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pH-Responsive Drug Delivery Systems For Cancer Treatment

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Abstract

pH-responsive Polymer-Based Systems like polymeric micelles, hydrogels, and lipid-based technologies can assist in cancer treatment where drugs are undergoing release only at certain regions within a tumor implant hence augmenting their delivery efficiency. pH-Responsive polymers and lipids can change their structures in response to the pH gradient of solid tumors; this permits stepwise medication delivery within the acidic TME. This review aims to discuss the different categories of pH-sensitive drug delivery systems based on the comparison of its working principle, the recent development of the concept, and the applications. Liposomes and pH-sensitive lipid nanoparticles such as Lipid-Based Systems employ triggered membrane disruption at pH to release the drugs. Quantum dots and mesoporous silica nanoparticles are examples of inorganic nanoparticles through encapsulation. These systems can enhance medication stability, pharmacokinetics, and therapeutic outcomes while reducing deleterious effects that could result from targeting.

Keywords: pH-responsive Polymers, Cancer Therapy, Polymeric Micelles, Hydrogels, Lipid-Based Systems, Drug Delivery Systems, Tumor Micro Environment (Tme), pH-Sensitive Liposomes, Inorganic Nanoparticles, Quantum Dots Mesoporous Silica Nanoparticles.

Authors:

Maida Noor: (Corresponding author)
Graduate, Department of Pharmacy, Quaid-i-Azam University, Islamabad, Pakistan.
ORCID: https://orcid.org/0009-0006-4785-5497
(Email: assetocorsa123@gmail.com)
Muhammad Saad Ali: Graduate, Department of Pharmacy, Quaid-i-Azam University, Islamabad, Pakistan.
Hafiza Arooba Shakeel: Graduate, Department of Pharmacy, Quaid-i-Azam University, Islamabad, Pakistan.

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Title

pH-Responsive Drug Delivery Systems for Cancer Treatment

Abstract

pH-responsive Polymer-Based Systems like polymeric micelles, hydrogels, and lipid-based technologies can assist in cancer treatment where drugs are undergoing release only at certain regions within a tumor implant hence augmenting their delivery efficiency. pH-Responsive polymers and lipids can change their structures in response to the pH gradient of solid tumors; this permits stepwise medication delivery within the acidic TME. This review aims to discuss the different categories of pH-sensitive drug delivery systems based on the comparison of its working principle, the recent development of the concept, and the applications. Liposomes and pH-sensitive lipid nanoparticles such as Lipid-Based Systems employ triggered membrane disruption at pH to release the drugs. Quantum dots and mesoporous silica nanoparticles are examples of inorganic nanoparticles through encapsulation. These systems can enhance medication stability, pharmacokinetics, and therapeutic outcomes while reducing deleterious effects that could result from targeting.

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Authors:

Maida Noor: (Corresponding author)
Graduate, Department of Pharmacy, Quaid-i-Azam University, Islamabad, Pakistan.
ORCID: https://orcid.org/0009-0006-4785-5497
(Email: assetocorsa123@gmail.com)

Muhammad Saad Ali: Graduate, Department of Pharmacy, Quaid-i-Azam University, Islamabad, Pakistan.

Hafiza Arooba Shakeel: Graduate, Department of Pharmacy, Quaid-i-Azam University, Islamabad, Pakistan.

Introduction

Polymer-Based Systems in pH-Responsive Drug Delivery

Smart polymer-based drug delivery systems have been well established as potentially targeted approaches to the delivery of therapeutics in the treatment of cancer. The polymers are not only compatible with the biological environment but also biodegradable, and they may be changed in response to alterations in the pH of the tumor.

Mechanisms of pH-Responsive Polymer-Based Systems

Polymer based drug delivery system can pH sensitive polymers which alter the conformation, swelling and degradation at an acidic site that is typical of tumor site.

Polymeric micelles are one of the most researched polymer-based systems. Self-assembled nanoparticle formation has been carried out by self-assembly of

amphiphilic block copolymers in solution conditions. These copolymers self-assemble into stable micellar structures at physiological pH and thus encapsulate hydrophobic drugs within the cores. However, in the case of pH-sensitive groups, there was protonation at the low pH found at the tumor site which is pH 5. 0 – 6. 5 hence making these blocks become cationic and destabilized to release the drug within micelles (Luo et. Al, 2016). Prior work of other researchers has described the pH-sensitive drug delivery mechanism of polymeric micelles. As a result, the poly(ethylene glycol)-b-poly(histidine) micelles contain histidine residues to be protonated at this lower pH to alter the shape and release the drug. They include Energy (Zhang et al., 2016).

Applications of pH-Responsive Polymer-Based Systems in Cancer Therapy

Another application of pH-responsive polymer-based devices is the targeted delivery of chemotherapeutic drugs to tumors. Cytotoxic pharmaceuticals can be incorporated into pH-sensitive nanoparticles or micelles to avoid interaction with normal cells and release the drug only at the tumor site. The consequence of the phenomenon is the lowering of the toxicity across the whole organism and the increase in the concentration of the drugs in the tumor tissues thereby increasing the therapeutic ratio of chemotherapy agents (Saxena et al., 2019). Additionally, cancers that are highly multidrug resistant may require the use of pH-responsive polymers-based systems. This is because MDR makes cancer cells resistant to many anticancer drugs; therefore, it becomes a major factor in chemotherapy (Saxena et al., 2019). Along the same line, nucleic acid-based therapeutics like small interfering RNA (siRNA), and microRNA (miRNA) for cancer gene therapy can be applied using pH-sensitive polymeric systems. These researchers can employ pH-sensitive nanoparticles containing nucleic acids to penetrate the cells and deliver therapeutic payloads to the tumor mass. It implies that there may be certain genes to be silenced, or genes may undergo certain changes in cancer cells resulting in suppression of tumor formation and metastasis.

Polymeric Micelles in pH-Responsive Drug Delivery

Polymeric micelles have been researched extensively as flexible drug carriers because they can greatly increase the solubility and efficiency of hydrophobic medicines when the pharmaceutical products are encapsulated into polymeric micelles.

Mechanisms of pH-Responsive Polymeric Micelles

In aqueous solutions, nanoparticles can form structures called polymeric micelles Copolymer: a polymer that has different monomers in its structure; the outside of a micelle is adjusted by hydrophilic segments, while hydrophobic segments are responsible for creating the core constituting the micelle. This is because the hydrophobic drugs can be fitted into the core-shell structure while the polymeric micelle can protect the drug from the aqueous environment. Undefined Polymeric micelles have been found to show pH-responsive behavior because of the presence of pH-sensitive moieties or functional groups in the polymer chains. For this reason, histidine, which becomes positively charged at low pH values, has been explored especially for pH sensitivity. Many papers and works published have widely described the responsiveness of polymers like poly (ethylene glycol)-b-poly(histidine) or peg-b-phis toward pH changes (Huang et al., 2017). However, the extracellular pH of the tumor is acidic in the range of 5.0-6.5, while the histidine residues in the tumor cell are in protonated form and thus change the charge distributions within the micelle. When they get protonated, micelles become unstable and ultimately, the core-shell structure collapses, which leads to the release of drug molecules encapsulated there. It is also possible to incorporate other pH-sensitive functional groups like amino groups or carboxylic acid into the polymer backbone to enhance its pH sensitivity. For instance, micelles derived from polymers with carboxylic acid groups demonstrate the alteration in the hydrophilic character that leads to micelles breakdown and drug release in acidic conditions. According to Lieu et al. (2016), the incidence is most likely responsible for reducing.

Recent Advancements in pH-Responsive Polymeric Micelles

Recently with the advances in polymer sciences and nanotechnology new more functional and sensitive pH-sensitive polymer micelles have been developed which has expanded the uses of pH-sensitive polymeric micelles not only in cancer treatment but also in other biological areas. Another area of success has been the construction of multifunctional polymeric micelles transporting drugs and at the same time providing diagnostic imaging (Li et al., 2017).

Applications of pH-Responsive Polymeric Micelles in Cancer Therapy

As they can release a drug under the acidic tumor microenvironment, pH-sensitive polymeric micelles hold high promise for targeted drug delivery. The presence of

the micelles also brings added two benefits that encompass lengthened circulation and diminishing system toxicity while exhibiting high tumor specificity. Therefore, pH-sensitive polymeric micelles have attracted a great deal of attention in recent years for the delivery of anticancer agents to the tumor site. Some of the literature evidence according to these points on how the researchers induced controlled release at tumor sites of hydrophobic encapsulated drugs with minimal side effects on normal tissues via pH-responsive polymeric micelles: By this therapeutic index, optimizable chemotherapies applied various approaches to concentrating the chemotherapy drugs in tumor tissues rather than systemic toxicities by increasing doses at diseased sites. (Luo et al., 2016)

pH-Responsive Hydrogels

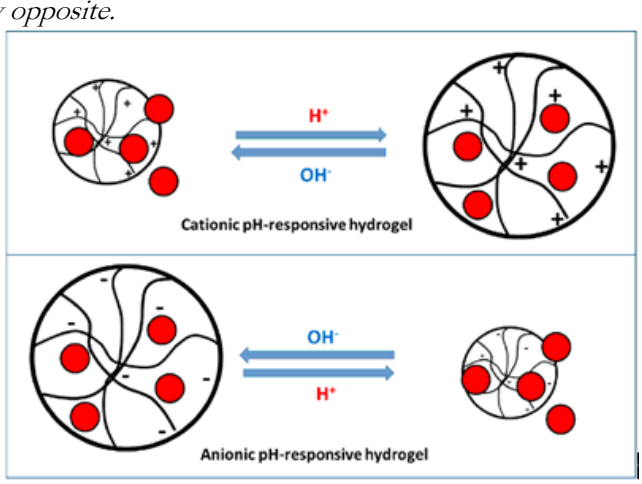
The application of hydrogels as drug delivery systems seems to keep on increasing due because of their water content, biocompatibility, and stimuli sensitivity. Something exceptional for the stimuli mentioned above is the swelling capability due to change in their pH environment, which gives relevance to this kind of smart material along with temperature-sensitive ones in cancer research.

Mechanisms of pH-Responsive Hydrogels

The hydrogel becomes pH-sensitive because of the swelling-deswelling behavior of the polymer network regulated by pH changes. The ionizable functional groups of the polymer chains such as carboxylic acids or amino groups contribute to the pH sensitivity. This is because an increase or decrease in pH facilitates protonation or deprotonation of the functional groups affecting hydrogel swelling (Ahmed et al. 2015). In polyacrylic acid (PAA), a pH-sensitive hydrogel where almost all carboxylic groups can be protonated at lower pH levels, dissociation of carboxylic acid groups occurs at pH 7 or above, allowing swelling of the polymer due to the electrostatic repulsion between polymer chains. However, with decreasing pH, protonation of carboxylic acid groups leads to the absence of electrostatic repulsion; thus, the hydrogel network collapses.

Figure 1

Pictorial presentation of the generalized action of pH-responsive polymer hydrogel in drug delivery application. Cationic hydrogel swells under acidic pH and shrinks at basic pH; thus, releasing its cargo. Either this is also for anionic hydrogels; only this scenario is completely opposite.



Recent Advancements in pH-responsive Hydrogels

Unique and novel features were added to create new pH-responsive hydrogels. Applications of these pH-responsive hydrogels are being examined in tissue engineering and regenerative medicine and as a carrier for applications of drug delivery. One path of development involves the generation of injectable pH-responsive hydrogels for tissue engineering and less invasive drug delivery. A second avenue of development would involve embedding bioactive molecules in the hydrogel matrix, such as growth factors or peptides, to enhance bioactivity and therapeutic efficacy. These functionalized hydrogels would thereby serve as bio carriers to mimic the natural extracellular matrix while tuning the condition for cell adhesion, proliferation, and differentiation. By modifying physiochemical characterization with respect to bioactive compound delivery standards and presenting them, special customized features can be made from hydrogels for specific biomedical applications (Chen et al., 2016). Next came an interest in developing smart hydrogels that

can feature programmable in vitro drug-release profiles or even on-demand responsiveness. In such hydrogels, a light, magnetic field, ultrasound, or another type of external stimulus is used to make the matrix release the medication in a pulsatile, sustained, or triggered manner. By embedding stimuli-responsive mechanisms into a hydrogel matrix, drug release could be placed under very accurate spatiotemporal control, thereby ensuring reduced adverse effects and maximized therapeutic efficacy (Zhang et al., 2017).

Applications of pH-Responsive Hydrogels in Drug Delivery

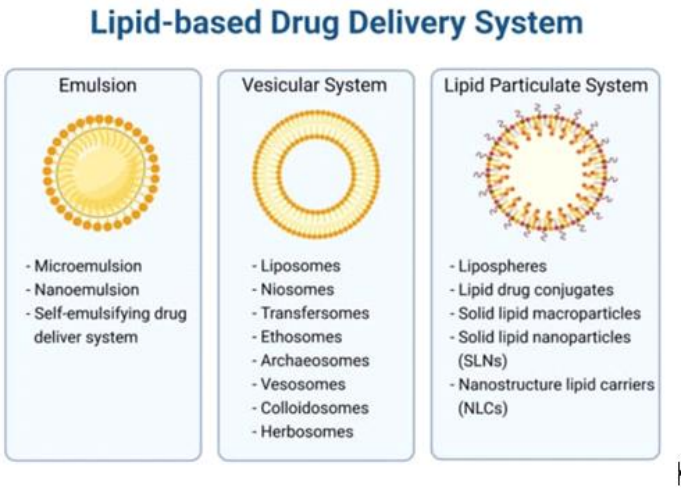
pH-responsive hydrogels represent an important matrix for drug targeting in regenerative medicine, cancer therapy, and other biomedical applications. There are many advantages of pH-responsive hydrogels of their own, such as high water content, biocompatibility, and pH response. Among the major applications of pH-responsive hydrogels are targeted drug delivery platforms against cancer. In this context, a specific strategy may increase the therapeutic index of the anticancer medications, which leads to reduced systemic toxicity with the administered larger drug doses in tumor tissues (Guo et al., 2016). By encapsulating drugs into nanoparticles or vesicles embedded in the hydrogel matrix, cell absorption and endosomal escape can be completed, and therefore researchers can achieve higher therapeutic efficiency against drug-resistant cancer cells. (Chen et al., 2016). Such pH-responsive hydrogels are also used in tissue engineering scaffolds and wound dressings. Bioactive molecules can be added to the hydrogel matrix by researchers to induce tissue regeneration, angiogenesis, and wound healing since the said molecules contain growth factors or antimicrobial peptides. Besides, humid and oxygen-rich environments for wound healing can be designed using pH-responsive hydrogels and, thereby, make the healing process faster with scars infrequently. (Guo et al., 2016).

Lipid-Based Systems in pH-Responsive Drug Delivery

Interest in lipid-based systems has been impending owing to its adaptability, biocompatibility, and the different range of therapeutic compounds it can encapsulate. Of the several lipid-based approaches for targeted drug delivery, especially in cancer therapy, pH-responsive lipid nanoparticles seem the most promising.

Figure 2

Various classes of Lipid-based Nanocarriers.



Mechanisms of pH-Responsive Lipid-Based Systems

pH-responsive lipid-based systems are those that use pH-sensitive lipids or surface modifications to achieve controlled drug release upon changes in pH, particularly in the acidic tumor microenvironment. These systems change the pH gradient between the tumor tissues, pH 5.0-6.5, and that of the normal physiological conditions, pH 7.4, so as to trigger drug release at specific sites. The most widely studied pH-responsive system based on lipids is the liposomes, which are self-assembled vesicles made up of lipid bilayers. pH-sensitive liposomes usually comprise lipids with ionizable functional groups, which are pH-dependent, such as phosphatidylethanolamine or cholesterol hemisuccinate. In this case, the lipids will remain non-chargeable at neutral pH and the structure of the liposome will be maintained. At this very pH level, the

ionizable groups start to become positively charged, by which the liposomal membrane becomes destabilized and then leads to drug release within the acidic tumor microenvironment (Al-Ahmady & Al-Jamal, 2018). Another pH-responsive lipid-based technology involves SLNs, wherein the lipid matrices are stabilized by surfactants. The incorporation of pH-sensitive lipids in the lipid matrix, like phospholipids or fatty acids, confers the development of pH-sensitive SLNs. At a neutral pH, these lipids retain their solid-state structure with the drugs encapsulated inside the nanoparticle matrix. However, at an acidic pH, drug release from the SLNs is caused by the phase change or hydrolysis of pH-sensitive lipids. (Ansari et al., 2011).

Recent Advancements in pH-responsive Lipid-Based Systems

This has been made possible by significant recent progress in lipid chemistry, nanotechnology, and drug delivery to create new pH-responsive lipid-based systems with improved properties and functionalities Area. These have, therefore, opened areas of pH-responsive lipid-based system use in cancer therapy and general other biomedical applications. The 1st development relates to the presentation of stimuli-responsive liposomes whereby various environmental conditions could be responded to, such as the pH, temperature, and redox potential. These multi-functional liposomes could be engineered into triggered systems for the release of the drug in response to the applied trigger, allowing for highly precise spatiotemporal control over drug release kinetics. Such incorporation of multiple stimuli-responsive mechanisms into liposomal formulations could improve therapeutic efficacy while reducing systemic toxicity (Gubernator et al., 2011). Combined with other major progress would be the introduction of stimulus-responsive lipid-based systems for combination treatment, co-loading therapeutic agents in one nanoparticle. By co-delivering the therapeutic agents with targeting ligands or those for imaging, one can achieve in vivo targeting and monitoring in real-time for the therapeutic response. The development in pH-sensitive lipid systems, combined with the pharmaceutical and diagnostics functions for application into theragnostic use, has gained great interest as the other advances in this field. Real-time monitoring of in vivo distribution and response to the drug treatment can be achieved through the incorporation of imaging agents such as fluorescent dyes or magnetic nanoparticles into liposome formulations. The introduction of available stimulus-responsive mechanisms within liposomal formulations will enable drug delivery and image acquirement on demand, further catering to personalized and precision medicine approaches in cancer therapies (Yuba et al., 2018).

Applications of pH-Responsive Lipid-Based Systems in Drug Delivery

Lipid-based pH-sensitive systems act effectively as tumor-targeted drug delivery systems for applications in cancer and other biomedical applications. Such systems, showing an improved performance than others, have higher stability, better biocompatibility, and tunable responsiveness of system properties toward environmental alterations. Among the most prominent pharmaceutical applications of pH-sensitive lipid carriers are the targeted drug delivery systems for cancer. In this regard, pH-sensitive lipid carriers such as liposomes or SLNs are used for the assisted site-specific delivery and targeted release of chemotherapy prodrugs at the tumor site to minimize the off-target effects on the normal tissues. The consequence of this will be to approximate to further enhance the therapeutic index of anti-cancer drugs, enabling hence higher dosing of the cancer tissue with lower systemic toxicity (Al-Ahmady & Al-Jamal, 2018).

Liposomes

Alec D. Bangham discovered liposomes in 1965, and since then, they have probably been the most studied nanocarrier for drug delivery. These liposomes consist of one or more phospholipid bilayers, which enclose an aqueous core inside, and they have specific advantages such as their biocompatibility, their ability to be engineered for drug encapsulation, and their varied physicochemical properties.

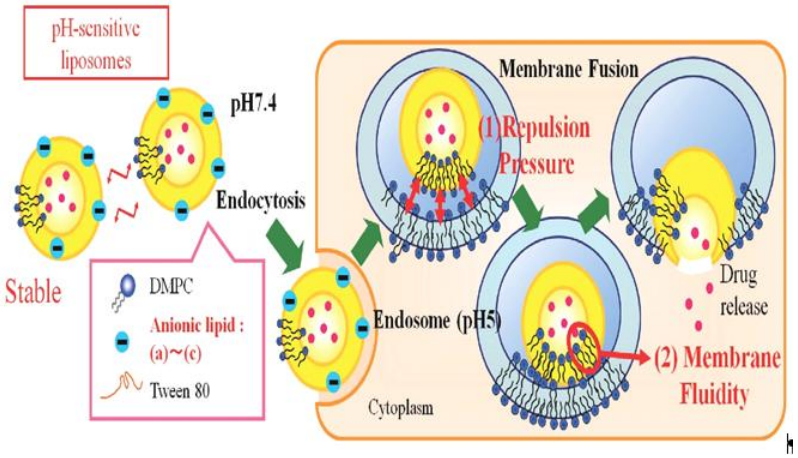
Mechanisms of Liposomal Drug Delivery:

Liposomes function as drug delivery vehicles because they can target, encapsulate, and release drugs under controlled conditions. The phospholipid bilayers of liposomes show a hydrophobic environment that can be used to encapsulate hydrophilic drugs in the aqueous core or hydrophobic medications within the lipid bilayer. This encapsulation increases the drug's solubility. It also prevents it from degrading and lengthens its in vivo circulation period (Allen & Cullis, 2013). Moreover, drugs can be delivered selectively to tissues or cells by making liposomes in such a way that they display passive or active targeting. Passive targeting is based on the enhanced permeability and retention (EPR) effect, which occurs when liposomes accrue in the leaky tumor vasculature

with poor lymphatic drainage leading to concentration in the tumor microenvironment. On the other hand, active targeting includes modifying the surface of liposomes with ligands. These include peptides, antibodies, or small molecules. These ligands can identify and attach to target cells because of their overexpressed receptors. Thus, they promote cellular uptake and intracellular drug delivery (Torchilin et al., 2013).

Figure 3

The strategy of inferring pH sensitivity of the anionic liposomes at acidic pH.



Applications of Liposomal Drug Delivery

There are many applications for liposomal drug delivery systems in the biomedical fields of cancer treatment, infectious diseases, inflammatory disorders, and regenerative medicine. These systems are the best options for enhancing treatment outcomes and patient compliance because they provide many advantages, such as improved drug solubility, stability, and targeting efficiency. Another use of liposomal drug delivery is in cancer treatment; liposomal formulations are studied for their ability to deliver chemotherapeutic medicines to tumor tissues in a targeted manner while decreasing systemic toxicity. Liposomal versions of anticancer medications have been licensed for use in clinical settings and have shown superior antitumor activity, improved pharmacokinetics, and fewer adverse effects when compared to conventional formulations. Additionally, liposomal formulations can overcome multidrug resistance mechanisms and increase drug accumulation in drug-resistant cancer cells, leading to improved treatment outcomes (Allen & Cullis, 2013). Moreover, liposomal formulations can encapsulate biologics. These include cytokines, growth factors, and antibodies, for the treatment of autoimmune diseases and inflammatory conditions. Liposomal formulations of anti-TNF antibodies have shown efficacy in reducing disease activity and improving clinical outcomes in patients with rheumatoid arthritis and inflammatory bowel disease (Allen & Cullis, 2013).

pH-Sensitive Lipid Nanoparticles

A class of adaptable drug delivery devices known as pH-sensitive lipid nanoparticles reacts to pH variations to release the drug at specified locations, especially in acidic tumor microenvironments.

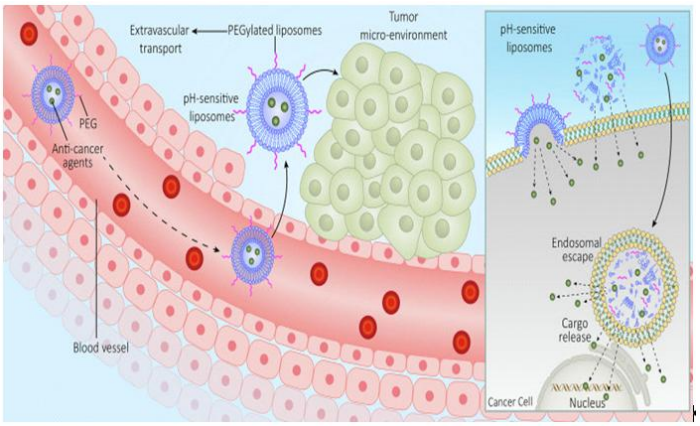
Mechanisms of pH-Sensitive Lipid Nanoparticles

pH-sensitive lipid nanoparticles respond to changes in pH by achieving controlled release of drugs using a range of ways. To release medications selectively at tumor sites, a pH gradient is created between malignant tissues (pH 5.0–6.5) and normal physiological conditions (pH 7.4). Among the pH-sensitive lipid nanoparticles that have been studied the most are liposomes. These nanoparticles consist of lipid bilayers surrounding an aqueous core, such as phosphatidylethanolamine (PE) and cholesterol hemisuccinate (CHEMS), and can be modified with pH-sensitive lipids. Because they are uncharged, these lipids maintain the stability of the liposomal structure at neutral pH. However, in the acidic tumor microenvironment, the pH-sensitive lipids get protonated, which makes the liposomal membrane unstable and releases the medication. (Torchilin, 2005Another technique for creating pH-sensitive lipid nanoparticles comprised of lipid matrices stabilized by surfactants is to create solid lipid nanoparticles (SLNs) or lipid nanoparticles (LNPs). by including polymers or lipids that are pH-sensitive in the lipid matrix. At a pH of neutral, these lipids maintain their solid-state form. They accomplish this by enclosing drugs

within the matrix of nanoparticles. However, the pH-sensitive lipids risk hydrolysis or phase shift at an acidic pH. This causes the drug to be released from the SLNs/LNPs. (Al-Ahmady & Al-Jamal, 2018).

Figure 4

The pH-sensitive liposomes in cancer drug delivery.



Applications of pH-Sensitive Lipid Nanoparticles in Drug Delivery

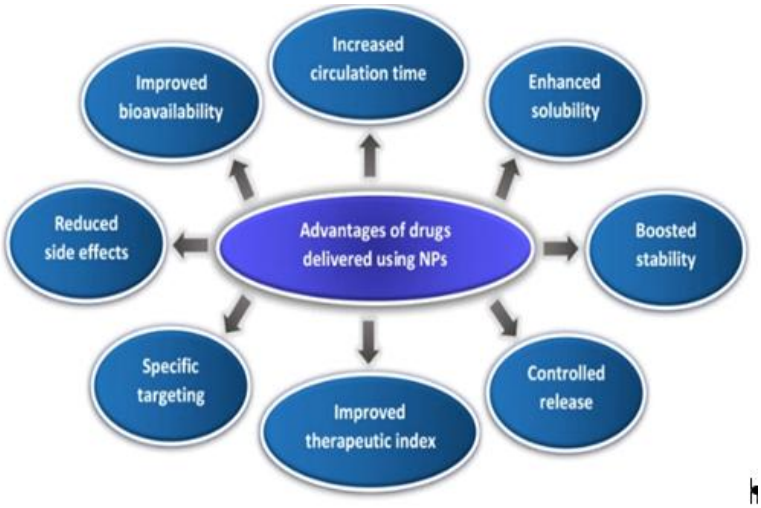
pH-sensitive lipid nanoparticles are a good option for targeted drug delivery in other biomedical applications, for example, in cancer treatment. The many benefits, such as improved stability, biocompatibility, and tunable reactivity to environmental signals, make them the best candidates to improve therapeutic outcomes and increase patient compliance. Among the main uses is the application of pH-sensitive lipid nanoparticles in the tailoring of drug delivery platforms designed for treating cancer. Chemotherapeutic drugs can be delivered, through encapsulation in pH-sensitive liposomes or SLNs/LNPs, to tumor tissues in a controlled and targeted manner with reduced side effects on healthy tissues. The specific approach increases the therapeutic index of the anticancer drugs. Therefore, lesser systemic toxicity would be caused by the administration of a higher amount of drug dosage to the tumor tissues. (Al-Ahmady & Al-Jamal, 2018).

It is possible to develop pH-sensitive lipid nanoparticles that will bypass these biological barriers and improve the therapeutic medicines' distribution into the cells. The encapsulation of drugs in targeting-ligand-modified liposomes or SLNs/LNPs can achieve effective cellular uptake and endosomal escape, which may potentiate the therapeutic efficacy against drug-resistant cancer cells. It is possible to increase the antitumor immune response and the treatment outcome for cancer immunotherapy by co-delivery of therapeutic drugs with immunomodulatory agents. (Yuba et al., 2018).

Another application of such pH-sensitive lipid nanoparticles is the development of stimuli-responsive drug delivery systems for personalized therapy. Researchers can change the composition and properties of lipid nanoparticles to respond to specific environmental stimuli, thus controlling the kinetics of drug release and therapeutic response. Furthermore, the incorporation of imaging agents into the formulation of lipid nanoparticles allows tracing of drug distribution and therapy response in a domicile manner, enabling the individualization of treatment plans and improvement of patients' outcome. (Al-Ahmady & Al-Jamal, 2018)

Figure 5

Different advantages of delivering drugs using NPs.



Inorganic Nanoparticles in Drug Delivery

Unique physicochemical properties, versatility, and tunability make inorganic nanoparticles exciting drug delivery agents. There are major advantages associated with these particles. These advantages include controlled drug release kinetics, large surface area-to-volume ratio, and ease of functionalization. They consist of materials such as silica, iron oxide, gold, silver, and quantum dots.

Mechanisms of Inorganic Nanoparticles in Drug Delivery

Inorganic NPs have been demonstrated to enhance drug delivery and therapeutic efficacy through several mechanisms. Small size and large surface area-to-volume ratio offer the best advantage in efficient drug loading and encapsulation in a nanoparticle matrix. Targeted delivery of medication, controlled release of therapeutic agents, and imaging can be realized by functionalizing inorganic NPs with stimuli-responsive components, targeting ligands, or imaging agents (Chen et al., 2013). This can be utilized to attain passive targeting of the inorganic nanoparticles in the tumor tissues through the enhanced permeability and retention effect. Inorganic nanoparticles are absorbed into the leaky vasculature of tumors and tend to remain there due to poor lymphatic outflow. This passive targeting minimizes off-target systemic toxicity to healthy tissue while facilitating the delivery of drugs into malignant tissue. (Hare et al., 2017). Another way is to modify the inorganic nanoparticle surface to actively target some cells or tissues by adding targeting ligands, such as antibodies, peptides, and small molecules. Targeting ligands recognize and bind with the overexpressed receptors or antigens on the target cells so that through this process, intracellular drug delivery and cellular uptake are facilitated. Conjugation of targeting ligands at the surface of inorganic nanoparticles could improve targeting specificity and therapeutic efficiency (Chen et al., 2013). It is possible to engineer inorganic nanoparticles to deliver medication at specific sites upon induction by pH, light, magnetic fields, or other types of external stimuli. Stimulus-responsive inorganic nanoparticles can destabilize the matrix of nanoparticles and therefore release drugs through their aggregation, breakdown, or alteration in structural makeup due to applied external stimuli.

Applications of Inorganic Nanoparticles in Drug Delivery

These nanoparticles are very attractive candidates for improving the outcome of treatment and patient compliance because of these numerous advantages. Among others, these include high drug loading capacity, customizable physicochemical features, and stimuli-sensitive behavior. One of the prime applications of inorganic nanoparticles in cancer treatment is the development of targeted drug delivery systems. By encapsulating the drugs for chemotherapy in inorganic nanoparticles, researchers achieve regulated and targeted drug release at areas where tumors exist without causing off-target effects on healthy tissues. An increased therapeutic index of the anticancer drugs reduces systemic toxicity after delivering an increased amount of the drug to the tumor tissues. (Huang et al., 2011). Inorganic nanoparticles can be designed to bypass biological barriers to enhance intracellular drug distribution. From targeting ligands to stimuli-responsive components, these functionalizations grant the nanoparticles efficient cellular uptake and endosomal escape, thus possibly bestowing improved therapeutic efficacy against drug-resistant cancer cells. Inorganic nanoparticle applications facilitate

the formation of theragnostic systems for personalized medicine. It envisages possibilities in controlled drug release and imaging triggered by stimuli-responsive components, thus offering a finer degree of control over the kinetics of drug delivery and therapeutic response. (Hare et al., 2017).

Drug Delivery with Mesoporous Silica Nanoparticles (MSN)

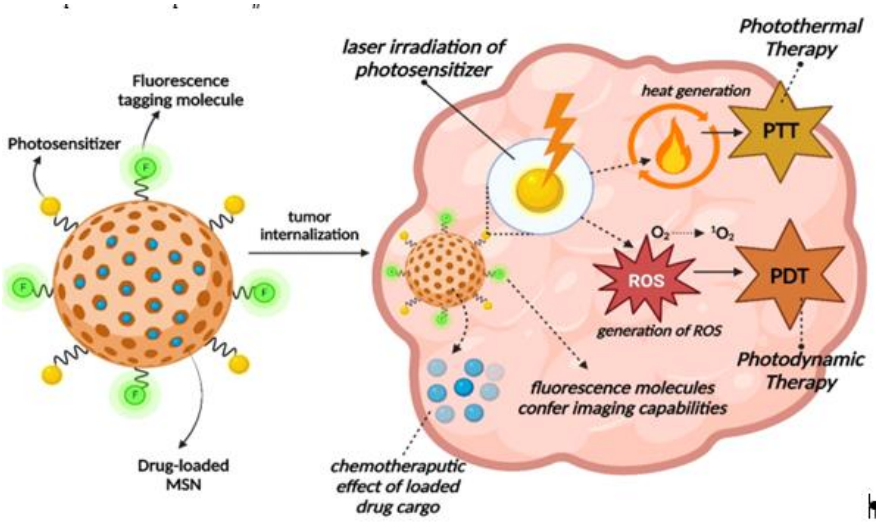
Mesoporous Silica Nanoparticles (MSN), with large pore volume, tunable pore size, and high specific surface area along with profound bioactivity have gained significant attention for the delivery of pharmaceuticals. The ability to provide the desired drug under this environment has numerous advantages in terms of controlled release, stimuli responsiveness, and a high enough loading capacity. In this review, we will discuss action mechanisms and design strategies of such nanocarriers developed in the past few years as well as breakthroughs and advancements in quality research related to mesoporous silica nanoparticles (MSNs) for drug delivery applications.

Mechanisms of Mesoporous Silica Nanoparticles in Drug Delivery

Different approaches that can be molecularly, or congressionally applied to mesoporous silica nanoparticles only choose improved therapeutic efficacy and drug delivery efficiency. This means that what a mesoporous structure in these nanoparticles implies is a great surface area and pore volume for drug loading and encapsulation. Depending on the physio-chemical properties of both the cargo molecule and the nanoparticle, the drugs can be embedded within mesopores inside the MSN structure through chemical conjugation, physical adsorption, or electrostatic interactions with the support prepared in this manner. (Marcazzan et al., 2008). It, therefore, utilizes these particles after loading drugs into them to be arrested from decaying too soon or cleaning off. The attached release of that drug is, hence, led by this marketing. Moreover, the porous framework of MSN facilitates diffusive-mediated controlled drug release or stimulus-responsive strategy. These can be finely adjusted and controlled for any of many design parameters and are tuned to create from triggered release profiles to sustained delivery kinetics (Wu et al., 2019). Besides, surface modifications like the attachment of the target ligand, imaging moieties, or the stimuli-responsive units can be done on the mesoporous silica nanomaterials to endow therapeutic targeting and imaging functions. On this basis, methods like surface modification to enhance cell uptake and efficacy via improved intracellular delivery have been designed.

Figure 6

Graphical representation of a drug-loaded theranostic MSN platform designed to have light-based triggers for therapeutic responses



Recent Advancements in Mesoporous Silica Nanoparticles for Drug Delivery

Scientific progress in mesoporous silica nanoparticles (MSNs) for the last few years has led to new formulations with better properties and behavior that enable their

application not only as drug delivery vehicles but also on theranostic, imaging methods or cancer therapies. These have been driven by advancements in surface engineering, cargo loading techniques, and synthesis methods. Advancements in the development of a series of multimodal mesoporous silica nanoparticles for theranostic properties, capable of co-delivering different therapeutic drugs or imaging agents. Researchers can see therapy unfold in real time and the imaging agents, nucleic acids, or chemotherapeutics get synergistic benefits by loading them in the same nanoparticle formulation. Mesoporous silica nanoparticles for combination therapy: Utilizing mesoporosity of both MCM-41 and SBA-15 to load several therapeutic drugs, the multicompartmental nanoparticle is another type synthesized in the clinical field which as such can provide the same carrier with multiple cisplatin-drug release that could circumvent drug resistance mechanisms reported via nanotechnology armamentarium approach (Sui et al., 2013). Multi-functional functional side chains decorated by diverse kinds of electromagnetic groups including reactive oxygen species or scavenger receptors like apoptosis-inducing protein have also been developed. MSN may benefit co-encapsulating immunomodulatory drugs, small molecule inhibitors as well as traditional chemotherapy agents for site-specific and synergistic delivery of therapeutics into the tumor. By adjusting the release kinetics of different medications, researchers can increase therapy efficacies and achieve therapeutic ratios in a way that has not previously been possible. (Chen et al., 2019). Also, over the years there have been a variety of interests to develop stimuli-responsive mesoporous silica nanoparticles for imaging and on-demand medication release. For example, pH-responsive MSN can be designed to release the cargo only after experiencing a shift in its inside pH and allowing a site-specific drug delivery while minimizing side effects. Using these MSNs as platforms for incorporation of imaging agents, researchers can track the distribution and response to therapy in real time providing personalized treatment plans leading ultimately to better patient outcomes (Rosenholm et al., 2016).

Applications of Mesoporous Silica Nanoparticles in Drug Delivery

Mesoporous silica nanoparticles are very good at targeted drug delivery of drugs in various biomedical areas like cancer therapy. To be clear, one rather pertinent problem associated with the application waves of the nanoparticles is the possibility that they might eventually lead to the initial development of either cancer or even some other similar illness. Nonetheless, these nanoparticles have pros of being able to solve health issues in the near future: they have been highly promising in drugs' good delivery, they are designed business-like, are easily shuffled into and or fit with existing technological and other health-based enterprises, and have recently been used successfully in the use of tumor cells, or, in engineering wherein they compete to combine different drugs to the cancer area than attaching to healthy tissues. The drugs packed into the pores of the nanocarrier are a good target for cancer therapy as the laser beams can precisely identify the tumor site without causing any damage to adjacent tissues. By using a tailored strategy, anticancer medications' therapeutic index is increased, resulting in less systemic toxicity when larger drug doses are administered to tumor tissues (Wu et al., 2019; Chen et al., 2019). Furthermore, one could theoretically create mesoporous silica nanoparticles for transporting the medicinal substances through the biological barriers toward the cell for the improvement of therapeutic effects. Researchers can accomplish effective cellular uptake and endosomal escape by functionalizing nanoparticles with stimuli-responsive components or targeting ligands. This can result in greater therapeutic efficacy against drug-resistant cancer cells. Furthermore, scientists can augment the antitumor immune response and treatment success in therapies by both co-delivering drugs and therapeutic immunomodulatory agents. Of course, the most direct scheme is the development of theranostic systems for customized medication that utilizes mesoporous silica nanoparticles. It is important to note that scientists can use imaging probes in these systems, which allow for imaging the delivery process of the drug and the drug's response. Individualized treatment plans along with improved patient outcomes are advantages of this technique. Furthermore, the integration of stimuli-responsive components enables researchers to perform on-demand drug release and imaging by which they get enough power to control the response of the drugs and hence the therapeutic duration. (Rosenholm et al., 2016).

Quantum points (QDs) in Medication

Although polymers and semiconductors have not meant this administration, QDs have made a trusted tool in drug delivery due to their phenomenal assets, like fluorescence, high photostability, and surface modification. The undisputed application of those semiconducting nanocrystals within precision medication and targeted drug delivery, particularly image-guided therapy (IGT) makes the exploitation of this shine sample especially

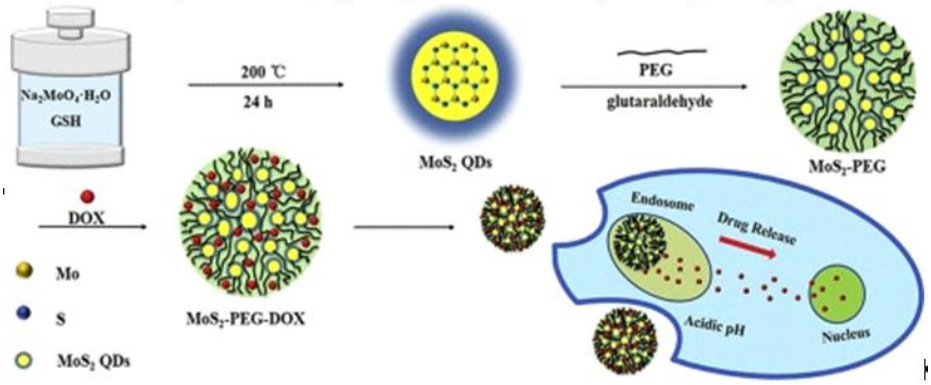
attractive. We can analyze the functioning of QDs in the design strategies for drug delivery systems, the applications of the latest innovations, and quantum dots in this article using knowledge derived from different peer-reviewed journals.

Mechanisms of Quantum Dots

Quantum dots serve as multi-functional delivery platforms, where they wrap therapeutic agents to target specific cells or tissues and allow monitoring of drug delivery in real time. QDs are great in drug delivery-limited applications such as controlled delivery, photothermal therapy, and fluorescence imaging due to their properties. Targeting ligands, stimulus-responsive polymers or imaging agents can all be utilized in quantum dots for the specific effect on drug delivery or therapeutic efficacy (Hossain et al., 2020). One way of approach is the surface loading of the quantum dots or their core with drugs, such as proteins, nucleic acids, therapeutics, and drugs QDs have an excellent drug loading capacity due to their surface area to size ratio and are light stable but then degraded moreover, compatibility ensures that the drugs are effectively delivered and released. Furthermore, real-time in vitro and in vivo monitoring of the drug release kinetics and therapeutic responses is facilitated through the fluorescence features of quantum dots (Chen et al., 2018). Another method for targeted drug delivery toward specific tissues or cells is the use of targeting ligands attached with aptamers, peptides, or antibodies on the surfaces of quantum dots. This led to intracellular chemical delivery and cell contraction. In addition to this, engineering the quantum dots for response to external stimuli such as pH, temperature, and light can trigger drug release locally or timely affording it the potential of reduced off-target effects at the surface enhancing the efficacy of treatment. (Hossain et al., 2020).

Figure 7

PEGylated MoS2 quantum dots for pH-responsive chemotherapeutic drug delivery



Recent Advancements in Quantum Dots for Drug Delivery

Advancements recently seen from quantum dots for drug delivery are active in the new generation of drugs with heightened potency and efficacy, thus increasing space in cancer therapy, imaging, and therapeutics. These further developments have been achieved based on personal innovation developed in chemical processes, surface engineering, and deposition processes. One area making remarkable advances is in excitatory quantum dots, which can control drug release with external responsiveness. For example, pH-responsive quantum dots can be designed to only selectively load in acidic tumor microenvironments and then stable at physiological pH conditions The incorporation of pH-sensitive linkers or gatekeepers into a quantum dot system paves the way for the development of pH change probes for drug release triggered in response, enable site-specific delivery of drugs and reduce off-target effects. (Hossain et al., 2020). Another idea development alongside the use of quantum dots for combined therapy, wherein multiple therapeutic agents are incorporated within one carrier to induce drug resistance mechanisms and thereby amplify therapeutic effects, is that the drugs can, in a sense, be jibed into a tumor-active organ. The quantum dots can be engineered to co-release chemotherapeutics, immunomodulators, and targeted therapies for synergy and the delivery of targeted agents/between-these-at agents to tumor tissue. Ratio and maximize therapeutic results (Chen et al., 2018).

Applications of Quantum Dots in Drug Delivery

Quantum dots have potential that extend to their use as targeted drug delivery nanocarriers in cancer therapies as well as in any form of biomedical applications. Besides

their scalability into fluorescence and great photostability, they can be surface modified, making them more flexible and offering room for improvement in the treatment outcome and patient compliance. Among the most popular applications of quantum dots are their progressive development into targeted drug delivery systems for cancer therapy. A therapeutic drug QD substrate allows researchers to achieve controlled and targeted release of the drug at sites inside a tumor thereby bypassing off-target effects on nonmalignant tissue. (Chen et al., 2018). A similar mechanism can be observed in anticancer medications that increase the therapeutic index reducing systemic toxicity within tumor tissues. These quantum dots can also be manufactured for improved intracellular drug delivery by overcoming biological barriers. Nanoparticles made of stimuli-responsive materials or targeting ligands increase efficiency in cell uptake and cellular escape (Hossain et al., 2020). This could have major implications for treating drug-resistant cancer cells. Moreover, researchers can co-deliver therapeutic agents with immunomodulatory factors to enhance both the anti-tumor immune response as well as the therapeutic effects of cancer immunotherapy (Hossain, et al., 2020).

Responsive Drug Conjugates

In the drug delivery field, responsive drug conjugates have been popular for their potential platform in exerting exactly the right control over drug release and therapeutic efficacy. Indeed, conjugates have been designed responsive to a specific stimulus, such as light, pH, or enzymes, and release the drug at the right time or at the right location. The review has sought to proffer limelight on mechanisms, design strategies, recent advances, and applications of responsive drug conjugates against the backdrop of insight garnered from a few relevant research publications.

Mechanisms of Responsive Drug Conjugates

Responsive drug conjugates have varying ways of exerting controlled release of their drug load with therapeutic efficacy. To this end, mechanisms are usually based on the design of structures within the conjugates that change in a specified manner upon contact with an external stimulus. The common mechanism involves pH-responsive drug conjugates in which changes in pH lead to the release of a drug from its conjugation structure. At acidic pH, the hydrolysis of a pH-sensitive linker or moiety or its protonation would cause destabilization of the conjugation and release of the medication. This kind of pH-sensitive activity brings about focused delivery in acidic tumor tissues but with less off-target results on healthy tissues. (Zhang et al., 2019).

Recent Advancements in Responsive Drug Conjugates

Responsive drug conjugates apply to areas within theragnostic, imaging, and treatment of cancer. One such example of the above-mentioned inventions is stimuli-responsive drug conjugates that release drugs in response to variations in a certain parameter or condition, such as the acidic tumor microenvironment. These conjugates can maintain stability under normal conditions of pH but release the loaded drugs following the alteration of environmental pH with the use of pH-sensitive linkers, thereby promoting targeted delivery which helps reduce off-target drug effects. (Zhang et al., 2019). The next significant changes are in responsive drug combinations that can be used together, where multiple therapeutic agents share a single carrier. Thus, it also allows the simultaneous delivery of immunomodulatory agents, targeted therapies, and chemotherapeutics all at once, leading to better treatment outcomes and overcoming drug resistance. This could be made possible by advances in stimuli-responsive materials, linker chemistry, and conjugation techniques. The rates of drug release can also be manipulated to better therapeutic outcomes and reach optimal therapeutic indexes (Cheng et al., 2018).

Applications of Responsive Drug Conjugates

Responsive drug conjugates open huge possibilities for applications for targeted cancer therapy and other fields of biomedicine. This will provide control over drug-release kinetics, enhance therapeutic efficiency, and reduce systematic toxicity, as encapsulation of the chemotherapeutic agents in the conjugates would help the researchers achieve a targeted release of the agents at the sites of the tumors, which minimizes off-target effects, and thus higher doses with lower systemic toxicity can be afforded. On this basis, conventional drugs shall be engineered to cross biological barriers and alter intracellular drug distribution by being formulated along with stimuli-responsive components or targeting ligands. This approach can ensure enhanced cellular uptake, endosomal escape, and therapeutic efficacy of the administered formulation against multidrug-resistant cancer cells. Furthermore, co-delivery of therapeutic and immunomodulatory agents can potentiate antitumor immune response thereby improving cancer immunotherapy outcomes (Zhang et al.,2019).

Prodrug Systems

Prodrug systems are advantageous, as they provide better pharmacokinetics and improved targeting in tissues while reducing the systemic toxicity. These are systems designed to undergo in vivo chemical or enzymatic changes that will release the active drug molecules at the target site.

Mechanisms of Prodrug Systems

Prodrug systems facilitate drug release in controlled manners which ultimately incorporate efficacy by numerous mechanisms. These are typically bio-reversible moieties or carriers designed to release the active drug upon metabolism in vivo. Enzyme-dependent Prodrug: In this strategy, inactive prodrugs are first activated through endogenous enzymes to exert their drug activity in tissues or cells overexpressed with some specific types of metabolic enzymes. Such selective receipt release serves to enhance treatment efficacy and can be achieved through hydrolysis, oxidation, reduction, or conjugation (Zhang et al., 2017). Non-toxic drug precursors are converted into active drugs by chemical activation, which is often a reaction with water (hydrolysis) or acid-catalyzed esterification, leading to stability and controlled release of the substances on specific cell walls. Prodrugs can also leverage physiological differences between cancerous and normal tissues, such as pH or redox potential, for selective drug release. PH-responsive prodrugs release their active form in an acidic environment, and redox-responsive prodrugs release drugs depending on variations of cellular oxidative stress state (Zhang et al., 2017).

Recent Advancements in Prodrug Systems

Both cancer therapy, imaging, and theranostics have developed a lot with ripe new prodrug systems. The underpinning mechanisms behind these advances have arisen mainly due to innovations in prodrug design, synthesis, and carrier technologies. For instance, enzyme-responsive prodrug systems were developed to selectively release drugs dependent on specific enzymatic activities overexpressed in diseased tissues which enhance therapeutic efficacy and minimize off-target effects and thus side toxicity (Zhang et al., 2017).

Applications of Prodrug Systems

Prodrug systems offer great benefits for targeted medicine delivery in biomedical applications, mostly in treating cancer. They improve pharmacokinetics, and tissue targeting, and minimize systemic toxicity thereby improving treatment outcomes as well as patient compliance. They enable drug release at tumor sites hence minimizing unintended effects and allowing a higher dose of the drugs to be used while reducing their systemic toxicity (Huttunen et al., 2011). This will hence allow the engineering of prodrugs that contain stimulus-responsive elements or targeting ligands to enhance the cell membrane permeability ability of the drug for effective action on chemotherapy-resistant cells. Prodrugs have been shown to enhance anti-tumor immune responses through combination therapy with therapeutic and immunomodulatory agents. Prodrugs that contain imagers will help the investigator see the course of treatment in real-time the distribution of medicines with the objective of tailoring the use of medicines for specific patients, and their manipulation becomes easier for delivering its effects.

Conclusion

Of course, the reason is that typical or classic chemotherapy often works poorly and entails side effects from the leakage of drugs and non-selective biodistribution. Nanotechnology and nanomedicine are an answer to this issue by creating new nano-carriers for drug delivery. Nanocarriers with such properties will demonstrate dual targeting by either employing the use of specific ligand molecules or exploiting the enhanced permeability and retention (EPR) property; hence, they can also tend to encapsulate drugs into very high volumes; controllable release components would include those capable of circulating longer, bioavailability, and overcoming drug resistance, thereby making chemotherapy much more effective and at the same time safer. An example showing current trends in targeting medicines is the pH-sensitive drug release system which helps to ensure accurate dosing while at the same time reducing side effects on the whole body. Drug conjugates, lipid-based systems, polymer-based systems as well as inorganic nanoparticles are still undergoing research aimed at improving personalizing and targeting the distribution of drugs.

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