Review Article

Stimuli-Responsive Nanocarriers for Targeted Drug Delivery: A Review

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Abstract:
Smart nanocarriers, which are also known as stimulus-responsive-dosing, are an advanced method of targeted and controlled drug administration that address many of the problems associated with traditional drug therapy. Traditional drug delivery methods have several limitations due to their inability to effectively deliver the drug (such as low bioavailability, nonspecific distribution of the drug, and systemic toxicity) because they do not release their drug based on a specific internal or external stimulus.

Internal stimuli for smart nanocarrier drug release are often associated with tumor microenvironments (e.g., an acidic tumor environment [pH=6.0], increased levels of reactive oxygen species (ROS), hypoxia, redox gradients, and levels of enzyme activity). External stimuli for drug release include temperature, light, magnetic fields, and ultrasound.

Smart nanocarriers utilize unique characteristics of the tumor microenvironment to achieve site-specific drug delivery based on high levels of ROS, low pH, and elevated levels of enzyme activity. This type of site-specific drug delivery enhances the therapeutic efficacy by minimizing the side effects of traditional delivery systems. The development of ROS-responsive and tumor-microenvironment-targeted nanocarrier systems has shown promise for improving the therapeutic efficacy of drugs used in cancer therapy.

Additionally, dual- or multi-stimuli responsive systems have been developed to improve the targeting accuracy and reduce the amount of time a drug is released from the system. Many of the nanocarrier systems used in these types of platforms include liposomes, polymeric nanoparticles, dendrimers, micelles, and lipid-based delivery systems. Although there has been considerable progress with regard to the development of smart nanocarriers, issues surrounding complexity, stability, scalability, and regulatory approval continue to hinder their translation into clinical practice.

Keywords: Stimuli-responsive nanocarriers, targeted drug delivery, tumor microenvironment, reactive oxygen species (ROS), controlled drug release, smart drug delivery systems, nanotechnology in pharmaceutics, multi-stimuli responsive systems

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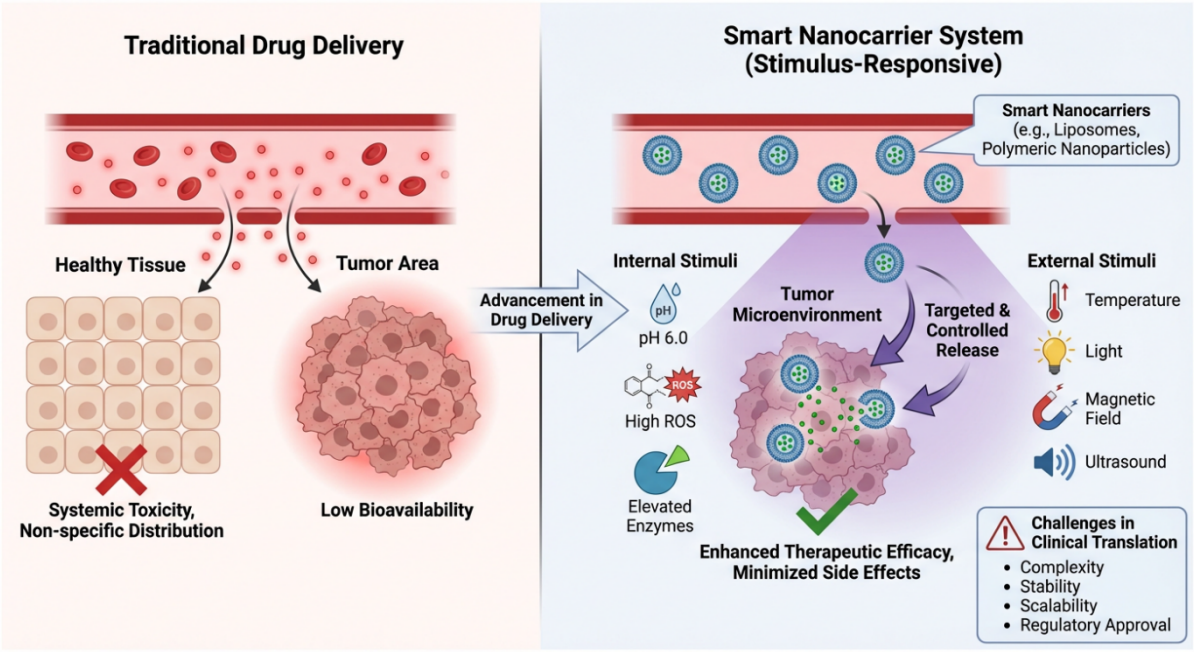
Graphical Abstract



1. Overview

Pharmaceutical research has long made the design of effective drug delivery systems one of its key objectives, as researchers face numerous challenges with current methods used to provide drugs to patients. Standard delivery methods (oral and parenteral) often yield compromised results, primarily because drugs administered via these methods often experience poor bioavailability, nonspecific distribution, rapid clearance from the body, and toxicity that depends on the amount of drug administered[1]. This is particularly true for the use of drugs to treat complex and chronic disease states (e.g. cancer, neurodegenerative diseases, inflammatory conditions) where precise placement of drugs at disease sites and the ability to release drugs at the time a dose is required are critical to producing a therapeutic response and minimizing potentially undesirable side effects.

In recent years, developments in the field of nanotechnology have provided an innovative mechanism that allows researchers to design and manufacture drug delivery platforms using drug delivery systems at the nanoscale level. Drug delivery systems (nanocarriers) such as liposomes, polymeric nanoparticles, dendrimers, micelles, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) have been shown to improve the solubility and stability of drugs as well as improve the pharmacokinetic (PK) profile of drugs. These drug delivery systems can encapsulate drug molecules that are either water-soluble or fat-soluble, protect the drug molecules from being degraded by enzymes, and use enhanced permeability and retention (EPR) in the target cancer cells to increase the likelihood that the chemotherapy agent will be accessible to the cancer cell for treatment. However, the use of passive targeting alone is often insufficient to achieve precise placement and controlled release of drugs[2].

In this regard, many researchers have become very interested in the development of smart drug delivery systems or stimuli-responsive nanocarriers for the purpose of creating improved methods for delivering precise, accurate, and controlled releases of therapeutic agents for patient use.Stimuli-responsive drug delivery systems are designed to respond to specific internal (endogenous) or external (exogenous) triggers in order to control the releasing and delivery of drugs from site-specific nanocarriers. The basic concept of stimuli-responsive nanocarriers is that responsive elements, which are present as part of the nanocarrier system, will undergo a physicochemical change in response to an external trigger causing the release of drug from the nanocarrier[3].

Internal stimuli-responsive drug delivery systems utilize the unique pathophysiological characteristics (such as changes in acidic pH, increased levels of reactive oxygen species (ROS), hypoxic conditions, or overexpression of certain enzymes like matrix metalloproteinases (MMPs)) that are exhibited by diseased tissue[4]. These physiological changes

create opportunities to use nanocarriers to selectively release drugs at target diseased tissues while avoiding release at healthy tissues[5]. Of these various internal stimuli-responsive systems, those that respond to pH or ROS have been extensively studied given their strong relevance to treating cancer and inflammatory diseases[6].

External stimuli-responsive drug delivery systems utilize external triggers (light, heat, ultrasonic waves, magnetic fields) to regulate the release of drugs. Using external triggers provides a mode of controlling drug release in a very specific and precise manner. For example, hyperthermia can be used to activate temperature sensitive nanocarriers; however, photoirradiation can be used to control the release of drugs from photo-responsive nanocarriers[7].

An important advancement in the field of drug delivery is the creation of multi-stimuli responsive nanocarriers that respond to two or more triggers for improved target specificity and to reduce the possibility of premature drug release. An example of this would be using a nanocarrier that is responsive to both pH and ROS, providing a more accurate targeting of the tumor tissue that exhibits both pH and ROS changes. By additionally including targeting ligands (antibodies, peptides, or small molecules), the target specificity and cellular uptake of these nanocarriers are significantly improved[8].

Although stimuli-responsive nanocarriers hold great potential for improving drug delivery, there are still many challenges that remain before these systems can be effectively translated into clinical practice. These challenges include complex synthesis processes, the difficulty in manufacturing large quantities of products, stability issues while being stored and circulated, as well as meeting regulatory requirements. Additionally, there is much variation in physiological characteristics between patients, which can also affect the efficacy of these nanocarrier systems requiring additional optimization/standardization[9].

However, continued research in the areas of materials science, nanotechnology, and biomedical engineering are being pursued to meet these challenges. Ongoing integration of advanced technologies, including artificial intelligence (AI), 3D printing, and nanorobotics, will likely improve the design and functionality of smart drug delivery systems. Overall, stimuli-responsive nanocarriers have the potential to transform modern therapeutics with precise, efficient, and personalized drug delivery[10].

2. Classification of Stimuli-Responsive Nanocarriers

Stimuli-responsive nano-carrier systems can be organized appropriately as a function of the causative mechanism that results in drug release. The classification of the systems as either internal (endogenous) or external (exogenous) stimuli-responsive nano-carriers is essential to understanding their design, behavior and application in different therapeutic conditions and has provided a basis for categorization by each type of triggering mechanism within those two broad categories[11].

The internal stimuli-responsive systems utilize the differences which exist between normal and diseased tissues from a physiological and biochemical perspective. These differences arise from changes in gene expression and/or enzyme activity associated with the development of disease. Some examples of the types of internal stimuli that have been studied and are most commonly studied are such as pH, reactive oxygen species (ROS), difference in redox state within an area and specific enzymes. For example, the extracellular pH found in tumor tissue is on the lower end of the pH scale (the environment or ‘milieu’) compared to what is normally found in healthy tissue. In addition, tumor cells typically show higher levels of oxidative stress associated with increased levels of ROS compared to other types of cells. Also, the expression of matrix metalloproteinases (MMPs) is higher or elevated than what is typically found in healthy tissue. Because of those three unique characteristics associated with tumor cells, they serve as a natural trigger to activate a collection of smart nano-carriers designed to selectively release their drug payloads at the disease site without the need for any outside intervention[12].

In the case of pH-responsive systems, the systems take advantage of the ionization of protonation or of the cleavage of acid-labile bonds as their mechanism for drug release. In the case of ROS-responsive systems, they use the mechanism of oxidative degradation of bonds designed to be sensitive linkers for drug release. Enzyme-responsive systems are designed to contain substrates that have been shown to be specifically cleaved by disease-related enzymes or proteins. The redox-responsive systems use disulfide bonds as their mechanism and therefore take advantage of the difference in05 glutathione (GSH) concentrations between

extracellular and intracellular environments for drug release by teaching it is possible to do this for generating the fulcrum for use in passive targeting utilizing the differences in the microenvironment of disease material relative to normally functioning cells[13].

In contrast to the internal stimuli-responsive systems that utilize intrinsic physiological properties of tissues or cells to trigger drug release, the exogenous systems utilize external physical stimulus (the application of energy in the form of temperature, light activation, magnetic field and/or ultrasound) to cause drug release from the delivery carrier into the disease and/or surrounding target site for regenerative therapy. The advantage of using exogenous stimuli as a triggering mechanism is that the position and timing of the drug release can be controlled. As a result, exogenous systems are especially useful for research and development of therapies that require localized therapy depending upon the target population. For example, temperature-responsive systems often use thermosensitive polymers as the basis for their construction, as they initiate and complete a phase change at a given temperature. Conversely, in many situations, light-responsive systems utilize photo-cleavable bonds and/or photothermal agents that respond to specific wavelength of light. Magnetic responsive systems make use of magnetic nanoparticles to be attracted to specific target sites through the application of external magnetic fields, in addition to providing localized heating using alternating magnetic fields. Ultrasound-responsive systems make use of mechanical energy (sound waves) to facilitate drug release from the drug delivery carrier and/or to enhance penetration of the drug through the tissue layer into the target site[14].

While both internal stimuli-responsive systems have potential to operate within the biological environment in a manner that is autonomous, inherent challenges for the internal systems exist, primarily in the consistency of physiological conditions among the patient population. External stimuli-responsive systems, on the other hand, provide superior levels of control, however; they require that supporting equipment(s) are in place in order to accomplish their intended purposes.To overcome the limitations of individual systems, recent research has focused on the development of dual or multi-stimuli responsive nanocarriers, which combine internal and/or external triggers. These hybrid systems provide enhanced specificity, improved control over drug release, and reduced risk of premature leakage[15]. For instance, a nanocarrier responsive to both pH and ROS can achieve more precise targeting in tumor environments where both stimuli coexist as shown in Table 1.

Table 1: Classification of Stimuli-Responsive Nanocarriers

Category	Stimulus Type	Trigger Mechanism	Key Features	Applications
Internal	pH	Protonation, acid-labile bond cleavage	Exploits acidic tumor environment	Cancer, oral delivery
Internal	ROS	Oxidative degradation of linkers	High specificity in diseased tissues	Tumor, inflammation
Internal	Enzyme	Enzymatic cleavage of substrates	Disease-specific targeting	Cancer, infection
Internal	Redox	Disulfide bond cleavage (GSH-mediated)	Intracellular targeting	Gene/drug delivery
External	Temperature	Polymer phase transition (LCST)	Controlled release via heat	Hyperthermia therapy
External	Light	Photo-cleavage, photothermal effect	Spatial and temporal control	PDT, cancer therapy
External	Magnetic	Magnetic guidance and heating	Targeted delivery, imaging	Theranostics
External	Ultrasound	Acoustic cavitation	Enhanced penetration	Local drug delivery

This classification provides a foundational understanding for designing advanced drug delivery systems tailored to specific therapeutic needs.

3. Internal Stimuli-Responsive Systems

Nanocarriers that respond to internal stimuli are considered to provide one of the best means of

achieving targeted drug-delivery because they take advantage of the different physiological and biochemical characteristics between healthy and diseased tissues. These types of systems are designed to be sensitive to endogenous triggers; examples include changes in pH, increases in (ROS), redox[16].

3.1 pH-Responsive Nanocarriers

pH-responsive nanocarriers are among the most extensively studied smart delivery systems due to the well-established pH gradients in the human body. Under normal physiological conditions, blood and healthy tissues maintain a pH of approximately 7.4. However, tumor tissues typically exhibit a slightly acidic extracellular pH (6.5–6.8) due to enhanced glycolysis and lactic acid production, a phenomenon known as the Warburg effect. Furthermore, intracellular compartments such as endosomes and lysosomes have even lower pH values ranging from 4.5 to 5.5[17].

These pH differences provide an effective trigger for designing nanocarriers that release drugs selectively in acidic environments. pH-responsive systems are generally based on two primary mechanisms:

- **Protonation of ionizable groups:** Polymers containing amine or carboxyl groups undergo protonation or deprotonation in response to pH changes, leading to swelling, destabilization, or disassembly of the nanocarrier.
- **Acid-labile bond cleavage:** Chemical linkages such as hydrazone, acetal, imine, and orthoester bonds are stable at neutral pH but degrade under acidic conditions, resulting in controlled drug release.

These systems have been widely applied in cancer therapy, where they facilitate drug release within tumor tissues or intracellular compartments following endocytosis. Additionally, pH-responsive nanocarriers are used in oral drug delivery for colon targeting, where pH variations along the gastrointestinal tract are exploited.

Despite their advantages, pH-responsive systems face certain limitations, including variability in tumor pH across patients and the possibility of premature drug release in mildly acidic environments[17].

3.2 ROS-Responsive Nanocarriers

Reactive oxygen species (ROS)-responsive nanocarriers have gained significant attention due to their ability to exploit oxidative stress conditions commonly observed in pathological environments. ROS, including hydrogen peroxide (H_2O_2), superoxide anions (O_2^-), and hydroxyl radicals (•OH), are present at elevated levels in cancer cells, inflamed tissues, and sites of infection.

These systems are designed using ROS-sensitive materials that undergo structural or chemical changes in the presence of high ROS levels, leading to drug release. The primary mechanisms include:

- **Oxidative cleavage of sensitive linkers:** Incorporation of ROS-cleavable bonds such as thioketal, disulfide, and selenium-based linkages.
- **Hydrophobic-to-hydrophilic transition:** Oxidation of certain polymers alters their solubility, causing destabilization of the nanocarrier.
- **Backbone degradation:** ROS-induced breakdown of polymer chains leads to carrier disintegration.

ROS-responsive systems are particularly advantageous in tumor-targeted drug delivery due to the significantly higher ROS levels in cancer cells compared to normal tissues[18]. They also show potential in treating inflammatory diseases, where oxidative stress plays a key role as shown in table 2.

Table 2: Common ROS-Sensitive Linkers Used in Nanocarriers

Linker Type	Mechanism of Action	Key Advantages	Limitations
Thioketal	Cleavage in ROS-rich environment	High specificity, stability in normal tissues	Moderate synthesis complexity
Disulfide bond	Redox-sensitive cleavage (GSH/ROS)	Biocompatible, widely used	May respond to non-specific redox changes
Selenium-based linkers	Oxidation-induced bond cleavage	Rapid and sensitive response	Potential toxicity concerns
Boronic esters	Oxidation by H_2O_2	High sensitivity to ROS	Stability issues in circulation

3.3 Enzyme-Responsive Nanocarriers

Enzyme-responsive nanocarriers deliver an active pharmaceutical compound to diseased tissue by providing a selective drug release triggered by the excessive expression of certain target enzymes in the tissue. Enzymes such as matrix metalloproteinases

(MMPs), cathepsins, phospholipases, and proteases are all known to be overexpressed in tumors, inflammatory and infectious diseases, etc.

The design of the nanocarrier utilizes the inclusion of enzyme-cleavable substrates within the structure of the nanocarrier, generally peptide sequences or ester bonds that are broken down by the specific enzyme in the targeted disease area[19]. The selective cleavage of these substrates will result in the release of the encapsulated drug. The methods involved in this process are:

- Degradation of carrier matrix - Breakdown of the nanocarrier by enzyme activity will result in the release of the encapsulated drug.
- Cleavage of protective coatings - Cleansing of the surface coating of the nanocarrier exposes either the drug or the targeting ligands.
- Activation of prodrugs - The enzyme-mediated change of an inactive prodrug into an active drug.

The specific expression of certain enzymes in diseased tissue provides enzyme-responsive systems with a high degree of specificity. MMP-responsive drug delivery systems are commonly used in cancer treatment because MMP's play an important role in tumor invasion and metastasis[20].

However, in order to achieve reproducible performance, there are several issues that must be addressed: variability of enzyme expression levels, possibility of off-target effects, and stability of enzyme-sensitive linkers.

3.4 Redox-Responsive Nanocarriers

Redox-responsive systems are based on the differences in redox potential between intracellular and extracellular environments. The intracellular environment, particularly in cancer cells, is characterized by high concentrations of reducing agents such as glutathione (GSH), which can be up to 1000 times higher than extracellular levels.

These systems typically incorporate disulfide bonds or other redox-sensitive linkages into the nanocarrier structure. Upon entering the intracellular environment, these bonds are cleaved by GSH, leading to the release of the drug[21].

Redox-responsive nanocarriers are particularly useful for intracellular drug delivery, including gene therapy and delivery of anticancer agents. They provide a high level of control over drug release and reduce the likelihood of premature release in the bloodstream.

Nevertheless, the design of redox-responsive systems requires careful consideration of stability and responsiveness to ensure efficient delivery[22].

4. External Stimuli-Responsive Systems

Nanocarriers designed to respond to external stimuli such as temperature, light, magnetic fields or ultrasound, are capable of controlled, localized release of drugs based on the application of a non-invasive or minimally invasive external physical signal. Compared to internal based drug delivery systems that rely on the inherent state of a physiological system, external stimuli based drug delivery systems offer greater precision to control spatial and temporal drug release.

The main area in which external stimuli-responsive systems will be effectively employed is in localized therapies for diseases such as cancer. Targeted drug delivery and precise dosing schedules are critical for the successful treatment of cancer.

External stimuli-based drug delivery systems can be activated using non-invasive or minimally invasive techniques, enabling the clinician to modulate (control) the timing and location of drug release. Effectiveness of these systems depends on tissue penetration and safety of the applied stimulus (i.e. heating device), availability of specialized equipment to stimulate the drug and tissue that contains the targeted disease.

4.1 Temperature Responsive Delivery Systems

Temperature responsive drug delivery systems consist of thermosensitive polymers that undergo a reversible phase change at specific (lower critical solution temperature) LCST temperatures. Temperature responsive delivery systems are one of the most heavily investigated classes of external stimuli responsive drug delivery systems.

Thermosensitive polymer poly(N-isopropylacrylamide) (PNIPAM) is a common example of a temperature responsive polymer that undergoes a hydrophilic to hydrophobic phase transition when temperature exceeds its LCST (approximately 32-40 degrees Celsius). Therefore, when the temperature is below the LCST, the polymer is swollen and hydrated, whereas when the temperature exceeds the LCST, the polymer collapses and the encapsulated drug is released[23].

Application of localized hyperthermia (40-45 degrees Celsius) can be utilized in the clinic to deliver a sustained and controlled release of drug from temperature responsive delivery systems to the site of cancer within the body through the use of an external heating device.ous cells whilst decreasing

the potential for exposure of healthy system components to the pharmaceutical. Some benefits of the method include:

- Controlled and reversible release of the pharmaceutical agent
- Compatibility with hyperthermia-based therapies
- Increased efficiency in targeting the pharmaceutical agent

The following are disadvantages of the method:

- There is a risk of injury to adjacent healthy tissues
- Difficult to achieve a uniform temperature profile
- Limited capability in the application of the method to deep-seated tumors.

4.2 Photoreactive nanoparticles

Photoreactive nanoparticles rely on the use of photoreaction materials to enable a highly precise method for the release of pharmaceutical products when exposed to a specific wavelength of light[23]. There are three mechanisms through which the phototherapeutic device functions:

- Bond cleavage through photocleavage (i.e., o-nitrobenzylic linkers) when exposed to ultraviolet (UV) or visible light;
- Thermal agents (i.e., gold nanoparticles and carbon-based) which convert light energy into thermal energy to cause the release of the pharmaceutical from the photoreactive nanoparticles;

4.2.1 Light Activation

Near-infrared (NIR) light has proven beneficial due to the depth of penetration into tissue as well as the reduction of phototoxicity in comparison to the use of UV or visible light, thus attracting significant research efforts in photodynamic therapy (PDT), photothermal therapy (PTT) and theranostic applications[24].

Benefit:

- Spatially and temporally precise
- Non-invasive activation method
- Capability to be used in conjunction with imaging (theranostic)

Disadvantage:

- Limited depth of penetration of light into tissues (particularly for UV or visible)
- Phototoxicity resulting from light
- Specialized light sources required for activation.

4.3 Magnetoreactive nanoparticles

Magnetoreactive nanoparticles are composed of primarily iron oxide (Fe_3O_4) magnetic nanoparticles capable of being attracted to specific sites in the target tissue with an external strong magnetic field attraction. Under alternating current fields, these nanoparticles produce localized heat through magnetic hyperthermia, which releases the pharmaceutical.

Magnetic nanoparticles, which are loaded with pharmaceuticals, can be directed to tumor tissue using static magnetic field attraction and will accumulate within the targeted area. When exposed to an alternating magnetic field, the temperature of the magnetically directed nanoparticles is increased, causing the release of the pharmaceutical[25].

In addition to the aforementioned method, theranostic imaging and therapeutic efficacy can also be achieved with the application of externally applied magnetic fields to direct the accumulations of pharmaceuticals.

4.3.1 Magnetic Activation

- Targeted accumulation of pharmaceuticals using magnetic fields
- Combination of imaging and treatment modalities
- Magnetic heating enables the controlled release of the pharmaceuticals.

Disadvantages:

- Limited magnetic field penetration into some tissues;
- Possible toxicity due to magnetic materials;
- Need for an external magnetic device.

4.4 Ultrasonic reactive nanoparticles

Ultrasonic reactive nanoparticles make use of acoustic energy (ultrasound) to facilitate the release of pharmaceuticals from nanoparticles. Ultrasonic energy induces (i) cavitation, (ii) mechanical stress and (iii) localized heat in order to disrupt the nanoparticles and release the pharmaceutical products.

Ultrasound (e.g., microscopic and nanoscopic) can be utilized in combination with ultrasonic energy to facilitate the delivery of pharmaceuticals. The mechanical forces of oscillation and destruction of microscopic and nanoscopic bubbles when exposed to ultrasound help to enhance the permeability of the cell

membranes inviting the delivery of pharmaceuticals to the cells.

Ultrasound has additional advantages including:

- Penetrable to sufficient depths into the tissues;
- Non-invasive and harmless;
- Increased cellular uptake of pharmaceutical products through sonoporation.

Disadvantages:

- Potential for tissue damage at higher intensities;
- Difficulty in dosimetry control of pharmaceuticals;
- Need for calibration of the equipment to be used.

5. Nanocarriers Used in Stimuli-Responsive Systems

Nanocarriers serve a major role in the design and performance of stimuli-responsive drug delivery systems. These nanoscale carriers are the vehicles used for encapsulation of therapeutic agents and can be tailored to respond to specific internal or external stimuli. The use of selected nanocarrier significantly affects the following drug loading capacity, release kinetics, targeting efficacy, stability, and biocompatibility. In stimuli-responsive systems various types of nanocarriers have been used, with each offering different structural and functional benefits[26].

5.1 Liposomes

Liposomes are spherical vesicles made up of one or more phospholipid bilayers that surround an aqueous core and are among the most commonly used nanocarriers due to their superior biocompatibility, biodegradability, and ability to encapsulate both hydrophilic and lipophilic drugs.

In a stimuli responsive system liposomes can be functionalized with pH-sensitive lipids or with temperature-sensitive materials that disrupt the lipid bilayer causing drug release. Thermosensitive liposomes, for example, are able to release their contents when exposed to mild hyperthermia, making them an excellent choice for treatment of cancer.

5.2 Polymeric Nanoparticles

Polymeric nanoparticles are solid colloidal systems made of biodegradable polymers such as PLGA, PEG, and chitosan. Polymeric nanoparticles can be designed as either nanospheres or nanocapsules and give an opportunity for controlled and sustained drug release.

In order to provide the mechanism for stimuli-responsiveness, functional groups or linkers that respond to either pH, ROS, or enzymes have been incorporated into the formulation.Polymer-based nanoparticles can be modified in terms of size, chemical composition, and surface charge to meet a variety of needs.

Dendrimers are highly branched macromolecules that have the potential to hold multiple drugs in one molecule due to their structural characteristics. They also allow for extensive control of functional group characteristics.

In a drug delivery system that is responsive to a stimulus, dendrimers can be modified with targeting ligands or linkers to facilitate controlled release and increased cellular delivery. Thus, dendrimers will play an important role in gene therapy and cancer treatment.

SLNs and NLCs are lipid-based nanoparticles that provide drug stability and controlled release. SLNs consist of solid lipids while NLCs are made from both solid and liquid lipids (i.e., NLC provides the ability to hold a larger drug amount and decrease the amount expelled).

SLNs and NLCs can also be designed to respond to various stimuli (e.g., temperature or pH) through the incorporation of responsive lipids and/or surfactants into the lipid matrix. SLNs and NLCs can therefore be utilized by oral, topical, and transdermal routes.

Polymer micelles are based on amphiphilic block copolymers that assemble into nanostructures. Polymer micelles consist of a hydrophobic inner core surrounded by a hydrophilic (i.e., super-hydrophobic) outer shell (making them a good vehicle for delivering poorly water-soluble drugs).

Polymer micelles allow for the controlled release of drug by altering the chemical structure of a polymer micelle (i.e., by destabilizing the core or losing the outer shell) when stimulated by a specific trigger (i.e., pH, temperature, or reactive oxygen species). Polymer micelles are much smaller than the RES and therefore can effectively target tumors. Table 3 provides information on the different characteristics of nanocarriers.

Table 3: Common Nanocarriers and Their Characteristics

Nanocarrier	Key Features	Stimuli Compatibility	Applications
Liposomes	Biocompatible, dual drug loading	pH, temperature	Cancer therapy
Polymeric nanoparticles	Controlled release, versatile	pH, ROS, enzyme	Targeted delivery

Dendrimers	High loading, precise structure	pH, enzyme	Gene delivery
SLNs/NLCs	Stable, scalable	Temperature, pH	Oral/topical delivery
Micelles	Amphiphilic, small size	pH, temperature	Hydrophobic drugs

After careful consideration of which nanocarrier to use will provide the basis for designing a successful delivery system that responds to different stimuli. Each type of nanocarrier has its own advantages and the ability to modify each type of nanocarrier to provide a means of response to each of the stimuli listed will ultimately lead to the development of advanced multifunctional nanocarriers which can ensure efficient drug delivery. Continued progress in the fields of polymer chemistry and nanotechnology will lead to new and innovative multifunctional nanocarriers.

6. The Tumor Microenvironment

The tumor microenvironment (TME) is now a focus area in the development of next-generation drug delivery systems, given the differences in biology and biochemistry between tumors and normal tissues. The characteristics of TME are unique and offer an avenue for bioengineering of stimuli-responsive drug nanocarriers that provide selective drug release within the tumor, leading to improved efficacy of the drug as well as reduced side effects.

The TME is a complex, dynamic environment consisting of heterogeneous populations of cancer cells, stromal cells, immune cells, extracellular matrix proteins and aberrant vascular structures. The most prominent features of TMEs include: the acidic extracellular pH (6.5-6.8), the presence of high levels of reactive oxygen species (ROS), the presence of large amounts of hypoxia and a high concentration of proteolytic enzymes (matrix metalloproteinases - MMPs). The characteristics arise from rapid tumor growth, abnormal tumor metabolism and lack of adequate blood flow to the tumor.

A hallmark of TME is the acidic extracellular pH (6.5-6.8) as opposed to the physiological pH of all other normal tissues (7.4). This acidosis is due to β-glycolysis and the production of lactic acid, as result of metabolic changes occurring in the tumor cells that can provide β-hydroxybutyric acid, which can provide pH-responsive nanocarriers as a mechanism by which the difference in pH of TME to normal tissues can serve as a basis for drug release from nanocarriers in the appropriate location and, thus, improve the selectivity of the drug.

Additionally, a characteristic of TME are the elevated amounts of ROS as a result of mitochondrial dysfunction and increased metabolic activity.Nanocarriers that are responsive to the tumor microenvironment can undergo oxidative degradation (oxidative breakdown) in that environment to provide a controlled release of drugs. Therefore, nanocarriers are an excellent platform for the delivery of chemotherapeutics, where they provide high specificity and reduced damage to non-cancerous tissues.

The tumor microenvironment is defined by several characteristics, with hypoxia (low oxygen levels) being another dimension associated with the tumor microenvironment. It is due to the inadequate supply of blood vessels to the tumor site and rapid growth of the tumor. To address hypoxia, there are hypoxia-responsive systems that are set to release drugs under low oxygen levels typically utilizing hypoxia-sensitive linkers including azobenzene and nitroimidazole derivatives. These systems enhance drug accumulation in poorly oxygenated regions of tumors that are often resistant to conventional therapy.

In addition to pH and ROS, there is also an overexpression of enzymes (e.g., MMPs, cathepsins, phospholipases) in the tumor microenvironment. Enzyme-responsive nanocarriers use substrates that can be cleaved by the respective enzymes at the target site and allow for site-specific drug release. MMP-responsive systems are frequently used to target the invasive border of tumors, as MMPs have an important role in both tumor progression and metastasis[27].

The enhanced permeation and retention (EPR) effect is also an important factor that allows for nanoparticle accumulation in tumors. The leaky vasculature and poor drainage in tumor tissues create a local excess of nanoparticles at the tumor site. Although the EPR effect provides for passive targeting of nanocarriers, there is considerable intertumoral and intratumoral heterogeneity in the EPR effect, which requires the implementation of stimulus-responsive systems due to the

heterogeneity associated with specific patient responses.

There is potential for the combination of active targeting strategies based on ligands and TME-responsive systems to increase the targeting efficiency of drug delivery. Targeting ligands, such as folic acid, transferrin, antibodies, and peptides, can bind receptors that are overexpressed on cancer cells, thereby promoting uptake of the nanocarriers and subsequent cellular release of the drug from the nanocarriers.

The development of multi-stimuli responsive nanocarriers that respond to multiple characteristics of the TME, such as pH and ROS or pH and enzyme action, has gained considerable attention in recent years. These systems have improved target specificity, decreased premature release rates, and provided significantly enhanced therapeutic benefit.

Thus, TME-responsive drug delivery systems represent a major advancement in targeted drug delivery systems for treatment of cancer. The ability to exploit the unique characteristics of the TME for selective release of drug, targeted delivery of drugs to cancerous tissues, and decreased systemic toxicity, provide opportunities for the advancement of TME-responsive drug delivery systems for the treatment of cancer. However, there are several hurdles that must be overcome to ultimately harness the clinical benefits of TME-responsive drug delivery systems including the heterogeneity of the TME and the variability in patient responses to therapy.

7. Dual and Multi-Stimuli Responsive System

Nanocarrier systems (NS) that respond to multiple stimuli (dual and multi) are used for a variety of applications, particularly drug delivery systems. When using NS that only respond to a single stimulus (i.e., single-stimulus responsive NS), several limitations exist, including premature drug release, low specificity for targeting the desired site, and variability of physiological conditions.

The design and development of novel dual/multi-stimuli responsive NS will improve the ability of delivery systems to be responsive to multiple internal and/or external stimuli in a sequential or simultaneous manner, thereby improving the precision and control of drug delivery, resulting in greater therapeutic efficacy.

Typically, dual-stimuli responsive NS are designed to exhibit two complementary stimuli (e.g., pH & ROS, pH & T, or enzyme and redox), thereby allowing the NS to respond to two different signals when the NS are used for targeted drug delivery. For example, NS targeting tumors can be designed to remain stable and intact at a physiological pH (7.4) but will partially activate in the mildly acidic environment of the tumor, and upon internalization in cancer cells, the elevated levels of ROS or the increased levels of glutathione will stimulate a complete release of drug from the NS. The stepwise activation mechanism of dual-stimuli responsive NS allows for reduced premature leakage of drug and substantially greater delivery of drug to the targeted site.

Multi-stimuli responsive NS can be designed to respond to three or more stimuli, resulting in advanced levels of delivery control. The multi-stimuli responsive NS will respond to both external and internal stimuli (e.g., pH, ROS, enzymes), resulting in either autonomous (self-initiated) or externally controlled release of drug. A prime example of this is when NS accumulate in tumors by some mechanism such as the EPR effect, then respond to acidic pH to initiate the first activation, and then are stimulated to release drug via photothermal therapy induced by exposure of the NS to NIR (near infrared radiation) light.

Multifunctional polymers, hybrid nanomaterials, and multilayered nanostructures allow for the integration of multiple responsive elements within one NS system (e.g., pH-activated linkers, ROS-cleavable bonds, thermosensitive polymers, and photoresponsive agents). The following table 4 summarizes potential dual/multi-stimuli responsive systems[28].

Table 4: Summarizes potential dual/multi-stimuli responsive systems.

System Type	Stimuli Combination	Mechanism	Application
Dual	pH + ROS	Acid-triggered swelling + oxidative cleavage	Cancer therapy

Dual	pH + Temperature	LCST transition + acidic degradation	Hyperthermia-based delivery
Dual	Enzyme + Redox	Enzymatic cleavage + GSH-triggered release	Targeted intracellular delivery
Multi	pH + ROS + Light	Sequential activation + photothermal release	Precision oncology
Multi	pH + Enzyme + Temperature	Multi-layered degradation	Controlled release systems

The advantages of dual/multi-stimuli responsive systems include:

- Increased specificity - The use of multiple stimuli reduces the chance of off-target drug release.
- Increased control - Sequential and/or combined activation mechanism provides for better control of the delivery of therapeutic agents.
- Decreased toxicity - Minimization of premature drug leakage reduces the potential for adverse events related to toxicity.
- Increased adaptability - The incorporation of multiple responsive mechanisms into one NS platform increases the use of NS in complex environments.

Challenges exist when using dual/multi-stimuli responsive systems in NS due to the complexity of the designs and synthesis, the higher cost of production, and the limited ability to reproduce and scale.

Dual/multi-stimuli responsive NS provide improved specificity and controlled release of therapeutic agents compared to traditional single-stimulus responsive NS. As additional research on dual/multi-stimuli responsive NS continues to expand, it is anticipated that clinical applications of these types of systems will facilitate the development of individualized therapeutic regimens resulting in enhanced success rates[29].

8. Aid in the Delivery of Drugs to Patients' Bodies

Nanocarriers that respond to stimuli have demonstrated a wide variety of applications in many areas of therapy because they enable controlled, directed, and efficient delivery of a drug. By responding to various types of stimulants (internal or external), nanocarriers improve therapy and reduce the overall toxicity of drugs to the whole patient. Because nanocarriers are versatile, they provide potentially effective treatment options for complicated diseases; particularly those in which conventional or standard methods of drug delivery fail.

Cancer continues to be the most researched area of application for nanocarriers that respond to stimuli. Stimuli-responsive nanocarrier systems are engineered to take advantage of specific characteristics of cancerous cells — very acidic pH, elevated levels of ROS (reactive oxygen species), hypoxia, and overexpression of enzymes. By enabling selective drug release from nanocarriers using these stimuli, it is possible to minimize damage done to healthy cells whilst delivering maximum amounts of the chemotherapeutic agent to the cancerous tissue.

Examples of stimuli-responsive systems that use either a pH or ROS stimulus to cause the release of the drug intracellularly following the endocytic process will increase the cytotoxicity of the chemotherapeutic agent to the cancerous material. On the other hand, external stimuli (other than pH and ROS) such as temperature (hyperthermia) and light (photodynamic and photothermal treatment) can also be used to improve the ability of the stimuli-responsive nanocarrier to directly target cancerous cells and effectively administer the appropriate therapeutic agents. In addition, the addition of imaging agents to the stimuli-responsive nanocarriers has led to the development of theranostic (therapeutic and diagnostic) platforms.

Nanocarriers that respond to stimuli have shown great potential for the delivery of genetic material (DNA, siRNA, and mRNA) and protect the nucleic acids from being degraded by nucleases and enable their transport across cellular barriers.

Redox-responsive (reduction-oxidation) nanocarriers are particularly useful for the delivery of genetic material because they will release the genetic material in the reductive intracellular environment (e.g., containing glutathione). Similarly, pH-responsive nanocarriers can deliver genetic material from the endosome to the cytoplasm (ensuring successful delivery of nucleic

acid). Therefore, nanocarriers that respond to stimuli have great potential as tools for gene therapy and genome editing[30].

In the event of an inflammatory process and infection, elevated levels of ROS and particular enzymes are common. Therefore, nanocarriers that respond to stimuli have the ability to target the delivery of anti-inflammatory drugs to areas where oxidative stress will improve the therapeutic outcome in diseases such as arthritis and inflammatory bowel disease.

Enzyme-responsive nanocarriers can deliver drugs to bacterial infections by using the enzymes produced by the bacteria as the target for the nanocarrier. This type of nanocarrier improves the localization of the therapeutic agent to the infected area while decreasing the systemic side effects for the patient, thereby improving patient safety and therapeutic efficacy. [28].

Nanocarriers that respond to stimuli have also been utilized in transdermal and topical drug delivery. Examples include smart hydrogels (that respond to pH, temperature, or light), microneedles, and nanofibers that can be used to control the release of a drug through the patient's skin to treat a localized area affected by disease or injury (including wound healing) or to relieve pain. [24]

Nanocarriers that respond to stimuli exhibit a wide range of possible applications, which have the potential to revolutionize drug delivery systems across different areas of therapy. The use of nanocarriers that respond to stimuli to provide targeted, controlled, and efficient delivery of drugs is anticipated to be of substantial value to modern medicine. Future progress in the field should only serve to further increase the utility of stimuli-responsive nanocarriers in the clinical setting.

9. Challenges and Limitations

The considerable potential of stimuli-responsive nanoscale carriers in targeted therapeutic delivery via stimulation has led to substantial progress in their use for the targeted treatment of disease. However, several challenges remain that impede their broader clinical implementation and commercialization, most of which need to be overcome to access all of the therapeutic advantages provided by these innovative delivery systems.

The principal impediment to usable stimuli-responsive carriers is the design and preparation of the carriers themselves. Most stimuli-responsive carrier systems require the incorporation of multiple functional components, linkers and targeting ligands, making the multi-step fabrication process technically complex. Thus, greater complexity increases the production costs of the carriers as well as the reproducibility and scalability of the carriers, which are critical features for commercial manufacturing[29].

Another limiting factor of the utilization of stimuli-responsive carriers for therapeutic delivery lies in the stability of the carriers throughout storage and circulation in the systemic circulation prior to being exposed to the appropriate stimulation. If they are subjected to unintended environmental conditions, e.g. oxidation or exposure to light, prior to achieving an expected response and during the time they are in systemic circulation, the release of the drug from the carrier will be either premature or occur not at all, thereby limiting the expected efficacy of the medicine and potentially resulting in the systemic toxicity of the medicine.

In addition to stability considerations, biological variability of the pathways used to create stimulation-response mechanisms represents another challenge to achieving an acceptable level of efficacy for the use of internal stimuli-responsive carriers. The successful use of internal stimuli-responsive carriers for the therapeutic delivery of drugs depends primarily on either the lack of consistency of physiological conditions (i.e., pH, levels of reactive oxygen species) within individuals, between the stages of a disease, and between different sites/tissues within of the tumor and the creation of the necessary signaling that ultimately results in triggering release of the drug from the carrier.

For external stimuli-responsive systems, limited tissue penetration of the delivery carrier, particularly of light-, heat- and/or ultrasound-based systems, represents the main challenge posed by their use in therapeutic delivery via stimulation. The use of these materials may also pose safety issues when responding to the aforementioned 3 types of external stimuli[26].

Finally, from a regulatory perspective, regulatory agencies require stringent safety, toxicity, pharmacokinetics and quality control requirements for the approval of the use of the carriers. In addition to the rigid evaluation and regulatory requirements, the lack of standardized evaluation protocols also adds to the difficulty of the approval process.

The clinical application of stimuli-responsive nanocarriers in the therapeutic delivery of pharmaceuticals offers distinct advantages, but

challenges exist in terms of the complexity of the carrier systems, stability/variability of the internal or external systems used to create an appropriate response, and/or the successful completion of the regulatory approval process for the commercial use of the carriers. Ongoing research and developments are necessary to overcome these challenges so that successful clinical translation of the carriers can occur.

10. Conclusion

With the advent of stimuli - responsive nano-carriers, the method of delivering medications to patients has changed dramatically. A nano-carrier can deliver drugs in a targeted manner and increase the overall efficacy of the treatment (as well as decrease any negative interactions with the body). The use of two of the more commonly identified types of responsive systems (tumor microenvironment responsive systems and reactive oxygen species (ROS) responsive systems) has provided great promise for cancer treatment due to their specific responses to the presence of disease/pathological conditions.

Advancements over existing responsive systems are systems that respond to multiple stimuli; these systems can provide solutions to the multiple limitations of previous single stimulus responsive systems. The most significant limitation of previously available single stimulus responsive pharmaceutical delivery systems is that they do not provide targeted drug delivery or controlled release of the drug.

While there have been many advances in the development of responsive, nano-carrier systems, several limitations remain that must be resolved before these carriers can be used in clinical practice. These include challenges related to formulation complexity, manufacture of scale-up, stability of the carrier, biological variation, and acquiring regulatory approval through interdisciplinary research and technological innovation.

Therefore, stimuli - responsive nano-carriers represent an exciting and much needed platform for future generations of drug delivery systems. Consequently, once these systems are implemented into clinical practice, they could enhance overall patient outcomes and help to advance the field of personalized medicine.

Ethical Approval and Consent to Participate

This article is a review study and does not involve any human participants or animals. Therefore, ethical approval and informed consent were not required for this work.

Consent for Publication

Not applicable.

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Compliance with Ethical Standards

This manuscript complies with all applicable ethical standards for research and publication.

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