Received: 14 July 2023 | Revised: 13 November 2023 | Accepted: 11 April 2024

DOI: 10.1002/hsr2.2065

NARRATIVE REVIEW

Health Science Reports Open Access WILEY

Current approaches in smart nano-inspired drug delivery: A narrative review

Sri Harsha Boppana[1] | L. V. Simhachalam Kutikuppala[2] | Sushil Sharma[2] | Madhavrao C[2] | Gaurav Rangari[2] | Arup Kumar Misra[2] | Venkataramana Kandi[3] | Snehasish Mishra[4] | Puneet Kumar Singh[4] | Ali A. Rabaan[5,6,7] | Ranjan K. Mohapatra[8] | Md. Kudrat-E-Zahan[9]

[1]Department of Anesthesia and Critical Care, Johns Hopkins School of Medicine, Baltimore, Maryland, USA

[2]Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), Mangalagiri, Andhra Pradesh, India

[3]Department of Microbiology, Prathima Institute of Medical Sciences, Karimnagar, Telangana, India

[4]School of Biotechnology, Campus-11, KIIT Deemed-to-be-University, Bhubaneswar, Odisha, India

[5]Molecular Diagnostic Laboratory, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia

[6]College of Medicine, Alfaisal University, Riyadh, Saudi Arabia

[7]Department of Public Health and Nutrition, The University of Haripur, Haripur, Pakistan

[8]Department of Chemistry, Government College of Engineering, Keonjhar, Odisha, India

[9]Department of Chemistry, Rajshahi University, Rajshahi, Bangladesh

Correspondence

Ranjan K. Mohapatra, Government College of Engineering, Keonjhar 758002, Odisha, India.
Email: ranjank_mohapatra@yahoo.com

Md. Kudrat-E-Zahan, Rajshahi University, Rajshahi 6205, Bangladesh.
Email: kudrat.chem@ru.ac.bd

Abstract

Background and Aim: The traditional drug delivery approach involves systemic administration of a drug that could be nonspecific in targeting, low on efficacy, and with severe side-effects. To address such challenges, the field of smart drug delivery has emerged aiming at designing and developing delivery systems that can target specific cells, tissues, and organs and have minimal off-target side-effects.

Methods: A literature search was done to collate papers and reports about the currently available various strategies for smart nano-inspired drug delivery. The databases searched were PubMed, Scopus, and Google Scholar. Based on selection criteria, the most pertinent and recent items were included.

Results: Smart drug delivery is a cutting-edge revolutionary intervention in modern medicines to ensure effective and safe administration of therapeutics to target sites. These hold great promise for targeted and controlled delivery of therapeutic agents to improve the efficacy with reduced side-effects as compared to the conventional drug delivery approaches. Current smart drug delivery approaches include nanoparticles, liposomes, micelles, and hydrogels, each with its own advantages and limitations. The success of these delivery systems lies in engineering and designing them, and optimizing their pharmacokinetics and pharmacodynamics properties.

Conclusion: Development of drug delivery systems that can get beyond various physiological and clinical barriers, as observed in conventionally administered chemotherapeutics, has been possible through recent advancements. Using multifunctional targeting methodologies, smart drug delivery tries to localize therapy to the target location, reduces cytotoxicity, and improves the therapeutic index. Rapid advancements in research and development in smart drug delivery provide wider and more promising avenues to guarantee a better healthcare system, improve

patient outcomes, and achieve higher levels of effective medical interventions like personalized medicine.

KEYWORDS
hydrogels, liposomes, micelles, nanoparticles, smart drug delivery, therapeutics

1 | INTRODUCTION

Drug delivery is a critical aspect of modern medicine that ensures effective and safe administration of therapeutic agents to the target site in the body.[1,2] Traditional drug delivery or systemic administration of a drug could have flaws such as nonspecific targeting, low efficacy, and inadvertent and obvious side-effects.[3,4] The emerging field of smart drug delivery aims to design and develop delivery systems to address these flaws to target specific cells, tissues, and organs better and minimize the off-target side-effects.[5,6]

The development of smart drug delivery systems has opened up new vistas for targeted drug delivery against numerous diseases including cancer, cardiovascular diseases, neurological disorders, and infectious diseases. Through precise delivery of therapeutic agents, smart drug delivery systems could potentially revolutionize the field of medicines in particular and healthcare in general.[7] Smart drug delivery systems adopt various approaches for improved specificity, efficacy, and safety of drug delivery. These include using nanoparticles (NPs), liposomes, micelles, hydrogels, and other such as biomaterials that can improve drug solubility, stability, and bioavailability. Also, designed smart drug delivery systems could respond to external or internal stimuli, and allow for controlled drug release at the target site.[8]

This review attempts to provide an overview of the current approaches and latest trends in smart drug delivery, various delivery systems, and their applications. The advantages and limitations of each approach are discussed, and the recent advances and challenges in the field are highlighted. The discussion extends to the future directions and potential applications of smart drug delivery systems beyond conventional therapeutics to personalized medicine and combination therapy. Supporting substrates, flexible circuitry, adhesive films, actuator components, thin-film sensor systems, data transmission systems, therapeutic systems, and energy-harvesting systems are typically included in smart wearable patch systems. By tracking numerous physical and biochemical characteristics on real-time basis and displaying an on-demand closed-loop drug release, smart wearable patch systems that are coupled with therapeutic components can enable personal healthcare and medication. Because they combine biosensors and stimuli-responsive carrier-based DDSs, these user-friendly, long-acting, noninvasive and self-administrable smart wearable patch systems have the potential to usher in an array of new-age healthcare platforms.[9]

2 | METHODOLOGY

To find the currently available papers and studies on the various strategies for smart nano-inspired drug delivery, a focused literature search was carrier out. The most pertinent and recent literature, as per the selection criteria, was concentrated on. The keywords and their combinations used while carrying out the targeted online search were “smart nano drug delivery,” “smart nano drug delivery system,” “nanostructured smart drug delivery,” “precise nano drug delivery,” and “personalized nano drug delivery.” The scientific databases searched were PubMed, Scopus, and Google Scholar. The requirements for an article to meet the inclusion criteria were: 1. studies or articles on smart nano drug delivery, 2. studies or articles published in the English language, 3. studies or articles published from the earliest possible date till June 2023, and 5. studies or publications with June 2023 or later as the publication time. A total of 69 articles were analyzed out of 240 collated after searching, and the references were validated and manually listed. Based on the above selection criteria, the most pertinent and recent items were included. The findings shed light on the progress in the field of smart nano-drug delivery. Patterns and consistency throughout the included literature may be found due to the narrative synthesis technique employed in the study. The irrelevant or less meaningful articles were excluded to avoid defocusing from the write-up. The potential publishing and linguistic bias, biasness due to high dependence on earlier reported research, the lack of generalizability, and the contradicting evidence are some of the limitations of this piece of work.

3 | NP-BASED SMART DRUG DELIVERY SYSTEM

NP-based smart drug delivery system is one of the most extensively improvised and widely applied approaches for targeted drug delivery. NPs are widely defined as particles with a 1–1000 nm size range having the ability to penetrate deep into the cells and tissues, providing enhanced drug delivery efficiency.[7,8] They can also be designed with specific surface properties like charge, hydrophobicity, or functionality, to enhance cellular uptake, extend circulation time, and target the specific cells or tissues better.[10,11]

NPs can be made from a variety of materials like polymer, lipid, metal, and inorganic material, each with its own advantages and limitations (Figure 1). For instance, polymer-based NP poly (lactic-co-glycolic acid; PLGA) and polyethylene glycol (PEG) are suitable for in vivo applications owing to their biocompatibility and biodegradability. Metal-based NPs like

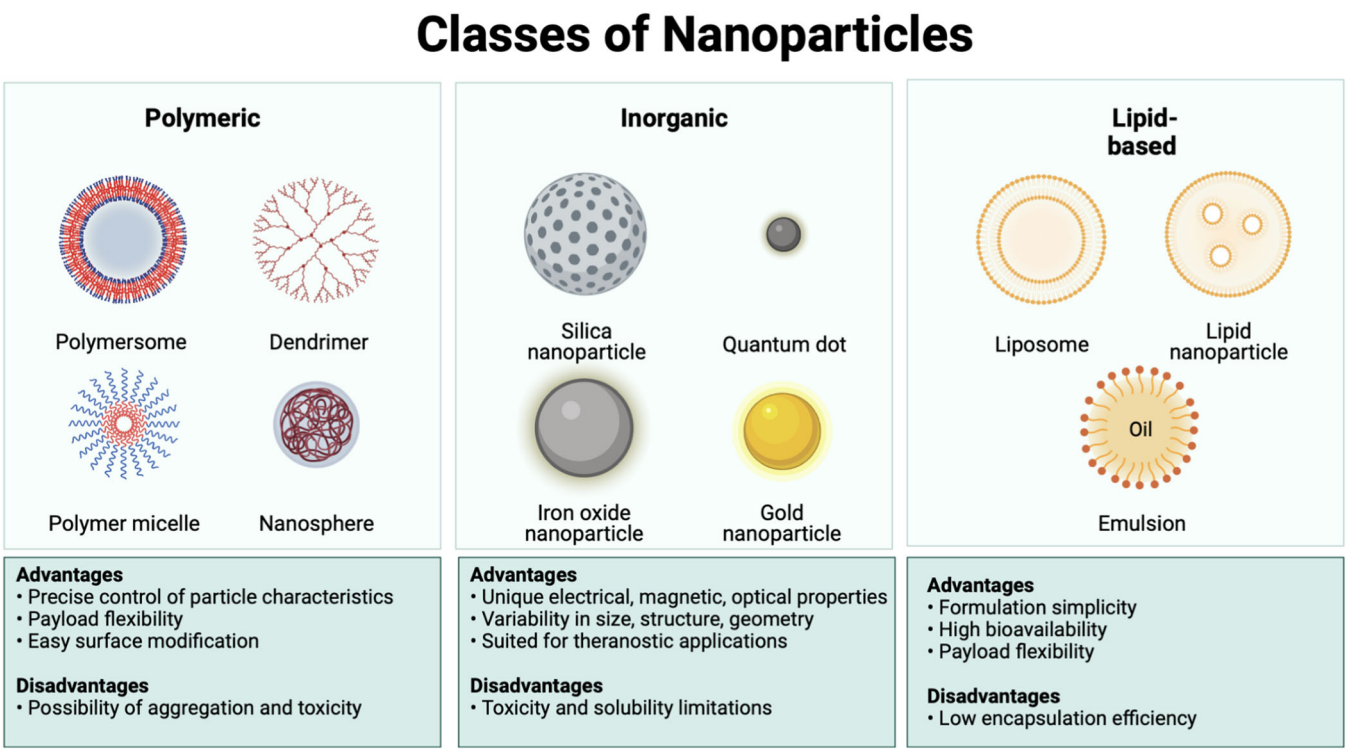

FIGURE 1 Classes of NPs for smart drug delivery and their advantages and disadvantages. NP, nanoparticle.

gold and iron oxide have unique optical and magnetic properties, useful for imaging and theranostic applications. Lipid-based NPs like liposomes and solid lipid NPs can mimic the structure of a cell membrane, enabling better cellular uptake and targeting.[12,13] NPs can also be functionalized with targeting ligands like antibodies, peptides, or aptamers to selectively bind to specific cell surface receptors and enhance drug delivery specificity. Also, the designed stimuli-responsive NPs release a drug in response to specific triggers such as an altered pH, temperature or enzyme activity, that ensures target-specific controlled drug release.[7]

Several NP-based smart drug delivery systems are developed against numerous diseases like cancer, cardiovascular diseases, and neurological disorders. For example, designed NP-based drug delivery systems target cancer cells by exploiting the overexpression of specific receptors or enzymes like folate receptors or matrix metalloproteinases that are abundant in onco-cells. Targeting strategies could improve the efficacy and reduce toxicity of chemotherapeutic agents like paclitaxel or doxorubicin.[14,15] Besides cancer, NP-based drug delivery systems are developed against cardiovascular and neurological ailments. Developed NP-based systems deliver anti-inflammatory agents like siRNA or curcumin to the vascular inflammation site to reduce inflammation and prevent the progression of atherosclerosis. NP-based drug delivery systems are developed to deliver drugs to the brain defying the blood-brain barrier to treat neurological disorders like the Alzheimer's disease.[15–17]

Despite the numerous advantages of NP-based smart delivery systems, several challenges are also there to address. For example, the synthesis and characterization of NPs could be complex, and their stability and toxicity need careful evaluation. The targeting and controlled drug release efficiency of NP-based delivery systems for specific applications also need optimization.[18]

4 | LIPOSOMAL DRUG DELIVERY

Liposomes are spherical lipid bilayer vesicles that could encapsulate hydrophilic or hydrophobic drugs. They are biocompatible, and biodegradable, and can be functionalized for improved specificity with targeting ligands. Liposomes can be engineered to respond to stimuli, such as altering pH, temperature, and light, to release drugs at the desired site of action. They can also be used to improve drug stability and solubility.[19,20]

On the other hand, polymeric NPs are composed of biodegradable or biocompatible polymers like PLGA and PEG. These can also be functionalized with targeting ligands and respond to pH, temperature, and enzyme stimuli. Polymeric NPs can encapsulate both hydrophilic and hydrophobic drugs, making them versatile drug carriers.[21] Both liposomes and polymeric NPs have been used in clinical trials for various diseases including cancer, infectious diseases, and inflammatory disorders and have shown astounding results at the preclinical stage.[22,23]

5 | MAGNETIC DRUG DELIVERY

Magnetic NPs having the ability to respond to magnetic fields have been explored for smart drug delivery. Such NPs can be functionalised with drugs and targeting ligands and delivered to target sites using an external

magnetic field thereby improving drug delivery specificity and efficacy, especially in the hard-to-reach areas such as the brain.[24] Magnetic NPs can also be used in hyperthermia therapy, where they are heated using an external magnetic field to induce tumor cell death. With promising results in preclinical trials, it holds great promise to improve cancer therapy.[25,26]

6 | MICELLES FOR SMART DRUG DELIVERY

Due to their unique structural and physicochemical properties, micelle NPs can be used as smart drug delivery systems. These are composed of amphiphilic molecules that could self-assemble in an aqueous solution to form stable colloidal particles with a hydrophobic core and a hydrophilic outer layer. The hydrophobic core could encapsulate hydrophobic drugs, enhance their solubility and stability by protecting them from degrading, while the hydrophilic outer layer could improve the stability and biocompatibility.[27,28]

One primary advantage of micelles smart drug delivery systems is their ability to selectively accumulate in a tumor microenvironment owing to the enhanced permeability and retention (EPR) effect. Tumors demonstrate leaky and disorganized blood vessels and impaired lymphatic drainage that result in the accumulation of high concentration of NPs in tumors as compared to normal tissues, a EPR phenomenon.[29] Micelles can be designed to exploit the EPR effect by incorporating targeting ligands like antibodies or peptides on their surface that would enhance the specificity and efficacy of drug delivery.[30–32]

Another advantage of micelles as smart drug delivery systems is their ability to respond to stimuli like the altered pH, temperature, or redox potential. Stimuli-responsive micelles can be designed to release the drug on the tumors in response to triggers like acidic environment or the presence of certain enzymes, allowing for target-specific controlled drug release. pH-responsive micelles release the drug in the acidic tumor microenvironment, reduce systemic toxicity, and improve drug efficacy.[33,34]

Despite these advantages, there are several challenges that need to be addressed. For example, the stability and biocompatibility of micelles, and the efficiency and specificity of drug delivery need to be carefully evaluated.[7] Additionally, micelles synthesis and characterization can be complex, and the scalability of the production process needs to be optimized. Nevertheless, the continued advancements in micelle-based drug delivery systems provide exciting opportunities for improved healthcare outcomes and ultimately achieve personalized medicine goals.[35]

7 | STIMULI-RESPONSIVE HYDROGELS-BASED SMART DRUG DELIVERY SYSTEMS

Owing to their unique properties of high-water content, biocompatibility and responsiveness to environmental stimuli, stimuli-responsive hydrogels have emerged as promising materials to design smart drug delivery systems.[36] Hydrogels are 3-D networks of cross-linked polymers that can absorb and retain large amount of water while their structural integrity is still retained. The responsiveness of hydrogels to external stimuli like temperature, pH, and ionic strength can be tailored by incorporating stimuli-responsive polymers like poly-N-isopropylacrylamide, poly-acrylic acid, or poly-ethylene glycol into the hydrogel matrix.[37,38]

Stimuli-responsive hydrogels as smart drug delivery are advantageous due to their ability to provide stimuli-specific controlled release of drugs. Temperature-responsive designed hydrogels release drugs in response to an altered temperature, like elevated temperature in tumors, allowing for localized sustained drug delivery. pH-responsive hydrogels could be designed to release drugs in response to the tumourogenic acidic microenvironment that enhance specificity and efficiency of drug delivery.[39] Additionally, ionic strength-responsive designed hydrogels release drugs in response to changes in the ionic strength of the surrounding environment, such as high ionic strength in the gastrointestinal tract, improving the bioavailability and therapeutic effect of the orally-administered drugs.[40]

Another advantage of stimuli-responsive hydrogels is their ability to be modified with targeting ligands or imaging agents, enabling targeted drug delivery and real-time monitoring of the drug release. Targeting ligands like antibodies or peptides could conjugate to the surface of hydrogels to enhance the specificity and efficiency of drug delivery to the target site. Imaging agents like fluorescent dyes or magnetic NPs can be incorporated into hydrogels for real-time in vivo monitoring of drug release and localization.[40,41]

Despite these advantages, there are several challenges to address for stimuli-responsive hydrogels as smart drug delivery systems. For instance, their stability and biocompatibility, the efficiency and specificity of drug delivery need to be carefully evaluated. Also, the synthesis and characterization of hydrogels and the scalability of the production process can be complex and need consideration. The ongoing advancements in hydrogel-based drug delivery systems nevertheless provide exciting opportunities and promise a better healthcare system.[42]

8 | BIOMIMETIC SMART DRUG DELIVERY SYSTEMS

Biomimetic smart drug delivery systems are designed to mimic the structure of biological systems such as cells or tissues and the natural process to improve drug delivery specificity and efficiency.[38] Biomimetic drug delivery systems could incorporate various biological system features, such as cell-penetrating peptides, extracellular matrix components, or biological signaling molecules, to enhance the targeting and uptake of drugs by the target cells or tissues. An advantage of biomimetic smart drug delivery systems is their ability to overcome biological barriers (like the blood-brain barrier or the mucus barrier in the respiratory and gastrointestinal tracts) that limit the efficacy of conventional drug delivery systems.[43]

An example of a biomimetic smart drug delivery system is the exosomes, naturally occurring cell-secreted vesicles, which play a role in intercellular communication. Engineered exosomes can encapsulate drugs and target specific cells or tissues by incorporating targeting ligands or fusing with the target cell membrane. Exosome-based drug delivery systems have shown promising results in preclinical studies to treat various diseases like cancer and neurological disorders.[36]

Liposomes are another example of a biomimetic smart drug delivery system. These are synthetic lipid-bilayer vesicles capable of encapsulating drugs and target specific cells/tissues.[33] These could be modified by targeting ligands like antibodies or peptides for enhanced drug delivery efficiency and specificity. Liposomes can be designed to respond to stimuli like the altered temperature or pH, thus allowing for controlled drug release at the target site.[44] Liposome-based drug delivery system has been approved for clinical use in treating diseases like cancer and fungal infections and continues as an active area of research and development. Figure 2 illustrates the drug loading strategies, modes of action, increased specificity, and half-life of liposome-based drug delivery.[45]

Despite the numerous advantages of biomimetic smart drug delivery systems, also there are several challenges that need to be addressed. For example, the complexity and variability of biological systems can make the designing and optimization of biomimetic drug delivery systems challenging. Also, the scalability and reproducibility of such systems, as well as their safety and toxicity need careful evaluation. However, similar to the other above-discussed delivery systems, the constant advancements in these drug delivery systems provide exciting opportunities.[46,47]

9 | MICRO-NEEDLES IN SMART DRUG DELIVERY

As drug delivery through transdermal route at the desired location is not efficiently carried out due to dermal barrier, micro-needles are suggested as a novel drug delivery mode.[48–55] Here, the skin is penetrated with micron-size needle for improved drug transportability to the desired location. Micro-needle drug delivery works more efficiently than conventional methods like topical ointments, transdermal patches, and hypodermic needles. Micro-needles also include multiple needles that ensure the delivery of large quantity of drugs by disrupting the dermal stratum corneum layer. Micro-needles are prepared from materials like silicon, stainless steel, platinum, palladium, nickel, palladium-cobalt alloy, ceramics, silica glass, carbohydrates (maltose, mannitol, trehalose, sucrose, xylitol, galactose, and polysaccharides), and biopolymers. Various types of micro-needles are solid type, coated micro-needle, those using hydrogel, dissolving micro-needle and hollow micro-needle.[48–55]

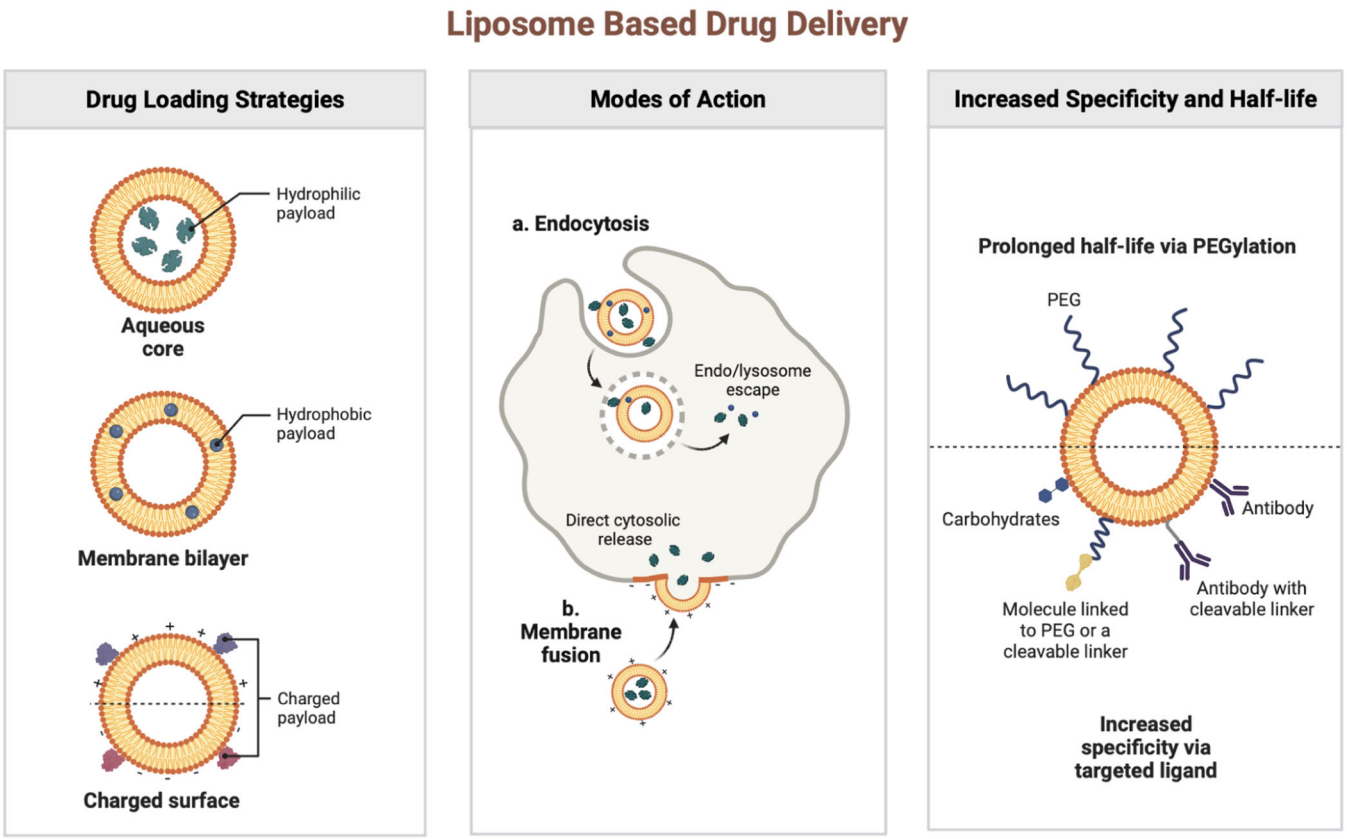

FIGURE 2 Drug loading strategies, modes of action, increased specificity, and half-life of liposome-based drug delivery systems.

Dermatological applications of micro-needles in managing skin diseases are huge. Micro-needle technology is useful in delivering anesthetics, vaccines, hormones like insulin, pain management drugs, inflammatory skin diseases, cancer and others.[48–55]

Micro-needle technology was recently applied in treating acne, wherein micro-needles were employed to deliver ultrasound-responsive zinc NPs to kill the *Propionibacterium* sp. responsible for acnes.[56] Patients with lung ailments like asthma, chronic obstructive lung disease, and cystic fibrosis develop breathing difficulties owing to infections and inflammation, usually treated through inhalation-type drugs dispensed through inhalers/nebulizers. The commonly used inhalation devices include nebulizer, pressurized metered-dose inhaler, breath-actuated metered-dose inhaler, dry powdered inhaler and soft mist inhaler.[57] Since the generated pressure by the device, lung deposition and inspiratory flow of a patient influence the efficiency of drug delivery, so selecting an effective drug delivery system is crucial to treat lungs disease.[58,59]

A recent study proposed the application of smart inhalers wherein the inhalers are fixed with smartphone applications. While being patient-friendly, it would enable physicians to track the medication adherence by the patient during management duration.[60] Given the associated drawbacks in traditional drug delivery systems, transdermal drug delivery approach has gained recognition in recent times.[61] Microarray patch (MAP) is a recently proposed novel transdermal drug delivery approach. Unlike the routine transdermal patches that release the drug instantly into the skin, MAP-based drug delivery systems are smart and are presumed to act on biological stimuli to release the drug. MAPs could also monitor the patients during drug therapy.[62] Smart drug delivery mechanisms like using porous particles and stimuli-responsive gatekeepers (smart gatekeepers) as carriers were proposed for improved drug delivery.[63] These methods notably enhance drug diffusion to the affected site and improve therapeutic efficacy of the drug.

10 | COMBINATION THERAPY USING SMART DRUG DELIVERY SYSTEMS

Combination therapy involves codelivering multiple drugs with various mechanisms of action to enhance the therapeutic efficacy while minimizing the adverse effects. Smart drug delivery systems to release drugs at different rates or in response to specific stimuli could be designed to allow precise control over the drug release profile and delivery timing. Combination therapy using smart drug delivery systems is promising to treat various diseases including cancer, cardiovascular disease, and neurological disorders at least at the preclinical stage.[47]

Codelivery of chemotherapeutics and immunomodulatory agents to treat cancer exemplifies combination therapy using smart drug delivery systems. While killing onco-cells, chemotherapy drugs also affect healthy cells, leading to severe adverse effects. Immunomodulatory agents can enhance immune response toward cancer cells and improve the efficacy of chemotherapy, but they could also cause immunotoxicity if not properly delivered. Designed smart drug delivery systems could co-deliver chemotherapy drugs and immunomodulatory agents at the tumor site, allowing for synergistic effects while minimizing the off-target (side-) effects.[64]

Another example of combination therapy using smart drug delivery systems is the codelivering drugs to treat complex diseases like Alzheimer's targeting multiple pathophysiological conditions. Alzheimer's disease involves multiple pathophysiological pathways including neuroinflammation, oxidative stress, and protein misfolding. Designed smart drug delivery systems can codeliver synergistic drugs targeting these different pathways for an improved therapeutic efficacy. Additionally, smart drug delivery systems can be designed to target specific regions of brain for more effective drug delivery and improved patient outcomes.[65,66]

Combination therapy with smart drug delivery system can potentially revolutionize the treatment of various diseases by improving therapeutic efficacy while minimizing the adverse effects.[67] The design and optimization of smart drug delivery systems for combination therapy needs a thorough understanding of the disease pathophysiology, drug pharmacokinetics, and interactions between the drugs and the delivery system. Despite challenges, advancements in such smart drug delivery systems pose exciting opportunities for healthcare and medical sciences.[31,68]

11 | ADVANTAGES AND LIMITATIONS OF SMART DRUG DELIVERY SYSTEMS

Smart drug delivery systems have gained significant attention in drug delivery due to their ability to improve therapeutic efficacy while minimizing adverse effects. Like any technology, smart drug delivery systems have their advantages and limitations. This section touches upon some major/wider and critical aspects regarding this.

11.1 | Advantages

1. *Enhanced therapeutic efficacy*: Smart drug delivery systems can be designed to target specific tissues/cells for enhanced therapeutic efficacy. Designed NPs can target onco-cell, allowing for higher drug concentrations at the tumor site and minimizing off-target side-effects.[19]
2. *Controlled drug release*: Along with enhanced drug targeting, smart drug delivery systems can ensure controlled release of drugs at specified rates or in response to specific stimuli, ensuring precise control over the profile and the timing of drug release/delivery. This could improve therapeutic efficacy and reduce adverse effects.[27]
3. *Improved patient compliance*: IT-enabled smart drug delivery systems could be designed to keep a track of the dosing by the consulting clinician from remote locations. Smart delivery

systems can be designed to deliver drugs over extended periods, reducing a need for frequent dosing and improving patient compliance.[21]

11.2 | Limitations

1. *Complex design*: The designing and optimization of smart drug delivery systems need a detailed knowledge of disease patho-physiology, drug pharmacokinetics and drug-delivery system interactions. It could result in complex and time-consuming design processes.[15]
2. *Limited drug loading capacity*: Some smart drug delivery systems have limited drug loading capacity that could affect their therapeutic efficacy. Also, drug loading capacity could affect its release kinetics.[15,16]
3. *Biocompatibility and toxicity concerns*: Biocompatibility and toxicity of smart drug delivery systems need careful consideration. Materials meant to design smart drug delivery systems, like NPs, can be cytotoxic that may lead to inadvertent adverse effects.[15] This needs to be addressed with due diligence and multiple compatibility and toxicity assays in vitro and in vivo before qualifying a potential material for designing a drug delivery system.

12 | FUTURE DIRECTIONS AND CHALLENGES

The field of smart drug delivery systems is rapidly evolving with multifarious future directions and challenges to address. Some of the key areas of research directions in future, and the various imminent and possible challenges to overcome are discussed here.

12.1 | Future directions

1. *Personalized medicine*: Personalized medicine is the future of healthcare and smart drug delivery systems will certainly play a catalytic role in it. Tailoring individualized drugs and their judicious delivery to a patient based on the genetic, biomarker, and lifestyle factors characteristics, such personalized medicine could improve treatment and minimize adverse effects.[31]
2. *Combination therapy*: Yet another emerging field is combination therapy involving the delivery of multiple drugs using smart drug delivery systems. Combination therapy could improve therapeutic efficacy, enhance bioavailability and reduce developing drug resistance, if any, in diseases such as cancer.[11]
3. *Integration with other technologies*: Smart drug delivery systems can be integrated with other technologies like biosensors, imaging modalities and artificial intelligence to create more advanced and precise drug delivery systems as also monitor the same remotely.[32]

12.2 | Challenges

1. *Regulatory approval*: The development and approval of smart drug delivery systems by regulatory agencies can be challenging due to the complex nature of these systems. The safety and efficacy of these systems need to be rigorously tested and validated before approval for human use.[66]
2. *Manufacturing scalability*: Developing manufacturing processes to produce large quantity of high-quality smart drug delivery systems at a reasonable cost is essential. Manufacturing of smart drug delivery systems can be challenging, and its production scalability is a significant challenge.[36,64]
3. *Biocompatibility and toxicity concerns*: Some materials used in smart drug delivery systems can be toxic to cells and tissues, leading to numerous unavoidable adverse effects later. Thus, biocompatibility and toxicity of such delivery systems need to be carefully considered.[64]

13 | CONCLUSION

Smart drug delivery systems hold great promise for targeted and controlled delivery of therapeutic agents for improved efficacy and reduced side-effects of conventional drug delivery approaches. Current approaches to smart drug delivery primarily involve NPs, liposomes, micelles, and hydrogels, having their own advantages and limitations. The success of these systems lies in their design and engineering marvels with optimized pharmacokinetics and pharmacodynamics properties. Smarter drug delivery systems can be designed to target specific cells, tissues, and organs by combining various advanced new-age materials and state-of-the-art technologies. Stimuli-responsive materials and biomimetic designs can enable controlled drug release and enhance therapeutic effects. Despite the obstacles that have prevented these delivery systems from being popular in medical set-ups as yet, these futuristic nano-devices still are very promising. Still, such systems will need to work in tandem with theoretical elaborations, laboratory studies, extensive research, and pharmaceutical and medical validation to achieve their full potential. Employing such treatments could significantly address bio-acceptability issues that drug delivery systems confront and will result in single, very effective dosage that will defy large drug build-up. Although still many challenges there are to overcome, rapid research and development advances in smart drug delivery could provide wider and promising avenues to guarantee improved patient outcomes and achieve high-end effective medical interventions such as personalized medicine.

AUTHOR CONTRIBUTIONS

Shri Harsha Boppana: Conceptualization; writing—original draft. **L. V. Simhachalam Kutikuppala**: Conceptualization; writing—original draft. **Sushil Sharma**: Writing—original draft. **Madhavrao C**: Writing—original draft. **Guarav Rangari**: Writing—original draft. **Arup Kumar Misra**: Writing—original draft. **Venkataramana Kandi**: Validation; writing—original draft. **Snehasish Mishra**: Writing—review and editing. **Puneet Kumar Singh**: Writing—original draft. **Ali A. Rabaan**: Writing—original draft. **Ranjan K. Mohapatra**: Supervision; writing—review and editing. **Md Kudrat-E-Zahan**: Project administration; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

TRANSPARENCY STATEMENT

The lead authors, Ranjan K. Mohapatra and Md. Kudrat-E-Zahan, affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA AVAILABILITY STATEMENT

Data Availability Statement is not available.

ETHICS STATEMENT

The authors declare no involvement of animal studies or human participants in the study.

ORCID

Venkataramana Kandi http://orcid.org/0000-0002-7197-0448
Snehasish Mishra http://orcid.org/0000-0002-3896-5831
Ranjan K. Mohapatra http://orcid.org/0000-0001-7623-3343

REFERENCES

1. Gupta AK, Naregalkar RR, Vaidya VD, Gupta M. Recent advances on surface engineering of magnetic iron oxide nanoparticles and their biomedical applications. *Nanomedicine*. 2007;2(1):23-39.
2. Barik SR, Mohapatra RK, Mohapatra PK, Mahal A, El-Ajaily MM. Recent developments in biopolymeric nanoparticles for drug delivery systems: an overview. *Micro Nanosyst*. 2022;14(2):92-100.
3. Desai DN, Mahal A, Varshney R, et al. Nanoadjuvants: promising bioinspired and biomimetic approaches in vaccine innovation. *ACS Omega*. 2023;8:27953-27968.
4. Dash R, Sahoo RN, Pattnaik G, et al. An open call for nano-based therapy to address COVID-19 and oncological clinical conditions. *Int J Surg*. 2023;110(4):2430-2432. doi:10.1097/JS9.0000000000000071
5. Torchilin VP. Recent advances with liposomes as pharmaceutical carriers. *Nat Rev Drug Discov*. 2005;4(2):145-160.
6. Zhang L, Gu F, Chan J, Wang A, Langer R, Farokhzad O. Nanoparticles in medicine: therapeutic applications and developments. *Clin Pharm Ther*. 2008;83(5):761-769.
7. Davis ME, Chen Z, Shin DM. Nanoparticle therapeutics: an emerging treatment modality for cancer. *Nat Rev Drug Discov*. 2008;7(9):771-782.
8. Jain KK. Advances in the field of nanobiotechnology: towards development of novel therapeutics. *Nanomedicine*. 2005;1(1):1-3.
9. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. *Nature Nanotechnol*. 2007;2(12):751-760.
10. Byrne JD, Betancourt T, Brannon-Peppas L. Active targeting schemes for nanoparticle systems in cancer therapeutics. *Adv Drug Deliv Rev*. 2008;60(15):1615-1626.
11. Pridgen EM, Langer R, Farokhzad OC. Biodegradable, polymeric nanoparticle delivery systems for cancer therapy. *Nanomedicine*. 2007;2(5):669-680.
12. Yoo JW, Chambers E, Mitragotri S. Factors that control the circulation time of nanoparticles in blood: challenges, solutions and future prospects. *Curr Pharm Des*. 2010;16(21):2298-2307.
13. Chauhan VP, Jain RK. Strategies for advancing cancer nanomedicine. *Nat Mater*. 2013;12(11):958-962.
14. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. *Nat Rev Cancer*. 2017;17(1):20-37.
15. Farokhzad OC, Langer R. Impact of nanotechnology on drug delivery. *ACS Nano*. 2009;3(1):16-20.
16. Torchilin VP. Multifunctional nanocarriers. *Adv Drug Deliv Rev*. 2012;64(4):302-315.
17. Vasir JK, Labhasetwar V. Targeted drug delivery in cancer therapy. *Technol Cancer Res Treat*. 2005;4(4):363-374.
18. Hrkach J, Von Hoff D, Ali MM, et al. Preclinical development and clinical translation of a PSMA-targeted docetaxel nanoparticle with a differentiated pharmacological profile. *Sci Transl Med*. 2012;4(128):128ra39.
19. Ganta S, Devalapally H, Shahiwala A, Amiji M. A review of stimuli-responsive nanocarriers for drug and gene delivery. *J Controlled Release*. 2008;126(3):187-204.
20. Du JZ, Du XJ, Mao CQ, Wang J. Tailor-made dual pH-sensitive polymer–doxorubicin nanoparticles for efficient anticancer drug delivery. *J Am Chem Soc*. 2011;133(44):17560-17563.
21. Mei L, Zhang Y, Zheng Y, et al. A multifunctional nanoplatform for imaging, radiotherapy, and the prediction of therapeutic response. *Small*. 2014;10(21):4343-4354.
22. Aryal S, Hu CMJ, Zhang L. Polymer–cisplatin conjugate nanoparticles for acid-responsive drug delivery. *ACS Nano*. 2010;4(1):251-258.
23. Aryal S, Hu CMJ, Zhang L. Combinatorial drug conjugation enables nanoparticle dual-drug delivery. *Small*. 2010;6(13):1442-1448.
24. Choi JH, Kim SW, Yun CO. Enhancement of tumor-specific uptake of magnetic nanoparticles by combination with targeting ligands. *J Control Release*. 2009;136(2):240-245.
25. Kim JH, Kim YS, Park K, et al. Antitumor efficacy of cisplatin-loaded glycol chitosan nanoparticles in tumor-bearing mice. *J Controlled Release*. 2008;127(1):41-49.
26. Soppimath KS, Aminabhavi TM, Kulkarni AR, Rudzinski WE. Biodegradable polymeric nanoparticles as drug delivery devices. *J Controlled Release*. 2001;70(1):1-20.
27. Jain AK, Swarnakar NK, Das M, Godugu C, Singh RP, Jain S. The effect of stimuli-sensitive hydrogels on the permeation of drugs. *Expert Opin Drug Deliv*. 2013;10(3):369-387.
28. Soppimath KS, Aminabhavi TM, Dave AM, Kumbar SG, Rudzinski WE. Stimulus-responsive "smart" hydrogels as novel drug delivery systems. *Drug Dev Ind Pharm*. 2002;28(8):957-974.
29. Khan I, Gothwal A, Sharma G, et al. Stimuli-responsive hydrogels in drug delivery and tissue engineering. *Drug Deliv*. 2018;25(1):766-784.
30. Shen J, Li Y, Zhuang X, et al. Biodegradable cationic PEG-PDMAEMA block copolymers for gene delivery. *Polym Chem*. 2013;4(1):169-178.
31. Li J, Li Y, Wang Y, et al. Development of hydrophobically modified chitosan nanoparticles with improved drug delivery efficiency. *Colloids Surf B Biointerfaces*. 2012;93:254-260.

32. Zhang Y, Li M, Li J, et al. Preparation and in vitro evaluation of the HUP nanoparticles for breast cancer therapy. *Int J Pharm*. 2010;385(1-2):62-68.
33. Faraji AH, Wipf P. Nanoparticles in cellular drug delivery. *Bioorg Med Chem*. 2009;17(8):2950-2962.
34. Li J, Li Y, Wang Y, et al. Investigation of the role of PEG chain in the preparation and characterization of hydrophobically modified chitosan nanoparticles. *Int J Pharm*. 2011;403(1-2):245-251.
35. Yoo JW, Irvine DJ, Discher DE, Mitragotri S. Bio-inspired, bioengineered and biomimetic drug delivery carriers. *Nat Rev Drug Discov*. 2011;10(7):521-535.
36. Patra JK, Das G, Fraceto LF, et al. Nano based drug delivery systems: recent developments and future prospects. *J Nanobiotechnol*. 2018;16(1):71.
37. Lee SM, O'Halloran TV, Nguyen ST. Polymer-caged nanobins for synergistic cisplatin-doxorubicin combination chemotherapy. *J Am Chem Soc*. 2010;132(51):17130-17138.
38. Wang H, Agarwal P, Zhao S, et al. Hyaluronic acid-decorated dual responsive nanoparticles of Pluronic F127, PLGA, and chitosan for targeted co-delivery of doxorubicin and irinotecan to eliminate cancer stem-like cells. *Biomaterials*. 2015;72:74-89.
39. Doppalapudi S, Jain A, Domb AJ, Khan W. Biodegradable polymers—assessment of recent advancements and drawbacks. *J Control Release*. 2016;240:5-22.
40. Li J, Li Y, Wang Y, et al. Preparation and characterization of hydrophobically modified chitosan nanoparticles as protein carriers. *Int J Pharm*. 2010;395(1-2):159-166.
41. Hu Q, Chen Q, Gu Z. Advances in transformable drug delivery systems. *Biomaterials*. 2018;178:546-558.
42. Xiong F, Mi Y, Yang X, et al. Hyaluronic acid-modified cationic nanoparticles for colon cancer-targeted delivery of 5-fluorouracil. *Int J Biol Macromol*. 2019;137:505-513.
43. Zhang L, Cao Z, Bai T, et al. Dopamine-melanin colloidal nanospheres: an efficient near-infrared photothermal therapeutic agent for in vivo cancer therapy. *Adv Mater*. 2014;26(26):4432-4438.
44. Karimi M, Bahrami S, Ravari SB, et al. Albumin nanostructures as advanced drug delivery systems. *Expert Opin Drug Deliv*. 2016;13(11):1609-1623.
45. Feng B, Zhou F, Hou B, et al. Smart nanovehicles based on hyaluronic acid for cancer therapy. *J Drug Target*. 2019;27(6):631-640.
46. Hao N, Li L, Tang F. Biodegradable nanoparticles for drug delivery in cancer treatment. *Curr Med Chem*. 2018;25(5):601-615.
47. Yu H, Chen Y, Xie X, et al. Rational design of cancer nanomedicine: nanoproperty integration and synchronization. *Adv Mater*. 2019;31(1):e1803544.
48. Aich K, Singh T, Dang S. Advances in microneedle-based transdermal delivery for drugs and peptides. *Drug Deliv Transl Res*. 2022;12(7):1556-1568.
49. Waghule T, Singhvi G, Dubey SK, et al. Microneedles: A smart approach and increasing potential for transdermal drug delivery system. *Biomed Pharmacother*. 2019;109:1249-1258.
50. Zaid Alkilani A, Abo-Zour H, Basheer HA, Abu-Zour H, Donnelly RF. Development and evaluation of an innovative approach using niosomes based polymeric microneedles to deliver dual antioxidant drugs. *Polymers*. 2023;15(8):1962.
51. Nguyen HX, Nguyen CN. Microneedle-mediated transdermal delivery of biopharmaceuticals. *Pharmaceutics*. 2023;15(1):277. doi:10.3390/pharmaceutics15010277
52. Ganeson K, Alias AH, Murugaiyah V, Amirul AAA, Ramakrishna S, Vigneswari S. Microneedles for efficient and precise drug delivery in cancer therapy. *Pharmaceutics*. 2023;15(3):744. doi:10.3390/pharmaceutics15030744
53. Pawar K. Recent updates in vaccine delivery through microneedles. *Adv Pharm Bull*. 2023;13(1):1-4. doi:10.34172/apb.2023.001
54. Tan G, Jiang F, Jia T, et al. Glucose-responsive silk fibroin microneedles for transdermal delivery of insulin. *Biomimetics*. 2023;8(1):50.
55. Dawud H, Abu Ammar AA. Rapidly dissolving microneedles for the delivery of steroid-loaded nanoparticles intended for the treatment of inflammatory skin diseases. *Pharmaceutics*. 2023;15(2):526.
56. Xiang Y, Lu J, Mao C, et al. Ultrasound-triggered interfacial engineering-based microneedle for bacterial infection acne treatment. *Sci Adv*. 2023;9(10):eadf0854.
57. Baloira A, Abad A, Fuster A, et al. Lung deposition and inspiratory flow rate in patients with chronic obstructive pulmonary disease using different inhalation devices: a systematic literature review and expert opinion. *Int J Chronic Obstruct Pulm Dis*. 2021;16:1021-1033. doi:10.2147/COPD.S297980; Erratum in: *Int J Chron Obstruct Pulmon Dis* 2021;16:2243.
58. González-Torralba F, Baloira A, Abad A, et al. FIDEPOC: consensus on inspiratory flow and lung deposition as key decision factors in COPD inhaled therapy. *Int J Chronic Obstruct Pulm Dis*. 2022;17:1005-1015.
59. Hagmeyer L, van Koningsbruggen-Rietschel S, Matthes S, Rietschel E, Randerath W. From the infant to the geriatric patient—strategies for inhalation therapy in asthma and chronic obstructive pulmonary disease. *Clin Respir J*. 2023;17(6):487-498.
60. Zhao L, Zhang C, Abu-Ershaid JM, et al. Smart responsive microarray patches for transdermal drug delivery and biological monitoring. *Adv Healthcare Mater*. 2021;10(20):e2100996.
61. Sorino C, Negri S, Spanevello A, Visca D, Scichilone N. Inhalation therapy devices for the treatment of obstructive lung diseases: the history of inhalers towards the ideal inhaler. *Eur J Intern Med*. 2020;75:15-18.
62. Wong WF, Ang KP, Sethi G, Looi CY. Recent advancement of medical patch for transdermal drug delivery. *Medicina*. 2023;59(4):778.
63. Thananukul K, Kaewsaneha C, Opaprakasit P, Lebaz N, Errachid A, Elaissari A. Smart gating porous particles as new carriers for drug delivery. *Adv Drug Deliv Rev*. 2021;174:425-446.
64. Bose RJ, Paulmurugan R. Nanoparticle drug delivery system for cancer therapy: advances and prospects. *Expert Opin Drug Deliv*. 2016;13(8):1117-1130.
65. Sheng J, Xu Z, Zheng W, et al. A review of nanocarrier-based therapy for pancreatic cancer: targeting, current status and future prospects. *Nanomedicine (Lond)*. 2019;14(9):1133-1152.
66. Li W, Li Q, Li J, et al. Recent advances in the applications of PLGA based nanomaterials for cancer photothermal therapy. *Biomater Sci*. 2019;7(11):4610-4627.
67. Aryal S, Hu CMJ, Zhang L. Polymer-cisplatin conjugate nanoparticles for acid-responsive drug delivery. *ACS Nano*. 2010;4(1):251-258.
68. Kharaziha M, Shin SR, Nikkhah M, et al. Tough and flexible CNT-polymeric hybrid scaffolds for engineering cardiac constructs. *Biomaterials*. 2014;35(28):7346-7354.

How to cite this article: Boppana SH, Kutikuppala LVS, Sharma S, et al. Current approaches in smart nano-inspired drug delivery: a narrative review. *Health Sci Rep*. 2024;7:e2065. doi:10.1002/hsr2.2065