REVIEW ARTICLE

Multifunctional Smart Nanoparticles A Game-Changer in Combinatorial Cancer Therapy a comprehensive review

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ABSTRACT

Multifunctional smart nanocarriers, as part of advanced drug delivery systems, have recently attracted much attention as a possible approach for utilizing combinations of cancer treatments. These new nanoparticles are designed to hit several regions of the tumor simultaneously; they are also able to attack the cancer-affected region more strongly. This involves coating the surface of the developed nanoparticles with various functional groups where specific chemical interactions, such as covalent bonds and van der Waals forces, are used to bond tailored site-specific drug molecules and be able to remain steady in the human body for specific durations. Another predictor of the formation of these nanoparticles is the incorporation of stimuli-sensitive polymers; this implies that the nanoparticles can be sensitive to factors such as pH or temperature. This allows rapid physio-chemical changes to be observed in the tumor microenvironment to facilitate the rapid diffusion of drugs and drug delivery. In this work, it became possible to define smart multifunctional nanoparticles as common nanoparticles whose properties can be predetermined to meet the requirements of some particular applications. The use of multifunctional smart nanoparticles for treating cancer has several advantages, including selectively attacking malignant cells, making the particles harmless to the body and releasing the fibers in the safest way. These nanoparticles may be designed with such a capacity that they will be oriented toward more localization of specific cancer cells, which will greatly reduce the probability of any undesired side reactions, hence increasing the general effectiveness of the treatment. It can also be prescribed in combination with other treatments to integrate it with other common cancer treatments, such as chemotherapy and radiotherapy.

Keywords Multifunctional Smart Nanoparticles, Combinatorial Cancer Therapy, Theranostic Functionality, Targeted Drug Delivery, Cancer Therapy

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INTRODUCTION

The increase in worldwide cancer incidence affects health and well-being considerably. Despite clinical and technological progress, cancer remains the second leading cause of loss of life globally following cardiovascular disease. A comprehensive survey of 37.5 million cancer patients from 2000 to 2014 revealed increased survival costs, even for malignant cancers. Cancer accounts for one in six deaths worldwide, with an estimated 19.3 million new cases in 2020 inflicting approximately 10 million deaths. Notably, over 70% of most cancer-related deaths arise in low- and middle-profit countries and are frequently connected to life elements such as tobacco use, weight problems, terrible food plans, inaction, and excessive alcohol intake.[1] The complexity of cancer origins poses challenges for remedies compounded by the development of multidrug-resistant cells, leading to remedy disasters and recurrences. Chemotherapy, radiotherapy, and surgical operations are common treatments, but they are limited by low tumor selectivity, toxicity, and drug resistance. A favorable prognosis is crucial for preventing remedy failure and recurrence, highlighting the need for customized remedy plans that integrate advanced diagnostic and therapeutic techniques.[2] Monoclonal antibody therapy focused on specific tumor antigens and antibody–drug conjugates offers promising targeted cancer treatments.[3] Researchers are exploring numerous techniques, such as natural chemistry, nanotechnology, and pharmacology, to overcome the restrictions of contemporary treatments. Nanotheranostics, which utilize nanotechnology, preferentially target tumor cells because of their small length and improved drug transport ability.[4] The capacity of nanotechnology to interact with mobile components holds promise for both in vivo and in vitro biomedical programs. Multifunctional smart nanoparticles have emerged as a revolutionary tool within the realm of combinatorial cancer therapy.[5] These nanoparticles, with their specific homes and abilities, are poised to transform the panorama of most cancer treatments. By integrating several features inside a single platform, they provide a flexible and focused approach to fighting most cancers at various tiers.[6] This assessment delves into the tricky mechanisms and promising packages of these nanoparticles for enhancing the efficacy and precision of cancer treatment.[7] Nanomedicine and immunotherapy have emerged as powerful tools in the fight against cancer, offering the

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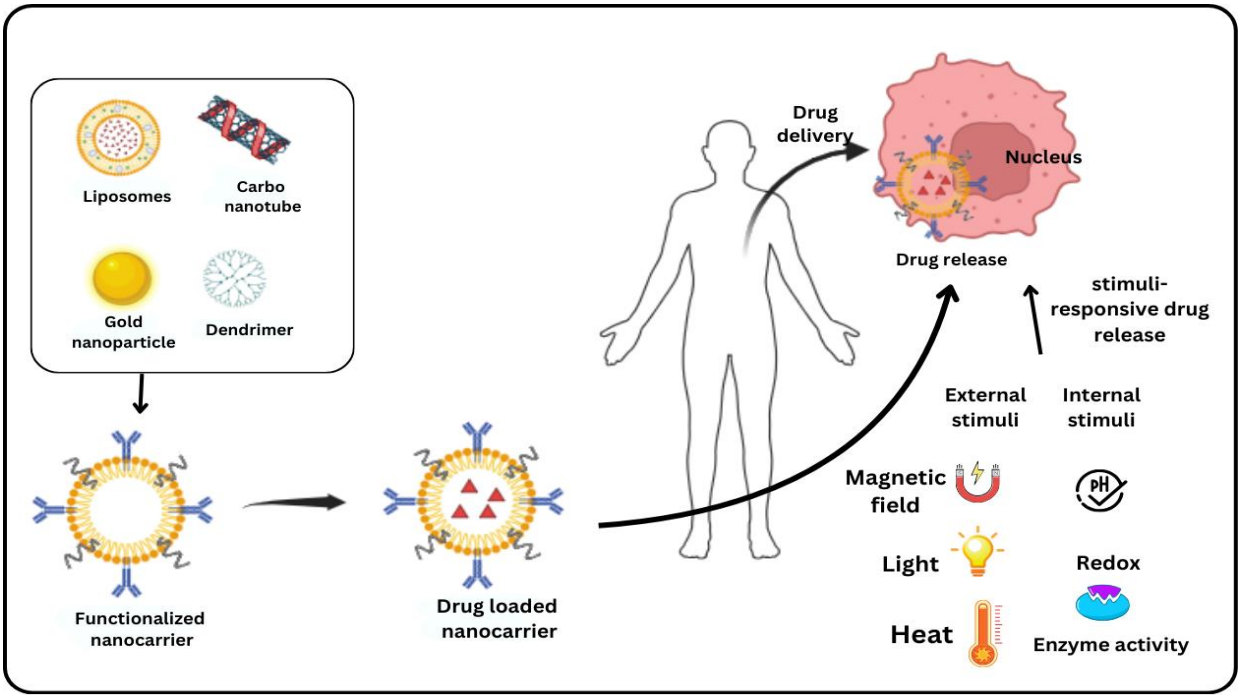

Figure 1: Graphical Abstract

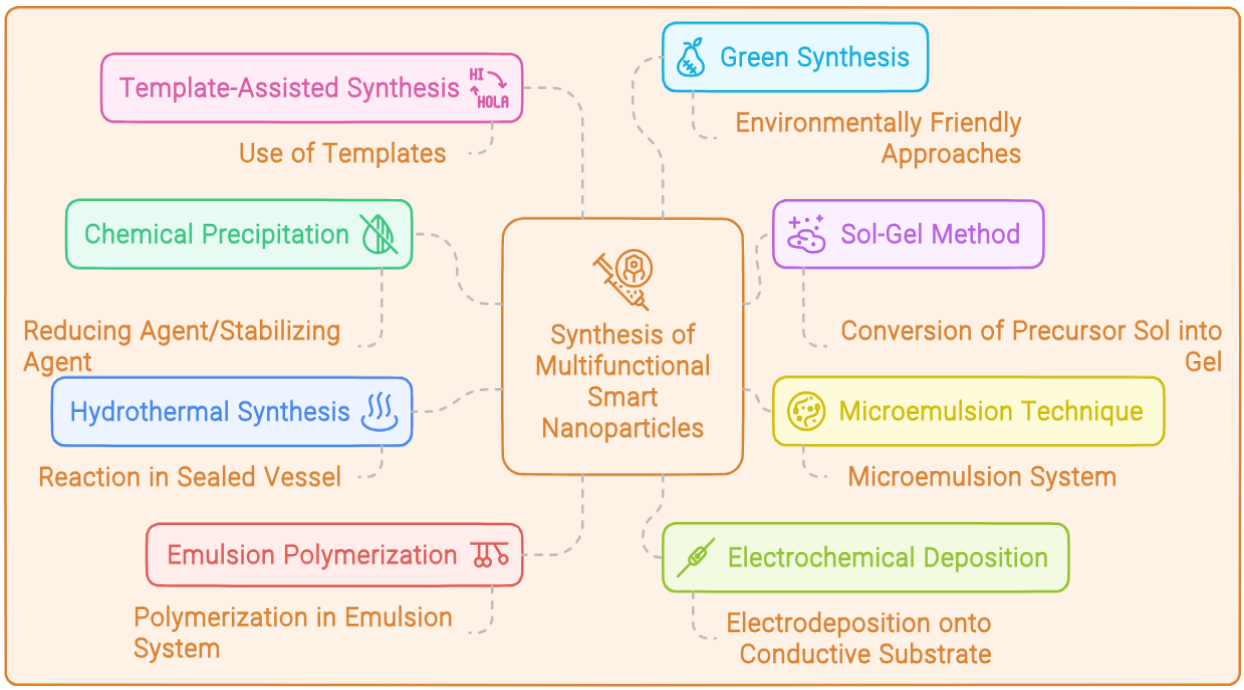

Figure 2**:** Various methods and techniques used for the synthesis of these nanoparticles

capacity to improve treatment efficacy.[8] The complicated interplay between cancer and the immune system is multifaceted and includes a delicate balance between tumor evasion and immune surveillance. Chemotherapy, radiotherapy, and surgical intervention are primary cancer remedies that have been the cornerstone of cancer care for decades. Although effective, they do not provide a whole therapy due to demanding situations, including low tumor selectivity, systemic toxicity, off-target outcomes, multidrug resistance, and considerable detrimental fitness influences.[9] Timely analysis is critical for preventing remedy failure, tumor recurrence, and metastasis.[10] Personalized treatment plans integrating diagnostic and healing techniques are critical for achieving superior clinical outcomes.[11]

By utilizing tumor-unique antigens (TSAs) and tumor-associated antigens (TAAs), monoclonal antibody therapy, particularly via antibody–drug conjugates (ADCs), offers a

central cancer remedy while minimizing damage to healthy cells. This method has transitioned efficaciously from studies to medical practice.[12] Researchers have explored diverse techniques, including natural chemistry, supramolecular chemistry, nanotechnology, oncology, and pharmacology, to improve most cancer treatments. The ability of nanotheranostics, which leverage the specific properties of nanotechnology, to correctly treat tumors and improve healing and diagnostic results is promising.[13] Nanotechnology allows the development of nanotherapeutics, providing excessive drug-loading capacities and particular interactions with cell components. NPs can be tailor-made to hold medicinal drugs efficaciously, displaying remarkable capability for in vivo and in vitro biomedical applications in cancer treatment.[14,15] A progressive shift is underway in cancer treatment, as scientists are turning their attention to combined cures that increase effectiveness while minimizing facet results. At the forefront of this breakthrough is the development of clever nanoparticles, which unite multiple capabilities in a single system, permitting the simultaneous shipping of focused treatments.[16] By harnessing these nanoparticles, researchers can overcome the long-standing hurdles of drug shipping, bioavailability, and tumor growth, particularly focused on the biological obstacles and drug resistance in which they are most effective. The number one goal of any tumor treatment is to attain perfect therapeutic drug awareness at tumor regions and remove most cancer cells without affecting ordinary cells. This life the idea is miles overbearing to generate unmarried mediators with an outstanding perspective to make the principal impact on most cancers' preclusion, detection, and remedies. The present-day knowledge of targeted delivery is focused on cancerous cells by affecting similar qualities of cancerous cells to permit their analysis and focus on potential.[17]

The following outlines the extent and recognition of this overview

The scope includes a comprehensive exploration of the transformative function of smart nanoparticles in revolutionizing most cancer treatments through a mixture of treatment options. The assessment will start with the aid of introducing the present-day demanding situations in cancer therapy, emphasizing the necessity for extrapowerful and less invasive treatments to mitigate the critical facet effects associated with conventional cures.[18] This research will then delve into the pivotal role of nanomedicine in growing biocompatible materials for diagnostic and healing functions, highlighting how nanoparticles decorate drug transport by improving bioavailability and awareness around tumor tissues. Furthermore, the bioengineering of extracellular vesicles and targeted remedy strategies for cancer treatment, in conjunction with improvements in immunotherapy and gene remedies for fighting cancer, are discussed. By studying the limitations and challenges of numerous modern cancer therapeutic approaches, including nanoparticles, extracellular vesicles, herbal antioxidants, targeted treatments, and gene therapy, this review aims to provide insights into the limitations and capacity areas for improvement in these strategies. Finally, the overview will finish with the aid of discussing the recent progress in most cancer remedy research, emphasizing the importance of continued exploration of multifunctional smart nanoparticles and proposing destiny research instructions and possibilities for in addition research on this dynamic discipline.[19]

Design and synthesis of multifunctional smart nanoparticles

Methods and techniques used for the synthesis of these nanoparticles

The design standards for multifunctional smart nanoparticles are rooted in the integration of various functionalities within a single nanoparticle system.[20] These concepts involve the strategic mixture of various substances, structures, and floor adjustments to obtain unique homes and behaviors. For instance, the incorporation of magnetic and fluorescent materials allows both imaging and targeting capabilities. Additionally, the use of stimuli-responsive polymers allows nanoparticles to trade their houses in response to environmental cues, including temperature or pH, which may be beneficial for controlled drug release. The surface amendment of nanoparticles focused on ligands, which include antibodies or peptides, enables unique popularity and binding to diseased cells or tissues, enhancing their therapeutic efficacy. Furthermore, the layout of nanoparticles with more than one functionality can also include the incorporation of healing sellers, together with capsules or genes, which may be released in a managed way to achieve the most favorable therapeutic outcomes. The optimization of nanoparticle size, form, and floor fee is likewise critical, as these parameters can affect nanoparticle biodistribution, cellular uptake, and interactions with biological structures. The use of computational methods and simulations can aid in the design and optimization of multifunctional nanoparticles with the aid of predicting their conduct and interactions under diverse conditions. Overall, the layout principles at the back of multifunctional smart nanoparticles involve a multidisciplinary technique that mixes the technological expertise, biology, and engineering of substances to create revolutionary healing and diagnostic tools.

The design standards at the back of multifunctional smart nanoparticles involve state-of-the-art structures with proper backbones, optimized modification sites, simple coaching strategies, and green feature integration.[21] These nanoparticles have advanced to meet numerous tumor websites concurrently, enhancing their aggressiveness and potency in cancer treatment.[22] Strategies for designing these nanoparticles encompass covalent or noncovalent changes in their surfaces, allowing web page-centered transport of medication and vitamins to unique cells.[23] Multifunctional clever nanoparticles are designed with specific ideas to improve their performance in diverse applications. One key layout principle is the incorporation of stimuli-sensitive/smart polymers that allow rapid physiochemical transitions inside the tumor microenvironment, as highlighted by Aram *et al*..[24] These smart polymers respond to external stimuli, consisting of modifications in pH or temperature, bearing in mind targeted drug transport and controlled release in the body. Furthermore, the layout of

multifunctional smart nanoparticles frequently entails the use of advanced materials and device configurations, as discussed by Li *et al*..[25] Using materials such as LiTi2(PO4)3 nanoparticles, researchers intend to improve the functionality and efficiency of aqueous rechargeable batteries. This technique demonstrates the significance of selecting suitable materials that can help multiple capabilities within an unmarried nanoparticle machine. In addition to cloth choice, the sensible layout of multifunctional nanoparticles also considers the integration of various functionalities, such as more suitable photodynamic therapy and bioimaging capabilities.[26]

The synthesis of multifunctional smart nanoparticles includes the introduction of nanoparticles with unique properties that can be tailored to unique programs.[27]

Template-assisted synthesis

Template-assisted synthesis is a flexible technique that utilizes templates, porous substances, or biological molecules to direct the boom of nanoparticles into unique shapes and systems.[28] By using these templates, researchers can exert precise control over the morphology of the nanoparticles being synthesized. This method offers a unique gain in tailoring the scale, shape, and floor residences of the resulting nanostructures, allowing the manufacturing of substances with enhanced functionalities and performance characteristics.[29] The use of templates in synthesis approaches plays a crucial role in dictating the final morphology and structure of nanoparticles. For example, in the fabrication of nickel nanoparticles, template-assisted synthesis has been used to obtain self-included nickel nanoparticles inside a porous community, demonstrating the importance of templates for controlling morphological and structural elements.[18] Similarly, in the synthesis of zinc oxide hollow microspheres, a sucrose-derived carbon template was used to research the impact of hole morphology on the photocatalytic pastime of the resulting microspheres.[30] This approach permits the correct tuning of the composition, size, and morphology of the synthesized materials, providing new opportunities for packaging in diverse fields. In the realm of supercapacitors, template-assisted synthesis has made considerable progress in the design and fabrication of porous carbons with excellent performance. Through the use of templates, inclusive of hard templates, researchers have been able to create porous carbon substances with tailored pore structures and greater electrochemical homes for power garage programs.[31] This level of manipulation over the synthesis procedure is vital for optimizing the overall performance of supercapacitors and advancing electricity garage technology. Moreover, template-assisted synthesis has been used to improve hierarchical porous carbon materials with amazing super capacitance residences. By utilizing salt templates, researchers have effectively improved the electricity garage ability of carbon-primarily based materials, demonstrating the effectiveness of template-guided techniques in improving overall fabric performance for strength garage applications.[32]

Chemical precipitation

Chemical precipitation is a widely used method in the synthesis of nanoparticles and involves the formation of nanoparticles from a chemical solution through the addition of a precipitating agent. This technique offers an honest and value-powerful method to provide a large array of nanoparticles with exactly controlled houses.[33] By adjusting the precursor concentration and pH, researchers can tailor the dimensions, shape, and composition of nanoparticles synthesized through chemical precipitation.[34] This level of control is crucial in various applications where specific nanoparticle characteristics are required for optimal performance. One of the key advantages of the chemical precipitation method is its versatility in producing nanoparticles of different materials. For instance, studies have demonstrated the successful synthesis of various nanoparticles, such as CeO2, ZnO, Fe3O4, and ZnS, using this technique.[35–37] This versatility highlights the broad applicability of chemical precipitation inside the subject of nanotechnology, permitting the fabrication of nanoparticles with numerous functionalities and properties. Moreover, the simplicity of the chemical precipitation system makes it a desirable choice for many researchers in nanoparticle synthesis. The technique's sincere nature, coupled with its fee-effectiveness, contributes to its massive adoption in both educational and commercial settings [38]. It is straightforward to scale up or increase the amount of chemical precipitation used; hence, this method is likely to be applied for large-scale production of nanoparticles. SK also has the advantages of being simple and adaptable to the needs of the synthesis process; chemical precipitation can effectively improve the physical and chemical characteristics of the resultant nanoparticles. In addition, if the synthesis conditions are suitably altered by the researcher, sodium nanoparticles that have met the desired size distribution special features and magnetic properties in addition to the ‘pleasant-tuning’ of reaction temperature and surface change.[36] This degree of control is essential because it allows for the deposition of films with specific properties tailored for use in specific sectors, including the biomedical, catalytic, and environmental sectors. After all, sectors require unique properties. Furthermore, the ability to manipulate drug nanoparticle formation through rapid precipitation is a sizeable benefit of the chemical precipitation approach in the pharmaceutical industry. Rapid precipitation techniques offer a way to modulate the size and stability of drug nanoparticles, influencing their efficacy and bioavailability in drug shipping structures. This finding underscores the importance of chemical precipitation not only in cloth science but also in the development of superior drug delivery technologies. Chemical precipitation is a powerful and versatile technique for the synthesis of nanoparticles with tailored properties. Its simplicity, fee-effectiveness, versatility, and capability to govern nanoparticle characteristics make it a useful tool for diverse scientific and commercial packages. Researchers continue to discover and optimize chemical precipitation approaches to develop a sphere of nanotechnology and harness particular nanoparticle solutions for a wide variety of progressive programs.[39]

Hydrothermal synthesis

Hydrothermal synthesis is a well-mounted method for the fabrication of metal oxide nanoparticles that involves the

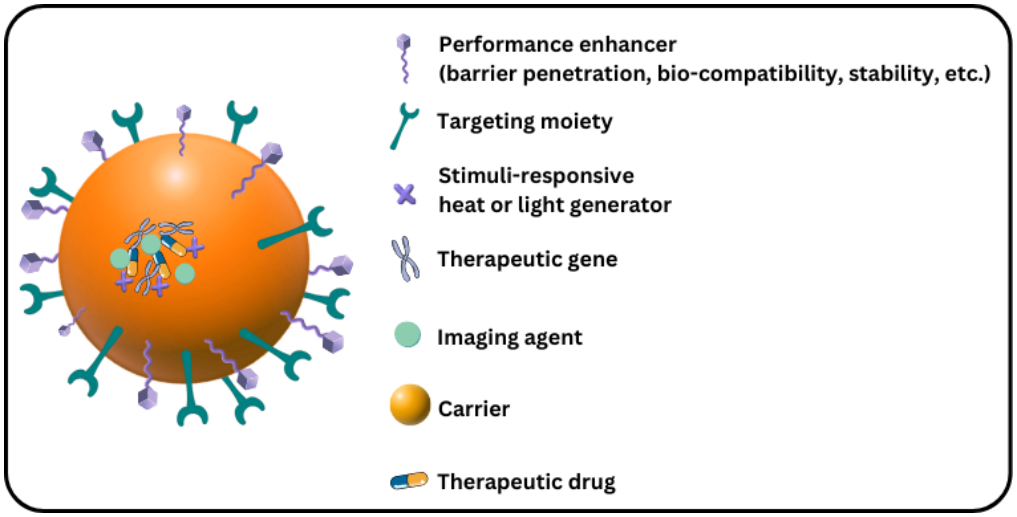

Figure 3: Design and development of multifunctional nanoparticles A, a prototypical multifunctional nanoparticle. Reproduced with permission.[67]

reaction of precursor substances in a vessel sealed beneath extended temperatures and pressures. This approach allows for the formation of nanoparticles, taking into account the appropriate manipulation of the size, morphology, and crystallinity of the synthesized substances.[40] The hydrothermal technique enables the synthesis of a large range of metal oxide nanoparticles, which are currently not limited to titanium dioxide (TiO2), zinc oxide (ZnO), or iron oxide (Fe2O3) and have tailor-made properties suitable for numerous applications in catalysis, sensing, and energy storage. One of the key benefits of hydrothermal synthesis is its ability to produce nanoparticles with excessive purity and uniformity. The effects of temperature, strain, and response time of the managed response situations are favorable for the SCR to formulate pure cylindrical meta-stable phase nanoparticles containing a minimum level of impurities.[41] This high purity is necessary, for instance, in those applications where even minimal concentrations of impurities can actively influence the characteristics of the nanoparticles. Furthermore, the hydrothermal method allows for the preparation of nanoparticles that can easily be organized into distinct crystal structures and with a determined size. Therefore, the possibility of managing the ease or increase of nucleation and, therefore, nucleation and increase procedures by the responders can be discussed regarding the formation of nanoparticles with certain phases and sizes.[42] Hydrothermal synthesis is a crucial process in manufacturing steel oxide nanoparticles with controlled crystal structures, and their length is useful for defining their properties suitable for photocatalysis and magnetic storage applications. In addition to the structural control of the homes from the nanoparticles, hydrothermal synthesis also offers a flexible system that can be tuned to incorporate dopants and surface modifications. This method can be used in the course of synthesis to endow nanoparticles with extraneous benefits that enhance their parametric value for catalytic or optical applications. As additional coatings for coatings or functional companies, the surface of nanoparticles can be further changed by hydrothermal treatments to balance and ensure good reactivity under these conditions. Additionally, due to the scale-up factor of hydrothermal synthesis, it stands out as the most suitable for large-scale production of steel oxide nanoparticles.[43] The synthesis of nanoparticles can be mastered at the macro level, and the regulation of homes is perfect for industrial applications where the characteristics of the nanoparticles produced are highly repetitive. This is because synthesis through hydrothermal processes is scalable for most major industrial uses, making it common for most industries, such as the electronics and healthcare industries. Hydrothermal synthesis is a versatile and effective approach for the controlled synthesis of metal oxide nanoparticles with tailored materials. Its ability to provide excessively pure nanoparticles with defined systems, sizes, and functionalities makes it a useful device for nanomaterial research and improvement. Continued advancements in hydrothermal synthesis techniques and information on reaction mechanisms will further increase the skills of this approach for the fabrication of superior metallic oxide nanoparticles with more desirable performance and applicability in diverse fields.[43]

Green synthesis

Green synthesis strategies have attracted considerable interest in the field of nanoparticle synthesis due to their environmentally friendly nature and sustainable practices. These techniques utilize natural sources such as plant extracts, microbial systems, and other biobased materials to provide nanoparticles without the need for unsafe chemical compounds or high-power input. Green synthesis offers a promising alternative to traditional chemical techniques by reducing the environmental impact of nanoparticle production and selling renewable resources for nanomaterial synthesis. One of the important advantages of inexperienced synthesis is its eco-friendly approach, which minimizes the amount of toxic byproducts and waste compared to traditional chemical methods.[44] By harnessing the reducing and stabilizing homes of plant extracts or microbial structures, green synthesis allows the formation of nanoparticles under slight response conditions, reducing the general environmental footprint of the synthesis procedure. This sustainable technique aligns with the ideas of inexperienced chemistry, emphasizing the importance of

designing chemical procedures that might be safe, green, and environmentally benign. Moreover, inexperienced synthesis methods provide versatility in nanoparticle fabrication, allowing the production of a large variety of nanoparticles with managed residences. The use of natural assets as lowering and capping retailers provides a platform for tailoring the size, shape, and floor characteristics of nanoparticles through simple and price-powerful methods.[45] The inherent range of bio based materials allows the synthesis of nanoparticles with particular functionalities and applications, expanding the scope of nanomaterial studies and improvement. In addition to their environmental friendliness, green synthesis strategies exhibit biocompatibility and biodegradability, making the resulting nanoparticles appropriate for biomedical and pharmaceutical applications. The use of herbal extracts and biomolecules in nanoparticle synthesis reduces the chance of cytotoxicity and promotes compatibility with biological systems, establishing opportunities for the development of nanomedicine, drug shipping systems, and diagnostic equipment. The biocompatibility of inexperienced-synthesized nanoparticles is especially fine for biomedical programs in which protection and compatibility with dwelling organisms are paramount. Furthermore, inexperienced synthesis contributes to the sustainable utilization of natural resources and promotes the integration of inexperienced technologies in nanomaterial manufacturing.[46] By harnessing the inherent homes of plant extracts, microorganisms, and different bioprimarily based substances, researchers can explore progressive strategies for nanoparticle synthesis that align with standards of sustainability and environmental stewardship. The development of green synthesis methods is no longer the most effective and reduces the reliance on conventional chemical methods; however, it also fosters a holistic approach to nanotechnology that prioritizes the proper well-being of the surroundings and society. Inexperienced synthesis techniques represent a promising method for the sustainable and environmentally friendly manufacturing of nanoparticles. By leveraging the specific properties of herbal sources and biobased total substances, inexperienced synthesis provides a greener opportunity for standard chemical strategies, with advantages ranging from reduced environmental effects to improved biocompatibility. The persistent exploration and development of green synthesis strategies hold notable potential for shaping the future of nanomaterial synthesis and promoting the adoption of sustainable practices in nanotechnology.[46]

Sol-gel method

The sol-gel approach is a flexible and widely used method for the synthesis of nanoparticles, specifically within the discipline of nanomaterials and thin films. This technique includes the transformation of an answer (sol) into a gel-like fabric through a sol-gel transition technique, followed by further processing to obtain nanoparticles with managed properties and characteristics. The sol-gel system offers numerous benefits, such as the ability to produce nanoparticles with specific management of length, form, composition, and shape, making it a useful device for nanoscience and nanotechnology research.[47] The sol-gel method typically starts with the use of a precursor solution containing metal alkoxides or other chemical precursors that may undergo hydrolysis and condensation reactions. These precursors are dissolved in a solvent to form a homogeneous solution called a sol. The sol is then subjected to a gelation system, in which the precursor molecules undergo polymerization and form a three-dimensional network, leading to the formation of a gel. The gel structure traps the nanoparticles inside its matrix, presenting a template for the subsequent processing steps. After the gelation step, the gel is processed to reap nanoparticles by using diverse strategies, including drying, calcination, or different thermal remedies. These publish-gel processing steps are crucial for transforming the gel into a strong cloth and removing the solvent to yield the favored nanoparticles [48]. The controlled drying and heat treatment conditions at some point of this degree have an impact on the final residence of the nanoparticles, together with their size, crystallinity, and surface characteristics. One of the important advantages of the sol-gel method is its capacity to provide nanoparticles with tailored homes through precise control of the synthesis parameters.[49] By adjusting elements, including the precursor, solvent composition, pH, temperature, and processing conditions, researchers can modulate the dimensions, morphology, and composition of nanoparticles, which is important for the development of materials with precise functionalities and applications. This tunability makes the sol-gel technique exceedingly versatile and adaptable to an extensive range of nanoparticle structures. Moreover, the sol-gel technique has the advantages of reproducing the sol-gel solution and its ability to produce a large quantity of nanoparticles, which makes it especially suitable for business programs. This is because the sol-gel technique is fairly simple but highly priced because of its ability to provide superior nanoparticles with stringently controlled properties, making sol-gel one of the most commonly used methods in electronics, catalysis, sensors, and biomedical fields, among others. The exceptional feature of the sol-gel technique makes it an affluent asset for the enhancement of superior nanomaterials possessing certain sturdy homes to fulfill specific technological necessities. In summary, the sol-gel method can be considered the most beneficial and efficient method for synthesizing nanoparticles with predetermined characteristics and desired functionality.[48] By manipulating the sol-gel transition, to form a gel matrix around nanoparticles, a systematically favorable synthesis environment can be achieved to produce materials with the required properties. The flexibility, size, and replicability of quartz glass are strengths of the sol-gel technique because it broadens the horizons of nanoscience and nanotechnology packages across multiple disciplines and industries.[47]

Microemulsion

Microemulsion techniques are versatile and effective approaches for the synthesis of nanoparticles, with particular management of their length, shape, and residence. In microemulsion structures, surfactants and cosurfactants are used to stabilize nanoscale droplets of 1 liquid segment inside another nonstop section, generating a

thermodynamically solid system. These nanoscale droplets act as nanoreactors wherein the synthesis of nanoparticles occurs in regions under controlled conditions, leading to the formation of nanoparticles with tailored traits. The formation of microemulsions entails the spontaneous introduction of surfactant molecules at the interface between the two immiscible stages (e.g., oil and water) to lessen interfacial anxiety and form a stable shape. The addition of a cosurfactant, in addition, increases the stability of the machine by promoting the formation of small and uniform droplets. The surfactant-cosurfactant combination creates a dynamic environment in which the droplets can grow and engage, facilitating the nucleation and growth of nanoparticles inside the confined areas of the droplets. One of the important benefits of microemulsion strategies is the ability to control the scale and morphology of the nanoparticles by adjusting the composition of the surfactant system, the nature of the precursors, and the reaction conditions. The limited environment furnished with the aid of nanoscale droplets permits better manipulation of the nucleation and boom strategies, leading to the formation of nanoparticles with slender length distributions and unique shapes. This degree of control is vital for tailoring the residences of nanoparticles for numerous applications, including catalysis, sensing, and biomedical imaging.[50] The use of microemulsion strategies also offers benefits in terms of scalability, reproducibility, and performance in nanoparticle synthesis. The homogeneous nature of the microemulsion system guarantees uniform reaction conditions throughout the nanoreactors, mainly to ensure consistent and reproducible nanoparticle residences on a massive scale.[51] Additionally, the ease of managing and manipulating microemulsion structures makes them appropriate for business programs in which unique management of nanoparticle synthesis is needed. Furthermore, microemulsion strategies permit the synthesis of an extensive range of nanoparticles, including steel, semiconductor, and magnetic nanoparticles, with tailored homes for particular packages. This makes it quite suitable for the introduction of different precursors and dopants, as we will see when discussing the process of making nanoparticles. Therefore, such microemulsion techniques are highly desirable for producing elite nanomaterials with the best home and performance indicators. Overall, the concept of creating a microemulsion can be beneficial for the synthesis of nanoparticles with a limited length, morphology, and length of stay. It is possible to achieve accurate control over the synthesis of nanoparticles through the formation of microemulsion systems employing surfactants and cosurfactants, and nanoscale droplets act as nanoreactors where these researchers have the ability to design and replace the residences of nanoparticles that will fit well for a given package. For these reasons of scalability, reproducibility and flexibility, microemulsion techniques will remain key instruments in the advancement of nanotechnology and nanoscience based on the applicability of this technique in many areas of study and invention.[52]

Explanation of the design principles behind multifunctional smart nanoparticles

The design ideas behind multifunctional smart nanoparticles involve an aggregate of superior materials science, nanotechnology, and biomedical engineering. These nanoparticles are engineered to perform several functions, including imaging, remediation, and focused delivery, by integrating various purposeful devices into a single platform.

Multimodal imaging capabilities

Multimodal imaging skills are important for multifunctional smart nanoparticles because they enable complete imaging at numerous length scales and remedy tiers. These nanoparticles can integrate special imaging retailers or probes onto their floor or inside their structure to provide additional particular information about the ailment nation and remedy reaction.[53] The integration of several imaging modalities allows for enhanced diagnostic accuracy and precision. For instance, gold nanoparticles are powerful assessment tools for optical imaging, photoacoustic imaging, and computed tomography (CT), providing a comprehensive imaging profile. Similarly, magnetic nanoparticles have been used in combination with other imaging moieties, including fluorescent molecules and radioisotopes, to offer multimodal imaging capabilities.[54]

The design of these nanoparticles entails the strategic integration of various imaging marketers or probes. For example, gold nanoshells and nanocages can be used for photothermal cures while also serving as imaging dealers. The floor chemistry and floor amendment strategies used to enhance these nanoparticles with imaging agents are essential for optimizing their performance [55].

There are numerous benefits of multimodal imaging. These methods permit the imaging of various regions with imaging techniques for men or women, facilitating more accurate ailment prognosis and prognosis. This is particularly important in cancer analysis, where the heterogeneity of tumors necessitates photoguided therapies. The development of multimodal imaging abilities is driven by advances in nanofabrication strategies and the desire for extracomprehensive imaging modalities. As the sector continues to evolve, we can assume the mixing of even extra superior imaging agents and probes, similarly enhancing the diagnostic abilities of multifunctional smart nanoparticles.[56]

Theranostic functionality

Theranostics systems that combine diagnostic and healing features into a single device have received much attention within the discipline of oncology. These platforms, often referred to as "smart Nano systems," are designed to diagnose, supply bioactive marketers, and reveal therapeutic reactions. By integrating healing functionalities with molecular imaging, theranostic techniques can aid in deciding on the precise therapy, making plans for treatment, tracking reactions, and guiding follow-up therapy based entirely on the precise molecular characteristics of an ailment.[57]

One vital theranostic approach is organic pretargeting. In targeted image-guided therapy, a target-precise bioligand first identified the goal, observed by way of a nanoscale or molecular drug that forms healing clusters through in situ

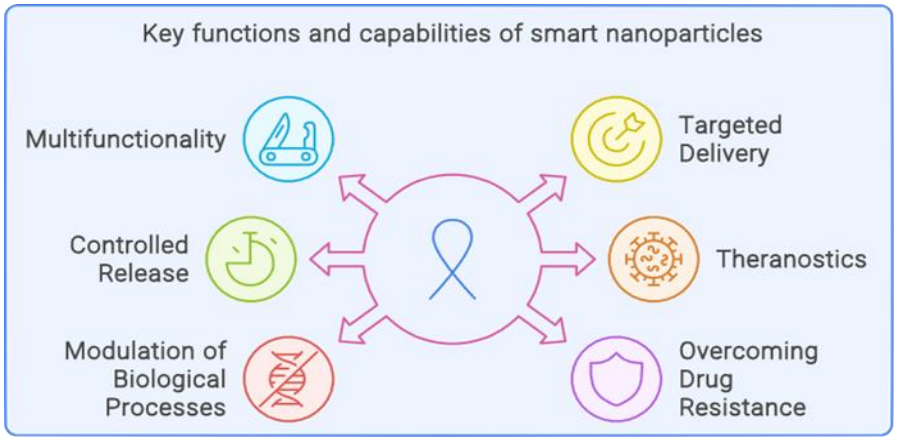

Figure 4: Key functions and capabilities of smart nanoparticles

conjugation reactions. If those targeted drug transport structures are categorized with multimodal imaging probes, they may be used as theranostics for diagnostic imaging and remedies. Optical and nuclear imaging techniques were utilized in proof-of-idea research with targeted theranostics.[58]

Theranostic probes can be designed to have the finest delivery, low renal clearance, reduced immunogenicity and antigenicity (e.g., by PEGylating the floor of theranostic nanoparticles), and excessive capability for therapeutic marketers. However, achieving green treatment may be difficult because of the need for uniform transport and distribution of theranostics to all malignant cells. Imaging can assist in improving the uniformity of delivery, but the design of therapeutic

machines should aid in the delivery and distribution of theranostics. One example of a theranostic platform is bismuth selenide (Bi2Se3) nanoplates, which can use near-infrared (NIR) laser light and successfully convert laser strength into heat for photothermal ablation of tumors. Bi2Se3 nanoplates also show strong X-ray attenuation and may be utilized for better X-ray computed tomography (CT) imaging. This observation highlights the potential of Bi2Se3 nanoplates as a promising platform for the prognosis and therapy of most cancers.[59]

Another in situ theranostic platform combines localized magnetic fluid hyperthermia, magnetic particle imaging, and 3D thermometry. This platform's objective is to reinforce invasive tactics by providing real-time remarks on the healing efficacy and safety of the treatment. The integration of these diagnostic and therapeutic features inside an unmarried system can lead to the development of extracenteredentred and customized cancer treatment approaches.[60]

Targeted delivery

Targeted drug shipping is a key factor of theranostic structures that aim to enhance specificity and decrease systemic toxicity. By incorporating concentrated ligands such as antibodies or peptides, theranostic structures can selectively bind to and deliver therapeutic agents to diseased cells or tissues. One approach is to use nanoparticles as drug providers and functionalize their floor with concentrated ligands. For example, gold nanoparticles (GNPs) can be optimized by attaching suitable floor ligands to maintain small dimensions while simultaneously retaining their fluorescent quenching sites for diagnostic imaging. The length of the nanoparticles affects their emission energies, fluorescence intensities, and peaks. The selection of an ideal nanovehicle and ligand is critical for successful drug transport to cancer cells.[61]

Targeted drug transport minimizes cytotoxic outcomes with the aid of therapeutic agents, especially for diseased cells. It also enables managed drug launches to avoid surprising damaging effects. Many targeted delivery procedures make use of membrane-specific cancer-unique antigens as goals. The use of nanocarriers has drastically advanced focused drug shipping for diagnostics and therapeutics. With respect to gastric cancer therapy, a theranostic nanomedicine platform was designed to overcome obstacles such as the pH, mucin layer, and extended stomach retention. The nanomedicine effectively added doxorubicin to most gastric cancer cells by targeting transferrin receptors. In vivo, research has shown the presence of nanoparticles and doxorubicin in tumor tissue for seventy-two hours, and mice treated with theranostic nanomedicine showed an 80% survival rate compared to those treated with pure doxorubicin.[62]

Targeted delivery is critical for attaining a uniform distribution of theranostics to all malignant cells. While passive delivery is based on the improved permeability and retention (EPR) effect, active concentration using ligands such as antibodies, antibody fragments, affibodies, or peptides is usually employed to enhance specificity. However, the "binding site barrier" can limit the penetration of focused theranostics into strong tumors. A careful layout of the theranostic platform, considering elements such as length and movement time, is important for overcoming these barriers and enabling powerful transport.[58]

Controlled release

To optimize remedy efficacy and limit side effects in managed release mechanisms, designing clever nanoparticles with pH-touchy or temperature-touchy residences is vital. These clever nanoparticles can provide centered drug delivery, managed launch, and more advantageous healing outcomes at the same time as reducing unwanted facet consequences. Smart nanoparticles with pH-sensitive traits can respond to the particular pH surrounding the goal site, bearing in mind the managed launch of medicine at the desired location.[63] On the other hand, temperature-sensitive nanoparticles can

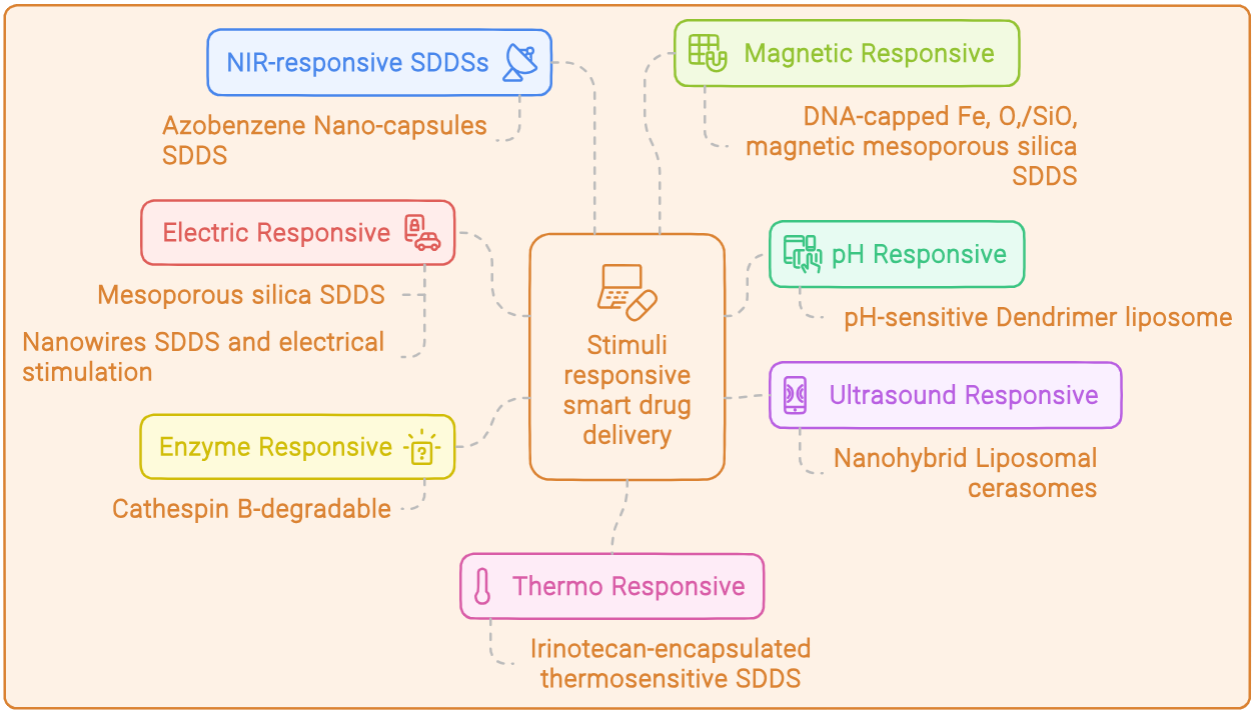

Figure 5: Stimuli-responsive smart drug delivery system

release drugs in response to changes in temperature, supplying a tailored and unique drug transport machine. By incorporating both pH-touchy and temperature-touchy properties into multifunctional clever nanoparticles, researchers can broaden superior drug shipping structures that offer controlled launch mechanisms. These systems can enhance remedy efficacy with the aid of ensuring that the medication is administered at the proper time and inside the right amount, mainly to improve healing outcomes. Furthermore, the use of stimuli-responsive carriers, such as pH-touchy polymers and temperature-sensitive substances, can aid the development of responsive drug shipping systems that may adapt to the particular situations of the target website online. This technique does not effectively improve the performance of drug delivery but additionally minimizes side effects by precisely controlling the release of therapeutic compounds.[18] The combination of pH-touchy and temperature-sensitive houses in multifunctional clever nanoparticles provides a promising approach for designing managed launch mechanisms that optimize remedy efficacy and limit side effects in drug shipping structures.

Multifunctionality of smart nanoparticles

Smart nanoparticles exhibit multifunctionality in most cancer remedies by integrating diagnosis and treatment, enhancing imaging resolution, and allowing precise tumor concentration.[64] These nanoparticles, including multifunctional nanoprobes, provide a sophisticated system with optimized amendment websites and green feature integration, making them powerful tools for competitive tumor targeting.[65] One of the important aspects of multifunctionality in smart nanoparticles is their potential for use in goal-specific cells or tissues. This is carried out through the functionalization of their surfaces with tumor-particular ligands such as antibodies, peptides, transferrin, and folic acid. These ligands permit the nanoparticles to selectively bind to cancer cells, increasing their uptake and enhancing their therapeutic effect.[66] The proper design of nanoparticles is important. Engineered nanoparticles are usually composed of biomedical payloads, nanocarriers and surface modifiers, as proven in Figure 3.

Smart nanoparticles also exhibit multifunctionality through their ability to perform multiple functions simultaneously. For example, they may be engineered to supply multiple therapeutic agents without delay, such as chemotherapy and immunotherapy, or to provide both diagnostic and healing capabilities via theranostics.[66]

In addition, the multifunctionality of smart nanoparticles is improved through their potential to interact with numerous organic molecules, such as DNA, proteins, and enzymes. This interplay permits them to modulate organic methods, consisting of gene expression and protein function, which can contribute to the development and progression of most cancers.[68]

Discussion on the various functions and capabilities of smart nanoparticles in cancer therapy

With precision and a response to the tumor microenvironment, they are valuable tools in the fight against cancer. One key feature of smart nanoparticles in most cancer therapies is centered drug delivery. By functionalizing nanoparticles with ligands that bind most cancer cell mobile markers, they can selectively accumulate in tumor tissues, sparing whole cells from the cytotoxic effects of chemotherapy drugs. This targeted approach improves drug efficacy and reduces systemic toxicity, mainly leading to increased treatment efficacy for patients.[69] Moreover, clever nanoparticles can carry more than one healing payload simultaneously, allowing aggregate therapy inside a single shipping device. This multifunctional functionality allows synergistic outcomes between unique pills, overcoming drug resistance mechanisms and improving the general healing impact. Additionally, nanoparticles may be engineered to launch

capsules in response to particular stimuli present within the tumor microenvironment, including pH, enzymes, or temperature, further optimizing drug transport and launch kinetics.[70]

Multifunctional clever nanoparticles offer several benefits in most cancer therapies. Some key functions and capabilities of smart nanoparticles are illustrated in Fig. 4. These nanoparticles can potentiate the capability of drug delivery structures, allowing focused and green shipping of therapeutic dealers to cancer cells.[71] They also provide blessings together with progressed biodistribution, which enhances the effectiveness of most cancer remedies. Additionally, multifunctional nanoparticles allow synergistic therapy via the combination of distinct treatment modalities, including chemotherapy, photodynamic therapy, siRNA remediation, and photothermal therapy, within an unmarried platform. Furthermore, clever nanoparticles can actively target precise molecular markers that are overexpressed on cancer cells, leading to more effective and unique treatments. These nanoparticles may be designed to respond to specific stimuli, taking into consideration controlled drug release on the tumor website and minimizing side effects on whole tissues.[72] The improvement of clever hyperthermia nanofibers demonstrates the capacity of multifunctional nanoparticles for developing revolutionary cancer therapeutics. Moreover, multifunctional nanoparticles can be applied for multimodal imaging, permitting both prognosis and treatment monitoring in most cancer patients. By incorporating modern photosensitizers and taking advantage of nanocomposite assemblies, these nanoparticles can offer theragnostic abilities, combining therapy and diagnostics for customized cancer remedies.[73]

Drug transport and clever nanoparticles can also be utilized for imaging and diagnostics in most cancer remedies. Nanoparticles functionalized with imaging agents such as fluorescent dyes or comparison marketers for MRI or CT scans can help in early detection, monitoring treatment response, and guiding surgical interventions.[66] This dual effect of nanoparticles on both prognosis and therapy is a widespread development in personalized cancer care. Furthermore, clever nanoparticles can be designed to overcome organic barriers that limit the effectiveness of traditional cancer treatments. For instance, nanoparticles can penetrate deep into tumor tissues through the impact of superior permeability and retention (EPR), bypassing the constraints of large-molecule pills.[74] They can also overcome multidrug resistance mechanisms in cancer cells by encapsulating pills in nanocarriers that evade efflux pumps and cell detoxing pathways. Another essential characteristic of smart nanoparticles in cancer therapy is their ability to enhance the efficacy of radiation therapy.[70] Radio-sensitizing nanoparticles may be used to increase the sensitivity of most cancer cells to radiation because decreased radiation doses can be used even to retain healing efficacy. This approach reduces harm to surrounding whole tissues and minimizes facet outcomes related to radiation treatment. Moreover, smart nanoparticles can modulate the tumor microenvironment to create an extra favorable environment for most cancer treatments.[75] By targeting additives of the tumor stroma, along with most cancer-associated fibroblasts or immune cells, nanoparticles can assist in conquering immunosuppression and enhancing antitumor immune reactions. This immunomodulatory characteristic of nanoparticles holds promise for improving the consequences of immunotherapy in most cancer patients. In conclusion, the multifunctional abilities of clever nanoparticles in most cancer therapies, including centered drug shipping, imaging, overcoming organic barriers, improving radiation therapy, and modulating the tumor microenvironment, represent a paradigm shift in most cancer remedies. These superior nanosystems can revolutionize the manner in which we diagnose, deal with, and manage cancer, supplying new wishes for patients and paving the way for customized and precision medicine in oncology.[75]

Examples of how these nanoparticles can target, deliver, and release therapeutic agents in a controlled manner

The targeted shipping and managed release of therapeutic dealers using nanoparticles have been significantly explored in diverse research. Here, we will discuss some examples of hit studies that show the efficacy of nanoparticles in focusing on, handing over, and liberating healing marketers in a controlled manner. One such approach is the use of gold nanoparticles (AuNPs) for the treatment of Alzheimer's disease. Researchers have correctly designed AuNPs that can selectively target and bind to amyloid-β peptide, a key factor in the pathology of Alzheimer's disease. These AuNPs were engineered to release a healing agent, which includes a small molecule or a protein, in a controlled manner, taking into consideration the focused remedy of the disease. The study confirmed that these AuNPs were powerful in reducing amyloid-β levels and improving cognitive features in animal models of Alzheimer's disease.[76]

Another example is the use of polymeric nanoparticles (PNPs) for treating cancer. PNPs have been designed to target most cancer cells by incorporating targeting molecules, including antibodies or peptides, on their surface. These PNPs can then supply healing retailers, which include chemotherapy pills or siRNAs, directly to cancer cells, reducing systemic toxicity and improving remedy efficacy. The use of PNPs loaded with a chemotherapy drug confirmed tremendous tumor regression and improved survival costs in animal models of cancer.[77] In addition, researchers have explored the use of liposomes and nanoemulsions for the targeted delivery of therapeutic agents. Liposomes are small vesicles composed of lipids that can encapsulate healing dealers and target unique cells or tissues. Nanoemulsions are similar but are composed of a combination of lipids and water. Both liposomes and nanoemulsions have been proven to be powerful in turning therapeutic sellers to specific sites within the body, including tumors or the mind.[78]

Furthermore, researchers have investigated the use of nanocarriers for the shipping of gene remedies. Nanocarriers are designed to guard and deliver genetic cloth, consisting of DNA or RNA, to unique cells or tissues. The use of nanocarriers loaded with a gene therapy agent

Table 1: Comprehensive overview of the various stimuli-responsive smart drug delivery systems and their potential applications in cancer therapy

Delivery Systems	Stimuli & Drug Release Mechanisms	Applications	Highlights	Reference
Nanoscale drug delivery systems	Respond to temperature, pH change, enzymes, light, magnetic field, ultrasound, or electrical stimuli	Cancer chemotherapy, gene therapy, theranostic applications	Enhanced selectivity, biocompatibility, tumor targeting, controlled release	[88]
Stimuli-responsive nanocarriers	Undergo physical incitement or molecular conformational change in response to specific stimuli	Control drug biodistribution in response to exogenous or endogenous triggers	Spatial-, temporal-, and dosage-controlled drug delivery	[89]
Enzyme-responsive nanocarriers	Sensitive to internal (temperature, pH, redox, enzyme reactions) and external (ultrasound, electric field, light, magnetic field) stimuli	Lung cancer therapy, drug release at designated localization	Utilization of unique tumor microenvironment for drug delivery	[90]
Polymeric nanocarriers	Act as a promising platform for efficient drug and gene delivery to targeted sites	Offer controlled drug release mechanisms	Imaging, theragnosis, targeted drug delivery	[91]
Hydrogel-based drug delivery systems	Respond to pH, temperature, or light stimuli	Cancer therapy, wound healing, tissue engineering	Biocompatibility, biodegradability, controlled release	[92]
pH-responsive dendrimers	Change conformation in response to pH changes	Cancer therapy, gene therapy	Enhanced selectivity, biocompatibility, controlled release	[89]
Temperature-responsive dendrimers	Change conformation in response to temperature changes	Cancer therapy, gene therapy	Enhanced selectivity, biocompatibility, controlled release	[90]
Enzyme-responsive dendrimers	Change conformation in response to enzyme reactions	Cancer therapy, gene therapy	Enhanced selectivity, biocompatibility, controlled release	[93]
Light-responsive dendrimers	Change conformation in response to light	Cancer therapy, gene therapy	Enhanced selectivity, biocompatibility, controlled release	[89]
Magnetic field-responsive dendrimers	Change conformation in response to magnetic field	Cancer therapy, gene therapy	Enhanced selectivity, biocompatibility, controlled release	[94]
Ultrasound-responsive dendrimers	Change conformation in response to ultrasound	Cancer therapy, gene therapy	Enhanced selectivity, biocompatibility, controlled release	[95]
Electric field-responsive dendrimers	Change conformation in response to electric field	Cancer therapy, gene therapy	Enhanced selectivity, biocompatibility, controlled release	[94]
Stimuli-responsive polymeric micelles	Respond to pH, temperature, or light stimuli	Cancer therapy, gene therapy	Enhanced selectivity, biocompatibility, controlled release	[90]
Stimuli-responsive liposomes	Respond to pH, temperature, or light stimuli	Cancer therapy, gene therapy	Enhanced selectivity, biocompatibility, controlled release	[96]
Stimuli-responsive nanoparticles	Respond to pH, temperature, or light stimuli	Cancer therapy, gene therapy	Enhanced selectivity, biocompatibility, controlled release	[97]

confirmed major developments in gene expression and healing efficacy in animal models of disease.[79]

Targeted drug delivery

The idea of targeted drug delivery involving the use of nanoparticles functionalized with focused ligands is certainly a promising approach in the field of drug delivery, particularly in cancer treatment.[80] Singh and Lillard highlighted the use of biodegradable nanoparticles for sustained drug launch within the online goal website over a period of days or perhaps weeks, demonstrating the capability for focused drug delivery in cancer therapy. NPs offer several benefits in drug shipping, including their small size, large floor area, and ability to be functionalized with specific ligands for targeting functions.[81] By functionalizing nanoparticles focused on ligands, researchers can enhance the specificity of drug delivery to the desired site, thereby decreasing off-goal results and enhancing therapeutic outcomes. In the context of cancer therapy, targeted drug delivery using nanoparticles can help in delivering therapeutic marketers at once to most cancer cells while minimizing publicity to healthy tissues.[82] This focused technique can enhance the efficacy of the remedy at the same time as lowering systemic facet outcomes commonly related to traditional chemotherapy. Moreover, the use of biodegradable nanoparticles permits sustained drug release at the target site, which could lead to prolonged therapeutic outcomes and doubtlessly reduce the frequency of drug management. This sustained release mechanism can also assist in preserving the finest drug concentrations at the target site, enhancing remedy effects. Overall, the mixture of nanoparticles functionalized with targeting ligands and biodegradable residences holds great promise for achieving centered drug delivery in cancer therapy, as proven with the aid of the look performed with the aid of Singh and Lillard.[83]

Controlled drug release

Nanoparticle-based drug shipping systems have been developed to enable controlled and centered drug release at specific sites within the body. Research via Dang and Guan highlights how those systems decorate efficacy by prolonging the half-life of medication, improving solubility, and facilitating precise drug launches at diseased websites, particularly in cancer remedies. These systems offer advantages, including improved balance, biocompatibility, and precise concentration, making them intelligent drug companies that respond to diverse stimuli for effective treatment. The capacity of nanoparticles to respond to organic cues or outside triggers permits tailored drug transport, addressing demanding situations such as drug resistance and enhancing treatment results in most cancer therapies.[84]

Stimuli-responsive smart drug delivery systems

Stimulus-intelligent drug delivery systems represent an innovative approach to drug delivery, enabling therapeutic drugs to be released in response to specific stimuli. These systems are designed to respond to a variety of stimuli, both internal (such as pH, temperature, redox, and enzymes) and external (including light, magnetic fields, and ultrasound), to enable the release of the target drugs at the desired site while minimizing side effects.[85] One of the key features of these systems is the pH response, which allows drugs to be released in acidic environments such as tumor cells or cells. Temperature-responsive systems use polymers such as poly(N-isopropylacrylamide) to release drugs based on temperature changes, with a low critical solution temperature (LCST) being an important parameter. Redox-responsive systems respond to changes in redox levels, especially in tumor cells with elevated levels of glutathione (GSH). Enzyme-responsive systems release drugs in the presence of specific enzymes such as matrix metalloproteinases (MMPs) found in the tumor microenvironment and use peptides with enzyme-cleavable peptides in their design.[86] Photosynthetic systems use light-sensitive molecules to release chemicals when exposed to light, whereas photoactive systems use an applied magnetic field to induce excessive heating and mobilize chemicals from nanocarriers. Ultrasound-responsive systems release drugs in response to ultrasound waves, enabling both drug extraction and imaging functions.[87] These novel drug delivery systems have shown tremendous potential in preclinical studies in cancer treatment and beyond, although further studies are needed to overcome challenges regarding clinical translation, scalability, and long-term safety management. The development of multiple stimulus systems capable of responding to a combination of stimuli holds promise for more accurate and effective drug delivery in the future. Figure 5 illustrates the stimuli-responsive smart drug delivery system.

pH-responsive stimuli

pH-sensitive drug delivery systems take advantage of the unique pH fluctuations in cellular compartments to stimulate efficient drug release. The pH of various cellular compartments, such as the cytosol, Golgi apparatus, endosomes, lysosomes, and tumor microenvironment, plays an important role in drug delivery. Polymers containing weak acid or base groups are used to develop pH-sensitive systems that rapidly change ionization over a specific pH range. By varying the comonomers used in polymer synthesis, the pH response of the system can be tailored accordingly.[98]

Hydrazone attachment of anticancer drugs to their carriers or targeting ligands enables the design of pH-responsive drug delivery systems that react in the acidic environment of tumor cells, facilitating controlled drug release. For example, the custom-designed dual pH-triggered polymer-drug system PCC-Hyd-DOX-DA was developed by Du *et al*. at pH 6.8 compared to pH 7.4.[99] Notably, polyacidic acid (PAAc) and polymethacrylic acid (PMAAc) are the major components of polyacidic pH-responsive systems. Researchers such as Saha and others have reported novel approaches such as pH-triggered autofluorescent polymeric nanoplatforms for the delivery of nonfluorescent drugs into cancer tumors.[100] Saha *et al*. reported the discovery of a pH-triggered autofluorescent polymeric nanoplatform for nonfluorescent aromatic nitrogen mustard chlorambucil (CBL) delivery in cancer tumors. In another study, Zhang *et al* combined doxorubicin and dextran with a hydrazone linker and targeted hepatocytes with folate.[101] While pH is widely used in smart drug delivery, it needs to be combined with other stimuli, such as temperature or redox, to achieve

more precise and accurate release in targeted environments. The use of acidic pH as a tumor microenvironment trigger has several drawbacks. First, the acidic pH of the peripheral regions is usually far from that of the blood, making nanoparticles ineffective. In addition, pH changes in healthy tissue and malignant tissue are usually similar.[102]

Redox-responsive stimuli

Redox homeostasis is important for survival and affects numerous cellular methods, with glutathione (GSH) playing a key role in maintaining the intracellular redox balance. The tremendously reductive and hypoxic microenvironment of tumor tissues results in notably greater intracellular GSH levels in tumor cells than in regular cells. This increase in GSH in tumor cells, combined with the incredible awareness gradient between the intracellular and extracellular environments, serves as a stimulus for tumor-centered intracellular drug transport. Various redox-responsive drug shipping systems (DDSs) have evolved to leverage this precise GSH gradient for targeted drug transport, particularly for the cytoplasmic delivery of healing products such as proteins and genes.[103] These systems often contain discount-sensitive bonds, consisting of disulfide bonds, which are cleaved by GSH, into their structures to permit controlled drug release in reaction to the intracellular redox environment. In the context of most cancer therapies, redox-responsive DDSs have shown promise in reversing multidrug resistance (MDR) through the delivery of therapeutic agents, especially to tumor cells [104]. For instance, a nanocomplex advanced with the aid of Wu and associates applied a disulfide bond to enable redox-responsive gene transport, mainly to reverse P-glycoprotein (P-gp)-mediated MDR and improve intracellular drug awareness for effective chemotherapy of cancer cells. Furthermore, tumor cells exhibit multiple ranges of reactive oxygen species (ROS) due to their hypermetabolism, making ROS-responsive DDSs appealing techniques for focused drug transport in cancer therapy. These systems use ROS-responsive linkages, which include thioketal bonds, to cause drug launches in reaction to the excessive ROS levels found in tumor tissues. The interplay between redox homeostasis, GSH levels, and ROS generation in tumor cells provides a basis for the development of revolutionary drug delivery structures that may target most cancer cells and enhance the efficacy of chemotherapy.[105]

Enzyme-responsive stimuli

The use of enzymes as catalysts in the development of stimuli-responsive drug delivery systems (SDDSs) has received considerable attention due to their unique advantages, including excellent substrate specificity and selectivity under moving conditions.[14] Enzymes, such as lipases, proteases, trypsins, glycosidases, phospholipases, and oxidoreductases, play important roles in the delivery of drugs to cancer cells. These enzymes facilitate drug delivery from specific target sites by enzymatic cleavage of smart carriers or ligands attached to the drug payload through encapsulation or covalent bonding. Drug release is catalyzed by several enzymes, including proteases that degrade proteins and peptides, providing an efficient mechanism for the release of drugs from liposomes [106]. Radhakrishnan and others. was the first to develop hollow nanocarriers that are stimulated by the trypsin/hyaluronidase enzyme to deliver anticancer drugs to cells.[107] The phospholipase A2 (PLA2) enzyme is used to release drugs or display targeted ligands from SDDSs using liposomes or small unilamellar vesicles (SUVs). In addition, cathepsin B, an intracellular cysteine protease, is overexpressed in tumor tissues and allows the H-Phe-Lys-OH peptide to break down. MMPs (matrix metalloproteases) are a well-known family of zinc-dependent endopeptidases that play important roles in cancer prognosis and have been extensively studied in drug delivery and imaging.[108] Zhu *et al*. developed MMP2-sensitive PEG lipid-conjugated liposomes with anti-nucleosome monoclonal antibodies on their surface to enhance cancer targeting [109]. In a separate study, Chen *et al*. developed multifunctional polymeric micelles incorporating doxorubicin to improve cancer cell uptake via endocytosis. Despite the advantages of enzyme-catalyzed SDDSs, precise control of the start-up time of the system remains a challenge.[110]

Light-responsive stimuli

Light stimuli, especially in drug delivery systems, have received considerable attention due to their noninvasive nature and precise controllability [111]. Researchers have explored the incorporation of photosensitizers into hydrogels to achieve controlled drug release through mechanisms such as photoisomerization, photochemical reactions, and photothermal reactions.[112] In addition, photoactive compounds such as those containing azobenzenes and spiropyrans enable the tailoring of drug delivery systems for advanced medical applications, including drug transport and release exchange. Recent advances in 3D printing technology have enabled the synthesis of polyelectrolyte hydrogels with high swelling capacity and tunable mechanical properties, exhibiting compelling drug delivery properties that can be used for screening with

stimulation or sequential consumption. These innovations highlight the potential of light stimulation in modifying standardized drug delivery regimens to improve clinical outcomes.[113]

Smart fluorescent drug delivery systems (SDDSs) have received considerable attention due to their ability to utilize natural sunlight and synthetic electromagnetic radiation at specific wavelengths between 2500 nm and 380 nm. These photoactive delivery systems offer several advantages over other stimuli, as photochemical synthesis does not require additional reagents or severe catalysts, and most if any side effects are harmless.[87] In light-responsive SDDSs, photosensitizers have mechanisms that turn on/off chemicals in response to strong radiation stimuli. These SDDSs are usually accompanied by a light-sensitive biomaterial or encapsulated in a therapeutic agent. The fluorescent materials absorb light (photons), causing changes in the smart carriers, drastically changing their structure and enabling the release of the packaging/combination at the desired location in a controlled manner. UV and visible light can originate from pharmaceuticals applied to the skin or circulate through

blood vessels near the body surface (e.g., the ocular system).[91] Drug delivery is usually triggered by reversible or irreversible photoinduced structural changes in smart carriers. Photo-separable fibers can be used to bind chemicals together for light sensitivity. For example, doxorubicin-encapsulated poly (lactic-co-glycolic acid) (PLGA) matrix particles with excess gold exhibited NIR excitation. When cancer cells are exposed to NIR light, doxorubicin is abruptly released, resulting in significant cancer cell toxicity and tissue ablation. These fluorescent SDDSs have the potential to revolutionize drug delivery by delivering controlled and targeted therapeutics, improving efficacy and reducing side effects.[85]

Ultrasound responsive

An ultrasound that triggers drugs from intelligent transporters to force drug delivery in diseased areas, especially tumors. Ultrasound, a type of high-frequency sound wave, can be adapted for different applications, and low frequencies are used to capture images and destroy intelligent carriers for material extraction when increased frequency concentrations may increase the permeability of cancer cell membranes. Ultrasound has gained popularity in clinical studies due to its advantages, such as lymph node penetration, improved spatiotemporal control, and increased safety.[114] It is widely used in hospitals for both diagnosis and treatment. The development of ultrasonic-sensitive nanocarriers has expanded the range of ultrasound techniques, making them successful tools for capturing drug carriers and triggering drug release at target sites by manipulating ultrasound by controlling parameters such as frequency, duty cycle, and duration. Researchers such as Kruskal *et al*. and Wang *et al*. have used ultrasound-sensitive nanocarriers to achieve tumor targeting and systemic drug distribution.[91] Jung *et al*. developed sonosensitive liposomes for doxorubicin delivery and magnetic resonance imaging.[115] In cancer therapy, ultrasound therapy in combination with micelles has shown promise, as shown by studies such as those of Husseini *et al*. Overall, ultrasound-based drugs, especially in combination with nanocarriers, offer a promising strategy for enhancing drug targeting, reducing systemic toxicity, and improving therapeutic efficacy in therapeutic settings, including cancer.[116]

Magnetic responsives

Magnetic-responsive drug delivery systems have emerged as promising noninvasive methods for monitoring the spatial and temporal proximity of carriers to their targets. This technology uses the unique properties of magnetic particles to deliver anticancer drugs or antibodies to specific organs or tissues that are altered by disease. The idea of using magnetic particles for targeting originated from the pioneering work of Freeman *et al*. in 1960, who proposed the idea of injecting fine metal particles through tissues and amplifying them in the body using a magnetic field.[117] MNPs have emerged as a major area of interest in this field due to their multifaceted ability to be synthesized with discretion for particular purposes. They have multiple magnetic properties and multiple biomolecular conjugations that allow design and construction with the ability to develop the kind of smart applications one desires. They include extended circulation time, the labeling of special tissues of the wound, and treatment. In the process of creating magnetic-responsive systems, different strategies, such as the use of nanoparticles and magneto-liposomes, are employed.[118] Similarly, Li *et al* synthesized a magneto thermally responsive nanocarrier/doxorubicin based on Mn-Zn-containing ferrite magnetic nanoparticles (MZF-MNPs) through the formation of a thermal copolymer shell that contains adsorbed drugs combined with the magnetothermal properties of MZF-MNPs to provide stimuli-responsive drug release in tumors using an AMF.[119] The potential of magnetic targeting and AMF treatment has been demonstrated in various studies. For example, magnetic targeting and AMF treatment in combination with MTRN/Dox showed a significant reduction in tumor volume compared to MTRN/Dox with magnetic targeting or AMF treatment alone when injected into nude mice within the bladder, suggesting a potential treatment for liver cancer. In addition to developing magnetic-responsive systems, researchers have focused on improving their manufacturing and characterization. For example, Fang *et al*. developed a highly controllable method for the synthesis of carbon-encapsulated magnetic nanoparticles (CEMNs) in an arc discharge plasma, allowing for better control of their size distribution and purity. The in vivo toxicity of CEMNs was evaluated using the human breast cancer cell line MDA-MB-231, and it was concluded that specific doses of CEMNs could be used in biomedical conditions such as MRI, cell migration site overheating, and chemical administration.[120]

Challenges and future perspectives

Some of the challenges of the Smart Drug Delivery System are as follows: To proceed, these difficulties must be evaluated and weighed to ensure their proper application in cancer treatment. These adverse effects render their use in SDDSs detrimental to the human body since their toxicity is inherent. This toxicity is best understood in proportion to the particle size; the smaller the particle size is, the more toxic it is. The formulation of low-toxicity nanocarriers remains a critical requirement for the effective implementation of SDDSs. Another will be the cost that this system will take to implement. The high cost of manufacturing and relatively low treatment scope for solid tumors are hindering factors in the use of SDDSs. In addition, the controlled release of drugs at the target site can also be hampered by premature release from nanocarriers, thereby compromising the therapeutic potential of the treatment regimen.[121] CSCs are a diverse type of disease and exhibit heterogeneity, which makes it difficult to design SDDSs that can address this type of disease appropriately. Every cancer is different and presents a certain set of features for which adequate therapeutic approaches should be used. This is worse because there is no specific regulation on how SDDSs should be conducted, which makes the formulation of such programmers and strategies complicated. Therefore, the selection of appropriate ligands and the development of suitable conjugation techniques constitute major challenges in SDDS design. As with all treatments involving ligands, the pharmacokinetic outcomes of these ligands must be closely controlled to

attain the ideal positive therapeutic impacts. The structure and functions of the products are also crucial in the determination of their actions in the body Fact sheet on the transporters, which also contains information on the physicochemical and pharmacological characteristics of the transporters. A few limitations of SDDSs include longer preparation times since, compared with PODs, preparation involves more steps in chemical synthesis and purification. Translation of these performances to similar human benefits remains restricted, meaning that clinicians ought to garner more different data sets to illuminate the potential advantages and disadvantages of the utility of these vehicles. Another issue that must be resolved is the flapping of functional groups and dynamic behavior in the cellular environment. pH-sensitive systems can be created to make or release drugs upon changes in pH, and redox-sensitive systems can be created to release drugs upon changes in the reductive components.[122] Furthermore, the impact of chronic toxicity resulting from the progressive accumulation of nanocarriers or other SDDDs within patients' needs to be explored. The attractiveness of SDDSs in translational medicine is enormous, but obstacles have to be surmounted for practice to occur. In the future, SDDSs will include diagnostics with targeted treatments in a single hub, which will increasingly enhance focused, effective, and 'easy' treatment. Future research should incorporate an emphasis on more clinical trials and a practicable framework for the broader implementation of these programs. Overall, SDDSs have several inherent difficulties, which, to different extents, seem to be rather intricate. Addressing these obstacles will involve considerations of toxicity interferences, costs, cancer variability, and compliance with regulatory frameworks. To achieve the full potential of SDDSs and apply them for cancer therapy, it is imperative to design new ligands, conjugation techniques and systems for delivery.[123]

CONCLUSION

Multiple functional properties of smart nanoparticles make them effective in cancer therapy because they have increased target specificity, less toxicity to the body, and a controlled drug release system. These advanced nanoparticles are employed in the coordination of chemotherapeutic agents to a variety of tumor localization sites, allowing for high rates of treatment success and a low incidence of side effects. The following are the details of the various synthesis methods used for synthesizing multifunctional smart nanoparticles: patent-assisted synthesis, chemical precipitation, hydrothermal synthesis, green synthesis, the sol-gel method and microemulsion. These methods define the chances of manipulating the basic characteristics of the nanoparticles, size, shape and the chemical properties of the product surface when synthesizing the nanoparticles for specific uses. Smartness is one of the important components for the development of these nanoparticles, especially when incorporating stimuli-sensitive polymers that undergo changes in pH or temperature. This creates a heterogeneous context that can convert a host of physicochemical properties of the immediate vicinity within the tumor environment for targeted drug delivery and depot formation. When creating composite smart NPs with more than one imaging component, the goal is to address the need to perform multiple imaging methods simultaneously, thereby enhancing the diagnostic resolution and target structure segmentation for accurate targeting, particularly in oncology, where malignant neoplasms are often heterogeneous. Combined diagnostic and therapeutic devices that include hassle-some structures as theragnostics have become fashionable in oncology. The potential for smart NFs is that they can be designed to identify diseases and deliver specific bioactive molecules for medical applications, which will assist in creating disease-specific therapies.

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