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Polymeric micelles in TKIs' delivery for cancer treatment

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Abstract

Polymeric micelles (PMs), one of the most popular nanotechnology platforms for the delivery of various kinds of chemotherapeutics, are aggregated colloids formed through the self-assembling of amphiphilic block copolymers in an aqueous solvent. The popularity of PMs is owing to several unique physicochemical characteristics such as small size, biocompatibility, core-shell arrangement, high drug loading capacity, and favorable solubility. There is a plethora of studies on the use of these nano-delivery systems over years to overcome the issues related to drug administration, like low water solubility.Tyrosine kinase inhibitors (TKIs) are targeted therapy agents that constitute a significant part of cancer treatment modality due to targeting key biological molecules (EGFRs, PDGFR, and HER2) largely involved in the progression of cancer. However, issues associated with TKIs such as water-insolubility, short circulation time, systemic toxicity, and drug resistance pose challenges in the way of cancer therapy. In the present review, in addition to providing an introduction to micelles and different types of block copolymers, we attempt to present the latest information on clinical and preclinical research on employing PMs to deliver different TKIs to various types of tumors.

Keywords: *Polymeric micelles, Nanocarriers, Drug delivery, Tyrosine kinase inhibitors, Cancer therapy*

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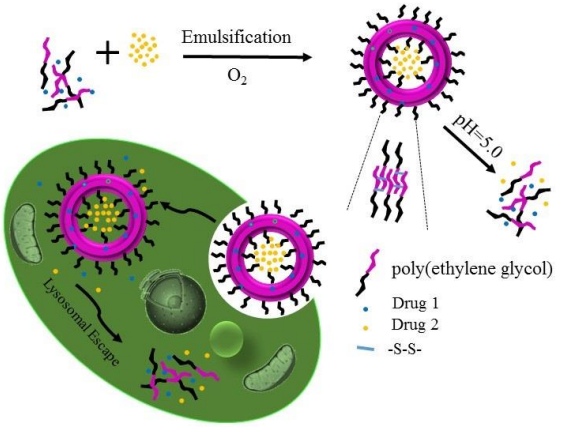
Graphical abstract



1. Introduction

Tyrosine kinases are enzymes that have a role in proteins phosphorylation and activate a signal transduction pathway that will lead to cell growth, differentiation and angiogenesis in normal cells. Inhibition of tyrosine kinases can block the signaling pathways and leads to cell death and inhibition of angiogenesis, and ultimately prevents the growth and proliferation of cancer cells [1-3]. Currently, approximately 90 different tyrosine kinases or tyrosine kinase receptors have been identified, which are classified into 20 different categories based on their receptors and ligands [4,5]. Oncogenic activation of these enzymes can cause tumor growth and malignant progression of solid tumors, such as lung cancer, especially NSCLC, breast, colorectal and prostate cancers. The mutations that cause activation of receptor tyrosine kinases mainly include "gain of function" mutation, high expression, gene amplification, change of chromosomal arrangement, kinase domain duplication and autocrine activation [6]. In addition to these mutations, there are other mechanisms for the activation of tyrosine kinases, including defects in the mechanisms of inactivation and activation through receptor dimerization [7]. Since different types of tyrosine kinases have significant roles in of cancer development, these enzymes have attracted the attention of many researchers as potential targets for cancer treatment.

More than 50 tyrosine kinase inhibitors have been approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), and more inhibitors are also in the process of clinical/preclinical trials [2]. These potent and well-tolerated drugs are either single- or multi-targeted inhibitors that interfere with function of TKIs including EGFR, VEGFR, FGFR, PDGFR, HER2, ALK, ROS1, NTRK, MET, RET, MEK, and KIT[8]. For about two decades, tyrosine kinase inhibitors have been used in the clinical treatment of many types of cancers [9-12]. Recent research on different anticancer drugs has also shown that tyrosine kinase inhibitors are the primary target group in the treatment of various types of cancer as they can provide precise targeted therapy options based on genetic alteration characteristics of each patient [13]. TKIs have had a great impact on patients' survival and quality of life and cause a shift in treatment paradigm of various solid tumors [8]. Despite many advantages of TIKs over other anticancer drugs, they are much more likely to develop resistance in patients after prolonged treatment. Patients develop resistance toward these drugs as a result of various reasons, mostly mutation. Such drug resistance leads to the development of generations of TKIs from first to third and even further. For example, in patients harboring a subgroup of lung

cancer named non-small cell lung cancer, after 10 to 14 months of therapy with first-generation EGFR-TKIs (e.g., gefitinib, erlotinib, and icotinib) and second-generation EGFR-TKIs (e.g., afatinib, dacomitinib) they demonstrate acquired resistance to these drugs, may resulting in the application of EGFR-TKIs from the third generation. However, due to the high efficiency of drugs such as gefitinib, erlotinib, and afatinib, another potential strategy to overcome acquired TKIs resistance is to make use of nanotechnology [8,14]. Various studies have shown that drugs based on nanotechnology have significant applications in diagnosis, treatment and drug release, especially in research related to cancer, and nanocarriers play an important role in overcoming the disadvantages of chemotherapy drugs [15-17]. The rational design of nanomedicine is an almost new therapy form that emphasizes replacing drug delivery and enhancing therapeutic effects while reducing adverse effects on normal tissues [18]. Recently, drug delivery technology has made it possible to target tumor cells for small molecules using nanoparticles [19], which include nanocarriers loaded with TKIs, and provide more drug solubility, increased systemic circulation time and tumor targeting, and a significant increase in the therapeutic effectiveness of these drugs.

Among the different types of nanoparticles, micellar nanoparticles (MNPs), i.e., polymer micelles (PMs), which are made from colloidal particles in nano dimensions (5-100 nm), have attracted the attention of many researchers [20]. Detailed information on PMs is presented in the following section of this article. With respect to the importance of this topic, in the present paper, we reviewed studies that have investigated the advantages and disadvantages of using micellar nanocarriers in the delivery of different types of TKIs drugs in the treatment of different types of cancer.

2. Polymer micelles

Micelles, the vesicles made up of amphiphilic surfactants (non-polymeric micelles) or amphiphilic copolymers (polymeric micelles), have recently attracted the attention of researchers as a novel drug carrier system for different types of organs. Compared to non-polymeric micelles, polymeric micelles have remarkable potential due to their higher solubilization power, higher loading capacity, higher stability in the bloodstream, and therapeutic potential and longevity[21-23].

Since the application of polymeric micelles as nano-scale drug delivery systems (nano-DDS) in the late

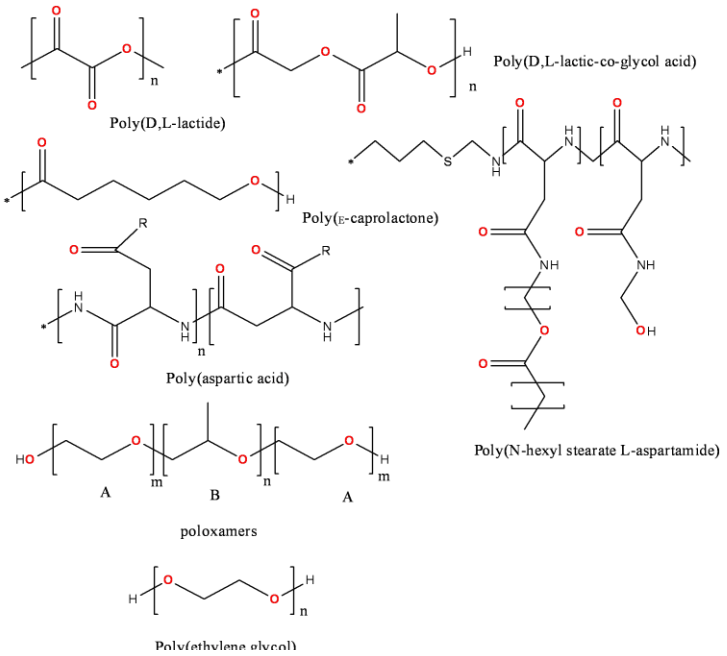


Figure 1. Chemical structure of the most commonly used poly(ester) and poly (amino acid)

core-forming blocks in polymeric

1980s, numerous polymer self-assemblies have been extensively developed with the aim of delivering various drugs, including low molecular weight anticancer drugs, tyrosine kinase inhibitors (TKIs), contrast/imaging agents, proteins, plasmid DNA, antisense DNA, and more recently short interfering RNA (siRNA) [24,25]. The hydrophilic outer shell provides the stability of micelles in the aqueous environment and prolongs their circulation time in the bloodstream, thereby protecting micelles from the reticuloendothelial system (RES) and facilitating their accumulation in specific areas with leaky vessels. Moreover, they were shown to facilitate brain delivery of low molecular mass drugs by escalating drug solubility and stability in plasma. [25,26].

Currently, several promising candidates are in clinical trials, e.g., doxorubicin (DXR)-encapsulated poly(ethylene glycol) (PEG)–poly(propylene oxide) (PPO)–PEG (Pluronic) micelle (SP1049C) in phase III, paclitaxel (PTX)-encapsulated PEG–polyaspartate block copolymermicelle (NK105) in phase II, PTX-encapsulated PEG–polylactide (PLA) block copolymer micelle (Genexol-PM) in phase II, SN-38 (the active form of irinotecan hydrochloride)-encapsulated PEG–polyglutamate block copolymer micelle (NK012) in phase II (Figure 1).

2.1 Structure and synthesis of micelles

The most common polymeric micelles used in drug delivery are amphiphilic di-block polymers (hydrophilic—hydrophobic) and tri-block polymers (hydrophilic—hydrophobic—hydrophilic) (Figure 2). In an aqueous system, the polymeric micelles are amphiphilic, where the hydrophobic part is kept outside the aqueous environment [23,27]. Additional structures include graft copolymers(hydrophilic-hydrophobic) and ionic copolymers (hydrophilic-ionic). Micelles possess core-shell structural designs with sizes ranging from 10 to 100 nm. The hydrophilic outer environment is mostly made up of polyethylene glycol (PEG), and the inner hydrophobic core is mainly composed of molecules such as polycaprolactone, polypropylene glycols, phospholipids, and fatty acids, which allow them to be loaded with hydrophobic drugs [28-31].

The defining characteristic of micelle systems is the ability of polymer units to self-assemble into nano-scale aggregates. Self-assembly is a thermodynamic process. The potential for self-assembly is determined by the mass and composition of the copolymer backbone, the concentration of polymer chains, and the properties of encapsulated or pendant drugs and targeting agents. The contributions of each of these factors are discussed in detail below [32].

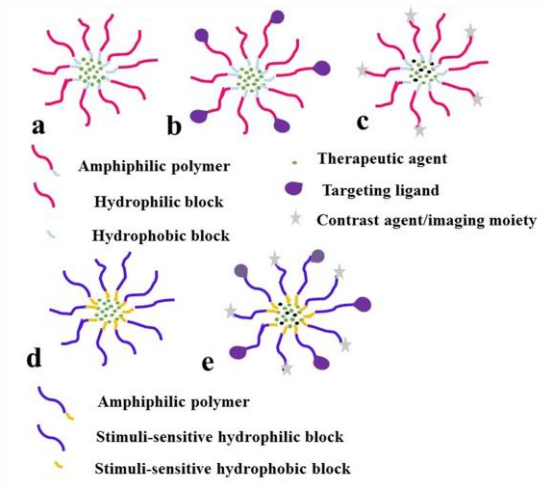


Figure 2. Schematic drawing of a polymeric micelle (a). Micelle conjugated with a targeting ligand (b). Micelle with incorporated contrast agent or chelated imaging components (c). Micelle improved for triggered drug release (d). Either the hydrophilic or hydrophobic polymer can be made thermo/pH/light/ultrasonic sensitive. Optimized micelles for cancer therapy carrying targeted ligands, contrast agents or imaging components, therapeutic agents and polymers suitable for triggered controlled release (e).

Polymer nanomedicines usually fall into one of two categories: (a) polymer-drug conjugates for increased drug half-life and bioavailability, and (b) degradable polymer architectures for controlled release applications. However, it should be noted that aspects of polymer chemistry are emerging in nearly all of the categories because many of the required components (e.g., amphiphilic block copolymers) can be designed and controlled through organic synthesis methods. The polymers themselves include those that are synthetic, pseudo-synthetic, and those arises from natural sources[21,33].

The hydrophobic segments of surfactant micelles used for drug delivery purposes vary widely in composition, unlike the hydrophilic segments. Broadly, the most commonly studied compounds making up the core-forming blocks of surfactant micelles are poly (propylene oxide), the poly (L-amino acid) s, poly(ether)s, and poly(ester)s [21,23].

These classes of block copolymers are reviewed with multiple examples of current research in which formulation techniques with polymeric micelles have been applied to some of the most challenging molecules in the pharmaceutical industry. The polymeric micelles used for drug delivery in these examples have shown the ability to attenuate toxicities, enhance delivery to desired biological sites and improve the therapeutic efficacy of active pharmaceutical ingredients [34].

Depending on the physicochemical properties of the block copolymer, two main classes of drug-loading procedures can be applied (Figure 3). The first class, direct dissolution, involves dissolving the block copolymer along with the drug in an aqueous solvent [35]. This procedure is mostly employed for moderately hydrophobic copolymers such as poloxamers and may require heating of the aqueous solution to bring about micellization via the dehydration of the core-forming segments. The direct dissolution method is also used to prepare PICM. Here, the copolymer and drug are dissolved separately in an injectable aqueous vehicle. Micelle formation is induced by combining the two solutions according to appropriate charge ratios of drug-polymer [36].

The second category of drug-loading procedures applies to amphiphilic copolymers which are not readily soluble in water and for which an organic solvent common to both the copolymer and the drug (such as dimethylsulfoxide, N, N-dimethylformamide, acetonitrile, THF, acetone or dimethylacetamide) is needed. The mechanism by which micelle formation is induced depends on the solvent-removal procedure. For water-miscible organic solvents, the copolymer mixture can be dialyzed against water, whereby slow removal of the organic phase triggers micellization [37].

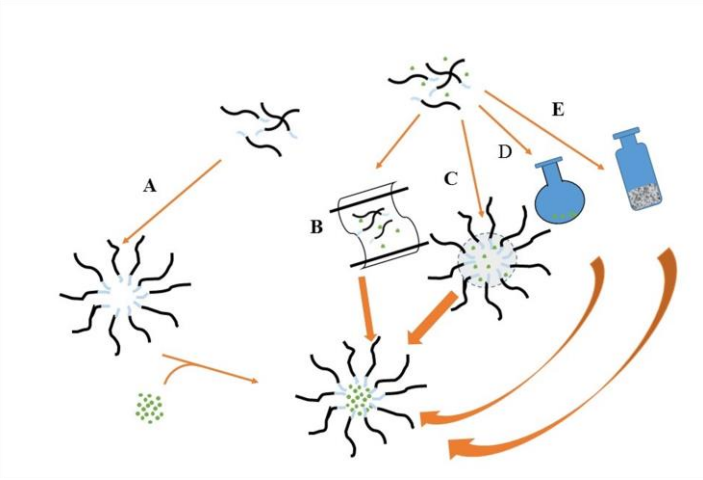


Figure 3. Common drug-loading procedures: (A) simple equilibrium, (B) dialysis, (C) O/W emulsion, (D) solution casting, and (E) freeze-drying.

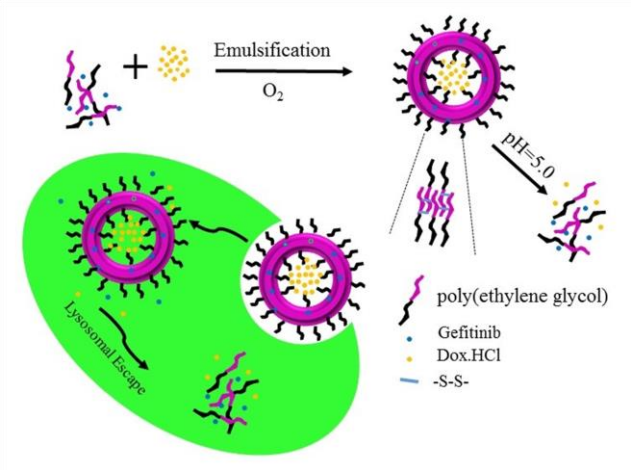


Figure 4. Illustration of nanovesicle preparation as well as the dual sensitive release of DOX and GEF inside the tumor cell.

Polyethylene glycol

micellar drug delivery and is also used for a wide variety of other biomedical and pharmaceutical applications (Figure 4) [32]. The common use of PEG stems from the fact that it is neutral, well-water-soluble, non-toxic, and FDA-approved for internal use [33]. PEG at a molecular weight of 4000 g/mol has been administered intravenously up to 16 mg/kg in multiple species of animals, with no major safety concerns noted. The PEG corona of micelles is a dense brush of highly hydrated chains that move rapidly and sweep out a large exclusion volume [34]. This barrier that the PEG chains form around the micelle core and its cargo serves to minimize interactions with proteins, enzymes and cells. Consequently, the encapsulated drugs avoid clearance by the reticuloendothelial system (RES) and mononuclear phagocyte system [35]. It has been shown that PEG chain length of micelles correlates inversely with protein adsorption and RES uptake. Micelles' shell may also help to protect its cargo from metabolic enzymes that would otherwise inactivate the drug. These properties make PEG ideal as a part of delivery systems aimed at increasing active drug circulation times and decreasing interaction with metabolic enzymes and phagocytic cells [36].

However, studies show that the mono micellar systems of PEG have multiple weak points for drug loading such as relatively low drug loading, larger particle size and low stability [37]. Through the mixing of different polymers and generation of mixed micellar systems, this issue can be addressed. An example in this regard is Vakil *et al.*'s study that showed mixed micelles of poly (ethylene glycol)-b-poly(ε-caprolactone) (PEG5000-b-PCLx) and 1,2-distearoyl-sn-glycero-3-phosphor Ethanolamine-N-methoxy poly (ethylene glycol) not only incorporate considerably higher levels of drug (amphotericin B) than the PEG5000-b-PCLx micelles but also produce small-sized and thermodynamically stable micellar structures [38].

Pluronics

The poloxamers are undoubtedly the most widely studied and characterized series of block copolymers available and continue to be produced today under the widely known name of Pluronics by BASF Corporation. The general chemical structure of the poloxamers is shown in Figure 1. The poloxamers differ from most other surfactants in that they are ABA triblock copolymer surfactants. In this scheme, the A stands for the hydrophilic PEG while the B stands for the relatively hydrophobic poly (propylene oxide) [39, 40]. Only one carbon marks the difference between the core-forming block and the coronaforming blocks, and the two are actually miscible when present as their respective ethylene glycol and propylene glycol monomers. There are over 20 poloxamers available for study in a variety of molecular weights, relative block lengths, and hydrophilic-lipophilic balances (HLB). The poloxamers have been studied and are used for a very broad range of applications, including biomedical

and pharmaceutical, agricultural, paper and coatings, photography, personal care, and detergents [41, 42]. The amount of work performed on the poloxamers is tremendous but has been comprehensively reviewed. The poloxamer referred to as Pluronic F68 is approved for intravenous use, though only as an additive up to 0.4% w/w. Many other poloxamers are FDA approved for ingestion and topical uses. A relatively well-characterized and positive safety profile is one of the strong advantages of the poloxamers, where the more hydrophilic ones especially have intravenous LD50s > 5 g/kg. Another distinct advantage of the poloxamers is that most are well soluble in aqueous systems and form micelles spontaneously upon direct addition to water, allowing for simple preparation. However, these surfactants do not biodegrade upon administration, typical of a poly(ether), where elimination must occur through renal clearance of the unimers [22].

Poly (D, L-lactic-co-glycolic acid)

Polylactide (PLA) and Poly (lactic-co-glycolic acid) (PLGA) are biodegradable, aliphatic polyesters that are prepared from the condensation of biological monomers such as lactic acid (i.e., PLA) or lactic acid and glycolic acid (i.e., PLGA). They possess favorable properties such as good degradability in the environment and biocompatibility so that they can undergo hydrolysis in the body and produce biodegradable metabolite monomers, glycolic acid, and lactic acid. Hence, these polymers have been approved by Food and Drug Administration (FDA) for application in the biomedical (e.g., tissue engineering, medical devices) and pharmaceutical field (e.g., drug delivery carriers). Drug encapsulation in PLGA NPs is one of the excellent approaches for improving bioavailability and enhancing the cancer treatment efficacy of EGFR-TKIs [38].

poly(ε-caprolactone)

Polymeric NPs composed of poly(ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone) (PCEC) have also been used as biocompatible nanocarriers for effective delivery of hydrophobic EGFR TKIs. In the study by Ni et al [39], PCEC nanoparticles loaded with gefitinib (PCEC-GEF) with an average size of 24 nm, zeta potential of -18 mV, drug loading of 9%, and entrapment efficiency of 92% were developed using a solid dispersion method. These PCEC-GEF NPs could release GEF slowly, and within 5 days, 80% of the charge molecules were released in a controlled and sustained manner. This may be the reason why PCEC-GEF has higher IC_{50} against lung cancer cells (A549) than GEF solution in vitro after 24 and 48 incubations. In vivo experimental results showed that intravenous injection of PCEC-GEF NPs resulted in significantly longer tumor growth delay, lower GEF-related side effects, and prolonged median survival time of about 23 days compared to the GEF-treated group. Subsequent flow cytometry and evaluation of Ki-67 and CD31 expression were performed to further investigate the mechanism of the anticancer effect of PCEC-GEF NPs in vivo. The results suggest that these GEF-NPs can effectively increase cellular apoptosis, reduce proliferation, and inhibit angiogenesis of a solid tumor in a xenograft mouse model induced by lung cancer cells [18].

Poly (oligo (ethylene glycol)

Poly (oligo (ethylene glycol) methyl ether methacrylate) (POEGMA) is a highly versatile polymer, as manipulation of its comb-type structure dimensions has a predictable effect on the conformation of its main and side chains, which can together or independently, be either extended or collapsed. This control, and the distinctive physical–chemical characteristics of POEGMA, are the common driving forces behind its tunable thermosensitivity properties, supramolecular assembly characteristics, and efficient protein repellency. due to these remarkable properties, POEGMA is increasingly being used within functional coatings, biosensors, drug delivery systems, biomaterials, etc. From a physical–chemical standpoint, this comb-shaped polymer is particular because its backbone is hydrophobic and its side-chains are amphiphilic. Modifying side-chain length alters hydrophilicity, which in turn can influence hydration state and conformation at a given temperature [40].

Apart from above-mentioned polymers, other shell-forming materials have been also studied for polymeric micelles, such as poly(N-isopropylacrylamide) and poly (methacrylic acid), which may be desirable for obtaining micelles with shells sensitive to pH or temperature [38]. In Table 1, we summarized different block copolymer surfactants have been used so far in micelle formation for TKIs' delivery.

Table 1. Examples of Drugs Encapsulated and Solubilized by Block Copolymer Surfactants

Surfactants	Mechanism of incorporation	Core-Forming Block or Surfactant	Solubilized Compound	Ref.
Poly (ester)s	Chemical	Poly (D, L-lactic acid-co-glycolic acid)	Dasatinib	[41]
	Physical	poly (D, L-lactide)	Osimertinib	[42]
		poly (D, L-lactide)	Apatinib	[43]
		poly (ε-caprolactone)	Erlotinib	[44]
			Gefitinib	[39]
poly(L-amino acid)s	Chemical	poly(L-aspartate)	Sunitinib	[45]
	Physical	poly(L-lysin)	Apatinib	[46]
Poly(ether)	Chemical	poly(ethylene glycol)-b-poly(aspartic acid)	Dasatinib	[47]
	Physical		Gefitinib	[48]
			Erlotinib	[44]
poloxamers	physical	Pluronic F-127	Ibrutinib	[49]

3. TKIs' delivery via polymeric micelles

3.1 Lung cancer

The prevalence of lung cancer has significantly increased in the last 20 years, particularly among women [50]. Frequent exposure to tobacco smoke, exogenous carcinogens such as diesel exhaust, radon, household fumes, and radiation in domestic and occupational environments are considered as lung cancer risk factors, increasing the incidence and prevalence rate [51]. The treatment regimen for lung cancer is determined by the stage of the disease and the physical condition of the patients. [52]. However, traditional treatment approaches usually cause undesirable short- and long-term side effects [53]. The recent development of nanotechnology made many breakthroughs in various aspects of science and industries, leading to the advent of further efficient drugs compared to traditional ones. In this respect, the application of nanocarriers for delivering localized therapeutic agents to target tumor tissues considerably enhances chemotherapy efficiency and minimizes adverse side effects[54,55]. In clinical practice, the treatment that specifically targets the oncogene-driving mutations can inhibit tumor progression and offer a promising prognosis. Epidermal growth factor receptors (EGFRs) activating mutations in lung cancer are a positive predictor for EGFR TKIs treatment [56]. First-generation (gefitinib, erlotinib) or second-generation (afatinib) TKIs are the recommended first-line treatments for patients with lung cancer who have EGFR-exon 19 deletions or an exon 21 Leu858Arg mutation (which together account for more than 80% of known activating EGFR mutations) (Figure 5). EGFR TKIs improve overall survival, time to progression, and response rates [57]. A wide variety of nano-formulations have been developed to assist lung cancer patients. One of the proper inhibitors of EGFR to enhance antitumor response for lung cancer therapy is gefitinib (GEF), which has shown antitumor activity and relief of symptoms in patients who have exhausted all standard chemotherapy [58]. It is widely assumed that modifying GEF's strong hydrophobicity and low bioavailability would not only improve its antitumor effects but also reduce its side effects [59]. For instance, Diao *et al.* [60] used the optimized PEG_{5k}-Fmoc-NLG919 micelles (with an even-size spherical morphology, 191.8 nm) as the carrier for loading GEF to treat lung cancer. Strikingly, the IC_{50} analysis revealed that GEF/PEG_{5k}-Fmoc-NLG919 was more effective than free GEF at killing lung tumor cells; besides, EGFR activity was found to be lower in GEF/PEG_{5k}-Fmoc-NLG919-treated cells than in free GEF-treated cells. This could be partially explained through the use of the cumulative GEF-releasing assay, which showed that GEF was slowly and gradually released from the micelles, which provides constant

proliferation stress for lung tumor cells. Furthermore, the long-term cumulative releasing assays showed that after 24 hours, approximately 90% of the GEF could be released from the PEG_{5k}-Fmoc-NLG919, indicating that delivering GEF with this nanocarrier did not impair the final dose when compared to administering GEF directly. In a nutshell, GEF/PEG_{5k}-Fmoc-NLG919 exhibited better antitumor and delivery efficiency, increased drug-loading capacity and formulation stability than the carrier or GEF alone. Likewise, Ling Ni *et al.* [61] indicated that using GEF-loaded PCEC nanoparticles (GEF-NPs) with smooth surface, spherical shape and an average diameter of less than 24 nm resulted in lower side effects, tumor growth inhibition, and longer survival time in *in vivo* animal models. The viability of A549 cells treated with GEF-NPs was higher than that of free GEF. This outcome could be attributed to the nanoparticles' slow GEF release rate; roughly 80% of GEF was slowly released from GEF-NPs in a sustained and controlled manner over five days, with no burst impact. After 24- and 48-h incubation, the IC_{50} values for free GEF were 29.03 and 5.6 g/mL, respectively, while the IC_{50} values for GEF-NPs were 37.8 and 8.1 g/mL. The results revealed that the GEF- nanoparticle formulation is much less cytotoxic in the cell culture system than free GEF, and hence represented an alternative therapeutic strategy for NSCLC treatment. Meanwhile, some studies have found that co-delivery of therapeutics via single NPs outperforms oral administration of the free drug combination in terms of tumor growth suppression. For example, Diao *et al.* [62] reported that GEF and Paclitaxel (PTX) loaded in PEG_{5k}-fmoc-NLG2 demonstrated significantly enhanced tumor cell-killing impact than the GEF alone on both 3LL and A549 cell lines. In general, when compared to free GEF alone, the carrier-loaded GEF/PTX was more efficient in inhibiting EGFR phosphorylation. Furthermore, such a strategy can be used in novel therapy that combines chemotherapy drugs with immune-modulating agents like PD-1 and CTLA4. Another study found that using a PEG-based nanocarrier (PEG-polylactic acid (PLA)) for co-delivery of GEF and Cyclosporin A (CsA) resulted in significantly improved drug stability, solubility, and augmented GEF potency in both GEF-sensitive and GEF-resistant cell lines. Characterization of the PEGylated nanoplatform revealed that the NPs had sub-50-nm diameters, allowing them to penetrate solid tumors deeply via the EPR effect. CsA also improves the cytotoxicity of GEF when co-delivered with NPs by inducing apoptosis. Moreover, in vivo results showed that CsA formulated in NPs sensitized GEF-resistant cells and GEF-resistant tumors to GEF treatment by inactivating the STAT3/Bcl-2 signaling pathway. This nanomedicine strategy not only offers an alternative route for the drugs of choice, but it also successfully reverses multidrug resistance (MDR), facilitating the development of effective lung cancer therapeutic modalities [63].

Additionally, chitosan-derived NPs can be used to overcome EGFR-T790M resistance by inhibiting downstream anti-apoptotic signal transduction while also persuading mitochondrial dysfunction and inhibiting miRNA expression. Huang *et al.* [64] synthesized a chitosan-derived nanocarrier DCAFP, to convey GEF and miR21 inhibitor (anti-miR21) to form Diglycolamide (DGA) nanoparticles. DGA

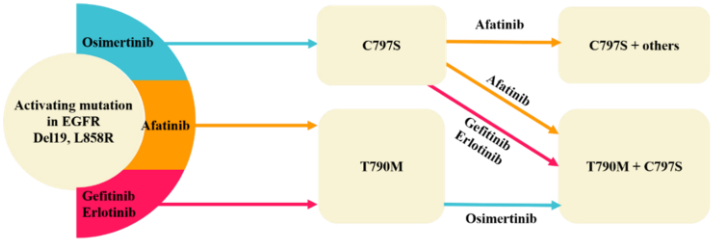


Figure 5. Typical mechanisms of acquired resistance in EGFR-mutant NSCLC patients following treatment with different EGFR-TKIs.

nanoparticles are highly sensitive to EGFR-T790M mutated NSCLC cells, with significant inhibition of tumor cell growth owing to superior antitumor therapeutic accumulation and synergistic blocking of downstream signal transduction via mitochondrial dysfunction and miRNA regulation. The in vivo study shows that EGFRT790M mutated lung cancer mouse models have superior safety and antitumor efficacy. These findings highlight the potential of DGA nanoparticles in improving GEF sensitivity to EGFRT790M NSCLC.

Osimertinib (OSI or AZD9291) is another third-generation EGFR-TKI that has been approved by FDA and EMA. It not only has a substantial effect on classical EGFR sensitizing mutations, but it can also inhibit EGFR T790M mutation. In a study by Hu rt al. [42] chitooligosaccharides (COS)-modified poly (lactic-co-glycolic acid) (PLGA) nanoparticles (AZD-PLGA-COS NPs) were developed, which can effectively enhance the impact of OSI and obtain better clinical application. They also promoted apoptosis by regulating endogenous proteins such as p-EGFR, PARP, Bak, caspase-9, Bax, and Bcl-2. Moreover, the NP's surface positive charge promotes cellular uptake by maximizing affinity with negatively charged cell membranes. COS, on the other hand, inhibited the expression of PD-L1 in H1975 cells, indicating that it could be used as an immunosuppressive agent. As a result, AZD-PLGA-COS NPs represent a promising method for combined targeted therapy and immunotherapy. Since patients treated with OSI eventually develop acquired resistance that prevents its long-term benefit for patients, combination therapy was a useful strategy for combating OSI resistance. Chen *et al.* [65] developed PEG-S-SEL conjugate for co-delivery of OSI and selumetinib (SEL) to treat OSI-resistant NSCLC effectively. Because drug molecules are conjugated with polymers via covalent bonds, it could attain good drug loading stability, high drug loading efficiency (100%), and minimize drug leakage or burst drug release. Wang *et al.* [66] used PEG5k-Cys4-L8-CA8 as a representative telodenrimer and created a biocompatible and versatile PTX- and OSI-loaded disulfide cross-linking micelles (DCMs) for NSCLC treatment. Drug-loaded DCMs were comparatively small (around 20 nm, allowing for excellent tumor penetration), had superb serum stability (a cross-linking strategy to prevent premature drug release), and had glutathione-responsive drug release. The drug loading efficiencies for PTX/OSI/DCMs were 82.5 and 83.7%, and showed strong synergistic impacts in both in vivo and cell line without additional toxicity. Therefore, this study has a high clinical translation potential, particularly for patients who developed T790M EGFR mutations following first-line EGFR-TKI treatment.

Research have found that temperature-responsive micelles have a high loading efficiency and a long-term controlled release rate, making them an efficient drug delivery system. Xu *et al.* [67] utilized BCM/HA multilayers with high stability, controlled structure, and good drug loading capacity. The films (with a thickness of 188 ± 28 nm) could efficiently load OSI in the hydrophobic cores of the BCMs. On-demand drug release profiles from the BCM/HA multilayers controlled by environmental temperature were also observed. The LBL films may be employed for programmable release of therapeutic compounds in medical devices, in the future, Gu *et al.* [68] also showed that combining a novel pH-sensitive shell–core nanoparticles CP@NP-cRGD with OSI showed significantly decreased the growth of NSCLC AZD9291 resistance-tumor xenografts and exhibited excellent targeting properties, sustained releasing potential, high encapsulation rate, good stability, and low toxicity. As a result, CP@NP-cRGD may be an effective and relatively safe alternative agent for overcoming OSI resistance.

3.2 Breast cancer

Breast cancer is one of the highest incidences of tumors in women and its morbidity and mortality are on the rise and tend to be younger [69,70]. The majority of the deaths from breast cancer are due to its potential of metastasis to distant organs.[71] There are several oncogenic receptor whose activation are involved in the modulation of breast cancer and its progression to metastasis, such as estrogen receptors (ERs), progesterone receptors (PRs), and human epidermal growth factor receptor 2 (HER-2) [72,73]. In this way, the epidermal growth factor receptors EGFR and HER2 are frequently over-expressed in several human cancers of epithelial origin and play essential roles in the development and progression of cancer. HER2 is over-expressed in several tumors, including breast and colorectal cancers. In normal cells, the HER proteins regulate cell growth, survival,

adhesion, migration and differentiation through a network of signaling pathways. The over-expression of this receptor in breast cancer is often associated with increased disease recurrence and a worse prognosis. Moreover, in patients where hormonal therapy is not effective, HER2 becomes a critical target for treatment. The epidermal growth factor receptors EGFR and HER2 are the main targets for tyrosine kinase inhibitors (TKIs). There is a variety of tyrosine-kinase inhibitors for treatment of breast cancer such as Dasatinib, Sunitinib, anlotinib, vandatanib, ponatinib, and Afatinib.

Dasatinib is an approved second-generation inhibitor of multiple tyrosine kinases, and literature data strongly support its use in the management of triple negative breast cancer (TNBC). However, dasatinib binds to plasma proteins and undergoes extensive metabolism through oxidation and conjugation. Bahman *et al.* synthesized and characterized a styrene-co-maleic acid (SMA) nanomicellar system encapsulating the TKI dasatinib. As a result of drug protection via this nanocarrier from the enzymatic degradation, dasatinib was about seven-fold more effective in controlling 4T1 implanted tumors in animal models of 4T1 TNBC [74]. Apart from encapsulating drugs into polymeric micelles, some studies conjugated this as prodrug into the structure of polymers to synthetized prodrug micelles. This technology is widely used not only to improve drug delivery efficiency but also reduce toxicity and side effects, and is one of the research focuses in the field of cancer treatment. In fact, prodrug micelle combines the advantages of both prodrugs (e.g., structural stability and technical simplicity) and micelles (e.g., efficient drug loading and high cellular uptake) for drug formulation. They can be also applied in purposes of combination therapy through being loaded with other therapeutic agents. H. Wang *et al.* have presented a compound micellar system composed of hyaluronic acid (HA)-dasatinib polymer, bonded by a pH-sensitive ester bond, and D-A-tocopherol polydiethylene glycol isosuccinate (TPGS), which provides great structural integrity to NPs for drug delivery process. Rosiglitazone was the drug encapsulated with a combination of the mentioned polymers. This nanoformulation showed a strong inhibitory effect on the proliferation and metastasis of breast cancer cells and reduced toxicity and side effects [47]. Similarly, J. Sun *et al.* developed a redox-sensitive, polymeric prodrug carrier containing poly(oligo(ethylene glycol) methacrylate) (POEG) hydrophilic blocks and dasatinib for codelivery of doxorubicin. The in vivo study indicated that the inhibitory effect of doxorubicin-loaded POEG-dasatinib, with redox-sensitive properties, on tumor growth was more significant than the codelivery of these two drugs through inert micellar carriers [75]. Another prodrug micelle that was evaluated in safety and efficacy contains crizotinib, a multi-target TKI targeting ALK gene recombination, MET gene amplification and ROS gene, and PEG polymers. Crizotinib has limited efficacy in the treatment of breast cancer due to its strong hepatotoxicity and inability to target tumor cells. However, the synthetized prodrug micelles enhanced the cumulation of crizotinib in the tumor [76].

Vandatanib (ZD6474), a dual TKI of EGFR and VEGFR, is associated with cell growth inhibition of NSCLC, head and neck, thyroid and breast cancers. In an attempt to enhance therapeutic index of this drug in breast cancer treatment using delivery vehicles, S. Sarkar *et al.* [84] used micellar networks to reduce and stabilize gold nanoparticles. AuNPs were synthesized by using non-toxic and non-ionic triblock copolymer PEG-PPG-PEG, and due to their low cytotoxicity and immunogenicity were an efficient nanocarrier for tissue- and site-specific drug delivery.

3.5 Colorectal cancer

Colorectal cancer (CRC) is the third most prevalent cancer, with the fourth highest mortality rate over all age groups globally.[77] Almost 694,000 people die from the disease annually. The incidence of CRC in young adults has been rising during recent years.[78] Along with the improvements in science, although numerous new diagnosis tools and specific drugs for therapy of CRC emerge continually, the 5-year survival rate of patients with late-stage CRC still remains only 12%. Overexpression of EGFR is common in many tumors. Specifically, in CRC, EGFR is estimated to be overexpressed in 60%-80% of tumors and is associated with a poor prognosis. Therefore, EGFR has been targeted as a locus for treatment with small molecule inhibitors and monoclonal antibodies, the latter of which has a role in the treatment of metastatic disease. Moreover, studies demonstrated that HER2 is another potential

therapeutic target for CRC, which can be detected in serum. Guan *et al.* investigated the protein levels/expressions of HER2 in sera and tumors from CRC patients and the therapeutic effect of afatinib on HER2-overexpressed CRC in vitro and in vivo. They demonstrated that HER2 is a CRC therapeutic target, and the measurement of serum HER2 is a potential tool for detecting HER2 expression in CRC. Afatinib, an irreversible EGFR/HER2 inhibitor, can specifically inhibit HER2-overexpressed CRC cell growth in vitro and in vivo. Afatinib-encapsulated micelles displayed higher cytotoxic activity in HCT-15 cells and were more effective for tumor growth suppression in HCT-15-induced tumor xenografts than afatinib performance alone. Regarding afatinib/micelles as an anti-tumor drug in HER2-overexpressed CRC therapy, other HER2-overexpressed cancer, such as gastric and ovarian tumors, could be a candidate in the future [79].

In another study done by Shih et al. the antitumor efficacy of sunitinib was evaluated against CRC. Sunitinib is an oral RTKI that is commonly used for the treatment of gastrointestinal stromal tumors (GIST), advanced renal cell cancer, and pancreatic cancer. Shih *et al*., however, applied Sunitinib as a therapeutic in CRC since it targets multiple receptors involved in tumor angiogenesis and tumor cell proliferation, which include platelet-derived growth factor receptors (PDGF-α and PDGF-β receptors) and vascular endothelial growth factor receptors (VEGF-1, VEGF-2, and VEGF-3 receptors). The anti-angiogenic effect of Sunitinib micelles could alleviate the abnormalities caused by angiogenesis and normalize vascularization. They also encapsulated Sunitinib along with SN-38 in polymeric micelles composed of Methoxy poly-(ethylene glycol)-poly(ε-caprolactone) (mPEG-PCL). In vitro and in vivo studies, the nanoscale SN-38/Sunitinib micelles could efficiently deliver the drugs into cancer cells, thereby increasing their cytotoxicity, and significantly improving their tumor accumulation and antitumor efficacy [80].

3.5 Leukemia

Leukemia is a cancer of white blood cells and is associated with bone marrow, a spongy, fatty tissue filling the medullary cavity of the bone. The microenvironment of bone marrow plays vital part in the development and progression of leukemia as well as the metastasis in other types of cancer. In treating bone marrow malignancies, the availability of systemically administered drugs in the bone marrow mainly faces problems. Sometimes they are metabolized even before they can affect their targets in the bone marrow tissue. In addition, the injected drugs are very likely to accumulate in other well-perfused organs, such as the liver and kidney, or be cleared by the body's excretory system before attaining the bone marrow. To overcome these limitations, drugs must be administered in high and/or frequent doses, resulting in inevitable systemic side effects. Hence, a rational drug design is required to secure that anticancer drugs selectively reach the tumor site inside the bone marrow [81].

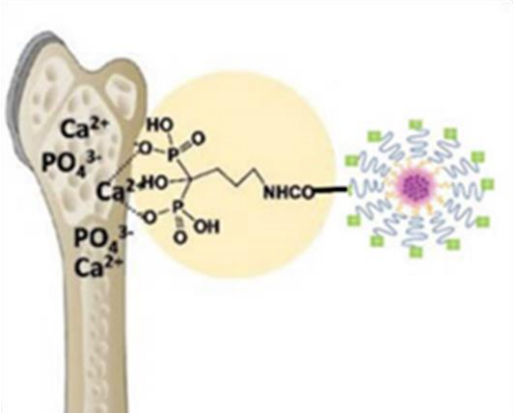


Figure 6. Active bone-targeted polymeric micelles for the treatment of therapy-resistant CML. The phosphate's oxygen atoms of bisphosphonates in alendronate molecular structure chelate the calcium ions in hydroxyapatite.

So, the accumulation of therapeutic agents inside the bone marrow can have a significant role in the successful treatment of leukemia. On the other hand, TKIs have limited accessibility into bone marrow, leading to a higher dose, severe cell toxicity, and nonspecific multi-kinase targeting. Several studies were conducted to evaluate targeted leukemia therapy via polymeric micelles loaded with different TKIs. One of the suitable targeting moieties used to modify the surface of micelles for leukemia treatment is alendronate. These moieties are absorbed into bone tissue through the high affinity for hydroxyapatite, a mineral form of calcium apatite found in bone tissue. The phosphate's oxygen atoms of bisphosphonates in alendronate molecular structure chelate the calcium ions in hydroxyapatite (Figure) [82].

In a study by Mu *et al*., alendronate was conjugated with PEG-PLA using a co-solvent evaporation method for the targeted delivery of TG101209, an inhibitor of the JAK2/STAT5 signaling pathway. Drawing a comparison between targeted and untargeted TG101209 formulation, they showed that 40 mg/kg of untargeted formulation has less accumulation rate in the bone marrow of leukemia C3H mice than of 20 and 40 mg/kg polymeric micellar formulation. However, the plasma concentration changes in mice after intravenous administration of both targeted and untargeted formulation is similar [41]. In a similar study, Mu *et al.* also encapsulated ponatinib and SAR302503 into alendronate-conjugated PEG3000-PLA2000. Ponatinib is the third generation of TKI that aims to treat Philadelphia chromosome–positive, acute lymphoblastic leukemia and chronic myeloid leukemia (CML), especially with T315I mutation. SAR302503 is a selective JAK2 inhibitor, used in combination with TKIs for CML therapy. The hydrophobic drugs were co-encapsulated inside the hydrophobic core of PEG-PLA micelles by the previous method. Combined TKIs alendronate-modified micellar formulation greatly enhanced drug availability inside the bone marrow and the efficacy of leukemia treatment. In vivo studies indicated that In terms of short-term high-dose exposure, oral administration is unfavorable in comparison to intravenous administration to achieve the same level of bioavailability [83]. The Bone-targeted injectable formulations in these two studies, containing polymeric micelles loaded with TKIs, showed a significant drug enrichment in the bone marrow, leading to dramatically decreased overall treatment dosage and drug exposure to normal tissues, and remarkable efficacy in leukemia treatment with no detectable cytotoxicity.

Another innovative strategy to target bone marrow for delivery of imatinib was used by Shah *et al*., in which iron oxide nanoparticles capped with EDTA were encapsulated with Pluronic-F127, an amphiphilic triblock copolymer, to fabricate micelles with the superparamagnetic feature (Figure 7). The rationale for selecting Fe_3O_4 as a vehicle to load imatinib and targeting bone marrow is associated with the process of erythropoiesis in the bone marrow. Since Fe^{+4} is the main component of hemoglobin, a large amount of Fe^{+4} is consumed during this process. Through the complex forming with transferrin, a blood-plasma glycoprotein, Iron can reach and enter the transferrin receptors located on the surface of bone marrow cells. So, Fe_3O_4 NPs can naturally accumulate in the bone marrow tissue and participates in erythropoiesis as a precursor of hemoglobin. Using this subject, Shah *et al*. apply their synthesized nanoformulation as both controlled drug delivery (therapeutic) and MRI contrast agents (diagnostics). The developed micellar

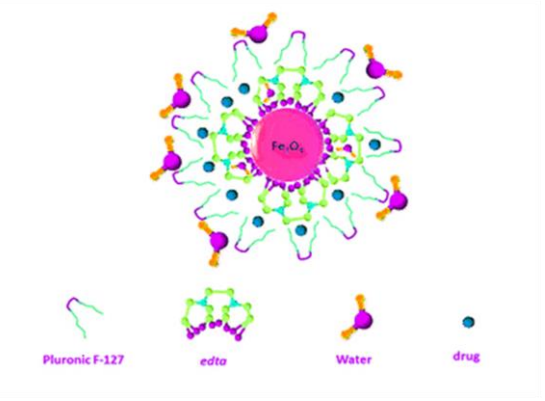


Figure 7. synthesized pluronic encapsulated and edta capped Fe_3O_4 magnetic micelle can be loaded with hydrophobic anti-cancer drug like imatinib in their hydrophobic shells [84].

nanoformulation showed a higher capacity to be internalized to human bone marrow K562 cell line than the pure Imatinib. The imatinib-loaded Fe_3O_4/edta/P NPs showed the IC_{50} value of 106 cells the 0.02 mg/mL, while pure Imatinib has 0.5 µg/µL IC_{50} of the same number of cells. It also has a great sustained drug release profile so that 30% of imatinib burst in the first 5 hours, and up to 60% was released at the end of 196 h [84].

3.5 Other types of cancer

In addition to the mentioned cancers, there are studies on TKI delivery using micellar systems to evaluate their efficacy on other types of cancers. These studies employ different strategies to enhance the cytotoxicity and anticancer effect of chemo drugs and improve drug loading and bioavailability.

For example, glioblastoma multiforme (GBM) is a fast and aggressive brain tumor defying the common cancer treatments of radiotherapy, chemotherapy and surgery. Hence, GBM is associated with a high fatality rate with a median survival of 14.6 months. A combination of Crizotinib and Dasatinib was found to exert the most potent effect on different GBM cell lines. However, to improve targeted therapy at the site of the tumor and avoid systemic toxicity, Greish *et al*. [85] exploited the enhanced permeability and retention effect by designing micellar formulations of these two TKIs. Crizotinib and Dasatinib were successfully encapsulated in poly(styrene-co-maleic acid) (SMA) micelles (SMA-Cr average size was 121 ± 59.9 and SMA-D 89.14 ± 55.3 nm). Micellar TKIs successfully abrogated multiple signaling pathways to overcome apoptosis resistance and pathological characteristics such as angiogenesis and invasion comparable to free TKIs. The combination maintained significant in vitro efficacy following encapsulation into a micellar system regarding the anti-proliferative effect, prevention of invasion, migration, angiogenesis, and vascular mimicry. The micellar encapsulation has improved the anticancer activity in vivo compared to free drugs, possibly due to increasing the accumulation of the TKIs at the tumor site and thereby increasing the efficacy of the treatments. These results are promising and warrant further investigation in in vivo models in combination with standard GBM treatment strategies. In another attempt for investigating combination therapy, Zong *et al*. have developed a dual-functional nanoformulation in which chemotherapy and photodynamic therapy (PDT) have been combined for a more effective treatment of liver cancer. They encapsulated lenvatinib along with halogeanted Boron-dipyrromethene (BODIPY) in Pluronic F127 polymeric micelles by π−π stacking effect between lenvatinib and halogenated BODIPY through the one-step nanoprecipitation method. BODIPY is a fluorescent dye widely used in PDT. PTD is a non-invasive treatment strategy in which a photosensitizer is administrated to cancer cells, and using a specific wavelength of light, they are stimulated to produce cytotoxic reactive oxygen species (ROS) and consequently induce cell apoptosis [86]. The fabricated nanodrug has a pH-responsive property that takes advantage of the fact that the cancer cells have a more acidic environment (pH 6.5−6.8) compared to blood and normal tissues (pH 7.0−7.4). Plus, the pH value in cellular endo/lysosomes is even lower (pH 4.5−5.0). So, in the response to the tumor microenvironment, the core−shell structure of the micelles is hydrolyzed, resulting in the release of lenvatinib (with a rate of 88.5 and 82.4%) and halogenated BODIPY, as well as reactive oxygen species (ROS) production. In vitro analysis such as the expression of apoptotic proteins and flow cytometry analysis showed that this multifunctional nanoformulation could effectively accumulate in hepatocellular carcinoma (HCC) cells and suppress the proliferation of tumor cells through ROS generation [87]. Synergistic combination of TKIs with a cytotoxic drug named hydroxycamptothecin (SN38) has been also explored in HCC treatment by Han *et al.* SN38 is a potent inhibitor of DNA topoisomerase I (TOP1). Molecules like SN38 with planar intrinsic structure and moderate polarity usually pose a challenge in their encapsulation inside the polymeric nanoparticles. Hence, in this study a PLA polymeric SN38 (pSN38) prodrug was synthetized to address that issue. PSN38 and apatinib then coassembled with a clinically approved amphiphilic copolymer mPEG5k-PLA8k and formed a nanodrug that showed ultrastable characteristics and highly sustained drug release (only <10% of the total drug after 5 days). These

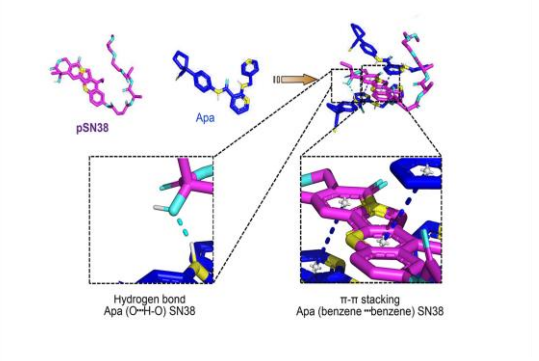


Figure 8. Strong π-π stacking interaction with PLA promioties of PSN38 in the core of micellar nanoparticles[43].

uniquefeatures are a result of π-rich hydrophobic cores within the nanoparticles. The aromatic structures of apatinib form strong π-π stacking interaction with PLA promioties of PSN38 in the NP's core (Figure 8). This simple nanosystem also demonstrated considerable antitumor activity so that a single injection of it containing a dose of 40 mg/kg apatinib and 10 mg/kg of SN38 equivalent concentrations to the preclinical metastasis model, could not only inhibit local primary tumor growth but also suppress metastasis to lymph nodes [43].

In addition to intravenous administration of nanosystems containing TKIs, the subcutaneous delivery of TKIs has been also explored by Soundararajan. They used a self-assembling polymer known as Molecular Envelope Technology (MET) to encapsulate a multi-targeted anticancer drug that simultaneously inhibits EGFR, HER2 and histone deacetylase (HDAC). This inhibitor, CUDC-101, is in the phase I clinical trial to treat head and neck squamous carcinoma patients (Figure 9). The required doses of CUDC-101 for these patients is approximately 400−500 mg of drug in a single injection, while the maximum dose administrated intravenously is between 225 and 275 mg. To achieve a high drug loading required for clinical application, MET NPs were chosen and coated by hyaluronidase (HYD)to facilitate the absorption of the drug through the subcutaneous route in high doses. HYD is an agent that is widely used for subcutaneous administration and is able to administer a volume higher than the normal 2 mL of drugs due to the degradation of the connective tissue by enzymatic activity that cleaves biopolymer components of extracellular matrix. Among three tested doses of CUDC-101, including 60, 90, and 120 mg kg^{-1}, the more efficient nanoformulation with a dose equivalent to 90 mg kg^{-1} CUDC-101 displayed a significant increase of median survival in murine A431 xenograft models from 15 days for control models treated with HYD alone to 43 days [88].

Most of the reported research has been on solid tumors in adults. However, cancer is also a leading cause of death in children over one year of age in Europe and the US. Most pediatric tumors follow different patterns from those common in adult tumors due to being of embryological origin. For instance, in solid adult cancer cells, there is a shift from mitochondrial glucose oxidation to fermentation of glucose to lactate, and as these cells have to compensate for high energy consumption the need for glucose to produce more ATP molecules for their proliferation enhances. In this circumstances, cancerous cells overexpress transmembrane glucose transporters (GLUTs) to supply glucose. However, only 10% of pediatric sarcomas are heterogeneous group avid glucose tumors. Bukchin *et al.* investigated for the first time the inhibitory effect of a TKI, dasatinib, on overexpression of GLUTs in patient-derived pediatric sarcomas. In this study, dasatinib was encapsulated within glycosylated polymeric micelles, including branched poly (ethylene oxide)-bpoly(propylene oxide) (PEO-PPO) block copolymers. Selective uptake of the glycosylated nanodrugs by glucose-avid cancer cells

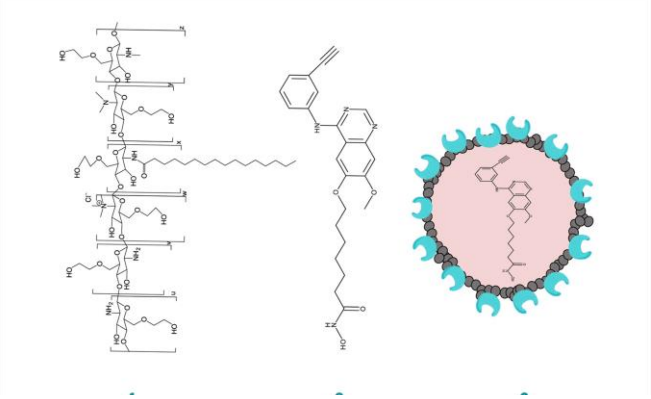


Figure 9. Chemical structures of polymer and drug: (a) N-palmitoylN-monomethyl-N,N-dimethyl-N,N,N-trimethyl-6-O glycolchitosan (molecular envelope technology, MET); (b) CUDC-101 [7-(4-(3- ethynylphenylamino)-7-methoxyquinazolin-6-yloxy)-N-hydroxyheptanamide] (NCBI, PubChem Database, CUDC-101, CID = 24756910); (c) schematic representation of CUDC-101 within a hyaluronidase coated polymer nanoparticle [88].

was shown, which was due to the permeation and retention (EPR) effect, also known as passive targeting. This resulted in a significant rise in the intratumoral drug bioavailability and the long-term median survival of mice bearing patient-derived pediatric tumors compared to untreated controls [89]. The conjugation of hydrophilic sugar residues to block copolymers stabilizes the self-assembled structure of polymeric micelles through the formation of H bonds with water molecules in the hydrophilic corona leading to a decrease in the CMC of the copolymer and micellization enhancement. Moreover, copolymer glycosylation also improves the capacity of encapsulation of different hydrophobic drugs compared to unmodified counterparts. In another study, Bukchin *et al*. also demonstrated that although glycosylation had a beneficial effect on the self-assembly, the extension of saccharide units from one to three per terminal block was detrimental for the aggregation, while it favored a more substantial binding to a soluble lectin-like receptor in vitro. Their results showed a significant increase in the aqueous solubility of imatinib encapsulated up to 100 folds and thermal stability in the Rh30 cell line [90]. Both studies done by Bukchin *et al*. showed that glycosylation of micellar NPs has a great effect on intracellular drug bioavailability and IC50 than unmodified counterparts. Although drug loading capacity can be increased due to surface-modification of polymers with sugar, this research team later illustrated that amphiphilic polysaccharides nanoparticles are much more efficient in drug loading capacity, so that 1% w/v hGM-PMMA28 (hydrolyzed copolymers of galactomannan grafted by 28% w/w poly(methyl methacrylate)) nanoparticles increased the water solubility of imatinib up to 212 times (from 3.4 to 720 μg/mL) as well as drug loading up to 11 folds compared to glycosylated PEO-PPO [91].

Unlike many TKIs, which are hydrophobic, there are some hydrophilic TKIs like imatinib mesylate, a hydrophilic chemotherapeutic agent applied in skin cancer and melanoma treatment. Designing a suitable carrier for efficient encapsulation of these types of drugs is considered a challenge due to their hydrophilic feature. One of the strategies that could be beneficial for these cases is using reverse micellar systems, i.e., micelles with inner hydrophilic and outer hydrophobic cores. In a study by Nithya *et al*., a reverse micelle was fabricated using lecithin and isopropyl myristate and used to encapsulate imatinib mesylate. To develop a formulation suitable for tropical application, they incorporated the drug-loaded reverse micelles into pluronic F 127 and converted it into organogels showing suitable physical properties and in vitro drug release of 46.02% after 8 hrs [92].

Due to the extent of research done in this field, i.e., TKIs' delivery via micellar nanosystems, we summarized them in table 2.

4. Conclusion

In this review, we aimed to provide comprehensive information on research done on the encapsulation of various TKIs into PMs for their delivery to different tumor cells, with emphasis on recent work.

One of the major problems in pharmaceutical formulations is related to delivering hydrophobic drugs, especially in a high dose. PMs are compatible and promising drug delivery vehicles for poorly water-soluble drugs like TKIs. These nanocarriers can provide a high loading capacity for such drugs in their hydrophobic cores: As the di- or tri-block copolymers self-assemble in an aqueous solution, a large volume of small drug molecules can be physically entrapped (solubilized) in the hydrophobic core. The shell part of the PMs consisting of hydrophilic polymers protects micelles and prevents the absorption of proteins and other adhesive cells. Moreover, PMs can efficiently enhance drug bioavailability via different routes of administration, including intravenous, intranasal, and subcutaneous. Studies indicate that the enrichment of TKIs in tumor tissue can lead to remarkable therapeutic efficacy and minimal toxicity by significantly decreasing drug exposure to normal tissues. Additionally, many preclinical animal studies have shown that cytotoxic chemotherapeutics rationally paired with TKIs can achieve additive or synergistic effects. Taking advantage of this matter, some studies assessed the efficiency of PMs loaded with TKIs and another cytotoxic agent. These multidrug-loaded PMs represent a new class of therapeutics that can effectively target both early- and late-stage tumors in a spatiotemporally controllable and synergistic manner with no need to increase the nanocarrier complexity.

Table 2. A summary of studies using PMs for TKIs' delivery into different tumor cells.

TKI	Nanocarrier	Cancer type	Particle size (nm)	Stability	Cytotoxicity	Drug release	Antitumor activity	Ref.
Gemcitabine	Genexol-PM	NSCLC	---	↑	Different outcomes	---	↑	[93]
Afatinib	HPGBCA	NSCLC	230	↑	↓	20% in buffer at pH 7.4	↑	[94]
Erlotinib	CE7Ns	NSCLC	234.2	↑	↓	Fast and late sustainable	↑	[95]
Erlotinib	Folate-(PNIPAAm-co-OA)-g-CS	NSCLC and pancreatic cancer	100	↑	No significant cytotoxicity impacts	Controlled and Temperature-dependent drug release ability	↑	[96]
Erlotinib	Incorporated PpIX into PEG-PCL micelles	Breast cancer	54	↑	↑	Less than 50% of encapsulated PpIX was released within 48 h	↑	[97]
Apatinib	mPEG5k−PLA 8k	Colon cancer and NSCLC	30	↑	No significant cytotoxicity impacts	Sustained and slow release	slightly enhanced antitumor activity	[43]
Apatinib + PTX	PA-ss-NP	Liver, lung, heart, and kidney cancer	90	↑	↑	Both <25%within 48 h	↑	[46]
Dasatinib	Zein-lactoferrin ANMs	Breast cancer	100	↑	↓	Initial burst release of dasatinib, which is followed by a linear sustained release pattern over 120 h	↑	[98]
Dasatinib	MMP/FR micelles	Ovarian and breast cancer	100-200	↑	↓	Sustained release without the burst release	↑	[99]
Sunitinib	dPGS-SS-PCL	Colon cancer	70	↑	↓	Sustained release of Sunitinib over 1 week.	↑	[100]
Sunitinib	STS/Epi/m micelles	Renal cell carcinoma	50	---	↑	Accelerated release of the drugs at an endosomal pH (pH 6.5–5.5)	↑	[45]
Sunitinib	PLGA-PEG-MBA	Skin cancer	73	↑	↑	Sunitinib base releases from micelles much more slowly at pH 7.4 than at pH 5.8	↑	[101]
Anlotinib	cRGD-AL-RM	Skin cancer	30	↑	↓	Good sustained release	↑	[102]
Ponatinib + JAK2 inhibitor SAR302503	Alendronate-PEG-PLA Micelles	Chronic Myeloid Leukemia	20-30	↑	↓	Release physically loaded drugs by disassembling and acting concurrently in bone marrow with minimum off-target effects	↑	[83]
nordihydroguaiaretic acid (NDGA) and a diaryl urea compound (PQ401)	PLGA	Breast cancer				An initial burst (~30% release within 3 hr) followed by slow release over several days	↑	[103]
Sorafenib + Nilotinib	SMA micelles	Prostate cancer	100	↑	↑	The release of both drugs was sustained over 96 hours with 9.7% and 10.7% sorafenib and nilotinib released from the micelles, respectively	↑	[104]
Lenvatinib	LBPNPs encapsulated by amphiphilic polymer F127	Liver cancer	75 ± 1.6 and 85 ± 2.4 nm	↑	↓	Good sustained release	↑	[87]

Although by the time this paper is written no TKIs-PM formulations have reached the clinical studies, there are some PMs that have either been approved by the FDA or are being evaluated in the clinical trial for delivery of other types of anticancer, such as paclitaxel and docetaxel [105], demonstrating outstanding features of PMs as versatile tumor-targeted nanocarriers with high translational potential. All of these micelles are based on PEG-b-poly(amino acid) copolymers which present several advantages to micellar systems, including: providing steric hindrance, reducing aggregation and physically stabilizing the preparations, reducing reticuloendothelial system clearance, improving the circulation half-life of drug and micelle and allowing it to reach the tumor site after intravenous injection. Generally, the versatility of polymers used in micelles' structure enables them to provide a suitable platform for gene delivery and theranostic applications of PMs.

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