce sustained selegiline release, with AP showing the most-sustained permeation. AP hydrogels exhibited linear permeation properties in transdermal delivery of selegiline.	(64)
Poloxamer/chitosan as vehicles for enhanced corneal permeation and sustained release of fluconazole.	The <i>in vitro</i> release studies showed sustained release of fluconazole from the poloxamer/chitosan formulation. The chitosan solutions alone showed the greatest <i>ex vivo</i> drug permeation; however, the poloxamer/chitosan formulation presented a similar <i>in vivo</i> performance to a chitosan solution at 1.0%.	(65)
PF-127 gel formulated with Ceragenin CSA-13 (synthetic mimic of cationic antibacterial peptides).	In the presence of PF-127, CSA-13 haemolytic activity was greatly reduced. PF-127 decreases the haemolytic, but not antibacterial, activity of CSA-13.	(29)
Topical HDL administration using 20% PF-127 gel (applied on the adventitial side of vein grafts).	Topical HDL administration on the adventitial side of vein grafts attenuates vein-graft atherosclerosis via increased incorporation of circulating progenitor cells in the endothelium, enhanced endothelial regeneration, and reduced intimal inflammation.	(28)

PLURONIC LECITHIN ORGANOGEL (PLO)

A hydrophilic gel is designated as a hydrogel or organogel depending on the nature of the liquid component: water in hydrogels and an organic solvent in organogels (66,67). Organogels are a vehicle base for the delivery of drugs through dermal and transdermal routes (67,68).

Pluronic lecithin organogel (PLO) 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 (lecithin gels slightly disorganise the structure of the skin, and thus permit the permeation of various substances) (66–69). It is a thermodynamically stable, viscoelastic, and biocompatible gel composed of phospholipids (lecithin), an organic solvent, and a polar solvent (66,68,70–72).

A PLO is an opaque, yellow preparation, composed of isopropyl palmitate (or, less commonly, isopropyl myristate), soya lecithin (a

permeation enhancer as it increases the fluidity of the stratum corneum - it is used as dispersing, emulsifying, and stabilising agent), water (acts as a stabilising and structure-forming agent in the process of PLO formation - it is also used for solubilising the PF-127 and polar drugs) and PF-127 (72–74).

PLO consists of an oil phase (lecithin dissolved in isopropyl palmitate in a 1:1 ratio) and an aqueous phase (aqueous solution of 20–30% of PF-127). The oil phase is prepared by mixing lecithin and isopropyl palmitate or isopropyl myristate (acts as a non-oleaginous emollient with very good spreading ability and also used for solubilising the lecithin) and allowing the mixture to stand overnight to ensure complete dissolution (72,75). The aqueous phase is prepared by adding PF-127 to ice-cold water, placing the mixture in a refrigerator and agitating periodically to ensure complete dissolution. Sorbic acid at 0.2% (w/w) or potassium sorbate is often added to the two phases as preservatives. The oil phase is then mixed with the aqueous phase (chilled before mixing) using a high-shear mixing method (75).

An important aspect is that the drug may be incorporated within PLO by either dispersing into prepared PLO or, more commonly, by dispersing in either the oil phase or the aqueous phase, depending on drug solubility, before mixing of the two phases. If the drug is lipophilic it is usually mixed with propylene glycol to form a paste, which is then mixed with the aqueous or oily phase (75).

Studies show that the increase in concentration of lecithin decreases the cumulative percentage of drug released, which might be due to the extensive formation of a network-like structure with very high viscosity (47).

Applications of PLO in pharmaceutical formulations

There are several drugs, or combination of drugs, that have been incorporated within PLO. Some examples are: hormones (estriol, estradiol, dehydroepiandrosterone, progesterone, testosterone), non-steroidal anti-inflammatory drugs (ketoprofen, piroxicam, diclofenac), selective serotonin reuptake inhibitors (fluoxetine, paroxetine), antipsychotic drugs (haloperidol, prochlorperazine), secretin, selegiline hydrochloride, levodopa, morphine,

dexamethasone, calcium channel blockers (diltiazem, nifedipine), Humulin N insulin, clonidine with gabapentin and ketamine hydrochloride, cyclopropazine with lidocaine, and methimazole (67,68,71,74–78).

Topical and dermal applications

The coexistence of organic and aqueous phases by means of a structurally well-defined micellar network of phospholipids, a large interfacial area, and the possibility to entrap solutes within the gel matrix, along with long-term stability, makes PLO gels useful for a variety of applications. The organised microstructural matrix, amphiphilicity, supersolubilising capacity and interaction of the biolipids with skin tissues, are some of the major promoting factors for an enhanced transport of drug molecules into or across the skin (74).

In vivo studies suggested that PLO gels were a good delivery vehicle for local action. PLO gels show excellent drug permeability by diffusion through the lipid intracellular matrix and by slight disorganisation of skin (70,79).

Table 2 shows many examples of the use of Pluronic lecithin organogels (PLO) in pharmaceutical systems over time.

Table 2. Examples of the use of Pluronic lecithin organogels (PLO) in pharmaceutical systems.

Pharmaceutical Formulations	Results	References
Ketoprofen in PLO gel.	Administration of ketoprofen in PLO gel offered convenience, produced fewer side effects, and alleviated pain in a specific location.	(80)
Topical formulation of 2% diclofenac in PLO in the treatment of chronic lateral epicondylitis.	When subjects used diclofenac PLO, pain was significantly less than that during the pre-treatment, wash-out, or placebo PLO periods. Topical 2% diclofenac in PLO appears to provide effective short-term reduction in elbow pain and wrist extensor weakness associated with chronic lateral epicondylitis.	(81)
Topical formulation of the 5-HT ₃ receptor antagonist ondansetron in PLO.	Application of PLO reduced the pain, mechanical hyperalgesia and inflammatory flare induced by intradermally injected capsaicin in a dose-dependent manner. Attenuation of nociceptive and inflammatory effects of intradermally injected capsaicin.	(82)
PLO formulated with ketamine.	Developed a PLO gel with ketamine, that when applied directly to the site of pain alleviates the sympathetic or neuropathic pain, while also avoiding the side effects associated with the drug.	(83)
Topical formulation of 2% diclofenac in PLO in the treatment of pain associated with mild to moderate osteoarthritis of the knee.	Topical formulation of 2% diclofenac in a PLO appears to have therapeutic value in patients with mild to moderate osteoarthritis of the knee. Patients experienced significantly less pain and stiffness when using diclofenac in PLO.	(84)

- Efficacy of PLO gels for topical use of local anaesthetics and nonsteroidal anti-inflammatory drugs (NSAIDs). It is inferred that for those orofacial disorders that are regional, near the surface, and chronic, PLOs are more advantageous over systemic administration of drugs because of the rapid onset of action with a low side-effect profile. (85)
- Transdermal formulation of testosterone in a PLO gel. The formulation of testosterone has been successfully prepared by incorporating the therapeutically effective amounts of micronised testosterone in a PLO gel. Plasma concentrations of testosterone increased after 20–30 days and reached an apparent steady state during the administration period. (86)
- In vivo* study of a single topical dose of ketoprofen 20% in a PLO. The relative bioavailability of ketoprofen was low and highly variable when the drug was administered as a single dose in a PLO-based ketoprofen 20% gel. (87)
- In vivo* study to determine the bioavailability of promethazine in a topical PLO. The topical promethazine, when applied in a PLO, was absorbed systemically and had serum concentrations much lower than after parenteral administration, with an absolute bioavailability of 2%. (88)
- PLO as a base for the delivery of bioactive polyunsaturated fatty acids from fish oil, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and ketoprofen. PLO was adapted to contain fish oil, ketoprofen, or both, with 1,8-cineole as penetration enhancer, and used to determine the *in vitro* permeation from infinite and finite dosing protocols across full-thickness porcine skin. A PLO-based gel is capable of delivering EPA and DHA via a repeat finite dosing regimen, although there is evidence for the retention of these very lipophilic molecules within the gel matrix. Although to a lesser extent than EPA and DHA, ketoprofen was also substantially retained. (89)
- In vivo* study using 1 mL of morphine compounded at 10 mg/mL in PLO (randomised, placebo-controlled, double-blind, crossover study of five volunteers). As morphine was seldom detected in plasma samples after topical administration and was unquantifiable when it was, the bioavailability of topical morphine was unquantifiable. The results suggest that topical administration of morphine compounded in a PLO base for transdermal drug delivery is unlikely to provide relief of cancer-related pain. (90)
- Topical formulation of ketamine hydrochloride (10%) in PLO. In several patients, ketamine treatment of the symptomatic limb inhibited allodynia due to brushing the ipsilateral forehead, suggesting that the mechanism that mediates allodynia in the symptomatic limb contributed to allodynia at more remote sites. The shows promise for the use of topical ketamine as opposed to parenteral and oral forms which often result in undesirable side effects. (69)
- Preparation, characterisation, and *in vitro* release of a topical formulation of methimazole in PLO. Studies of release *in vitro* were carried out showing that the selected excipients do not pose an obstacle to the cession of methimazole. (91)
- PLO formulated with flurbiprofen (prepared using PF-127, lecithin, flurbiprofen, isopropyl palmitate, water, sorbic acid, and potassium sorbate). Stability studies and freeze–thaw thermal cyclic tests were carried out, showing no phase separation of gel, and thus good gel stability. The formulation showed a statistically significant anti-inflammatory activity and is a non-irritant to the skin. (92)
- In vivo* study using methadone (MTD) in PLO applied topically. The objective of this study was to compare serum MTD levels achieved after topical and oral administration to The topical application of an MTD-PLO gel in doses <45 mg/day did not result in trough MTD serum concentrations associated with analgesia. An observer placebo response may explain the perceived benefit of MTD applied topically as a PLO gel in doses <45 (93)

hospice patients.

mg/day. The evaluation of systemic absorption of MTD-PLO gel in doses >45 mg/day is warranted.

In vivo study using lorazepam, diphenhydramine, and haloperidol (ABH) in PLO applied topically.

No lorazepam or haloperidol was detected in any sample from any of the 10 volunteers down to a level of 0.05 ng/mL.

Diphenhydramine was found in multiple plasma samples at concentrations >0.05 ng/mL in three patients, with the highest concentration of 0.30 ng/mL in one person at 240 minutes.

Overall, five out of ten patients exhibited detectable diphenhydramine in one or more samples, supporting limited absorption.

(94)

As commonly used, none of the lorazepam, haloperidol, or diphenhydramine in ABH gel is absorbed in sufficient quantities to be effective in the treatment of nausea and vomiting.

CONCLUSIONS

PF-127 and PLO gels present unique characteristics including their gelation behaviour and micellar properties. These characteristics make these polymers excellent carriers with the ability to administer an efficient concentration of drugs at the right time and location, reducing the adverse systemic reactions and increasing the patient's adherence to the therapeutic regimen, thereby also allowing for a reduction in the drug dose and, consequently, the costs.

These polymeric systems have the advantage of being thermodynamically stable, viscoelastic, biocompatible, and have specific and localised actions, thus increasing the potential effectiveness of the drugs.

PF-127 and PLO gels appear to be effective alternative vehicles for delivering drugs through topical and transdermal routes as these systems exhibit excellent drug permeability via diffusion through the lipid intracellular matrix and by slight disorganisation of skin.

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