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Lipid-based nanoformulations for TKIs delivery in cancer therapy

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Abstract

Cancer therapy faces many challenges, such as inadequate drug loading, low solubility, leakage before reaching the target cells and killing healthy cells. Furthermore, severe side effects resulting from conventional chemotherapy and the other therapeutic methods for cancer treatment are the main reasons for finding more effective methodologies. Thanks to nanomedicine, various nanoparticles (NPs) are designed to overcome the previously mentioned issues. Among these NPs, lipid-based ones are popular with a high potential to be used in cancer therapy. On the other hand, Tyrosine kinase inhibitors (TKIs), with crucial properties for inhibiting the growth of cancerous cells, are the drug of choice in many different types of cancers. In this regard, different lipid-based NPs are being used as nano-drug delivery systems for carrying TKIs.
In this review paper, current research on those novel systems describes how significantly some systems were able to deliver TKIs. In particular, solid lipid nanoparticles (SLNs) are discussed, and their advantages and disadvantages in different drug delivery systems for TKIs were mentioned.

Keywords: Lipid-based nanoparticles, Tyrosine kinase inhibitors (TKIs), Solid lipid nanoparticles, Cancer therapy

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1. Introduction: an overview of TKIs

According to GLOBOCAN 2020, cancer is still the main cause of death and a major factor in reducing life expectancy around the world [1]. Hence, finding effective methods in the treatment of cancer have become a prominent issue for communities, physicians and scientists. Beside the traditional methods such as surgery, chemotherapy, and radiotherapy, a new generation of cancer therapy with high specificity to cancer cells is targeted therapy. As the method's name implies, therapeutic agents belonging to this method specifically target the molecules implicated in causing malignancy in tumor cells. They can distinguish between normal cells with rapid division and cancer cells, which is not the case with conventional chemotherapeutic agents. So, targeted therapy provides more efficient treatment with less systemic side effects compared to chemotherapy.

Various types of targeted therapies include monoclonal antibody, antisense inhibitors of growth factor receptors, and tyrosine kinase inhibitors (TKIs). The latter is a group of small molecules or peptides that restrain tyrosine kinases, a family of proteins involved in a broad range of biological processes, especially growth signaling. Tyrosine kinases (TKs) are enzymes that selectively phosphorylate their protein substrates and thus transmit various signals such as cell growth, differentiation and angiogenesis to different parts of the cell. There are two classes of TKs, including receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (NRTKs), with about 58 and 32 members, respectively. Oncogenic activation of these enzymes is associated with developing tumor characteristics in cells. Accordingly, tyrosine kinases are a key target in cancer treatment and their inhibition contributes to inhibition of cell growth, proliferation, angiogenesis and metastasis as well as induction of apoptosis.

The advent of TKIs has revolutionized the treatment of cancer by meliorating the response rate and overall survival. Since 2001, when Imatinib as the first TKI received the FDA approval for the treatment of chronic myeloid leukemia, approximately 67 FDA-approved small molecules have been developed as TKIs in three generations [2]. The development of each new generation of TKIs has been the result of drug resistance to previous generations in cancer patients with tyrosine kinase mutations so the fourth generation is currently developing [3].

In competition with adenosine triphosphate (ATP) or substrate, these inhibitors can bind reversibly or irreversibly to tyrosine kinases to prohibit their activity, thereby hampering signal transduction. Irreversible TKIs such as afatinib, osimertinib, and ibrutinib represent a promising therapeutic effect in non-small cell lung cancer (NSCLC) and Mantle cell lymphoma (MCL). These inhibitors form a permanent covalent bond with enzymes, and thus they may cause toxicity through off-target modifications. Other classes of covalent but reversible inhibitors are classified into five distinct classes (type I-V) depending on the binding state, the conformational state of the enzyme, and the target site [4]. Inhibitors of types I, II, and III directly target enzymes' active site, while the target site of type IV is remote from the active site of enzymes. Type I inhibitors such as erlotinib and gefitinib, in competition with ATP binds to the ATP-binding site. Type II TKIs open up an allosteric pocket in the active site of inactive kinases and form many similar interactions with the type I inhibitors. Imatinib and crizotinib are two examples of type II TKIs. In type III, inhibitors exclusively bind to an allosteric site near the active site without any interaction with the ATP-binding site, unlike the previous two forms. TKIs targeting mitogen-activated protein kinase (MEK) belong to this class of inhibitors. Type IV TKIs can allosterically target any part of the kinase remote from the ATP-binding site. There is less information about type IV inhibitors of TKs, but ON012380 is a small-molecule TKI following this inhibitory mode [5]. Type V of TKIs includes bivalent inhibitors exhibiting a combination of these inhibitory modes. In figure 1, four types of the reversible binding mode of TKIs are illustrated.

Apart from the inhibitory mechanism, TKIs are also classified based on the TK family they target. EGFR-TKIs are a significant class of TKIs inhibiting the epidermal growth factor receptor (EGFR) family. The oncogenic activation of EGFRs is commonly detected in cancers such as breast cancer, metastatic colorectal cancer, head and neck cancer, glioblastoma, and especially NSCLC[6]. A large number of NSCLC patients (%15 to %50) harbor sensitizing mutation in EGFRs, which about those EGFR-TKIs have been approved as the first-line treatment by the FDA. They include gefitinib and erlotinib from the first generation and afatinib from the second generation. Compared to

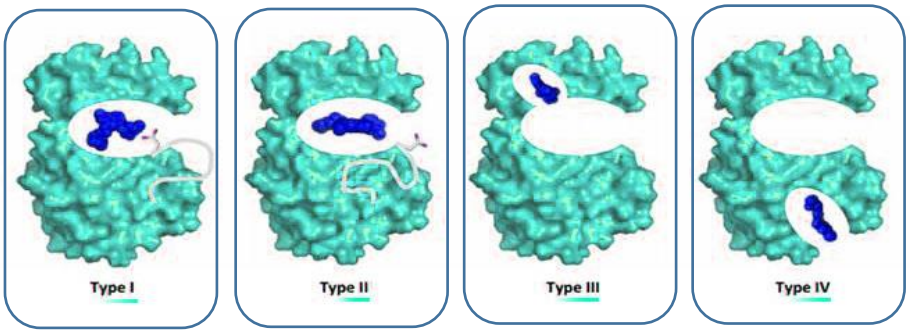

Figure 1. Different types of reversible small-molecule TKIs. Type I inhibitors bind to the active conformation of the TK in the ATP-binding pocket through the aspartate residue (white backbone) of the DFG motif; type II inhibitors bind to the inactive conformation of the enzym by flipping the aspartate residue facing outward of the binding pocket; type III inhibitors take up an allosteric pocket adjacent to the ATP-binding pocket with no overlapping with it; type IV inhibitors occupy an allosteric pocket remote from the ATP-binding pocket [7].

conventional chemo-drugs, these TKIs display a more prolonged progression-free survival (PFS) and response rate in patients with advanced NSCLC. Even though these drugs demonstrate a prolonged response at first, after about one year, these patients develop resistance to EGFR-TKIs [8]. Studies in NSCLC patients with EGFR mutation have shown that erlotinib is not significantly superior to gefitinib in PFS and response rate.[9], whereas afatinib outcomes showed a significant improvement compared to gefitinib [10]. In addition, the combination of first-generation EFGR-TKI with chemotherapy [11] and anti-angiogenic antibodies [12] has been effective in the treatment of NSCLC due to synergistic effects. Acquired resistance to standard EGFR-TKIs is mainly due to the Thr790Met point mutation in EGFRs, for which osimertinib has been designed and developed to target this mutation in the second line of NSCLC treatment [13]. Moreover, according to FLAURA Trial outcomes, osimertinib as the first-line treatment in patients with metastatic NSCLC and EGFR mutation has excellent superiority in comparison with standard EGFR-TKIs [14]. It also has remarkable efficacy relative to platinum therapy plus pemetrexed in patients with T790M-positive advanced NSCLC cancer with or without brain metastases [15]. Another class of TKIs is ALK-TKIs, which are used for a unique mutation in a small population of NSCLC patients, including the fusion gene of echinoderm microtubule-associated protein-like4 and anaplastic lymphocyte kinase (EML4-ALK). Crizotinib is the first generation of ALK-TKIs. Despite its excellence over chemotherapy, it illustrated some limitations in controlling brain metastasis which led to the development of the second generation of ALK-TKIs (ceritinib, alectinib, and brigatinib) [3]. Upon progression of ALK–positive lung cancer, mainly as the result of ALK^{G1202R} mutation, the treatment procedure is followed by the third-generation ALK-TKIs lorlatinib [16]. Other classes of TKIs targeting various TKs comprise FGFR-TKIs, HER2-TKIs, VEGFR-associated multi-targeted TKIs, RET-TKIs, MET-TKIs, MEK-TKIs, ROS1-TKIs, Tropomyosin RTK inhibitors, and Bruton's TK inhibitors [3].

Resistance to TKIs can be intrinsic or acquired after the initial response. The most common cause of resistance to TKIs is various kinds of point mutations in the kinase domains, such as T790M and T315I, which decrease in the affinity of the inhibitor for this domain. Other mechanisms contributing to resistance to TKIs are related to developing modified signaling pathways by cancer cells, changing gene copy numbers, and their expression [17]. Moreover, long-term treatment with TKIs can lead to activation of efflux transporters which in turn cause cells to pump the drugs out. It is proven that TKIs are the transported substrate of ATP-binding cassette (ABC) transporters. Through the interaction with TKIs, these transporters influence their bioavailability, their removal from liver and kidney, plasma exposure, and their accumulation in tissue[18]. However, In recent years, some studies

demonstrated that some TKIs such as imatinib, afatinib, osimertinib, and crizotinib could reverse multi-drug resistance (MDR) via the inhibition of P-gp, ABCG2, and a few other ABC transporters [19].

Like other conventional chemotherapeutics, the high daily dose of TKIs displays a broad range of adverse effects in patients [20], some of which are due to off-target changes, potentially inhibiting other TK receptors [21]. However, since TKIs are delivered over a more extended period of time, their side effect profile differs from conventional treatment strategies [22]. Studies indicate that some TKIs, such as imatinib and nilotinib, adversely affect the metabolism of glucose, lipid, bone, and endocrine system function [21]. Generally, side effects of TKIs are dose-dependent, and each inhibitor possesses its own side effects. However, a different class of TKIs may show similar side effects due to the similarity in their targets. The most commonly reported side effect of EGFR-TKI is related to skin drug reactions that result from the role of EGFR in the natural integrity of the skin. An essential factor in the survival and metastasis of cancer cells is angiogenesis induced by vascular endothelial growth factor (VEGF). Inhibition of their corresponding receptor by TKIs causes some detrimental cardiovascular effects such as hypertension, systemic vascular resistance, pro-coagulant changes, and in the long term, thrombosis and hemorrhage. In addition to the skin and cardiovascular system, other organs are affected by TKIs including lungs, liver, gastrointestinal tract, kidneys, and thyroid. However, especially compared to chemotherapy, TKIs are a well-tolerated treatment strategy. Choosing the optimal TKI at the optimal dose is critical in reducing toxicity and side effects [20]. Due to poor solubility, the majority of TKIs belong to classes II and IV of the Biopharmaceutical Classification System (BCS), which are characterized by high and low permeability, respectively [23]. As oral agents, they also have poor and variable bioavailability that may lead to variation in plasma levels and, consequently, reduce response to treatment. Several factors are responsible for this issue, individually or in combination with other factors, including physicochemical factors, food and drugs interactions with the administered TKI, metabolizing enzymes in the intestine and liver, and as mentioned earlier efflux transporters. Additionally, since the solubility of TKIs is inversely related to pH, in the small intestine with relatively high pH the absorption of TKIs is problematic [24].

Accordingly, despite being a real breakthrough, the use of TKIs in clinical treatments poses challenges. Over the recent decade, many efforts have been made to take advantage of nanotechnology to improve TKIs' functionality and obviate their drawbacks. One attractive strategy has been the encapsulation or complexation of TKIs with nanoparticles. Nanoparticles (NPs) provide an appropriate delivery platform for conventional chemo-drugs to compensate for their limitations in treatments. They can pass through the physiological barriers, retain drugs till reaching to target cells, prolong the blood circulation time of the drug, overcome drug resistance, and generally enhance the bioavailability and efficiency of anti-cancer drugs. Moreover, nano-carriers provide opportunities for combining different treatment strategies. For instance, to improve the efficiency of targeted therapy, scientists combined TKIs with immunotherapy by using an immunostimulatory nano-carrier [25]. Various types of NPs have been designed and tailored for TKIs, including inorganic NPs, polymeric NPs, polymeric micelles, protein-based NPs, lipid-based NPs, and other nanoformulation [23, 26]. Lipid-based NPs, due to their outstanding features such as high biocompatibility, non-immunogenicity, high drug loading capacity, and scalability, have attracted much more attention than other types of NPs to deliver TKIs into cancer cells [26, 27].

In this regard, this review aims to discuss recent research about using various lipid-based nanoparticles that contribute to cancer therapy using TKIs.

2. Types of lipid-based nanoparticles

Various nanopharmaceuticals have emerged by utilizing nanotechnology science in medicine to meet health-related problems. Although there have been different polymers, magnets, sugar-based materials, and other materials used as nanocarriers for cancer therapy[28, 29], lipid-based nanoparticles exhibited the highest success in getting FDA approvals and making their way to the market [30, 31]. As illustrated in Figure 2, this group of compounds generally consists of five subcategories: liposomes, niosomes,

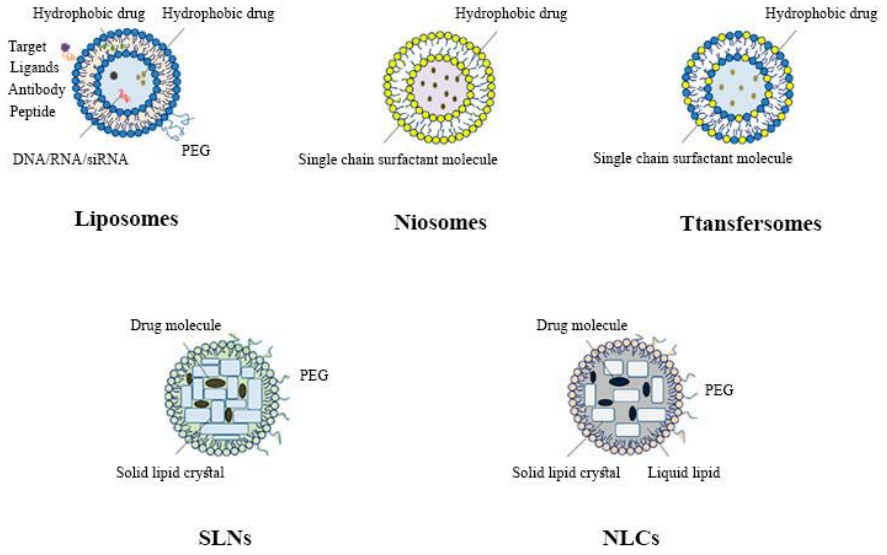

Figure 2. Different types of lipid-based nanoparticles [30].

transfersomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs).

Lipid nanoparticles with outstanding biocompatibility, stability, and low toxicity have been considered useful vehicles for the delivery of various drugs. They are also called "nanosafe carriers" regarding their low side effects [32, 33].

Either bilayer or multilayer forms of lipid nanoparticles with the hydrophilic core can be used to encapsulate conventional hydrophilic and hydrophobic drugs and biomaterials while no chemicals are involved in the procedure. Typically, hydrophilic drugs go through the core of these lipid-based nanoparticles, and lipophilic drugs travel through the external bilayers.

The most conventional lipid structures are liposomes constructed of phospholipids and cholesterol and the size range of 25nm-2.5μm. However, there are different forms of liposomes according to their size, composition, synthesis, and surface charge [34, 35]. With such a structure, they can show high drug protection and targeting capability, controlled release of drugs, in line with decreasing toxicity and boosting efficacy [36-38]. However, they failed to penetrate the stratum corneum, leading to limited dermal delivery. Besides, liposomal nanoparticles cannot strongly bind with hydrophilic drugs in the core, so they suffer from inadequate stability and drug leakage in their path for delivering specific drug(s).

As for niosomes, they are made of cholesterol and nonionic surfactants such as alkyl-ether, esters, and amides in aqueous conditions that cause better stability and longer shelf life. Although there is a neutral shell in niosomes construction that practically illustrates higher compatibility than positively charged liposomes, the lack of ionic repulsion in their structure makes it difficult for drug stability through leakage and aggregation. These issues played an important role in losing ground of being FDA-approved materials.

Transfersomes comprising phospholipids, edge activators (EA), and cholesterol are deformable nanoparticles. However, this type of lipid-based nanoparticles shows the highest penetration and entrapment for lipophilic drugs. Structurally, they may be a good candidate for different goals, but they cost much, and their oxidative degradation needs to be solved first.

The remained disadvantages, such as inadequate stability, low degree of loading, and toxicity were considered unsolved issues related to lipid nanoparticles for widening their applicability domain. In this regard, scientists developed a novel class of

spherical lipid-based nanoparticles as solid lipid nanoparticles (SLNs) formed of solid fats and surfactants. The differences in the structure of SLNs make some valuable properties that led to increasing the stability and efficacy of encapsulation of hydrophilic drugs [32, 36].

NLCs possess a core matrix of a mixture of both solid and liquid lipids in various ratios. Although there is not much difference between the preparation methods of SLNs and NLCs, NLCs are prepared with less or no crystalline in the core, while the core matrix of SLNs is crystallized. The common preparation methods for the two mentioned types are cold homogenization, hot homogenization, and hot emulsification-ultrasonication. In SLNs, drugs solubilize in the solid lipids or are incorporated straightly into them. In contrast, in NLCs, drugs are dissolved and/or melted in the mixture of liquid and solid lipids based on the thermal stability of the drug, and then in the presence of surfactant, they are dispersed in the aqueous phase. The presence of oil and solid lipid in NLCs avoids the formation of complete crystals and the escape of drugs into the aqueous phase. Therefore, the amorphous matrix in NLCs increases the drug loading capacity. These nanoparticles have recently been widely evaluated for various therapeutic applications such as ocular drug delivery, pulmonary drug delivery, and drug delivery for treating different cancer types [23, 37, 39]. All in all, researches showed that the preparation conditions and scaling-up processes provide a good opportunity to use SLNs over liposomes in drug delivery systems for nanomedicine [36]. However, more clinical processes should be done to provide reliable awareness of any side effects.

3. Application of lipid nanocarriers in TKIs delivery: advantages and disadvantages

NLCs have so far been a subject of interest to be studied for their structure, preparation methods, benefits, and drawbacks (see, e.g., Subramanian et al.[34], Ghasemiyeh et al.[40], Li et al.[41], and Jaiswal et al.[42]). However, not much is known about the advantages and against of utilizing NLCs in tandem with inhibitors of protein tyrosine kinases (PTKs) in the treatment of various cancers. In this context, a plethora of evidence reports promising results for NLC-PTK therapeutic systems. Sorafenib is a well-established PTK inhibitor employed against many cancers such as renal cell carcinoma (RCC) [43, 44], hepatocellular carcinoma (HCC) [45], and gastric cancer [46]. Nevertheless, sorafenib suffers from low bioavailability due to its poor water solubility [47, 48]. In addition, high daily doses of sorafenib come with adverse outcomes such as gastrointestinal irritation, diarrhea, anorexia, and skin reactions [49, 50]. To avoid these adverse effects, sorafenib is widely considered to be incorporated in nanomedicine-based platforms. For example, Duan and colleagues reported that incorporating sorafenib into lipid NPs allows higher drug distribution in tumors than in other tissues, such as the heart and kidneys, especially within 48 hours. This may result from the potential of NPs for sustained and targeted drug delivery into the affected sites, culminating in minor side effects during tumor treatment [51]. N-acetylgalactosamine (NAcGal) targets hepatic cancer cells where asialoglycoprotein receptors (ASGPRs) are overexpressed. This study scrutinized the targeted delivery of NAcGal with doxorubicin (DOX) and sorafenib (SOR). It was found that SOR is released from SOR-loaded NAcGal-DOX lipid nanoparticles (NAcGal-DOX/SOR LNPs) much more slowly than from DOX-SOR LNPs and SOR LNPs. The cellular uptake efficiency of NAcGal-modified LNPs was quite higher than that of non-modified LNPs. The best synergistic effect was observed at the weight ratio of 2:1 (DOX: SOR). Dually functionalized LNPs, i.e., LNPs having both DOX and SOR, exhibited better efficacy than LNPs decorated with one of the two. The most potent antitumor activity was observed when using NAcGal-DOX/SOR LNPs. Dayani et al. evaluated albumin lipid nanoparticles (ALNs) targeted with lactobionic acid (LA) for targeted drug delivery of sorafenib in cancer patients. Their assay was based on previous studies on the expression of asialoglycoprotein (ASGP) receptors on Hepatic carcinoma cells such as HepG2 cells, the use of galactose, LA, and galactosamine as ligands for ASGP receptors, as well as research on utilizing ALNs for the delivery of poor water-soluble cytotoxic drugs to cancer cells [52-55]. To monitor the cellular uptake of SOR, coumarin-6 was loaded as a fluorescence probe in targeted and non-targeted ALNs. Targeted ALNs exhibited higher cell uptake than the others. Furthermore, HepG2 cell survival was diminished dose-dependently in the presence of free SOR and targeted and non-targeted ALNs. Both SOR-loaded targeted and non-target ALNs showed greater cytotoxicity against HepG2 cells than SOR alone at the same concentration. The IC50 values showed that SOR-loaded targeted ALNs

possess a greater anticancer effect than non-targeted ALNs and SOR alone. As with the results, SOR-loaded targeted ALNs can improve the therapeutic effect of SOR and avoid its side effects at high concentrations [56]. Yang and co-workers showed that drug-carrying lipid nanosuspensions (LNSs), as a drug delivery system, possess outstanding properties such as uniform size distribution and sustained drug release [57]. In this study, lipid nanosuspensions were utilized, possessing high drug-loading capacities, which allow an improved drug concentration at the target sites and fix the problem of low loading capacity and drug leakage that are visible in other nanocarriers such as liposomes [58]. SOR possesses high lipophilicity; thus, phospholipids are the suitable stabilizers to assure superb compatibility with SOR [59]. In this study, 45.75% of the SOR was released during the first 48 hours. Such a sustained release could largely be due to the gradual dissolution of the lipid skeleton of the LNS. On the contrary, the cumulative release of SOR from the SOR solution was 34.53%, which is remarkably lower than that of SOR-LNSs. This implies the poor water solubility of SOR. SOR-LNSs showed higher cytotoxicity than the SOR solution at higher relative concentrations. In addition, the IC50 value of SOR-LNSs was significantly lower than that of the SOR solution. Likewise, it was found that it is feasible to improve the interaction and intracellular localization by the lipid components, contributing to the higher in vitro cytotoxicity of SOR-LNSs. Similarly, Zhang and colleagues outlined superior properties for such LNSs, including improved efficacy, elevated stability in drug release, enhanced cell internalization, and prolonged blood circulation time [60]. In this study, hybrid LNSs were utilized mostly for their improved drug solubility and dispersibility, no drug leakage, and a chance to merge different carriers [61-63]. Research has further revealed that hyaluronic acid (HA) can specifically bind to CD44 receptors overexpressed on the surface of various cancer cells, including hepatic cancer cells and gastric cancer cells [57, 64, 65]. Thus, HA was employed in the present study. The IC50 in HA-SOR-cLNS assembly was significantly lower than that of the SOR solution. The specific recognition of HA-SOR-cLNS by CD44 surface receptors culminated in active-targeting efficiency to HepG2 cells, leading to more elevated cytotoxicity. In the presence of free HA, the cellular mean fluorescence intensity (MFI) was significantly diminished in HA-cLNS, presumably due to the specific binding of free HA receptors and CD44. The results revealed that HA-cLNS had been internalized by CD44-mediated endocytosis which has led to efficient drug delivery. The strongest tumor inhibition was found in the HA-SOR-cLNS group in which the mean tumor volume (MTV) was significantly lower than in the other SOR-treated groups. Bondi et al showed that Nanosystems shield sorafenib against being metabolized and/or binding to plasma proteins, thus enhancing its bioavailability. SOR-containing NLCs remarkably improve the therapeutic efficiency of loaded cargoes [66]. Wang and co-workers found that Solid lipid NPs enhance the bioavailability of sorafenib and its capability for hepatic targeting in patients under investigation [67]. Solid lipid nanoparticles (SLNs) are novel drug carriers best suited to carry payloads with poor water solubility [68]. Compared to conventional nanocarriers (e.g., NPs and polymer NPs), SLNs possess improved biocompatibility, stability, and oral absorption [69]. Therefore, they were employed in this study. The mean drug selectivity index (DSI) in the SOR-SLN group was 2.20 times greater than in the suspension group. Similarly, the mean residence time (MRT) in mice following oral prescription of SOR-SLNs was 1.77 times greater than oral prescription of SRF suspension, implying sustained drug release upon using SOR-SLNs. In addition, the peak plasma drug concentrations (Cmax) and the area under the concentration-time curve revealed that the oral bioavailability of SOR-SLNs is inflated by 66.7% compared to the SOR suspension. In a similar study, Yang et al. reported a greater antitumor activity of sorafenib when being loaded onto NPs, presumably due to the reduced drug collapse at circulating and enhanced volume of drug accumulated in tumor sites. They further found less toxicity in treatment with drug-containing NPs compared to the drug alone due to lower levels of liver and kidney enzymes [70]. In addition, Yang et al. utilized HA that can specifically bind to CD44 receptors on the surface of gastric cancer cells.

Other PTK inhibitors, such as afatinib, imatinib, brigatinib, and erlotinib, have also attracted burgeoning attention in treating cancers, especially lung tumors. In a study, Fu et al. showed that afatinib-encapsulated NPs possess improved therapeutic efficacy than the afatinib alone in cell viability, apoptosis, cell migration, and cell cycle analysis [71]. Lipid–polymer hybrid NPs (LPHNPs) contain a biodegradable hydrophobic core surrounded by a phospholipid monolayer. Ideally, LPHNPs enclose a

pair of drugs. This study used LPHNPs to load cisplatin (CDDP) and afatinib drugs. Flow cytometry (FC) results showed a significant gradual uptake of ACD-LP NPs by tumor cell lines HONE-1. After 24 h of incubation, AFT significantly reduced cell viability more than CDDP. CDDP and AFT alone induced apoptosis in 10 to 12% of cells, while the CDDP+AFT assembly inflicted apoptosis in 30% of cells. The consequences of CDDP and AFT on nasopharyngeal carcinoma (NPC) cell migration were assessed separately or in combination using the wound healing procedure. ACD-LP NPs significantly hampered cell migration of HONE1 lines due to synergistic anticancer activity and dual drug pathways. Likewise, Molaahmadi et al. reported that the imatinib activity is sustained when loaded into LNCs. The capacity of Lipid nanocapsules (LNCs) for sustained drug delivery can potentially reduce the demand for high doses of the drug and, consequently lowering side effects [72]. LNCs require a simpler and affordable preparation method, better stability of encapsulated drugs, lower toxicity and good biocompatibility, and higher drug loading capacity and physical stability than liposomes and/or SLNs [73-77]. Therefore, they were utilized in this study. Ahmed et al. found that solid lipid nanoparticles (SLNs) containing brigatinib(BG) allow sustained drug release and potential efficacy against A549 lung cell lines, qualifying it as a promising drug delivery system for the treatment of non-small cell lung cancer (NSCLC) [78]. Notably, there was a significant difference in cell viability between the samples of pure BG suspension and samples of BG-loaded SLNs with 275 mg stearic acid and 27.5 mg soy lecithin (BS5-SLN). The IC50 values for pure BG suspension and BS5-SLN suspension were 89.9 and 43.85, respectively, implying the higher cytotoxicity of BS5-SLN and its efficacy at a 48.7% lower dose than the BG suspension. Similarly, Mandal and colleagues reported satisfactory serum stability of erlotinib for nearly 12 hours, as well as a significant increase in erlotinib accumulation in A549 cells after 72 hours when loaded onto NPs compared to erlotinib alone [79].

Numerous failures in cancer treatment inflicted by drug resistance and lower quality of life have provoked researchers to adopt multi-component NLCs, instead of single-component ones; and to explore the chance for the simultaneous application of multiple drugs with PTK inhibitors to achieve improved therapeutic results owing to the synergistic effect of drugs, decreased drug resistance, and diminished adverse toxicity by reducing the dose of drugs prescribed [33, 60, 70, 71, 80-84]. Moreover, novel drug delivery systems are also strongly in play, in tandem with NLCs, including dry powder inhalers (DPI) in refractory lung cancer studies (see, e.g., Yang et al.[80] for afatinib, and Bakhtiary et al. [85] for erlotinib). Furthermore, the bioavailability of tyrosine kinase inhibitors (TKIs) and the stability of NLC-based drug delivery systems are of utmost importance. In this context, numerous modalities have been explored to modify the surface of nanocarriers with polyethylene glycol (for example) to diminish interaction with serum proteins and protect the immune system [81, 86, 87]. Generally speaking, NLC-based drug delivery systems have shown outstanding properties such as versatile particle size, polydispersity index, zeta potential, entrapment efficiency, and the potential to be monitored by transmission electron microscopy (TEM) in the case of TKIs. In conclusion, NLC-based drug delivery systems possess unprecedented properties, including 1) sustained release of TKIs and prolonged blood circulation, 2) improved efficiency of TKIs and tumor targeting, 3) elevated bioavailability of TKIs, 4) reduced side effects of TKIs, 5) simultaneous application of multiple drugs into a single platform to improve synergistic effects, reduce the drug resistance, and minimize adverse toxicity of drugs, and 6) the chance to develop novel modalities for efficient drug delivery. All of these are the footstone for future applied studies in cancer research. Therefore, it seems the advantages of such drug delivery systems will soon allow their widespread application in the treatment of various cancers. However, the therapeutic efficiency of nanoformulations has been less explored in clinical applications [88]. This is while, it seems, advantages of such drug delivery system will soon allow their widespread application in the treatment of various cancers.

4. The excellence of solid lipid nanoparticles in TKIs delivery

As mentioned earlier, several challenges are associated with TKIs formulation. Solid lipid nanoparticles (SLNs) are one of the drug delivery platforms providing a lucrative hotbed to approach these challenges and improve the efficacy of cancer treatment with TKIs. So, it seems mandatory to discuss SLNs characteristics that take the edge of drug delivery in cancer treatment.

Although various nanocarriers exhibit promising effects in the improvement of TKIs efficiency, there are still different limitations that do not allow these nanoformulations to be introduced to the clinic. One of the major concerns in the application of nanocarriers is the toxicity issue related to a polymeric material or solvent residue, particle shape and size, surface area, agglomeration, and solubility. The lack of methods for large-scale production and polymer costs are other limitations that hinder the entry of nanoformulations into clinical trials [89, 90].

Generally, lipid-based NPs are appropriate platforms for loading both hydrophilic and lipophilic therapeutic agents. They are a well-tolerated nanocarrier system, constituting out of physiological materials and due to being biodegradable. However, in the case of liposomes, factors such as drug loading capacity, drug leakage, and vascular instability limit their use in some cases. In contrast, SLNs, integrate many advantages of liposomes and polymeric NPs without many of their drawbacks. Many SLNs have been developed for oral, ocular, pulmonary, intravenous, and intranasal administration [91]. SLNs are highly versatile, safe, biocompatible, cost-effective, and more stable nanocarriers than other NPs, even liposomes. The procedures of sterilization and production on a large scale for SLNs are convenient [92, 93]. Dispersed solid lipids in aqueous environments with the help of surfactants are stabilized and prevented from agglomeration. Also, SLNs are capable of loading an extensive amount from a broad range of therapeutic agents. Immobilized drugs within solid lipids are protected from photochemical, oxidative and chemical reactions [31].

Overall, SLNs are effective delivery systems for increasing the bioavailability of anticancer drugs in various ways. Belonging to class II and IV of BCS, TKIs' bioavailability issue is mainly associated with the low dissolution rate. Conventional approaches to enhance drugs' dissolution rate include the use of surfactants, cyclodextrin complexes, salt formations, nanoparticles, solid dispersions, lipids, and permeation enhancers [94]. The SLNs are favorable nanoparticles for improving the bioavailability of poorly water-soluble drugs by encapsulation of them in the lipid core of SLNs, which is stabilized by surfactant. When drugs are in the lipidic matrix of SLNs, the crystallization is reduced as a result of being in an amorphous state, which in turn improves the solubility and dissolution rate of drugs [78]. SLNs show a remarkable encapsulation efficiency and drug loading capacity for TKIs. For example, a dry powder of gefitinib-loaded SLNs conjugating with glucosamine as a targeted agent was prepared for lung cancer treatment and showed a remarkable encapsulation efficiency of 97.31% [39]. Another study that prepared erlotinib-SLNs in dry powders containing inhalable microparticles showed an encapsulation efficiency of 78.21% [85]. Moreover, sorafenib encapsulation into SLNs prepared by Zhang et al. represented almost 93 % efficiency [95]. Sorafenib has also been encapsulated in an SLN-based tranostatic nanodevices developed for delivery to the tumor site using a remote magnetic field, with an efficiency of about 90% [96]. The amount of lipid components is proportional to the efficiency of encapsulation. Due to its lipophilic nature, the higher the amount of lipid component, the more hydrophobic drugs are accepted. However, Ahmed et al. elucidated that a further increase in lipidic content reversely affects the encapsulation efficiency because lipids are removed from SLNs through crystallization [78].

A novel approach in the formulation of SLNs, designed for the delivery of sorafenib, has shown a significant improvement in drug solubility. In this study, Benizri *et al.* stabilized SLNs formation by nucleolipids with positive and negative charges. In the absence of nucleolipids, extensive amounts of sorafenib (about 90%) were lost in different formulation processes, possibly due to the low water-solubility of sorafenib. In the presence of nucleolipids, sorafenib due to its hydrophobic feature interact with nucleolipids through the heterocycles, hydrogen bonds, and ionic bonds. Nevertheless, such interactions were seen more in anionic SLNs which also justify their great stability in different temperatures (4 and 37 °C). While positively-charged SLNs exhibit no stability in a high temperature (37 °C) due to repulsive coulombic interactions that occur between the positive charges of both sorafenib and cationic nucleolipids. However, both cationic and anionic SLNs loaded with sorafenib exhibited potent cytotoxicity on liver and breast cancer cells [97]. It is worth mentioning that the drug release kinetics need to be investigated. Sorafenib-loaded SLNs, prepared through a simple combination of high-speed shearing and ultrasonic treatment, increase oral bioavailability up to 66.7% with longer MRT(0-∞) compared to sorafenib suspension. This is probably due to drug encapsulation in a solid lipid matrix that keeps

sorafenib from metabolic enzymes and reduces drug release. In addition, extended systemic circulation time lowers doses of nanoformulation required to obtain the same pharmacological effects of the SRF-suspension, which in turn reduces SRF-induced side effects in patients [67].

Ranging from 50-1000 nm, the particle size of SLNs offer a good option for TKIs delivery for the following reason. Small-sized particles have weak interactions with blood proteins as well as circumvent the physiological barrier of the GI tract. However, particles less than 70 nm are prone to hepatic aggregation. It is shown that the SLNs between 70 to 200 nm with a suitable surface area are appropriate NPs in absorption and through which they can enhance the bioavailability of the small molecule TKIs [67, 95]. Although the particle size is directly dependent on the level of lipid components, an increase in the surfactant reduces the particle size [78].

Oral administration of drugs and their absorption through intestinal mucosa exposes them to first-pass metabolism and hepatic metabolic enzymes with two degradation phases. Some TKIs such as erlotinib lose their pharmacological activity through oxidative reactions of phase I mediated by cytochrome P4503A4 (CYP3A4) [98]. Hence, SLNs would preserve the pharmacological activity of TKIs until the delivery to target cells. On the other hand, there is an alternative route for uptake of lipidic materials that occurs through ducts of the lymphatic system by Peyer's patch mechanism. The lymphatic vessels mediate lipids absorption through the digestion of lipids and chylomicron formation. Therefore, in this way, lipid-based nanoparticles increase drug bioavailability via bypassing the first-pass metabolism. The uptake of lipophilic drugs can further increase by co-administration of fatty foods [89]. However, the digestion of lipid nanocarriers mediated by the collision of fatty droplets and the action of different lipases, colipases, and bile salts on the joint surface of lipids and water raises problems. So, the controllable digestion of lipid-based nanocarriers is of great importance in the bioavailability and controlled release of drugs. In this respect, a coated layer of polyethylene glycol (PEG) upon SLNs effectively addresses this problem. Ban et al. demonstrated that SLNs covered with large-chained PEGylated emulsifiers are more efficient in preventing lipolysis than small-chained PEGylated emulsifiers are [99]. Compared to simple SLNs, PEGylated SLNs have been shown to penetrate the intestinal mucosa much more easily and are more stable in intestinal fluids. They also represent an extended systemic circulation time and almost twice bioavailability more than simple SLNs [100].

Besides the enhanced bioavailability, using SLNs in TKIs' delivery affects the variability in the pharmacokinetic profile of TKIs. For example, Rampaka et al. have recently shown that in addition to significant improvement in bioavailability, SLNs can highly reduce the pharmacokinetic variability of erlotinib resulting from the presence or absence of food [101].

SLNs also provide a sustained drug release profile attributed to the mobility retardation of drugs entrapped into the lipid matrix. Therefore, it can be considered as a superiority of SLNs over lipid nanoparticles with liquid oil core. Drug release from SLN occurs through three pathways: initial rapid release or burst effect, diffusion of the drug, and erosion/degradation of the lipid matrix. Initially, drugs that are weakly bound or on the surface of the SLN are released explosively. Subsequently, much more drugs are released in a controlled and slow manner as a result of their zero/first-order diffusion in the lipid core of the SLN or erosion/degradation of SLNs [92]. The optimized brigatinib-SLNs were prepared by Ahmed. et al. represent a biphasic release pattern for brigatinib that involves an 8-hour rapid release at first followed by a slower release up to 24 hours in a sustained manner [78]. Sorafenib-loaded SLNs are parenterally administrated to rabbits and had a slow elimination rate (0.14 times slower than the sorafenib solution) due to the retardation in drug release, leading to extended blood circulation time [95]. In a study on the co-delivery of afatinib-loaded SLNs and paclitaxel using PLGA porous microspheres, the inhalable microspheres showed an attractive profile of drug release. Since paclitaxel and afatinib are prescribed in clinics for the treatment of EGFR-TKIs resistant NSCLC, Yang et al. were inspired and designed a pulmonary microspheres system that first and rapidly releases paclitaxel within 2 days, followed by a slow and sustained release of afatinib (2 weeks). The insertion of afatinib-loaded SLNs into porous microspheres contributes to decreasing the initial burst release of afatinib [80]. Imatinib-loaded SLNs optimized by Plackett-Burman design and Box-Behnken design showed a sustained release in physiological pH and a rapid release at pH 5. The in vitro release mechanism for this nanoformulation

involved a drug diffusion from the lipid matrix and degradation of the lipid core [102].

In terms of cytotoxicity, TKIs delivery via SLNs displayed a significant reduction in IC_{50} and an enhancement in cell toxicity effect on various cancer cell lines. IC_{50} refers to the concentration of a drug that diminishes the viability of cells up to 50%. For example, in Benizri et al.'s study, two types of sorafenib-SLNs were prepared with positive and negative charges and showed IC_{50} values of 15 and 50 µM on MDA-MB-134 cells (breast cancer cell line), respectively. On the othe hand, at the concentration of free sorafenib, which has the maximum water solubility (5µm), no cytotoxicity was observed [97]. Another example is Ahmed et al.'s work in which their optimized brigatinib-SLNs showed a remarkable enhancement in cytotoxicity effect. According to their results, the blank-SLN and the optimized brigatinib-SLNs showed the IC_{50} of 89.9±2.4 and 43.85±1.8, respectively, and the IC_{50} for pure brigatinib-suspension was 58.53±1.3 µg/mL. In addition to being more cytotoxic, the optimized formulation is also efficient in 74.91 % less dosage as that the drug suspension [78].

As briefly mentioned earlier, once the SLNs are prepared, during storage, it is very likely that the solid matrix forms highly ordered crystals. This crystallinity can decrease the available space for the incorporation of drugs, leading to drug loss. A new generation of SLNs namely NLC has been developed as a potential drug delivery system to overcome such shortcomings in SLNs. Figure 3 illustrates a brief comparison among SLNs and NLC structurally. In a study conducted by Varshosaz et al., a series of NLCs were designed and fabricated for the co-delivery of imatinib and curcumin for non-Hodgkin lymphoma treatment. They evaluated the effect of the type of lipid and oil as well as the oil percentage on the physical properties of nanoparticles. They used glyceryl monostearate (GMS) and lecithin for solid lipid and oleic acid and Labrafac for liquid lipids in %15 and %25. Although all eight designed NLCs exhibited significant encapsulation efficiency (98 to 100% and 86 to 97% for curcumin and imatinib, respectively), only the combination of lecithin with higher content of oleic acid represented the best physical properties. The optimized formulation conjugated with a targeted agent (rituximab) reduced the IC_{50} of imatinib from 4.3 ± 0.1 to 1.4 ± 0.0 l g/ml. Furthermore, co-administration of these drugs reduces the amount of imatinib required for treatment and its side effects due to the synergistic effect [82]. Another study done by Makeen et al. characterized gefitinib-loaded NLCs to treat colorectal cancer. The optimized gefitinib-NLCs with an encapsulation efficiency of >95% showed a prolonged and sustained drug release and 4.5-fold enhancement in cytotoxicity compared to free gefitinib [104]. Moreover, Sorafenib loading in NLCs containing tripalmitin as solid lipid and Captex 355 EP/NF or Miglyol 812 as liquid lipids has been studied. The results showed that sorafenib has much better loading and encapsulation in NLCs containing Captex 355 EP/NF which was attributed to better solubility of sorafenib due to longer fatty acids chains compared to Miglyol 812. This nanoformulation also exhibited a better antitumor effect on various hepatocarcinoma cell lines [66]. Recently, a

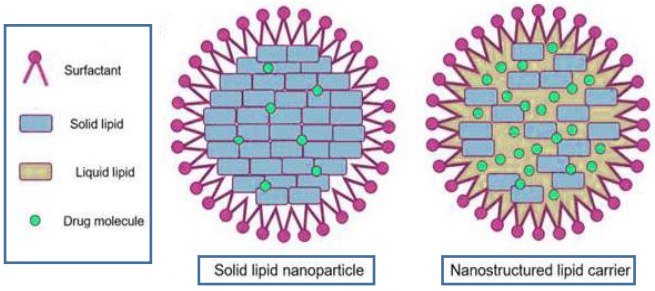

Figure 3. Schematic illustrations of SLNs and NLCs. The available space for drug loading in SLNs compared with NLCs is much less. The addition of liquid lipid to a completely solid matrix provides ample pace for drug molecules in NLCs [103].

multifunctional theranostic NLC system has been developed for co-delivery of multiple moieties, including anticancer drugs of gefitinib and/or paclitaxel, a siRNA targeting EGFR mRNA, an imaging agent, and cancer-targeting agents to target the NSCLC tumors. This synthesized NLC showed high aqueous stability through the storage for 60 days in 4°C in buffer with pH 7.4 without any significant change. For both the gefitinib and paclitaxel-loaded NLCs, 5 to 10 times improvement in anticancer activity was reported in the treatment of a series of NSCLC cell lines [33].

5. Conclusion

The increasing demand for efficient cancer treatment methods with the lowest side effects is the main reason for utilizing nano-drug delivery systems. Therefore, TKIs, one of the most valuable groups of drugs in cancer therapy, are used as the chosen drug to be carried with NPs, and these nanosystems have been investigated.

PH-sensitive nanoparticles can cover TKIs and protect them while passing through healthy and cancerous cells and releasing the drugs when they reach the cancerous cells.

Although many nanovesicles have been established to fulfill this need, the most published studies successfully got FDA-Approval, belong to lipid-based nanoparticles. These brilliant nanocarriers stand out for high efficiency in cancer treatment, especially by improving the solubility and stability of different drugs, including TKIs. However, studies showed lipid-based nanocarriers could deliver various TKIs. However, some drawbacks still need more effort to eradicate and decrease the side effects to an acceptable level to create a low-cost and optimized anticancer drug available on the market.

Conflict of interest

The authors declare that they have no conflict of interest.

6. References

1.H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA: a cancer journal for clinicians, 209-249, 71 (2021).

2.C. Bournez, F. Carles, G. Peyrat, S. Aci-Sèche, S. Bourg, C. Meyer, P. Bonnet, Comparative assessment of protein kinase inhibitors in public databases and in PKIDB, Molecules, 3226, 25 (2020).

3.L. Huang, S. Jiang, Y. Shi, Tyrosine kinase inhibitors for solid tumors in the past 20 years (2001–2020), Journal of hematology & oncology, 1-23, 13 (2020).

4.K.J. Cox, C.D. Shomin, I. Ghosh, Tinkering outside the kinase ATP box: allosteric (type IV) and bivalent (type V) inhibitors of protein kinases, Future medicinal chemistry, 29-43, 3 (2011).

5.P. Negi, R.S. Cheke, V.M. Patil, Recent advances in pharmacological diversification of Src family kinase inhibitors, Egyptian Journal of Medical Human Genetics, 1-16, 22 (2021).

6.P. Wee, Z. Wang, Epidermal growth factor receptor cell proliferation signaling pathways, Cancers, 52, 9 (2017).

7.P. Wu, T.E. Nielsen, M.H. Clausen, FDA-approved small-molecule kinase inhibitors, Trends in pharmacological sciences, 422-439, 36 (2015).

8.M. Takeda, K. Nakagawa, First-and second-generation EGFR-TKIs are all replaced to osimertinib in chemo-naive EGFR mutation-positive non-small cell lung cancer?, International journal of molecular sciences, 146, 20 (2019).

9.Y. Urata, N. Katakami, S. Morita, R. Kaji, H. Yoshioka, T. Seto, M. Satouchi, Y. Iwamoto, M. Kanehara, D. Fujimoto, Randomized phase III study comparing gefitinib with erlotinib in patients with previously treated advanced lung adenocarcinoma: WJOG 5108L, Journal of Clinical Oncology, 3248-3257, 34 (2016).

10.K. Park, E.-H. Tan, K. O'Byrne, L. Zhang, M. Boyer, T. Mok, V. Hirsh, J.C.-H. Yang, K.H. Lee, S. Lu, Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial, The Lancet Oncology, 577-589, 17 (2016).

11.C. Pottier, M. Fresnais, M. Gilon, G. Jérusalem, R. Longuespée, N.E. Sounni, Tyrosine kinase inhibitors in cancer: breakthrough and challenges of targeted therapy, Cancers, 731, 12 (2020).

12.E. Ichihara, K. Hotta, N. Nogami, S. Kuyama, D. Kishino, M. Fujii, T. Kozuki, M. Tabata, D. Harada, K. Chikamori, Phase II trial of gefitinib in combination with bevacizumab as first-line therapy for advanced non–small cell lung cancer with activating EGFR gene mutations: the Okayama Lung Cancer Study Group Trial 1001, Journal of Thoracic Oncology, 486-491, 10 (2015).

13.S.L. Greig, Osimertinib: first global approval, Drugs, 263-273, 76 (2016).
14.J.-C. Soria, Y. Ohe, J. Vansteenkiste, T. Reungwetwattana, B. Chewaskulyong, K.H. Lee, A. Dechaphunkul, F. Imamura, N. Nogami, T. Kurata, Osimertinib in untreated EGFR-mutated advanced non–small-cell lung cancer, New England journal of medicine, 113-125, 378 (2018).
15.T.S. Mok, Y.-L. Wu, M.-J. Ahn, M.C. Garassino, H.R. Kim, S.S. Ramalingam, F.A. Shepherd, Y. He, H. Akamatsu, W.S. Theelen, Osimertinib or platinum–pemetrexed in EGFR T790M–positive lung cancer, New England Journal of Medicine, 629-640, 376 (2017).
16.J.F. Gainor, L. Dardaei, S. Yoda, L. Friboulet, I. Leshchiner, R. Katayama, I. Dagogo-Jack, S. Gadgeel, K. Schultz, M. Singh, Molecular mechanisms of resistance to first-and second-generation ALK inhibitors in ALK-rearranged lung cancer, Cancer discovery, 1118-1133, 6 (2016).
17.T. Kosaka, E. Yamaki, A. Mogi, H. Kuwano, Mechanisms of resistance to EGFR TKIs and development of a new generation of drugs in non-small-cell lung cancer, Journal of Biomedicine and Biotechnology, 2011 (2011).
18.S. Durmus, J.J. Hendrikx, A.H. Schinkel, Apical ABC transporters and cancer chemotherapeutic drug disposition, Advances in cancer research, 1-41, 125 (2015).
19.K.K. To, M. Wu, C.W. Tong, W. Yan, Drug transporters in the development of multidrug resistance in colorectal cancer, Drug Resistance in Colorectal Cancer: Molecular Mechanisms and Therapeutic Strategies, Elsevier2020, pp. 35-55.
20.R.J. Thomson, M. Moshirfar, Y. Ronquillo, Tyrosine Kinase Inhibitors, StatPearls [Internet], (2021).
21.M. Breccia, M. Molica, G. Alimena, How tyrosine kinase inhibitors impair metabolism and endocrine system function: a systematic updated review, Leukemia research, 1392-1398, 38 (2014).
22.S.C. Sodergren, A. White, F. Efficace, M. Sprangers, D. Fitzsimmons, A. Bottomley, C.D. Johnson, Systematic review of the side effects associated with tyrosine kinase inhibitors used in the treatment of gastrointestinal stromal tumours on behalf of the EORTC Quality of Life Group, Critical reviews in oncology/hematology, 35-46, 91 (2014).
23.Z. Moradpour, L. Barghi, Novel approaches for efficient delivery of tyrosine kinase inhibitors, Journal of Pharmacy & Pharmaceutical Sciences, 37-48, 22 (2019).
24.M. Herbrink, B. Nuijen, J.H. Schellens, J.H. Beijnen, Variability in bioavailability of small molecular tyrosine kinase inhibitors, Cancer treatment reviews, 412-422, 41 (2015).
25.D. Diao, J. Zhai, J. Yang, H. Wu, J. Jiang, X. Dong, A. Passaro, B. Aramini, S. Rao, K. Cai, Delivery of gefitinib with an immunostimulatory nanocarrier improves therapeutic efficacy in lung cancer, Translational Lung Cancer Research, 926, 10 (2021).
26.X. Zhou, K. Shi, Y. Hao, C. Yang, R. Zha, C. Yi, Z. Qian, Advances in nanotechnology-based delivery systems for EGFR tyrosine kinases inhibitors in cancer therapy, Asian journal of pharmaceutical sciences, 26-41, 15 (2020).
27.J.E.N. Dolatabadi, Y. Omidi, Solid lipid-based nanocarriers as efficient targeted drug and gene delivery systems, TrAC Trends in Analytical Chemistry, 100-108, 77 (2016).
28.A. Akbari, F. Rahimi, Z.A. Radmoghaddama, S. Honarmand, T. Godarya, M.G. Toudeshkchouei, S. Akbari, β-Cyclodextrins-based nano carriers for cancer therapy, NanoScience Technology, 1-11, 1 (2021).
29.Z. Jafaria, S. Honarmanda, F. Rahimia, A. Akbaria, S. Akbari, Mesoporous Silica Nanoparticles as Versatile carrier platforms in therapeutic applications, NanoScience Technology, 40-61, 1 (2021).
30.S.-Y. Chuang, C.-H. Lin, T.-H. Huang, J.-Y. Fang, Lipid-based nanoparticles as a potential delivery approach in the treatment of rheumatoid arthritis, Nanomaterials, 42, 8 (2018).
31.E. Russo, A. Spallarossa, B. Tasso, C. Villa, C. Brullo, Nanotechnology of Tyrosine Kinase Inhibitors in Cancer Therapy: A Perspective, International Journal of Molecular Sciences, 6538, 22 (2021).
32.S. Samimi, N. Maghsoudnia, R.B. Eftekhari, F. Dorkoosh, Lipid-based nanoparticles for drug delivery systems, Characterization and biology of nanomaterials for drug delivery, 47-76, (2019).
33.J. Majumder, T. Minko, Multifunctional Lipid-Based Nanoparticles for Codelivery of Anticancer Drugs and siRNA for Treatment of Non-Small Cell Lung Cancer with Different Level of Resistance and EGFR Mutations, Pharmaceutics, 1063, 13 (2021).
34.P. Subramanian, Lipid-Based Nanocarrier System for the Effective Delivery of Nutraceuticals, Molecules, 5510, 26 (2021).
35.Y. Namiki, T. Fuchigami, N. Tada, R. Kawamura, S. Matsunuma, Y. Kitamoto, M. Nakagawa, Nanomedicine for cancer: lipid-based nanostructures for drug delivery and monitoring, Accounts of chemical research, 1080-1093, 44 (2011).
36.T.T.H. Thi, E.J. Suys, J.S. Lee, D.H. Nguyen, K.D. Park, N.P. Truong, Lipid-based nanoparticles in the

clinic and clinical trials: from cancer nanomedicine to COVID-19 vaccines, Vaccines, 359, 9 (2021).
37. J. Buse, A. El-Aneed, Properties, engineering and applications of lipid-based nanoparticle drug-delivery systems: current research and advances, Nanomedicine, 1237-1260, 5 (2010).
38. B. Foroughi-Nia, J. Barar, M.Y. Memar, A. Aghanejad, S. Davaran, Progresses in polymeric nanoparticles for delivery of tyrosine kinase inhibitors, Life Sciences, 119642, 278 (2021).
39. N. Satari, S. Taymouri, J. Varshosaz, M. Rostami, M. Mirian, Preparation and evaluation of inhalable dry powder containing glucosamine-conjugated gefitinib SLNs for lung cancer therapy, Drug Development and Industrial Pharmacy, 1265-1277, 46 (2020).
40. P. Ghasemiyeh, S. Mohammadi-Samani, Solid lipid nanoparticles and nanostructured lipid carriers as novel drug delivery systems: applications, advantages and disadvantages, Research in pharmaceutical sciences, 288, 13 (2018).
41. Q. Li, T. Cai, Y. Huang, X. Xia, S.P. Cole, Y. Cai, A review of the structure, preparation, and application of NLCs, PNPs, and PLNs, Nanomaterials, 122, 7 (2017).
42. P. Jaiswal, B. Gidwani, A. Vyas, Nanostructured lipid carriers and their current application in targeted drug delivery, Artificial cells, nanomedicine, and biotechnology, 27-40, 44 (2016).
43. B. Escudier, T. Eisen, W.M. Stadler, C. Szczylik, S. Oudard, M. Siebels, S. Negrier, C. Chevreau, E. Solska, A.A. Desai, Sorafenib in advanced clear-cell renal-cell carcinoma, New England Journal of Medicine, 125-134, 356 (2007).
44. D. Jäger, J. Ma, J. Mardiak, D. Ye, E. Korbenfeld, M. Zemanova, H. Ahn, J. Guo, N. Leonhartsberger, K. Stauch, Sorafenib treatment of advanced renal cell carcinoma patients in daily practice: the large international PREDICT study, Clinical genitourinary cancer, 156-164. e151, 13 (2015).
45. J.M. Llovet, S. Ricci, V. Mazzaferro, P. Hilgard, E. Gane, J.-F. Blanc, A.C. De Oliveira, A. Santoro, J.-L. Raoul, A. Forner, Sorafenib in advanced hepatocellular carcinoma, New England journal of medicine, 378-390, 359 (2008).
46. T. Li, Y. Zhang, Y.-P. Meng, L.-S. Bo, W.-B. Ke, MiR-542-3p appended sorafenib/all-trans retinoic acid (ATRA)-loaded lipid nanoparticles to enhance the anticancer efficacy in gastric cancers, Pharmaceutical research, 2710-2719, 34 (2017).
47. R. Poojari, S. Kini, R. Srivastava, D. Panda, Intracellular interactions of electrostatically mediated layer-by-layer assembled polyelectrolytes based sorafenib nanoparticles in oral cancer cells, Colloids and Surfaces B: Biointerfaces, 131-138, 143 (2016).
48. Z. Zhang, B. Niu, J. Chen, X. He, X. Bao, J. Zhu, H. Yu, Y. Li, The use of lipid-coated nanodiamond to improve bioavailability and efficacy of sorafenib in resisting metastasis of gastric cancer, Biomaterials, 4565-4572, 35 (2014).
49. B. Vincenzi, D. Santini, A. Russo, R. Addeo, F. Giuliani, L. Montella, S. Rizzo, O. Venditti, A.M. Frezza, M. Caraglia, Early skin toxicity as a predictive factor for tumor control in hepatocellular carcinoma patients treated with sorafenib, The oncologist, 85-92, 15 (2010).
50. G.M. Keating, A. Santoro, Sorafenib, Drugs, 223-240, 69 (2009).
51. W. Duan, Y. Liu, Targeted and synergistic therapy for hepatocellular carcinoma: monosaccharide modified lipid nanoparticles for the co-delivery of doxorubicin and sorafenib, Drug design, development and therapy, 2149, 12 (2018).
52. Y. Yang, S.-X. Yuan, L.-H. Zhao, C. Wang, J.-S. Ni, Z.-G. Wang, C. Lin, M.-C. Wu, W.-P. Zhou, Ligand-directed stearic acid grafted chitosan micelles to increase therapeutic efficacy in hepatic cancer, Molecular pharmaceutics, 644-652, 12 (2015).
53. E.F. Craparo, C. Sardo, R. Serio, M.G. Zizzo, M.L. Bondì, G. Giammona, G. Cavallaro, Galactosylated polymeric carriers for liver targeting of sorafenib, International journal of pharmaceutics, 172-180, 466 (2014).
54. L. Fiume, G. Di Stefano, Lactosaminated human albumin, a hepatotropic carrier of drugs, European journal of pharmaceutical sciences, 253-262, 40 (2010).
55. H. Gao, S. Cao, Z. Yang, S. Zhang, Q. Zhang, X. Jiang, Preparation, characterization and anti-glioma effects of docetaxel-incorporated albumin-lipid nanoparticles, J Biomed Nanotechnol, 2137-2147, 11 (2015).
56. L. Dayani, M. Dehghani, M. Aghaei, S. Taymouri, A. Taheri, Preparation and evaluation of targeted albumin lipid nanoparticles with lactobionic acid for targeted drug delivery of sorafenib in hepatocellular carcinoma, Journal of Drug Delivery Science and Technology, 103142, 69 (2022).
57. S. Yang, B. Zhang, X. Gong, T. Wang, Y. Liu, N. Zhang, In vivo biodistribution, biocompatibility, and efficacy of sorafenib-loaded lipid-based nanosuspensions evaluated experimentally in cancer, International journal of nanomedicine, 2329, 11 (2016).
58. F. Danhier, B. Ucakar, M.-L. Vanderhaegen, M.E. Brewster, T. Arien, V. Préat, Nanosuspension for the delivery of a poorly soluble anti-cancer kinase

inhibitor, European Journal of Pharmaceutics and Biopharmaceutics, 252-260, 88 (2014).
59. L. Wang, Z. Liu, D. Liu, C. Liu, Z. Juan, N. Zhang, Docetaxel-loaded-lipid-based-nanosuspensions (DTX-LNS): preparation, pharmacokinetics, tissue distribution and antitumor activity, International journal of pharmaceutics, 194-201, 413 (2011).
60. J. Zhang, J. Hu, H.F. Chan, M. Skibba, G. Liang, M. Chen, iRGD decorated lipid-polymer hybrid nanoparticles for targeted co-delivery of doxorubicin and sorafenib to enhance anti-hepatocellular carcinoma efficacy, Nanomedicine: Nanotechnology, Biology and Medicine, 1303-1311, 12 (2016).
61. B. Sierra-Martin, A. Fernandez-Barbero, Inorganic/polymer hybrid nanoparticles for sensing applications, Advances in Colloid and Interface Science, 25-37, 233 (2016).
62. Y. Zhong, J. Zhang, R. Cheng, C. Deng, F. Meng, F. Xie, Z. Zhong, Reversibly crosslinked hyaluronic acid nanoparticles for active targeting and intelligent delivery of doxorubicin to drug resistant CD44+ human breast tumor xenografts, Journal of controlled release, 144-154, 205 (2015).
63. O. Mezghrani, Y. Tang, X. Ke, Y. Chen, D. Hu, J. Tu, L. Zhao, N. Bourkaib, Hepatocellular carcinoma dually-targeted nanoparticles for reduction triggered intracellular delivery of doxorubicin, International Journal of Pharmaceutics, 553-568, 478 (2015).
64. V.B. Lokeshwar, S. Mirza, A. Jordan, Targeting hyaluronic acid family for cancer chemoprevention and therapy, Advances in cancer research, 35-65, 123 (2014).
65. K. Ghaffarzadehgan, M. Jafarzadeh, H.R. Raziee, H.R. Sima, E. Esmaili-Shandiz, H. Hosseinnezhad, A. Taghizadeh-Kermani, O. Moaven, M. Bahrani, Expression of cell adhesion molecule CD44 in gastric adenocarcinoma and its prognostic importance, World journal of gastroenterology: WJG, 6376, 14 (2008).
66. M.L. Bondì, C. Botto, E. Amore, M.R. Emma, G. Augello, E.F. Craparo, M. Cervello, Lipid nanocarriers containing sorafenib inhibit colonies formation in human hepatocarcinoma cells, International journal of pharmaceutics, 75-85, 493 (2015).
67. H. Wang, H. Wang, W. Yang, M. Yu, S. Sun, B. Xie, Improved oral bioavailability and liver targeting of sorafenib solid lipid nanoparticles in rats, AAPS PharmSciTech, 761-768, 19 (2018).
68. R. Müller, S. Runge, V. Ravelli, A.F. Thünemann, W. Mehnert, E. Souto, Cyclosporine-loaded solid lipid nanoparticles (SLN®): Drug–lipid physicochemical interactions and characterization of drug incorporation, European journal of pharmaceutics and biopharmaceutics, 535-544, 68 (2008).
69. L. Hu, X. Tang, F. Cui, Solid lipid nanoparticles (SLNs) to improve oral bioavailability of poorly soluble drugs, Journal of Pharmacy and Pharmacology, 1527-1535, 56 (2004).
70. F. Yang, A. Li, H. Liu, H. Zhang, Gastric cancer combination therapy: synthesis of a hyaluronic acid and cisplatin containing lipid prodrug coloaded with sorafenib in a nanoparticulate system to exhibit enhanced anticancer efficacy and reduced toxicity, Drug design, development and therapy, 3321, 12 (2018).
71. D. Fu, C. Li, Y. Huang, Lipid–Polymer Hybrid Nanoparticle-Based Combination Treatment with Cisplatin and EGFR/HER2 Receptor-Targeting Afatinib to Enhance the Treatment of Nasopharyngeal Carcinoma, OncoTargets and therapy, 2449, 14 (2021).
72. M.R. Molaahmadi, J. Varshosaz, S. Taymouri, V. Akbari, Lipid Nanocapsules for Imatinib Delivery: Design, Optimization and Evaluation of Anticancer Activity Against Melanoma Cell Line, Iranian Journal of Pharmaceutical Research: IJPR, 1676, 18 (2019).
73. S. Safwat, R.M. Hathout, R.A. Ishak, N.D. Mortada, Augmented simvastatin cytotoxicity using optimized lipid nanocapsules: a potential for breast cancer treatment, Journal of Liposome Research, 1-10, 27 (2017).
74. B. Saliou, O. Thomas, N. Lautram, A. Clavreul, J. Hureaux, T. Urban, J.-P. Benoit, F. Lagarce, Development and in vitro evaluation of a novel lipid nanocapsule formulation of etoposide, European Journal of Pharmaceutical Sciences, 172-180, 50 (2013).
75. J. Varshosaz, V. Hajhashemi, S. Soltanzadeh, Lipid nanocapsule-based gels for enhancement of transdermal delivery of ketorolac tromethamine, Journal of drug delivery, 2011 (2011).
76. O. Thomas, F. Lagarce, Lipid nanocapsules: a nanocarrier suitable for scale-up process, Journal of Drug Delivery Science and Technology, 555-559, 23 (2013).
77. P. Sanchez-Moreno, P. Buzon, H. Boulaiz, J. Peula-García, J. Ortega-Vinuesa, I. Luque, A. Salvati, J. Marchal, Balancing the effect of corona on therapeutic efficacy and macrophage uptake of lipid nanocapsules, Biomaterials, 266-278, 61 (2015).
78. M.M. Ahmed, F. Fatima, M.K. Anwer, M.F. Aldawsari, Y.S.M. Alsaidan, S.A. Alfaiz, A. Haque, A. Alanazi, K. Alhazzani, Development and characterization of Brigatinib loaded solid lipid nanoparticles: In-vitro cytotoxicity against human

carcinoma A549 lung cell lines, Chemistry and Physics of Lipids, 105003, 233 (2020).
79. B. Mandal, N.K. Mittal, P. Balabathula, L.A. Thoma, G.C. Wood, Development and in vitro evaluation of core–shell type lipid–polymer hybrid nanoparticles for the delivery of erlotinib in non-small cell lung cancer, European journal of pharmaceutical sciences, 162-171, 81 (2016).
80. Y. Yang, Z. Huang, J. Li, Z. Mo, Y. Huang, C. Ma, W. Wang, X. Pan, C. Wu, PLGA porous microspheres dry powders for codelivery of afatinib-loaded solid lipid nanoparticles and paclitaxel: novel therapy for EGFR tyrosine kinase inhibitors resistant nonsmall cell lung cancer, Advanced Healthcare Materials, 1900965, 8 (2019).
81. P. Zhao, M. Li, Y. Wang, Y. Chen, C. He, X. Zhang, T. Yang, Y. Lu, J. You, R.J. Lee, Enhancing anti-tumor efficiency in hepatocellular carcinoma through the autophagy inhibition by miR-375/sorafenib in lipid-coated calcium carbonate nanoparticles, Acta biomaterialia, 248-255, 72 (2018).
82. J. Varshosaz, S. Jandaghian, M. Mirian, S.E. Sajjadi, Co-delivery of rituximab targeted curcumin and imatinib nanostructured lipid carriers in non-Hodgkin lymphoma cells, Journal of liposome research, 64-78, 31 (2021).
83. F. Yugui, H. Wang, D. Sun, X. Zhang, Nasopharyngeal cancer combination chemoradiation therapy based on folic acid modified, gefitinib and yttrium 90 co-loaded, core-shell structured lipid-polymer hybrid nanoparticles, Biomedicine & Pharmacotherapy, 108820, 114 (2019).
84. J.Y. Choi, T. Ramasamy, S.Y. Kim, J. Kim, S.K. Ku, Y.S. Youn, J.-R. Kim, J.-H. Jeong, H.-G. Choi, C.S. Yong, PEGylated lipid bilayer-supported mesoporous silica nanoparticle composite for synergistic co-delivery of axitinib and celastrol in multi-targeted cancer therapy, Acta biomaterialia, 94-105, 39 (2016).
85. Z. Bakhtiary, J. Barar, A. Aghanejad, A.A. Saei, E. Nemati, J. Ezzati Nazhad Dolatabadi, Y. Omidi, Microparticles containing erlotinib-loaded solid lipid nanoparticles for treatment of non-small cell lung cancer, Drug development and industrial pharmacy, 1244-1253, 43 (2017).
86. S. Schöttler, G. Becker, S. Winzen, T. Steinbach, K. Mohr, K. Landfester, V. Mailänder, F.R. Wurm, Protein adsorption is required for stealth effect of poly (ethylene glycol)-and poly (phosphoester)-coated nanocarriers, Nature nanotechnology, 372-377, 11 (2016).
87. J.V. Jokerst, T. Lobovkina, R.N. Zare, S.S. Gambhir, Nanoparticle PEGylation for imaging and therapy, Nanomedicine, 715-728, 6 (2011).
88. A. Zinger, G. Baudo, T. Naoi, F. Giordano, S. Lenna, M. Massaro, A. Ewing, H.R. Kim, E. Tasciotti, J.T. Yustein, Reproducible and Characterized Method for Ponatinib Encapsulation into Biomimetic Lipid Nanoparticles as a Platform for Multi-Tyrosine Kinase-Targeted Therapy, ACS Applied Bio Materials, 6737-6745, 3 (2020).
89. S. Satapathy, C.S. Patro, Solid Lipid Nanoparticles for Efficient Oral Delivery of Tyrosine Kinase Inhibitors: A Nano Targeted Cancer Drug Delivery, Advanced Pharmaceutical Bulletin, (2021).
90. R. Awasthi, A. Roseblade, P.M. Hansbro, M.J. Rathbone, K. Dua, M. Bebawy, Nanoparticles in cancer treatment: opportunities and obstacles, Current drug targets, 1696-1709, 19 (2018).
91. J.-S. Baek, Y.-G. Na, C.-W. Cho, Sustained cytotoxicity of wogonin on breast cancer cells by encapsulation in solid lipid nanoparticles, Nanomaterials, 159, 8 (2018).
92. A.A. Attama, C.E. Umeyor, The use of solid lipid nanoparticles for sustained drug release, Therapeutic delivery, 669-684, 6 (2015).
93. M.I. Alam, S. Baboota, A. Ahuja, M. Ali, J. Ali, J.K. Sahni, Intranasal administration of nanostructured lipid carriers containing CNS acting drug: pharmacodynamic studies and estimation in blood and brain, Journal of psychiatric research, 1133-1138, 46 (2012).
94. K. ČERPNJAK, A. Zvonar, M. Gašperlin, F. Vrečer, Lipid-based systems as promising approach for enhancing the bioavailability of poorly water-soluble drugs, Acta pharmaceutica, 427-445, 63 (2013).
95. H. Zhang, F.-M. Zhang, S.-J. Yan, Preparation, in vitro release, and pharmacokinetics in rabbits of lyophilized injection of sorafenib solid lipid nanoparticles, International journal of nanomedicine, 2901, 7 (2012).
96. A. Grillone, E.R. Riva, A. Mondini, C. Forte, L. Calucci, C. Innocenti, C. de Julian Fernandez, V. Cappello, M. Gemmi, S. Moscato, Active targeting of sorafenib: preparation, characterization, and in vitro testing of drug-loaded magnetic solid lipid nanoparticles, Advanced healthcare materials, 1681-1690, 4 (2015).
97. S. Benizri, L. Ferey, B. Alies, N. Mebarek, G. Vacher, A. Appavoo, C. Staedel, K. Gaudin, P. Barthélémy, Nucleoside-lipid-based nanocarriers for sorafenib delivery, Nanoscale research letters, 1-8, 13 (2018).
98. H.-J. Klümpen, C.F. Samer, R.H. Mathijssen, J.H. Schellens, H. Gurney, Moving towards dose

individualization of tyrosine kinase inhibitors, Cancer treatment reviews, 251-260, 37 (2011).
99. C. Ban, M. Jo, S. Lim, Y.J. Choi, Control of the gastrointestinal digestion of solid lipid nanoparticles using PEGylated emulsifiers, Food chemistry, 442-452, 239 (2018).
100. H. Yuan, C.-Y. Chen, G.-h. Chai, Y.-Z. Du, F.-Q. Hu, Improved transport and absorption through gastrointestinal tract by PEGylated solid lipid nanoparticles, Molecular pharmaceutics, 1865-1873, 10 (2013).
101. R. Rampaka, K. Ommi, N. Chella, Role of solid lipid nanoparticles as drug delivery vehicles on the pharmacokinetic variability of Erlotinib HCl, Journal of Drug Delivery Science and Technology, 102886, 66 (2021).
102. B. Gupta, B.K. Poudel, S. Pathak, J.W. Tak, H.H. Lee, J.-H. Jeong, H.-G. Choi, C.S. Yong, J.O. Kim, Effects of formulation variables on the particle size and drug encapsulation of imatinib-loaded solid lipid nanoparticles, Aaps Pharmscitech, 652-662, 17 (2016).
103. B. Subramaniam, Z.H. Siddik, N.H. Nagoor, Optimization of nanostructured lipid carriers: Understanding the types, designs, and parameters in the process of formulations, Journal of Nanoparticle Research, 1-29, 22 (2020).
104. H.A. Makeen, S. Mohan, M.A. Al-Kasim, I.M. Attafi, R.A. Ahmed, N.K. Syed, M.H. Sultan, M. Al-Bratty, H.A. Alhazmi, M.M. Safhi, Gefitinib loaded nanostructured lipid carriers: characterization, evaluation and anti-human colon cancer activity in vitro, Drug delivery, 622-631, 27 (2020).