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Poloxamers based nanocarriers for drug delivery system

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ABSTRACT

In last few decades, there has been a considerable research interest in the area of drug delivery using polymer based particulate delivery systems as carriers for small and large molecules. Particulate systems like nanoparticles and micelles have been used as a physical approach to alter and improve the pharmacodynamic and pharmacokinetic profiles of various types of drug molecules. Due to the wide compatibility with drug candidates of diverse nature and ingredients in formulations, poloxamers serve to be excellent polymer for drug delivery vehicles by different routes of administration. This review will highlight the poloxamers-based micelles/nanoparticles that have been developed to date.

Keyword: Poloxamers, Nanoparticles, Drug delivery, Micelles, Nanocarrier.

INTRODUCTION

Polymers are the substances of high molecular weight having repeating monomer units. They are widely used in pharmaceutical systems as suspending, adjuvants, adhesives, emulsifying agents and coating material for controlled and site specific drug delivery systems. Polymer molecules may be branched or linear and separate linear or branched chains may be joined by crosslinks. The chemical reactivity of polymers depends upon the chemistry of monomer units but their properties depend to large extent on the way of arrangement of the monomers. Polymers having identical monomeric units are referred to as homopolymers; those formed from more than one monomer type are called copolymers. Arrangements of various monomers units, say A and B lead to formation of varieties of copolymers. The copolymers may be described as alternating copolymers, graft copolymers or block copolymers. Pluronic is one of the most widely used block copolymer and forms heterogels [1,2].

Nanomaterials have been the subject of increasing research concentration in recent years because of their potential biomedical and life science applications. Polymer nanomaterials have sparked a significant interest as vehicles used for diagnostic and therapeutic agents; research in nanomedicine has not only become a frontier movement but is also a revolutionizing drug delivery field [3].

Poloxamers are interesting copolymers as nanocarrier having amphiphilic characters. Due to large solubility differences between hydrophobic and hydrophilic moieties, in aqueous medium they are able to self-assemble into polymeric micelles characterized by mesoscopic size range. These micelles consist of water-insoluble cores and water-soluble shells. Depending on blocks length, core can assemble into various supramolecular structures characterized by different morphologies [4-6]. This review describes the characteristic features of poloxamers along with its applicability in nano-targeted drug delivery systems.

Characteristic and Properties of Poloxamers

The amphiphilic block copolymer named 'Pluronics or poloxamers' is triblock A-B-A type poly(ethylene oxide)-poly(propylene oxide)-poly-(ethylene oxide) (PEO-PPO-PEO) arrangement, which is non-ionic in nature [7,8]. The block copolymers with different numbers of hydrophilic ethylene oxide and hydrophobic propylene oxide units are characterized by different hydrophilic-lipophilic balance (HLB) values. They consist of a central block of relatively hydrophobic polypropylene oxide (PPO) surrounded on both sides by the blocks of relatively hydrophilic polyethylene oxide (PEO) [9,10]. They form micellar structures above critical micelles concentration in aqueous solvents due to the PEO/PPO ration of 2:1 [11,12].

Generally, pluronic are waxy, white granules of free flowing in nature and are practically tasteless and odorless [13]. Their aqueous solutions in presence of acids, alkalis and metal ions are very stable. The poloxamers are readily soluble in aqueous, nonpolar and polar organic solvents. Poloxamers has been extensively studied as a potential drug delivery vehicle due to their excellent biodegradability and thermosensitivity [14,15]. Due to this fact, Pluronics have been established themselves as a preferred molecule in the formulation and drug delivery techniques. The poloxamers copolymers are available in various grades (Table 1**)** differing in molecular weights and physical forms. Depending upon the physical property, the grades are assigned as F for flakes, L for liquid, P for paste.

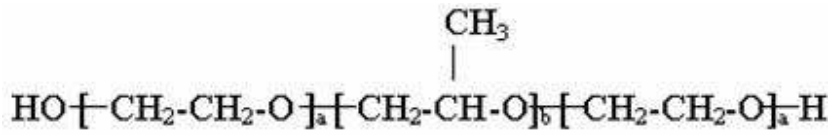

Fig. 1 General structure of Pluronic

Table 1: Pluronic grades and their chemical composition [14,16-17]

Poloxamer	Pluronic®	Physical form	a	b	Content of Oxyethylene (Percent)	Molecular Weight
124	L 44 NF	Liquid	12	20	44.8-48.6	2090-2360
188	F 68 NF	Solid	80	27	79.9-83.7	7680-9510
237	F 87 NF	Solid	64	37	70.5-74.3	6840-8830
338	F 108 NF	Solid	141	44	81.4-84.9	12700-17400
407	F 127 NF	Solid	101	56	71.5-74.9	9840-14600

F127 based Nano-carriers

Due to the long hydrophobic PPO segments and amphiphilic property, F127 can efficiently encapsulate hydrophobic agents with a compact core to efficiently prevent contact of conjugated polymers molecules with oxygen and water to reduce the quenching effect [18].

The gemcitabine loaded nanoparticles have been prepared by an ionic gelation method using chitosan and pluronic F-127 as a carrier and had a spherical shape mean diameter ranging between 80 to 170 nm. The *in vitro* drug release study at 37°C in phosphate-buffered saline (pH 7.4) exhibited controlled release profile for chitosan-pluronic F127 nanoparticles. The cytotoxicity of the gemcitabine loaded nanoparticles was assayed in the HT-29 colon cancer cell line showed increase in the cytotoxicity of gemcitabine embedded in the nanoparticles in comparison to drug alone. The mucoadhesion study reveals that nanoparticles could be considered as an efficient oral formulation for colon cancer treatment [19].

A targeted drug delivery system using folate-conjugated pluronic F127/chitosan core-shell nanoparticles was prepared to deliver doxorubicin to the target cancer cells. First, doxorubicin was encapsulated in pluronic F127 micelle cores in the presence of sodium dodecyl sulfate by self-assembly method. A shell of either chitosan or folate-conjugated chitosan was deposited onto the pluronic F127 micelles with encapsulation efficiency approximately 58.1± 4.7%. The average size of the prepared nanoparticles was 37.4±2.0 nm, while zeta potential was 12.9±2.3mV, indicated the presence of a shell layer and more stable nanoparticles. The *in vitro* doxorubicin release study represents an initial burst release, followed by sustained release, was observed within 24 hours. In addition, the core-shell nanoparticles showed superior cytotoxicity towards MCF-7 cells than free doxorubicin, suggesting a better therapeutic efficacy in treating cancer [20].

The critical micelle concentration (CMC) of pluronic F127 is about 0.26-0.8 wt% [21-22] so that the usefulness of F127 in nanotechnology based drug delivery system is limited since the nano-sized micelles could dissociate upon dilution. The stearic acid (SA) was coupled to F127 between the carboxyl group of SA and the hydroxyl group of pluronic F127, which formed a novel copolymer named as SA-coupled F127, with considerably lower CMC (6.9×10^{-5} wt%). SA-coupled F127 self-assembled to stable nanoparticles with Zeta potential -36 mV. Doxorubicin loaded nanoparticles were prepared with drug loading 5.7 wt% and Zeta potential -36 to -39 mV and the size distribution of nanoparticles was from 20 to 50 nm. Doxorubicin loaded nanoparticles were relatively stable and exhibited doxorubicin dependant cytotoxicity toward MCF-7 cells *in vitro*. These results suggested that SA-coupled F127 potentially could be applied as a nano-technology based drug delivery method [23].

An thermosensitive mixed micelles were prepared from pluronic F127-b-poly(ε-caprolactone) block copolymer by mixing with hydrophilic bovine serum albumin (BSA) and hydrophobic polylactic acid (PLA). Pure micelles with different lengths of caprolactone undergo morphology transition from the rods to the sphere. The addition of PLA and BSA can influence the thermosensitive and drug loaded behaviors of the micelles. Doxorubicin HCl loaded pure and mixed micelles have characteristics ideal for the selective sustained release of doxorubicin HCl in mildly acidic physiological environments rather than at pH 7.4. As observed from cell cytotoxicity, the block polymers showed excellent biocompatibility and the doxorubicin HCl loaded pure and mixed micelles were effective to inhibit the growth of HepG2 tumor cell lines. Therefore, the properties of the micelles can be adjusted by mixing either hydrophilic or hydrophobic molecules and the thermosensitive block polymeric micelles may be an attractive vehicle for doxorubicin HCl delivery [24].

PLGA containing half shells nanostructures were prepared by oil-in-water emulsion solvent evaporation method by adding pluronic F127 to the organic phase. They showed sequential events including phase separation, fast solidification and water escape. These nano-half-shells nanostructures possessed low densities, so the possibility of being used as carriers for pulmonary drug delivery system [25].

Honokiol, a multi-functional drug possessed low water solubility and has great potential in cancer therapy [26-32]. Honokiol micelles based on poly(ethylene glycol)-poly(ε-caprolactone)-poly(ethylene glycol) and pluronic F127 copolymer were prepared which underwent thermosensitive sol-gel-sol transition. Due to high hydrophobic character, honokiol could not be well-disperse in the composite hydrogel to form homogeneous solution. Above mentioned problem were solved by preparing honokiol micelles. The obtained honokiol micelles with average particle size of 33.34 nm and polydisperse index of 0.036 could be well dispersed in water with good stability. Cytotoxicity assay was conducted by using human HEK293 cells and suggested biocompatibility with low cell cytotoxicity [33].

In another study, honokiol nanoparticles were prepared with pluronic F127 by emulsion- solvent evaporation method. The obtained honokiol showed amorphous character and well dispersed in water [34]. The pluronic block copolymers were shown to be potent biological response modifiers capable of sensitizing and overcoming multidrug resistance (MDR) in cancer therapy and enhancing drug transport across cellular barriers, such as polarized intestinal epithelial cells, brain and Caco-2 endothelium [3,35-36]. From the above fact, the prepared honokiol nanoparticles might be anti-MDR formulation for cancer therapy.

Poly(lactic acid)-b-pluronic-b-poly(lactic acid) (PLA-F127-PLA) vesicular nanoparticles as oral delivery carrier for insulin were reported [37]. These polymeric vesicles aggregate with complicated onion-like structure containing three layers, which possessed microstructure similar to many biological systems. The biphasic release behavior was observed for the *in vitro* release of insulin from PLAF127-29 vesicles. In diabetic mice tests the blood glucose concentration of oral insulin-loaded PLA-F127-29 vesicles decreased from 18.5 to 5.3 mmol/L within 4.5 hours and the minimum blood glucose concentration about 4.5 mmol/L were achieved after 5 hours. This blood glucose concentration was maintained for at least an additional 18.5 hours. Due to prolonged hypoglycemic effect, PLA-F127-PLA vesicles could be promising polymeric carriers for oral insulin delivery application [38].

F68 based Nano-carriers

Paclitaxel loaded poly(ε-caprolactone)(PCL)/pluronic F68 (F68) nanoparticle formulation was prepared by solvent evaporation method as an intratumoral delivery system to assess its potential for future neoadjuvant chemotherapy application in the treatment of breast cancer [39]. Pluronic F68 incorporated into the PCL matrix acted as both pore-forming agent and to enhance drug release from the particles [40]. The murine breast cancer model has shown that

when using equivalent paclitaxel doses, paclitaxel loaded PCL/F68 nanoparticles administered by a single intratumoral injection were more efficient in impeding tumor development than conventional paclitaxel injections administered by multiple intraperitoneal injections [39].

The doxorubicin loaded pluronic F68 nanoparticles in size range of 632.8 nm were prepared in a molten mixture of doxorubicin dissolved in soybean oil/Tween 80 mixtures and pluronic F-68 through temperature induced phase. For detailed understanding of the tumor microenvironment, elevated interstitial tumor pressure and dense tumor extracellular matrix have been known as formidable barriers to the extravasation of nanoparticles. The increased targeting at tumor and effective extravasation into interior cells in the tumor tissue were demonstrated using pluronic nanoparticles using high-intensity focused ultrasound (HIFU) exposure. This approach transiently enhance the effective pore size of tumor tissue with the increased permeability of pluronic nanoparticles through non-thermal mechanisms and was confirmed by observing the *in vivo* biodistribution of pluronic nanoparticles with HIFU exposure. The results demonstrated that HIFU exposure through non thermal mechanisms can aid the extravasation of nanopartcles into interior cells in tumors and increase the therapeutic effect in targeted cancer therapy [41].

Curcumin loaded mixed micelles (Cur-PF), composed of Pluronic P123 (P123) and Pluronic F68 was prepared using the thin-film hydration method. The nano-sized micelles improved the solubility and biological activity of the drug. The *in vitro* cytotoxicity assay showed that the IC_{50} values on MCF-7 cells for Cur-PF and free curcumin in DMSO solution were 5.04 g/mL and 8.35 g/mL, while 2.52 g/mL and 8.27 g/mL on MCF-7/ADR cells [42].

Nisin loaded tripolymeric nanoformulation was synthesized using three biocompatible polymers viz. chitosan, sodium alginate and pluronic F68 by ionotropic pre-gelation method followed by polycationic cross linking. The controlled and sustained *in vitro* release profile of nisin was achieved. The used polymers and nisin exhibited synergistic antimicrobial activity that was retained over a prolonged period [43].

Silver nanoparticles (AgNps) co-stabilization with the bioactive copolymer pluronic F68, was shown improved antimicrobial activity against gram-negative microorganisms (*E. coli* and *P. aeruginosa*) in comparison to unstabilized AgNps [44].

The protein-pluronic covalent conjugates described were antibodies and insulin attached to pluronic analogs, which were used as targeting moieties for the delivery of polymeric micelles to the brain [45]. Pluronic P85 is an amphiphilic block copolymer with a molecular mass of ca. 4600 dalton having approximately equal by mass content of PPO and PEO chains. The unconjugated pluronic P85 was formulated with haloperidol (neuroleptic drug) in the form of polymeric micelles and then blended either with pluronic P85 modified insulin or antibodies. The protein molecules get incorporated into the PEO shell of the polymeric micelles while the solubilized drug remained in the core of micelle formed by PPO chains. The antibodies used in this study included either brain specific antibodies against alpha-2-glycoprotein or brain non-specific antibodies against alcohol dehydrogenase. The micelles were intraperitoneally administered into mice and biological activity was determined. All haloperidol micelle formulations showed better central response than the haloperidol alone. Among micelle groups, the most pronounced augment of haloperidol action was observed with the micelles linked to the brain specific antibody, followed by insulin linked micelles and then non-specific antibody or untargeted micelles. Similar micelles incorporated with fluorescence dye confirmed that the dye was in fact delivered to the brain parenchyma [46-47].

CONCLUSION

The difunctional block copolymer, poloxamers exhibits various desired characteristics of pharmaceutical formulations like its amphiphilic micellar behavior, desirable delivery rate, thermo-sensitivity and biocompatibility. The amphiphilic characteristics of micelles makes delivery systems capable of solubilizing poorly soluble or water insoluble drugs and of protecting labile molecules such as peptides and proteins. There has been remarkable progress in development of poloxamers based nano-carriers drug delivery systems. The new wave of pharmaceutical products will definitely make use of this polymer and a range of formulation problems incurred will get solved.

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