REVIEW PAPER

Pluronic as nano-carier platform for drug delivery systems

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ABSTRACT

A usual method to build a nano-drug delivery system is incorporating the drug within the nano-carrier to high solubility, improved circulation time, and metabolic stability. However, recent studies indicate that the polymeric nanomaterials can be applied more than the inert carrier functions based on the biological response modifiers. Tri-block copolymers of Pluronic as one of these polymeric materials that they cause different functional alterations within cells. The key characteristic related to the biological activity of Pluronics is their ability to incorporate drug into membranes followed by subsequent translocation into the cells and then affecting the different cellular functions such as ATP synthesis, mitochondrial respiration, activity of drug efflux transporters, gene expression, apoptotic signal transduction and so on. As a result, Pluronics cause effective sensitization to the different anticancer agents based on the multidrug resistant (MDR) and resulting increase in the drug transport across the blood brain and intestinal barriers that it causes transcriptional activation of gene expression both *in vitro* and *in vivo*. On the other hand, there is an increasing interest in the area of drug delivery systems by using polymers as carrier for small and large molecules. Particulate systems like polymeric nanoparticles and micelles have been applied as a physical method to improve the pharmacokinetic and pharmacodynamics profiles of the different drug molecules. It is widely that Pluronics are excellent polymer for nano-drug delivery vehicles by different routes of administration due to their wide compatibility with different drug candidates This review is aimed to highlight the Pluronics -based nanomicelles/ nanoparticles that have been developed to date.

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INTRODUCTION

In recent years, by using nanotechnology, the nanometer-sized objects and nanomaterials were designed and fabricated that they offers the suitable tools to delivery of different drugs and other bioactive agents [1-9]. In pharmaceutical and drug delivery system (DDS), by using nanotechnology, the therapeutically active agents were formulated in various Nano form objects such as Nano particles, Nano capsules and micellar systems that demonstrated many advantages in drug delivery [3]. Among these approaches, the polymeric micelles illustrated a remarkable potential to encapsulate poorly water-soluble drugs inward the hydrophobic core.

Emulsion is a fine dispersion of minute droplets of one liquid in another in which it is not soluble or miscible On the other hand, suspension is a mixture in which particles such as drugs are dispersed throughout the bulk of a fluid. Because of thermodynamic instability of these forms, they demonstrated phase separation upon storage. In contrast, micelles and microemulsions are stable and transparent and have lower dispersed phase size

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(≤ 200 nm) than emulsions. Microemulsions show many advantages such as stability, transparency, low viscosity, ease of preparation and improved drug delivery systems. Furthermore, they considerably are used as drug delivery vehicle in pharmaceutical applications and treatment of diseases owing to their unique features [10]. Currently, a number of polymers conjugates that are biologically active were provided in clinical development [11]. Polyethylene glycol(PEG), poly(D,L-lactideco-glycolide) PLGA, poly(lactic acid) (PLA), N-(2-hydroxypropyl)-methacrylate HMPA copolymers are the most copolymers that utilized for medicinal applications [12,13]. The widespread utilization of amphiphilic copolymers in the medicine and pharmaceutical applications is due to their intrinsic biological activities and properties that these properties solve problems related to drug delivery. .Among various types of formulations, formulations based on pluronics have gained intense attention. Pluronic is an amphiphilic copolymers that includes a poly(propylene oxide) as hydrophobic block and poly(ethylene oxide) as a hydrophilic block. Above the critical micellar concentration (CMC), they form nanosized micellar structures. In these systems, the hydrophobic agents were encapsulated within the micellar spacious core or the hydrophilic moieties were conjugated on the surface of nanoparticles [14]. There are unique points and features associated with pluronic copolymers based delivery systems. Firstly, athwartof numerous drug delivery systems which only act as simplex vehicles, poloxamers function/work as pharmacologically active polymers and modulate the response of cancerous cells [15,16]. Insomuch pluronic are vastly classified as polymerized drugs [17]. Secondly, pluronic own tunable/flexible physicochemical properties, therefore its characteristics can be: due to tunable physicochemical characteristics of pluronic copolymers, their properties can be modified and optimized. The tunable chemical properties of these polymers is considered as a unique advantage to develop the targeted delivery systems (or can caused the development of targeted delivery systems). Thirdly, pluronic based systems can be utilized for delivery of combinational therapeutic regimes more than singlet payloads. These combinational therapeutic regimens provide a platform for pharmacokinetics synchronization and pharmacodynamics synergism. Fourthly, the pluronic polymers haven't any acute-chronic toxicity and these polymers are biocompatible and safe-to-administer agents [17,18]. Polymeric micelles illustrated several basic properties and advantages that desirable for nano-DDS [20,21]. A surrounded drug-loaded core with hydrophilic shell which provided solubilization of water insoluble drugs and also protected the incorporated agents such as protein or nucleic acid from their degradation at off-target sites. Microemulsion based formulations is one of the solubilization approaches to deal with low solubility drugs [22]. Micro emulsions have the illustrious/topping solubilization capacity for both hydrophilic and hydrophobic drugs which is contain high level of water, oil and large amount of emulsifiers (15-25%) [23]. A micro emulsion system could be formed spontaneously when fitting/suitable ratios of water, oil and a surfactant/co-surfactant are reached. Microemulsoin showed several preferences for pharmaceutical use, included high solubilization capacity for hydrophilic and lipophilic drugs, thermodynamic and long-term stability, improved drug delivery and simple preparation which these advantages make the microemulsion superior to emulsion. For treatment of diseases, drugs are introduced into the body by various routs: parenteral, oral and other mucosal delivery. The oral delivery, in all of these ways, has attracted a considerable attention and become superior route as oral forms include 60% of all medical products on the mart that are due to safety, wide acceptability and price [24]. Oral chemotherapy has become an important issue in medicinal field in the 21st century which may alter the prevalent issue of chemotherapy and powerfully improved the quality and condition of life of patients. Currently, for chemotherapy of the sick, the injection of anticancer drugs was used. Such a route led to great peak above the maximum tolerable concentration (MTC) of the used drug within the plasma and a limited area-under-the curve (AUC) resulted due to quick excretion of the drug from the circulate system of the body and resulting a large part of AUC would be contributed with high drug concentration above the MTC that causes the serious and important side effects. In contrast, chemotherapy by using oral route can maintain a sustained moderate concentration of the drug in the circulation system and resulting the long time exposure of cancerous cells to the drug as well as avoiding high peak above MTC.

Also, oral chemotherapy reduced prices and medicinal expenses and especially the oral chemotherapy has an overmuch importance for

cancer patients at the latest steps treatment, when sicks are too weak [25-28].

Pluronic as nanocarier for drug delivery

In the early 1960s, the emergence of lipid vesicles led to conceptual advance so that paved the way for the progress of nanomedicines. Such development caused the approval for clinical and therapeutic of a dozen of nanothechnological products. Among these, the polymeric nanoparticles attracted particular interest and attention because of their tunable properties. They utilized as drug delivery system due to their potential to navigate the drug cargo in vivo environment. Ashore this ability of NPs, they possess several advantages such as potential targeting and controlling the drug concentration and dispensation at the tissues, cells and sub cellular levels [29]. They also can control the drug solubility and increased the circulation time in blood compound to the corresponding naked drug and provided platform for multidrug delivery and theranostics [30]. The using of pluronic® as drug delivery system are not only recent but also, the mixture of the doxorubicin as an anticancer drug (DOX) whit of pluronic® L61 and F127 micelles was the first anticancer micellar system [31]. In 2013, Kabanov, researcher of supratek pharma, Inc., and co-workers reported a research that in their work mentioned to the ability of SP1049C to deplete cancerous stem cells and decreasing the tumorigenicity of cancerous cells in vivo, evolved abroad spectra of operation for SP1049C. By the encapsulation of DOX in micellar pluronic® systems, the bio distribution of DOX shifts, therefore compared to the free drug the accumulation of micellar drug in the tumors improved. The utilization of pluronic® copolymer micelle for encapsulation of anticancer drugs is the other clinical application of anticancer drugs. Docetaxel that is a semi-synthetic analog of paclitaxel, possess a potential and ability in the war against the various solid tumors bur shows disadvantages such as poorly solubility in water, fast phagocytic activity, emulgent clearance and non-election distribution. In clinical usage of docetaxel, it formulated with the non-ionic surfactant tween 80 (poly sorbate 80) which named taxotere® and the FDA approved this formulation, in 2004. However, taxotere® system illustrated serious side traces including nephrotoxicity, hypersensitivity and neurotoxicity [32]. physicochemical characteristics of some of the Pluronic® block copolymers is shown in Table 1.

In 2013 [34], a mixture of the DTX with pluronic® P105 and F127 micelles, were fabricated by Fang and co-workers that displayed a cytotoxicity toward A549-taxol resistant cancer cells more than taxotere® injections. There with, the micellar system of DTX-loaded P105/F127 demonstrated 1.58× longer blood circulation time and 3.82 × bigger areas below the plasma concentration-time curve and also in vivo therapeutic was improved. Pluronics® as surfactants, and gelation and coating agents for pharmaceutical formulation

Pluronics® tri-block copolymer are categorized as polymorph materials that depending on the molar mass ratio between the poly ethylene oxide (PEO) and poly propylene oxide (PPO) blocks can be covered arrange of gelation states from liquid to paste and solid. This versatile structure of Pluronics® are attractive due to their applications as emulsifier, solubilizing agent and dispersive ingredients for pharmaceutical formulation [35]. U.S. and British pharmacopoeias had listed the poloxamer copolymers as an excipient for variety of clinical applications [36,37]. According to the amphiphilicity and surfactant properties of poloxamer copolymers they have become suitable agent for decoration of up-conversion nanoparticles (UCNPs). UCNPs polymer coating technology led to increasing the aqueous solubility and stability of UCNPs and also provided possibility of functionalization their surface. There are

Table 1. physicochemical characteristics of some of the Pluronic® block copolymers [33].

pluronic®	Average no. of EO units (x)	Average no. of PO units (y)	Molar Mass	Cloud point 1 % Aqueous solution (℃)	HLB	CMC (M)
L61	4.55	31.03	2000	24	3	1.1×10^{-4}
L121	10.0	68.28	4400	14	1	1.0×10^{-6}
F127	200.45	65.17	12600	>100	22	2.8×10^{-6}
F68	152.73	28.97	8400	>100	29	4.8×10^{-4}
F87	122.50	39.83	7700	>100	24	9.1×10^{-5}
P105	73.88	56.03	6500	91	15	6.2×10^{-6}
P123	39.20	69.40	5750	90	8	4.4×10^{-6}

several methods for achieving stable and efficient decorations including electrostatic adsorption [38], ligand oxidation [39], ligand exchanging [40] and surface grafting [41].

Morphism of each copolymer (liquid (L), paste (P), and flake (F)) related to Pluronic® triblock copolymer has been reported in the literature [42-43].

In 2012, [44-45], the Pluronic® F127 was utilized for coating UCNPs which played role of an oil-to-water phase transfer. This oil-to-water phase transfer coating was displayed with $NaYF_4$:Yb,Er (Tm) NPs. Using this method, a highly stable up-conversion NPs was produced that illustrated many benefits such as low general toxicity, strong luminescence characteristic and high biocompatibility. By introducing this method and according to this advantages opens new perspective for capability of UCNPs, as bio-imaging ingredients.

Hong-Ru lin and coworkers were reported a poluronic-chitosan micelles for lung delivery using lactose as excipient [46]. In this study the prepared pluronic-chitosan nanomicelles were subjected to spray-dryer to produced microencapsulated nanomicelles and used their system for lung delivery, in addition the physicochemical characterization of nanomicelles was investigated such as diameter, surface charge, morphology and stability. Due to stability of these micelles, they restore back to nanomicelles when they enter to the lung and demonstrated high stability in the lung. Also, evaluation of the in vitro drug release behavior of quercetin-loaded microencapsulated nanomicelles displayed that they have good flow ability sustained drug release behavior [46].

Doxetal (DTX) drug is one of the most important anticancer drugs that as a semi-synthetic analog of paclitaxel was used in clinical therapeutic. The DTX inhibites the microtubule depolymerization of free tubulin and has high potential in the war against a variety of solid tumors but its clinical usage is extremely hampered due to some feature of DTX such as poorly water solubility, fast phagocytic activity, renal clearance, and non-elective distribution. To overcome on these problems and improve the aqueous solubility of DTX, various drug delivery systems have been developed. Liangcen Chen and co-workers has reported a novel polymeric mixed-micelles that composed of plorunic P105 and F127 block copolymers loaded DTX against Taxol-resistant non-small cell lung cancer [46]. By using Central Composite Design, the preparation process was optimized and drug solubility and also micelle stability improved. The in vitro cytotoxicity assay displayed that the DTX-loaded P105/F127 mixed micelles has a superior hypersensitivity effects and the mixed-micelle formulation showed a 1.85 fold longer mean residence time in blood circulation according to the in vivo pharmacokinetic study. In addition, in this system the therapeutic improvement of polymeric mixed micelles in vivo against A549/Taxol was obtained. These micelles showed tumor inhibition rate about 69.05% versus 34.43% for taxotere ($P<0.01$). The results of this investigation demonstrated that DTX-loaded P105/F127 mixed nanomicelles can use an antitumor DDS to overcome multidrug resistant in lung cancer [47].

In 2013, Bandyopadhyay and co-workers encapsulated the hydrophobic drugs including ibuprofen, aspirin and erythromycinin the hydrophobic cores of spherical pluronic F127 micelles and also, the effects of drug hydrophobicity of solution temperature and pH were investigated [47].

According to the literature [48], for all the encapsulated drugs, R_H (hydrodynamic radius) of nanomicelles decreases as a function of temperature, also at the lower temperatures the polydispersity parameter of samples subsequently increases.

The morphological features of micelles are extremely depends to the molecular architectures and hydrophobicity of their constituents. With the loading of drugs into the micelles, the radii of the micelles increases, that is in the agreement with previous experiments and reports [49-51]. At temperature ≥ 40 , the higher hydrophobicity of drugs ensures more compact packing of the molecules within the micellar core of pluronic. Among these drugs, aspirin, which has the least hydrophobicity, forms the largest micelles, while ibuprofen, as the most hydrophobic drug, caused the formation of the smaller and more compact micelles. In this study, a strong pH dependence on drug-encapsulated micelles was observed, with increasing of solution pH from 4.65 to 6.1, the drug molecules were ionized and led to formation of larger micelles, due to repulsive interactions within the micellar core. Subsequently, by achieving the pH=11.36 drug molecules released in the solvent.

CONCLUSION

In summary, the conducted studies focus on polymer nanoparticles have highlighted importance and key role of different polymers

specially pluronic in drug delivery systems.

Along with the design of drug delivery systems based on new Pluronics as well as development of formulations containing Pluronic, considerable efforts have also been devoted to elaborate their role in the activity increase of the encapsulated drug.

In the current review, we have tried to present recent advances in the utilization of Pluronic ® block copolymers as nano-drug delivery systems.

Reported studies confirm that there is a widespread potential to design innovative Pluronic® formulation by using various types of poloxamers to tune the biological properties according to mixed micelles. We believe that Pluronic ® block copolymers will play a key role in the design of Nano drug delivery systems based on Pluronic in future.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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