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Review Article

Smart Nanocarriers in Targeted Drug Delivery: Advances, Challenges, and Future Directions

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ABSTRACT

Nanocarrier-assisted Smart Drug Delivery Systems (SDDS) are one of the most revolutionary advances in contemporary medicine. Nanodelivery systems have been developed for improved therapeutic accuracy, higher bioavailability, and lower systemic toxicity. Different from conventional formulations, the smart nanocarriers respond to stimuli and incorporate surface engineering, molecular targeting and controlled drug release toward improved PK-PD performance. In the past 10 years, progress in material science, lipid technology, polymer chemistry and knowledge about nanobio interface have allowed the formulation of novel nanocarrier systems. These systems consist of liposomes, polymeric NPs, dendrimers, nanogels, Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs), metallic nanoparticles, and biomimetic nanosystems as well as hybrid multifunctional constructs. These carriers can respond to both internal (pH, redox, enzymes, hypoxia and reactive oxygen species) and external (light, heat, magnetic fields, ultrasound, and electric fields) stimuli in a smart way, leading to controlled release and better therapeutic efficacy. Smart nanocarriers have shown excellent capacity for delivering cancer-targeted therapy, neurotherapy, infectious disease management, metabolic disorder management, cardiovascular diseases treatment, immunotherapy, gene therapy, and vaccination. Recent progress can be noted in the cell membrane-coated nanoparticles, lipid nanoparticle for mRNA vaccine, CRISPR/Cas9 carrier and AI-assisted design of nanocarriers, nanotheranostics and nanorobotic targeting. Despite their promising aspects, challenges remain in nanotoxicology, mass production, regulatory uniformity and evidence of long-term safety. This review provides an in-depth discussion on SDDS, including their mechanisms of action, stimulus-response mode, therapeutic applications and technological progress, for the period from 2020 to 2024, as well as safety considerations, regulatory aspects, challenges in the translation, and future directions. A structured approach incorporating PubMed, Scopus, ScienceDirect, and other electronic databases was adopted to extract the latest literature. In general, smart nanocarriers are appearing as the design elements that could revolutionize personalized medicine and targeted treatments.

Keywords: Controlled Release, Lipid Nanoparticles, Nanocarriers, Nanomedicine, Smart Drug Delivery, Stimuli-Responsive Systems, Targeted Therapy.

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INTRODUCTION

Drug delivery science has undergone a technological revolution-from traditional "dumb" conventional formulations to highly engineered, nanoscale systems that potentially could be precisely controlled therapeutic tools. Conventional DDSs have many drawbacks, resulting in inefficient therapeutic efficacy with poor drug solubility, rapid blood clearance, and nonspecific tissue distribution, and inability to penetrate biological barriers, nonsustained release patterns, and systemic toxicity (Singh *et al.*, 2022). These are severe limitations in diseases such as cancer, neurodegenerative disorders, chronic infections, autoimmune diseases, and metabolic conditions since targeted delivery and long-lasting exposure of the drug is a precondition for successful treatment.

In this context, nanotechnology has enabled the design of drug carriers at molecular and supramolecular levels to address these issues. Smart DDS, also called intelligent, stimuli-responsive, or programmable nanocarrier system, is a novel concept in the therapeutic field. While traditional nanocarriers *per se* were passive medicine release systems, Smart Drug Delivery Systems (SDDS) is capable of sensing biological cues and responding to the disease microenvironment for on-demand drug enrichment compared with conventional release patterns (Zhang *et al.*, 2021).

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The "smart" functions of SDDS are realized by several basic principles

1. Stimuli-responsiveness: its ability to respond toward the physiological stimuli including pH, glutathione concentration, enzymes, hypoxic conditions, and Reactive Oxygen Species (ROS).
2. Sensitivity to an external stimulus-ultrasound, light, electric field, temperature, and magnetic fields.
3. The ability to target overexpressed disease-specific receptors, a unique property of surface functionalization.
4. Programmable release kinetics afford temporal control, such as instant, sustained, pulsatile, or multistage release.
5. Enhanced barrier crossing to facilitate transport across blood-brain, mucosal, and tumor extracellular matrices (Zhao *et al*., 2023).

Smart nanocarriers exploit these mechanisms to a great extent and lead to marked enhancement in the pharmacokinetic and pharmacodynamic properties. This comprises improvement of drug absorption, prolonged serum half-life, enhanced tissue retention and drug delivery as well as at intracellular site.

Targeted Therapy in Synchrony with Smart Nanocarriers

Several drugs which play a key role in treatment like anticancer drugs, antibiotics, peptides and proteins, and so on, experience many barriers for their drug delivery. These include:

- Poor aqueous solubility,
- Low permeability across membranes,
- High susceptibility to degradation,
- Extensive first-pass metabolism,
- Severe systemic toxicity,
- Inability to selectively concentrate in abnormal tissues,
- Very short plasma half-life (Joshi *et al*., 2023).

Smart nanocarriers address these problems by

- Targeted delivery,
- Reduced off-target exposure,
- Less Systemic Toxicity,
- Greater Therapeutic Index,
- On-Demand or Site-Specific Release (Chaurasia *et al*., 2022),
- Evolution of Smart Drug Delivery Systems.

SDDS development can be divided according to technology generation into five generations:

First generation

- Conventional nanocarriers.

Liposomes, micelles and polymeric nanoparticles: primarily for enhanced solubility and stability (Maeda, 2021).

Second generation

- Ligand-targeted systems.

Surface-functionalized nanoparticles that are conjugated to antibodies, folate, RGD peptides, aptamers etc. (Rathi *et al*., 2021).

Third generation

Stimuli-responsive nanocarriers nanocarriers of pH-, redox-, enzyme-, ROS- or temperature-sensitivity (Luo *et al*., 2020).

Fourth generation

Biomimetics and hybrid system (Kumar *et al*., 2022).

Cell membrane-coated NPs, exosomes, and lipid-polymer hybrids are largely immune-evasive with good penetration.

AI engineering and nanorobotics advance toward best design trends (Ahmed *et al*., 2023).

There are also the computationally designed nanoparticles, self-propelled nanorobots and the precision systems: Imaging + therapy (theranostic).

This development demonstrates an advancement in comprehension of pathophysiology of diseases, nanobio interactions, and stimulus-responsive materials (Yadav *et al*., 2020).

Mechanism Based on Smart Nanocarrier Functionality

Smart nanocarriers combine several targeting mechanisms:

Passive Targeting

Use of the enhanced permeability and retention effect in tumors, inflammation, and infection.

Active Targeting

Various surface ligands, for example, antibodies (HER2), peptides (RGD), transferrin, folic acid, aptamers, and carbohydrates can guide the nanocarrier to a specific receptor.

Intracellular Delivery Strategies

- Endosomal Escape Mechanisms,
- pH-responsive membrane destabilization,

- Proton Sponge Effect,
- Redox-triggered release in the cytosol (Liu *et al*., 2021).

Programmable Release

Intelligent nanocarriers can be designed for:

- Burst Release Immediately,
- Sustained Release,
- Multistage Sequential Release,
- Stimulus-Responsive Release in the disease microenvironment.

Clinical Translation and Industrial Application

Some of the above smart nanocarriers have already had an important clinical application. Examples include:

- Lipid NPs for mRNA vaccines, COVID-19 (Pfizer-BioNTech and Moderna),
- Doxil® (liposomal doxorubicin), which was found to decrease the incidence of cardiotoxicity (Pandey *et al*., 2022),
- Abraxane® (albumin-bound paclitaxel) that enhanced bioavailability,
- Vyxeos® (daunorubicin and cytarabine liposome for injection) that extends survival for patients with blood cancer (Sharma and Jain, 2020).

These successful examples demonstrate the potential to enhance efficacy and reduce toxicity through smart delivery. This advancement brings new types of therapies, such as mRNA, siRNA, and CRISPR gene-editing constructs (Jain *et al*., 2023).

Justification of Reviewing Smart Nanocarriers

Although thousands of research articles have been published in this field, rapidly evolving technologies include-stimuli-responsive polymers, hybrid materials, biomimetic coatings, nanotheranostics and AI-empowered designs with gene delivery systems as the next generation. Therefore, an earlier review and thorough understanding is of vital necessity to: list up-to-date developments (2020-4); describe technological principles; illustrate targeting and stimuli-responsive systems.

Focus on clinical applications and regulatory challenges show prospects of precision medicine in the future offer guidance to researchers, developers, and patients. The purpose of this review is to provide a one-stop reference source that highlights recent developments, modes of action, therapeutic implications, hurdles, and projected advances in the smart nanocarrier-based drug delivery systems (Santos and Araujo, 2021).

METHODOLOGY

The methodological strategy used in this narrative literature review was rigorously planned to achieve systematic rigor, scientific validity, and up-to-date information on the subject of smart nanocarrier-triggered drug delivery systems.

As a review article, not original research, this study was conducted using a systematic and reproducible approach to improve its transparency and trustworthiness.

Literature Search Strategy

We conducted an electronic search in several scientific databases including the following:

- PubMed/MEDLINE,
- Scopus,
- Google Scholar,
- Wiley Online Library,
- SpringerLink,
- ACS publications,
- Taylor & Francis online.

A search was conducted for articles published between 2010 and 2024 with particular emphasis on recent advances (from 2018 to 2024), that is, a period characterizing fast growth and very intensive improvement in stimuli-responsive nanocarriers and advanced smart material engineering.

Keywords and Search Terms

To cover all potential resources, we used a combination of MeSH terms and Boolean operators.

- Smart drug delivery systems,
- Stimuli-responsive nanocarriers,
- Targeted drug delivery,
- Nanotechnology in therapeutics,
- Polymeric nanoparticles,
- Liposomes,
- Nanomicelles,
- Dendrimers,
- Hybrid nanocarriers,
- Biomimetic nanoparticles,
- Tumour microenvironment-responsive systems,
- Controlled release formulations,
- Theranostic nanocarriers,

- "Nanomedicine clinical trials".

Combinations of keywords such as (smart nanocarriers) AND (targeted therapy), and also (stimuli-responsive nanoparticles) AND (drug release), were used to retrieve highly relevant and impactful studies.

Inclusion Criteria

Inclusion criteria were as follows for the articles:

1. Research papers, review articles, meta-analysis and book chapters.
2. Articles addressing the design, fabrication, mechanism, targeting strategy, applications and advantages of smart nanocarriers.
3. Studies on polymeric, lipid-based, hybrid, biomimetic and inorganic nanocarriers.
4. Investigations of stimuli-responsive or intelligent release systems.
5. Investigations on clinical applications, regulatory aspects and translational issues.

The Process of Selection

A methodical three-phase screening approach was employed:

1. Title confirmation: initially, titles that have nothing to do with the research topic-such as nanomaterials or cosmetic applications-are eliminated.
2. Abstract screening: evaluation based on applicability to targeted or intelligent nanocarriers.
3. Full-text screening: review of the retained articles to find if they meet the inclusion and exclusion criteria established.

In the first search, approximately 2000 records were identified and 214 full-text articles were screened. These included original-research articles, clinical studies, systematic reviews, and high-quality experimental data.

Data Extraction and Synthesis

Extracted data included:

- Type of nanocarrier,
- Preparation and Design Strategies,
- Mechanisms of Stimuli-Responsive Behavior,
- Surface Modification and Targeting Ligands,
- Drug Loading and Release Characteristics,
- *In vitro* and *in vivo* performance,
- Clinical Translation Progress,
- Advantages and Limitations,
- Future Directions for Smart Drug-Delivery Systems,
- Safety, Toxicity, and Regulatory Issues.

Overview of SDDS

SDDS represents a major advancement in pharmaceutical nanotechnology, providing programmable, site-specific, and stimuli-responsive delivery of therapeutic agents. In contrast to traditional drug-delivery system, which rely on passive diffusion and exhibit nonselective tissue distribution, SDDS should have an active interface with biological microenvironment, retaining the drug until it meets particular internal or external triggers. Thus, the intelligent responses of SDDS enable maximized therapeutic effectiveness while minimizing systemic toxicity incurred in addition to overcoming multiple physiological barriers which natural drugs are powerless against.

Origin and Evolution of Smart DDS

The concept of smart drug delivery was pioneered to overcome certain limitations of conventional nanocarriers, such as uncontrolled release, rapid systemic clearance, and inability to respond to physiological signals. To overcome these limitations, early researchers began integrating responsive polymers, biochemical sensors, and functional ligands into these systems, enabling them to:

- Biological Cue Detection,
- Structural Transitions,
- Dynamic Drug-Release Modulation,
- Tissue-Specific or Receptor-Specific Targeting.

Mechanism of Action of Smart Nanocarriers

Smart drug-delivery systems function through several integrated mechanisms:

Stimuli-Responsive Behavior

SDDSs are designed to respond to either endogenous (internal) or exogenous (external) stimuli.

Common internal triggers include:

- pH gradients: tumors, stomach, endosomes,
- Redox potential: cancer cells with high glutathione,
- Overproduction of enzymes: (MMPs, phospholipases, cathepsins),
- Hypoxia,
- ROS (Rajan *et al.*, 2023).

External triggers include:

- Light (UV/NIR),

- Ultrasound,
- Magnetic fields,
- temperature,
- Electric fields (Sharma and Singh, 2023).

These nanocarriers, being smart, change conformation or chemistry upon sensing these triggers, leading to controlled drug release.

Mechanisms for Targeted Delivery

Targeting increases specificity and also enhances the accumulation of nanoparticles in diseased sites.

Smart nanocarriers use:

- Passive Targeting via Enhanced Permeability and Retention (EPR) effect,
- Active Targeting through ligand-receptor interactions,
- Magnetic or ultrasound-guided targeting,
- These stratagems concentrate the drug at the target site with very low exposure to systemic tissues.

Controlled or Programmable Release

For example, smart nanocarriers can be designed to:

- Environmental-Responsive Release,
- Release over Periods of hours to days,
- Pulsatile Release, Mimicking Physiological Rhythms,
- A Multitiered release, where one stimulus triggers another responsive layer,
- This Programmable release is important in diseases, for which delicate pharmacokinetic control is required.

Classification of Smart Drug Delivery Systems

- Smart nanocarriers can be classified according to the following aspects,
- Types of drugs/drug-loading approaches,
- Various types of drugs are used on the basis of which different smart carriers are selected.

Material Composition

1. Polymeric Platforms-PLGA, chitosan, PEG-PLA,
2. Lipid-based systems: liposomes, Solid Lipid Nanoparticles (SLNs), Nanostructured Lipid Carriers (NLCS),
3. Inorganic nanoparticle carriers: gold, silica, iron oxide (Das *et al*., 2022),
4. Hybrid nanoparticles: lipid-polymer and biomimetic particles (Bhatia and Narain, 2023),
5. Biological systems: exosomes and cell membrane-coated nanoparticles (Fang *et al*., 2022).

Responsiveness

1. pH-responsive (tumors, infection sites),
2. Redox-Responsive (Intracellular GSH levels),
3. Enzyme-Responsive (protease-rich microenvironments),
4. Photo-Responsive,
5. Magneto-Responsive,
6. Ultrasound-Responsive.

Therapeutic Uses

1. Oncology,
2. Infectious disease,
3. Neurological disorders,
4. Cardiovascular therapy,
5. Metabolic disorders,
6. Gene therapy,
7. Immunotherapy.

This classification highlights the flexibility and adjustability of SDDS for different therapeutic requirements.

Benefits of Smart Drug Delivery Systems

The above smart nanocarriers have the following advantages in terms of conventional systems:

- Improved specificity due to a targeted and stimuli-responsive manner,
- Reduced toxicity, as healthy cells are spared,
- Enhancement of the bioavailability of poorly soluble drugs,
- Labile molecule protection: peptides, proteins, nucleic acids,
- Bypassing physiological barriers (Blood-Brain Barrier [BBB] and tumor ECM),
- Reduced dosing frequency,
- Capability of cotherapy: two or multiple drugs loadings,
- Theragnostic potential: dual imaging and therapy.

These are among the properties that render smart nanocarriers most suitable for precision medicine (Mohan *et al*., 2024).

Limitations and Hurdles for Smart Nanocarriers

Despite significant achievements, a number of obstacles are still encountered by the SDDS:

- Nanotoxicity and long-term biodistribution issues,
- Complex synthesis and scale-up difficulties,
- Expensive materials,
- Potential immunogenicity or Reticuloendothelial System (RES) clearance,
- Regulatory challenges due to multimodal character,
- Only minimal clinical translation has been achieved; most systems remain at the preclinical stage,

Addressing these challenges would be critical for broader clinical translations (Bera *et al*., 2021).

Clinical Consideration and New Developments

Smart nanocarriers are increasingly entering clinical investigation with success seen in:

- mRNA vaccine lipid nanoparticle. (Pfizer, moderna),
- Liposomal anticancer formulations. (Doxil, Vyxeos).

Nanocarriers of siRNA and gene editing, Patisiran-the first FDA-approved siRNA therapy (Patel *et al*., 2021).

Types of Smart Nanocarriers

Advanced drug delivery technologies, such as smart nanocarriers, such as smart nanocarriers, represent a significant advancement in modern medicine, as their site-specificity and on-demand precision enable targeted therapeutic control. In contrast to the mainstream delivery vehicle for drugs, including core products in a nonspecified way in the body, smart nanocarriers can be designed to identify some specific biological signs and make a response, then unload the drug only at the target region. This approach enhances the therapeutic efficacy, reduces toxicity and improves patient compliance. The developed smart nanocarriers so far are with diversified properties and functions.

Polymeric Nanoparticles

Polymeric nanoparticles are the most investigated among the nanocarrier systems, because of their good biocompatibility, biodegradability and inbuilt drug-loading capacities. Nanoparticles are commonly developed using natural polymers, including chitosan and alginate, as well as synthetic polymers like PLGA, PEG and PCL. Polymeric nanoparticles offer protection from early drug degradation by encapsulating both hydrophilic and lipophilic drugs.

Recent developments include polymeric systems that respond to Ph, enzymes, or temperature stimuli, enabling active, site-specific drug delivery. Such systems are promising for treating difficult conditions like cancer and chronic inflammation (Dutta *et al*., 2024).

Liposomes

Liposomes are spherical vesicles composed of phospholipid bilayers and may entrap various therapeutic agents such as small drugs, proteins and nucleic acids. They exhibit low drug toxicity and increased circulation time when pegylated.

More advanced smart liposomes are thermosensitive liposomes, which release the drugs upon mild heating, pH-responsive liposomes that target the tumor and ligand-coupled (ligand-incorporated) liposome, that is receptor-mediated. Clinical application potential of such systems is demonstrated by FDA-approved liposomal formulations (i.e., liposomal doxorubicin).

Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

SLNs and NLCs are second generation lipid-based nanocarriers that have the benefit of both polymeric nanoparticles and conventional lipid systems. SLNs enhance the stability, sustained release, and drugs protection against chemical degradation. Although SLNs have relatively slower drug-loading, second-generation NLCs compensate by incorporating both solid and liquid lipids. Due to their great biocompatibility and capability of improving the bioavailability of highly hydrophobic, poorly water-soluble drugs, these carriers are widely used in transdermal, oral, or ocular delivery systems.

Dendrimers

Dendrimers are a class of highly branched macromolecules, which have very reactive surface functional groups and are in the size range of nm. Owing to their three-dimensional tree-like morphology, dendrimers' size, shape, and surface chemistry can be easily tailored. Therefore, dendrimers are able to accommodate numerous drug molecules, imaging agents and targeting ligands simultaneously and are thus ideal for multifunctional theragnostic purposes. The surface modification with PEG, antibodies or peptides improves targeting and reduces toxicity. PAMAM dendrimers are one of the most widely studied classes of dendrimer systems (Banerjee and Gohil, 2021).

Carbon-Based Nanocarriers

Of these carbon nanomaterials, CNTs, GO, and fullerenes have become promising candidates mainly attributed to their very high mechanical strength, large surface area as well as superior penetrating ability into cellular membranes. In the case of functionalized CNTs and GO, high-efficiency drug delivery for anticancer drugs as well as nucleic acid and peptides are possible, but long-term biocompatibility and toxicity concerns remain and

encourage further studies regarding safe surface modifications (Wang *et al*., 2024).

Metallic and Inorganic Nanocarriers

Metal nanoparticles, like gold, silver, and iron oxide and inorganic systems such as silica or calcium phosphate have some unique characteristics that give them an advantage over others: magnetic responsiveness and photothermal activity as well as high drug-loading capacity. Gold and iron oxide nanoparticles can deliver targeted phototherapies and magnetically guided to specific tissues. Mesoporous silica nanoparticles are among the most extensively studied systems because of their controllable pore structure and drug promising multidrug-carrying capacity.

Exosomes and Biomimetic Nanocarriers

Exosomes are cell-derived endogenous nanovesicles, which play an essential role in intercellular communication. Biomimetic nanocarriers such as cell membrane-coated nanoparticles, combine synthetic systems with biological camouflage to enhance circulation time and evade the immune system.

Targeting Mechanisms and Stimuli Responsiveness

Intelligent nanocarrier-mediated drug delivery systems are designed to interact with the biological environment, aiming at transporting therapeutic molecules where they are required and when needed. Their targeting capacity, which is based on passive and active targeting mechanisms, as well as on the response to specific internal or external stimuli. These mechanisms serve not only to enhance drug accumulation at the disease site but also decrease systemic exposure, thus increasing efficacy and reducing side effects.

Passive Targeting

Passive targeting is based on the inherent physiological properties of the body, which allow nanocarriers to accumulate in diseased tissues (e.g., tumors and inflammatory sites). This is primarily enabled by the EPR effect, in which tumor-associated vasculature and their lymphatic drainage accumulate nanocarriers hundreds of nm in size, moved. Induced vascular permeability, as occurs in inflammatory diseases, also enables passive accumulation. Passive targeting is particularly attractive for use in cancer therapy, as it avoids the need to make specific surface modifications or conjugations for targeting, and instead utilizes particle size, shape, and circulation time to improve biodistribution.

Active Targeting

Active targeting: This approach is the attachment of some specific ligands on the nanocarrier surface, and is used for selective binding with overexpressed receptors in target cells. Ligands may include antibodies, peptides, aptamers, folic acid, transferrin and the like. When the ligand is bound to the target receptor, receptor-mediated endocytosis occurs in relation to nanocarrier and can markedly promote the intracellular drug delivery. Active targeting introduces more specificity and decreases nonspecific toxicity. It is not only for anticancer drugs but also for antiviral molecules. For example, folate-targeted nanomaterials are extensively used because the folate receptor is overexpressed in various cancers.

Stimuli-Responsive Targeting

Stimuli-responsive nanocarriers release their therapeutic payload in the presence of certain internal or external triggering factors. Such smart systems ensure that drugs are not released prematurely but are activated only at their target sites.

Internal stimuli

Internal stimuli are the physiological parameters that differ between normal and diseased tissues. The pH-sensitive systems are designed for drug liberation in the acidic environment, such as that of the tumor microenvironment or endosomes and lysosomes. These enzyme-responsive nanocarriers would break up and release drugs in response to the presence of disease-associated enzymes, such as MMPs or esterase enzymes. Multiple redox-responsive mechanisms activate in response to the high levels of GSH inside cancer cells and thereby can result in selective intracellular drug release. Internal stimuli-centered targeting works very well in cancer, inflammation, and ischemic diseases.

External stimuli

The drug release can be triggered by various external stimuli very efficiently and specifically in space and time:

- Thermosensitive responsiveness nanocarriers can mediate drug release at 40-42 °C in response to mild hyperthermia,
- Light-stimulated platform utilizes UV, visible and NIR to activate drug release or for heat-producing photothermal therapy,
- Nanocarriers that respond to a magnetic field can be directed to particular tissues or used to kill the tumor cells contained in these tissues (magnetic hyperthermia),
- Ultrasound-sensitive systems increase permeability and induce controlled drug release by means of cavitation.

These systems, triggered externally, are of great value in targeted cancer therapy and localized drug delivery.

Cellular Uptake Mechanisms

Once nanocarriers arrive at the target site, they must be internalized efficiently by cells. Smart nanocarriers use various internalization mechanisms to improve intracellular drug accumulation:

- Clathrin-Mediated Endocytosis,

- Caveolae-Mediated Endocytosis,
- Macropinocytosis,
- Phagocytosis, Especially for Immune Cells.

Surface charge, particle size, and hydrophobicity show remarkable effects on cellular endocytosis. Nanocarriers can also be tailored to escape the endosome by exhibiting proton sponge effects or pH-buffering functionality, allowing drug delivery into the cytoplasm or nucleus.

Controlled and Sustained Drug Release

The beneficial effect of using smart nanocarriers is the controlled drug release, which can avoid peak-trough variations and enhance therapeutic efficacy. The various controlled-release systems available are:

- Diffusion-Controlled Release,
- Degradation-Controlled Release,
- Swelling-Controlled Release (in polymers),
- Stimuli-Triggered Release,
- This leads to sustained drug levels at the site of action, permitting less dosing frequency, better patient compliance and reduced toxicities.

Overcoming Biological Barriers

In particular, smart nanocarriers configurations will drive the breakthrough in several biological bottlenecks associated with current drug delivery approaches:

- Mucosal Barriers (respiratory, gastrointestinal, vaginal),
- BBB,
- Tumor Microenvironment Barriers: thick extracellular matrix,
- Immune Clearance, through PEGylation or biomimetic coating.

Emerging strategies such as cell membrane-coated nanomaterials and exosome-like carriers or surface-modified nanocarriers further aid in immune evasion by prolonging circulation time (Singh *et al*., 2023).

Smart Nanocarrier Applications

Smart nanocarriers have fundamentally altered the field of therapeutics by offering tailored, site-specific, and regulated drug delivery for a range of clinical conditions. They are versatile platforms due to their tunable physicochemical properties, capability to overcome biological barriers, and responsiveness to both internal and external stimuli. This section describes the major therapeutic applications of smart nanocarrier-based drug delivery systems.

Cancer Therapy

Tumors are ideal candidates for both passive and active targeting strategies due to their leaky vasculature, hypoxic conditions, and disrupted metabolic pathways (Li *et al*., 2023).

Contagious Illnesses

The efficacy of antimicrobial, antiviral, and antiparasitic drugs, especially in infections requiring targeted delivery, is improved through the use of nanocarrier-based delivery systems (Singh *et al*., 2024).

Neurological Disorders

Smart nanocarriers offer strategies to enhance the transport of drugs across blood brain barrier.

BBB penetration and targeting

To overcome the blood-brain barrier, intelligent nanocarriers employ cell-penetrating peptides and receptor-mediated transport via transferrin and insulin receptors.

Regenerative and neuroprotective treatments

Neurotrophins, antioxidants, anti-inflammatory drugs, or genetic materials can be delivered by nanocarriers to promote neuronal survival and repair.

Cardiovascular Diseases

Smart nanocarriers potentially provide a novel strategy for the treatment of cardiovascular diseases by transporting drugs to damaged or inflamed vessels. These systems enable targeted drug delivery to atherosclerotic plaques. Nanocarriers can be tailored to target overexpressed molecules in atherosclerosis, such as VCAM-1, ICAM-1 or scavenger receptors (Li *et al*., 2024).

Diabetes and Metabolic Disorders

Intelligent nanocarriers offer novel approaches to enhance the delivery of insulin, peptides, and oral antidiabetic drugs (Khan *et al*., 2022).

Oral insulin and peptides

Nanocarriers protect insulin from enzymatic degradation in the gastrointestinal tract and enhance lymphatic or mucosal absorption.

Controlled and sustained release

Polymeric and lipidic nanovehicles provide sustained drug release, enhancing glycemic control and improving patient compliance.

6.6 gene delivery/gene therapy

Nanocarriers are vehicles for delivery of therapeutic nucleic acids, including siRNA, mRNA, plasmids and CRISPR components.

Protection and targeted delivery

Smart nanocarriers protect genetic materials from nuclease digestion, enhance cellular uptake and facilitate targeted intracellular release, resulting in efficient gene silencing or editing.

Applications in precision medicine

Gene-editing nanocarriers are being tested for treating inherited disorders, cancers, and viral infections.

Immunotherapy and Vaccine Delivery

Intelligent nanocarriers can significantly augment vaccine efficacy by promoting antigen targeting to immune cells.

Targeting dendritic cells

Functionalized nanocarriers deliver antigens to dendritic cells, enhancing immunity and vaccine effectiveness.

Nucleic acid vaccines and adjuvants

Lipid nanoparticles, including those used for the mRNA vaccine such as COVID-19 vaccine, are among the best examples of how smart nanocarriers have revolutionized global vaccination strategies.

Regenerative Medicine

Nanocarriers also promote tissue regeneration by maintaining growth factors, stem cell modulatory molecules, and biomolecules on damaged tissues.

Pulmonary and Inhalation Delivery

Smart nanoparticles could be inhaled for the treatment of respiratory diseases (asthma, COPD, pulmonary tuberculosis and lung cancer).

Ophthalmologic and Dermatologic Uses

Nanocarriers facilitate drug penetration across ocular and skin barriers, thus enhancing their therapeutic effect.

Recent Advancements (2020-4)

During the of 2020-4, research on smart nanocarriers has observed tremendous growth. This is attributed to the continuous advancements in the fields of nanofabrication, materials science, artificial intelligence, and other elements of precision medicine. Such advancements have transformed the potential of nanocarriers in disease diagnosis, monitoring, and treatment with unparalleled accuracy, safety, and efficacy.

The following are other key advancements that define the contemporary smart nanocarrier technology.

AI-Powered Nanocarrier Design and Optimization

Key advancement:

- Enhanced Prediction of Nanoparticle-Cell Interactions,
- Enhanced optimization of particle size, charge, and shape,
- ML-guided modeling of drug release,
- Drug Release Mechanism prediction,
- Automated Prediction of toxicity,
- AI-Driven ligand selection for targeted delivery.

Biomimetic and Cell-Membrane-Coated Nanocarriers

Research on biomimetic nanocarriers has grown tremendously since 2020, focused on the immune evasion characteristics.

2020-4 road map:

- RBC Membrane Coated Nanocarriers with prolonged circulation,
- Nanocarriers Coated with Cancer Cells for homotypic tumor targeting,
- Targeting Inflammation and Infection with platelet and macrophage coated vesicles,
- Reducing the formation of protein corona,
- Enhancing immune evasion and biocompatibility,
- In Addition, biomimetic carriers mimic the structures and surfaces of the biological carriers, leading to better targeting and longer circulation times.

Multifunctional (Theranostic) Nanocarriers

Theranostic, or the seamless integration of therapy with diagnostics, is one of the most rapidly advancing technology areas.

Innovations:

- Nanocarriers with engineered drug release and subsequent imaging by MRI, CT or fluorescence,
- Photothermal or photodynamic therapy integrated with chemotherapy,
- Imaging-enabled nanoparticles for real-time control of drug distribution,
- Adjusting drug dose in real time based on imaging feedback,
- These Systems can simultaneously detect a problem, deliver a solution, and provide ongoing surveillance.

CRISPR, mRNA, and Gene-Editing Nanocarriers

Research on genetic nanomedicines has increased significantly due to the success of mRNA vaccines in the COVID-19 pandemic.

2020-4 highlights:

- Lipid Nanoparticles for mRNA delivery,

- Novel Lipid-Based and polymeric delivery systems for CRISPR/Cas9 with improved endosomal escape, stability, and effectiveness,
- Targeted Gene Editing for viral infections, hemoglobinopathies and cancer,
- All These Advances indicate a shift toward the design of therapies at the genetic level,
- pH-, Redox-, and Enzyme-Responsive Smart Nanocarriers.

Stimuli-responsive technology has significantly matured

Major improvements:

- More Rapid and accurate release in the acidic tumor microenvironment,
- Enhanced Reactivity of redox-triggered systems to high levels of intracellular glutathione,
- Enzyme-Responsive Nanocarrier systems triggered by MMPs, cathepsins, or β-lactamases,
- Multiresponsive systems that combine pH + ROS + enzyme triggers to minimize the risk of premature release and to enhance the intracellular delivery of the drug.

Advances in Nanocarrier Penetration Across Biological Barriers

Research from 2020 to 2024 has focused on overcoming challenging physiological barriers.

Key breakthroughs:

- Transferrin- and insulin-receptor-targeting nanoparticles for blood-brain barrier delivery,
- Nasal and intrathecal nanocarriers for noninvasive CNS delivery,
- Improved mucus-penetrating nanoparticles for pulmonary and gastrointestinal diseases,
- Nanoenabled transport across tumor stroma and fibrotic tissues.

Smart Hydrogels, Nanogels, and Injectable Nanomaterials

Research of hybrid systems and nanogels expanded considerably following 2020.

Recent advancements:

- Location-Specific, injectable nanocomposites for controlled release,
- Nanogels Responsive to temperature and glucose for diabetes management,
- Tumor Targeting with pH-sensitive dissolution of nanogels,
- Improved Capture and retention of antibodies, proteins, and peptides.

Hydrogels and their nanoscale advantages were synergistically integrated into these systems.

Microfluidic and 3D Printed Nanocarriers

Recent improvements in microfabrication technology have increased the accuracy and repeatability in the production of nanocarriers.

2020-4 advancements:

- Uniform-sized nanoparticles synthesized from microfluidic chips,
- 3D-printed scaffolds for nanocarriers in regenerative medicine,
- Continuous flow fabrication systems for easy scaling,

These systems respond to prior challenges with manufacturing and scaling.

Targeted Nanoimmunotherapy

The use of nanotechnology for immunotherapy to boost immune response has grown considerably.

Recent progress:

- Nanocarriers with PD-1 and CTLA-4 checkpoint inhibitors,
- Nano vaccines to activate and enhance dendritic cells,
- Nanoparticles containing neoantigens from tumors,
- Immunomodulatory nanoparticles that respond to ROS,
- These innovations contribute to the goal of personalizing cancer immunotherapy.

Green and Biodegradable Nanocarriers

Recent advancement:

- Nanoparticles biosynthesized using plant extracts,
- Polymeric nanocarriers that are fully biodegradable,
- Reduced use of heavy metals,
- Sustainable strategies for nanofabrication,
- Reduced toxicity and environmental impact compared to conventional nanocarriers.

Difficulties and Limitations

Despite the impressive progress in smart nanocarrier-based drug delivery systems with promising therapeutic potential, still exist many barriers and limitations for their broad clinical translation due to toxicity, stability, cost, regulations, scalability,

and unexpected biological interactions. The development of safe, efficacious, and clinically translatable nanocarrier systems should be based on knowledge of these challenges.

Safety and Nanotoxicity Concerns

Unanticipated toxicological effects may result from interactions of nanocarriers with cells at the cellular and subcellular levels.

Organ toxicity and cytotoxicity

Some nanomaterials induce inflammation, oxidative stress, mitochondrial injury or membrane disturbance. Examples include metal nanoparticles (e.g., Au, Ag, Fe-oxide NPs) causing the death via ROS generation.

Immunogenicity

Surface charge, size and composition influence the nature of immune responses. Nanoparticle carriers (e.g., pegylated ones) can induce hypersensitivity responses or complement system activation.

Accumulation during prolonged treatments

Nondegradable nanoparticles may accumulate over time in the organs (liver, spleen, kidneys and lungs) which would be hazardous.

Physiological and Biological Barriers

Many *in vivo* challenges are associated with the distribution, stability, and therapeutic potential of intelligent nanocarriers.

RES clearance

The RES clears foreign particles rapidly by the liver and spleen's macrophages. Nanoparticles could not effectively target the tissues without the right surface modification, that is, PEGylation or bio-inspired coating.

Protein corona formation

Immediately upon entering the circulation, proteins attach to nanoparticle surfaces, which leads to the formation of a protein corona, modifying targeting specificity, biodistribution, therapeutic activity, and immunogenicity. This renders *in vivo* behavior unpredictable.

Heterogeneous tumor microenvironment

Nanoparticle penetration and distribution within tumors are thus limited by variable vascular permeability, high interstitial pressure, and hypoxic regions.

Stability and Drug Loading Associated Challenges

Nanocarriers need to maintain structural integrity in fabrication, storage, and physiological circulation.

Early drug leakage

The drug's therapeutic efficacy may be diminished if it is released before it reaches the target site due to poor encapsulation or unstable polymer/lipid matrices.

Poor drug loading efficiency

Poor loading of either hydrophobic or hydrophilic drugs limits the clinical utility of some nanocarrier systems.

Aggregation and degradation

Variations in pH, ionic strength, and temperature of the medium can distort the nanoaggregates.

Manufacturing and Scalability

A challenge remains in the industrially scaled production of smart nanocarriers while maintaining their quality and reproducibility.

Complex manufacturing processes

Smart nanocarriers require the following sophisticated fabrication techniques:

- Microfluidics,
- Self-Assembly,
- Layer-by-Layer Deposition,
- High-Pressure Homogenization,
- These Methods may lack scalability or consistency.

High production costs

Purification, characterization, and formulation significantly increase production costs, making commercialization very difficult.

Reproducibility limitations

Minor variations in the manufacturing processes can cause substantial differences in the size, charge and behavior of nanoparticles.

Ethical and Regulatory Challenges

Regulation of the field of nanomedicine is in flux.36373839

Lack of regulatory guidelines

There is a lack of standardized guidelines for nanoparticles since they are more complex than drugs or devices, which makes it difficult to fit them within the existing regulatory system.

Long-term lack of safety information

Comprehensive long-term toxicity and ecologic effect studies, necessary for regulatory purposes, are time-consuming and expensive.

Ethical issues

Nano waste, patient consent, and the use of advanced technology raise ethical issues.

Obstacles to Clinical Translation

Few nanocarriers make it to clinical use, despite the fact that many exhibit outstanding preclinical outcomes.

Distinctions between humans and animal models

Human outcomes are difficult to predict because immune responses and nanoparticle distribution differ significantly between species.

Restricted clinical research

The quantity of nanocarriers entering clinical trials is decreased by high development costs and intricate design specifications.

Human studies failure

Lack of Efficacy, unpredicted toxicity or poor patient acceptability may cause some nanocarriers to fail in human studies.

Environmental and Disposal Concerns

Production of synthetic nanoparticles and their large-scale use can be environmentally toxic (World Health Organization, 2022).

Difficulties with Biodistribution and Targeting

- Effects off-target,
- Proteins and nanoparticles can interact, causing particles to be rerouted to off-target locations,
- Restricted infiltration in dense tissues.

The distribution of nanoparticles may be restricted by fibrotic or calcified tissues, which would lessen the therapeutic benefit.

Future Perspectives

The future lies in the following advancements:

- AI-designed nanocarriers,
- Personalized nanomedicine,
- Nanorobotics-based targeting,
- Multifunctional theranostic systems,
- Biodegradable Next-Generation polymers,
- Gene-Editing Nanoplatforms,
- Immuno-Nanomedicine.

CONCLUSION

Smart nanocarrier-based drug delivery systems are revolutionizing modern therapeutics by offering precision, controlled release, and targeted drug action. Integration of nanotechnology with biotechnology, materials science, and artificial intelligence continues to expand its potential. While challenges remain in biosafety and regulatory translation, SDDS holds promise for becoming a cornerstone of personalized, safe, and effective therapy.

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ABBREVIATIONS

ABIPER: Aditya Bangalore Institute of Pharmacy Education & Research; **AI:** Artificial Intelligence; **BBB:** Blood-Brain Barrier; **CHMP:** Committee for Medicinal Products for Human Use; **CNTs:** Carbon Nanotubes; **COPD:** Chronic Obstructive Pulmonary Disease; **CRISPR:** Clustered Regularly Interspaced Short Palindromic Repeats; **CT:** Computed Tomography; **CTLA-4:** Cytotoxic T-Lymphocyte-Associated Protein 4; **DDS:** Drug Delivery System; **EPR:** Enhanced Permeability and Retention; **FDA:** Food and Drug Administration; **GSH:** Glutathione; **GO:** Graphene Oxide; **ICAM-1:** Intercellular Adhesion Molecule 1; **MMPs:** Matrix Metalloproteinases; **ML:** Machine Learning; **MRI:** Magnetic Resonance Imaging; **mRNA:** Messenger Ribonucleic Acid; **NIR:** Near-Infrared; **NLCs:** Nanostructured Lipid Carriers; **NPs:** Nanoparticles; **PAMAM:** Polyamidoamine; **PCL:** Polycaprolactone; **PD-1:** Programmed Cell Death Protein 1; **PEG:** Polyethylene Glycol; **PEG-PLA:** Polyethylene Glycol-Polylactic Acid; **Ph:** Potential of Hydrogen; **PK-PD:** Pharmacokinetic-Pharmacodynamic; **PLGA:** Poly (lactic-co-glycolic acid); **RES:** Reticuloendothelial System; **RGD:** Arginine-Glycine-Aspartic Acid; **ROS:** Reactive Oxygen Species; **SDDS:** Smart Drug Delivery Systems; **siRNA:** Small Interfering Ribonucleic Acid; **SLNs:** Solid Lipid Nanoparticles; **UV:** Ultraviolet; **VCAM-1:** Vascular Cell Adhesion Molecule 1; **WHO:** World Health Organization.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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AUTHOR CONTRIBUTIONS

Navitha GA: Conceptualization, literature review, data extraction, manuscript drafting, referencing, and final editing.

Likitha K. literature review, data compilation, critical revision of manuscript sections, and proofreading.

All authors have read and approved the final version of the manuscript.

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