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Effective nano Cyclodextrin-TKIs drug delivery for cancer therapy

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Abstract

Nanotechnology-based studies pursuing the innovative cancer treatment methods, particularly using drug delivery systems, have significantly increased over the past few years. Some of the impacts of using such systems include the increased cytotoxic activity of drugs, reduced unwanted side effects, and a more stable and controlled release of drugs. Particularly using the targeted delivery systems with helping novel nanocarriers made it possible to kill cancer cells specifically. Meanwhile, Cyclodextrins were known as natural cyclic oligosaccharides which serve the intended purposes. Many cancer researchers were interested in them due to the multiple advantages of a variety of materials utilized as nanocarriers for medication delivery. Regarding their unique structure, they can benefit hydrophobic and hydrophilic drugs. On the other hand, tyrosine kinase inhibitors, with their properties to inhibit the growth of cancer cells, are the valuable drugs of choice for various types of cancer. In this regard, cyclodextrins were used as nano-drug delivery systems to transport tyrosine kinase inhibitors in recent studies by researchers. In this review, some recent medical applications of cyclodextrin-based nanocarriers for the delivery of tyrosine kinase inhibitors and the synthesis methods of cyclodextrin-based compounds have been discussed, and the advantages and disadvantages of using cyclodextrin along with tyrosine kinase inhibitors in the treatment of various cancers were mentioned.

Keywords: *Cyclodextrin, Nanocarrier, Cancer therapy, Drug delivery, Tyrosine kinase inhibitors, Targeted therapy*

Table of Contents

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1. Introduction

Tyrosine kinase (TK) is an enzyme which participates in protein phosphorylation and triggers a signal transduction pathway in normal cells leading to cell proliferation, differentiation, and angiogenesis. The inhibition of tyrosine kinase can block signaling pathways which lead to apoptosis and inhibition of angiogenesis, which in turn prevent cancer cell growth and proliferation [1-3]. Tyrosine kinase inhibitors (TKIs) were used in the clinical treatment of many cancers for approximately two decades [4-7]. Recent research on many anti-cancer drugs was shown that TKIs are the primary target group in cancer treatment [2].

On the other hand, new approaches have recently emerged to reduce the side effects of conventional chemotherapy, known as delivery systems, in which anti-cancer drugs or genes are supplied via the carriers. Using nanoparticles (NPs), drug delivery technology has made it possible to target tumor cells for small molecules, killing only malignant cells [8]. Up to now, various kinds of nanocarriers were examined and the most popular of them are mesoporous silica nanoparticles (MSNs), cyclodextrin-based nanocarriers (CD), lipid-based nanocarriers, and micelles [9-11]. Increased solubility, longer systemic circulation, and tumor targeting are all key benefits of using nanocarriers loaded with tyrosine kinase inhibitors. Consequently, they have resulted in a significant increase in the therapeutic efficacy of medications for cancer therapy [12], and finally, many novel nanocarriers were considered potential drug delivery systems. Targeted delivery systems deliver medications and/or genes to their intended target and prevent them from being removed or destroyed [13,14]. Targeted nanoparticles have a greater impact on drug cytotoxic activity and cell death in diverse malignancies than non-targeted nanoparticles [15,16].Two well-known targeting strategies i.e. passive and active targeting mechanisms of nanoparticles result in increased drug accumulation and decreased drug outflow from cancer cells alongside playing a crucial role in increased drug concentration in cancer cells [17-19]. Moreover, most studies have compared drug release between targeted and non-targeted nanoparticles. They showed that targeted and non-targeted nanoparticles lead to a more sustained release and controlled release of drugs with higher efficiency than pure drugs [20,21]. In this process, cyclodextrin molecules which are cyclic oligomers linked by an α-1 and 4-glycoside bond and have a hydrophilic outer surface and a hydrophobic inner cavity showed valuable results. Their unique structure has led to the ability to carry lipophilic molecules, increased solubility in water, and improved stability of guest molecules [22-24]. Some other advantages of CDs include high drug loading, low production costs, reducing the toxicity of drug system, and improving the bioavailability of anticancer drugs [25-28].

Consequently, this study aims to explore the most advanced cancer-related therapies based on using tyrosine kinase inhibitors in combination with CDs, as well as the roles that cyclodextrins may play in developing more successful formulae in this scope. The mechanism of action of tyrosine kinase inhibitors was originally defined in this work to better understand the benefits and drawbacks of targeting this class of medications. Then, the synthesis of CDs and their application in biomedicine were investigated. Finally, the advantages of different nanocarriers of cyclodextrin with TKs were presented to show the effectiveness of using CDs combined with TKIs for cancer therapy.

2. Tyrosine kinase inhibitors: mechanisms of action

TKIs are targeted agents whose application in chemotherapy shows favorable selectivity, efficiency, and safety in terms of hampering specific molecular targets involved in the growth or progression of the tumor, tyrosine kinases [29]. Since 2001, when the first

TKI- Imatinib- was approved by FDA, about 67 small-molecule tyrosine kinase inhibitors were approved so far (http://www.brimr.org/PKI/PKIs.htm). To understand the importance of targeting tyrosine kinases in malignancies treatment, a brief description of their role in the cell is provided below.

TKs are enzymes with a crucial role to regulate a plethora of biological processes, such as cell cycle, cell differentiation, transcription, translation, and immune response. Approximately 90 members from this family were recognized, of which 58 are receptors, and others are non-receptors. RTKs are cell surface transmembrane proteins that dimerize upon binding to their N-terminal extracellular domains. They then activate the catalytic site of their intracellular C-terminal domain. RTKs themselves are classified into several families, containing epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), insulin receptor (IR), and platelet-derived growth factor receptors (PDGFR). The other class of tyrosine kinases, non-receptor tyrosine kinases (NRTKs), include intracellular cytoplasmic proteins and bound proteins to the cell membrane, which activate downstream intracellular signals from extracellular receptors. ABL proteins, Iron-sulfur (FeS) proteins, Tyrosine-protein kinase Tec, Spleen tyrosine kinase (SYK), Focal-adhesion kinase (FAK), JAK, ACK, SRC, and CSK family of kinases are proteins belonging to the NRTKs class. In general, the enzymatic function of tyrosine kinases comprises selective phosphorylation of a particular tyrosine residue in a specific protein substrate via breaking γ phosphate group of ATP through which extracellular signals can be conveyed to the cytoplasm and nucleus [29-31]. Under the normal physiologic condition, there is a balance between the level of TKs activity, cell growth, and apoptosis. However, oncogenic activation of these enzymes, especially RTKs, can cause tumor growth and progression of malignancy in solid tumors, such as non-small cell lung cancer (NSCLC), and cancers of breast, colorectal, and prostate. Gain-of-function mutations, overexpression, gene amplification, chromosomal rearrangement, kinase domain duplication, and autocrine activation are the most common activating mutations in RTKs [31].In addition to these mutations, there are other responsible mechanisms to activate TKs, including the excess of ligand expression, defect in inactivation mechanisms, and transactivation through receptor dimerization [32].

Structurally, TKs typically share a similar 3D structure in their kinase domain, particularly in their highly conserved active site. This domain is a bilobate structure consisting of a β-sheet-rich N-terminal lobe, an α-helix-rich C-terminal lobe, and a connecting hinge loop. ATP binding pocket is located between these two lobes. In the vicinity of ATP binding site, there is a flexible activation loop with a triple conserved motif Asp-Phe-Gly (DFG) responsible to regulate access to the pocket [33]. To inhibit TKs, many TKIs interfere with ATP binding via interaction with this site or its surrounding. TKIs are divided into two primary groups, reversible and irreversible, depending on how the inhibitor molecule interacts to the enzyme. The later forms of TKIs form covalent bonds with a nucleophilic target (a sulfhydryl group of a cysteine residue) next to the ATP pocket. Reaching selective targeting is a problematic issue and it is very liable to toxicity through persistent off-target modifications. To avoid such problems, tremendous efforts were made to develop a new class of reversible covalent inhibitors. Reversible TKIs bind differently based on the confirmation of the binding pocket and DFG motif near the kinase active site. They are categorized into five major types (Types I-V). Types I, II, and III inhibitors directly target the active site of TKs in different forms of the enzyme. Type I inhibitors exclusively block the ATP pocket in competition with ATP via binding with the Asp residue of the DFG motif in the active form of kinases. TKIs of type II bind to the inactive form of enzyme with Asp, but reverse the orientation of DFG motif. Through this orientation change, the inhibitor molecule gains access to an allosteric pocket adjacent to the ATP-binding site and docks a hydrophobic substituent. The third type of TKIs stabilizes the inactive conformation of the enzyme via exclusive binding to an allosteric pocket near the ATP-biding site but without any overlap or interaction with the ATP cleft. Type IV inhibitors are merely allosteric ones that, despite former types, target all sites of kinase except the active site. These TKIs, regardless of structural similarity of the kinase catalytic domain, allosterically bind to a region far from the ATP-binding pocket. Some reversible TKIs display a combination of these inhibitory modes. To discriminate between these inhibitors and others, they are fallen into a distinct category (type V). Type V TKIs are bivalent inhibitors that can simultaneously bind to a different region of the enzyme via covalent attachment [35,36]. Many TKIs exhibit a favorable

selectivity profile but do not show a high affinity for TKs, which can be seen in inhibitors type I-III. It can be explained by the fact that many of the allosteric sites used by these inhibitors so be covered via the protein-protein interaction that small molecules of inhibitors have hardly access to them [36]. Using bivalent inhibitors can overcome this issue, as while one moiety maintains the selectivity, the other moiety amplifies affinity toward the allosteric site. Moreover, there is an excellent potential for developing optimized inhibitors. Type V inhibitors, based on their target site, are divided into two subcategories: type Va and Vb. Type Va includes bisubstrate inhibitors in which one moiety binds to the ATP-binding site, and the other moiety attaches to the substrate-binding domain. TKIs belonging to Type Vb are generic bivalent inhibitors binding to any targetable region of kinases [35].

3. Synthesis and characterization of CDs

Cyclodextrins glycosyltransferase are initially produced from starch or starch derivatives [37]. In general, CDs are classified into two essential groups: biological and synthesized. α, β, and γ CDs are three natural species having six, seven, and eight glucopyranose units in their cyclic structures which are connected by α(1,4)-linkages [38,39]. The internal cavity diameter of CDs depends on the number of glucopyranose units. So, when the height of the truncated cone of α, β, and γ-CD is 7.8 Å, their internal cavity diameters are 5.7, 7.8, and 9.5 Å, respectively.

The basic structure of natural CDs includes two types of hydroxyls named primary and secondary. These hydroxyls are both located on the exterior surface of the CD, but the first one is on the narrow side of the ring molecule, and the second one is on the wider side. However, the cavity of CDs contains water molecules; it is a kind of apolar, and their water solubility changes to 145, 18.5, and 232 g/L for α, β, and γ-CD, respectively [40,41]. Figure 1 shows the schematic structures of native CDs.

By modifying CDs characteristics via chemical reactions, different reagents can be used to obtain specific properties. For instance, selectively functionalizing one hydroxyl at position 6 in CD's structure with tosyl group creates a new structure with unique properties of the synthesized CDs. Moreover, amination, esterification, or etherification, can provide various modified compounds based on CD with maintaining its basic macrocyclic framework. The most popular derivatives belong to hydroxypropyl-, sulfobutylether-, and carboxymethyl-type of β –CDs [42-44].

There are some methods used to form CD complexes, such as co-precipitation, spray drying, freeze-drying, kneading, slurry complexation, paste complexation, damp mixing, heating method (sealed-heating), extrusion method, dry mixing, microwave treatment, and supercritical carbon dioxide [45]. When drug complexes with CDs are constructed, no covalent bonds are formed or broken during the formation

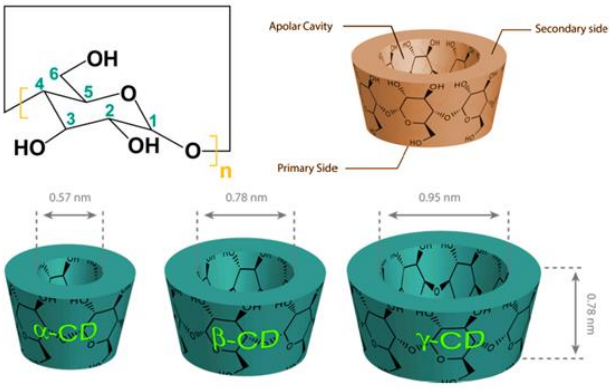

Figure 1. Different structures of native CDs [34].

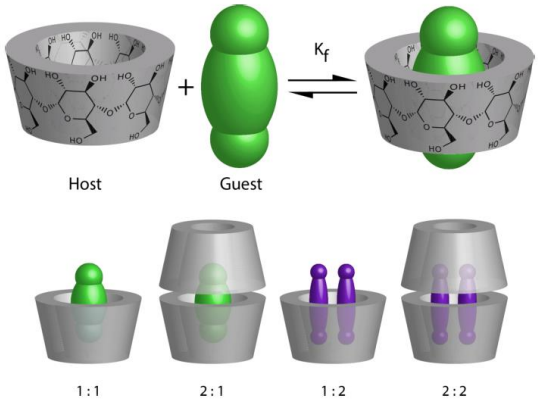

Figure 2. Inclusion of guest molecules in CDs with different ratios [34].

process. Free molecules in the solution are in fast equilibrium with the drug entities. Moreover, because of the hydrophobicity of the cavity structure of CDs, hydrophobic or lipophilic drugs have a higher affinity to building complexes with CDs [23].

The weakness of bonding between CDs and drugs inclusion entraps the drug temporarily in the cavity of CDs, resulting in enhanced solubility and bioavailability [46]. The whole structure or part of the apolar molecules can reversibly entrap into the hydrophobic cavity of CDs and make inclusion complexes. The chemical reactions between CDs and lipophilic compounds follow an equilibrium reaction as follows:

Free CD + free guest ↔ CD/guest (1)

In the mentioned equation, there is a stability constant, or affinity constant (M^{-1}) as K_f [41]. Besides, different ratios of guest molecules can be complexed with CDs, as described in figure 2.

Methods to detect the complex's details include spectroscopic methods, such as UV/VIS spectroscopy, fluorescence spectroscopy, circular dichroism spectroscopy, and nuclear magnetic resonance (NMR) spectroscopy. Some other techniques like pH potentiometric titration, microcalorimetry, and surface tension are not so standard, but these tools were used in the literature [23].

3.1 Cyclodextrin-based nanosponges synthesis

To enhance the bioavailability, solubility, and stability of active pharmaceutical ingredients, abundant modifications were applied with some crosslinkers. Mainly a bunch of bifunctional crosslinkers leads to forming networks of nanopores that are named CD nanosponges. Although they were used to deliver camptothecin, resveratrol, erlotinib, tamoxifen, and some other compounds, there are some issues related to the interaction between crosslinked CD nanosponges and the biological membrane. So, an alternative and improved type of CD, amphiphilic CD (AMCD), have shown up. The key structural differences between AMCD and the nature CD are the hydrophobic alkyl chains which are replaced with hydroxyl (-OH) groups in the CD structure. Some of their influences on the application of CDs are reported such as improving the interaction between CDs and biological membranes and increasing water solubility. Besides, they created various nanostructures like nanospheres, nanoparticles, and nanocapsules. One of the most essential efficiencies of AMCD is its usage as a nanocarrier without any leakage. As mentioned in the literature, one big problem of nanocarriers is leakage in the AMCD nanocarriers. Stable self-assembled AMCD nanostructures eradicate this problem. Figure 3 illustrates the synthesis of AMCD based on βCD. This path includes dry DFM, adding trimethylamine and lauroyl chloride, temperatures 30˚C, and 24h under a nitrogen environment [47].

Some basic strategies for synthesizing other modified CDs for different goals include deprotonation,

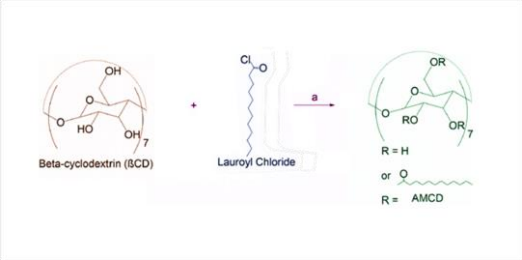

Figure 3. The schematic synthesis process of AMCD [47].

dehydration, and condensation. In these methods, the modification of hydroxyl groups plays a significant role. For the deprotonation, the acidic hydroxyl group will be reacted with a powerful base that results from an anion. This product will construct a polymer structure using SN2-polymerization method or the most popular cross-linker, epichlorohydrin. The dehydration method will be accomplished by building a reaction through polyethers or polyesters between CDs and diol or diacid in sulphuric acid solution. To produce CD-based inclusion, some bi-functional linkers like diisocyanate can react with CDs directly in the condensation method. In fact, the kind of inclusion structures depends on the linkers [48].

3.2 Synthesis of CD-conjugated polymers

There are some typical methods for polymerization, such as ring-opening polymerization (ROP), atom transfer radical polymerization (ATRP), and reversible addition-fragmentation transfer (RAFT) polymerization. The synthesis of polymers with CDs as essential compounds requires finding a suitable method which leads to desired compositions, topologies, and favorite functional applications. By helping different polymerization methods or click chemistry, various CD-based derivatives with grafted polymer chains and CD cores can be produced. Hence, there are two different techniques named grafting-from and grafting-to approaches. In the first method, some 21-arm polymer complexes will be synthesized using ROP of cyclic esters like ε-caprolactone (CL) and D, L-lactide, with β-CD as a macroinitiator.

Further modifications can occur with the functionalization of the end OH group in each chain by RAFT or ATRP to generate new blocks. Some other compounds, such as alkyne end-capped polymers and azide-modified CDs, will be synthesized in the grafting-to approach. CD-cored star polymers are generated when these compounds are linked to CDs using a click reaction. Other complexes called CD-cored Janus-like were derived using a combination of grafting-from and grafting-to approaches. One of the different forms of CD-based polymer structures is supramolecular. In fact, the host-guest interaction between CDs and the guest molecules allows to construct threaded linear polymers. The most typical guest molecules are included phenyl groups, adamantine (AD), azobenzene (AZO), ferrocene (Fc), lithocholic acid (LA), and cholesterol [43]. As an example of the supramolecular, polyrotaxanes (PRs) are built using multiple CDs threaded on the polymer chains, and the end of them are capped by bulky molecules [49]. As 23 α-CD rings can be threaded with PEG chains, poly(ethylene glycol) (PEG) is introduced here as an appropriate compound for threading α-CDs. However, for the larger β-CDs, poly(propylene glycol) (PPG) is used as a suitable threading option.

Moreover, different hydroxyls of the threaded CDs can be modified to obtain targeted CD-based complexes [43].CD-capped polymers are produced when CDs are introduced at the ends of polymers (one or multiple endings).They place in two groups CD-terminated polymers and CD-pendent polymers, as shown in figure 4.

The most effective factor for forming CD-terminate polymers is CD-based macroinitiators. Furthermore, they can be synthesized when linear polymers are conjugated in the reactive sites at the end with CDs. As for the CD-pendent polymers, they can be obtained when CD-based monomers form polymers directly or post-functionalize CDs on the side chains of polymers [49].

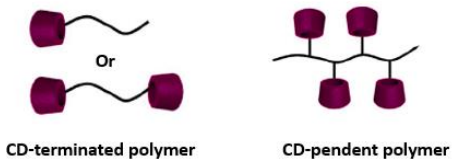

Figure 4. Two common forms of CD-capped polymers [49].

4. Application of CDs in biomedicine

Using CDs in biomedicine and pharmaceutical concepts has an extended history. As mentioned above, CDs are composed of a hydrophobic cavity and a hydrophilic exterior surface. Because of these unique structures, CDs belong to cage molecules, and they can encapsulate different compounds in their cavities via host-guest interactions. So, CDs and their derivatives were used in practical applications in various fields, such as foods, cosmetics, chromatography, biotechnology, nanotechnology, the textiles industry, pharmacy, and medicine, especially in drug delivery, cancer therapy, gene delivery, and biosensing. As host molecules, delivery systems, and complexing factors in drug production, they have been approved in the literature for use in biomedicine [45,46].

However, there are 56 pharmaceutical products with a CD basis, but they are still novel substitutes in pharmaceutical compounds, drug delivery systems, and anti-aggregation agents [50]. CDs are frequently-used compounds in drug delivery research to design carriers in medical scopes. They improve many active molecules' aqueous solubility and chemical stability against hydrolysis, dehydration, oxidation, and photodegradation. When drugs are entrapped in the CD structures, the construct inclusion complex enhances the stability of the drug, and prevents unwanted interactions between drugs and vehicles. Therefore, the native structure of drug will remain unchanged. It is the inclusion of complex formation between CDs and drugs which is fundamental. Depending on the shape and size of guest molecules, there are different types of complexes based on CDs. The strength of interactions between CD structure and drugs are the most decisive factors that determine the potential and stability of the complexes [51,52].

Around the world, CD-based complexes were widely used as drug formulations. Different administration methods are used for these drugs, including the oral, nasal, sublingual, dermal, parental, and ocular routes. During the treatment procedure, the primary objective is to deliver drugs to a specific point or site in the tissue. So, scientists proposed using a CDs-based drug delivery system that needs to be combined with a nanotechnology basis and targeting purposes for cancer therapy. Specifically for the complexes of CD molecules, there are compounds in the forms of nanoparticles, polymer hydrogels, and liposomes which are extensively reviewed in the literature [53].

In recent years, CDs were distinguished as advantageously functional materials in nanoparticle-based drug delivery systems in biomedicine and bioengineering [46]. NPs were used in key forms, such as drug delivery systems, drug structure substituents, and imaging and therapeutic applications in biomedicine. They can be made from soft and hard materials. It means they can be made of some compounds like polymers, lipids, and also, metals. The key reasons to use NPs can be listed below:

The similarity in the size of NPs and biological substituents,

Containing a metallic core that can be manipulated for imaging,

Large surface area,

Ability to functionalize with various ligands for targeting delivery [54].

Another important function of CDs as NPs is to target the NPs to tumor tissues and enhance drug loading capacity, in addition to increasing solubility, stability, and bioavailability. Many CDs were complexed with polymeric NPs for targeting drug delivery in anti-cancer purposes and siRNA delivery systems. Reported results illustrated lipid-based NPs, such as liposomes, SLNs, and NLCs improved drug loading with better targeting for cancer therapeutics.

According to the US Food and Drug Administration (USFDA), a few parent CDs (γ-CD in intravenous injection, β-CD in oral and topical delivery) and CD-based derivatives (HP-γ-CD for topical application, SBE-β-CD for injection, HP-β-CD for oral delivery and injection) were approved. Progress in drug delivery systems using NPs and CDs, make it necessary to do more scientific works on CDs-based complexes [49]

5. CDs and delivery of TKIs

Various studies surveyed the effect of CD on permeability, solubility, cytotoxicity, bioavailability, side effects, and, in general, the anti-cancer activity of tyrosine kinase inhibitors. Hence, the most popular TKIs carried by CDs for cancer therapy purposes were described.

Erlotinib is a tyrosine kinase inhibitor approved by the Food and Drug Administration for NSCLC and metastatic pancreatic cancer. It inhibits cellular signaling in competition with adenosine triphosphate (ATP) for EGFR, leading to the anti-cancer effects of this drug [55-57]. It was shown that it causes several side effects, including skin rash, diarrhea, and intestinal disorders, as well as Stevens-Johnson syndrome [58]. ERL-RAMEB complex was able to improve dissolution rate, cytotoxicity in the A549 cell line, and permeability in Caco-2 cells in the Erdoar et al. research on erlotinib.The decrease shown in cell viability in A549 cells in the ERL-RAMEB complex-treated group is thought to be in terms of the synergistic effect of cholesterol-lowering ability and high affinity for RAMEB membrane cholesterol, which reduces IC_{50}. Increased intestinal permeability and improved solubility showed a similar effect to the new formulation of erlotinib at a lower dose [59]. A study by Vaidya et al., on erlotinib, found that the new combination of the drug with cyclodextrin improved its anti-cancer activity against NSCLC by promoting apoptosis as well as inhibiting autophagy. To study the mechanism of improving the efficacy of erlotinib-loaded nanoformulations, cell cycle analysis was performed by measuring DNA content with propidium iodide (PI) staining with helping flow cytometry. The achieved results illustrated that treatment of A549 cancer cells with nano-erlotinib leads to induction of apoptosis, which stems from increased DNA fragmentation. Nano-erlotinib showed 2-fold induction of apoptosis compared to free erlotinib solution, while 4-fold induction of apoptosis was observed compared to uncontrolled A549 cells. The encapsulation of erlotinib in PLGA nanoparticles significantly enhanced its cytotoxicity, as evidenced by the smaller IC_{50} in resistant cell lines after 72 h of incubation. Western blot was performed to confirm further the mechanism of improving the anti-cancer activity of the nanoformulation against NSCLC cells. The results showed that nano-erlotinib induced apoptosis by increasing the expression of apoptotic proteins, i.e., PARP and caspase. It was also observed that nanocapsule erlotinib significantly inhibited autophagy in NSCLC-resistant cancer cells because the expression of autophagy protein markers, microtubule-associated protein 1-light chain 3 (LC3B), and p62 increased after the nanoparticle treatment [60]. In another study, Devasari et al. showed that ERL-SBE-β-CD[2] had improved bioavailability compared to pure drugs. In vitro dissolution and in vivo studies on ERL-SBE-β-CD confirmed a 3.6-fold increase in oral bioavailability of erlotinib. This complex showed a 3.2-fold increase in Cmax with a 5.4-fold decrease in T_{max} (0.5 ± 0.2 vs. 2.7 ± 0.8 h) compared to pure erlotinib [61]. In the study of Varan et al., after 48 hours, nanoparticles significantly reduced the IC_{50} value of erlotinib in cell lines. It means that anti-cancer efficacy can be achieved by using less erlotinib. Amphiphilic cyclodextrin nanoparticles were evaluated in cell culture for their lower cholesterol level. It is thought that the root cause higher anti-cancer activity showed by nanoparticles in A549 cells may be related to the cellular cholesterol content. Amphiphilic CD derivatives made synergistic effects on cancer cells in terms of their cholesterol affinities, and this was higher in A549 cells with higher cholesterol levels [62]. In the study of Dora et al., it was seen that the CD-based nano-sponge formula increased the solubility, dissolution efficiency, and consequently, the oral bioavailability of erlotinib. This formulation showed higher cytotoxicity against pancreatic adenocarcinoma cell lines. Therefore, it may be concluded that this combination may result in dosage decrease and adverse consequences connected to the dose. The relative bioavailability was about double that of pure erlotinib. In vitro cytotoxicity was also assessed by treating pancreatic MIA PaCa-2 and PANC-1 cells for 24, 48, and 72 hours and measuring cell viability with MTT. It was found that the new compound is more cytotoxic against cells MIA PaCa-2 and PANC-1 than free erlotinib [63].

Ibrutinib is a new irreversible inhibitor of Bruton's tyrosine kinase (BTK) and has shown significant efficacy against several B cell malignancies. It can covalently bind to Cys-81 and thus inhibit kinase activity [64-66]. Like many oral medications, IBR is mainly absorbed through the small intestine. Poor solubility leads to very low oral bioavailability (3.9% in the fasting state) and requires high doses. Consequently, increasing drug toxicity and side effects can be obtained [67-70]. Zhao et al. conducted a study on Ibrutinib by showing that the drug's release in vitro was stable and pH-independent in the gastrointestinal tract. This study indicated that the potential

[2] Erlotinib sulfobutyl ether beta-cyclodextrin complex

nanoformulation maintains drug activity and demonstrates sustained-release properties [71]. In the study by Surendar et al., the pharmacokinetic parameters of ibrutinib after oral administration in Wister rats were evaluated. The Cmax of the nano-sponge formula increased 4-fold compared to the pure drug, and the AUC0-t of the nano-sponge formula increased 5-fold compared to the pure drug. The concentration of the drug in the blood indicated better systemic absorption of ibrutinib in the β-CD nano-sponge formulation. In brief, this study showed that CD nano-sponges could be used to improve the physicochemical properties, oral bioavailability, and therapeutic efficacy of ibrutinib, the anticancer drug [72].

Sorafenib is known as an oral multikinase inhibitor that targets Raf kinases, vascular endothelial growth factor (VEGFR) -2/-3, platelet-derived growth factor receptor-β (PGFRβ), and Fms-like-3 tyrosine kinase (Flt-3) and c-Kit [73,74]. The drug was approved by USFDA in 2006 to treat patients with advanced renal cell carcinoma and liver cell carcinoma. Sorafenib also exhibits antitumor activity in various tumors, including renal, hepatic, breast, thyroid, and colorectal cancers [75]. In Giglio et al.'s study on sorafenib, CD-sorafenib complexes were found to be able to inhibit cell proliferation and stimulate apoptosis in the cell lines. In general, this study showed that cyclodextrin polymers could be a new formulation strategy for the delivery of sorafenib to increase its bioavailability and reduce its systemic toxicity [76].

Regorafenib is a multikinase inhibitor as well, that targets a wide range of kinases involved in angiogenesis and oncogenesis, such as VEGFR-2, PDGFR-β, and mitogen-activated protein kinases (MAPKs). It also has significant benefits in preventing the progression of colorectal cancers [77,78]. In a study by Bai et al., on regorafenib, γ-CD was modified with mannose to impart colon cancer targeting capacity. RG-M-γ-CD CNPs[3] reduced inflammation and prevented the activation of tumor-associated macrophages (TAMs) by targeting macrophages. It is a targeted, safe, and effective anti-tumor nanodrug that suppresses tumor cell proliferation, lesion neovascularization, and tumor microenvironment (TME) regeneration. Plasma concentration profiles showed that CNP nanomedicines (RG-γ-CD and RG-M-γ-CD) had 2.38-3.45-fold more AUC0-24 compared to regorafenib, confirming long-term circulation and lower elimination. Decreased contact of RG-M-γ-CD with the liver and kidney was also observed, which may reduce the systemic toxicity of kinase inhibitors in these tissues. The antitumor activity of RG-M-γ-CD was demonstrated in vitro against colorectal cancer cells. Within 4 hours, the compound had similar lethal effects. After 12 hours of treatment, CNP formulation (RG-γ-CD and RG-M-γ-CD) induced a significant rate of cell death relative to free regorafenib. Considering the fact that colorectal cancer cells express mannose receptors, mannose γ-CD modification can be an effective targeting strategy [79]. To evaluate the targeting potential, rhodamine (Rho) was used as an indicator and formulated with CNP. Cell internalization of Rho-M-γ-CD and Rho-γ-CD CNPs using confocal laser scanning microscopy (CLSM) and fluorescence-activated cell sorting (FACS) showed that both CNPs could be absorbed by colorectal cancer cells CT26 and HT29 within 2 hours. When the cells were pretreated with free mannose, the fluorescence accumulation induced by internal Rho-M-γ-CD was significantly reduced, confirming that colorectal cancer targeting was derived from specific binding between mannose groups [80].

Nintedanib is a kinase inhibitor approved by the FDA for treating idiopathic pulmonary fibrosis (IPF) [81]. It inhibits platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), vascular endothelial growth factor receptor (VEGFR), and Fms-like-3 tyrosine kinase (FLT3) [82,83]. In the study done by Vaidya et al., on Nintedanib, it was found that when the nintedanib-CD complex was incubated with SIF[4] and PBS[5], nintedanib remained stable in both fluids longer than the plain drug. It indicated increased nintedanib stability in the intestinal environment and improved intestinal permeability and consequently, higher bioavailability of the new compound [84].

6. Conclusion

The enzyme tyrosine kinase activates a signal transduction pathway which leads to cell growth, differentiation, and angiogenesis. Targeting and

[3] Channel-type nanoparticles
[4] Simulated intestinal fluid
[5] Phosphate buffered saline

controlling tyrosine kinase seems to be a promising strategy for treating cancer. Over the past two decades, tyrosine kinase inhibitors were studied for the clinical treatment of many cancers. The increasing incidence of cancer and the problems associated with current cancer treatment methods, such as high drug toxicity and unwanted side effects, have prompted researchers to focus on cancer treatment methods with fewer disadvantages and more effectiveness. Advances in nanotechnology-based drug delivery systems resulted in the successful therapeutic delivery of numerous drug molecules. There has been recently unprecedented growth in nanotechnology studies and applications in targeted drug delivery. Among them, Cyclodextrins are appropriate for drug delivery in terms of their beneficial properties, such as biocompatibility, stability, permeability, solubility, and improved bioavailability. Among the studies conducted by a number of researchers, the effects of using cyclodextrin along with erlotinib are more pronounced than those of other tyrosine kinase inhibitors. Erlotinib is a tyrosine kinase inhibitor that is used to treat various cancers, including NSCLC. Increased dissolution rate, cytotoxicity, intestinal permeability, bioavailability, and reduction of dose-dependent side effects are among the benefits of this association. Other studies have shown that using cyclodextrin leads to a more stable release and higher bioavailability. It reduces the systemic toxicity of other tyrosine kinase inhibitors in treating various cancers. In combination with cyclodextrin, Tyrosine kinase inhibitors could lead to future breakthrough therapies in biomedicine and cancer. However, there is a lack of clinical studies on cancer patients in researchers' research.

7. References

1. 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, 298-308, 12 (2021).
2. R. Roskoski, Jr., Properties of FDA-approved small molecule protein kinase inhibitors: A 2021 update, Pharmacol Res, 105463, 165 (2021).
3. N. Makrilia, T. Lappa, V. Xyla, I. Nikolaidis, K. Syrigos, The role of angiogenesis in solid tumours: an overview, European journal of internal medicine, 663-671, 20 (2009).
4. N. Sinlikhitkul, P. Toochinda, L. Lawtrakul, P. Kuropakornpong, A. Itharat, Encapsulation of plumbagin using cyclodextrins to enhance plumbagin stability: computational simulation, preparation, characterization, and application, Journal of Inclusion Phenomena and Macrocyclic Chemistry, 229-243, 93 (2019).
5. K.S. Bhullar, N.O. Lagarón, E.M. McGowan, I. Parmar, A. Jha, B.P. Hubbard, H.P.V. Rupasinghe, Kinase-targeted cancer therapies: progress, challenges and future directions, Molecular Cancer, 48, 17 (2018).
6. A. Arora, E.M. Scholar, Role of tyrosine kinase inhibitors in cancer therapy, J Pharmacol Exp Ther, 971-979, 315 (2005).
7. S. Sigismund, D. Avanzato, L. Lanzetti, Emerging functions of the EGFR in cancer, Mol Oncol, 3-20, 12 (2018).
8. Y.-H. Cheng, C. He, J.E. Riviere, N.A. Monteiro-Riviere, Z. Lin, Meta-Analysis of Nanoparticle Delivery to Tumors Using a Physiologically Based Pharmacokinetic Modeling and Simulation Approach, ACS Nano, 3075-3095, 14 (2020).
9. Z. Jafaria, S. Honarmanda, F. Rahimia, A. Akbaria, S. Akbari, Mesoporous Silica Nanoparticles as Versatile carrier platforms in therapeutic applications, Nano Science Technology, 40-62, 1 (2021).
10. A. Akbari, F. Rahimi, Z. Radmoghaddam, S. Honarmand, T. Godary, M. Ghasemi Toudeshkchouei, S. Akbari, β-Cyclodextrins-based nano carriers for cancer therapy, Journal of Nanoscience and Nanotechnology, 1-11, 01 (2021).
11. Z. Abbasi Radmoghaddam, S. Honarmand, M. Dastjerdi, S. Akbari, A. Akbari, Lipid-based nanoformulations for TKIs delivery in cancer therapy, NanoScience Technology, 11-27, 3 (2022).
12. 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).
13. S. Muro, Challenges in design and characterization of ligand-targeted drug delivery systems, Journal of Controlled Release, 125-137, 164 (2012).
14. W. Gu, C. Wu, J. Chen, Y. Xiao, Nanotechnology in the targeted drug delivery for bone diseases and bone regeneration, Int J Nanomedicine, 2305, 8 (2013).
15. H. Kulhari, D. Pooja, S. Shrivastava, V. Naidu, R. Sistla, Peptide conjugated polymeric nanoparticles as a carrier for targeted delivery of docetaxel, Colloids and Surfaces B: Biointerfaces, 166-173, 117 (2014).

16. M.S. Suh, J. Shen, L.T. Kuhn, D.J. Burgess, Layer-by-layer nanoparticle platform for cancer active targeting, International Journal of Pharmaceutics, 58-66, 517 (2017).
17. Y. Zhuang, H. Deng, Y. Su, L. He, R. Wang, G. Tong, D. He, X. Zhu, Aptamer-Functionalized and Backbone Redox-Responsive Hyperbranched Polymer for Targeted Drug Delivery in Cancer Therapy, Biomacromolecules, 2050-2062, 17 (2016).
18. X. Qi, Y. Fan, H. He, Z. Wu, Hyaluronic acid-grafted polyamidoamine dendrimers enable long circulation and active tumor targeting simultaneously, Carbohydr Polym, 231-239, 126 (2015).
19. B. Yang, X. Ni, L. Chen, H. Zhang, P. Ren, Y. Feng, Y. Chen, S. Fu, J. Wu, Honokiol-loaded polymeric nanoparticles: an active targeting drug delivery system for the treatment of nasopharyngeal carcinoma, Drug Deliv, 660-669, 24 (2017).
20. S. Jiang, X. Wang, Z. Zhang, L. Sun, Y. Pu, H. Yao, J. Li, Y. Liu, Y. Zhang, W. Zhang, CD20 monoclonal antibody targeted nanoscale drug delivery system for doxorubicin chemotherapy: an in vitro study of cell lysis of CD20-positive Raji cells, Int J Nanomedicine, 5505-5518, 11 (2016).
21. A. Jain, P. Kesharwani, N.K. Garg, A. Jain, S.A. Jain, A.K. Jain, P. Nirbhavane, R. Ghanghoria, R.K. Tyagi, O.P. Katare, Galactose engineered solid lipid nanoparticles for targeted delivery of doxorubicin, Colloids Surf B Biointerfaces, 47-58, 134 (2015).
22. X. Guan, Y. Chen, X. Wu, P. Li, Y. Liu, Enzyme-responsive sulfatocyclodextrin/prodrug supramolecular assembly for controlled release of anti-cancer drug chlorambucil, Chemical Communications, 953-956, 55 (2019).
23. P. Jansook, N. Ogawa, T. Loftsson, Cyclodextrins: structure, physicochemical properties and pharmaceutical applications, Int J Pharm, 272-284, 535 (2018).
24. S. Göktürk, E. Çalışkan, R.Y. Talman, U. Var, A Study on Solubilization of Poorly Soluble Drugs by Cyclodextrins and Micelles: Complexation and Binding Characteristics of Sulfamethoxazole and Trimethoprim, The Scientific World Journal, 718791, 2012 (2012).
25. N. Qiu, X. Li, J. Liu, Application of cyclodextrins in cancer treatment, Journal of Inclusion Phenomena and Macrocyclic Chemistry, 229-246, 89 (2017).
26. T. Higashi, Cyclodextrin-Based Molecular Accessories for Drug Discovery and Drug Delivery, Chem Pharm Bull (Tokyo), 289-298, 67 (2019).
27. M. Chen, R.L. Pérez, P. Du, N. Bhattarai, K.C. McDonough, S. Ravula, R. Kumar, J.M. Mathis, I.M. Warner, Tumor-Targeting NIRF NanoGUMBOS with Cyclodextrin-Enhanced Chemo/Photothermal Antitumor Activities, ACS Applied Materials & Interfaces, 27548-27557, 11 (2019).
28. P. Bakshi, V. Londhe, Widespread applications of host-guest interactive cyclodextrin functionalized polymer nanocomposites: Its meta-analysis and review, Carbohydrate Polymers, 116430, 242 (2020).
29. A. Arora, E.M. Scholar, Role of tyrosine kinase inhibitors in cancer therapy, Journal of Pharmacology and Experimental Therapeutics, 971-979, 315 (2005).
30. A. Azevedo, S. Silva, J. Rueff, Non-receptor Tyrosine Kinases Role and Significance in Hematological Malignancies, Tyrosine Kinases as Druggable Targets in Cancer, IntechOpen2019.
31. Z. Du, C.M. Lovly, Mechanisms of receptor tyrosine kinase activation in cancer, Molecular cancer, 1-13, 17 (2018).
32. G. Vlahovic, J. Crawford, Activation of tyrosine kinases in cancer, The oncologist, 531-538, 8 (2003).
33. M. Tong, M.A. Seeliger, Targeting conformational plasticity of protein kinases, ACS chemical biology, 190-200, 10 (2015).
34. G. Crini, Review: a history of cyclodextrins, Chem Rev, 10940-10975, 114 (2014).
35. 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).
36. M.R. Arkin, A. Whitty, The road less traveled: modulating signal transduction enzymes by inhibiting their protein–protein interactions, Current opinion in chemical biology, 284-290, 13 (2009).
37. J.M. López-Nicolás, P. Rodríguez-Bonilla, F. García-Carmona, Cyclodextrins and antioxidants, Critical reviews in food science and nutrition, 251-276, 54 (2014).
38. S.R. Gandhi, J.S.S. Quintans, G.R. Gandhi, A.A.S. Araújo, L.J. Quintans Júnior, The use of cyclodextrin inclusion complexes to improve anticancer drug profiles: a systematic review, Expert Opin Drug Deliv, 1069-1080, 17 (2020).
39. B. Tian, Y. Liu, J. Liu, Smart stimuli-responsive drug delivery systems based on cyclodextrin: A review, Carbohydr Polym, 116871, 251 (2021).
40. Z. Liu, L. Ye, J. Xi, J. Wang, Z.-g. Feng, Cyclodextrin polymers: Structure, synthesis, and use as drug carriers, Progress in Polymer Science, 101408, 118 (2021).
41. D. Duchêne, A. Bochot, Thirty years with cyclodextrins, Int J Pharm, 58-72, 514 (2016).

42. J.Y. Liu, X. Zhang, B.R. Tian, Selective modifications at the different positions of cyclodextrins: a review of strategies, Turk J Chem, 261-278, 44 (2020).
43. X. Yao, J. Mu, L. Zeng, J. Lin, Z. Nie, X. Jiang, P. Huang, Stimuli-responsive cyclodextrin-based nanoplatforms for cancer treatment and theranostics, Materials Horizons, 846-870, 6 (2019).
44. W. Tang, C. Zou, C. Da, Y. Cao, H. Peng, A review on the recent development of cyclodextrin-based materials used in oilfield applications, Carbohydr Polym, 116321, 240 (2020).
45. G. Crini, S. Fourmentin, É. Fenyvesi, G. Torri, M. Fourmentin, N. Morin-Crini, Fundamentals and applications of cyclodextrins, Cyclodextrin fundamentals, reactivity and analysis, Springer2018, pp. 1-55.
46. H. Shelley, R.J. Babu, Role of Cyclodextrins in Nanoparticle-Based Drug Delivery Systems, J Pharm Sci, 1741-1753, 107 (2018).
47. M.R. Patel, D.A. Lamprou, P.R. Vavia, Synthesis, characterization, and drug delivery application of self-assembling amphiphilic cyclodextrin, AAPS PharmSciTech, 1-16, 21 (2020).
48. Á. Haimhoffer, Á. Rusznyák, K. Réti-Nagy, G. Vasvári, J. Váradi, M. Vecsernyés, I. Bácskay, P. Fehér, Z. Ujhelyi, F. Fenyvesi, Cyclodextrins in Drug Delivery Systems and Their Effects on Biological Barriers, Scientia Pharmaceutica, 33, 87 (2019).
49. X. Yao, P. Huang, Z. Nie, Cyclodextrin-based polymer materials: from controlled synthesis to applications, Progress in Polymer Science, 1-35, 93 (2019).
50. G. Crini, S. Fourmentin, É. Fenyvesi, G. Torri, M. Fourmentin, N. Morin-Crini, Cyclodextrins, from molecules to applications, Environmental chemistry letters, 1361-1375, 16 (2018).
51. P. Dhiman, M. Bhatia, Pharmaceutical applications of cyclodextrins and their derivatives, Journal of Inclusion Phenomena and Macrocyclic Chemistry, 171-186, 98 (2020).
52. M. Řezanka, Synthesis of substituted cyclodextrins, Environmental Chemistry Letters, 49-63, 17 (2019).
53. A. Abdolmaleki, F. Ghasemi, J.B. Ghasemi, Computer-aided drug design to explore cyclodextrin therapeutics and biomedical applications, Chem Biol Drug Des, 257-268, 89 (2017).
54. R. Mejia-Ariza, L. Graña-Suárez, W. Verboom, J. Huskens, Cyclodextrin-based supramolecular nanoparticles for biomedical applications, Journal of Materials Chemistry B, 36-52, 5 (2017).
55. J. Gupta, H.A. Safdari, M. Hoque, Nanoparticle mediated cancer immunotherapy, Semin Cancer Biol, 307-324, 69 (2021).
56. S.T. Kim, J. Lee, J.H. Kim, Y.W. Won, J.M. Sun, J. Yun, Y.H. Park, J.S. Ahn, K. Park, M.J. Ahn, Comparison of gefitinib versus erlotinib in patients with nonsmall cell lung cancer who failed previous chemotherapy, Cancer, 3025-3033, 116 (2010).
57. V.D. Cataldo, D.L. Gibbons, R. Pérez-Soler, A. Quintás-Cardama, Treatment of non-small-cell lung cancer with erlotinib or gefitinib, N Engl J Med, 947-955, 364 (2011).
58. 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 : official journal of the European Federation for Pharmaceutical Sciences, 162-171, 81 (2015).
59. N. Erdoğar, S. Akkın, G. Varan, E. Bilensoy, Erlotinib complexation with randomly methylated β-cyclodextrin improves drug solubility, intestinal permeability, and therapeutic efficacy in non-small cell lung cancer, Pharm Dev Technol, 797-806, 26 (2021).
60. B. Vaidya, V. Parvathaneni, N.S. Kulkarni, S.K. Shukla, J.K. Damon, A. Sarode, D. Kanabar, J.V. Garcia, S. Mitragotri, A. Muth, Cyclodextrin modified erlotinib loaded PLGA nanoparticles for improved therapeutic efficacy against non-small cell lung cancer, International journal of biological macromolecules, 338-347, 122 (2019).
61. N. Devasari, C.P. Dora, C. Singh, S.R. Paidi, V. Kumar, M.E. Sobhia, S. Suresh, Inclusion complex of erlotinib with sulfobutyl ether-β-cyclodextrin: Preparation, characterization, in silico, in vitro and in vivo evaluation, Carbohydr Polym, 547-556, 134 (2015).
62. G. Varan, S. Akkın, N. Demirtürk, J.M. Benito, E. Bilensoy, Erlotinib entrapped in cholesterol-depleting cyclodextrin nanoparticles shows improved antitumoral efficacy in 3D spheroid tumors of the lung and the liver, J Drug Target, 439-453, 29 (2021).
63. C.P. Dora, F. Trotta, V. Kushwah, N. Devasari, C. Singh, S. Suresh, S. Jain, Potential of erlotinib cyclodextrin nanosponge complex to enhance solubility, dissolution rate, in vitro cytotoxicity and oral bioavailability, Carbohydr Polym, 339-349, 137 (2016).
64. A. Novero, P.M. Ravella, Y. Chen, G. Dous, D. Liu, Ibrutinib for B cell malignancies, Exp Hematol Oncol, 4, 3 (2014).
65. A. Aalipour, R.H. Advani, Bruton's tyrosine kinase inhibitors and their clinical potential in the treatment of B-cell malignancies: focus on ibrutinib, Ther Adv Hematol, 121-133, 5 (2014).

66. E.B. Haura, U. Rix, Deploying ibrutinib to lung cancer: another step in the quest towards drug repurposing, J Natl Cancer Inst, 106 (2014).
67. E. Marostica, J. Sukbuntherng, D. Loury, J. de Jong, X.W. de Trixhe, A. Vermeulen, G. De Nicolao, S. O'Brien, J.C. Byrd, R. Advani, J. McGreivy, I. Poggesi, Population pharmacokinetic model of ibrutinib, a Bruton tyrosine kinase inhibitor, in patients with B cell malignancies, Cancer Chemother Pharmacol, 111-121, 75 (2015).
68. E. Scheers, L. Leclercq, J. de Jong, N. Bode, M. Bockx, A. Laenen, F. Cuyckens, D. Skee, J. Murphy, J. Sukbuntherng, G. Mannens, Absorption, metabolism, and excretion of oral ^{14}C radiolabeled ibrutinib: an open-label, phase I, single-dose study in healthy men, Drug Metab Dispos, 289-297, 43 (2015).
69. R. de Vries, J.W. Smit, P. Hellemans, J. Jiao, J. Murphy, D. Skee, J. Snoeys, J. Sukbuntherng, M. Vliegen, L. de Zwart, E. Mannaert, J. de Jong, Stable isotope-labelled intravenous microdose for absolute bioavailability and effect of grapefruit juice on ibrutinib in healthy adults, Br J Clin Pharmacol, 235-245, 81 (2016).
70. C.S. Lee, M.A. Rattu, S.S. Kim, A review of a novel, Bruton's tyrosine kinase inhibitor, ibrutinib, J Oncol Pharm Pract, 92-104, 22 (2016).
71. L. Zhao, B. Tang, P. Tang, Q. Sun, Z. Suo, M. Zhang, N. Gan, H. Yang, H. Li, Chitosan/Sulfobutylether-β-Cyclodextrin Nanoparticles for Ibrutinib Delivery: A Potential Nanoformulation of Novel Kinase Inhibitor, Journal of Pharmaceutical Sciences, 1136-1144, 109 (2020).
72. G. SURENDAR, B. RAMESH, Formulation & In Vivo Evaluation Of Ibrutinib Loaded Cyclodextrin Nanosponges, NVEO-NATURAL VOLATILES & ESSENTIAL OILS Journal| NVEO, 1434-1447, (2022).
73. S.M. Wilhelm, C. Carter, L. Tang, D. Wilkie, A. McNabola, H. Rong, C. Chen, X. Zhang, P. Vincent, M. McHugh, Y. Cao, J. Shujath, S. Gawlak, D. Eveleigh, B. Rowley, L. Liu, L. Adnane, M. Lynch, D. Auclair, I. Taylor, R. Gedrich, A. Voznesensky, B. Riedl, L.E. Post, G. Bollag, P.A. Trail, BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis, Cancer Res, 7099-7109, 64 (2004).
74. O. Brunetti, A. Gnoni, A. Licchetta, V. Longo, A. Calabrese, A. Argentiero, S. Delcuratolo, A.G. Solimando, A. Casadei-Gardini, N. Silvestris, Predictive and prognostic factors in HCC patients treated with sorafenib, Medicina, 707, 55 (2019).
75. O. Huillard, E. Boissier, B. Blanchet, A. Thomas-Schoemann, A. Cessot, P. Boudou-Rouquette, J.P. Durand, R. Coriat, J. Giroux, J. Alexandre, M. Vidal, F. Goldwasser, Drug safety evaluation of sorafenib for treatment of solid tumors: consequences for the risk assessment and management of cancer patients, Expert Opin Drug Saf, 663-673, 13 (2014).
76. V. Giglio, M. Viale, V. Bertone, I. Maric, R. Vaccarone, G. Vecchio, Cyclodextrin polymers as nanocarriers for sorafenib, Invest New Drugs, 370-379, 36 (2018).
77. G.D. Demetri, P. Reichardt, Y.K. Kang, J.Y. Blay, P. Rutkowski, H. Gelderblom, P. Hohenberger, M. Leahy, M. von Mehren, H. Joensuu, G. Badalamenti, M. Blackstein, A. Le Cesne, P. Schöffski, R.G. Maki, S. Bauer, B.B. Nguyen, J. Xu, T. Nishida, J. Chung, C. Kappeler, I. Kuss, D. Laurent, P.G. Casali, Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial, Lancet, 295-302, 381 (2013).
78. T. Waddell, D. Cunningham, Evaluation of regorafenib in colorectal cancer and GIST, Lancet, 273-275, 381 (2013).
79. M. Xiong, Q. Lei, X. You, T. Gao, X. Song, Y. Xia, T. Ye, L. Zhang, N. Wang, L. Yu, Mannosylated liposomes improve therapeutic effects of paclitaxel in colon cancer models, J Microencapsul, 513-521, 34 (2017).
80. H. Bai, J. Wang, C.U. Phan, Q. Chen, X. Hu, G. Shao, J. Zhou, L. Lai, G. Tang, Cyclodextrin-based host-guest complexes loaded with regorafenib for colorectal cancer treatment, Nature communications, 1-18, 12 (2021).
81. M.E. Mazzei, L. Richeldi, H.R. Collard, Nintedanib in the treatment of idiopathic pulmonary fibrosis, Ther Adv Respir Dis, 121-129, 9 (2015).
82. B. Vaidya, R. Patel, A. Muth, V. Gupta, Exploitation of Novel Molecular Targets to Treat Idiopathic Pulmonary Fibrosis: A Drug Discovery Perspective, Curr Med Chem, 2439-2458, 24 (2017).
83. G.J. Roth, R. Binder, F. Colbatzky, C. Dallinger, R. Schlenker-Herceg, F. Hilberg, S.L. Wollin, R. Kaiser, Nintedanib: from discovery to the clinic, J Med Chem, 1053-1063, 58 (2015).
84. B. Vaidya, S.K. Shukla, S. Kolluru, M. Huen, N. Mulla, N. Mehra, D. Kanabar, S. Palakurthi, S. Ayehunie, A. Muth, V. Gupta, Nintedanib-cyclodextrin complex to improve bio-activity and intestinal permeability, Carbohydr Polym, 68-77, 204 (2019).