Available online on 15.4.2025 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

Open Access to Pharmaceutical and Medical Research

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Review Article

Stimuli-Responsive Nanocarriers for Site-Specific Drug Delivery System

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A B S T R A C T

Stimuli-responsive nanocarriers have emerged as a promising tool for site-specific drug delivery, offering improved therapeutic efficacy and reduced side effects. These nanocarriers can respond to various internal and external stimuli, such as pH, temperature, light, and enzymes, to release therapeutic agents in a controlled manner. The design and synthesis of different types of stimuli-responsive nanocarriers, including liposomes, polymeric nanoparticles, micelles, and hydrogels, are discussed. The applications of these nanocarriers in cancer therapy, treatment of inflammatory arthritis, gene therapy, and management of neurological diseases are also explored. The benefits and challenges of using stimuli-responsive nanocarriers for site-specific drug delivery are highlighted, and future directions for research and development are outlined. The potential of stimuli-responsive nanocarriers to revolutionize the field of medicine by providing targeted and controlled drug delivery is emphasized.

Keywords: Stimuli-responsive nanocarriers, Site-specific drug delivery, Cancer therapy, Gene therapy, Neurological diseases

A R T I C L E I N F O: Received 24 Dec. 2024; Review Complete 27 Jan. 2025; Accepted 14 March 2025. ; Available online15 April. 2025

Cite this article as:

Gawai AY, Hatwar PR, Bakal RL, Nehar KN, Bhujade PR, Stimuli-Responsive Nanocarriers for Site-Specific Drug Delivery System, Asian Journal of Pharmaceutical Research and Development. 2025; 13(2):100-106, DOI: http://dx.doi.org/10.22270/ajprd.v13i2.1547

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INTRODUCTION:

It is commonly known that to increase therapeutic efficacy and minimize or prevent side effects, drugs must be delivered to target sites in a controlled manner. Stimulus-based drug delivery systems showed a great deal of interest in this regard for efficiently delivering active drug moieties. The first-time thermosensitive liposomes were used to deliver drugs was in 1978[1]. Designing and developing materials with sizes ranging from approximately 1 nm to even hundreds of nanometers is the focus of nanotechnology, which makes it possible to create materials with a specific structural molecular architecture[2]. The ability of a range of stimuli, such as temperature, pH, redox state, light, and magnet fields, to alter a material's characteristics, interactions, structure, and/or dimensions is being studied. The pharmacokinetic and pharmacodynamic profiles can be enhanced by NPs [3]. To enhance the results of diagnosis and treatment, nanocarriers provide a flexible platform for loading a variety of payloads, such as imaging agents, nucleic acids, anticancer medications, photosensitizers, and antibodies, among others [4]. Due to their ability to alter their physicochemical characteristics in response to various stimuli, including low pH, enzymes, redox agents, hypoxia, light, temperature, magnetic fields, ultrasound, and so forth, stimuli-responsive polymeric nanoplatforms are receiving increasing attention [5]. From drug delivery systems to diagnostics and treatment, stimuli-responsive materials have a wide range of uses in the biomedical industry[6]. When it comes to targeted drug delivery and on-demand release of cargo drug molecules, stimuli-responsive nanocarriers provide distinct advantages over typical drug delivery systems (DDSs)[7]. Both chemical and physical stimuli-responsive drug delivery systems can be categorized as stimuli-responsive drug delivery systems [8]. Imaging agents for cancer diagnosis and development of novel anticancer medications and tactics have been the primary uses of these novel drug-delivery and targeting systems[9].

Types of Stimuli -Responsive Nanocarriers

1. **pH responsive nanocarriers:**

One of the most widely used delivery stimuli is pH-responsive nanocarriers, which can be applied to specific organs (such as the gastrointestinal tract or vagina) or to organelles (such as lysosomes, golgi, and endosomes). It has also been used to release drug moieties in altered pathological conditions, such as inflammation, cancer, or ischemia with visible pH changes [1].

- **Benefits:**

a) Increases drug delivery efficiency.
b) Controls drug release rate.
c) Boosts cell uptake as needed.
d) Greater anti-cancer effects in a tumor model in mice[10].

2. **Ultrasound-responsive nanocarriers**:

Ultrasound has a number of benefits, including superior tissue penetration, safety, ease of use, and non-vasiveness. As a result, targeted drug delivery has made extensive use of ultrasound-responsive nanomedicines [11]High-frequency sound waves like ultrasound have an ability to influence nanocarriers for regulated drug release at diseased sites, such as tumors[4]. Imaging, kidney stone disruption, blood circulation analysis, lipectomy, tumors, leiomyomas, and dentistry are just a few of the medical uses for ultrasound [8]. Both medical diagnosis and treatment have been transformed by ultrasound. Additionally, it has been used to promote and increase the healing of soft tissue injuries, including bone fractures[12].

3. **Temperature responsive nanocarriers**:

Drug delivery and cancer treatment have made extensive use of temperature-sensitive nanocarriers [4]. Both internal and external temperature stimuli are possible [13]. Because of their phase transition behaviorin response to temperature changes, temperature-responsive materials have been extensively studied for smart drug delivery applications. When a pathological condition (such as a tumor or inflammation) causes a local temperature increase, temperature can either act as an external stimulus (heat applied from the outside) or as an internal stimulus. Tumor tissues, for instance, are marginally hyperthermic, meaning they are 1-3 degrees Celsius warmer than normal tissue [14].

- **Benefits:**
  - Increases EPR effect and radiotherapy and chemotherapy responsiveness.
  - Wide applicability and ease of synthesis characterize temperature-sensitive nanoparticles[15].

4. **Light-responsive nanocarriers:**

In the clinical treatment of a number ofdiseases, light is a commonly employed exogenous stimulus[16]. Compared to other stimuli, light stimulators have the advantage of being immediate highly precise, and able to provide spatial and temporal control using less invasive methods [6]. LRDDS are primarily used in photodynamic therapy (PDT), a combined therapy that uses light and photoactivatable photosensitizer in the presence of tissue oxygen [8]. It is one of the most studied stimuli in DDSs due to its low toxicity and ease of administration [17].

- **Benefits**

a) High accuracy.
b) Inexpensive.
c) Minimal disturbance
d) Ionizing radiation is absent[15].

5. **Thermoresponsive nanocarriers**:

A stimuli-responsive drug delivery method for severaldiseases, thermoresponsive systems is extensively studied. Typically composed of a single temperature-sensitive component, a thermoresponsive nanocarrier can release the drug it contains in response to changes in the surrounding temperature [18]. The ability of a material or substance to significantly change at least one of its physicochemical properties in response to temperature changes is known as thermoresponsiveness[19]. Since its first report in 1967, PNIPAAm, the most successful thermoresponsive polymer, has been that the individual of much research [11].

6. **Enzyme-responsive nanocarriers:**

Enzymes are crucial for biological processes, and their uncontrolled expression in cancerous conditions may serve as a catalyst for the delivery of drugs that respond to enzymes [4]. To help deliver drugs to cancer cells, a variety of enzymes have been employed, including lipase, protease, trypsin, glycosidase, phospholipase, oxidoreductase, and others [1]. The two components of the enzyme-responsive nano-drug delivery system are (i) a nanomaterial scaffold with the enzyme-sensitive part that breaks down when it comes into contact with enzymes; and (ii) encapsulated therapeutic agents that are either conjugated via electrostatic interaction between the active ingredient and the charged carrier or bound to the outer lipid membrane or lipid core, or biodegradable (like ester) bonds [10].

7. **Magnetic Nanocarriers:**

MNCs have attracted a lot of attention lately because of their huge potential as heat regulators for the treatment of hyperthermia and their capacity to deliver medications in a targeted way that can lessen systemic effects[20].

Ideal characteristics of MRDDS's:

1) They should be composed of nanoparticles to enable capillary-level perfusion.
2) They should be sufficiently magnetically responsive.
3) They should be able to transport a broad range of active therapeutic agents.
4) They can be made to serve as targeted or controlled drug delivery systems.
5) They have low levels of toxicity and antigenicity.
6) They are highly biocompatible and biodegradable [8].

8. **Carbon-Based Nanomaterial:**

Because of their special biological, physical, and chemical properties, carbon nanotubes (CNTs), which are long cylindrical structures with flexible NCs characteristics, have attracted interest as drug delivery molecules [20]. Carbon nanotubes range in diameter from 0.8 to over 100 nm and in length from 100 nm to several centimeter[5].

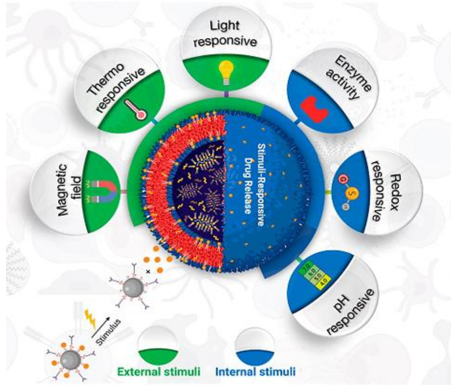

Figure 1: A schematic representation types of stimuli-responsive Nanocarriers [20].

Materials Used To Design Stimuli-Responsive Nanocarriers:

1. Liposomes:

The British hematologist Dr. Alec D. Bangham and associates at the Babraham Institute, University of Cambridge, made the initial discovery of liposomes in the 1960s. The first report on the subject was published in 1964 (Bangham and Horne, 1964) [21]. The spherical concentric vesicles known as liposomes were created by combining the Greek words "Lipos," which means fat, and "Soma," which means body [22]. One of the earliest types of nanoparticle candidates utilized as drug delivery systems in clinical applications, liposomes are made of phospholipids [23]. Both hydrophilic and hydrophobic medications can be delivered by the lipid bilayers and the aqueous core of liposomes [18]. Liposome nanoemulsions are commonly used nanoparticles in nanomedicine primarily because of their safe excipients, high drug loading efficiency, stability, ease of synthesis, and high bioavailability [24].

Liposome benefits include:

a) Betterdelivery to the disease site.

b) A reduction in the free drug's systemic toxicity[20].

c) Increased circulation time [15].

2. Quantum Dots:

These nanoscale semiconductor materials have excellent optical, electrical, and photoluminescent qualities, making them ideal for image-guided drug delivery applications [18]. The shell core structure of quantum dots is usually made up of elements from the II VI or III V groups of the periodic table [25].

Benefits:

1) Advantageous fluorescent characteristics
2) Drug delivery to the intended site, easy detection, and monitoring [15].

3. Dendrimers:

A new class of polymer materials, dendrimers are named after the Greek word "dendron," which means tree. They are macromolecules with branched repeating units that expand from a central core and contain external functional groups [26].

4. Gold nanocarriers:

Gold nanocarriers, or AuNCs, have been used as anticancer agents in photothermal therapy (PTT) because of their exceptional ability to convert light into heat [20].

Their advantages include:

1) Increased loading, biocompatible, ease of synthesis and conjugation of multiple bioactive agents, control of particle size, and optimized pharmacokinetics and biodistribution [15].
2) Improved selectivity to brain [27].

5. Hydrogel:

Hydrogels and nanogels are a significant class of materials used in thermoresponsive carriers. Networks with a highwater content that are cross-linked chemically or physically are called hydrogels. Three-dimensional networks of polymers dissolved in water form hydrogels, which are semi-solid materials with a composition of over 99% water [9]. Because of their superior qualities, including nontoxicity, biocompatibility, and biodegradability, hydrogels are being used extensively in biomedical fields for drug delivery [28].

Benefits:

1) Simple administration[15].
2) A variety of drug delivery applications, such as wound healing and cell delivery [15].

6. Micelles-

Micelles are amphiphilic surfactant molecules that consist of lipids and amphiphilic molecules. The diameter of micelles ranges from 10 100 nm [25]. Both hydrophobic and hydrophilic interactions produce a thermodynamic equilibrium that protects the core-shell structure of micelles. Micelles are tiny particles with hydrodynamic diameters ranging from 5 to 100 nm [29].

Advantages:

1) Biodegradable and biocompatible
2) Extravasation is encouraged by small size
3) Surface functionalization is possible [12].
4) Reduced systemic toxicity of free drug; enhanced delivery to disease site [20].

7. Polymeric nanocarriers:

In 1975, the idea of delivering therapeutically active substances via polymers was first proposed [30]. Because polymeric nanoparticles are highly biocompatible, biodegradable, and structurally versatile, they have been used extensively as drug and bioimaging agents [5].

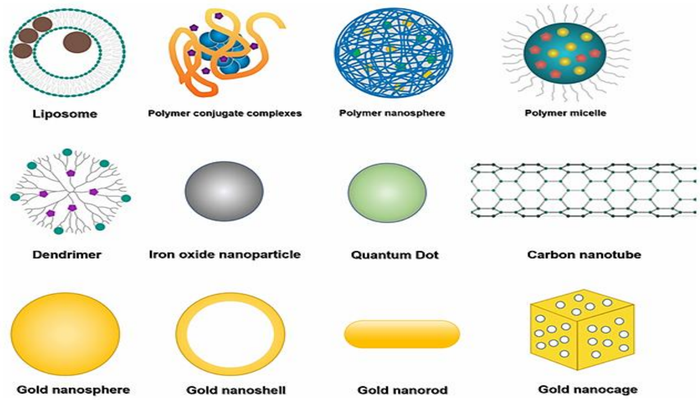

Figure 2: Structure of nanocarriers [5]

APPLICATIONS

1. **Cancer therapy**:

Uncontrolled growth of cells that are irregular that have the potential to spread to other parts of the body is a characteristic of cancer, which includes over 80 diseases [14]. Nanoparticles' high specific surface area, ease of modification, and potent targeting capabilities have made them popular in antitumor research[31]. Because of their potential for targeting, stimuli-responsive nanoparticles are a rapidly developing area of study in the treatment of cancer [32]. Stimuli-responsive drug delivery systems have become promising instruments for advanced cancer treatment[33]. The use of nanomedicine appears to be a great strategy that can overcome a number of issues that are usually observed in the conventional cancer therapy methods, such as low specificity, rapid drug clearance, biodegradation, and very limited targeting property [34].

The ideal nanomedicine would cure cancer without causing any side effects [11]. One of the most commonly used stimuli-responsive nano systems for cancer therapy is pH sensitive nanocarriers [34]. Of the various stimuli-responsive systems, temperature-responsive systems are the most investigated, especially in the field of oncology. In recent years, a new strategy known as targeted drug delivery systems was introduced that could enhance the selectivity of cancerous tumor and decrease the toxicity effects of the chemotherapeutic agents [8].

2. **Treatment for inflammatory arthritis**:

Inflammatory arthritis is a chronic condition that causes joint pain and significantly limits a patient's ability to perform daily tasks [10]. The immune system's biological reaction to defending living things against harmful substances is inflammation. However, a number of harmful chronic diseases, including atherosclerosis, are linked to excessive and uncontrolled inflammation[35]. One of the main causes of disability in the elderly is inflammatory arthritis. This disorder, which is mostly brought on by osteoarthritis (OA) and rheumatoid arthritis (RA), results in joint pain, loss of function, and a decline in quality of life[22].

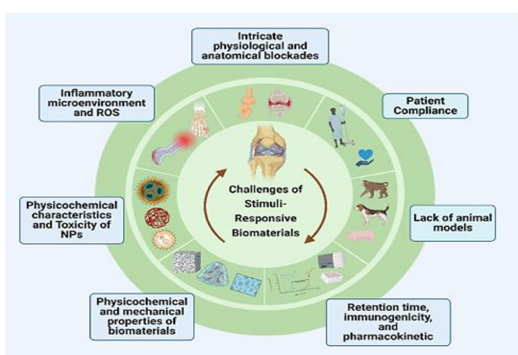

Figure 3: Depicted various potential challenges of "Smart" stimuli-responsive biomaterials for the management of inflammatory arthritis [36].

3. **Gene therapy**:

Genetic alterations are linked to a number of human diseases. A significant advancement in the treatment of these genetically modified diseases, gene therapy sets the course for future research into diseases that traditional medicine is unable to treat[37]. Conventional gene therapy typically uses gene modification in conjunction with high-dose chemotherapy, antagonizing antioncogenes, expressing suicide genes, or enhancing host anticancer immunity [38]. One promising approach to treating complex diseases and monogenetic disorders is gene therapy [37]. Stimuli respond to various internal and external stimuli in order to participate in the transfection of nucleic acids. An interesting prospect for drug and gene delivery is provided by stimuli-responsive nanocarriers, in which the delivery system takes an active role in therapy optimization rather than serving as a passive vehicle[39].One of the most effective systems for gene therapy and stimulus-responsive cancer is redox responsive DDS [40].

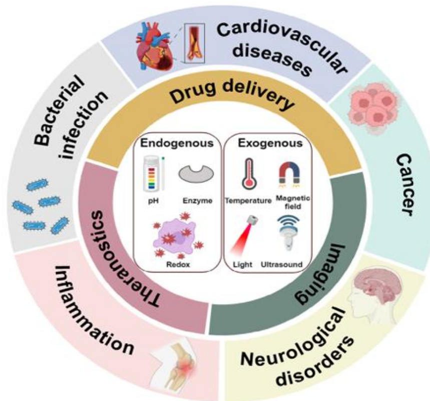

Figure 4: Biomedical applications of stimuli-responsive nanomaterials [41].

4. **Management of neurological diseases**:

Traumatic brain injury (TBI), Alzheimer's disease, Parkinson's disease, dementia, epilepsy, schizophrenia, stroke, depression, and glioblastoma (GBM) are among the primary neurological disorders that have a high incidence. The three-dimensional cross-linked polymer structure of stimuli-responsive hydrogels gives them special qualities that make them appropriate for treating a range of brain disease issues[42]. Nanotechnology's sensitivity, specificity, and accuracy can be very helpful in identifying even trace amounts of biomarkers linked to neurological disorders. It is therefore widely used in diagnostics. The only substance that allows for the most effective use of small dosages of medications to produce the best results is nanomaterials[27].

In response to internal or external stimuli or physiological or pathological environmental stimuli, stimuli-responsive hydrogels can change their structures, functions, and properties either irreversibly or reversibly, which enhances their therapeutic effects on illnesses [29]. Although QDs' capacity to cross the blood-brain barrier has been demonstrated, their possible toxicity may still need to be evaluated [27].

The following points encapsulate the benefits of using biomaterials to treat neurological disorders. Because biomaterials can easily pass through the blood-brain barrier (BBB), they offer promising new avenues for neurological disease diagnosis and treatment.

- Most significantly, biomaterials' exceptional biocompatibility eliminates the possibility of toxicity, which is currently a significant drawback of synthetic nanomaterials.
- Because hydrogels are so porous, there is currently no better option for drug delivery systems or scaffolds that bind stem cells and may pass through the blood-brain barrier [43].

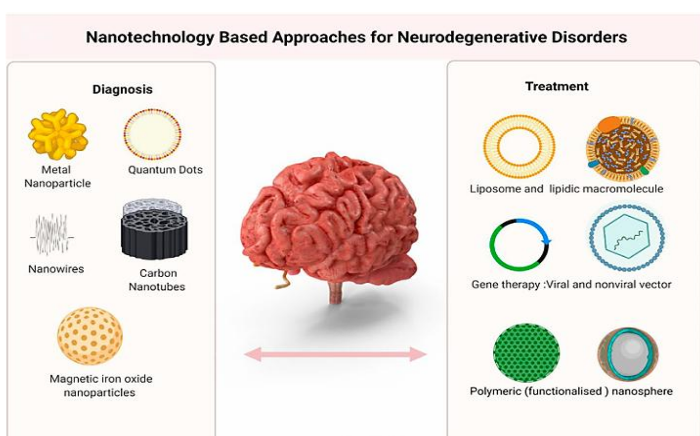

Figure 5: Different form of NPs and their Application to treat and control Neurological Disorder [43].

CONCLUSION:

Stimuli-responsive nanocarriers have shown great promise for site-specific drug delivery in various diseases, including cancer, inflammatory arthritis, and neurological disorders. These nanocarriers can be designed to respond to specific stimuli, such as pH, temperature, or light, to release therapeutic agents in a controlled manner. While there are still challenges to be addressed, the benefits of using stimuli-responsive nanocarriers for site-specific drug delivery make them an attractive option for future research and development. There is a need for additional research to thoroughly investigate the potential of these nanocarriers and to convert them into clinical applications.

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