REVIEW ARTICLE

Stimuli-responsive nanomaterials: Innovations in on-demand drug release systems

Vepamani Siva Sai Bharath Kumar[1], Kateregga Ismael[2], P. Harathi[1], M. Jayalakshmi[1], B. Abhishek[1], S. Dadu Basha[1], R. Dinesh[1], Nawaz Mahammed[1]*

[1]Department of Pharmaceutics, Raghavendra Institute of Pharmaceutical Education and Research-Autonomous, Anantapuramu, Andhra Pradesh, India, [2]Department of Industrial Pharmacy, Raghavendra Institute of Pharmaceutical Education and Research-Autonomous, Anantapuramu, Andhra Pradesh, India

Abstract

Stimuli-responsive nanoparticles (SRNs) provide an innovative method in pharmaceuticals, facilitating accurate, on-demand drug release systems customized for particular therapeutic requirements. These sophisticated materials react to internal (pH, enzymes, and redox potential) or exterior (temperature, light, and magnetic fields) stimuli, enabling regulated drug release while reducing adverse effects. Recent developments in the design and engineering of SRNs have improved their sensitivity, biocompatibility, and drug-loading efficiency, rendering them optimal candidates for customized therapy. Notwithstanding their potential, issues related to stability, possible cytotoxicity, and scalability impede their clinical application. Contemporary research emphasizes surmounting these obstacles using multistimuli-responsive systems and the use of developing technologies such as artificial intelligence. This review elucidates the processes, material developments, and pharmacological applications of SRNs, addresses significant limits, and examines prospective avenues for their advancement. By tackling these issues, SRNs possess the capacity to revolutionize contemporary drug delivery methods, providing unparalleled precision and efficiency in therapeutic treatments.

Key words: Immediate drug liberation, Pharmaceutical nanotechnology, Regulated drug administration, Stimuli-responsive nanomaterials, Tailored medicine

INTRODUCTION

Conventional drug delivery systems, such as oral tablets, injectables, and transdermal patches, often face significant challenges in achieving optimal therapeutic outcomes.[1] These systems rely on passive drug release mechanisms, leading to issues such as poor bioavailability, off-target effects, and inconsistent therapeutic levels.[2] Many pharmaceuticals deteriorate in the gastrointestinal tract or experience significant first-pass metabolism, diminishing their effectiveness. Moreover, systemic drug distribution may induce adverse effects by impacting healthy tissues in addition to sick regions. The absence of site-specific targeting and regulated release profiles impedes their efficacy, especially in chronic diseases and disorders necessitating localized treatment.[3]

Stimuli-responsive nanoparticles (SRNs) have emerged as a transformative solution to address the limitations of conventional drug delivery.[4] These advanced systems are designed to release drugs in response to specific stimuli, such as pH, temperature, light, or enzymes, ensuring site-specific and controlled delivery.[5] By responding to pathological changes or externally applied triggers, SRNs provide precise temporal and spatial drug release, minimizing systemic exposure and reducing side effects. Moreover, their nanoscale size allows for better cellular uptake and accumulation at target sites, enhancing therapeutic efficacy. This adaptability positions SRNs as a promising tool in precision medicine.[6]

Address for correspondence:
Nawaz Mahammed, Department of Pharmaceutics, Raghavendra Institute of Pharmaceutical Education and Research-Autonomous, Anantapuramu, Andhra Pradesh, India.
E-mail: mohammednawaz151@gmail.com

Received: 08-02-2025
Revised: 18-03-2025
Accepted: 30-03-2025

On-demand drug release systems refer to delivery platforms that release therapeutic agents in a controlled manner only when triggered by specific stimuli. These systems allow for tailored dosing schedules, accommodating patient-specific needs and disease dynamics.[7] In pharmaceutics, on-demand systems are particularly valuable for conditions requiring pulsatile or sustained drug delivery, such as cancer, diabetes, or inflammatory disorders.[8] By offering controlled release at the right time and place, these systems enhance drug efficacy while minimizing toxicity and dosing frequency. Their relevance lies in bridging the gap between conventional systems and the need for precise therapeutic intervention.[9,10]

This review seeks to elucidate the design, development, and uses of stimuli-responsive nanoparticles in on-demand medication delivery systems. This will investigate the processes of stimuli-responsiveness, material improvements, and engineering solutions to enhance drug delivery. The evaluation will analyze pharmaceutical applications, constraints, and viable solutions to address issues. This work aims to underscore the transformational potential of SRNs in contemporary pharmaceutics by summarizing recent accomplishments and exploring future prospects, so providing a valuable resource for researchers, physicians, and industry stakeholders.

MECHANISMS OF STIMULI-RESPONSIVENESS

Intrinsic stimuli

Drug delivery systems responsive to internal cues are engineered to leverage the distinctive physiological conditions present in sick tissues or cells. These systems depend on particular biochemical and biophysical alterations that transpire in the body throughout illness progression, facilitating targeted and regulated medication release.[11]

pH gradients in pathological tissues

A notable physiological characteristic utilized by stimuli-responsive nanomaterials is the pH disparity between healthy and sick tissues. Tumors typically exhibit a higher acidic microenvironment (pH 6.5–6.8) relative to normal tissues, partly attributable to increased glycolysis in rapidly growing cancer cells. Likewise, inflammatory tissues and specific intracellular compartments, like lysosomes and endosomes, display acidic environments. Nanomaterials engineered to react to these pH gradients discharge their therapeutic payload in acidic conditions. Substances like pH-sensitive hydrogels, polymers, or nanoparticles featuring acid-labile linkers (e.g., hydrazone or imine bonds) can decompose or modify their structure in reaction to low pH, facilitating drug release precisely at the target location while reducing systemic exposure and adverse effects.[12]

Enzyme activity pertinent to pathological conditions

Specific illness states, including cancer, inflammation, and bacterial infections, are characterized by the overexpression of certain enzymes. Enzymes such as matrix metalloproteinases (MMPs) and cathepsins destroy extracellular matrix components and proteins, rendering them suitable targets for enzyme-responsive drug delivery systems. Nanomaterials can be engineered with enzyme-sensitive linkers or substrates to facilitate medication release through enzymatic cleavage at the disease location. In cancer, where MMPs are overexpressed, pharmacological agents are released upon the cleavage of peptide-based linkers by MMPs. This technique facilitates precise medication release, reducing unintended harm to healthy tissues.[13,14]

Redox potential variations in cellular environments

Redox-responsive drug delivery methods exploit the disparities in redox potential between healthy and sick cells. In healthy tissues, the extracellular environment sustains a low quantity of glutathione (GSH), whereas internal levels of GSH are much elevated, frequently by a factor of 1000. Cancer cells, specifically, demonstrate heightened GSH levels attributable to augmented metabolic activity. Nanomaterials with redox-sensitive linkers, like disulfide bonds, can be cleaved in high GSH concentrations, thereby releasing their therapeutic payload specifically within target cells. This technique guarantees accurate intracellular drug delivery, enhancing the therapeutic efficacy while minimizing adverse side effects.[15]

External stimuli

Drug delivery systems responsive to external stimuli are designed to release their therapeutic agents in reaction to controllable physical or environmental variables. These devices provide geographic and temporal regulation of medication delivery, facilitating improved targeting, and less side effects. The three primary external stimuli employed in controlled drug release are temperature variations, light exposure, and magnetic or electric fields.[16]

Temperature changes

Temperature-sensitive drug delivery devices utilize temperature fluctuations that arise in specific situations, such as fever, inflammation, or external heating. These systems frequently employ thermos-responsive polymers, such as poly(N-isopropylacrylamide) (PNIPAM), which experience a phase shift at a designated temperature.[17] At reduced temperatures, these polymers exhibit solubility in water; conversely, at elevated temperatures, they become insoluble and experience a gel-to-sol transition, resulting in drug release. These systems can be triggered by slight temperature variations in affected tissues, exemplified in cancer treatment when hyperthermia is utilized to selectively release drugs

at the tumor location. The capacity to regulate drug release by temperature fluctuations offers an efficient, non-invasive approach for targeted delivery.[18]

Light irradiation

Light-sensitive drug delivery systems utilize light as an external stimulus to regulate medication release. These systems generally integrate light-responsive moieties such as azobenzene or spiropyran, which experience conformational alterations when subjected to particular wavelengths of light (ultraviolet or visible light).[19] This structural alteration may either liberate the medication from the nanomaterial or induce the material's degradation. Light irradiation provides the benefit of non-invasive and accurate regulation of drug distribution at designated locations, particularly when utilized with external light sources capable of penetrating deep tissue. These devices are exceptionally beneficial in targeted therapies, such as ophthalmology or superficial cancers, where light can be concentrated on the treatment site.[20]

Magnetic or electric fields

Magnetic and electric fields are utilized in controlled drug delivery systems to initiate drug release by leveraging the characteristics of magnetic or electrically responsive materials. Magnetic nanoparticles can be infused with therapeutic substances and guided to the target location with an external magnetic field. Upon localization at the target site, the magnetic field can facilitate drug release by modifying the nanoparticle's characteristics or by inducing thermal effects (magnetic hyperthermia). Electric fields are utilized in electroporation devices, wherein the introduction of an electric field transiently permeabilizes cell membranes, facilitating enhanced medication entry into cells.[21] Magnetic and electric field-responsive technologies offer precise localization in drug delivery, minimizing systemic toxicity and improving therapeutic efficacy.[22,23]

MATERIALS FOR STIMULI-RESPONSIVE NANOMATERIALS

Stimuli-responsive nanoparticles (SRNs) consist of diverse materials engineered to respond to particular physiological or environmental stimuli, facilitating regulated medication release. The primary constituents of SRNs comprise polymers, lipids, metallic nanoparticles, and hybrid materials, each presenting distinct benefits derived from their chemical composition and functionalization.

Polymers and their functionalization

Polymers are among the most extensively utilized materials in SRNs owing to their versatility, biocompatibility, and simplicity of functionalization. Polymers such as poly(lactic acid), poly(ethylene glycol), PNIPAM, and poly(caprolactone) can be customized for pH, temperature, or enzyme-responsive release. The functionalization of these polymers with certain chemical groups (e.g., carboxyl, amine, or thiol groups) or targeted ligands facilitates improved drug encapsulation, stability, and release kinetics.[24] For instance, pH-sensitive polymers may deteriorate or experience structural alterations in acidic conditions, such as those present in tumors or inflamed tissues, thereby releasing the encapsulated medicine. Polymers may be conjugated with bioactive compounds or antibodies for the purpose of targeted drug delivery.[25]

Lipids and lipid-based carriers

Lipids, encompassing phospholipids and cholesterol derivatives, are essential constituents in the development of lipid-based carriers, including liposomes, solid lipid nanoparticles, and nanostructured lipid carriers.[26] Lipid-based materials provide superior biocompatibility, biodegradability, and the capacity to encapsulate both hydrophilic and hydrophobic pharmaceuticals.[27] Liposomes can be engineered to react to particular stimuli, such as pH, temperature, or ionic strength, facilitating regulated medication release. Furthermore, lipids can be modified by targeting ligands, thereby improving the specificity of medication delivery to pathological locations. Lipid-based carriers are particularly effective for transporting therapeutic medicines to delicate tissues, such as the brain or liver, by surmounting biological obstacles like the blood–brain barrier.[28]

Metallic nanoparticles and their properties

Metallic nanoparticles, such as gold, silver, iron oxide, and platinum-based variants, are extensively utilized in SRNs owing to their distinctive optical, magnetic, and catalytic characteristics. Gold nanoparticles (AuNPs) are exceptionally adaptable and can be functionalized with many ligands for targeting and response to stimuli.[29] Iron oxide nanoparticles are frequently utilized in magnetic-responsive drug delivery systems, wherein an external magnetic field facilitates the guidance and regulation of the drug's release.[30] Metallic nanoparticles can undergo alterations in size, shape, or surface charge in response to stimuli, facilitating precise drug release. Their extensive surface area offers an optimal foundation for drug loading, and their characteristics can be adjusted for certain applications, like cancer treatment or imaging.[31]

Hybrid materials combining multiple components

Hybrid materials integrate multiple distinct components, including polymers, lipids, and inorganic nanoparticles, to produce SRNs with improved functionality.[32] These materials leverage the unique capabilities of each component

to enhance medication delivery efficiency, targeting precision, and response to stimuli. Hybrid materials composed of polymeric micelles and AuNPs can provide synergistic advantages, including enhanced drug loading capacity, stability, and targeted delivery.[33] Hybrid systems facilitate multi-stimuli responsiveness, enabling concurrent reactions to pH, temperature, and magnetic fields. Hybrid SRNs enhance control over release profiles and improve treatment outcomes by merging diverse materials, rendering them suitable for complicated disorders such as cancer or chronic inflammation.[34]

DESIGN AND ENGINEERING OF STIMULI-RESPONSIVE SYSTEMS

The design and engineering of stimuli-responsive drug delivery systems necessitate meticulous structural and functional modification to enhance responsiveness, accuracy, and release profiles. Various tactics can be utilized to improve the efficacy of these systems and guarantee they fulfill particular therapeutic requirements [Figure 1].[35]

Structural and functional customization for stimuli responsiveness

The architectural design of stimuli-responsive systems is essential for their efficacy. Customization commences with the selection of materials that exhibit the requisite reactivity to a particular stimulus, such as pH, temperature, light, or enzymes.[36] Polymers or hydrogels can be crosslinked to create networks that either expand or disintegrate in response to particular environmental conditions. The functionalization of the material surface with responsive groups (e.g., carboxyl, amine, and thiol) facilitates more precise interactions with stimuli. Moreover, the inclusion of targeting ligands such as antibodies, peptides, or aptamers facilitates site-specific drug release, guaranteeing that medications are administered alone at the intended site. Structural alterations, including the fabrication of nanoparticles with core-shell topologies, can boost stability and facilitate multi-stimuli response.[5]

Strategies for enhancing precision and minimizing premature drug release

To improve accuracy and minimize premature medication release, the system design must guarantee that stimuli activate drug release alone under appropriate conditions. One method involves employing "protective" mechanisms, such as the fabrication of "drug-loaded" particles including drug-containing reservoirs that are encased in responsive coatings (e.g., pH-sensitive polymers). These coatings inhibit the premature release of the medication in non-target regions and facilitate release alone when encountering the appropriate stimulus. Moreover, modifying the size of the polymer or nanoparticle helps control drug release rates and inhibit leakage into the systemic circulation. Creating systems that necessitate several triggers for release significantly reduces inadvertent drug discharge, guaranteeing that medications are released solely when the exact combination of elements is present.[37]

Approaches for achieving tunable and sustained release profiles

Achieving tunable and sustained drug release profiles is essential for effective long-term treatment.[38] This can be accomplished by engineering materials with controlled degradation rates or by embedding drugs within carriers that release their payload over extended periods. For example, crosslinking polymers at varying densities or incorporating biodegradable materials can allow for controlled breakdown over time.[39] Moreover, blending different materials with distinct release characteristics (e.g., combining slow-degrading and fast-degrading components) can create systems that exhibit prolonged and predictable drug release profiles. Encapsulation techniques such as nanoencapsulation, layer-by-layer assembly, or micelle formation can also be employed to modulate the release rate, allowing for sustained release over days or weeks, depending on the disease requirements.[40] The integration of feedback mechanisms, where drug release is regulated by environmental conditions (e.g., temperature or pH), can further enhance the tunability of the release profile, offering both short-term and long-term therapeutic solutions.[41]

LIMITATIONS AND CHALLENGES

While stimuli-responsive nanomaterials (SRNs) hold significant promise for revolutionizing drug delivery, several challenges and limitations remain in their development, storage, and clinical application. These obstacles must be addressed to fully harness the potential of SRNs for therapeutic use.[42,43]

Stability issues during storage and transport

One of the main challenges with SRNs is ensuring their stability during storage and transport. These materials are often sensitive to changes in temperature, pH, and humidity, which can affect their structure, integrity, and drug release behavior.[44] For example, pH-sensitive nanomaterials may degrade or lose their responsiveness if exposed to extreme conditions, leading to compromised therapeutic performance. In addition, SRNs containing hydrophobic drugs or biologics may undergo aggregation or phase separation during storage, affecting drug loading and release kinetics. To mitigate this, researchers are exploring stabilizing formulations and packaging strategies, such as lyophilization, encapsulation in protective coatings, and optimizing storage conditions to maintain SRN efficacy and stability during long-term storage and transport.[45]

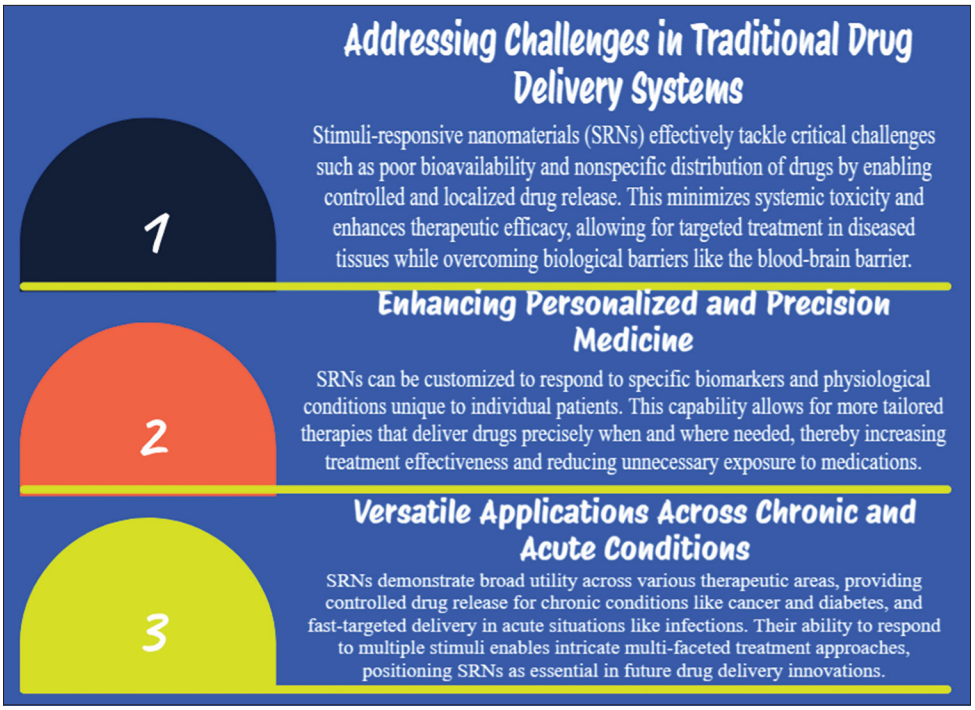

Figure 1: Pharmaceutical applications of stimuli-responsive nanomaterials

Potential toxicity and immunogenicity concerns

The use of nanomaterials in drug delivery raises concerns about potential toxicity and immunogenicity. Despite their small size and the ability to target specific tissues, SRNs can trigger immune responses or accumulate in non-target organs, leading to adverse effects.[46] The materials themselves, such as polymers or metallic nanoparticles, may induce inflammatory responses, oxidative stress, or cytotoxicity. Moreover, the breakdown products of SRNs may also pose risks if not carefully designed for safe degradation. Ensuring the biocompatibility of SRNs requires rigorous preclinical testing to evaluate their toxicity profiles and to minimize risks of unintended immune activation or long-term accumulation in the body.[42]

Manufacturing hurdles, such as reproducibility and scalability

The manufacturing of SRNs faces significant challenges, particularly in achieving reproducibility and scalability.[47] While small-scale laboratory synthesis may allow for precise control over size, composition, and drug loading, translating these processes to industrial-scale production remains a complex task.[48] Variability in the synthesis process, such as inconsistent particle size or surface functionalization, can lead to batch-to-batch differences that affect the quality and effectiveness of SRNs. Furthermore, scaling up the production of SRNs while maintaining quality and uniformity requires the development of efficient, cost-effective, and robust manufacturing processes. Solutions such as automated production systems and continuous flow synthesis are being explored to overcome these hurdles and meet the demand for large-scale production of SRNs.[49]

Challenges in clinical translation and regulatory approval

One of the most significant challenges for SRNs is their clinical translation and regulatory approval. The use of nanomaterials in humans is highly regulated, with strict guidelines governing their safety, efficacy, and manufacturing.[49] Clinical trials involving SRNs must demonstrate not only that these materials are safe and effective but also that they can be consistently produced at scale. In addition, the potential for long-term side effects, such as accumulation in organs or unexpected immunological responses, must be thoroughly assessed.[50] Regulatory bodies, such as the food and drud administration and European medicines agency, require extensive data on the pharmacokinetics, toxicity, and biocompatibility of SRNs before approval for clinical use.[51] Meeting these regulatory requirements while demonstrating the advantages of SRNs over traditional drug delivery systems presents a significant challenge for researchers and pharmaceutical companies.[52]

FUTURE PERSPECTIVES

Stimuli-responsive nanomaterials (SRNs) represent a rapidly evolving field with immense potential for revolutionizing drug delivery.[51] As research advances, several emerging trends and opportunities are shaping the future of SRNs in pharmaceutical applications.

Emerging trends in multi-stimuli-responsive systems

One of the most exciting emerging trends in SRNs is the development of multi-stimuli-responsive systems. These systems are designed to respond to multiple environmental factors simultaneously, such as pH, temperature, light, and specific enzymes or redox conditions.[53,54] By combining different stimuli, multi-responsive systems can offer greater precision and control over drug release, adapting to complex disease microenvironments.[55] For example, cancer tissues often present a combination of acidic pH, oxidative stress, and overactive enzymes, making multi-stimuli-responsive SRNs particularly advantageous for targeted therapy.[56] These systems can also be tailored for more efficient drug release in challenging conditions such as biofilms or hypoxic regions, which are common in chronic infections.[57,58] By harnessing multiple triggers, these SRNs could improve therapeutic outcomes while minimizing side effects.[59]

Integration of SRNs with advanced technologies, such as artificial intelligence (AI), for real-time monitoring and control

The integration of SRNs with advanced technologies such as AI and machine learning holds great promise for optimizing drug delivery.[60,61] AI could facilitate real-time monitoring of SRN behavior, tracking drug release *in vivo* and adjusting parameters such as drug dose or timing based on individual patient responses.[62] Machine learning algorithms could help design more efficient SRNs by predicting how these materials will interact with specific disease conditions or stimuli.[63] This integration could also enable personalized treatment plans by analyzing patient data to determine the most effective drug release strategy.[64,65] Furthermore, AI-powered sensors could monitor SRN activity and provide feedback to dynamically control drug release, offering unprecedented precision and adaptability in therapeutic applications.

Prospects for SRNs in advanced drug delivery systems

The future of SRNs lies in their ability to play a pivotal role in next-generation drug delivery systems.[44] Innovations such as self-healing nanomaterials, nanorobots, and gene-delivery platforms could be incorporated with SRNs for even more advanced therapeutic strategies.[66] For instance, self-healing materials could repair themselves in response to mechanical stress, improving the stability and longevity of the drug delivery system. Nanorobots or "smart" nanoparticles could be designed to interact with cellular targets in response to external cues, offering ultra-targeted drug delivery.[67,68] In addition, SRNs can be applied in combination therapies, where multiple drugs are delivered simultaneously or sequentially, allowing for synergistic effects and better therapeutic outcomes.[69,70] The ability of SRNs to deliver both traditional pharmaceuticals and biologics (such as proteins, RNA, or CRISPR-based therapies) further expands their utility in next-generation treatments.[71]

Pathways for enhancing clinical translation and commercialization

To fully realize the clinical potential of SRNs, several pathways must be explored to enhance clinical translation and commercialization.[72] First, addressing the stability, scalability, and reproducibility challenges associated with SRNs is crucial for ensuring consistent performance in clinical settings.[73] Collaborations between academic researchers and industry partners can help streamline the manufacturing process and reduce production costs.[74] In addition, extensive preclinical studies, coupled with the development of standardized protocols for testing SRNs, will be critical in gaining regulatory approval.[75,76] Regulatory agencies may also benefit from adopting flexible guidelines specific to nanomedicine, as traditional approval pathways may not be well suited to the unique properties of SRNs.[77] Finally, addressing concerns related to toxicity and immunogenicity will be vital for safe clinical use. Clinical trials will need to demonstrate that SRNs offer a clear therapeutic benefit over conventional treatments, which will drive their acceptance and widespread use in the market.

CONCLUSION

Stimuli-responsive nanoparticles (SRNs) signify a revolutionary development in drug delivery, presenting considerable potential for on-demand drug release systems. By reacting to particular environmental stimuli, like pH, temperature, light, or enzyme activity, SRNs provide targeted and localized drug release, addressing numerous constraints inherent in traditional drug delivery systems. Their capacity to provide medications exclusively at the target location, along with improved bioavailability and diminished systemic toxicity, renders them exceptionally promising for the therapy of intricate diseases such as cancer, persistent infections, and neurodegenerative disorders. SRNs are set to revolutionize contemporary pharmaceuticals by enhancing medication targeting, reducing adverse effects, and facilitating personalized therapy. Their use of sophisticated technology, including AI, amplifies their capabilities by enabling real-time monitoring and regulation of medication release, thereby maximizing therapeutic results. The future of SRNs depends on their capacity to tackle new healthcare difficulties, such as multi-stimuli responsiveness and the administration of complicated biologics. Despite ongoing obstacles concerning stability, toxicity, and clinical translation, persistent research and development, coupled with collaborative initiatives

among academia, industry, and regulatory entities, will facilitate their commercialization and clinical integration. The prognosis for SRNs is favourable, presenting novel opportunities for more efficient, individualized therapies.

ACKNOWLEDGMENT

The authors are extremely thankful Raghavendra Institute of Pharmaceutical Education and Research for their extreme support and knowledge.

REFERENCES

1. Adepu S, Ramakrishna S. Controlled drug delivery systems: Current status and future directions. Molecules 2021;26:5905.
2. Qindeel M, Ullah MH, Fakhar-Ud-Din, Ahmed N, Rehman AU. Recent trends, challenges and future outlook of transdermal drug delivery systems for rheumatoid arthritis therapy. J Control Release 2020;327:595-615.
3. Singh AP, Biswas A, Shukla A, Maiti P. Targeted therapy in chronic diseases using nanomaterial-based drug delivery vehicles. Signal Transduct Target Ther 2019;4:33.
4. Dutta G, Manickam S, Sugumaran A. Stimuli-responsive hybrid metal nanocomposite -a promising technology for effective anticancer therapy. Int J Pharm 2022;624:121966.
5. Karimi M, Ghasemi A, Zangabad PS, Rahighi R, Basri SM, Mirshekari H, *et al.* Smart micro/nanoparticles in stimulus-responsive drug/gene delivery systems. Chem Soc Rev 2016;45:1457-501.
6. Zhang M, Hu W, Cai C, Wu Y, Li J, Dong S. Advanced application of stimuli-responsive drug delivery system for inflammatory arthritis treatment. Mater Today Bio 2022;14:100223.
7. Sankula MK, Bodavula SS, Rao MN, Vadapalli RR. Drug Delivery Systems. Uttar Pradesh: JEC Publication;2025.
8. Gao J, Karp JM, Langer R, Joshi N. The Future of Drug Delivery. United States: ACS Publications; 2023. p. 359-63.
9. Zheng PP, Li J, Kros JM. Breakthroughs in modern cancer therapy and elusive cardiotoxicity: Critical research-practice gaps, challenges, and insights. Med Res Rev 2018;38:325-76.
10. Sorger PK, Allerheiligen SR, Abernethy DR, Altman RB, Brouwer KL, Califano A, *et al.* editors. Quantitative and Systems Pharmacology in the Post-genomic Era: New Approaches to Discovering Drugs and Understanding Therapeutic Mechanisms. In: An NIH White Paper by the QSP Workshop Group. United States: NIH Bethesda; 2011.
11. Liu M, Du H, Zhang W, Zhai G. Internal stimuli-responsive nanocarriers for drug delivery: Design strategies and applications. Mater Sci Eng C Mater Biol Appl 2017;71:1267-80.
12. Karimi M, Eslami M, Sahandi-Zangabad P, Mirab F, Farajisafiloo N, Shafaei Z, *et al.* pH-sensitive stimulus-responsive nanocarriers for targeted delivery of therapeutic agents. Wiley Interdiscip Rev Nanomed Nanobiotechnol 2016;8:696-716.
13. Li M, Zhao G, Su WK, Shuai Q. Enzyme-responsive nanoparticles for anti-tumor drug delivery. Front Chem 2020;8:647.
14. Hu Q, Katti PS, Gu Z. Enzyme-responsive nanomaterials for controlled drug delivery. Nanoscale 2014;6:12273-86.
15. Mirhadi E, Mashreghi M, Maleki MF, Alavizadeh SH, Arabi L, Badiee A, *et al*. Redox-sensitive nanoscale drug delivery systems for cancer treatment. Int J Pharm 2020;589:119882.
16. Vinchhi P, Rawal SU, Patel MM. External stimuli-responsive drug delivery systems. In: Drug Delivery Devices and Therapeutic Systems. Netherlands: Elsevier; 2021. p. 267-88.
17. Papadakis CM, Niebuur BJ, Schulte A. Thermoresponsive polymers under pressure with a focus on poly(N-isopropylacrylamide) (PNIPAM). Langmuir 2023;40:1-20.
18. Zheng F, Xiong W, Sun S, Zhang P, Zhu JJ. Recent advances in drug release monitoring. Nanophotonics 2019;8:391-413.
19. Stoychev G, Kirillova A, Ionov L. Light-responsive shape-changing polymers. Adv Opt Mat 2019;7:1900067.
20. Sahoo PR. Light responsive materials: Properties, design, and applications. In: Stimuli-Responsive Materials for Biomedical Applications. United States: ACS Publications; 2023. p. 101-27.
21. Wang Y, Kohane DS. External triggering and triggered targeting strategies for drug delivery. Nat Rev Mater 2017;2:1-14.
22. Chen Y, Chen N, Feng X. The role of internal and external stimuli in the rational design of skin-specific drug delivery systems. Int J Pharm 2021;592:120081.
23. Choudhary S, Guleria V, Gupta G. Electric field responsiveness of nano-drug delivery. In: Smart Micro- and Nanomaterials for Drug Delivery. United States: CRC Press; 19. p. 244-64.
24. Liarou E, Varlas S, Skoulas D, Tsimblouli C, Sereti E, Dimas K, *et al*. Smart polymersomes and hydrogels from polypeptide-based polymer systems through α-amino acid N -carboxyanhydride ring-opening polymerization. From chemistry to biomedical applications. Prog Polym Sci 2018;83:28-78.
25. Abd Ellah NH, Abouelmagd SA. Surface functionalization of polymeric nanoparticles for tumor drug delivery: approaches and challenges. Expert Opin Drug Deliv 2017;14:201-14.
26. Mishra DK, Shandilya R, Mishra PK. Lipid based nanocarriers: A translational perspective. Nanomedicine 2018;14:2023-50.
27. Wang G, Wang J, Wu W, Tony To SS, Zhao H, Wang J. Advances in lipid-based drug delivery:

Enhancing efficiency for hydrophobic drugs. Expert Opin Drug Deliv 2015;12:1475-99.
28. Susa F, Arpicco S, Pirri CF, Limongi T. An overview on the physiopathology of the blood-brain barrier and the lipid-based nanocarriers for central nervous system delivery. Pharmaceutics 2024;16:849.
29. Nejati K, Dadashpour M, Gharibi T, Mellatyar H, Akbarzadeh A. Biomedical applications of functionalized gold nanoparticles: A review. J Clust Sci 2021;33:1-16.
30. Ajinkya N, Yu X, Kaithal P, Luo H, Somani P, Ramakrishna S. Magnetic iron oxide nanoparticle (IONP) synthesis to applications: Present and future. Materials 2020;13:4644.
31. Liu X, Yang Y, Urban MW. Stimuli-responsive polymeric nanoparticles. Macromol Rapid Commun 2017;38:1700030.
32. Vogler-Neuling VV, Saba M, Gunkel I, Zoppe JO, Steiner U, Wilts BD, *et al*. Biopolymer photonics: From nature to nanotechnology. Adv Funct Mater 2024;34:2306528.
33. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. Nat Rev Drug Discov 2021;20:101-24.
34. Pourjavadi A, Heydarpour R, Tehrani ZM. Multi-stimuli-responsive hydrogels and their medical applications. New J Chem 2021;45:15705-17.
35. Hu S, Zhao R, Shen Y, Lyu B. Revolutionizing drug delivery: The power of stimulus-responsive nanoscale systems. Chem Eng J 2024;496:154265.
36. Yang P, Zhu F, Zhang Z, Cheng Y, Wang Z, Li Y. Stimuli-responsive polydopamine-based smart materials. Chem Soc Rev 2021;50:8319-43.
37. Ahmadi S, Rabiee N, Bagherzadeh M, Elmi F, Fatahi Y, Farjadian F, *et al.* Stimulus-responsive sequential release systems for drug and gene delivery. Nano Today 2020;34:100914.
38. Benhabbour SR, Kovarova M, Jones C, Copeland DJ, Shrivastava R, Swanson MD, *et al.* Ultra-long-acting tunable biodegradable and removable controlled release implants for drug delivery. Nat Commun 2019;10:4324.
39. Van Bochove B, Grijpma DW. Photo-crosslinked synthetic biodegradable polymer networks for biomedical applications. J Biomater Sci Polym Ed 2019;30:77-106.
40. Balkundi S. Micro, Nano Encapsulation Methods for Sustained Release Drug Formulations and Biomimetic Applications. United States: Louisiana Tech University; 2009.
41. Zhang Y, Yu J, Bomba HN, Zhu Y, Gu Z. Mechanical force-triggered drug delivery. Chem Rev 2016;116:12536-63.
42. Comanescu C. Recent advances in surface functionalization of magnetic nanoparticles. Coatings 2023;13:1772.
43. Umadevi K, Sundeep D, Vighnesh AR, Misra A, Krishna AG. Current trends and advances in nanoplatforms-based imaging for cancer diagnosis. Indian J Microbiol 2024;64:1-40.
44. Rout SR, Manu KR, Kaur G, Abishek KG, Alsayari A, Wahab S, *et al*. Recent advances in drug delivery aspects using organogel: Exploring a viscoelastic system as a platform for the next-generation therapeutics. Eur Polym J 2024;214:113184.
45. Bhatia S. Natural Polymer Drug Delivery Systems. Germany: Springer; 2016.
46. Ilinskaya AN, Dobrovolskaia MA. Understanding the immunogenicity and antigenicity of nanomaterials: Past, present and future. Toxicol Appl Pharmacol 2016;299:70-7.
47. Othman NH, Alias NH, Fuzil NS, Marpani F, Shahruddin MZ, Chew CM, *et al*. A review on the use of membrane technology systems in developing countries. Membranes 2021;12:30.
48. Herdiana Y, Wathoni N, Shamsuddin S, Muchtaridi M. Scale-up polymeric-based nanoparticles drug delivery systems: Development and challenges. OpenNano 2022;7:100048.
49. Çiçekler M, Akın M. Advances and Challenges in the Integration of Cellulose Nanocrystals in Paper Manufacturing. In: 2nd International Conference on Modern and Advanced Research (ICMAR 2025), Konya; 2025.
50. Zhang Y, Bai Y, Jia J, Gao N, Li Y, Zhang R, *et al.* Perturbation of physiological systems by nanoparticles. Chem Soc Rev 2014;43:3762-809.
51. Dachani SR, Vashi A, Mundada AB, Mundada PA, Rudrangi SR, Rudrangi S, *et al*. Innovative polymers in pharmaceutical chemistry: Revolutionizing drug delivery systems. Polym Plast Technol Mater 2024;19:1-23.
52. Banda JM, Evans L, Vanguri RS, Tatonetti NP, Ryan PB, Shah NH. A curated and standardized adverse drug event resource to accelerate drug safety research. Sci Data 2016;3:160026.
53. Taheri Z, Mozafari N, Moradian G, Lovison D, Dehshahri A, De Marco R. Integrin-specific stimuli-responsive nanomaterials for cancer theranostics. Pharmaceutics 2024;16:1441.
54. Falsafi M, Saljooghi AS, Abnous K, Taghdisi SM, Ramezani M, Alibolandi M. Smart metal organic frameworks: Focus on cancer treatment. Biomater Sci 2021;9:1503-29.
55. Jia R, Teng L, Gao L, Su T, Fu L, Qiu Z, *et al*. Advances in multiple stimuli-responsive drug-delivery systems for cancer therapy. Int J Nanomedicine 2021;16:1525-51.
56. Zhou L, Wang H, Li Y. Stimuli-responsive nanomedicines for overcoming cancer multidrug resistance. Theranostics 2018;8:1059-74.
57. Benoit DS, Koo H. Targeted, Triggered Drug Delivery to Tumor and Biofilm Microenvironments. United Kingdom: Taylor and Francis; 2016. p. 873-9.
58. Smith AW. Biofilms and antibiotic therapy: Is there a role for combating bacterial resistance by the use of novel drug delivery systems? Adv Drug Deliv Rev 2005;57:1539-50.
59. Wiraswati HL, Ma'ruf IF, Hidayati NA, Ramadhanti J, Calina D, Sharifi-Rad J. Harnessing

the anticancer potential of *Piper nigrum*: A synergistic approach to chemotherapy enhancement and reduced side effects. Discov Oncol 2025;16:10.
60. Segun AF. Integrating machine learning into regulatory frameworks and safety assessment for advanced medical therapeutics. Int J Res Publ Rev 2024;5:7262-76.
61. Malviya R, Ghinea G, Balusamy B, Sundram S. Deep Learning for Targeted Treatments: Transformation in Healthcare. United States: John Wiley and Sons; 2022.
62. Poomari DK. Intelligent support for cardiovascular diagnosis. In: Using Traditional Design Methods to Enhance AI-Driven Decision Making. United States: IGI Global; 2024. p. 64.
63. Janssen RJ, Mourão-Miranda J, Schnack HG. Making individual prognoses in psychiatry using neuroimaging and machine learning. Biol Psychiatry Cogn Neurosci Neuroimag 2018;3:798-808.
64. Marques L, Costa B, Pereira M, Silva A, Santos J, Saldanha L, *et al.* Advancing precision medicine: A review of innovative *in silico* approaches for drug development, clinical pharmacology and personalized healthcare. Pharmaceutics 2024;16:332.
65. Serrano DR, Luciano FC, Anaya BJ, Ongoren B, Kara A, Molina G, *et al.* Artificial intelligence (AI) applications in drug discovery and drug delivery: Revolutionizing personalized medicine. Pharmaceutics 2024;16:1328.
66. Hasanzadeh A, Ebadati A, Saeedi S, Kamali B, Noori H, Jamei B, *et al.* Nucleic acid-responsive smart systems for controlled cargo delivery. Biotechnol Adv 2024;74:108393.
67. Sun L, Liu H, Ye Y, Lei Y, Islam R, Tan S, *et al.* Smart nanoparticles for cancer therapy. Signal Transduct Target Ther 2023;8:418.
68. Mendes PM. Cellular nanotechnology: Making biological interfaces smarter. Chem Soc Rev 2013;42:9207-18.
69. Tonse R, Tom MC, Mehta MP, Ahluwalia MS, Kotecha R. Integration of systemic therapy and stereotactic radiosurgery for brain metastases. Cancers 2021;13:3682.
70. Kareliotis G, Tremi I, Kaitatzi M, Drakaki E, Serafetinides AA, Makropoulou M, *et al*. Combined radiation strategies for novel and enhanced cancer treatment. Int J Radiat Bio1 2020;96:1087-103.
71. Nazir A, Hussain FH, Raza A. Advancing microbiota therapeutics: The role of synthetic biology in engineering microbial communities for precision medicine. Front Bioeng Biotechnol 2024;12:1511149.
72. Aguilera-Cobos L, Rosario-Lozano MP, Ponce-Polo A, Blasco-Amaro JA, Epstein D. Barriers for the evaluation of advanced therapy medicines and their translation to clinical practice: Umbrella review. Health Policy 2022;126:1248-55.
73. Eshbekova N, Sowndarya A, Thangadurai TD, Lee YI. Recent advancements in Raman instrumentation and capabilities for pharmaceutical and biomedical applications. Appl Spectrosc Rev 2024;59:798-849.
74. Sanders A, Elangeswaran C, Wulfsberg JP. Industry 4.0 implies lean manufacturing: Research activities in industry 4.0 function as enablers for lean manufacturing. J Indust Eng Manage 2016;9:811-33.
75. Bhogal N, Combes R, Balls M. Preclinical drug development planning. In: Preclinical Development Handbook. United States: Wiley; 2008. p. 1-64.
76. Shepherd RK, Villalobos J, Burns O, Nayagam DA. The development of neural stimulators: A review of preclinical safety and efficacy studies. J Neural Eng 2018;15:041004.
77. Abbott KW, Marchant GE, Sylvester DJ. A framework convention for nanotechnology? Policy review. Environ Law Report 2008;38:10507-14.

Source of Support: Nil. **Conflicts of Interest:** None declared.