REVIEW ARTICLE

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Poloxamers: Promising Block Co-Polymers in Drug Delivery

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Poloxamers/Pluronic block copolymers are recognized pharmaceutical excipients listed in US and British Pharmacopeias. Because of the thermo-reversible gelation property and low toxicity they are widely used in a variety of pharmaceutical formulations including delivery of low molecular weight drugs and high molecular weight polypeptides. This review describes recent reports of applications of poloxamers in drug delivery, gene therapy, tissue engineering and in neuroprotection.

Pluronic block copolymers, which are also termed as poloxamer or synperonic, consist of ethylene oxide (EO) and propylene oxide (PO) blocks arranged in a triblock structure. PEO-PPO-PEO block copolymers have been widely used in pharmaceutical formulations because of their ability to self-aggregate thereby forming micelles and liquid crystalline phases[1,2]. The core of the micelles is hydrophobic consisting of polypropylene oxide, while a hydrophilic corona consists of ethylene oxide[3,4]. Self-assembly is temperature dependent and at a given polymer concentration a critical micellization temperature (cmt) exists[2]. Gelation behavior is also affected by the factors such as copolymer composition, molecular weight, concentration and the presence of co-solutes like surfactants, electrolytes and hydrophobic substances[2,5-7].

Triblock copolymers form micelles, which equilibrate with poloxamer unimers at low temperature above the critical micelle concentration (CMC), of about 1 mg/ml[1]. As the temperature increases, the equilibrium shifts from unimers to spherical micelles, reducing the number of unassociated unimers in solution, leading to an increase in critical volume fraction >0.53, i.e. where the micelles are locked into a hard spherical crystalline structure due to their high volume density[8,9]. The transition from sol to gel at high temperatures is relatively poorly understood and could be related to the shrinkage of PEO corona of the micelles due to the effect of temperature on PEO solubility and the interaction of PEO chains with the PPO hard core[10,11].

Poloxamers have been widely used in pharmaceutical industry for solubilizing water insoluble drugs. They are also used in solid dispersion technique to improve the solubility and bioavailability of poorly soluble drugs. The low melting point renders them suitable for melt granulation technique with added advantage of solubility enhancement. Due to the thermo-reversible property, poloxamers are widely used as *in-situ* gel for ocular delivery of drugs, periodontal delivery and for delivery of proteins and peptides through parenteral administration. This review incorporates all the significant applications of poloxamer with particular emphasis on the recent advances in applications besides chemical nature and gelation behavior.

CHEMISTRY OF POLOXAMER

Poloxamer consists of EO and PO blocks arranged in a triblock structure EO being hydrophilic and PO hydrophobic. This arrangement results in an amphiphilic copolymer, in which the number of hydrophilic EO (x) and hydrophobic PO (y) units can be altered to vary the size, hydrophilicity and lipophilicity[2]. The chemical structure of poloxamer is presented in fig.1

Pluronic or poloxamer nomenclature includes one letter, 'F', 'P' or 'L', followed by a two or three digit numeric code. The letters stand for solid (F), paste (P) or liquid (L) The numeric code defines the structural parameter of the

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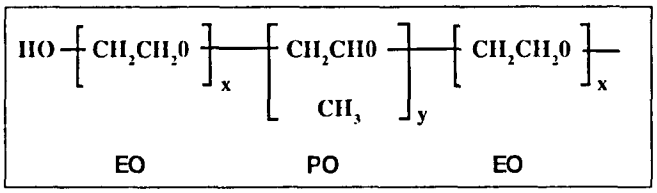

Figure 1: Chemical structure of poloxamer

The poloxamer contains hydrophilic EO block and hydrophobic PO blocks (available from BASF)

block copolymer. The last digit of this code approximates the weight content of EO block in tens of weight percent (for example, 80% weight if the digit is 8 or 10% weight if the digit is 1). The remaining first one or two digits encode the molecular mass of the central PO block. To obtain the molecular mass in Da, the number is multiplied by 300. For example the code 'F127' defines the block copolymer as the solid with PO block of 3600 Da (12x300) and 70% weight of EO[11].

GELATION

Mechanism of gelation:

The mechanism of thermo-reversible gelation of poloxamer solutions still remains a controversial issue. In the early 1980s, an intrinsic change in the micellar properties, such as aggregation number and micellar symmetry with increase in temperature was thought to cause gelation of aqueous poloxamer solutions. This hypothesis was based on the observation of a decrease in the critical micelle concentration with increasing temperature[12].

A little later it was proposed on the basis of C-NMR study that the dehydration of poly (propylene oxide) (PPO) caused the gelation of aqueous poloxamer solutions with temperature. The study demonstrated the change in the chemical shift and peak broadening of PPO methyl group at the transition temperature, which was interpreted as the dehydration of PPO from the existing micelles resulting in the increasing friction between polymer chains followed by viscosity increase, resulting in the gel phase[13]. In another study the change in entropy caused by locally ordered water around the core PPO was claimed to be responsible for sol-to-gel transition[14].

Estimation of gelation temperature:

Various techniques have been reported for evaluation of gelation process. In recent years, mechanistic studies on the phase transition and characterization of the solution and gel state of poloxamers were reported using number of instrumental techniques, such as dynamic light scattering (DLS), small angle neutron scattering (SANS), differential scanning calorimetry (DSC), rheometry, dielectric constant measurement and microcalorimetry.

Temperature scanning diode array UV spectroscopy:

The aqueous phase aggregation of poloxamer was studied using two indicators I_2 and 1,6-diphenyl-1,3,5-hexatriene (DPH) by temperature scanning diode–array UV spectroscopy[15]. Depending on the poloxamer concentration 10-50 µl (iodine standard) and 100-200 µl (DPH standard) were added to 10 ml of poloxamer solution and absorbance was measured at 366 nm (for iodine standard) and 356 nm (for DPH standard) over a certain temperature range, at a scan rate of 0.33° min^{-1}. Aggregation was demonstrated by the increase in absorption intensity with increasing solution temperature, maximum absorbance being at the temperature of maximum aggregation (T_m).

Differential scanning calorimetry:

Scherlund *et al.*[16] investigated gelation temperature of poloxamer gel using DSC. In this study weighed samples hermetically sealed in aluminum containers were scanned in the temperature range of −10° to 50° with a scanning rate of 5° per min and thereafter heat transfer was measured. Measurements resulted in an endothermic peak upon increase in temperature, where cmt (critical micelle temperature) was taken as the onset of the endothermic peak.

Small-angle neutron scattering (SANS) and dynamic light scattering (DLS):

SANS is used for characterization of sol-gel transition because of the presence of heterogeneities in the gel phase. Strong excess scattering is observed in gel phase at low angles in small-angle-X ray and neutron scattering as compared to the scattering from the corresponding polymer solution. The heterogeneities are observed as speckles when a laser light irradiates a gel[17,18].

DLS measures the scattering of the laser beam when the probe particles diffuse in a confined geometry. In a solution phase, the probe particle can explore the entire configurational space of the system and hence the time averaged dynamic structure factor measured through dynamic light scattering gives an ensemble averaged picture of the whole system. In the cross linked networks of a gel, geometrical constraints cause the probe particle to get con-

fined and move about its mean position, thus it cannot explore the entire configurational space and the time averaged dynamic structure factor no longer is representative of the whole ensemble of the system[19].

Rheology:

Rheology is an important tool in determining the macroscopic behavior of polymer solution and its temperature dependence. By subjecting a sample to oscillating shear between a cone and a plate, the elastic modulus (G') and loss modulus (G") can be measured at different temperatures and frequencies. Scherlund *et al.*[20] used a StressTech Rheometer (Reologica, Sweden) with a cone/plate and solvent trap system to measure the rheological behavior of poloxamer containing formulations. The cone diameter and angle were 40 mm and 4°, respectively. The temperature unit had a stability of ±0.1° and a temperature range of 5° to 90°. The measurements included oscillation stress sweep in the linear viscoelasticity region (LVER), oscillation temperature sweep from 10-40° with constant stress in the LVER, the temperature of gelation and the elastic (G') and loss moduli (G") of the formulations. Both the G' and G" were found to increase with temperature and reach to a maximum value at T_m. The viscosity and elastic modulus of the isotropic phase was low whereas that of hexagonal phase was high.

Glass bulb method[21]:

In this method about 0.25 g of poloxamer solution was placed with help of the syringe in a glass bulb having 3.5 cm long neck and 2 mm inside diameter. The neck was then sealed with micro flame torch. The bulb was then inverted and placed in an ice-cold water bath for few minutes and then into the hot water bath in order to form an immobile gel. The neck of the gel as attached to a glass rod and then placed into the jacketed beaker with the stirring bar. The temperature in the jacketed beaker was maintained at a higher value than T_m. The bath temperature was then reduced at the rate of 6°/h, and the temperature at which the gel started melting was considered as the transition temperature.

APPLICATIONS OF POLOXAMERS

Owing to the non-toxic nature and the unique sol-gel transition, poloxamers have attracted considerable attention as excellent polymers for controlled release, ocular, nasal, rectal, and peptide delivery and in gene therapy. Apart from drug delivery, poloxamers have also been explored as potential candidates for tissue engineering and neuroprotection in recent years.

Parenteral drug delivery:

Recent advancement in biotechnology has focused attention towards the effective delivery of bioactive agents and peptides/proteins to target cells or organs. Most of the proteins and peptides are administered by parenteral routes, such as intravenous and subcutaneous, however, patients have poorly accepted this form of delivery. Many approaches have been used to improve the existing parenteral dosage forms. One of these approaches is the use of pluronic F-127 (PF 127) gels. The unique sol-gel transition has made this system attractive as a depot-forming injectable drug delivery for the delivery of proteins/peptides such as insulin, urease, interleukin-2, and epidermal growth factor.

The use of PF127 gels for parenteral delivery of insulin by subcutaneous administration in rats has been evaluated[22]. The concentration of PF127 was 20 or 30%. The *in vitro* results demonstrated that higher the concentration of PF127 in the formulation, the slower was the release of insulin from the matrices. *In vivo* results indicated that by loading insulin in PF127 gels, a slower and more prolonged hypoglycemic effect of insulin was obtained in an inverse proportion to the polymer concentration.

An injectable poloxamer gel of lidocaine HCl and ibuprofen Na was formulated with additives, such as HPMC, sodium CMC and dextran[23]. *In vitro* release study showed cellulose derivatives to prolong the release of ibuprofen as compared to the gel containing poloxamer alone. Release of vancomycin was also studied from poloxamer 407 gels. Two types of gels, one with vancomycin being dispersed and another with vancomycin solubilised in the poloxamer, were formulated. *In vitro* studies demonstrated prolonged release from the dispersed form with lower diffusion coefficient for vancomycin than the solubilised form. A single dose resulted in the local concentration for 24 h, followed by lower but effective antibacterial levels for at least another 8 d[24].

In order to examine the efficacy of paclitaxel after local administration at the tumor site, a thermo-reversible gelling formulation in poloxamer 407 (Pluronic F-127) solution was developed by Amijii *et al.*[25] Paclitaxel was incorporated in poloxamer 407 [20% (w/w)] at 0.5 and 1.0 mg/ml concentrations. Control and paclitaxel-poloxamer 407 formulations were administered intratumorally at a dose of 20 mg/kg in

B16F1 melanoma-bearing mice. Significant enhancement in the anti-tumor efficacy was noted following intratumoral administration of paclitaxel-poloxamer 407 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 poloxamer 407 gel survived on day 15 post-administration, as compared to 58% in the control group.

Ocular delivery:

In ocular drug delivery, many physiological constraints prevent a successful drug delivery to the eye due to its protective mechanisms, such as effective tear drainage, blinking and low permeability of the cornea[26,27]. Thus conventional eye drops containing a drug solution tend to eliminate rapidly from the eye and the drugs administered exhibit limited absorption (1-2%), leading to poor ophthalmic bioavailability. Additionally, their short-term retention often results in a frequent dosing regimen to achieve the therapeutic efficacy for a sufficiently long duration. These challenges motivated researchers to develop drug delivery systems that can provide a prolonged ocular residence time of the drugs. In that respect *in-situ*-forming hydrogels were found attractive because of their use in dosing as a liquid, and their long-term retention property as a gel after dosing.

A pluronic F127 (PF127)-containing formulation of pilocarpine hydrochloride (PHCL) was formulated for sustained-release ocular delivery of PHCL[28]. The PF127 formulations of PHCL containing methylcellulose (MC) or hydroxypropylmethylcellulose (HPMC) were assessed for the *in vivo* performance using miosis in the rabbit eye produced by PHCL as a measure of ocular bioavailability. The PF127 formulations of PHCL having MC or HPMC as an additive showed considerable potential as sustained-release ocular delivery for PHCL. In another study, the same authors prepared a biodegradable polyisobutylcyanoacrylate (PIBCA) colloidal particulate system of pilocarpine and incorporated it into a pluronic F127 (PF127)-based gel delivery system[29]. The system was evaluated for its ability to prolong the release of pilocarpine. The mitotic response of PIBCA-NC dispersion of 1% pilocarpine alone (I) and pluronic F127 gel delivery system (II) was compared against 1% pilocarpine incorporated into a PF127 gel containing 5% methylcellulose (PF127MC) (III) in the albino rabbits. Statistical analysis indicated a rank-order for both the duration and intensity of miosis of II>III>>I, with all differences being significant ($p<0.05$).

The literature also reports development of a controlled release formulation of a model oligonucleotide (pdT16) for ocular delivery. The drug contained in liposomes was dispersed in thermoreversible gel of poloxamer 407. In this study effect of poloxamer concentration on stability of the liposomes and release of drug was studied[30].

El-Kamel reported development of Pluronic F127 (PF127) based formulations of timolol maleate (TM), aimed at enhancing its ocular bioavailability[31]. In an attempt to reduce the concentration of PF127 without compromising the *in situ* gelling capabilities, various viscosity-enhancing agents were added to PF127 solution containing 0.5% TM. The viscosity of formulations containing thickening agents was in the order of PF-MC 3%>PF-HPMC 2%>PF-CMC 2.5%>PF127 15%. The slowest *in vitro* drug release was obtained from 15% PF127 formulations containing 3% methylcellulose. *In vivo* study showed that the ocular bioavailability of TM, measured in rabbits, increased by 2.5 and 2.4 fold for 25% PF127 gel formulation and 15% PF127 containing 3% methylcellulose, respectively, as compared with 0.5% TM aqueous solution.

Rectal delivery:

The rectal route has been used primarily, for local treatment of diseases associated with the rectum, such as hemorrhoids. Additionally, it is well known that drugs absorbed from the lower part of the rectum drain into the systemic circulation directly thus, the rectal route is a useful administration route for drugs suffering heavy first-pass metabolism. A problem associated with rectal administration using conventional suppositories is that drugs diffuse out of the suppositories in an uncontrolled manner and are unable to be sufficiently retained at a specific position in the rectum, and sometimes migrate upwards to the colon leading to a variation of the bioavailability of certain drugs, particularly, drugs with extensive first-pass elimination. In this context, *in situ* gels with sufficient bioadhesive property that can be easily administered in liquid form and gels at body temperature may offer a valuable way to overcome the problem with conventional suppositories. With the biotechnological development, various peptide and protein molecules as potential therapeutic agents have been emerged, but their low bioavailability due mainly to degradation by protease enzymes in the gastrointestinal tract, high molecular weight and poor lipophilicity are problems that limit their use by the oral route. Reduced polypeptide degradation and partial avoidance of hepatic first-pass metabolism have been cited as some advantages for rectal administration of

peptide and protein drugs[32].

The PF127 depot can be easily administered rectally as a solution, which then forms a rigid semisolid gel network as it warms with the body temperature. Barichello *et al.*[33] prepared various insulin-loaded PF127 gel formulations containing unsaturated fatty acids such as oleic acid, eicosapentaenoic acid and docosahexaenoic acid to enhance the absorption of insulin and compared their pharmacological availability following rectal administration. In addition, pharmacokinetic parameters of insulin from the various PF127 formulations were also compared. Rectal insulin absorption in rats was markedly enhanced and marked hypoglycemia was induced by all PF127 gels (insulin dose, 5 U/kg) containing different unsaturated fatty acids.

To decrease the loss of active materials in the colonic lumen and thereby optimize their absorption, thermoreversible gel for rectal administration of short-chain fatty acids was formulated. Five thermogels were prepared with poloxamer 407 at concentrations ranging from 17% to 20%. Short-chain fatty acid release was studied using Guyot cells. Short-chain fatty acid release from the 18% polymer gel was decreased by 60% compared to the rectal solution. Thus 18% poloxamer 407 concentration provided a solution that was liquid at room temperature that gelled at 37°, possessed adhesive properties and controlled short-chain fatty acid release[34].

A poloxamer gel containing diclofenac sodium could not be developed using bioadhesive polymers, as the drug was precipitated in this preparation. To counter this difficulty, a poloxamer gel using sodium chloride was prepared. Pharmacokinetic study was performed on diclofenac sodium delivered by the poloxamer gel in rats. The poloxamer gels with less than 1.0% sodium chloride, in which the drug was not precipitated, were inserted into the rectum without difficulty and there was no leakage, The gels retained in the rectum of rats for at least 6 h. Furthermore, poloxamer gel gave significantly higher initial plasma concentrations and faster Tmax of diclofenac sodium than did solid suppository, indicating that drug from poloxamer gel could be absorbed faster[35].

Very recently Yong and coworkers[36] reported improvement in the bioavailability of poorly water-soluble ibuprofen in the rectum with poloxamer and menthol. The effects of menthol and poloxamer 188 on the aqueous solubility of ibuprofen were also investigated. The studies also included dissolution and pharmacokinetic evaluation of ibuprofen delivered by the poloxamer gels composed of poloxamer 188 and menthol. The poloxamer gel with menthol/ibuprofen ratio of 1:9 and higher than 15% poloxamer 188 showed the maximum solubility of ibuprofen, up to 1.2 mg/ml. Menthol improved the dissolution rates of ibuprofen from poloxamer gels. Furthermore, the poloxamer gel with menthol (poloxamer/menthol/ibuprofen (15%/0.25%/2.5%)) gave significantly higher initial plasma concentrations, Cmax and AUC of ibuprofen than did solid suppository, indicating that the drug from poloxamer gel was better.

Tissue engineering:

In recent years, artificial materials are of growing importance in medicine and biology. A modern scientific interdisciplinary field known as Tissue Engineering has been developed to design artificial biocompatible materials to substitute irreversibly damaged tissues and organs. In addition, biomaterials are important for fundamental scientific research as relatively simple and physicochemically well-defined artificial templates of extracellular matrix (ECM), allowing studies of ECM signals controlling cell adhesion, spreading, growth, differentiation, functioning, viability, and matrix degradation[37-44].

The most recent trend in tissue engineering aims at creation of hybrid bioartificial organs. This strategy is used for construction of artificial vessels, bone, cartilage and parenchymatous organs like pancreas or liver. The artificial component of these constructs is designed as a three-dimensional scaffold promoting control in growth and maturation of cells. It could be colonized under *in vitro* conditions with patient's own cells obtained by biopsy prior to the planned surgery, or even with stem cells guided to a certain differentiation pathway[38-40,42,44,45]. The surfaces preventing cell adhesion have been generated using various natural or synthetic molecules, such as antiadhesive protein albumin[42], hydrogels based on hyaluronic acid[39]or poly (hydroxylethylmethacrylate)[46], polyvinyl alcohol, polyacrylamide, dextran[44], and particularly poly (ethylene glycol) (PEG)[40,44]or poly (ethylene oxide) (PEO)[42,47]. Due to their poor mechanical properties, the latter two compounds have often been applied in a form of a pendant side chains attached to a backbone, represented e.g. by latexes[40], poly (methyl methacrylate)[45], polyurethane[42], poly (L-lysine)[44] and particularly polylactides[41,43,48-51].

A report also suggests the application of poloxamers in tissue engineering[52]. In this study an autologous chondrocyte was isolated from porcine auricular elastic cartilage and was suspended in 30% w/v of PF127. The formu-

lation was then injected on the ventral surface of the pig from which the cells were isolated. A circumferential sub dermal suture was used to•support the contour of the implant, which also assisted in its projection in the form of human nipple. As a control equal number of injections were made using either cells or hydrogels alone. After 10 w, all specimens were excised and examined both grossly and histologically. On visual inspection of the chondrocyte-PF127 hydrogel, implant sites revealed a closely resembled human female nipple-areolar complex. Temperature-sensitive HA/Pluronic composite hydrogels were synthesized[53], that gradually collapsed with increasing temperature over the range of 5-40 ° . Incorporation of recombinant human growth hormone in the hydrogel resulted in a sustained release profile, which followed a mass erosion pattern. Recently, grafting of poloxamer onto the hyaluronic acid for application of tissue engineering oriented ophthalmic drug delivery system has been reported[54]. The gelation temperature of graft copolymers was dependent on the content of HA and the concentration of poloxamer. *In vitro* studies revealed sustained release of ciprofloxacin from the poloxamer-g-hyaluronic acid hydrogel due to the *in situ* gel formation of the copolymer and viscous properties of HA.

Gene therapy:

The field of non-viral gene therapy has recently gained increased interest[55]. It is widely believed that non-viral gene therapy can overcome some problems inherent to current viral-based therapies, including immune and toxic reactions as well as the potential for viral recombination[56]. One major approach, in non-viral gene therapy is based on 'polyplexes', complexes formed by mixing DNA with synthetic polycations. A variety of polycation molecules have been proposed for polyplex formation[57,58]. An alternative approach for gene delivery evaluates nonionic polymers, such as poly(vinyl pyrrolidone), which enhance gene expression of naked DNA in tissues, such as skeletal muscle[59,60]. Poloxamers appear to be very valuable for gene delivery in skeletal muscle. Furthermore, Poloxamers have proven to be useful elements in polyplexes on the base of the polycation and DNA complexes that have a potential in a variety of gene therapy applications.

Increase in transgene expression by poloxamer:

The relatively low level of gene expression limits the applicability of naked DNA as therapeutic agent, therefore, an alternative approach has been to identify compounds that can enhance gene expression in the muscle. It was recently discovered that certain pluronic block copolymers significantly increase expression of plasmid DNA in skeletal muscle in mice[61]. A formulation based on the mixture of the block-?copolymers, pluronic L61 and pluronic F127, has been identified that increased gene expression by 5–20-fold compared to naked DNA. This formulation was termed SP1017. Two reporter genes, luciferase and beta-galactosidase, and one therapeutic gene, erythropoietin, were injected intramuscularly with and without SP1017 into C57Bl/6 and Balb/C mice and Sprague-Dawley rats. SP1017 increased gene expression by about 10-fold and maintained higher gene expression compared with naked DNA[61].

Nasal administration of plasmid DNA is emerging as a new route of delivery for therapeutic genes and DNA vaccines. To improve the intranasal absorption of plasmid DNA, delivery systems composed of *in situ* gelling (poloxamers) and mucoadhesive polymers {polycarbophil (PC) or polyethylene oxide (PEO)} were designed[62]. At 3 h postdose, the nasal tissue levels of plasmid DNA given in Pol/PC and Pol/PEO 0.8% were 10 and 40-fold higher relative to saline.

Pluronic -polycation conjugates for gene delivery:

Some recent reports suggest that pluronic block copolymers can be useful as the components of novel self-assembling gene delivery systems. Astafieva *et al.*[63] demonstrated that pluronic block copolymers can enhance polycation-mediated gene transfer *in vitro*. In this study, a synthetic polycation, poly (*N*-ethyl-4 vinylpyridinium bromide) was used to prepare complexes with a plasmid DNA, and then these complexes were evaluated for DNA intracellubiologicallar uptake and transgene expression in cell culture models. When poly (*N*-ethyl-4-vinylpyridinium bromide) and DNA were mixed with 1% pluronic P85 and then the cells were exposed to the resulting formulation, both the DNA uptake in the cells as well as the transgene expression were significantly increased compared to the cells treated with the poly(*N*-ethyl-4-vinylpyridinium bromide) and DNA complex alone. A recent study reported that the receptor-mediated gene delivery to hepatic cell line, HepG2 using complexes of a plasmid DNA with an asialo-oroso-mucoid-poly(L-lysine) conjugate was increased four fold in the presence of pluronic F127[64]. Similar efficiency was demonstrated in the presence of pluronic F127 when the cervical cancer cell line, C-33A was transfected with the polycation /DNA complex[65]. In a recent report, poly-L-lysine-g-pluronic (PLL) was evaluated for its efficiency as a possible non-viral gene carrier candidate. pCMV-beta-gal

was used as a reporter gene, and the *in vitro* transfection efficiency was measured in HeLa cells. Compared with unmodified PLL, PLL-g-pluronic showed about 2-fold increase in transfection efficiency with similar cytotoxicity specifically at the 1:1 weight ratio of polymer: DNA[66].

Neuroprotection:

Increasing mortality due to traumatic brain injury has lead to the intense experimental and clinical research to identify the efficient neuroprotective agents to combat these disorders. Selection of potential therapeutic targets critically depends on a better understanding of the cellular and molecular events in designing new pharmacological approaches for treatment. Extracellular glutamate release has been observed as the first pathological process following traumatic injury[67]. The extracellular release of glutamate acts postsynaptically by activating N-methyl-D-aspartate (NMDA) and non-NMDA types of glutamate receptors, which, in turn, results in an excessive calcium (Ca2+) influx into neuronal cells and leads to calcium mediated cell death following the trauma[68]. Many neuroprotective strategies for limiting neuronal injury in recent years, therefore, focused on reducing the release of glutamate from presynaptic terminals and on preventing its actions at postsynaptic receptors.

Recently, poloxamers have been proved to have potential neuroprotective activity. In a recent study, neuroprotective effects of poloxamer 188 (P188) on neuronal survival after stimuli resulting in neuronal necrosis have been investigated[69]. In this study, 12 d old embryonic (E17) rat hippocampal pyramidal neurons were exposed to 300 μ mol NMDA for 15 min in buffered saline. After 48 h of exposure, survival was measured. NMDA exposure significantly reduced neuronal survival to about 33.8%, however when P188 was added to the culture medium, after incubation in NMDA, 48 h survival was increased to 73.3%. P188 was also tested for neuroprotection against non-NMDA receptor activation-induced injury. In this study hippocampal cultures were exposed to severe oxidative injury with menadione or tert-butyl-hydroperoxide and embryonic purkinje neurons (12 d *in vitro*) to kainate for 15 min. After 48 h of exposure it was revealed that survival fell from > 70% to 30-50% depending on the toxin. When P188 was added to the culture medium after exposure to toxin, 48 h survival after all stimuli markedly increased with survival approaching control levels[70]. The membrane sealing ability of P188 helped in restoration of membrane integrity and viability after electroporation[69,70].

Membrane repair of damaged neurons by surfactant poloxamers has been noted in experimental spinal cord injury and *in vitro* excitotoxicity[71]. Quinolinate was infused into the stratum, and 4 h later P-188 was administered either i.v. or intracisternally (i.c.), or by vehicle. Mean neuronal loss after 7 d in control animals was 50% greater ($P < 0.01$) than after i.c. P-188 treatment. This robust protection against glutamate toxicity may predict P-188-mediated neuroprotection against a broad range of clinically relevant neural insults.

OTHER APPLICATIONS OF POLOXAMER

Pluronics (polyoxyethylene polyoxypropylene block copolymers) have the capability to self-assemble into polymeric micelles (fig.2). For drug delivery purposes, hydrophobic drugs may be solubilised within the core of the micelle or, alternatively, conjugated to the micelle-forming polymer. Recently solubility and dissolution of poorly water-soluble drug ibuprofen has been increased from poloxamer gel (P188) using eutectic mixture with menthol[72]. The low melting point poloxamers enabled them to be used as binders in melt granulation with the advantage of also improving the drug solubility. Ibuprofen-poloxamer 188 granules were prepared by melt granulation in order to improve its dissolution rate[73].

Poloxamer has also been proved as a successful candidate for periodontal drug delivery particularly for periodontal anaesthesia. Lidocaine and prilocaine in combina-

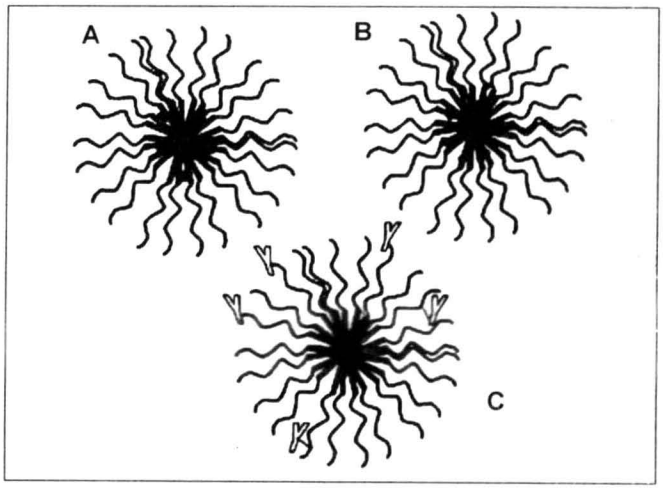

Fig. 2: Polymeric micelles

Polymeric micelles containing A. Drug solubilised in the hydrophobic core, B. Drug covalently linked to hydrophobic core and C. Micelles carrying antibodies attached to the hydrophilic chain.

tion have been formulated as the local anaesthetic using PF127 and PF68[74].

In addition to the use of pluronic block copolymers as structural components of micellar drug formulations, selected pluronic block copolymers have been used extensively as immunadjuvants[75-78]. Studies suggested significant enhancement of both cell-mediated and humoral immune response induced by addition of the block copolymer formulations with respect to a very broad spectrum of antigens.

Polymeric micelles bearing targeting ligands (fig. 2C) may also be used as drug targeting agents. Cationic liposomes modified by different pluronic block copolymers have been prepared and the influence of pluronic on the cellular uptake of antisense oligonucleotides (ODN) based on cationic 3beta[N-(N', N'-dimethylaminoethan)-carbamoyl] cholesterol (DC-Chol) liposomes was studied by flow cytometric analysis[79]. It showed that DC-Chol liposomes containing Pluronic gave 1.7-2.3 times higher capacity of cellular uptake of ODN. Poloxamers also inhibit the postoperative adhesion of bacteria. In orthopedic surgery polymethylmethacrylate (PMMA) is used as the acrylic cement but it has the disadvantage of promoting bacterial adherence. A report suggests the antiadhesive effect of poloxamer 407(P407), together with modifications in the antimicrobial susceptibility of residual adherent staphylococci[80].

CONCLUSIONS

With bright expectations of new developments in near future, poloxamers can be used as the structural elements in novel self-assembling gene delivery systems that may be superior to the currently known vectors. Furthermore, pluronic copolymers are the molecules that can be used in designing of artificial biocompatible materials.

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