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Poloxamer: A Novel Functional Molecule For Drug Delivery And Gene Therapy

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Abstract:

Aim: Poloxamer a block copolymer is well known for its thermoreversible property also has several other properties used in several formulations for its advantage over optimising the drug release from its formulation with a sol-gel transition property.

Methods: Poloxamer exhibits in a sol state at less than room temperature and gets converted to a gel state at body temperature (37.2°C) thus modifying drug release characteristics. Poloxamer formulations were also evaluated for other therapeutic properties for both *in-vitro* and *in-vivo* based on its specific property. Poloxamer is frequently used polymer, which showed a good solubilisation capacity and an enhanced release profile of many poorly soluble drugs for several route of administrations such as oral, topical, ocular, rectal, vaginal, nasal and parenterals. Even inclusion of active ingredients in liposomes, micro and nano formulations were performed and showed more satisfying results. The recent inventions gave a good breakthrough in Poloxamer market due to its agreeable application in gene therapy and cytotoxicity studies.

Conclusion: This work extensively concentrates on the different grades of Poloxamer for its physical and biological applications.

Keywords: Cytotoxicity, Liposomes, Nanoformulation, Poloxamer, Sol-Gel transition, Thermoreversible.

INTRODUCTION

Poloxamer with its synonym as polyethylene-propylene glycol copolymer and trade names as Supronic, Pluronic or Tetronic have been introduced in 1950 as a non-ionic triblock copolymer.[1] They were since then very famously used in diverse pharmaceutical applications. Chemically poloxamer is α-Hydro-ω-hydroxypoly (oxyethylene)$_a$ poly (oxypropylene)$_b$ poly (oxyethylene)$_a$ block copolymer and they consisted of two hydrophilic chains of ethylene oxide chains (PEO) that sandwiched one hydrophobic propylene oxide chain (PPO) giving a chemical formula $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$ where a and b have the values as shown in the Table 1. The varying length of polymer blocks giving rise to different polymers identified as 124, 188, 237, 338 and 407 showing a slight difference in their properties. The common representation of Poloxamer is indicated as 'P' succeeded by three digits where the first two digits are to be multiplied by 100 and that gives the molecular mass of the hydrophobic propylene oxide and the last digit is to be multiplied by ten that gives the content of hydrophilic ethylene oxide in percentage. The common trade name used is Pluronic and the usual copolymer representation denotes its physical appearance (L-Liquid, P-Paste and F-Flake). The trade name coding is given as poly for Pluronic, followed by a single letter representing the physical form and then by two digits. In these two digits the first digit is to be multiplied by 300 to give molecular mass of propylene oxide, and the next digit is multiplied by ten to get the ethylene oxide in percentage.[2]

Poloxamers usually have an efficient thermoreversible property with characteristic sol-gel transition temperature that is used widely in the thermogelling system. Below the transition temperature it is present as a solution and above this the temperature the solution results in interaction of the copolymer segment which leads to gelation. Poloxamers incorporated in a drug delivery systems are administered through oral, parenteral, topical routes and observed to be used as solubiliser, emulsifier and stabiliser. Poloxamers are non-toxic and non-irritant and so, it is also used as wetting agents in ointments, suppository bases and gels.[3] In this work the various physical and biological properties of Poloxamers with their different application studies are highlighted. This review gives a clear idea on the different formulation approaches where the polymer is used for its distinct property that helps in the drug delivery leading to better therapeutic activity through novel drug delivery system

GELLING AGENT

The block copolymer poloxamer in aqueous media exhibits micellar structures which can convert into gel like structures based on their length, concentration and temperature as shown in Fig 1. The increase of temperature above the critical micelle concentration (CMC) and critical micelle temperature (CMT) leads to the reduction of solubility of propylene oxide chain (PPO) blocks in aqueous solution and simultaneous increase of concentration and temperature will lead to the core shell type of micelle formation. The dehydrated micelle core helps in the incorporation of hydrophobic drug in aqueous poloxamer solution. After the incorporation of drug, the gelation process can be achieved by increasing the temperature and concentration above the critical gel temperature (CGT) and critical gel concentration (CGC) respectively. Here the physical entanglement and packing of micellar structures are the reason for gelation. This is a reversible process which is a specific advantage for the administration through smaller orifices where the polymer remains fluid below the CGT.[4,5] There were also several works performed with different drugs by *in-situ* delivery system as shown in Table 2.

A sub-gingival delivery system using poloxamer block copolymer was developed for perodonyal intrapocket administration. Formulation in the form of solution was administered where a gel transition is reached in the

periodontitis region leading to improved drug release and therapy followed by elimination through normal route from the body indicating a biocompatible system.[6] Prolonged residence time of drugs was observed by using poloxamer 407 in formulation at a concentration of 25 % w/w leading to a reversible thermal gelation helping in low diffusion co-efficient of drugs.[7, 8] Another extensive study of *in- situ* gel was performed with a combination of poloxamer 407 (28% w/w), Chitosan (CT) and Sodium Tripolyphosphate (TPP) that showing a decreased dissolution rate. By varying the composition of TPP, Chitosan and Poloxamer the gels were obtained with specific proportions and their pH was controlled for solubilisation of drug at specific site.[9] A thermo-sensitive gel was developed using poloxamer 188 at 10-15% w/w by a direct dispersion method. Here 0.1 % w/w of Carageenam and Sodium chloride solutions were prepared and added together with the poloxamer gelling system to obtain a 3-fold increase in gel strength. An *in-vitro* drug release experiment for an injectable controlled release platform achieved satisfactory results for a formulation with poloxamer 188 and poloxamer 407.[10] A gel formulation of 5-aminolevulinic acid (ALA) as active agent increased its permeation across the human stratum corneum when poloxamer 407 was combined with Dimethyl isosorbide (DMIS), Isopropyl alcohol (IPA) and Propylene glycol dicaprylocaprate (MIG) with constant ratio of water. A thermo gel formulation for dermal delivery was evaluated with different ratios of the additives which showed that the combination of Poloxamer 407 with MIG and water had better permeation than others.[11]

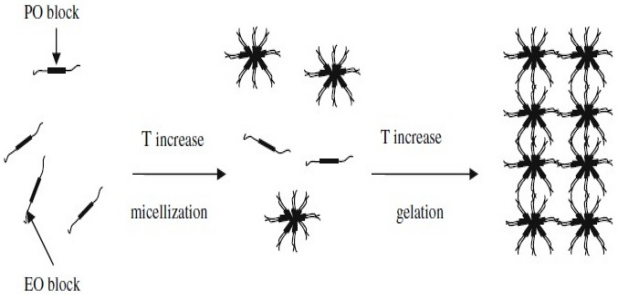

Fig 1: Illustration of micellar mechanism of Poloxamer [6]

SURFACTANT

The mechanism of Poloxamer 407 as shown in Fig 2 shows its ability to hydrolyze the circulating triglyceride (TG) by lipoprotein lipase (LPL) study was performed *in-vitro* which showed that incubation of LPL and Poloxamer 407 inhibited enzyme activity at 24 µm and showed an activity loss of 50%. When concentration of Poloxamer 407 exceeded 350 µm there was a complete inhibition of LPL activity. The *in-vivo* studies on rats at a single 300 mg dose of Poloxamer 407 showed an increased LPL suppression of above 95% in post heparin plasma within 3 hrs and it was observed that Poloxamer 407 acts as a surfactant by reducing the rate of TG to be hydrolyzed by the heparin-releasable LPL inhibition leading to the increase in circulation of TG.[20] The surfactant property of poloxamer 188 (1.5 %) and poloxamer 407 (3 %) showed modification in surface properties of polystyrene particles. The Poloxamer coated polystyrene particles showed an increased particle diameter, measured by photon correlation spectrometry.

Table 1: Poloxamer grades and their pharmacopeial specifications.

Poloxamer[1]	**Pluronic**	**Physical form**	**Ethylene oxide units (n)[a]**	**Propylene oxide units (n)[a]**	**Average molecular mass**	**Weight % of Oxyethylene**		**Unsaturation (mEq/g)**
			(a)	*(b)*	*PhEur 2005/ USPNF 23*	*PhEur 2005*	*USPNF 23*	*USPNF 23*
124	L 44	Liquid	10-15	18-23	2090-2360	44.8-48.6	46.7± 1.9	0.020±0.008
188	F 68	Solid	75-85	25-40	7680-9510	79.9-83.7	81.8± 1.9	0.026±0.008
237	F 87	Solid	60-68	35-40	6840-8830	70.5-74.3	72.4± 1.9	0.034±0.008
338	F108	Solid	137-146	42-47	12700-17400	81.4-84.9	83.1± 1.7	0.031±0.008
407	F127	Solid	95-105	54-60	9840-14600	71.5-74.9	73.2± 1.7	0.048±0.017

[a] The average numbers of EO and PO units were calculated using the average molecular weights.

Table 2: Poloxamer as gelling agent.

Poloxamer	**Active ingredient**	**Route of administration**	**ReferenceNo**
407	Mebeverine hydrochloride, Metoprolol, Doxycycline and BMS-A and BMS-B, Vancomycin	Sustained Oral delivery	[12, 9, 13,8]
407	Nimesulide	Rectal	[14]
407 & 188	Clotrimazole	Vaginal	[15]
407 & 127	Ciprofloxacin, Peurarin	Opthalmic	[16, 17]
407	Chitosan salt	Buccal	[18]
407 & 388	5-aminolevulinic acid, Lecithin	Topical	[5, 19]
407	Proteins and peptide drugs, Ibuprofen octyl ester	Parenteral	[20, 4]

The uptake of polystyrene particles in small and large intestine was inhibited due to the poloxamer adsorption on the polystyrene particles. [21] In topical ocular delivery system, poloxamer 407 with an active agent Indomethacin (IND) gave a micellar solution. The *in-vivo* study was done using rabbits and an increased bioavailability of the drug and immediate onset time was observed compared to the commercially available IND product Indocin. It also showed an enhanced miotic response and more effective with a single dose when compared to the commercially available aqueous solution.[22]

Different drug delivery as in combination with Poloxamers were performed and sorted in Table 3. Poloxamers 338, 407 and Dimyristoyl Phosphatidyl Choline (DMPC) in combination was developed as liposomes where the poloxamer was observed to have an interaction with the phospholipid bilayer leading to a decrease in phase transition temperature. The solubilisation of phospholipid to mixed micelles was possible at high temperature and high concentration of surfactant poloxamer.[23] Poloxamer 407 in combination with Sodium caprylate and Ethyl butyrate was used in a nanoreservoir complex which caused a greater interfacial area of the emulsion that showed an improved bioavailability in animal models.[24, 25, 26]

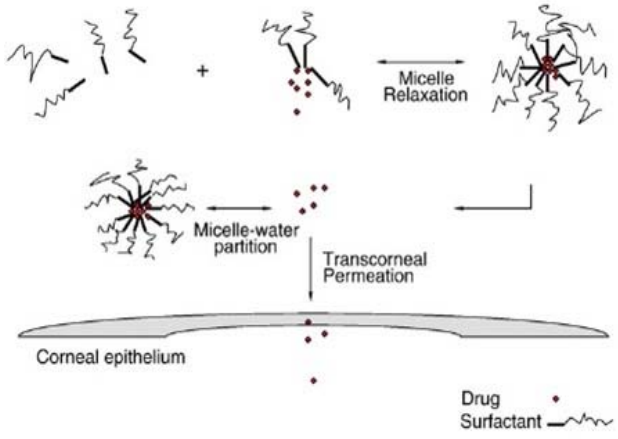

Fig 2: Topical ocular drug absorption through micellar system [22]

STABILIZING AGENT

The block copolymer PEO-PPO-PEO compositions with high PEO content are expected to have very low toxicity and higher solubilising capacity in different formulations with drugs as shown in Table 4. Poloxamer 188 used in a formulation that was developed and then in human plasma and whole blood showed that showed an increased whole blood permeability of networks and it was also observed that the increased fibrin permeability was due to fibrin fibres arrangement. The alterations of fibrin are the main reason to increase the mechanical stability contributing to antithrombotic and rheological effects.[30, 31] The drug loaded mixture of Pluronic F127and Pluronic P123 form a micelle solution which was prepared by a method of thin film hydration. The micelle stability was focused here especially by introducing Pluronic F127 of 33 wt % into Pluronic P123 micelle system. It was observed that this system significantly increased the stability of drug loaded mixture. The *in-vivo* studies also showed that the IC_{50} of the formulation was much lower than a standard (Taxol) used. There was also increase in stability of the gel formulation using Poloxamer with organic solvents such as ethanol, propylene glycol, glycerol and PEG 400. Poloxamer 407 in the presence of these organic solvents, self assembles into two liquid crystal structures namely micellar cubic and hexagonal structures that are thermodynamically stable. The stability range of these gel phases differs extensively with the organic solvents used. Based on the macro and microscopic view of the structures it was classified these organic solvents into two groups were PEG 400 and glycerol in one group as these do not undergo swelling of PEO blocks and are located at polar domains and on the other hand, propylene glycol and ethanol caused swelling of PEO and PPO blocks, and also they undergo a polar formation at the interface. The relative polarity of these solvents indicated as partition co-efficient or solubility was related to stability of the gel formulation. This help in the modulation of phase behaviour of these polymers based on polarity.[32] Poloxamer 407 in combination with a liposome showed an increase in stability of liposome formulation by increasing half life, preventing aggregation and fusion of phosphatidylcholine multilamellar vesicles.[33] In a comparative study, Pluronic F68 showed better stability than phospholipids Epikwon 145 V a standard used in the formulation with bile salts.[34] The thermoresponsive sustained release delivery system with cubosomes and poloxamer 407 showed sol- gel transition, whereas when Pluronic K (25R4) was added with this sustained release formulation, it increased the gelation temperature with a free flow in liquid at 22°C and gelled immediately at 37°C body temperature and also showed better stability in aqueous environment.[35] The low stability of poloxamer hydrogel in an aqueous solution lead to the combination development of poloxamer 407 with acrylate and thiol groups of 17.5 wt % at body temperature. It was observed with an immediate crosslinking formed between acrylate and thiol that modified poloxamer 407 property, giving rise to a remarkable increase in stability of drugs about four times and for its potential application in controlled drug release.[36]

Table 3: Poloxamer as a surfactant.

Poloxamer	Active ingredient	Route of administration	Reference No
338, 188, 407	^{125}I-fibrinogen, Polystyrene, Heat- denatured hen egg white lysozyme	Oral	[27, 7, 13]
188 and 407	Polysorbate 80	Ocular	[19]
188, 407, 207	Poly(lactic-co-glycolic acid), Omnipaque^{TM} 300, Bupivacaine	Parenteral	[28, 29, 17]

Table 4: Poloxamer as a stabilizing agent

Poloxamer	Active ingredient	Route of administration	ReferenceNo
407, 188, 127	Phytantriol cubosomes, Fibrin network structures, Polyglycolyzed oils, Glycols	Oral	[10, 20, 27, 21]
188, 407, 127	Bile salts, Egg lecithin, Indocyanine green	Parenteral	[24, 37, 38]

Table 5: Poloxamer as a solubilising agent.

Poloxamer	Active ingredient	Route of administration	ReferenceNo
407, 188, 388	Triamcinolone acetonide, Ciclopirox olamine, Cyclosporine, Felodipine	Oral	[33, 30, 46]
407	Atrial natriuretic factor	Nasal delivery	[47]
407	Methotrexate, Acrylate and Thiol groups	Topical	[48]
188	Ibuprofen	Rectal	[31]

Table 6: Miscellaneous Poloxamer properties.

Property	Poloxamer	Active ingredient	Route of administration	Reference No
Meltable binder	188	Praziquantel, Ibuprofen	Oral	[34, 35, 58]
Wetting agent	188	Hydrochlorothiazide, Most BCS class II drugs	Oral	[37, 36]
Suppository base	407, 188, 124	Propranolol, Acetaminophen, Diclofenac sodium	Rectal	[39, 28, 29]

SUPPOSITORY BASE

A suppository formulation was developed by loading drug with poloxamer to enhance the dissolution and the anti-tumor activity. The formulation with anti-cancer drug showed better anti tumor activity and also observed with decreased hepatotoxicity when compared to conventional oral formulation. Thus Poloxamer based suppository was observed to be an effective rectal dosage formulation with less irritation and damage to the rectal tissues. The conventional suppositories create leakage at the rectum causing discomfort to patients. The problems encountered with solid suppositories without mucoadhesivity was overcome by an *in-situ* gelling and mucoadhesive liquid suppository with a combination of Poloxamer 407 and Poloxamer 188 at a concentration of 15-20 % which gelled at 34-35°C.[39] The suppository base developed by a combination of poloxamer, carbopol and polycarbophil adjusted the physical property of gel strength and bioadhesive force that showed drug retainment in rectum for around 6 hrs when tested *in-vivo*.[40] The Poloxamer based suppository formulation composed of Poloxamer 124 and Poloxamer 188 showed that even a very small amount of Poloxamer 188 can affect the melting point and the dissolution rates of drug, and the dosage form retained in the rectal tissue for >4 hrs and did not cause any irritation or damage to the rectal tissues of the rats.[41] There were several studies referred showing formulation with different drugs as in Table 6.

SOLUBILIZER

Solubility enhancement of drugs was achieved using poloxamer 188 at different concentration as polymer (4-22g/L) and at different temperatures (10-50°C) and work with different drugs was concentrated in Table 5. When temperature was increased with increasing poloxamer concentration, a higher hydrodynamic radius and better distribution of size was observed due to micelle formation. This showed that Cyclosporine A had a better solubility in aqueous polymer solution than water.[42] Ibuprofen loaded liquid suppository was prepared using methanol and Poloxamer 188. It was found that the liquid suppository with methanol showed an increase in solubility of the formulation in methanol to Ibuprofen ratio of 0:10 to 4:6 but above 4:6 ratios there was an abrupt decrease showing that there was the formation of an eutectic mixture with four parts of Ibuprofen with six parts of methanol. Simultaneously the formulation with poloxamer 188 showed an increase in solubility and for ratio 4:6 there was a 6 fold increase in Ibuprofen solubility compared to solution with methanol alone. So a methanol Ibuprofen ratio of 1:9 in a Poloxamer gel of 15 % showed maximum solubility. The aqueous solution of the thermosensitive gels were observed to be of low toxicity with good solubilisation capacity and can be highly compatible for a topical drug delivery system.[43,44] Poloxamer 407 was used as a solubilisation agent in a thermoreversible hydrogel formulation, but its solubilisation capacity was observed to be less in some poorly soluble drugs. So, to increase the solubilisation effect, along with poloxamer 407 a complexation with cyclodextrin was performed giving rise to a complex called as poly-pseudorotaxanes due to the threading in the ring cavity of cyclodextrin. Therefore when P407-drug thermosensitive hydrogels cannot solubilise the drug dose completely, cyclodextrin was used to increase drug solubility and to modulate release property.[45]

MELTABLE BINDER

The fluidised hot melt (FHMG) granulation procedure in pharmaceutical industry was a novel technology mainly adopted for water sensitive materials. This process eliminates the wetting and drying phases finally giving an advantage of energy and time consumption. Poloxamer 188 was used as a meltable binder for granulation process indicating that there was high influence of the binder in the nucleation mechanisms.[49,50] Namely, immersion and

dispersion when the binder drop is large compared to the other particles present in the formulation there will be an immersion of the smaller particle into the larger droplet giving saturated pore nuclei. On the other hand for smaller droplets of binder there will be a complete distribution of these binders to the surface of the large particles and then it slowly starts to unite. There might be trapped air created between the nuclei causing a voidage. Different concentrations of 4-8 % (w/w) of Poloxamer 188 were used to make formulations at a specified air speed of 1.50 ms^{-1} at a constant temperature of 80°C.[51,52] It was observed that viscosity of meltable binder showed a significant influence with FHMG formulations resulting in an increase in size of the granules. So the results of the particle size analysis of the granules showed an increase in mean particle size with increase in these binder concentrations. [53] Drugs showing low aqueous solubility and high permeability of the mass evaluated using melt granulation technique with poloxamer 188 as a meltable binder and was observed to show a significant increase in dissolution rate. [54, 55] Drugs with different routes were evaluated and sorted in Table 6.

DISINTEGRATING AGENT

The tablets prepared with poloxamer as a disintegrating agent showed a direct relation of its concentration to the disintegration time. Here it was made as a comparative study with Aospovidone a standard disintegrating and poloxamer where the hydrophilicity was observed to be better in Poloxamer and it lead to swelling showing poloxamer a better disintegrating agent than the standards used. It was observed that the increase in the Poloxamer concentration enhanced the drug dissolution.[56, 57] Different drugs were used in formulations as disintegrating agent and showed in Tablet 6.

BIOLOGICAL PROPERTIES

Apart from the properties of pluronic with the above discussed pharmaceutical applications, they also signify a wide range of advantages in biological and chemical fields.

GROWTH OF CALLUS AND PROTOPLAST

Pluronic F68 showed significant effect on the growth of callus and protoplasts which was studied by using *Solanum dulcamara L*. It was observed that the roots of the plant showed a better tolerance to Poloxamer than the animal cell cultures. Generally Pluronic F68 was used to protect mechanical damage of animal cell cultures with its interaction with the cell membrane. Here the work was done with 3 different concentrations of Pluronic 68 to study the growth of the callus. It was observed that at low concentration range of 0.01% (w/v) of Poloxamer there was no development in callus growth whereas at an intermediate concentration of 0.1% (w/v) showed a significant increase in the growth of callus. At a higher concentration of 1 % (w/v) or above it was observed that there was an inhibitory effect on growth of callus. This work helped in optimising the concentration of poloxamer to enhance the growth of callus and protoplast.[59, 60] Protoplasts of *Albino petunia hybrid* was also grown in aqueous culture medium where the mean plating efficiency was observed to elevate about 37 % at the interface but remain unaltered in the presence of perfluorodecaline or oxygen separately. The mean plating efficiency at the interface of albino petunia hybrid was increased to 57 % by growing the callus in presence of perflurodecaline and oxygen along with the copolymer Pluronic F 68 at 0.01 % (w/v) concentration. This concentration of Pluronic was selected due to the growth stimulating effect observed in *Solanum dulcamara L.* Here Pluronic played an important role in decreasing the interfacial tension between perfluodecalin and water (about 40 %) leading to a maximum protoplast contact to interface. It was also observed that these supplementations increased the mean division frequency than control showing that the Pluronic F68 with perfluorodecaline gave a repeated mitotic division of protoplast.[61, 62]

TRANSGENE EXPRESSION IN SKELETAL MUSCLES

A novel gene therapy to enhance immunization during DNA vaccination was developed in combination with pluronic block polymers to deliver the DNA plasmid. The naked DNA delivery to the skeletal muscles has shown meaningful gene expression.[63] It was also possible for the delivery of DNA by encoding it with proteins such as Erythroprotein and Interleukin-5, [64, 65] and also with Fibroblast growth factor and Endothelial growth factors.[66] But in all these cases a relative low level of gene expression was encountered leading to an alternative approach. It was the delivery of naked DNA along with Poly (vinyl pyrrolidone) and Cationic DNA, but in both these cases condensation of DNA was observed.[67, 68] So to overcome these problems Pluronic block copolymer was used in combination with plasmid DNA. The observed results showed that the gene expression increased to 5-20 fold compared to the naked DNA and also showed no traits of DNA condensation as of Cationic DNA or Poly (vinyl oyrolidone) formulations. It was also observed that the maximum stimulation of gene expression was observed at a relative optimum concentration of 0.01 % wt that was also found to be in a 500 fold safety margin level in animals.[69, 70]

POLY-CATION OF PLURONIC CONJUGATES IN GENE DELIVERY

A novel gene delivery system with Pluronic block polymer showed, poly-cation mediated gene transfer *in-vitro*. A synthetic polycation complex was prepared with plasmid DNA and Poly (N-ethyl-4-vinyl pyridinum bromide) that showed minimum DNA uptake and transgene expression. Latter DNA plasmid with Poly (N-ethyl-4 vinyl pyridinium bromide) was complexed with Pluronic P85 of 1 % which showed a significant increase in DNA uptake and transgene expression.[71,72] A recent study have shown a fourfold increase in gene expression when a receptor mediated gene delivery with plasmid DNA in the presence of pluronic F127 was performed.[73] Pluronic F127 in cervical cancer cell line showed a better transfection efficiency when a polycation of DNA complex was prepared with the copolymer.[74] Pluronic P123 combined with polyethyleneimine by a covalent conjugation gave a complex of [P123-g-PEI (2K)] forming a small and firm complexe with DNA finally giving a high transfection activity. [75]

OLIGONUCLEOTIDE DELIVERY USING PLURONIC

The delivery of oligonucleotides with plasmid DNA was designed using poly (etheleneoxide)-g- polyethyleneimine [PEO (8K)-g-PEI (2K)] in an *in-vivo* polycation system.[76, 77] Recently a complex of Pluronic P85 and polyethyleneimine [P85-g-PEI (2K)] was prepared and was observed to show a better stability than the complex without pluronic. The IV administration of both complex *in-vivo* was studied and the results showed that PEO(8K)-g-PEI(2K) complex gave an accumulation mainly in kidney whereas the P85-g-PEI(2K) gave an accumulation of DNA mainly in hepatocytes and little observed in lymphocytes. These results showed that PEO (8K)-g-PEI (2K) complex formulation had an oligonucleotide distribution that was based on the hydrophilic- lipophilic balance of the polyethylene chain, whereas P85-g-PEI (2K) complex showed enhanced oligonucleotide accumulation at specific compartments supporting targeted delivery.[78]

PLURONIC AS EFFLUX PUMP INHIBITORS- BLOOD BRAIN BARRIER (BBB)

Pluronic P85 (4600 Da) has been extensively studied in the area of efflux pump inhibitory action in BBB drug delivery system. The mechanism behind was believed to be ATP depletion and ATPase inhibition and its extensive effect on membrane fluidization. Delivery of Rhodamine 123 with Pluronic in brain endothelial cells gives a better efficient BBB delivery and a concentration dependent inhibitory activity.[79, 80] *In-vivo* efficiency data provided results on enhanced BBB transport influenced by pluronic to efflux pump substrates. Pluronic P85 was also used in combination with digoxin in wild type mice models. The study showed that pluronic P85 played an important role in prolonging the residence time and caused an increase in drug concentration level in brain.[81] Rhodamine 123 a P-gp substrate was formulated with and without Pluronic P85 that showed an enhanced Rhodamine 123 accumulation with even low polymer concentration. It was observed that when Pluronic P85, concentration was above CMC level there was micelle formation of the drug leading to a very less amount of free Rhodamine 123 present for uptake. Whereas, when Pluronic P85 was below CMC concentration it caused a better uptake of Rhodamine 123 due to the P-gp inhibition mechanism.[82]

PLURONIC IN CANCER THERAPY

Poloxamers are efficiently used in cancer therapy either by inhibiting efflux transporter proteins or by circumventing efflux pump transport. Doxorubicin was formulated with pluronic and both *in-vitro* and *in-vivo* studies were performed which showed an increased drug accumulation in brain with pluronic contained formulation showing that there was an increased P-gp expression with polymer solution causing this mechanism.[83, 84] There was also a comparative study on a multidrug resistance gene 1 (MDR1) transfected cells and non transfected cells with Pluronic showing an enhancement of Pluronic accumulation and permeation of P-gp substrates. The inhibition of multidrug resistance protein 1 (MRP1) and multidrug resistance protein 2 (MRP2), in efflux pumps was a significant observation showing the lesser P-gp ATPase activity in these efflux pumps when compared to the formulation with pluronic.[85, 86]

CONCLUSION:

Poloxamer, a commonly identified polymer for its thermogelling property is also universally accepted for its various other special properties and applications. Past 50 yrs the polymer has been in market but its various other properties than gelling capacity, surfactant and solubilizer were not well explored. This paper clearly evidences the physicochemical and biological properties of Poloxamer and its different mechanisms in different administrations. The efflux pump inhibitory mechanisms in BBB and Cancer therapy are gaining of utmost importance as Poloxamer shows a better application in gene therapy. The new trend also suggests the combination of other polymers with Poloxamer to develop better pharmaceutical aids still an extensive future work is needed in human clinical trials based on its benefit and risk ratio.

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