

MINI REVIEW

Pluronic based nano-delivery systems; Prospective warrior in war against cancer

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ABSTRACT

Common cancer therapeutics suffer from serious drawbacks such as multidrug resistance and off target effects. These problems would lead to reduced patient compliance and low survival rates. There is an urgent need for more effective therapeutics for treatment of cancers patients. Pluronic based nano-particulate systems are innovative platforms for delivery of anti-cancer agents. These systems due to their pharmacological properties and suitable physicochemical characteristics are great opportunity for development cancer therapeutics. Pluronic based delivery systems are used for delivery of combinatorial therapeutic regimens as well. This mini-review tries to provide a more detailed overview on the currently available pluronic based drug delivery systems. In the section 2, pharmacological characteristics of pluronic as a therapeutic polymer are assessed. In section 3, pluronic based formulations for hydrophobic payloads and surfaced modified targeted delivery systems are analyzed. The combinatorial pluronic based systems are summarized in section 4 and at last but not least the challenges and future prospective are discussed within section 5.

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INTRODUCTION

Cancer is one of the leading causes of death worldwide [1]. Recent progress on prevention, diagnosis and treatment of cancer seems to be so promising. However, more effective therapeutics are required to increase survival rate and quality of life of the cancer patients. Common treatments suffer from serious drawbacks such as off-target effects and low efficacy especially during metastatic stages. Emergence of nanotechnology promoted a wide spread optimism. Nano-scaled delivery systems actively and passively target the chemotherapeutic payload to the cancer cells while minimizing side effects on the normal cells [2]. Furthermore, these systems could be used for formulation of hydrophobic molecules which lack

suitable physicochemical characteristics required for development of stable pharmaceutical dosage form. Among various types of drug delivery systems, pluronic based formulations have gained significant attention by drug delivery scientists [3]. Pluronic is an amphiphilic polymer consisted of poly (ethylene oxide) (hydrophil) and poly (propylene oxide) (hydrophobe) blocks. Above critical micelle concentration (CMC), pluronics form nano-sized micellar structures. These structures could be used for encapsulation of hydrophobic agents within the micelle's spacious core or conjugation of the hydrophilic moieties on the surface of nanoparticle. Due to thermo-responsive characteristics of the pluronic, it can be used for development of *in situ* forming hydrogels, as well [4]. *In situ*

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forming hydrogels are suitable for both local and systemic drug delivery. Pluronics are easily mixed, conjugated or adsorbed by other widely-used polymers in the field of drug delivery such as chitosan, PLA, PLGA and etc. [5-7]. So the mixed delivery systems consisted of pluronic and another polymeric constituents are very common.

What are the unique points associated with pluronic based delivery systems? Firstly, unlike many other drug delivery systems which merely act as a simple carrier, pluronics are pharmacologically active polymers which can modulate the response of cancer cells [8, 9]. So pluronics are mainly categorized as polymeric drugs [10]. Secondly, pluronics possess tunable physicochemical characteristics; so its properties can be modified and optimized according to the therapeutic payload. The tunable chemistry of pluronic polymers is a unique opportunity for development of targeted delivery systems by addition of targeting moieties on the surface of nanoparticles. Thirdly, pluronic based systems can be used for delivery of combinatorial therapeutic regimens rather than singlet payloads. Combined pluronic based delivery systems provide a platform for pharmacokinetics synchronization and pharmacodynamics synergism. Fourthly, from nano-toxicological point of view, pluronics unimers are readily excreted via glomerular filtration while nano-particulate pluronic based delivery systems are mainly eliminated by hepatic pathway [11]. Up to our knowledge, there is not any report on acute-chronic toxicity of these polymers [12]. So pluronics could be regarded as a biocompatible and safe-to-administer agent. US Food and Drug Administration (FDA) have approved various pluronic polymers for pharmaceutical usage and even intravenous administration [13]. A commercial pluronic F127/L61 micellar system have been developed by Supratech Pharma Inc. [14]. This system which has been developed for delivery of doxorubicin for treatment of Adenocarcinoma, has successfully completed phase 1 and 2 clinical studies. It seems that in near future more and more pluronic based delivery systems are introduced to the clinical level.

This mini-review tries to provide a more detailed overview on the currently available pluronic based drug delivery systems. In the section 2, pharmacological characteristics of pluronic as a therapeutic polymer are assessed. In section 3, pluronic based formulations for hydrophobic payloads and surfaced modified targeted delivery

systems are analyzed. The combinatorial pluronic based systems are summarized in section 4 and at last but not least the current challenges and future prospective are discussed within section 5.

Pluronics as a therapeutic polymer

Pluronics are not mere carriers; Pluronics could alter the target cells response via various cell-polymer interactions. These cell-polymer interactions affect various critical mechanisms within target cells such as apoptosis, oxidative phosphorylation and the chemo-resistance. Resistance is the main challenge upon efficacy of chemotherapeutic agents. Resistance is mainly caused by efflux pumps which reduce the intracellular levels of chemotherapeutic agents [15]. Efflux mediated drug resistance can be overcome by pluronic based systems. Several studies report that pluronic alters the lipid microenvironment of P-glycoproteins (P-gp) which cause the reduced efflux activity. Pluronic polymers decrease the membrane microviscosity which permeabilize cancer cells to the chemotherapeutic agents [16-18]. Furthermore, the pluronics destabilize the mitochondrial membrane which leads to a serious ATP depletion within cancer cells [17]. ATP depletion blocks the normal function of P-gp which require a sufficient amount of energy reservoir. The magnitude of pluronic effects is not limited to P-gp inhibition. Pluronics cause a rapid storm in cancer cell's metabolism and also trigger critical apoptotic pathways. Kabanov research group has reported that pluronics are capable of blocking electron transfer chain in mitochondria (complexes I and IV), which may increase the reactive oxygen species (ROS) levels within target cancer cells [17]. Elevated ROS levels disturbs the normal structure of the mitochondrial membrane and initiate the release of intrinsic apoptotic pathway mediators [17, 19, 20]. Pluronic mediated release of cytochrome c, Apoptosis Inducing Factor (AIF) and endonuclease G could trigger fast activation of other apoptotic mediators within programmed cell death process.

Another important characteristic of pluronic as a therapeutic polymer is metastasis inhibition. Efficacy of common therapeutic agents is negligible in metastatic cancers. Unfortunately, systemic administration chemotherapeutic regimens in these patients often leads to serious- life threatening side effects. It is reported in literature that pluronic polymers with medium hydrophilic-lipophilic balance (HLB) would block cancer

cells migration and invasion [21]. Huiping Sun et al. reported significant pulmonary metastasis inhibition in 4T1 tumor bearing mice model via pluronics effect [21]. Interestingly, pluronic anti-metastatic properties are related to down regulation of matrix metalloproteases such as MMP-9. In addition, significant synergistic anti-metastatic effect has been reported for pluronic-doxorubicin combination in the aforementioned research work. In another analogous study, 5-Fluorouracil (5FU) loaded pluronic P85 copolymer micelles have been developed for inhibition of metastasis in colon cancer [22]. In these series of studies, the 5FU loaded micelles successfully blocked epithelial-mesenchymal transition (EMT). EMT is observed frequently in liver metastasis caused by colon cancer.

Pluronic based delivery systems as a carrier for hydrophobic molecules and a platform for targeted delivery

The core of pluronic based delivery systems is consisted of a hydrophobic microenvironment suitable for encapsulation of lipophilic molecules such as Taxanes (Table 1). It seems that pluronics based delivery systems are a suitable platform to increase solubility of such hydrophobic molecules. A mixed pluronic F127/P105 micellar system has been developed for delivery of docetaxel [23]. This formulation enhanced the solubility of docetaxel without using toxic-immunogenic cosolvents. Curcumin is another hydrophobic agent which is highly potent against cancerous cell. Recently, a novel pluronic F68 curcumin conjugated delivery system has been formulated [24]. These micelles

had an acceptable encapsulation efficacy and superior toxicity compared to the naked drug. Gemcitabine is another anti-cancer agent which is used in several chemotherapeutic regimen. A novel chitosan-pluronic oral delivery system is reported by Dinarvand research group [25]. Due to the mucoadhesive properties, aforementioned system could be used to increase the oral bioavailability of gemcitabine. Another innovative pluronic based system is introduced by Ying-chi Yang et al. for delivery of sorafenib in treatment of gastric malignancies [26]. Despite of proper anti-proliferative effects via blocking tyrosine kinase receptors, sorafenib suffers from low intrinsic solubility. Aforementioned delivery system is a heparin functionalized pluronic nanoparticle which significantly enhanced the *in vivo* anti-tumor efficacy of sorafenib in tumor xenograts models.

Pluronic based delivery systems have gained widespread attention for development of targeted therapies. Hydrophilic shell of pluronic nanoparticles could be used for conjugation of targeting moieties such as folate, aptamers and monoclonal antibodies (Fig. 1). Penetration enhancers such as cell penetrating peptides (CPP) could be attached as well to secure the nanoparticle transport across biological barriers. Pluronic composite micelles have been functionalized with AS1411 aptamer [27]. AS1411 aptamer has been reported to selectively target the nuclein protein overexpressed in many subtypes of cancer [28]. *In vivo* real time imaging analyses have been proved the efficacy of AS1411 as a targeting moiety. There are several folate conjugated pluronic delivery system which demonstrated significant tumor accumulation. Folate pluronic/ poly lactic acid nanoparticles and

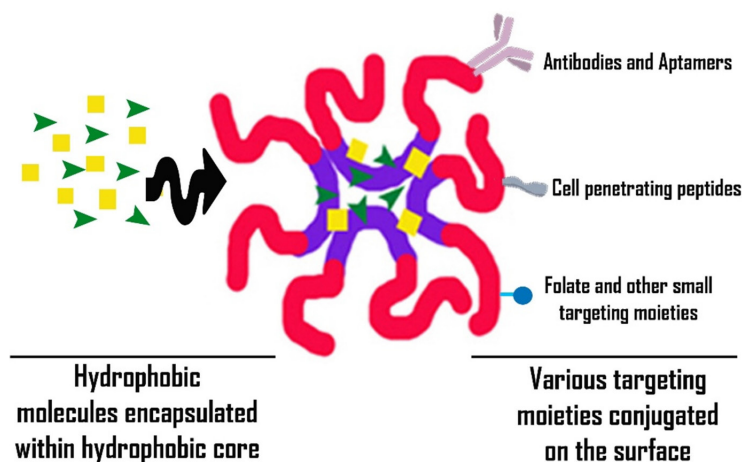


Fig. 1. Pluronic based delivery system; a novel platform for formulation of hydrophobic molecules and targeted delivery

folated cross linked pluronic micelles have been developed for delivery of paclitaxel and doxorubicin, respectively [29, 30]. Another innovative nanocarrier is RVG (Rabies virus glycoprotein) conjugated pluronic nanoparticles [31]. RVG conjugated particles successfully target blood brain barrier and consequently improved the brain bioavailability of its therapeutic payload. Such a system can be used for treatment of various types of brain tumors and CNS malignancies. Tumor targeting capability of pluronic based delivery systems can be used for targeting special cellular side-populations within tumor tissue. For instance cancer stem cells; an important side-population responsible for tumor relapse and drug resistance can be targeted by functionalized pluronic based systems [32]. Hyaluronic decorated pluronic nanoparticles have been used for targeting and eradicating cancer stem cells. The hyaluronic moieties interact with CD-44 receptors overexpressed on cancer stem cells. The developed system effectively suppresses the cancer stem cell population both *in vitro* and *in vivo* [33].

Pluronic based delivery systems as a carrier for combinational therapeutic payloads

Pluronic based delivery systems due to flexible and tunable physicochemical properties could be used as a vehicle for delivery of combinational regimens

(Table 2). Combinatorial regimens are more effective compared to monotherapy due pharmacodynamics synergism and lower required therapeutic dose. However, the desirable pharmacodynamics synergism is not achieved within many cancer patients due to unsynchronized pharmacokinetics. The synchronized pharmacokinetics and consequently pharmacodynamics synergism could be achieved by pluronic based delivery systems. Delivery systems control the release of therapeutic combinational payload and protect it from hazardous enzymes within plasma. So it seems that biodistribution and biological fate of drug loaded pluronic based delivery systems are more controllable compared to their naked counterparts.

Several combinational pluronic based delivery systems have been developed. Our research group have recently developed a novel Pluronic F127 micellar system for co-delivery of paclitaxel and lapatinib (Fig 2) [38]. Paclitaxel acts as a microtubule stabilizer while lapatinib blocks epidermal growth factors receptors (EGFR). Furthermore, lapatinib and pluronic inhibit the efflux pumps which synergize the paclitaxel cytotoxic effect. The system demonstrated a superior *in vitro* cytotoxic effect on T-47D cell line compared to binary mixture of naked drugs. The results show that delivery system provides the required intracellular concentrations required for pharmacodynamics synergism (at least during *in vitro* analyses). A thermo-responsive

Table 1. Pluronic based delivery systems (single agent carrier)

Delivery system	Therapeutic payload	Disease	Reference
AS1411 aptamer targeted Pluronic F127/cyclodextrin linked polymer composite micelles	Doxorubicin	Breast cancer/MCF-7	[27]
Heparin-functionalized Pluronic nanoparticles	Sorafenib	Gastric cancer/ BGC-823	[26]
Folate decorated bioreducible cross-linked Pluronic micelles	Doxorubicin	Cervical cancer/HeLA	[30]
Pluronic F68–curcumin conjugate micelles	Curcumin	Breast cancer/ MDA-MB-231	[24]
Hybrid biomaterial based on porous silica nanoparticles and Pluronic F-127	Sildenafil	Prostate cancer/-	[34]
Pluronic P105/F127 mixed micelles	Docetaxel	Non-small-cell lung cancer/ A459	[23]
Doxorubicin-loaded Vitamin E-Pluronic Micelles	Doxorubicin	Hepatocellular carcinoma/HepG2	[35]
Folated Pluronic/Poly(lactic acid) Nanoparticles	Paclitaxel	Ovarian cancer/OVCAR3	[29]
Chitosan–F127 Pluronic nanoparticles	Gemcitabine	Colon cancer/HT-29	[25]
F127-polyethylenimine-folate micelle	Paclitaxel	Epithelial carcinoma /HeLA	[36]
Pluronic P85 Copolymer Micelles	5-Fluorouracil	Colon cancer/ RKO and AT116	[22]
vitamin E succinate functionalized pluronic micelles	Paclitaxel	Glioblastoma/U87	[37]

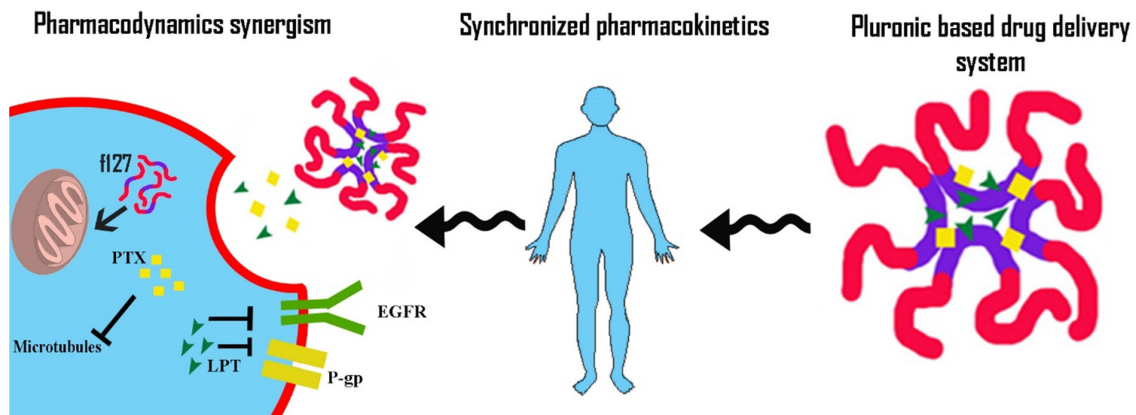


Fig. 2. Paclitaxel- lapatinib loaded pluronic micelle; a combined pluronic based delivery system

Table 2. Pluronic based combinational delivery systems with multiple payloads

Drug delivery system	Therapeutic combination	Disease/cell line	Reference
Hyaluronic acid-decorated dual responsive nanoparticles of Pluronic F127, PLGA, and chitosan	Doxorubicin and irinotecan	Prostate and breast cancer/Cancer stem cell/PC-3, MDA-MB-231	[33]
c(RGDyK)-decorated Pluronic micelles	Paclitaxel and doxorubicin	Brain glioma/ U87	[41]
F127-P105 mixed pluronic micelles	Paclitaxel and doxorubicin	Multidrug resistant breast cancer/ MCF-7/ADR	[40]
Pluronic P85-PEI/TPGS complex nanoparticles	shRNA and paclitaxel	Breast cancer/ 4T1	[42]
F127 pluronic micelle	Paclitaxel and lapatinib	Metastatic breast cancer/ T47-D	[38]
Pluronic <i>in situ</i> forming hydrogel	Paclitaxel and lapatinib	Breast cancer/ MCF-7 ADR, BT474	[39]

hydrogel for codelivery of paclitaxel and lapatinib have been assessed by another research group [39]. Paclitaxel nanoparticles and Lapatinib microparticles were incorporated in to pluronic based gel. The system increased the survival rate of tumor bearing mice significantly with lower levels of toxicity. Yanzuo Chen et al. have introduced a mixed pluronic paclitaxel and doxorubicin loaded micelles for multidrug resistant breast cancer chemotherapy [40]. *In vivo* analyses demonstrated significant anti-tumor efficacy in MCF-7/ADR tumor bearing mice. This might be regarded as a proof concept that pluronic based delivery systems would guarantee synchronized pharmacokinetics and pharmacodynamics synergism. In another study, paclitaxel- doxorubicin loaded pluronic RGD coated nanoparticles were analyzed for treatment of gliomas [41]. RGD peptide was used as

penetrating enhancer to cross blood brain barrier. *In vitro* transport analyses and apoptosis studies on U87 malignant glioblastoma cell line demonstrated the superior efficacy of developed system compared to the control group. *In vivo* fluorescent analyses proved the intra cranial accumulation of developed system which seems to be in line with *in vitro* studies.

Pluronic based delivery systems could be used for delivery of chemotherapeutic agents along with siRNA, miRNA and shRNA. Jianan Shen et al. have reported a pluronic based system for codelivery of paclitaxel and shRNA [42]. The system proved efficient cytotoxicity and RNA interference. Biodistribution analyses proved that nanoparticulate system possess extended circulation half time. Furthermore, aforementioned enhanced pharmacokinetics properties have led to tumor

growth suppression and metastasis inhibition. Another gene/chemotherapeutic combinatorial system is developed for delivery of paclitaxel and anti BCL-2 siRNA [43]. This combinatorial system demonstrated significant anti-tumor synergism. It seems that more pluronic based combinatorial systems are going to be introduced in the future. However, more effective pharmacological combinations should be selected to be studied. In addition in case of combinatorial pluronic based system more detailed pharmacokinetics studies are required to prove the synchronization.

CONCLUSION

Pluronic based delivery systems have gained widespread attention and huge amount of optimism. Up to now, SP1049C (pluronic based micellar formulation of doxorubicin, Supratech) is the only clinically applied pluronic based delivery system. There are major challenges ahead for commercialization of these delivery systems. From industrial pharmacy point of view, scale up procedure for pluronic based delivery systems due their complexity seems to be difficult [44]. Multi-parametric nature of these formulations, especially in case of surface modified nanoparticles and combinatorial systems should be considered in scale up process. Another key challenge is regulatory issues associated with nanomedicines [45, 46]. Quality criteria seems to be more sophisticated compared to small molecules or even protein based formulations. Quality by design approach should be developed for quality assessments of these pharmaceutical products. Furthermore, there is an urgent need for more elucidate quality guidelines by FDA, EMA and other local regulatory agencies. With practical solutions for the aforementioned challenges, the pluronic based delivery system might be turn into real warriors in war against cancer.

CONFLICT OF INTEREST

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

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