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Review Article

FUNCTIONALIZED POLYMERIC NANOPARTICLES: A NOVEL TARGETED APPROACH FOR ONCOLOGY CARE

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ABSTRACT

Popular cancer therapies face extreme disadvantages, including multimedicament tolerance and non-target impact. These issues will lead to poorer patient conformity and poor levels of survival. Successful medical therapies for cancer patients are desperately required. Nano-particulate structures with a pluronic base represent revolutionary platforms for anti-cancer agent provision. These structures provide great potential for the advancement of cancer therapy due to their pharmacological properties and sufficient physicochemical characteristics. This review aims to offer a more detailed description of the pluronic drug delivery mechani sms that are currently available and explains pluronic as a medicinal polymer. Hydrophobic payload formulations and updated, targeted distribution mechanisms are explained based on pluronic formulations. This analysis offers a rundown of the current situation art related to the theranostic application of polymer micelles targeting the microenvironment of cancer cells. Some guidelines for the future scope and possible opportunities are also been addressed.

Search criteria: Primary sources such as Medline a principal component of PubMed, an online, searchable, and biomedical and life science research literature database has been used. It brings readers to almost any area of interest with research and journal articles. One of the internet resources of importance to get scientific publications is specialized scientific search engines known as Google Scholar a database of research material that can be searched for. I have used the online electronic access portal of Elsevier, such as Science Direct to its publications. Scopus is the biggest abstract and peer-reviewed literature database for scientific journals, books, and conference work. Keywords like Cancer, Pluronic, Nanoparticles, Chemotherapy, Cancer, Theranostic, Targeted, Micelles, and Core-shell are crucial as they notify search engines of the content of the site.

Range of years: 1992-2020.

Keywords: Cancer, Multimedicament, Tolerance, Nanoparticulate, Pluronic, Drug delivery, Hydrophobic, Micelles, Theranostic, Microenvironment

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INTRODUCTION

Every year, cancer causes millions of deaths globally and while there have been significant strides in treatment, several problems need to be solved to strengthen cancer therapy. Therefore, oncological science strives extremely hard to discover alternative and innovative drugs that can mitigate the important side effects that are induced by traditional therapies. Various innovations are being tested or have already been implemented into clinical use in clinical trials. Although nanomedicine helps create biocompatible materials for both diagnostic and therapeutic purposes, the bioengineering of extracellular vesicles and patient cells allowed ad hoc systems and univocal targeting strategies to be designed [1]. Employing nanotechnology in the field of drug delivery has led to the advent of Nano pharmaceuticals. Nano pharmaceuticals are bound to surmount various obstacles that the field of pharmacy is currently facing by offering various advantages thereby, promising potential to formulate advanced medicines with fewer adverse effects [2]. In this study, we will discuss in detail the latest developments in basic and applied nanotechnology, theranostic approach that have led to the development of developed nanoscale materials as ground breaking prototypes for biomedical applications and tailored targeted treatment for cancer [3].

Existing cancer prevention strategies

Cancer is one of the most frequent illnesses globally, killing about seven million a year. For the past two decades, the outlook for cancer therapy has shifted significantly. New developments in the treatment of cancer, which are based largely on tumor molecular characteristics, are emerging. Treatment of cancer has been made more tumor-specific and less toxic by using modern cancer-centric therapy based on medicinal antibodies or small molecules [4]. However, chemotherapy, surgeries, radiation, or a mixture of these drugs are used in the procedures used for cancer. The foregoing are the various advanced cancer treatments.

Chemotherapy

The application of chemotherapy to cure cancer started to decrease the chemical list by improving ways to diagnose it using transplantable tumors in mice at the turn of the 20th century. Since the late 1940s, chemotherapy has been used to cure many different forms of cancer successfully and to increase survival rates [5]. However, it is not very precise in general and thus endangers normal tissue and organs [6]. Nausea, fatigue, hair loss, anemia, diarrhea, constipation, low blood count, fertility, and more are the major harmful effects of chemotherapy. Often chemotherapeutic agents affect the activity of the brain by direct/indirect pathways, but there are assurances for systemic blood-brain barrier therapy of the brain. Chemotherapy has an intensive and chronic effect on cognitive function, but the cause remains unclear [7]. Several medications, such as Gemcitabine, Azacitidine, Pemetrexed, Paclitaxel, Docetaxel, and many others, are used in chemotherapy. Tablets, capsules, and parenteral (intramuscular, intravenous) are the different routes from which anticancer medications are taken [8].

Radiation therapy

The bulk of people who undergo radiation therapy after their course of the disease continue to receive cancer care as a central factor, leading to a 40% cure of cancer. The treatment with radiation takes away the ability of cancer cells to replicate [9]. High-energy radiation in radiation therapy is used to reduce cancers and destroy cancer cells. X-rays, gamma rays, and charged particles are different sources of radiation used for the treatment of cancer. It destroys cancer cells by destroying the molecules known as Deoxyribonucleic Acid (DNA) in cells and conveys genetic information for the killing of cancer cells from generation to generation [10].

Surgical therapy

The turn of the 20th century marked the beginning of the advancement of cancer operating methods, and in 1908 Miles conducted the first abdominoperineal resection and the first lobectomy in 1912 [11]. The current operation improved dramatically, with non-invasive procedures like laparoscopic colectomy (for colon cancer removal) and thoracic video techniques replacing Halstedian procedures [12]. Sentinel node removal has been used to boost esthetic outcomes and to prevent lymphedema [13]. The use of laryngoscopic laser procedures on early laryngeal cancer is another example of traditional surgery [14]. The most recent breakthrough is Da Vinci®, which is a robot device for the treatment of prostate and renal cancer [15].

Proton therapy

It has wonderful promise as a therapy for multiple tumors. Public interest in proton therapy has risen to a large degree since the Food and Drug Administration (FDA) approved it in 2001. In children with multiple cancers, Proton Therapy is most effective in people with organs with tumors such as kidney, bladder, brain, spine, lungs, back, and leg. Proton therapy is more common. Proton Therapy centers continue to assess their use for more cancers in science [16]. Nevertheless, we do not neglect the value of proper patient preparation, precise science analysis, including contrasts with other technologies, ethical challenges, and economic performance [17].

Thermotherapy

Thermotherapy has been used for at least 4000 y to treat tumors and even before that point, to destruct the tumor masses. Extreme temperature (hyperthermia) can cause tumors to break down by destroying tumor cells and damaging proteins and structures within cancer cells [18]. In many clinical trials, hyperthermia has been used in conjunction with radiation therapy and varicose vein treatment chemotherapy. Thermotherapy is a treatment of body tissue with high-temperature penetration up to 113 degrees F [19, 20].

Photodynamic therapy (PDT)

In 1903, the first scientific use of photodynamic therapy in cancer therapies was discovered for eosin to be aimed at basal cell carcinomas (BCC). For photodynamic therapy, a medicament known as a photosensitizing agent or photosensitive agent with a particular wavelength of light is used. Photosensitizing agent emits a kind of oxygen that destroys surrounding cells on exposure to a certain wavelength of light [21, 22]. PDT can be combined with other medications, for example, chemotherapy, radiation, or surgery. Many clinical experiments are ongoing to test the use of PDT for different forms of cancer [23]. The only way to be able to use nanoparticles as a photo-sensitizing carrier is to me*et al.* l of the needs of an optimal PDT agent [24].

Laser therapy

Lasers are most widely used for cancers and precancerous development to shrink or kill. The most prevalent application with laser therapy is peripheral disorders, including cancer of the skin of basal cells in the very early stages of multiple cancers, such as non-small cell lung cancer, vulvar, ovarian, penile, and cervical cancer. Laser therapy can also mitigate various signs of cancer, such as bleeding or obstruction. In combination with various other therapies, including surgery, chemotherapy, or radiation therapy, laser therapy can be used. Furthermore, laser treatment can be used to scan the lymph vessels to reduce swelling and minimize the metastasis for tumor cells [25]. Three types of laser are used more commonly in different tumor types, including the neodymium of yttrium-aluminum-garnet (Nd: YAG), argon lasers, and carbon dioxide (CO2). Laser therapy may also evaluate nerve endings to relieve pain after treatment [26].

Immunotherapy

Recent advances and clinical tests have shown that adoptive antitumor-infiltering tumor therapy in about 50–75% of Multiple Myeloma (MM) patients will effectively cause tumor regression [27, 28]. Antitumor Tumor-Infiltrating Lymphocyte (TIL) may also be used to expand adoptive cell transplant therapy to treat patients with other types of cancer, including brain, renal, and lung. However, combination therapies such as Dendritic Cell-Cytokine-Induced killer (DC-CIK) in combination therapy in patients with metastatic breast cancer may enhance their longevity free of relapse and overall survival [29]. Tumor regressions in 72 % of patients with metastatic melanoma can result in adoptive cell therapy in tandem with non-myeloablative chemical therapy and complete body irradiation, whereas TIL adoptive immunotherapy with non-myeloablative chemotherapy in only 52 % of treated patients can cause tumor regression [27].

Gene therapy

To regain lost functionality and eliminate viruses, gene therapies seek to cure diseases through the insertion of DNA and Ribonucleic Acid (RNA), minor interfering RNA, and antisense oligonucleotides into special target cells or tissues. The therapeutic genes are supplied to certain target cells with effective vectors aimed at retaining stable, regulated gene expression without causing undesirable side effects [30]. Transforming viruses into genetic shuttles to provide the cell gene of interest is one of the fundamental concepts of gene therapy [31]. Gene transfer is a modern cancer therapy approach that incorporates new genes into a tumor cell or the tissue around to induce apoptosis or delay tumor growth.

Nanotherapeutics

Latest efforts have centered on designing functionalized therapeutic nanoparticles that are over-expressed to various cancer cells for particular molecular purposes. Possible benefits of engineered nanoparticles in terms of therapeutic therapies include the potential to transform undesirable physical and chemical properties of the bioactive molecules into desired biopharmacology patterns; increase therapeutic distribution through biologic boundary areas; monitor bioactive agent release; increase therapeutic effectiveness, through administering therapeutics to biological targets selectively; and, by integrating multimodal imaging and simultaneous testing and treatment, execute theranostic functions on multifunctional platforms. The multifunctional framework focused on pluronic nanoparticles with the potential of integrating imaging with therapy as well as incorporating multiple receptor targeting has been providing new insights using novel nanomaterial's for cancer care (fig. 1). Moreover, a photothermal approach to the removal of cancer cells or tumor tissue, which may have significant promise in the therapeutic environment, has been included in most research on pluronic nanoparticular cancer therapy [32, 33].

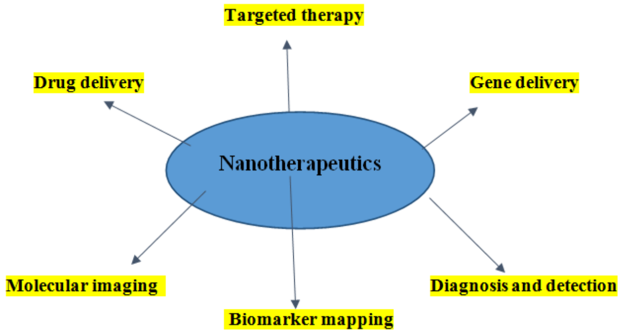

Fig. 1: Biomedical applications of nanotherapeutics

Polymeric nanoparticles

The development of nanoparticle-based clinical treatment methods has resulted in significant pharmacological advancements that have decreased adverse effects and improved the safety, resolvability, Pharmacokinetics, and biodistribution of cytotoxic drugs. Polymeric nanoparticles remain popular in cancer therapy because they are a good platform for the study of hydrophilic as well as hydrophobic drugs [3, 34-35]. But most medicines are released into the extracellular matrix; their efficacy relies on tissue diffusion and their use is limited by their poor *in vivo* specificity. Therefore, promising progress in cancer science is the latest site-specific targeting of nanoparticles. Table 1 lists several examples of polymeric nanoformulation [36]. To improve the biodistribution of antitumor agents, NPs have been designed for optimal size and surface characteristics to increase their circulation time in the bloodstream. They are able to carry and deliver their active drug payloads to cancer cells, by passive targeting mechanisms, such as the EPR effect as well as by active targeting mechanisms using ligands directed against selected determinants differentially over expressed on the surface of tumor cells [37]. One promising solution is the BIND-014 technology, made from docetaxel loading polymeric nanoparticles able to detect prostate cancer by targeting Prostate-specific membrane antigen (PSMA), prostate cell prostate cancer tumor antigen, and non-prostate solid tumor vasculature. In Phase II clinical trials, BIND-014 has shown greater antitumor efficacy in the lower doses of advanced or metastatic non-small-cell lung cancer than normal documentation for the use of non-small-cell lung cancer [3, 38].

Table 1: Drug-loaded polymer nanoparticles in clinical trials or clinical use

Product	Drug	Applications	Status	Reference
Abraxane	Paclitaxel	Breast cancer, non-small cell lung cancer, pancreatic cancer	Approved	36
BA-003	Doxorubicin	Hepatocellular carcinoma	Phase III	
Mitoxantrone-loaded Polybutylcyanacrylate (DHAD-PBCA-NPs)	Mitoxantrone	Hepatocellular carcinoma	Phase II	
ProLindac	Dichloro(1,2-diaminocyclohexane)platinum(II) DACHPt	Advanced ovarian cancer	Phase III	
ABI-008	Docetaxel	Metastatic breast cancer, prostate cancer	Phase II	
ABI-009	Rapamycin	Solid tumors	Phase II	
ABI-011	Thiocolchicine dimer	Solid tumors, lymphoma	Phase II	
BIND-014	Docetaxel	Non-small cell lung cancer	Phase II	
Cyclosert	Camptothecin	Solid tumors, rectal cancer, renal cell carcinoma, non-small cell lung cancer	Phase II	
CALAA-01	siRNA targeting	Solid tumors	Phase I	
Docetaxel-PNP	Docetaxel	Solid tumors	Phase I	
Nanotax	Paclitaxel	Peritoneal neoplasms	Phase I	

NP targeting strategies

Ideally, the target applies rather than indiscriminate delivery across the entire body, to the precise localization of NPs to the desired site. These target NPs need to resolve external obstacles, path barriers, and cellular barriers before the site being accumulated [39]. There have been two main techniques for targeting tumors–passive and active targeting, shown in fig. 2.

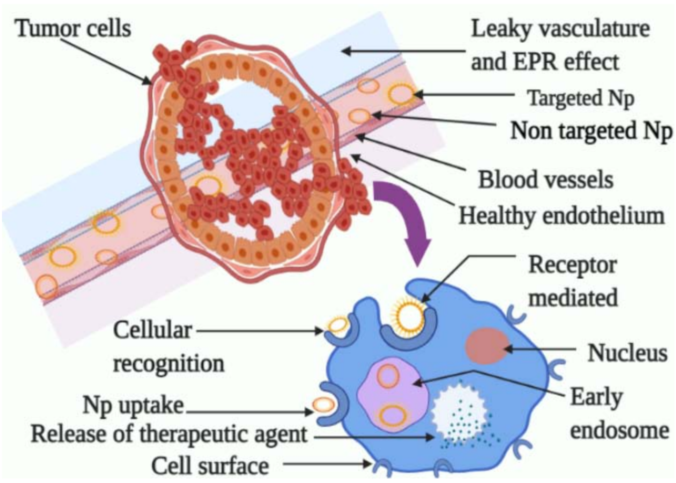

Fig. 2: Schematic representation of passive and active targeting approaches. EPR, enhanced permeability and retention; np, nanoparticle [39]

Passive targeting

It benefits from diseased tissues, usually tumor, pathophysiological properties, while active targeting by the drug carrier initially uses passive targeting to gather in the tumor zone and then bind to the target cells using ligands to internalize the NPs to the cells [40, 41]. The passive targeting of therapeutics from nanocarrier depends on the tumor microenvironment, the enhanced permeability and retention (EPR) effect, and the tumor pH. Tumor cells expand and proliferate more quickly than normal cells are well established. This cell proliferation has a metabolic rate that requires more nutrients and a larger amount of oxygen. The architecture of normal cells is disturbed and replaced by tumor cells to compensate for nutrients [42]. Passive targeting helps NPs to build up in the tissue through EPR [43]. Ground Shift in PEG NPs. Enhanced NP hydrophobicity associated with higher particle-partisan aggregation and blood opsonization steric deficiency was found [44, 45]. Poloxamins, poloxamins, Polyethylene Glycol (PEG), Poly-Caprolactone (PCL), Poly D, L-lactic-co-Glycolic Acid (PLGA) are the polymers widely used in the manufacture of sterically stable stealth nodes and to improve hydrophillicity [46].

Active targeting

The therapeutic medication can be obtained with or without the use of coupling agents by mixing medicine or nanocarrier with a cellular targeting motive known as ligands. These target moieties have a special affinity with cell surface antigens (for example, receptors) and can be differentiated among normal and tumor cells based on levels of receptor or antigen expression [43]. The use of targeted Herceptin NPs helped distinguish positive and negative cell breast cancer epidermal growth factor 2 (HER2) in humans. The successful targeting of HER2 receptors with NPs has been verified in over-expressed cells [47]. In designing a targeted delivery system, the specific properties of cancer cells may be used. For example, cancer cells frequently overexpress tumor antigens, structures similar to carbohydrates, or receptors of the growth factor (e. g., epidermal growth factor receptor). Different ligands may be used as active targeted molecules such as antibodies, polysaccharides, aptamers, peptides, transfers, folate, and other small molecules, based on this definition [48]. Table 2 offers some examples of target ligands connected to NPs and their respective targets. Ligand selection depends on the targeted cells [49].

Table 2: An overview of different targeting ligand decorated PLGA NPs

Nanoparticles type	Targeting ligand	Loaded drug	Cell line/Animal model	Reference
PEG-PCL	Angiopep-2	Paclitaxel	U87 MG, Brain Capillary Endothelial Cells (BCECs)	50
PLGA	g7 Peptide	Loperamide, Rhodamine-123	Tail vein in rats	51
PLGA	Trastuzumab	Paclitaxel	Caco-2, SK-BR-3	52
PLGA	Humanized anti-DC-SIGN (hD1)	Fluorescein Isothiocyanate Titanus Toxoid (FITC-TT) Peptide, Dye Quenched-Bovine Serum Albumin (DQ-BSA)	Granulocytes, Peripheral Blood Mononuclear Cells (PBMCs)	53
PLGA-PEG	A10 Prostate-Specific Membrane Antigen **(**PSMA) aptamer	Cisplatin	LNCaP, PC3	54
PLGA-PEG	Pep TGN	Coumarin-6	bEnd.3	55
PLGA-PEG	c-Arginyl Glycylaspartic Acid (RGD) peptide A-10	Doxorubicin	MDA-MB-231,B16F10 MCF-7	56
PLGA-PEG	2-fluoropyrimidine RNA aptamers	Docetaxel	LNCaP	57
PLGA-PEG	Folate binding protein	Docetaxel	SKOV3	58
PLGA-TPGS	Tocopheryl Polyethylene Glycol Succinate (TPGS)	Docetaxel	Caco-2, MCF-7	59
PLGA-TPGS	Vitamin E TPGS-folate	Doxorubicin	MCF-7, C6 glioma	60

Table 3: Structural features and CMC of some poloxamers (Pluronic®) commercially available

Copolymer	Molecular weight (Da)	Total average polyethylene oxide units	Total average polypropylene oxide units	Hydrophilic–lipophilic balance	Critical micelle concentration (mm)	Reference
L10	3200	7.3	49.7	12–18	---	71
L35	1900	21.6	16.4	18–23	5.3	
F38	4600	83.6	15.9	>24	---	
L42	1630	7.4	22.5	7–12	---	
L43	1850	12.6	22.4	7–12	2.2	
L44	2200	20.0	22.8	12–18	3.6	
L61	2000	4.55	31.0	1–7	0.11	
L62	2500	11.4	34.5	1–7	0.40	
L64	2900	26.4	30.0	12–18	0.48	
P65	3400	38.6	29.3	12–18	---	
F68	8400	152.7	29.0	>24	0.48	
F77	6600	105.0	34.1	>24	---	
L81	2750	6.3	42.7	1–7	0.023	
P84	4200	38.2	43.5	12–18	0.071	
P85	4600	52.3	39.7	12–18	0.065	
F87	7700	122.5	39.8	>24	0.091	
F88	11400	207.3	39.3	>24	0.25	
L92	3650	16.6	50.3	1–7	0.088	
F98	13000	236.4	44.8	>24	0.077	
L101	3800	8.6	59.0	1–7	0.0021	
P103	4950	33.8	59.7	8–12	0.0061	
P104	5900	53.6	61.0	12–18	0.0034	
P105	6500	73.9	56.0	12–18	---	
F108	14600	265.5	50.3	>24	0.022	
L121	4400	10.0	68.3	1–7	0.0010	
L122	5000	22.2	69.0	1–7	---	
P123	5750	39.2	69.4	7–12	0.0044	
F127	12,600	200.5	65.2	18–23	0.0028	

What are pluronic?

The Baden Aniline and Soda Factory (BASF), under the trade names Pluronics and Tetronics (also named Poloxamers and polyamines, respectively), commercialized Ethylene oxide-propylene oxides (EO-PO) based block of Copolymers some Decades ago [61]. Poly Ethylene Oxide (PEO) is a hydrophilic section that contributes 70% of the block copolymer, while PEO is a water-soluble nonionic class A-B A and B-A-B triblock copolymers, A is (PEO) and B is polypropylene oxide (PPO), with PPO being hydrophobic, and PPO is a contributing 30% of block copolymer [62]. The monomers of the copolymer blocks (e. g., polar and nonpolar) are chemically distinct and thus the block copolymers are amphiphilic and induce active surface properties. Interesting nanostructures that are spontaneously produced by solution result from the block separation (self-assembly). Based on the PEO water solubility and PPO insolubility, Poloxamers demonstrated an amphiphilic character in aqueous solutions. Thus hydraulic are the PEO bricks, and hydraulic is the PPO stone. In many applications, they have been made useful by their size and composition as well as their adsorption, including drug distribution, nanoparticles synthesis, cosmetics and emulsion formulations, efficient ink/pigment dispersants as flexible anti-biofouling shielding, amongst other items [63-70]. Poloxamers are commonly studied in pharmaceutical trials. Of the numerous pluronic F127 (PF127) types, the wide variety of biomedical applications has provided considerable interest. A full range of molecular weights and PPO/PEO ratios are given with Poloxamers. Examples of commercially available Pluronic® are presented in table 3 [71]. They show strong cell compatibility and do not cause major inflammation following administration (e. g., intraperitoneal) or topical administration [41, 72]. Although PEO-PPO materials do not degrade under conditions of physiology, renal filtration eliminates copolymers with molecular weights lower than 15 kDa [73]. The useful features pave the way for the approval of the United States Food and Drug Administration (US FDA) and European Medicines Evaluation Agency (EMEA) for some linear PEO-PPO-PEO triblock in the food, pharmaceutical, and agricultural industries.

Several drug resistance mechanisms are affected by pluronic

Inhibition of P-glycoprotein (Pgp) drug efflux system

The increased cytotoxicity of Pluronic in anthracycline drug-resistant cancer, doxorubicin, seems related to the effects of copolymers on the transportation of the Pgp drug efflux system. This is confirmed by the observation that the doxorubicin accumulation in intracellular resistant cancer cells which express Pgp can greatly increase [74, 75]. No alterations in the use of drugs in Pluronic presence were identified with non-Pgp-expressing carcinogenic cells, i.e. the Pgp-controlled transportation routes in Multidrug-resistant (MDR) cells were especially affected with copolymers.

Effects on other drug transporters

Proof that pluronic block copolymers alone can be inhibited by the Pgp efflux pump is rising. There is increasing data. In recent years it has been concluded that other organic anion carriers, including Multidrug resistance-associated Protein (MRP2), could also occur in Panc-1, in addition to Pluronic can thus also inhibit these conveyors, resulting in increased aggregation of fluorescein in Panc-1 cells [76].

Effects on drug sequestration within cytoplasmic vesicles

Drug in the MDR cells can be sequestrated inside cytoplasmic vesicles and then expressed from the cell until the drug can function on the cell as expected, which is a further possible challenge in the treatment of tumors that are immune [77-81]. The protection of abnormally high pH gradients across organelle membranes by H1-Adenosine Triphosphate (ATP), a pump based on ATP, achieves drug sequestration in MDR cells [82]. Pluronics were shown to be capable of hyper-Sensitizing multiple MDR tumors, increasing their antitumor activity by 2 to 3 times to the activity of antineoplastic agents. The effect below the CMC was noticed in a dose-dependent analysis and was finally due to the free unimer chains.

Effect on glutathione (GSH) and glutathione S transferases system (GST)

Multidrug resistance-associated protein (MRP) prescription flush transporters are closely related to the detoxification mechanism in MDR cells with respect to several substrates [77]. Studies have also started on GSH/GST device effects of Pluronic block copolymers. For example, after exposure to different pathways for drug resistance, including those cells, to P85, substantial decreases in both GSH and GST intracellular levels were observed in Madin-Darby Canine Kidney (MDCK) cells expressing PRP.

Self-assembly of pluronic

The concentration and temperature of pluronic are mainly modulated in an aqueous medium. In principle and laboratory experiments, the technique has respectively been named lyotropic and thermotropic micellization. If pluronic are combined with water, that's fine for the PEO block and bad for the PPO block; pluronic are micelles in an aqueous shape according to pluronic concentration and the temperature shown in fig. 3 [83]. The pluronic solution behavior with the coarse grain model has been described previously [84, 85]. The L44 monolayer displayed a brush-like behavior where water reached the entire PEO region. Conversely, it seems that the PPO air-region-oriented unit is aimed at reducing water interaction. Of special interest is the fact that all PEO blocks are exposed to water and the central PPO block to the vacuum by means of a U-shape conformation [86]. As the number of unimer exceeds the Critical Micelle Concentration (CMC), micelle, polymer, and lyotropic liquid crystalline phases are formed by self-assembly [87, 88].

The mechanism includes complex molecular exchanges between micelles and bulk solvents and micelles [89]. Very hydrophobic pluronic do not micellize yet at a cloud stage (<20 % PEO) constitute unsteady vesicular structures. The hydrophobic, relatively atomized copolymers form narrowly dissipated micelles of the heart at ambient temperature. Calorimetric differential scanning studies have shown that the migration of unimer to micelles is an endothermic process. PEO block is primarily governed by a temperature-dependent pluronic aggregation. Its character varies between hydrophilic and hydrophobic as the temperature increases, which means critical micelle temperature (CMT) dominates CMC [90]. The hydrophobicity in higher temperatures of the PEO and PPO blocks in combination with the reducing opportunities of H bond formation (the proportion of the anhydrous methyl groups) increases. The shift in the hydrodynamic size of aggregates can be tested for temperature-dependent micellization and de-micellization [91].

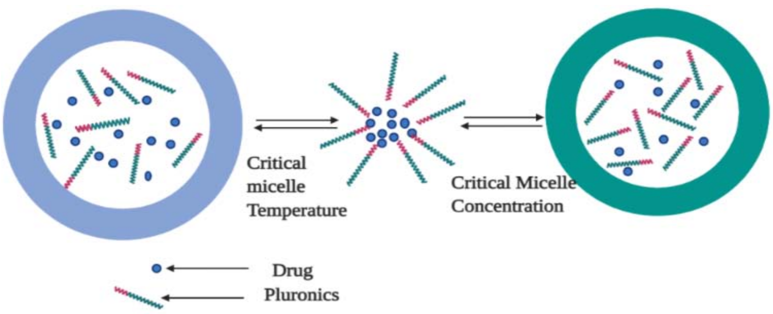

Fig. 3: The development of pluronic micelles in the watery medium according to Pluronics and temperature concentration [82]

Modulation in aggregation behavior of pluronic micelles

In the presence of salt, Micelles will typically expand around the cloud point or display a transformation to rod-like assembling [92]. These transitions primarily rely on temperature and additive existence or hydrophobicity and on copolymer concentration. Like electrolytes (inorganic salts, ionic liquids), nonelectrolytes (urea, sugar, alcohol), and amphiphilic compounds (hydrotropes and ionic surfactants with low molecular weight and other copolymers) additives [93-97]. The CMC or CMT is reduced by dehydration of PEO–PPO interface by additives with beneficial interactions with water. On the opposite, micellization of mixed solvents gives greater solvency for copolymers is disadvantaged. For e. g., with the addition of 40v/v percent ethanol in water, Alexandridis and coworkers showed double increases in CMC P105-F127 [98]. Pluronics solution behavior can also be modified by chemical alteration. Depending on demand, neutral hydrophilic blocks can be cationized or anionised [99]. In pentablock copolymers made of poly (N-isopropyl acrylamide) and poly (lactic acid-co-glycolic acid) and separate end blocks, major changes were recorded in step actions [100, 101]. Mixed pluronic structures with ionic surfactants form small micelles that are rich in surfactants and increase surfactant concentration [102]. Mixing of pluronic with other nonionic surfactants containing PEO as hydrophilic block reported synergistic results [103-106].

Drug solubilization in pluronic micelles

Restricted aqueous solubility of medicines remains a problem, especially given the increasing trends in molecular synthesis with high molecular weights, melting points, and lipophilicity [107]. The bioavailability is constrained by the dissolution of poorly soluble anticancer drugs. Through the use of micellar structures, this can be greatly circumvented. Pluronic metabolism is desirable for both topical and systemic administration, owing to its low immunogenic and special core-shell structures. Without embolism risk, micelles may be injected. The hydrophobic center makes it possible to integrate several medicinal products while the hydrophobic corona protects against aggregation, protein adsorption, and soluble locus, and coordination of the loaded molecules depends on their composition and their relative hydrophobicity [108-110]. The first depends primarily on the presence of pluronic, hydrophobic blocks to ensure the superior involvement of drug molecules [111, 112].

Tumor-selective drug targeting with pluronic

The transportation of drug transporters in the extracellular region from tumor interstitial to target cells can be increased with high-affinity interactions. This can be achieved by means of ligands, which display selective binding on cancer cellular surface to an upregulated molecular target. This technique increases cell absorption, off-targeting effects and amplifies clinical benefits by withdrawing the target cells from within. Despite their high specificity, anti-compound targeting is limited in large-scale development due to their large molecular sizes, immunogenic, and complexity. Its large size hinders carrier trafficking, particularly in solid tumors [113]. On the other hand, low molecular weight compounds are inexpensive, non-immunogenic, and have superior regulation of the density on the surface of the carrier. Terminal hydroxyl groups of pluronic were used to attack ligands in literature papers [68, 114-116]. The approach involves the immediate binding of ligands to more volatile aldehyde, carboxylic acids, and primary amine terminals or the derivation of hydroxyl groups. The latter can be used to bind molecules sensitive to stimuli and targets. Crosslinkable groups are often inserted into the hydrophilic block to reduce premature drug-loaded release that may otherwise take place by de-micellizing unnecessarily diluting micelles. Despite phase transition, the pluronic with low CMC values have been selected as modifiers of biological responses, as seen in fig. 4. Pluronics triggered the cytochrome C release with increased cytosolic reactive oxygen levels in the cytoplasm, which resulted in a pro-apoptotic signal being strengthened or a resistance against acupuncture in MDR cells being decreased [117]. Pluronic unimer built into the mitochondrial membranes has also been suggested to alter membrane structure due to elevated cytochrome C and Reactive Oxygen Species (ROS) levels contributing to mitochondrial apoptosis. Pluronic P85 with Doxorubicin (DOX) and Breast Cancer Resistance Protein (BCRP) plays a critical role in increasing the signal pro-apoptotic and restricts the anti-apoptotic cell machinery in cellular levels in MDR cells [118]. However, DOX alone will simultaneously activate both the pro-apoptotic signal and cellular defense against responsive DOX cancer cells [119].

pH-responsive micelles

The carriers have clear pH differences as a result of their path from the blood into the tumor microenvironment, cells, and subset cells. While their environment is a little bit acidic (6.5 to 7.2), pH decreased considerably on endosomes (5.5–6.0) and lysosomes (4.0–5.0) have been reported [120, 121]. The goal is that drug cleavage and release should occur on latter endosomes or lysosomes and tumor tissue [122-124]. Acid-labile bonds including ketal, acetal, hydrazone, imine, cis aconytil, and orthoester were explored. Compared to those focused on the behavior of lysosomal proteases, conjugates constructed with pH-sensitive bonds are superior. The synthetic solution requires the direct attachment of the medication to or trapping in pH-sensitive block micelles using pH. The first was demonstrated by the covalent attachment of curcumin utilizing a cis-aconytil anhydride connector on hydrophilic blocks of F68. The covalent relation of pH-responsive poly (β-amino ester), as a biodegradable polymer, is used in another approach. While low pH makes it possible to release drugs within the cell, the key challenge remains improving micelle affinity for cancer cells. This can be done by the latest demonstration by Xu *et al.*, of identifiable ligands on micelles. A possible target of such transports is tumor cells over-expressing sialic acid residues in the extracellular domain. In contrast with free doxorubicin, hybrid micelles have more than 3.4 times improved the potency of tumor inhibition. On Folic acid attachment, similar changes were observed in the anti-tumor effect of pH-sensitive F127 micelles. Rather recently, as P123 has been connected to a molecule believed to enhance the solubilization of medicine (P115), Tange and coworkers confirm selective oxidative damage to cells of cancer; they have increased intracellular reactive oxygen species, interrupting with mitochondrial activity. Drug molecules escaped the lysosome successfully and were located near the nucleus, which translated into apoptotic death of the tumor cells [125-127].

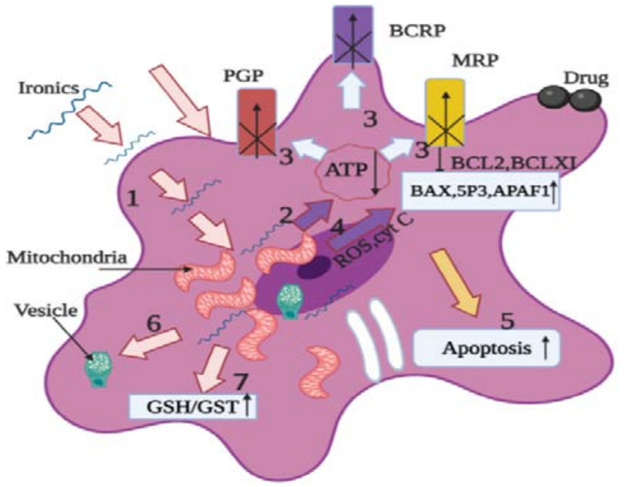

Fig. 4: Effect of pluronics in MDR cancer cells: (1) entrance of Pluronics, (2) ATP depletion, (3) drug efflux inhibition, (4) cytochrome C release and elevation of ROS in the cytoplasm, (5) pro-apoptotic signaling elevation and lower anti-apoptotic defense, (6) inhibition on the glutathione/glutathione S-transferases detoxification system, and (7) elimination of drug sequestration within cytoplasmic vesicles [116]

Redox sensitive micelles

The uncontrolled proliferation and a high metabolic rate of cancer cells contribute to high reactive oxygen species development. ROS speeds up cancer mutation rates and causes irregular signals [128]. While the intracellular, extracellular redox cells actively configure their state, a safeguard device acts at the same time. The development of GSH, a tripeptide-containing thiol (μ-glutamyl-cysteinyl-glycine), effectively controls the latter. GSH mediates electrical, free radical, and ROS neutralization [129, 130].

Ultrasound-sensitive micelles

The reversible endothelium permeability and focused drug release can be manipulated at the tumor site by acoustic waves. Tumor simulation and drug release activation can be performed concurrently here. The tumor interstitium will discharge a high payload within the pluronic micelles by ultrasound-induced interference. The destruction of micelles and the payload release has been demonstrated that the power output change can be remotely controlled [131]. The copolymer was synthesized using azide-completed PEO and alkyne-completed PPO, which contains 1, 2, 3 triazole movement and four ester bonds at the junction site. The breakage of crossroads caused by High-Intensity Focused Ultrasound **(**HIFU) has been verifiable by a change in average micelle diameter (from 26 nm to 90 nm). In addition, the authors confirmed that cleavage was superior to the triazole ring, at the central ester relation [132]. Pluronic F127 was recently used to create a new theranostic nanobubble (NB), which combines ultrasound and fluorescent pictorial tracking with Photodynamic therapy (PDT) [133].

Radiation responsive micelles

PDT uses chemical photosensitizer (PS), which, when irradiated with a particular wavelength, generates singlet oxygen and other ROS in tumor cells. During molecular interaction of active PS with intracellular oxygen, these radicals are formed. Tumor and healthy cells are classified by their metabolism. Increased metabolic and mitochondrial dysfunction allows cancer cells to exercise more oxidant stress through the oncogenic transition. Further anti-cancer effects of PDT occur by vascular shut-down, cell membrane de-stabilization, local immune system activation, and the injection of tumor antigen into infiltrating immune cells. Burst release and fast clearance of tumor area micelle can be overcome through the transformation of sole-to-gel [134-137].

Pluronic-based mixed polymeric micelles as drug solubilizing/ stabilizing carrier

The polymeric micelles allow the integration and protect against the inactivation of poorly water-soluble drugs into the biological media and strive to provide effective medication and targeting capabilities [135-138]. Several experiments have shown that the cytotoxicity of anti-cancer bioactive agents with MDR in tumor tissues can be improved by mixtures of pluronic and other polymers [116, 139, 140]. The self-assembly property of PF127 in the form of micelles was also assessed for the targeted supply of drugs. Nano-size pluronic micellar structures which be used to encapsulate hydrophobic agents on the surface of a nanoparticle inside the micelle's broad center or conjugate the hydrophilic moieties. It may also be used to grow hydrogels forming in situ, owing to thermo reacting features of the pluronic [141-145]. Hydrogels are ideal in situ for local as well as the systemic distribution of drugs. The pluronic agents are easily mixed, combined, or adsorbed by other common polymers such as chitosan, Polylactic Acid (PLA), PLGA, and so on in the field of drug delivery. Polymeric micelles are formed with lower levels and demonstrate greater thermodynamic and kinetic resilience relative to the micelles of standard surfactants to tolerate thermodynamic therapeutic dilution, as well as improved drug solubilization and stabilizing capacity [138, 146, 147]. Moreover, micelles in which hydrophilic blocks consist of PEO are sterically stabilized and macrophages are less feasible to consume [148]. Drug trapping in the micellar structure limits bond access to an external medium and thus, the drug-copolymer bond hydrolyze rate is much less than for the typical drug-polymer conjugates [149]. Only released drug molecules are anticipated to be pharmaceutical in a mechanically trapped environment, even though the micelle impacts cellular and body delivery [150].

The thermal transformation of Paclitaxel (PTX) to Pluronic-based NPs, with a core/shell configuration, was conducted in a mixture from the Pluronic F-68 to the liquid polyethylene glycol (PEG); molecular weight: 400). As PTX solubilizers, Liquid PEG and Pluronic F-68 are used for nanoencapsulation PEG containing PTX. In addition, emulsions made from PEG containing PTX and liquidized Pluronic F-68 were produced at nanometer level by extracting the melted mixture at a transition temperature (120 °C) as defined in fig. 5 [151]. The PEG containing PTX pluronic F-68 nanoencapsulation was finished with the liquid mixture being cooled to 0 °C. The formation of the PTX equipped Pluronic NPs with core/shell configuration has been clearly revealed by FE (field emission)-Scanning Electron Microscopy (SEM), cryo-transmitting electron microscopy (TEM), and by size distribution analysis. The sustained circulation in the bloodstream of the PTX-charged Pluronic NPs, resulting in improved tumor tissue targeting ability, was predicted to increase over that of the surfactant-based PTX, due to PEO blocks in pluronic F-68.

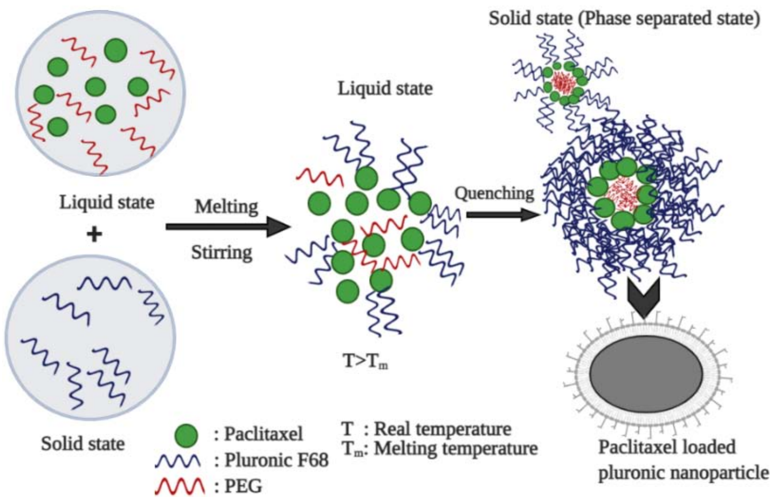

Fig. 5: The formation of Pluronic-based NPs with a core/shell structure. The core is composed of a mixture of PEG (molecular weight: 400) and PTX (or DTX) and the shell is composed of Pluronic F-68 [151]

Core/shell np composed of a pluronic composite

A temperature-induced phase change in the mixture between PLGA and Pluronic F-127 core/shell NPs with PLGA core and pluronic shells is prepared for a PTX carrier [152]. The liquidized mixtures of PLGA, PTX, and Pluronic F-127 were prepared at 600c on a stepped basis in response to temperature changes, with the result that the temperature was decreasing to 250C. Based on the actions of the PLGA and Pluronic F-127. SEM has been used to monitor the phase-separated state and check the identity of the PLGA center. When this mixture was spread into water, aqueous media is suppressed of the Pluronic-coated PLGA NPs (core/shell NPs with PLGA core). Fig. 6 explains the development of PLGA NPs with pluronic coating. On the surface of the PLGA heart, the pluronic shell tracked PTX from the core/shell NPs [153]. PLGA NPs were developed without the use of a poisonous organic solvent with the liquidized pluronic F-127 as a solvent. As the pluronic F-12, pluronic-coated PLGA NPs with a core/shell structure were not evaporated during preparation. The PTX and Docetaxel (DTX) models for small molecules were chosen and the vascular endothelial growth factor (VEGF) and HGH models were picked as protein-based medicines. They included both PTX and DTX. A pattern of continuous release of both model drugs has been found that the presence of a Pluronic coating on the liposome core surface mediated the release of the model drug.

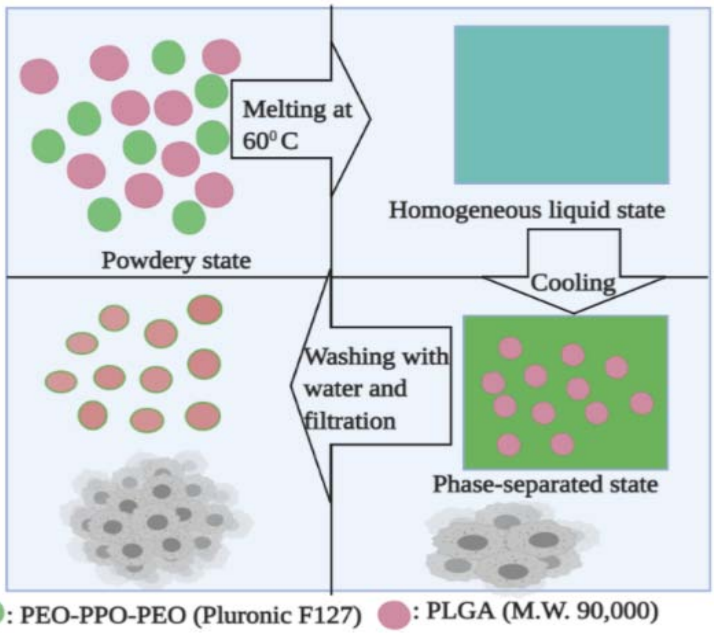

Fig. 6: Temperature-induced phase transition in the melt mixture of PLGA and Pluronics [153]

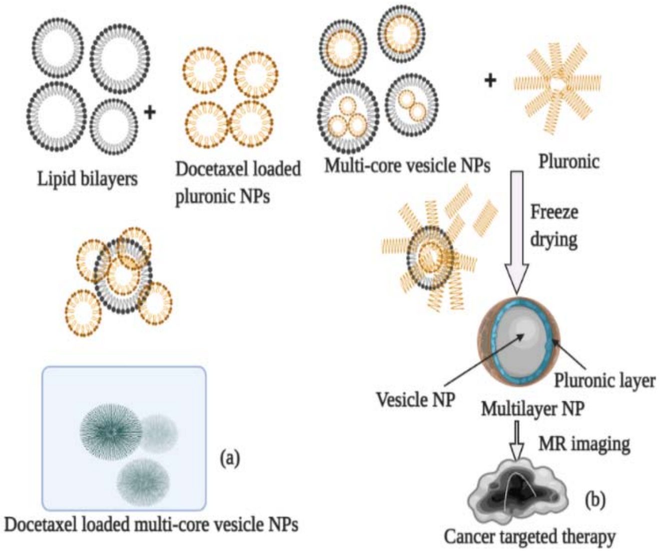

Fig. 7: (a) Stabilization of Pluronic NPs by vesicle fusion (forming vesicular NPs) and (b) layer by layer approach stabilization of vesicle NPs [154]

Pluronic based NPs with a Core/Shell structure for cancer-targeting therapy

In the preparation of the NPs of Pluronic-based, temperature-induced phase transformation was very helpful. However, during the development of DTX charged Pluronic NPs during the previously mentioned temperature-induced transformation, the oxidation of DTX was observed [151]. The temperature-induced phase shift was rendered in a milder environment to protect DTX from oxidation (90 °C for 10 min). Though DTX oxidation was low, instability of DTX charged Pluronic NPs was observed with DTX precipitation within 10 min from the NPs in the aqueous medium.

The Pluronic NPs demonstrated a fast release pattern of precipitation of DTX in the release medium before being integrated into the vesicle [154]. In vesicle NPs, the release rate drop was controlled because the DTX released was penetrated through the lipid bilayer by the Pluronic NPs (fig. 7).

The multilayer NPs revealed a more deleted release rate for DTX as the external Pluronic layer was a further obstacle against DTX release. A calculation of anti-tumor effectiveness by tumor-bearing muzzles has observed the therapeutic functionality of the multilayer NPs. The DTX filled multi-layer NPs are more successful than those injecting free DTX (Commercial DTX (Taxotere®)), Empty NPs (Multilayer No-DTX), or Saline (200 L) [155, 156]. Due to their tumoral objective potential based on the EPR effect, the multilayer NP has demonstrated improved anti-tumor effectiveness [157]. This research prepared and injected multilayer NPs with iron oxide NPs in the tail veins of tumor-bearing mice to validate the ability of the multilayer NPs to target the tumor. There was a large improvement in MR strength at the tumor site relative to Resovist in the multi-layer iron oxide NPs. This shows that multilayer NPs can be used as nanocarriers with tumor-targeting capabilities for molecular imaging [158].

Building blocks for targeted chemotherapy using pluronics

The issues with conventional chemotherapy, such as a lack of precise targeting of the tumor and drug resistance, have been resolved with NP, whereby traditional chemotherapy has been improved [159-161]. Of these pluronic NPs, promising carriers have been identified in targeted cancer therapy. Due to Pluronics micellization in aquatic solution, polymeric micelles have been developed and their cores have been used as depots for different treatment agents and methods of diagnosis [162]. A Temperature Induced Phase Transition (TIPT), as defined in fig. 8, was prepared for pluronic NPs loaded by Paclitaxel (PTX). Images from Cryo TEM revealed Pluronic NPs' core/shell structure (fig. 8b).

Because the pluronic F-68 was mostly protected by the surface of NPs and PEOs, it was predicted that pluronic NPs would be retained in systemic circulation for a prolonged permeation and retention effect (EPR). This is the prerequisite. The high targeting efficiency near the tumor can be explained by the *in vivo* biodistribution in terms of the EPR effect. In Phase II clinical trials, esophageal adenocarcinoma was tested for the antitumor potency of the DOX formulation, composed from pluronic (L61 and F127) and DOX [163-165]. This technique was designed to test the multifunctional properties of the DOX-controlled pluronic/heparin-np-system. MB or DEVD-S-DOX was then achieved in the tumor-tissue mixture after photo-irradiation by the release of MB or DEVD-S-DOX from the NP (fig. 9). Table 4 illustrates several clinical trials involving Pluronic® polymer-containing formulations. Pluronic and heparin NPs were predicted to accumulate in tumor tissues caused by the EPR effect [166, 167]. Some medicines solubilized in poloxamer micelles used for cancer chemotherapy are presented in table 5 [71].

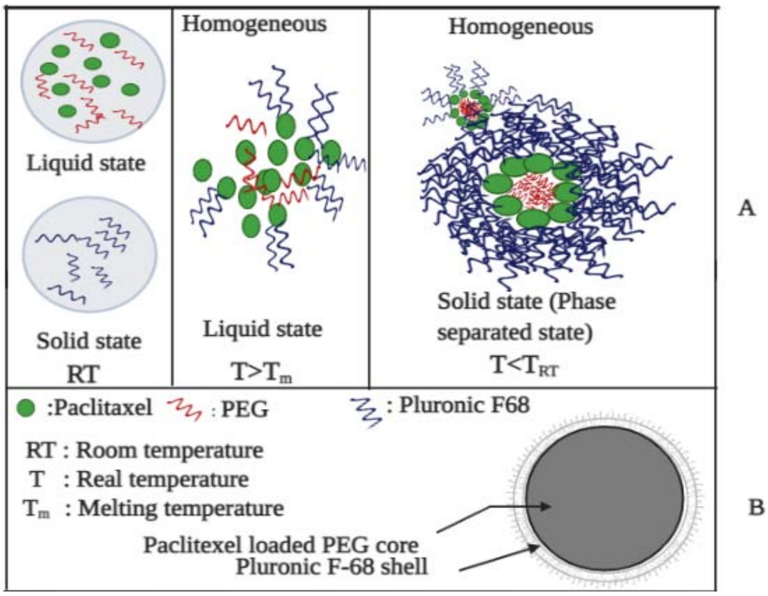

Fig. 8: (A) Formation of Pluronic nanoparticles by the TIPT method, (B) cryo-TEM image of paclitaxel-loaded Pluronic NPs [162]

Table 4: Some examples of pluronic®-containing formulations in clinical trials

Industry/sponsor	Pluronic® containing formulation	Use	Stage	Reference
Supratek Pharma Inc.	SP1049C: Doxorubicin+Pluronics® L61 and F127	Advanced esophageal adenocarcinoma	Phase III	168
Mast Therapeutics, Inc.	Purified Poloxamer 188 (based on Pluronic® F68)	Vaso-occlusive crisis	Phase III	
British Columbia Cancer Agency	Topical amitriptyline 2%, ketamine1%, and lidocaine 5% in Pluronic® lecithin organogel	Neuropathic pain secondary to radiation therapy	Phase III Completed	
CoDa Therapeutics, Inc.	Nexagon®: Pluronic® gel	Persistent corneal epithelial defects	Phase II	
Sancilio and Company, Inc.	SC401B (Pluronic® F87 as a surfactant)	Severe hypertriglyceridemia	Phase III	
Valentis	VLTS-934 (Pluronic®Poloxamer 188)	Peripheral vascular disease	Phase II Completed	

Pluronics as a therapeutic polymer

The biggest challenge for the success of chemical agents is tolerance. Resistance comes primarily from efflux pumps minimizing chemical therapeutic intracellular levels [169]. The therapeutic resistance induced by Efflux can be resolved by pluronic systems. Several studies record Pluronic alterations that induce decreased efflux activity in the lipid microenvironment of P-gp. The pluronic polymers suppress the membrane microviscosity that permeates the cancer cells to chemotherapeutic agents. Also, the mitochondrial membrane is destabilized by pluronic and induces significant ATP depletion in cancer cells. The Kabanov research group notes that pluronic can block the mitochondrial electron transfer chain (Complexes I and IV), which could increase the ROS level within the target cancer cells [170]. High ROS disturbs the mitochondrial membrane's normal configuration and initiates the release of apoptotic mediators Intrinsic [163, 171]. Pluronic cytochrome-mediated release c, Apoptosis-Inducing Factor (AIF), and Endonuclease G can cause other apoptotic mediators to be swiftly triggered within the programmed cell death protocol. Metastasis suppression is another essential function of the pluronic as a medicinal polymer. In metastatic cancers, the efficacy of normal medicinal substances is marginal. Pluronic polymers with medium hydrophilic-lipophilic equilibrium (HLB) have been documented to block the migration and invasion of cancer cells. In the 4T1 tumor-carrying mice model, a major inhibition of the lung metastasis by a pluronic effect was reported [172]. Oddly, pluronic Antimetastatic characteristics are linked to a decrease in matrix metaloproteases (MMP) such as MMP-9 control. Moreover, the above-mentioned study has documented substantial synergistic anti-metastatic activity for the combination of pluronic-doxorubicin. In another related analysis, the P85 pluronic copolymer micelles loaded with a 5-Fluorouracil (5FU) were produced for colon cancer inhibition [173]. There has recently been a new pluronic F68 conjugated delivery system [174]. The potency and toxicity of these micelles concerning naked drugs were appropriate. Gemcitabine is a 70-gent anti-cancer drug used in multiple chemo regimes. Dinarv and the study community reveal a novel chitosan-pluronic oral delivery system. Pluronic nanoparticles hydrophilic shells can be used to conjugate target moieties such as folates, aptamers, and monoclonal antibodies (fig. 10). There is numerous folate-conjugated pluronic framework for the transmission of paclitaxel and doxorubicin, which has shown substantial tumor aggregation folate cross-connected pluronic micelles [175, 176]. Rabial Glycoprotein Virus (RVG) conjugates pluronic nanoparticles is another groundbreaking nanocarrier. RVG has effectively conjugated particles aim at the blood-brain barrier and has thus increased the biological bioavailability of the brain. The treatment of different brain tumors or Central Nervous System (CNS) malignancies may be achieved with such a method. Pluronic supply systems could be used as a vehicle for the supply of combinatorial regimens because of versatile and tunable physicochemical properties [177]. Paclitaxel-loaded pluronic Arginyl Glycylaspartic Acid (RGD)-plated nanoparticles for the treatment of gliomas have been analyzed in another report [178]. RGD peptide has been used to cross the blood-brain barrier as a penetration enhancer.

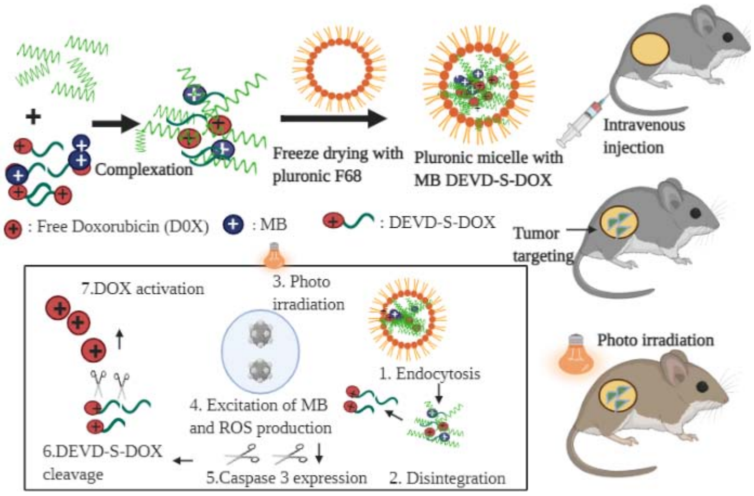

Fig. 9: An illustrative description of chemo-photodynamic combination therapy [76, 119]

Table 5: Anticancer agents formulated in poloxamer-based polymeric micelles

Drug	Copolymer	Performance	Reference
Epirubicin	L61, P85, F108	Lifespan of animals and inhibition of tumor growth considerably increased with drug/copolymer compositions.	71
Doxorubicin	P105	Lower *in vitro* proliferation of MatLu rat prostate carcinoma cells with micellar system.	
	P85	A formulation containing Pluronic® P85 and DOX prevents the development of MDR in the MCF7 human breast carcinoma cell line.	
Camptothecin	F127, L92 versus materials modified with Polyacrylic acid (PAA) blocks	3-to 4-fold higher solubility. Amount of camptothecin solubilized per PPO greater in the Pluronic-PAA than the parent, suggesting solubilization by the hydrophobic cores and hydrophilic shells. Enhanced stability.	
	F127, F68, P85	Improved oral absorption estimated *in vitro*.	
Megestrol	F127/l61 mixed micelles versus materials modified with PAA blocks	Bioadhesive tablets for gastrointestinal retention and enhanced bioavailability.	
Paclitaxel	P123	Enhanced solubility, prolonged blood circulation and modified biodistribution. Plasma half-life was 2.3-fold higher. Increased accumulation of PTX in ovary, uterus, lung, and kidney; but decreased accumulation in liver and brain.	
Octaethylporphine	F127, F68, P85	Improved oral absorption estimated *in vitro*.	
Epidermal growth factor	F127	Gel was evaluated as a potential topical vehicle.	
Tyrphostin 47	F127	Sustained local delivery does not result in a reduction of neointimal proliferation in the rat carotid injury model.	
Rapamycin	F127	Treatment of experimental vein grafts is associated to increased apoptosis in the vascular wall and reduction of neointimal hyperplasia.	
Methotrexate	F127	Potential direct administration into solid tumors	

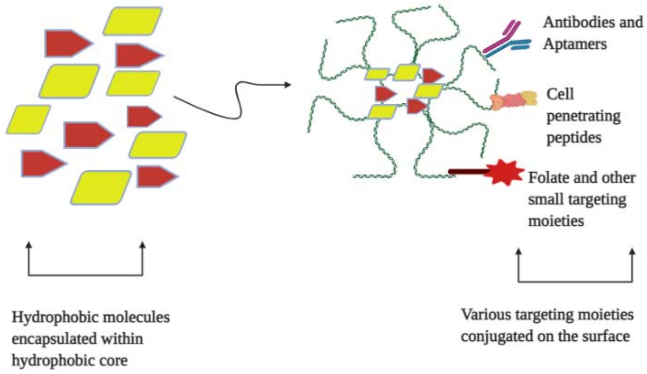

Fig. 10: Pluronic based delivery system; a novel platform for formulation of hydrophobic molecules and targeted delivery [174]

Pluronic nanocarrier: a theranostic approach

Nanoscale theranostic such as polymeric micelles are commonly explored as promising gold standards in a personal medicine context for the purpose of diagnosis, treat and track the growth of tumors simultaneously [179]. Theranostic functional pluronic polymer micelles have shown tremendous promise in contrast to traditional therapies to enhance and track medication delivery after administration, which can improve drug effectiveness and mitigate off-target toxicity. Latest studies have indicated that the tumor microenvironment (TME), including malignancy, invasion, and metastasis, is a central orchestrator of cancer progression [180, 181]. A significant biological factor in which cohesive and polarized epithelial cells turn over nonpolarized and highly mobile, mesenchymal-like cells remains an important element of epithelial-mesenchymal transfer [182]. The innovative design of nanomedicine continues to be relevant as the tumor barriers to drug accumulation (altered flux, thick matrix, efflux pumps.) are multiple and highly effective. In particular, the use of nano-caregiators, adorned with the most adequate targeting vector and with the most suitable therapeutic agent, all selected in the light of genetic knowledge for the recipient, is a means of successful transmission to the cells involved, while the protection and efficacy of the therapy are far-reaching [183, 184]. The hydrated pluronic PEO shell induces sterical repulsion and leads to a strongly activated protein adsorption strength barrier [185, 186]. Some examples of pluronic micelles for cancer diagnosis are been listed in table 6. It thus minimizes the formation of protein corona that contributes to the prolonged blood circulation and bio-imaging performance of the nanocarrier for theranostic (fig. 11) [187].

The Pluronic P94 was studied to direct the intravenous and intratumoral injections of radionuclides [188]. In for the hybrid Single-Photon Emission Computerized Tomography (SPECT)/ Computed Tomography (CT) imaging pluronic F68 micelles incorporating Near-Infrared (NIR) Cy 5.5 and DOX is found useful in the diagnosis and treatment of targets. Pluronic F127 is safe against protein adsorption. Table No.6 outlines recent techniques for multi-factor therapies, medications, and/or theranostic of cancer, including Pluronic structures alone and as a mixed method. In combination with biomethodologies, pluronic intelligent nano micelles will open the door for understanding the pathways of cancer that are at the core of the diseases, including the Epithelial-Mesenchymal Transition (EMT)-related methods.

Table 6: Overview of some pluronic micelles for cancer diagnosis; theranostic approach

Pluronic	Imaging						
	Agent	**Modality**	**Drug**	**Theranostic model**	**Result**	**Purpose**	**Reference**
Pluronic F68	Cyanine5.5 (Cy5.5) dye	NIR	DTX	HIFU	*In vitro* SCC-7 cells, murine *in vivo* male C3H/HeN mice	Targetable/Triggering nanosystems for the solid tumors. PMs triggering release into tumor cells occurs under HIFU exposure through nonthermal mechanisms, which increase the therapeutic effect.	189
F127	β-thiophene-fused-BF2 azadi-pyrromethene (aza BDTP)	NIR	PTX	Photoacoustic imaging and photothermal	*In vitro* 4T1 cells, mouse breast cancer cell line	Co-loading of aza-BDTP and PTX (BDTP/PTX micelles show promising *in vitro*/*in vivo* results as nanotheranostic vehicles.)	190
F127	AuNPs	NIR	PTX	chemo-photothermal therapy	*in vitro* MDA-MB-231 cells *in vivo* female Balb/c nude	*In vitro* and *in vivo* studies using the combined strategy. (The pluronic-PLL-Au micellar carrier can cause a synergistic effect that is promising for chemo-photothermal therapy.)	191
F127	AuNPs IR780 iodide	NIR1 05	IR780	photodynamic and photo-thermal therapies and surface-enhanced reso-nance Raman scattering	*in vitro* C26 cells, murine colon carcinoma cell line	The use of the AuNPs-F127-IR780 micellar system indicates synergistic effects by simultaneous photodynamic and photothermal activity.	191
P123 F127	rhodamine-B dye	NIR	Verte-porfin	Photodynamic therapy	*in vitro* MCF-7 cells, human breast cancer cell line PC3 cells, human prostate cancer cell line	Multifunctional pluronic P123/F127 mixed micelles show promising results for the encapsulation and delivery of the photodynamic therapy.	192

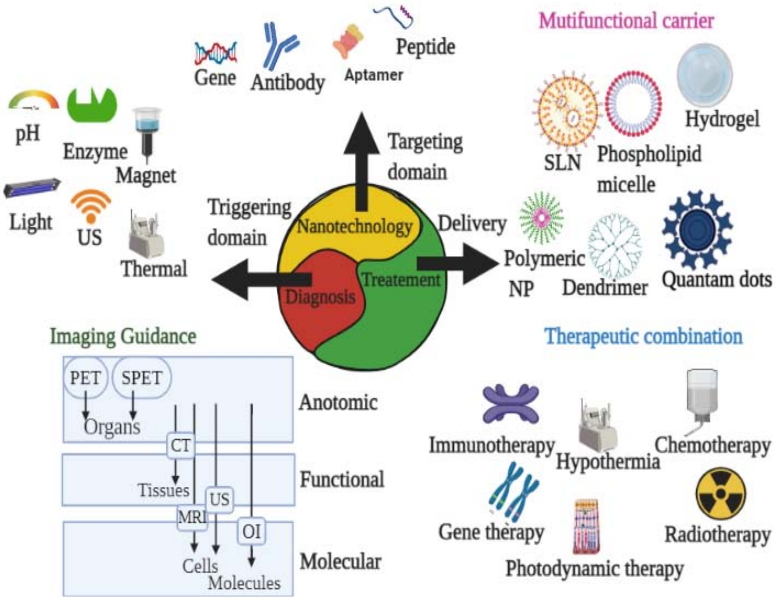

Fig. 11: Multifunctional theranostic and bio imaging nanosystems. PET, positron-electron transmission; SPECT, single-photon emission computed tomography; CT, computed tomography; MRI, magnetic resonance imaging; NPs, nanoparticles; US, ultrasounds; OI, optical imaging [187]

Future prospective

In clinical trials as vehicles of cancer therapies, there are some promising practical pluronic micelle formulations. The clinical translation of the nano-medicines is still a problem. However, their use in theranostic has not yet been translated into clinical trials [193]. The copolymer concentration can decay below the CMC, for example, after intravenous administration and subsequent formulation dilution, resulting in micellar dissociations and premature release of medicines. Polymer micelles must also be programmed for extended blood circulation to ensure a proper concentration of the loaded therapeutic product and the photographic material collecting in the target area. While it is possible to use multi-target nano delivery schemes, the still enormous distance between preclinical and clinical outcomes requires the introduction of general and logical translation protocols [194-197]. The main concern of future research can be done in the preparation of nanoparticles that can further withstand the biological diversities and thus further improve drug stability in the biological environment and hence its bioavailability [198].

CONCLUSION

Conventional cytotoxic medications induce some side effects partly as a result of existing treatment protocols dependent on several administrative periods. The effectiveness of the strategy is dependent on the combination of recent trends in nanomedicine care with targeted cytotoxic drug nanocarrier allowing for sustained release, site-specific delivery, and dissemination, reduction, or even elimination. One of the most brilliant cancer therapy techniques has been the advancement of nanoparticles-based treatment strategies as a drug delivery method. The conjugation of ligands on the surface of nanoparticles for cell recognition has resulted in the development of a new generation of nanoparticles (targeted nanoparticles). The use of differentially expressing molecules such as polymeric nanoparticles on the surrounding tumors could be achieved in the targeted nanoparticles offering sufficient cytotoxic release. The use of tailored and functionalized NPs promises to advance in emerging therapy groups. A multifunctional theranostic approach in the drug delivery system can be successful against cancer with different therapeutic cargo. These forms of formulations can be investigated in clinical trials.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

Declared none

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