Applications of thermo-reversible pluronic F-127 gels in pharmaceutical formulations

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APPLICATIONS OF THERMO-REVERSIBLE PLURONIC F-127 GELS IN PHARMACEUTICAL FORMULATIONS

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ABSTRACT. It is, sometimes, desirable to maintain a constant plasma drug concentration within the therapeutically effective concentration range. The use of high viscosity hydromiscible vehicles such as hydrophilic gels, is one of various approaches for controlled drug delivery, and represents an important area of pharmaceutical research and development. Of these systems, Pluronic F-127 (PF-127) provides the pharmacist with an excellent drug delivery system for a number of routes of administration and is compatible with many different substances. Gels containing penetration enhancers have proven to be especially popular for administering anti-inflammatory medications since they are relatively easy to prepare and very efficacious.

INTRODUCTION

It is well known that gels are swollen networks possessing both the cohesive properties of solids, and the diffusive transport characteristics of liquids. 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 (1). They are porous solids and tend to be soft elastically, and osmotically reactive (2). Reversible gels refer to those that have the capacity to make, break, and modify the bonds responsible for holding the network together. Gels that do not have this capability because they are held together by covalent bonds are termed permanent gels.

Pluronic F-127 (Poloxamer 407, PF-127) is a thermoreversible gel (3-6). This characteristic has allowed PF-127 to be used as a carrier for most routes of administration including oral, topical (7,8), intranasal (9), vaginal, rectal (10-12), ocular (13-20), and parenteral routes (21). The potential use of PF-127 as an artificial skin has also been reported (3).

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 behavior is preferred.

Classification of gels

Gels or jellies are semisolid systems consisting of suspensions of small inorganic particles or large organic molecules interpenetrated by a liquid. Gels are generally classified as a two-phase system, if the particle size of the dispersed phase is large; or as single phase gels, when the organic macromolecules are uniformly distributed throughout a liquid such that no apparent boundaries exist between the dispersed macromolecules and the liquid (22).

As shown in Table 1, PF-127 is included in the group of hydrogels. One of the main characteristics of hydrogels is that they contain ingredients that are dispersible as colloids or are water-soluble.

Characteristics and properties of poloxamer 407 (pluronic F-127)

Poloxamer 407 (PF-127) is a nonionic surfactant composed of polyoxyethylene-polyoxypropylene copolymers in a concentration ranging from 20-30%. In general, poloxamers are composed of white, waxy, free-flowing granules that are practically odorless and tasteless (23).

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Table 1. General classification and description of gels. From reference 23 with permission.

Class	Description	Examples
Inorganic	Usually two-phase systems	Aluminum hydroxide gel; bentonite magma
Organic	Usually single phase systems	Carbopol®; tragacanth
Organogels	Hydrocarbon type Animal/vegetable fats Soap bases greases Hydrophilic	Petrolatum lard, cocoa butter aluminum stearate Carbowax®
Hydrogels	Organic hydrogels Natural & synthetic gums Inorganic hydrogels	Pectin paste methylcellulose, Sodium CMC, PF-127® bentonite gel, Veegum®

At low concentrations (10^{-4}–10^{-5} %) they form monomolecular micelles, but higher concentrations result in multimolecular aggregates consisting of a hydrophobic central core with their hydrophilic polyoxyethylene chains facing the external medium (24).

Micellization occurs in dilute solutions of block copolymers in selected solvents above the critical micellar concentration, at a given temperature. At higher concentrations, above a critical gel concentration, the micelles can order into a lattice. These scenarios are illustrated in Figure 1.

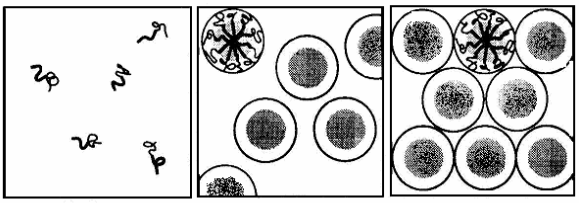

Figure. 1. Illustration of the critical micelle concentration (cmc) and critical gel concentration (cgc) in a block copolymer solution. From reference 1 with permission.

Aqueous solutions of poloxamers are stable in the presence of acids, alkalis, and metal ions. Commonly used poloxamers include the 188 (F-68 grade), 237 (F-87 grade), 338 (F-108 grade) and 407 (F-127 grade) types, which are freely soluble in water. The "F" designation refers to the flake form of the product. PF-127 has a good solubilizing capacity, low toxicity and is, therefore, considered a good medium for drug delivery systems.

PF-127 is a commercially available polyoxyethylene-polyoxypropylene triblock copolymer of general formula E_{106} P_{70} $E_{106,}$ with an average molar mass of 13,000 (25,26). It contains approximately 70% ethylene oxide, which accounts for its hydrophilicity (27-29). It is one of the series of poloxamer ABA block copolymers, whose members share the chemical formula shown in Figure 2.

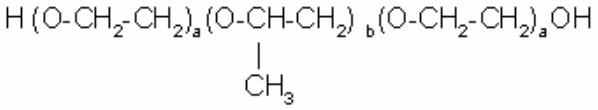

Figure 2. Chemical structure of Pluronic F-127 (a, ethylene oxide portion b, propylene oxide portion).

The polymers are produced by condensation of ethylene oxide and propylene oxide (30). PF-127 is more soluble in cold water than in hot water as a result of increased solvation and hydrogen bonding at lower temperatures (4). PF-127 aqueous solutions of 20 to 30% w/w have the interesting characteristic of reverse thermal gelation (5,31), i.e., they are liquid at refrigerated temperatures (4-5°C), but gel upon warming to room temperature. The gelation is reversible upon cooling (32).

At low temperatures in aqueous solutions, a hydration layer surrounds PF-127 molecules. However, when the temperature is raised, the hydrophilic chains of the copolymer become desolvated as a result of the breakage of the hydrogen bonds that had been established between the solvent and these chains. This phenomenon favors hydrophobic interactions among the polyoxypropylene domains, and leads to gel formation. Because of the dehydration process, the hydroxyl groups become more accessible (33,34). It is thought that the gel is micellar in nature. A liquid micellar phase is stable at low temperatures but transforms into the cubic structure by increasing the temperature (35). At higher temperatures, a phase of hexagonal-packed cylinders is formed (Figure 3). These compounds are surface active and form micelles and liquid lyotropic crystalline phases (36,37). Ultrasonic and light-scattering measurements (38-40) have indicated a micellar association for PF-127 over the temperature range 10-40°C. Other techniques such as NMR (41), rheology, and fluorescence have also shown the micellar arrangement of block copolymers. Gelation of PF-127 is thought to occur as a result of dehydration of the polymer leading to increased chain friction and entanglement, producing a hydrophobic association (41).

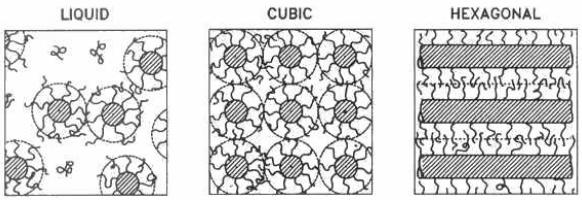

Figure 3. Schematic illustration of micellar phases formed by the Pluronics® with increasing temperature. From reference 1 with permission.

Reverse thermal gelation and low toxicity (42) have been the basis of research into the use of PF-127 as a possible drug delivery system in man (43). It has been considered for topical delivery of lidocaine (44), anti-cancer agents (5,45), and for the covering of burnt wounds (46). Investigations into ophthalmic use have been performed using pilocarpine as the model drug and PF-127 as the vehicle (13). Finally, PF-127 has been studied as a potential vehicle for injectables by both the intramuscular and subcutaneous routes (47, 48).

PF-127 is of particular interest since concentrated solutions (>20% w/w) of the copolymer are transformed from low viscosity transparent solutions to solid gels on heating to body temperature. The reversible thermal behaviors of both, dilute and concentrated PF-127 solutions have been extensively studied (32,49-51). This phenomenon, therefore, suggests that when poured onto the skin or injected into a body cavity, the gel preparation will form a solid artificial barrier and a sustained release depot. Furthermore, PF-127 has been reported to be the least toxic of commercially available copolymers (4).

Applications of Pluronic F-127

The unique thermoreversible and promising drug release characteristics of PF-127 render it an attractive candidate as a pharmaceutical vehicle for drugs through different routes of administration. This is emphasized in Table 2, which summarizes the research into PF-127 uses in pharmaceutical formulations.

Topical and Dermal applications

Analgesic/Anti-inflammatory drugs

Many authors have suggested PF-127 gels as potential topical drug delivery systems (28, 52-69) having advantages over traditional bases in terms of ease of application, and drug release characteristics. It is interesting that many studies have focused in the development of topical/dermal formulations containing analgesic or anti-inflammatory drugs (28, 55-59) due to the fact that the possibility of delivering these drugs through the skin for local pain and inflammations at low doses is attractive. However, in many cases penetration enhancers may be present in the topical/dermal formulations because otherwise only small amounts of drug pass through the skin.

Miyazaki et al. (28) evaluated thermally reversible gels of PF-127 as vehicles for the percutaneous administration of indomethacin. *In vivo* percutaneous absorption studies using a rat model suggested that a 20% aqueous gel may be of practical use as a base for topical administration of the drug. The addition of isopropyl myristate or (+) - limonene to the gel formulation significantly improved percutaneous absorption, particularly when the gel was applied using an occlusive dressing technique.

Table 2. Research of PF-127 gel in pharmaceutical formulations.

Author (Ref.)	Research	Outcome
Miyazaki, et al (5, 28,45).	Indomethacin, anticancer agents, (adriamycin,5 flurouracil), and mitomycin C in PF127.	PF-127 is a good vehicle for topical and rectal administration of Indomethacin and excellent for sustained–release of mitomycin.
Lenaerts, et al (31).	Rheological study of PF-127.	Exponential relationship between viscosity and temperature.
Wang, et al (52).	*In vitro* and *in vivo* skin absorption of capsaicin and nonivamide from hydrogels.	Moderate correlation between *in vitro* skin permeation and *in vivo* erythema responses of topically applied capsaicin and nonivamide.
Kattan, et al (53).	Effect of four terpene enhancers on the percutaneous permeation of ketoprofen.	The highest increase in the ketoprofen permeation was observed using limonene followed by nerolidol, fenchone, and thymol.
Chi, et al (54).	Anti-inflammatory and analgesic transdermal gel.	Prolonged anti-inflammatory and analgesic activities.
Fang, et al (55).	*In vitro* topical application and *in vivo* pharmacodynamic evaluation of nonivamide hydrogels using Wistar rat as an animal model.	Hydrogel formulations of nonivamide delivered more drug to the skin and produced greater pharmacodynamic activities than cream bases of capsaicin did.
Shin, et al (56).	Effects of non-ionic surfactants as permeation enhancers on piroxicam from the poloxamer gel through rat skin.	Skin pretreated with the PF-127 gels containing various surfactants showed a loosely layered stratum corneum and wide intercellular space.
Liaw,et al (57).	PF-127 as a release vehicle for percutaneous administration of fentanyl.	PF-127 is useful for percutaneous delivery of fentanyl.
Escobar-Chávez, et al (58)	Effect of Azone® and Transcutol® on skin permeation of sodium naproxen formulated in PF-127 gels.	Combination of Azone® and Transcutol® in PF-127 gels enhanced sodium naproxen penetration, with enhancement ratios of up to two-fold compared with the formulation containing only Transcutol®.
Eurokova, et al (59).	Effect of PF-127 on permeation of weak acids and bases through bilayer lipid membranes.	PF-127 facilitates the permeation of large molecules across lipid bilayers.

Table 2. continued

Pillai, et al (60).	Transdermal delivery of insulin from poloxamer gel: *ex vivo* and *in vivo* skin permeation studies in rat using iontophoresis and chemical enhancers.	*Ex vivo* studies, both linoleic acid and menthone in combination with iontophoresis showed a synergistic enhancement of insulin permeation.
Nair, et al (61).	PF-127 gel as vehicle for transdermal iontophoretic delivery of arginine vasopressin: evaluation *in vivo* in rats.	The use of iontophoresis improves the delivery of arginine formulated in PF-127 gels.
Zhang, et al (62).	Development and evaluation *in vitro* of sustained release PF-127 gel formulation of ceftiofur.	The overall rate of release of ceftiofur is controlled by dissolution of the PF-127.
Kadar, et al (63).	Treatment of skin injuries induced by sulfur mustard with calmodulin antagonists, using the pig model.	Topically applied Pluronics® base ointments containing lidocaine or pentamide produce beneficial effects when applied immediately after short-term sulfur mustard exposure to pig skin.
Fowler, et al (64).	*In vivo* effects of Pluronics® combined with either an allograft or an alloplast on the healing of critical-sized calvarial defects.	Pluronics® may be considered as carriers for osseous graft materials.
Nalbadian, et al (65).	Use of PF-127 in third- degree thermal burns.	Accelerated rate of healing.
Di Biase, et al (3,66).	Epidermal growth factor (EGF) in PF-127.	Feasible to develop a topical product with EGF.
Shin, et al (67).	Bioadhesive gels containing triamcinolone acetonide using different enhancers.	Permeation of triamcinolone through buccal mucosa was best using deoxycholate as an enhancer.
Morishita, et al (68).	Release profiles of insulin from PF-127 gel containing unsaturated fatty acids and the hypoglycemic effect of insulin following the buccal administration of the gel formulations in rats.	PF-127 gels containing unsaturated fatty acids are potential formulations for the buccal delivery of insulin.

Table 2. continued

Bourre, et al (69).	Efficacy of a delta 5-aminolevulinic acid (ALA) thermosetting gel formulation for use in photodynamic therapy of lesions of the gastrointestinal tract.	ALA-PF-127 is a suitable formulation for treatment of Barrett's esophagus, allowing good adhesion in the esophagus in gel form, with efficient diffusion of ALA into treated mucosa.
Hokket, et al (70).	Enhanced rate of human gingival fibroblast spreading and attachment.	PF-127 is beneficial in early postsurgical wound healing.
Charreaue, et al (71).	PF-127 as a thermogelling and adhesive polymer for rectal administration of short-chain fatty acids.	The 18% PF- 127 concentration provided a solution that was liquid at room temperature, and gelled at 37 ºC, possessed adhesive properties, and controlled short-chain fatty acid release.
Fawaz, et al (72).	Development and evaluation *in vivo-in vitro* in rabbits of two rectal quinine pediatric formulations to treat malaria attack.	Quinine bioavailability of the mucoadhesive gel was higher than the thermosensitive gel.
Kim, et al (73).	rhEGF/HP-beta-CD complex in poloxamer gel for ophthalmic delivery.	rhEGF may be retained in the pre-corneal area for a prolonged period. Therefore, the Pluronic® gel could be applicable for the development of effective ophthalmic delivery.
Desai, et al (74).	Prepare biodegradable polyisobutylcyanoacrylate particulate pilocarpine system, to incorporate it into a PF-127 gel delivery system, and to evaluate its ability to prolong the release of pilocarpine.	The PIBCA-NC of pilocarpine dispersed in the PF-127MC gel delivery system has considerable potential for achieving a prolonged delivery for pilocarpine and other more hydrophobic drugs.
Westerink, et al (75).	Effect of mucosal administration of tetanus toxoid (TT) in the presence of a non-ionic block copolymer, PF-127, with chitosan on the systemic and mucosal immune response.	PF-127/chitosan represents a novel mucosal vaccine delivery system that appears to exert an additive or synergistic effect on the immune response.
Moghimi (76).	Modulation of lymphatic distribution of subcutaneously injected PF-127-coated nanospheres: the effect of the ethylene oxide chain configuration.	Lymphatic distribution of interstitially injected PF-127-coated nanospheres is controlled by surface configuration of the ethylene oxide (mushroom-like configuration).

Table 2. continued

Paavola, et al (77).	Long acting, single dose gel injection to improve epidural pain treatment. The possibility of using liposomal systems to control the release and dural permeation of ibuprofen was investigated *in vitro.*	The liposomal gel controlled ibuprofen release and dural permeation *in vitro* showed a permeation pattern favorable for maintaining constant drug levels.
Wenzel, et al (78).	PF-127 gel formulations of deslorelin and GnRH reduce drug degradation and sustain drug release and effect in cattle.	PF-127 gel formulations can sustain peptide release and reduce peptide degradation.
Kabanov, et al (79).	Evaluation in phase I clinical trials following validation using *in vitro* and *in vivo* models of a formulation containing doxorubicin and Pluronic mixture (L-61 and F-127).	Drastic sensitization of these tumors with respect to various anticancer agents.
Amiji, et al (80).	Development of a thermo-reversible gelling formulation in PF-127 solution containing Paclitaxel (Taxol, Bristol-Myers Squibb)	Significant enhancement in the anti-tumor efficacy was noted following intratumoral administration of paclitaxel-PF-127. Initial tumor growth rate was delayed by 67%.
Paustin, et al (81).	Use of PF-127 intravenously in rats to heal burnt wounds.	Skin appeared markedly less damaged.
Xia, et al (82).	Experimental study of tissue engineered autologous cartilage by using an injectable polymer	The autologous cartilage could be generated by using a tissue engineering technique, with the histological characteristics similar to natural cartilage
Veyries, et al (83).	Control of staphylococcal adhesion to polymethylmethacrylate and enhancement of susceptibility to antibiotics by PF-127.	Combination of PF-127 with antibiotics could be a promising approach to the prevention of infection of foreign material.
Barichello, et al (84).	Use of PF-127 gels, polylactic-co-glycolic acid nanoparticles and their combination for parenteral delivery of peptides and proteins having short half-lives using insulin as a model drug.	PF-127 gel formulations containing either drug or drug-nanoparticles could be useful for the preparation of a controlled delivery system for peptides and proteins having short half-lives.
Bentley,et al (85).	Influence of lecithin in rheology and permeation properties	The presence of lecithin in PF-127 gel generates skin retention of lipophilic drugs

Wang et al. (52) designed a study to investigate the *in vitro* and *in vivo* skin absorption of capsaicin and nonivamide from hydrogels. Various commercialized creams of capsaicin were also compared with hydrogels. Both, skin stripping technique and Mexameter® were applied to evaluate the level of capsaicin and nonivamide retained in stratum corneum (SC) and skin erythema *in vivo*. The partition of drug between skin and the hydrogel matrix was considered to play an important role in the permeation process. The *in vitro* permeation of capsaicin from hydrogels depends on the physicochemical nature and the concentration of the polymer used. The incorporation of nonionic PF-127 polymer into hydrogels resulted in a retarded release of capsaicin. On the other hand, the *in vitro* capsaicin permeation showed higher levels with cationic chitosan and anionic carboxymethyl cellulose hydrogels than with cream bases. The permeation of nonivamide was retarded in the *in vitro* application. The cream induced *in vivo* skin erythema depending on the drug concentration. However, the dose-dependence was not observed in hydrogels. Nonivamide-treated skin showed stronger erythema than capsaicin-treated skin. The study indicates that there is a moderate correlation between *in vitro* skin permeation and *in vivo* erythema responses of topically applied capsaicin and nonivamide. The correlation between drug amount in SC and skin erythema test *in vivo* was also observed.

Kattan et al. (53) studied and evaluated the effect of enhancer lipophilicity, and ethanol concentration using hydroxypropyl cellulose and two PF-127 gel formulations on the percutaneous permeation of ketoprofen. All experiments were conducted using hairless mouse skin *in vitro*. Data recorded over 24 hr was compared with that for control gels (containing no terpene) using Franz diffusion cells. In the three gel formulations, the highest increase in the ketoprofen permeation was observed using limonene followed by nerolidol, fenchone, and thymol. Relationships were established between terpene lipophilicity, enhancement ratios for ketoprofen flux, and the cumulative amount of ketoprofen after 24 h from the three gel formulations. However, no correlation was established between terpene lipophilicity and ketoprofen skin content values at 24 h. Ethanol had a synergistic effect on the enhancing activity of the terpenes. Increasing the concentration of ethanol from 10% to 50% was associated with an increase in the permeation of ketoprofen.

Chi et al. (54) formulated a transdermal gel comprising ketoprofen as the active ingredient, PF-127, 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, water or a buffer solution. The gels possess prolonged anti-inflammatory and analgesic activities and physicochemical stability, with less systemic side effects and gastric irritation, compared to the oral administration.

Fang et al. (55) investigated the *in vitro* percutaneous absorption of nonivamide from gels of various polymers (PF-127, chitosan and carboxymethylcellulose) using Wistar rat as an animal model. The pharmacodynamic responses in skin after *in vivo* topical application of these hydrogels were determined. Their experimental data suggest that chitosan hydrogels produce the highest nonivamide permeability across the skin and the greatest cumulative amount trapped in the skin. Dose-dependent permeability and skin distribution of nonivamide were also observed. The *in vivo* effects of capsaicin and nonivamide on cutaneous responses were shown to differ depending on dose and duration after application. A significant correlation between non-invasive measurements of barrier perturbation, as measured by TEWL and the *in vitro* skin distribution of nonivamide was found. Thus, the higher the skin distribution of topical applied nonivamide, the more significant responses of skin perturbations seen.

Shin et al. (56) evaluated the enhancing effects of non-ionic surfactants on the permeation of piroxicam from the poloxamer gels using Franz diffusion cells fitted with excised rat skin**.** The effectiveness of penetration enhancers and the ratio of piroxicam flux in the presence or absence of enhancers were defined as the enhancement factor. Among the various non-ionic surfactants tested, polyoxyethylene-2-oleyl ether showed the highest enhancing effects with an enhancement factor of 2.84.

Liaw et al. (57) studied the feasibility of PF-127 gel as a release vehicle for percutaneous administration of fentanyl *in vitro* and *in vivo*. A cellulose membrane (Cell.Sep® T1, molecular weight cut-off 3500) and nude mouse skin with different concentrations of PF-127 were used to examine the sustained-release pattern and permeation of fentanyl. The *in vivo* percutaneous absorption was examined using rabbits to evaluate

the preliminary pharmacokinetics of fentanyl with 46% PF-127 formulation patches. The micelle formation ability and the penetration ability of PF-127 over time were also studied by pyrene fluorescence probe methods and the dynamic light scattering test. At a concentration of 46% at 37 ºC, PF-127 formed a gel and showed a pseudo-zero-order sustained-release profile. With increasing concentration of copolymer in the cellulose membrane transport, the apparent release flux of fentanyl decreased. Assessment of the effect of the copolymer on nude mouse skin also showed a decrease in the apparent permeability coefficient [(PH_2O) 2.24 ± 0.47 X 10^{-6} cm s^{-1} vs. (*P 46% block copolymer*) 0.93 ± 0.23 X 10^{-7} cm s^{-1}]. The preliminary pharmacokinetics of the fentanyl patch was shown to be in steady state within 24 h, and this was maintained for at least 72 h with an elimination half-life ($t_{1/2}$) of 10.5 ± 3.4 h. A fluorescence experiment showed polymeric micelle formation of PF-127 at 0.1% (w/w) within 50 nm micelle size and the PF-127 copolymers were able to penetrate nude mouse skin within 24 h. Thus, it appears that fentanyl preparations based on PF-127 gel might be practical for percutaneous delivery.

Escobar-Chavez et al. (58) determined the penetration of sodium naproxen, formulated in PF-127 gels containing Azone® and Transcutol® as penetration enhancers, through human skin *in vivo*. It was found that the combination of Azone® and Transcutol® in PF-127 gels enhanced sodium naproxen penetration, with enhancement ratios of up to two-fold compared with the formulation containing only Transcutol®. These results were confirmed by TEWL and ATR-FTIR spectroscopy, suggesting a synergic action for Azone® and Transcutol®. Due to the thermo-reversible behavior of Pluronic gels, the influence of the components added to gel formulations on viscosity as a function of temperature, was also studied.

It is also remarkable that there is an emerging interest of delivering different kind of drugs such as anti-cancer agents, hypoglycemic agents, antibiotics, and antiseptics throughout the skin (4,5, 59-63).

Anti-tumoral drugs

Topical administration of the anticancer agents, 5-flurouracil and adriamycin, was evaluated by Miyazaki et al (5). The effects of drug and PF-127 concentration, as well as temperature, on the release rate were studied by means of *in vitro* release tests using a cellulose membrane. With increasing concentration 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, as well as an increase in drug concentration.

Erukova et al. (59 have made important contributions studying the effects of Pluronics® on the permeability of several weak acids and bases through bilayer lipid membranes. Their results demonstrated that Pluronics® facilitated the permeation of comparatively large molecules (such as 2-n-undecylmalonic acid and doxorubicin) across lipid bilayers, whereas the permeation of small solutes (such as ammonium and acetic acid) remained unaffected. Pluronics® also accelerated the translocation of large hydrophobic anions (tetraphenylborate). The effect of Pluronics® correlates with the content of propylene oxide units: it is enhanced when the portion of polypropylene oxide block in the copolymer is increased. The action of the Pluronic on lipid membrane permeability differs from the effect of the conventional detergent Triton X-100, which does not affect doxorubicin transport if added at concentrations similar to those used for Pluronics®. It has been proposed that Pluronic accelerates the process of solute diffusion within lipid bilayers (in a structure-dependent manner) rather than influencing the rate of solute adsorption/desorption on the membrane surface.

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 big molecular weight. However, the use of enhancing-transport technology such as iontophoresis in combination with chemical enhancers gives us the possibility of delivering this kind of drugs through the skin with increasing permeation (60, 66).

Pillai et al. (60) used insulin like a model peptide for large peptides in the molecular weight range of 3-7 kDa. A gel formulation of insulin was formulated using PF-127 and was evaluated by *ex vivo* and *in vivo* skin permeation studies in rats with chemical enhancer and/or iontophoresis. The PF-127 gel was physically and chemically stable during the storage period. In *ex vivo* studies, both linoleic acid and menthone in combination with iontophoresis showed a synergistic enhancement of insulin permeation. The plasma insulin concentration (PIC) was the highest with linoleic acid pre-treatment, in

agreement with *ex vivo* permeation studies, but the reduction in plasma glucose levels (PGL) was comparable to iontophoresis. Menthone pre-treatment resulted in rapid attainment of peak PIC, but the reduction in PGL was less than other treatment groups. There was no direct relation between PIC and PGL and this is attributed to the fact that a cascade of cellular mechanisms mediates the action of insulin, before a reduction in PGL is observed. However, iontophoresis, either alone or in combination with linoleic acid, produced a reduction in PGL to the extent of 36-40%. Nevertheless, it should be taken into account that a combination of chemical enhancers and iontophoresis may cause greater skin irritation than when either of them is used alone.

Antidiuretic drugs

Nair et al. (61) described pharmacokinetic and pharmacodynamic activity of arginine vasopressin (AVP), a nanopeptide with antidiuretic activity, on being delivered by transdermal iontophoresis. PF-127 was used to form stable gels that did not reduce the release of AVP. The release rate from the gel followed Higuchi kinetics indicating that the dominant mechanism of release is diffusion. Iontophoresis alone or in combination with chemical enhancers, was used to augment the transdermal permeation of AVP. The results of both pharmacokinetic and pharmacodynamic studies emphasize the dimension of 'rapid onset' achieved by iontophoresis. The correlation between pharmacokinetic data and pharmacodynamic activity was only qualitative. Histopathological studies revealed that skin toxicity caused by either iontophoresis or chemical enhancers when used alone could be reduced by using a combination of both techniques in tandem.

Antibiotics

Zhang et al. (62) developed sustained release PF-127 gel formulations of ceftiofur for treating foot infections in cattle. The formulations contained 25-35% (w/v) PF-127 alone or with polyvinyl pyrrolidone (PVP), carboxymethylcellulose (CMC), or hydroxylpropyl methylcellulose (HPMC) as an additive. The *in vitro* release profiles of ceftiofur from the PF-127 formulations and the gel dissolution profiles were obtained. Ceftiofur release followed zero order kinetics and correlated well with the weight percentage of PF-127 dissolved; indicating that the overall rate 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. However, it appears that other factors may have also affected the drug release rate. Inclusion of PVP, CMC, and HPMC in the gel decreased the rate of release of ceftiofur to some extent.

Antiseptic drugs

Gilbert et al. (4) have focused their investigations on the release of benzoic acid and related compounds from PF-127 gels, using an *in vitro* release model through a Celgard® 2500 microporous engineering film. Release of the model drugs was shown to decrease with increasing PF-127 concentration, probably due to an increase in the size and number of micelles and a subsequent decrease in size and number of aqueous channels.

Calmodulin antagonist drugs

Kadar et al. (63) investigated the beneficial effects of topical treatments with calmodulin antagonists against HD (sulfur mustard) skin lesions in the pig model. Neat HD, either in liquid form (0.2-1 micro droplets) or as vapour, was applied to the back skin of female pigs (Large White & Landrace, 10-12 kg) for various exposure durations. Evaluation was based on quantitative analysis of the degree of erythema and area of the lesions, as well as histological evaluation. Calmodulin antagonists (10% pentamide, 1% trifluoperazine, 2% thioridazine) and anaesthetics (20% lidocaine and 3% benoxinate) were dissolved in PF-127 base, and were applied either topically as ointments or by intradermal injection, as early as 5 min post-exposure (twice a day for at least 3 days). The results demonstrated that topically applied PF-127 base ointments containing lidocaine or pentamide produce beneficial effects when applied immediately after short-term HD exposure to pig skin.

Wound and burn healing

The unique properties of PF-127 have also been used in bone wound healing in calvarial defects (64), and besides, PF-127 gels sufficiently mimic normal functions of the skin epidermis acting not only as an “artificial skin” (65) but also as a vehicle to carry small mitogenic proteins such as

epidermal growth factor (EGF) (3, 66) to accelerate wound healing in thermal burns that constitute a major medical problem all over the world.

DiBiase et al. (3) evaluated PF-127 gel as a potential topical vehicle for EGF. Modifications to the formulation were made to improve physical characteristics and chemical stability. The authors concluded that it was feasible to develop a topical product with EGF in PF-127 gel with a shelf life of at least 3 months when stored in a refrigerator.

Fowler et al. (64) determined the *in vivo* effects of Pluronics® combined with either an allograft or an alloplast on the healing of critical-sized calvarial defects. PF-68 or PF-127 was administered either topically or systemically and in conjuction with demineralized bone powder (DBP), tricalcium phosphate (TCP) or non-grafted controls. Pluronics® are easily mixed with either DBP or TCP to improve handling ease. Calvaria were harvested at 12 weeks postsurgery and evaluated histomorphometrically, by contact radiography with subsequent densitometric analysis, through energy spectrometry utilizing a scanning electron microscope, and by fluorescent microscopy. Although there were isolated differences, the overall trend was that the Pluronics® and the mode of administration did not result in a significant change in bone wound healing as measured by the percentage of bone fill. However, Pluronics® may be considered as carriers for osseous graft materials.

Nalbandian et al. (65) designed a blind study to provide qualitative and quantitative evaluation of the possible therapeutic benefits of the use of PF-127 as a substitute skin in standardized third-degree thermal burns. Three separate burns were induced on the shaved backs of young, anesthetized pigs. Biopsies confirmed that third-degree burns were achieved. The pigs were observed for 30 days. The rate of healing of third-degree thermal burns was significantly accelerated over control sites when treated with PF-127 plus propylene glycol. Thus, PF-127 was able to enhance significantly the rate of wound healing, possibly by stimulation of epithelial growth factor, although the precise mechanism of action remains unknown.

DiBiase et al. (66) went on to identify and designed those formulations with the essential physicochemical characteristics, to be used as potential pharmaceutical bases for delivery of epidermal grow factor (EGF) into open wounds. The exact flux of EGF required for therapeutic effect has yet to be determined and little data has been published on this subject. Nevertheless, gel formulations of Carbopol and 25% w/w PF-127 showed similar average EGF release rates of 16.55 and 17.12 μ_g /cm^2/h respectively across Celguard® 2500 45% porosity isotactic polypropylene membrane. A vanishing cream formulation similar to the commercial product Silvadane® showed much slower release of 0.5 μg/cm^2/hr.

Buccal applications

Anti-inflammatory drugs

Shin et al. (67) prepared bioadhesive gels containing triamcinolone acetonide (TA) using two polymers: carbopol 934 and PF-127. The drug release profiles from the gels were studied as a function of drug concentration and temperature. Different enhancers such as bile salts, glycols and non-ionic surfactants were used for the enhancement of its permeation through buccal mucosa. Among the enhancers used, sodium deoxycholate showed the best enhancing effects. The PF-127 and carbopol 934 can be used as a reservoir from which TA or other drugs are released when topically applied, since it forms a soft bioadhesive gel at body temperature.

Hypoglycemic drugs

Morishita et al. (68) investigated the release profiles of insulin from PF-127 gel containing unsaturated fatty acids such as oleic acid (18:1), eicosapentaenoic acid (20:5) or docosahexaenoic acid (22:6) and the hypoglycemic effect of insulin following the buccal administration of the gel formulations in normal rats. Insulin release from the gels decreased in the presence of unsaturated fatty acids. Remarkable and continuous hypoglycemia was induced by all PF-127 gels (insulin dose, 25 IU /kg) containing unsaturated fatty acids. PF-127 gels containing oleic acid showed the highest pharmacological availability (15.9 ± 7.9%). Their findings demonstrate that 20% PF-127 gels containing unsaturated fatty acids are potential formulations for the buccal delivery of insulin, and they would offer sustained release profile for buccally administered drugs due to its depot function. The ability of free insulin or that associated with unsaturated fatty acids, to diffuse through the buccal mucosa in normal rats, is an important finding in the search and development of a mucosal dosage form for insulin or any other peptide drug.

Anti-wart drugs

Bourre et al. (69) developed and evaluated, in an *in vivo* mouse model, an ALA (5-aminolevulinic acid) thermosetting gel PF-127, for potential use in photodinamyc therapy of Barrett's mucosa. *In vivo* relationships between ALA doses and fluorescence were studied to determine the optimal concentration. Fluorescence measurement *in vivo* showed that ALA concentration and time had a nonlinear influence on protoporphyrin IX synthesis.

Human gingival fibroblast

Hokett et al. (70) examined the speed of human gingival fibroblast (HGF) spreading and attachment. The purpose of this study was to determine the *in vitro* effects of Pluronics® on the growth and attachment of HGF to dentin and plastic surfaces using established tissue culture techniques. Pluronics®, in very low dosages may be beneficial in early postsurgical wound healing by facilitating early attachment and enhancing the growth rate of HGF.

Rectal applications

Anti-inflammatory drugs

Miyazaki et al. (10) evaluated Pluronics® as a vehicle for the rectal administration of indomethacin. Indomethacin gels, administered in rabbits, did not show a sharp peak in plasma concentration and produced a sustained plateau level from 10 to 15 hours. Thus, indomethacin preparations based on PF-127 aqueous gels appeared to be practically useful as a rectal preparation with prolonged action and with reduced side effects.

Short-chain fatty acids

Charrueau et al. (71) gelled a rectal solution of short-chain fatty acids to decrease the loss of active materials in the colonic lumen and thereby optimize their absorption. Five thermogels were prepared with PF-127 at concentrations ranging from 17% to 20%. Their viscosities were measured at room temperature and 37 ºC, and their gelling temperatures were determined. The adhesive properties of each gel were assessed *in vitro* at 37 ºC. Short-chain fatty acid release was studied using Guyot cells. From the threshold concentration of 17.5%, the solutions showed a Newtonian behavior at room temperature (50-80 mPa x s) and gelled at 37 °C. The higher the concentration, the higher the viscosity (1750 to 49,000 mPa x s) and, the lower the gelling temperature (27.6° C to 23.4 °C), the stronger the work of adhesion (2.2 to 4.5 mJ). Short-chain fatty acid release from the 18% polymer gel was decreased by 60% compared to the rectal solution. The 18% PF-127 concentration provided a solution that was liquid at room temperature, gelled at 37 °C, possessed adhesive properties, and controlled short-chain fatty acid release.

Anti-malaria drugs

Fawaz et al. (72) developed and evaluated rectal quinine paediatric formulations to treat acute uncomplicated malaria attack. Developed dosage forms must be able to assure a prolonged release in the rectum but not too much so as to avoid product expulsion by the child anus. Two quinine rectal gels, namely mucoadhesive (MA) gel and thermosensitive (TS) gel, containing 20 mg quinine base/g were developed and evaluated *in vitro* and *in vivo* in rabbits. The MA and the TS gels contained hydroxypropyl methylcellulose 4000 and PF-127, respectively. The calculated *in vitro* release exponent (n) values suggested that drug was released from both gels by non-Fickian diffusion. Both gels exhibit practically similar dissolution, which was not reflected in the plasma, and therefore, quinine bioavailability from MA gel was found to be higher than that obtained from TS gel and their $AUC_{0-\infty}$ were statistically different ($P = 0.0006$). The $t_{1/2}$ values of quinine were significantly higher for hydrogels than for IV and rectal solutions. Mean residence time values displayed by TS gel and MA gel were not statistically different but were about 3.8 and 1.3-fold, respectively, larger than those obtained for IV solution and rectal solution, respectively. These results confirm the sustained-release behaviour of both hydrogels in the rabbit. Tolerability study of hydrogels didn't show any damage on the rectal mucosa of the rabbit.

Ophthalmic applications

Epidermal growth factor

Kim et al. (73) prepared a chemically and physically stable Epidermal Growth Factor (EGF)/poloxamer gel to investigate its possible application as ophthalmic delivery system. The EGF/HP-beta-CD complex markedly increased

EGF stability compared with EGF solution at 4 ºC. The poloxamer gel was composed of PF-127 (16%) and PF-188 (14%). Addition of EGF/HP-beta-CD complexes increased the gelation temperature: 0.5% EGF/HP-beta-CD complex exhibited a suitable gelation temperature (35.5 ºC). The gel strength and bioadhesive force decreased by increasing the EGF and HP-beta-CD ratio from 1:4 to 1:20 in the complex. The *in vitro* release of EGF from poloxamer gel containing 1:4 EGF/HP-beta-CD complex was much slower than that of EGF solution and faster than that of 1:20 EGF/HP-beta-CD complex. After ocular administration of poloxamer gels in the rabbit, the concentration of EGF in tear declined at a first-order elimination. The poloxamer gel containing EGF/HP-beta-CD complex increased the area under the concentration-time curve of EGF in tears fluid compared with gel containing EGF solution.

Parasympathomimetique drugs

Desai et al. (74) prepared a biodegradable polyisobutylcyanoacrylate (PIBCA) colloidal particulate system of pilocarpine, to incorporate it into a PF-127-based gel delivery system, and to evaluate its ability to prolong the release of pilocarpine. Polyisobutylcyanoacrylate nanocapsules (PIBCA-NC) of pilocarpine were prepared by interfacial polymerization. Physicochemical characterization of the colloidal dispersion of PIBCA-NC was performed by measuring pilocarpine loading, particle size analysis, and scanning electron microscopy. Approximately 13.5% of pilocarpine was loaded onto the PIBCA-NC. The PIBCA-NC dispersion of 1% pilocarpine alone (I) and after its incorporation into the PF-127 gel delivery system (II) were compared against 1% pilocarpine incorporated into a PF-127 gel containing 5% methylcellulose (PF-127MC) alone (III). Measurements of the miotic response in the albino rabbit eye were performed. Statistical analysis indicated a rank-order for both the duration and intensity of miosis of II > III >> I, with all differences being significant. Thus, it appears that II increases the contact time of pilocarpine with the absorbing tissue in the eye, thereby improving ocular bioavailability. The PIBCA-NC of pilocarpine dispersed in the PF-127MC gel delivery system has considerable potential for achieving a prolonged delivery for such drugs as pilocarpine and other more hydrophobic drugs.

Intranasal applications

Tetanus toxoid

Westernik et al. (75) examined the effect of mucosal administration of tetanus toxoid (TT) in the presence of PF-127, with chitosan or lysophosphatidylcholine (LPC) on the systemic and mucosal immune response. Balb/c mice, immunized intraperitoneally with TT and boosted intranasally with TT in PF-127/chitosan, demonstrated a significant enhancement in the systemic anti-TT antibody response compared to mice boosted intranasally with TT in PBS or mice boosted intranasally with TT in PF-127/LPC. They determined the antigen specific IgA response in the nasal and lung washes of these animals and found a significant increase in anti-TT mucosal IgA response in the group boosted with TT in PF-127/chitosan. Similarly, mice immunized and boosted intranasally with TT in PF-127/chitosan had a significant enhancement of their systemic anti-TT IgG and mucosal IgA antibody responses compared to the animals immunized and boosted intranasally with TT in PBS or TT in PF-127/LPC. The results of these studies suggest that PF-127/chitosan represents a novel mucosal vaccine delivery system, consisting of two components that appear to exert an additive or synergistic effect on the immune response.

Subcutaneous applications

Moghimi S M. (76) demonstrated that lymphatic distribution of interstitially injected PF-127-coated nanospheres (45 nm in diameter) is controlled by surface configuration of the ethylene oxide (EO) segments of the adsorbed copolymer. At low poloxamer surface coverage, EO tails spread laterally on a nanosphere surface and assume a 'flat or mushroom-like' configuration. Such entities drain rapidly from the subcutaneous site of injection into the initial lymphatic, when compared to uncoated nanospheres, and subsequently are captured by scavengers of the regional lymph nodes. In vitro experiments have also confirmed that such entities are prone to phagocytosis. When the equilibrium poloxamer concentration is at 75 μg/ml or greater the EO chains become more closely packed and project outward from the nanosphere surface. These surface-engineered nanospheres drain faster than those with EO chains in mushroom configurations into the initial

lymphatic, escape clearance by lymph node macrophages, reach the systemic circulation, and remain in the blood for prolonged periods. These experiments provide a rational approach for the design and engineering of nanovehicles for optimal lymphatic targeting.

Intramuscular applications

Analgesic drugs

Paavola et al. (77) developed a long acting, single dose gel injection to improve epidural pain treatment. The possibility of using liposomal systems to control the release and dural permeation of ibuprofen was investigated *in vitro*. The liposomal gel controlled ibuprofen release and *in vitro* dural permeation showed a permeation pattern favorable for maintaining constant drug levels. The liposomal poloxamer gel represents a new formulation approach to increase the local epidural availability of ibuprofen.

GnRH agonist drugs

Wenzel et al. (78) compared the effectiveness of intramuscular sustained release PF-127 gel formulations of deslorelin, a potent GnRH agonist, and GnRH to their solution formulations in inducing the release of luteinizing hormone and formation of luteal tissue in cattle. Injectable gel formulations of deslorelin and GnRH were prepared using PF-127 (25%, w/w). PF-127 gels sustained the *in vitro* release of deslorelin as well as GnRH at similar rates and reduced drug degradation in muscle tissue when compared to the solution formulations. Deslorelin, as well as GnRH, elicited desirable elevations in plasma LH and progesterone concentrations *in vivo*. When compared to the solution formulations, the gel formulations of both drugs induced a broader peak of LH. Also, the peak LH levels were lower and the peak times were delayed with the gel formulations compared to the solution formulations. While the solution dosage form of deslorelin and GnRH elicited similar responses, the PF-127 gel formulation of deslorelin induced peak LH levels at an earlier time (3 h for deslorelin versus 5.25 h for GnRH). The results indicate that, deslorelin exerts a pharmacological effect in cattle. The LH response to deslorelin as well as GnRH can be altered by controlling the input or the release rate of the drug. PF-127 gel formulations can sustain peptide release and reduce peptide degradation.

Anti-tumoural drugs

Kabanov et al. (79) describes novel applications of Pluronics® in the treatment of drug-resistant tumors. It has been discovered that Pluronics® interact with multidrug-resistant cancer (MDR) tumors resulting in drastic sensitization of these tumors with respect to various anticancer agents, particularly, anthracycline antibiotics.

Amiji et al. (80) examined the efficacy of paclitaxel (Taxol, Bristol-Myers Squibb) after administering it locally at the tumor site, they developed a thermo-reversible gelling formulation in PF-127 solution. Control and paclitaxel-PF-127 formulations were administered intratumorally at a dose of 20 mg/kg in B16F1 melanoma-bearing mice. The change in tumor volume as a function of time and the survival of treated animals were used as measures of efficacy. In vitro paclitaxel release from PF-127 gels was very slow (only 6.1% after 6 hr) probably due to the poor aqueous solubility of the drug. Significant enhancement in the anti-tumor efficacy was noted following intratumoral administration of paclitaxel-PF-127 formulation. The initial tumor growth rate was delayed by 67% and the tumor volume doubling time was increased by 72% relative to saline control. In addition, more than 91% of the tumor-bearing animals that received paclitaxel in PF-127 gel survived on day 15 post-administration as compared to 58% in the control group. This study shows significant benefit of paclitaxel for solid tumor when administered locally in an in situ gelling poloxamer.

Intravenous applications

Burn wound healing

Paustin et al. (81) showed a dramatic improvement in full skin thickness burn wounds in rats treated intravenously with PF-127. Anaesthetized male rats (300-320g) received full skin thickness burns by immersion of the anterior chest wall. Thirty minutes after the burn, half the animals received equal volumes of either saline or PF-127 via the tail vein. The animals autopsied at 48h showed a significant reduction in the degree of wound contraction and the wound appeared grossly less damaged in the PF-127-treated animals.

Intraperitoneal applications

Anticancer drugs

Miyazaki et al. (45) also evaluated PF-127 gels as a sustained-release vehicle for intraperitoneal administration of mitomycin C (MMC) in order to enhance the therapeutic effects of MMC against a Sarcoma-180 ascites tumor in mice. The *in vitro* release experiments indicated that PF-127 might serve as a rate-controlling barrier and be useful as a vehicle for sustained-release preparations of MMC to be administered intraperitoneally.

Other applications

Xia et al. (82) investigated the proper cell density of tissue engineered autologous cartilage to indicate the clinical application. The chondrocytes, isolated from mini swines' ears, were mixed with an injectable biocompatible matrix (PF-127) to make the cell suspensions with the densities of 10,20, 30,40,50,60,70 x 10^6/ml. The chondrocyte-polymer complex was injected into the subcutaneous tissue of swines' abdomens. Each specimen was harvested and evaluated with body-mass, histological examination, glycosaminoglycan content and type II collagen tests, after 6 weeks *in vivo*. The histological examination showed that the neo-cartilage was solid homogenous cartilage when using 50 million chondrocytes/cc for 6 weeks. The samples with 10 and 30 million chondrocytes/cc showed that the area of the cartilage was incomplete and separated by the remnant polymer. The mass of the samples was ranged from 30-110 mg after 6 weeks. The glycosaminoglycan content was lower from 5.8 to 9.0 percent, compared to the 9.2 percent of the normal auricular cartilage. Western-Blot presented the type II collagen in all samples.

Veyries et al., (83) studied the antiadhesive effect of PF-127, together with modifications in the antimicrobial susceptibility of residual adherent staphylococci. Bacterial adherence was markedly inhibited (77% to more than 99.9%) whether polymethylmethacrylate was exposed to PF-127 before or during the adherence assay. Furthermore, residual adherent staphylococci appeared to be more susceptible to antibiotic activity, suggesting that combination of PF-127 with antibiotics could be a promising approach to the prevention of infection of foreign material.

Barichello et al. (84) evaluated the use of PF-127 gels, polylactic-co-glycolic acid (PLGA) nanoparticles and their combination for parenteral delivery of peptides and proteins having short half-lives using insulin as a model drug. The *in vitro* insulin release profiles of various PF-127 formulations were evaluated at 37 °C using a membraneless *in vitro* model. *In vivo* evaluation of the serum glucose and insulin levels was performed following subcutaneous administration of various insulin formulations in normal rats. The *in vitro* results demonstrated that the higher the concentration of PF-127 in the gel, the slower the release of insulin from the matrices, independent of the vehicle. By loading insulin into PF-127 gels, a slower and more prolonged hypoglycemic effect of insulin was obtained in inverse proportion to the polymer concentration. PF-127 gel formulations containing insulin-PLGA nanoparticles had the most long-lasting hypoglycemic effects of all formulations. From the current *in vitro* and *in vivo* study, they concluded that PF-127 gel formulations containing either drug or drug-nanoparticles could be useful for the preparation of a controlled delivery system for peptides and proteins having short half-lives.

Rheological studies

Due to the thermoreversible property of the PF-127 solutions, different studies focus on the effect of additives on the rheological behavior of these gels.

Bentley et al. (85) investigated the influence of the addition of lecithin, a permeation enhancer, on the rheological behavior and *in vitro* permeation properties of PF-127. Increased concentrations of lecithin increased the thixotropy, yield value, apparent viscosity and the gelation temperature of the gels. Light microscopy showed that formation of micellar structures by the addition of lecithin, may account for changes in rheological properties. They found that the presence of lecithin in PF-127 gels decreased the flux of a lipophilic drug through the skin, increasing its skin retention.

Lenaerts et al. (31) conducted a rheological study of PF-127 aqueous solutions (15-30%) at temperatures ranging from 15 to 35°C. An exponential relationship was found between viscosity and temperature, with a 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. The proposed hypothesis, therefore, invokes the creation of a cross-linked network.

Conclusions

The thermoreversible gel PF-127 can be considered as a suitable drug carrier, which has unique characteristics. Its micellar properties and gelation behavior, renders systems with excellent solubility as well as suitable delivery rate.

Administration of PF-127 formulations in the liquid state provides convenience of application and allows an intimate contact between the preparation and the biological tissue, before the formation of a non-occlusive gel on warming. The thermal gelation of PF-127 is able to form a depot increasing the contact time which produces a prolonged pharmacology action. In addition, PF-127 water-based polymeric gels offer several advantages over traditional oleaginous bases in terms of ease of application, cosmetic acceptability (colorless and water-washable) and desirable drug release characteristics.

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