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Poloxamers: A pharmaceutical excipients with therapeutic behaviors

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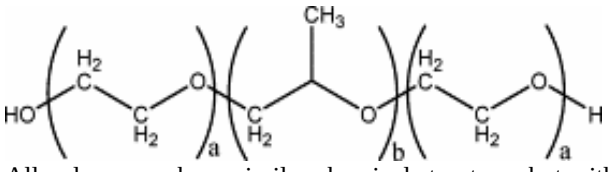
Abstract: The effect of excipients for synergistic effect or any combinational therapy is became a one of the best alternative for the dosage form development in the current research. Here we have reviewed on the different category of poloxamers as novel polymer for the drug delivery. Apart from the very good excipient properties, poloxamers showed a clinical and therapeutic uses for cure and treatment of various physiological condition. It is used in the various DNA technology, brain injury, cardiovascular, microbiological, burn injury and ophthalmic treatment also. The goal of this review is to improve the used of poloxamers to achieved economic treatment with less side effect.

Key words: Poloxamers, Copolymers, Pharmaceutical ingredient, Therapeutic effect

1. Introduction:

Poloxamers are non-ionic poly (ethylene oxide) (PEO)–poly (propylene oxide) (PPO) copolymers. They are used in pharmaceutical formulations as surfactants, emulsifying agents, solubilizing agent, dispersing agents, and in vivo absorbance enhancer [1]. Poloxamers are often considered as "functional excipients" because they are essential components, and play an important role in the formulation[2]. Poloxamers are synthetic triblock copolymers with the following formula:



All poloxamers have similar chemical structures but with different molecular weights and composition of the hydrophilic PEO block (a) and hydrophobic PPO block (b). Two of the most commonly used poloxamers are poloxamer 188 (a=80, b=27) with molecular weight ranging from 7680 to 9510 Da, and poloxamer 407 (a=101, b=56) with molecular weight ranging from 9840 to 14600 Da. Despite their wide range of applications, limited analytical techniques have been reported in literature for characterizing poloxamers and few are targeted to quantify poloxamer contents in formulations with desired sensitivity and accuracy.

Poloxamer is available in different grade based on the physical parameter like Molecular Weight, Weight % of oxyethylene etc. The common available grades are poloxamer (68, 88, 98, 108, 124, 188, 237, 338, and 407) [3].

Their surfactant property has been useful in detergency, dispersion, stabilization, foaming, and emulsification[4]. Some of these polymers have been considered for various cardiovascular applications, as well as in sickle cell anemia. Two polymers from this class, poloxamer 188 and poloxamer 407, show inverse thermosensitivity; therefore, they are soluble in aqueous solutions at low temperature, but will gel at higher temperature [5].

2. Poloxamers as Pharmaceutical excipients

Poloxamers possesses properties which appear to make it suitable for use in the formulation of topical dosage forms. Poloxamer 407 had been used in vehicles for fluorinated dentifrices, eye applications and contraceptive gels. A poloxamer based dental gel product has been in use several years for treating patients with sensitive gums and teeth. Moreover, P-407 gel has been shown to possess many favorable characteristics for use as a burn dressing. Not only does the gel provide a non-toxic

detergent covering to the wound, but specific studies suggest that the pluronic gel itself may have a beneficial action, accelerating wound healing over controls[6] . This makes P-407 a very suitable vehicle for gels intended to be applied for ulcers and traumatic lesions.

For example, the formulation of conventional suppository, a polyethylene glycol (PEG)-based suppository, which may softens or melts lately in the rectum due to its relatively high melting point, can not be rapidly absorbed in the rectal mucous membranes. Furthermore, such a PEG-based suppository, which may reach the end of the colon, has a loss of drug at colonic level and may also allow the carried drugs to undergo the first-pass effect. In this study, as a base of novel poloxamer-based suppository, a mixture of poloxamer 124 (P 124) and poloxamer 188 (P 188) with the melting point of about 15 and 55 °C, respectively, has been selected. In addition, P 124 and P 188 are known to have suitable mucoadhesive force, low toxicity, less skin irritation, good drug release characteristics and compatibility with other chemicals[7] .

Apart from this so many activities of poloxamer as formulation excipients, here we have planned to review the specific use of poloxamer in treatment of some disease state and as an alternative substitute for the therapy.

3. Important clinical applications of Poloxamers in different field

3.1 Biotechnological activity

Poloxamer hydrogel is used for the assessment of bio film susceptibility towards biocide treatments. Here for this type of activity a Chilled poloxamer was mixed with an inoculum of Pseudomonas aeruginosa and placed as 100 µl drops onto separate glass cover-slips. These were placed into sealed Petri dishes containing moistened cotton wool and incubated at 35°C. SDS-PAGE of cell envelope preparations showed the poloxamer-grown cells to exhibit a biofilm rather than planktonic phenotype. Susceptibility towards various concentrations of chlorhexidine, iodine and hydrogen peroxide was assessed for 10 min at 35°C for suspensions of broth-grown cells and for incubated poloxamer-gels (1 and 16 h). The gels were immersed in biocide, on their glass supports, before transfer to neutralizer at 10°C where dissolution was complete within 5 min. The gel populations mimic the localized high cell densities observed in biofilms and will also be subject to the same nutrient and chemical gradients as found within natural biofilms. Thermoreversible gelation enables complete recovery of the test inoculum without further trauma [8] .

In vitro studies suggested that poloxamer 407 enhances transfection efficiency of adenoviral vectors in vascular smooth muscle cells. Gene transfer was performed in balloon-injured rat carotid arteries using E1- adenoviral vectors diluted in either poloxamer 407 or phosphate buffered saline (PBS). Transfection efficiency was significantly higher in rats transfected using a nuclear -galactosidase expressing adenovector diluted in poloxamer 407 versus PBS. Moreover, in the presence of poloxamer 407, it was possible to reduce the incubation time of adenoviral vectors from 20 to 10 min without compromising transfection efficiency. Poloxamer 407 did not evoke specific tissue toxicity. Site-specificity of arterial gene transfer, assessed by PCR, was not altered by administration of poloxamer 407. These findings suggest that poloxamer 407 may be useful to improve the efficiency of adenovirus-mediated arterial gene transfer[8] .

3.2 Brain injury treatment

Surfactant poloxamer 188 decreases inflammation and tissue damage after experimental brain injury in rats. The surfactant, poloxamer 188 has been found to protect against tissue injury in various experimental models. Its protective mechanism may involve the effects of the surfactant against oxidative stress and inflammation. Here in this investigation the role of P- 188 is the reduction of tissue injury and macrophage response in the rat striatum. Fifteen Sprague-Dawley rats underwent stereotactic injection of 120 nmol of quinolinic acid into the striatum and received intracisternal injection of vehicle or P-188 (40 mg/kg) at 10 minutes and 4 hours post injury. Rats were killed after 1 week, and the histological score was determined based on the degree of overall tissue injury (Grades 1-4) at the lesion site. The number of macrophages within the lesioned striatum was compared with that found within the striatum on the non operated contra lateral side. Striatal injection of the toxin produced a lesion characterized by necrosis and inflammation surrounding the injection site in all six control animals. The rats that received intracisternal surfactant also had significantly less macrophage infiltrate than control animals. The surfactant P-188 reduces tissue loss and macrophage infiltrate after excitotoxic brain injury in the rat. Possible mechanisms of this effect may include direct surfactant modulation of inflammatory cell membrane fluidity[10].

3.3 DNA Delivery

Electroporation has been reported to facilitate naked DNA gene transfer in skeletal muscle, but has also been implicated in the pathogenesis of electrical injuries. To assess the effects of electroporation on gene transfer, mouse quadriceps muscles were injected with the luciferase reporter plasmid VR1255 and electroporated with caliper electrodes. Intramuscular luciferase expression was increased 10- to 70-fold by electroporation, depending on the DNA dose and injection volume used. In the absence of plasmid DNA injection, electroporation of quadriceps muscles resulted in rapid elevations in serum creatine phosphokinase activity, but did not elicit visible muscle damage. However, in muscles injected with plasmid DNA and electroporated, visible lesions consistently developed in

the areas proximal to electrode placement when field strengths optimal for gene transfer (300 volts/cm) were applied. Co-injection of poloxamer 188 (pluronic F68) with VR1255 substantially reduced elevations in serum creatine phosphokinase activity following electroporation, but did not inhibit the development of muscle lesions. In non-electroporated muscles, co-injection of poloxamer 188 increased luciferase expression threefold. Poloxamer 188 may thus constitute a useful excipient for intramuscular delivery of naked DNA[11] .

3.4 Microbiological activity

There is a reported study for the Reversion of Amphotericin B Resistance in Leishmania donovani by Poloxamer 188 in Vitro. A micellar formulation of amphotericin B (AmB) solubilized with poloxamer 188 was evaluated against an AmB Leishmania donovani-resistant line. A concave isobologram showed a synergistic effect of this association against promastigotes. This result was confirmed with amastigotes since the 50% effective concentration of the new formulation was 100 times less than that of the control AmB formulation. The increase in the activity of AmB against the wild-type WT amastigotes, even when poloxamer 188 does not modify the activity of free drug at the membrane level, could be a consequence of the surfactant's effect on the AmB aggregation. This fact may improve drug uptake by macrophages and drug availability for the parasite[12] .

3.5 Cardiovascular treatment with poloxamers

3.5.1. Temporary vascular occlusion with poloxamer 407

There is a need for safe and reversible occlusions during percutaneous endovascular procedures. Poloxamer 407 is a non-ionic surfactant with rapid reversible sol–gel transition behavior. The safety and efficacy of this polymer as a temporary embolic agent was investigated. First, dissolution time after gelation of poloxamer was determined in an in vitro model. Then, transient poloxamer occlusion of renal and pulmonary arteries of seven dogs was followed by serial angiograms. Macroscopic and pathological changes were studied 1 week later. This experiment was repeated in similar arteries in one pig, and in auricular arteries of two rabbits. Poloxamer dissolution after in vitro polymerization was completed within 1–20 h, depending on concentrations. In vivo poloxamer 22% injections led to complete occlusion, followed by full recanalization within 10–90 min without complication. The only biochemical effect of poloxamer occlusions was transient elevation of triglyceride levels. There were no pathological abnormalities at 1 week. Poloxamer 407 could be used as an embolic material for temporary occlusions also[13].

3.5.2. As a new therapeutic approach for duchenne muscular dystrophy

Duchenne muscular dystrophy (DMD) is a devastating progressive disease of striated muscle deterioration. This fatal X-linked disorder results from the loss of the protein dystrophin, which in turn causes striated muscle membrane instability. Cardiac dysfunction is a growing problem in patients with DMD, but relatively little is known about the pathophysiology of the dystrophic heart. At present, there is no effective treatment for DMD and the current clinical approaches are primarily supportive in nature. The tri-block poloxamers, specifically poloxamer 188 (P188), are able to stabilize the membranes of dystrophic myocardium in animal models and may offer a new therapeutic approach for cardiac disease in DMD[14].

3.6 Other uses of Poloxamers in general conditions

3.6.1 As a postsurgical materials

Poloxamer 407 is used as an intraperitoneal barrier material for the prevention of postsurgical adhesion formation and reformation in rodent models for reproductive surgery. Contemporary adhesion-prevention regimens for infertility surgery emphasize the use of barrier materials to effect physical separation of injured surfaces before reperitonealization. Poloxamer 407 is a biocompatible polymer that displays reverse thermal gelation characteristics; that is, the material exists as a liquid at room temperature and as a solid at body temperature. These properties make it an ideal material for use in laparoscopic surgery[15].

3.6.2. Improvement in capillary blood flow in the zone of stasis after burn injury

Cutaneous burn injury causes blood flow reduction in regions near the site of the injury, collectively termed as the zone of stasis. Blood flow, in this zone, ceases after 24-48 hours resulting in an expansion of the injured area. CD-1 male mice (30 g) were fitted with skin flap chambers and capillary blood flow was visualized by intravenously injecting fluorescently labeled red blood cells into the mice. Playback image analysis showed that there was a reduction in blood flow near the site of burn injury immediately (0-2 hrs.) after the injury and away from the site of injury there was no change. Intravenous injection of Poloxamer-188 (0.1 ml, 200 mg/kg) greatly improved blood flow in the zone of stasis[16].

3.6.3. Interaction with lipid monolayers

The mechanism by which poloxamer 188 (P188) seals a damaged cell membrane is examined using the lipid monolayer as a model system. X-ray reflectivity and grazing-incidence x-ray diffraction results show that at low nominal lipid density, P188, by physically occupying the available area and phase separating from the lipids, forces the lipid molecules to pack tightly and restore the barrier function of the membrane[17] .

3.6.4. Lens refilling with poloxamer hydrogel

The appropriate concentration of poloxamer hydrogel was determined for injection by examining the transparency and gelling temperature of this material, assessing the lens capsule refilling technique, and

studying the postoperative findings in a rabbit model[18] Two different methods have been used to refill the lens capsule after endocapsular phacoemulsification. One involves the implantation of the refilled endocapsular balloon, and the other direct lens filling. However, currently, the balloon implantation seems to be no longer a topic of study. The reason is because the technique is limited in terms of the discrepancy between the shape of the individual lens capsule and that of the preformed balloon, wrinkling of the anterior and posterior capsule-balloon surfaces, and the technical complexity of the surgery which is shown in figure no.1.

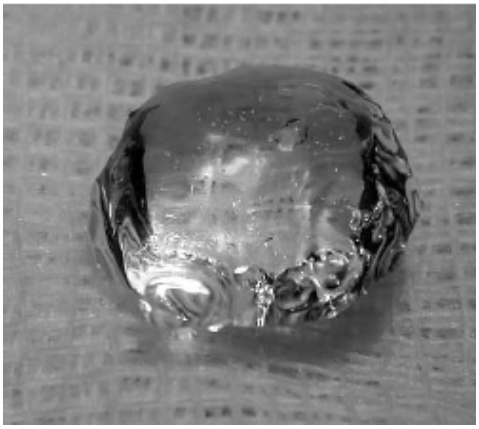


Figure 1: Rabbit lens filled with poloxamer hydrogel immediately after operation.

3.6.5. Prevention of adult skeletal muscle cells necrosis

It has been shown that several multi-block copolymer surfactants (i.e. poloxamers) can induce sealing of damaged membranes following reperfusion injury, electroporation, heat shock and traumatic injury[19] . Acute cellular necrosis occurring minutes to hours after massive ionizing radiation exposure (IR) results from rapid membrane lipid peroxidation, blebbing and membrane breakdown. Specifically, the efficacy of the amphiphilic surfactant Poloxamer 188 in preventing acute necrosis of adult rat skeletal muscle cells after high-dose IR was studied.

4. Conclusion

The use of pharmaceutical excipients for the drug delivery as well as therapeutic agent is one of the best alternatives for the new dosage form development. It is also imparting the synergistic effect with active medicament to treat the disease and some change in physiological condition of human body. So, as a part of this review we have tried to stress on the future use of poloxamers and there is a best option for the researchers to develop the better technique containing Poloxamers as a basic ingredients. Inspite of pharmaceutical properties, the thermoreversible nature of poloxamer is of the utmost interest in optimising drug formulation which promote the prolonged release of pharmacological agents. As compare to other polymers characteristics, it has shown a promising option for the delivery of drug through various drug delivery technologies. A constant improvement with drug delivery technology should be there to improve the effect of dosage form and make it more suitable at there relevant site. In addition, new findings have demonstrated immuno-modulation and cytotoxicity-promoting properties of Poloxamers revealing significant pharmacological interest and, hence, human trials are in progress to specify these potential applications.

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