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PLURONIC F127 AND ITS APPLICATIONS

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Abstract

Drug delivery is a main challenge in the field of pharmaceutical industry. Many techniques are available nowadays for improving the drugs' pharmacokinetic and pharmacodynamics profiles. One of the most famous and success techniques for controlling drug delivery is the use of Pluronic F-127 (PF-127). This approach depends on the use of high viscosity hydro miscible vehicles such as hydrophilic gels that provide an excellent drug delivery system for a number of routes of administration and is compatible with many different substances. PF-127 is a thermo reversible gel that was usefully used for administering many types of drugs through most routs of administration including as a carrier for most routes of administration including oral, topical, intranasal, vaginal, rectal, ocular, and parenteral routes. The potential use of PF-127 as an artificial skin has also been reported.

Keywords: *Drug delivery, Pluronic, viscosity , gel.*

Introduction

Gels 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 [1] .

Poloxamers, available also under the trademark Pluronics®, are a class of water-soluble

Non-ionic A-B-A and B-A-B triblock copolymers, where A is poly (ethylene oxide) (PEO) and B is poly (propylene oxide) (PPO).

Tetronic® block copolymers, comprise four PPO-PEO chains, which extend outward from an amine-terminated central chain. While traditional surfactants are low molecular weight, block copolymers are long chains (several thousand Da). The monomers comprising the copolymer blocks are chemically dissimilar (e.g., polar and non-polar), rendering the block copolymers amphiphilic and leading to surface active properties. The block segregation gives rise to interesting and useful nanostructures, which are spontaneously formed in solution (self-assembly).

Poloxamers exhibit an amphiphilic character in aqueous solution on the basis of the PEO solubility in water and the PPO insolubility. The PEO blocks are thus hydrophilic, while the PPO block is hydrophobic. The use of poloxamers in pharmaceutical research is widely researched. Recent reviews have covered various drug delivery forms (thermosensitive gels, micelles), specific applications (ophthalmic, oral chemotherapy, lung cancer treatment, gene delivery) and multi-drug resistance (MDR) reversal. Types of Pluronic polymers and their physiochemical properties are illustrated in Table 2

PF-127 is classified as a hydrogel that they contain ingredients that are dispersible as colloids or are water-soluble. PF-127 is a commercially available polyoxyethylene-polyoxypropylene triblock copolymer of general formula E106 P70 E106, with an average molar mass of 13,000. It contains approximately 70% ethylene oxide, which accounts for its hydrophilicity [2] .

It is one of the series of poloxamer ABA block copolymers, whose members share the chemical formula shown in Figure 1. Configurations of Pluronic® F127 is shown in figure 2. It is spherical with a core-shell structure. Fluorescence probe studies using pyrene show that the micelle core is hydrophobic and dominated by PPO blocks, while the corona, in contact with the bulk aqueous environment, is comprised of hydrated PEO blocks. The heat-induced micellization process has been observed to take place over a range of about 5 C, attributable to polydispersity in poloxamer systems. As the temperature is increased beyond the cmt, the aggregation number (i.e., average number of block copolymer chains comprising one micelle) increases, while the overall micelle hydrodynamic radius remains approximately constant. The hydrodynamic radius corresponds to the equivalent hard sphere model radius [3] .

Applications of Pluronic F-127:

A main advantage of pharmaceutical biotechnology includes the synthesis of optimal polymers which can increase the bioavailability and thermostability of incorporated biotherapeutic agent. Therapeutic efficacy, bioavailability, and stability of the drugs to be incorporated within polymers are of major concern in pharmaceutical research. There are many drugs that have an ideal therapeutic efficacy but because of their poor bioavailability and water-solubility, their clinical use is rather difficult. PF127 has shown to increase the therapeutic efficacy and thermostability of various incorporated therapeutic proteins using different routes for brain disorders and tumor-targeted delivery. Similarly, PF127 has also shown to improve the pharmacokinetic and pharmacodynamic parameters of incorporated drugs by increasing the oral bioavailability of various poorly water-soluble drugs. In the following sections, we will discuss different therapeutic approaches that have been adopted for the efficient delivery of various therapeutic proteins and peptides using PF127-based thermosensitive gels [4].

PF127-Based Thermosensitive Gel for Subcutaneous Delivery of Recombinant Hirudin Variant-2

In this study, they investigated thermo-sensitive Pluronic(P) F127 (PF127) hydrogel for the controlled release of peptide and protein drugs after subcutaneous injection, using an antithrombotic polypeptide, recombinant hirudin variant-2 (rHV2), as the model drug. The in vitro release experiment performed with a membrane-less model at 37C showed that the release of antithrombotic activity of rHV2 from PF127 gel followed zero-order kinetics and correlated well with the weight percentage of PF127 dissolved, indicating a dissolution-controlled release mechanism. The in vivo result obtained after subcutaneous injection of rHV2-loaded PF127 gel in normal rats demonstrated that PF127 gel improved the bioavailability, prolonged the antithrombotic effect of rHV2, and induced detectable plasma rHV2 concentration for a longer time in comparison with rHV2 aqueous solution. Differential scanning calorimetry, dynamic light scattering and Fourier transform infrared spectroscopy provided evidence of the interaction between PF127 and rHV2, but such interaction was unlikely to interfere the feasibility of this drug delivery system. In vitro and in vivo study suggested that PF127 gel may be useful as an injectable delivery vehicle for peptides and proteins with short half-lives to prolong their therapeutic effect, increase their bioavailability and improve the clinic outcome (Table 3) [5].

PF127-Based Thermosensitive Gel for Controlled Release of Recombinant Human Growth Hormone

Deficiency of growth hormone in children has usually been treated with recombinant human growth hormone (rhGH) which is usually administered via the parenteral route. Because of its short circulation half-life and rapid clearance, parenteral delivery of rhGH requires once daily or three times/week injection. They prepared thermosensitive gel of rhGH using PF127 and evaluated the in vitro and in vivo sustained release of rhGH from PF127 gel. The in vitro release of rhGH from thermosensitive gel of PF127 continued till 72 h via embraneless dissolution method. However, in the in vivo the release of rhGH from PF127 thermosensitive gel was observed till one week following either subcutaneous and/or intramuscular route in rats. No significant difference was observed between the in vivo release of rhGH from PF127-based thermosensitive gel given by either routes(Fig. 3) [6].

Furthermore, they also loaded rhGH in PF127 gel and administered it to mixed breed dogs via subcutaneous route. This route of administration attained the maximum plasma concentration within 9 h and maintained the plasma concentrations of rhGH within therapeutic range till 132 h compared to rhGH solution alone. The rhGH loaded in PF127 gel required more time to reach the maximum plasma concentration as compared to rhGH solution alone. On the other hand, Cmax of rhGH released from PF127 gel was less than the Cmax of rhGH solution alone. Although PF127 significantly prolonged the sustained release of rhGH till 132 h but it could not overcome the initial burst release of rhGH. Although PF127 has many advantages over the other biodegradable polymers but it has some shortcomings including its rapid dissolution when placed in excess amount of buffer which is due to the reason that below the CGC, PF127 is immediately diluted. Owing to this limitation, high concentrations of PF127 are required for its transformation into gel at body temperature. To overcome this limitation of PF127, stereo complexed crystalline domains of D-lactide and L-lactide oligomers were introduced at the ends of copolymer chains of PF127 which helped to crosslink the hydrophilic part (PEO) of PF127 in a more stable manner. D-lactide and L-lactide oligomers have already shown to produce stable thermosensitive polymers and have demonstrated sustained release of therapeutic proteins [7].

Keeping in view the advantages of D-lactide and L-lactide oligomers, Chung et al. prepared stereo complexed pluronic multi-block copolymers for sustained delivery of rhGH. Briefly, they crosslinked the D-lactide and L-lactide oligomers at the end of PF127 copolymers to form in situ stereo complexed thermosensitive gel (Fig. 4). This attempt helped by providing additional crosslinking points which substantially increased the gel strength. The stereo complexed multi-block PF127 copolymer resulted in increased mechanical strength and prevented rapid dissolution of gel in aqueous media with relatively lower CGC and temperature compared to PF127 alone. When they incorporated rhGH in this stereo complexed multi-block PF127-based thermosensitive gel, the in vitro release of rhGH from stereo

complexed multi-block PF127-based thermosensitive gel followed zero order release kinetics model for 13 days by erosion-controlled mechanism [8].

Kim and Park synthesized thermosensitive gel of hyaluronic acid (HA) with PF127 by photopolymerization of vinyl group modified HA with acrylate group end-capped with tri-block copolymer PF127. Briefly, methacrylate HA was synthesized by the interaction of carboxylic acid group of HA with vinyl monomer whereas the two carboxylic groups in PF127 were end-capped with two units of acrylate monomer to form di-acrylate PF127 [9].

PF127-Based Thermosensitive Gel for Subcutaneous Delivery of Insulin.

The first attempt was made by Barichello et al. to formulate insulin with PF127 thermosensitive gel using insulin either alone or as PLGA-based nanoparticles of insulin. They investigated the in vitro release characteristics of insulin using the membraneless dissolution method and in vivo release characteristics using Wistar-rats as animal model. The in vitro release of insulin from PF127 gel was dependent on the concentration of PF127 used. When compared with insulin loaded in PF127 and/or insulin solution alone, the insulin loaded in PF127 gel administered in the form of insulin-nanoparticles showed slower and prolonged hypoglycaemic effects. It was concluded that PF127-based thermosensitive gel containing either insulin or insulin-nanoparticles could sufficiently prevent the initial burst release of insulin and may prolong the hypoglycaemic effects of insulin for a sufficient period of time (Table 4) [10].

Conclusion:

The benefits of PF127 as a thermoreversible polymer having unique biopharmaceutical significance for the sustained and/or controlled delivery of various therapeutic proteins and peptides without any known toxicity. Therapeutic proteins and peptides loaded in either PF127 or PF127 in combination with other polymer additives showed increased thermostability, prolonged therapeutic efficacy via sustained release phenomenon, and displayed minimal toxicity at injection site. Keeping in view the weak mechanical strength and short residence time of PF127 in biological fluid, significant attempts have been made to overcome these shortcomings. Summarizing the aforementioned studies using PF127 as thermosensitive gel for sustained delivery of various therapeutic proteins and peptides with no known toxicity, PF127 continues to show its prospective effects for sustained delivery of therapeutic proteins and peptides. But still, there is a need to synthesize new multiblock copolymers of PF127 with short GT and strong mechanical strength to prolong the sustained release of incorporated therapeutic proteins [11].

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Table 1. General classification and description of gels.

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®

Pluronic® Notation	MW	PO Units	EO Units	cmc at 25 °C (% *w/v*)	cmc at 30 °C (% *w/v*)	cmc at 35 °C (% *w/v*)
L64	2900	30	26	n/a	1.5	0.4
P65	3400	17	36	n/a	4	1
P84	4200	43	38	2.6	0.6	0.15
P85	4600	40	52	4	0.9	0.2
F88	11,400	39	206	n/a	n/a	1.7
P103	4950	60	34	0.07	0.01	0.002
P104	5900	61	54	0.3	0.04	0.008
P105	6500	56	74	0.3	0.025	0.005
F108	14,600	50	264	4.5	0.8	0.15
P123	5750	69	38	0.03	0.005	0.001
F127	12,600	65	200	0.7	0.1	0.025

Table 2. Physicochemical properties of Pluronic® PEO-PPO-PEO block copolymers often used in drug formulation. Data obtained from [40]. cmc, critical micellization concentration; L, liquid; P, paste; F, flake.

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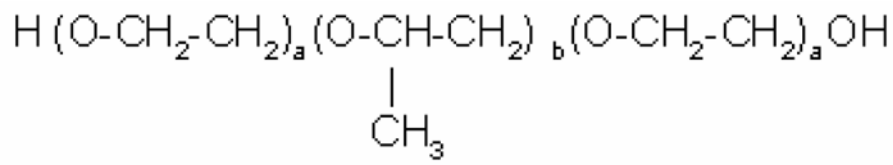

Figure 1. Chemical structure of Pluronic F-127 (a, ethylene oxide portion b, propylene oxide portion).

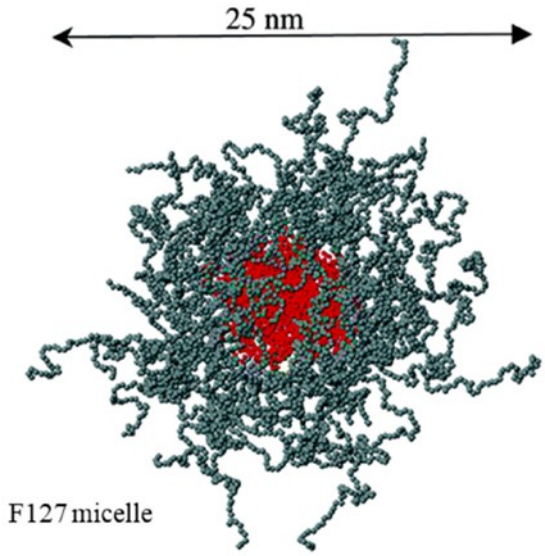

Figure 2. Configurations of Pluronic® F127 (EO100PO65EO100)

Table 3

Comparison of the pharmacokinetic and pharmacological parameters of rHV2 following subcutaneous administration of various formulations containing rHV2 in rats with the dose of 10 mg l kg (n=5–6, mean±S.D.)

Formulation	rHV2 solution	rHV2-loaded 20% PF127	rHV2-loaded 25% PF127
C_{max}(μg/mL)	16.57±1.55	8.50±0.94**	10.45±0.01**†
T_{max}(h)	1.1±0.2	1.3±0.7	5.2±0.5**†
MRT(h)	2.25±0.18	4.38±0.68**	5.71±0.16**†
Bioavailability (%)		196.9±12.3**	228.5±17.2**†
Pharmacological bioavailability (%)			
APTT		126.3±33.7	210.8±48.2 €†
PT		138.8±44.0	169.1±52.8 €
TT		122.8±31.3	130.7±11.0 €

** Highly significant different compared with rHV2 solution (p<0.01, t-test).
† Significantly different when compared with rHV2-loaded 20% PF127 gel (p<0.05, t-test).
€ Significantly higher than the bioavailability of the solution group (set as 100%) (p<0.05, t-test).

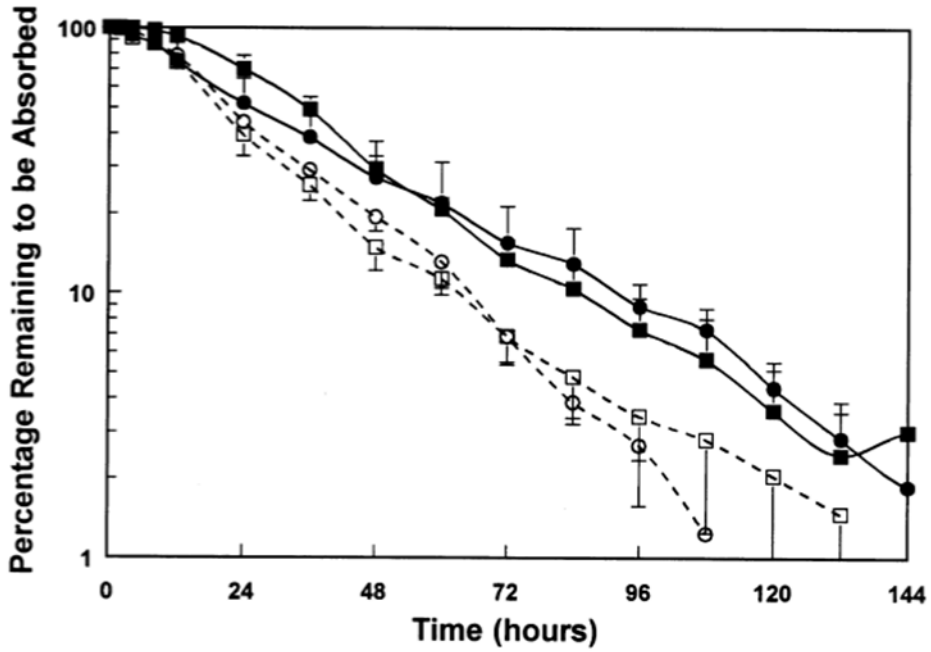

Fig. 3. Controlled release of rhGH from poloxamer gels in rats injected through intramuscular and subcutaneous route (● i.m. gel; ○ i.m. control; ■ s.c. gel; □ s.c. control).

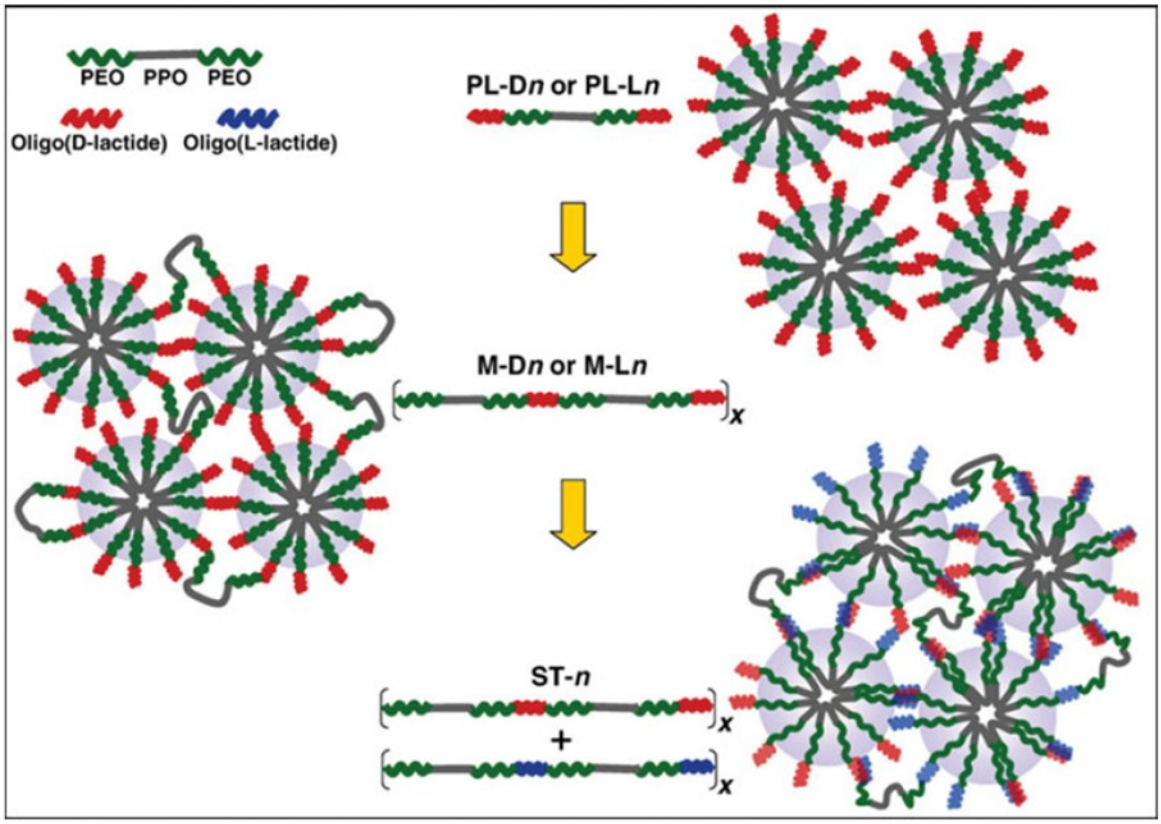

Figure 4: Proposed mechanism for the synthesis of stereocomplexed pluronic multi-block copolymers. A series of multi-block PF127 copolymers were synthesized by crosslinking the PF127 with end-capped to D-lactide and L-lactide oligomers to form in situ stereocomplexed thermosensitive gel. PF127; Pluronic F127.90

Formulation	$AUC_{insulin}$ (μU·h·ml^{-1})	C_{max} (μU/ml)	t_{max} (h)	MRT (h)
Insulin solution	114.4 ± 14.3	130.9 ± 11.6	0.5 ± 0.1	0.9 ± 0.2
INP	248.4 ± 26.5**	150.2 ± 20.6	1.2 ± 0.4*	1.3 ± 0.3*
20% PF127	294.4 ± 34.0**	102.7 ± 16.0*	2.4 ± 0.8**	2.8 ± 0.5**
30% PF127	315.7 ± 17.6**	61.7 ± 11.3**	4.0 ± 0.9**	4.6 ± 0.3**
INP-loaded 20% PF127	355.9 ± 36.7**,†	189.8 ± 49.2	1.4 ± 0.5*	2.1 ± 0.4**,†
INP-loaded 30% PF127	355.8 ± 30.8**,†	97.2 ± 13.4**,†	3.6 ± 0.8**,†	3.8 ± 0.5**,†

[a] Each value represents the mean of five rats ± SD.
* Significant difference ($P<0.05$) in the mean value compared with insulin solution using the Students' t-test.
** Significant difference ($P<0.01$) in the mean value compared with insulin solution using the Students' t-test.
† Significant difference ($P<0.01$) in the mean value compared with INP using the Students' t-test.

Table4: Comparison of the pharmacokinetic parameters of insulin following subcutaneous administration of various formulations containing insulin in normal rats