IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A REVIEW ON NANOPARTICLE DRUG DELIVERY SYSTEMS FOR CANCER THERAPY: CURRENT ADVANCES AND APPLICATIONS

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Abstract

Applications for nanoscale materials can be found in nanomedicine and nano-delivery systems, where they can be precisely targeted to specific areas and used as regulated carriers for pharmaceuticals and diagnostic equipment. Because nanotechnology makes it possible to precisely deliver medications in a targeted, site-specific manner, it provides various benefits in the treatment of chronic human diseases. Recently, chemotherapeutic medicines, biological agents, immunotherapeutic agents, and other noteworthy applications of nanomedicine have been used to treat a wide range of disorders. The application of nanoparticles as a drug delivery system (NDDS) holds considerable potential for the treatment of cancer. Because of several significant benefits, drug delivery systems (DDS) based on nanoparticles are more effective than conventional DDS. First of all, it can extend the half-lives of medications and proteins that are easily broken down. Second, it can increase the hydrophobic medications' solubility, which will increase their therapeutic efficacy. Finally, it makes it possible to precisely and carefully distribute medications at the precise location of the illness, providing individualized treatment plans.

Keywords: Nanomedicine, nanomaterials, controlled release, targeted distribution, drug delivery system, nanoparticle, cancer treatment

1. INTRODUCTION

Cancer is a major global cause of mortality, with chemotherapy serving as a key treatment method. It targets fast-growing cancer cells, but the collateral damage to healthy, fast-growing cells limits its effectiveness. Furthermore, multi-drug resistance (MDR) hinders chemotherapy's success, as cancer cells evolve resistance to cytotoxic drugs.[1,2] These limitations have prompted the development of Smart Drug Delivery Systems (SDDSs), utilizing smart nanocarriers. SDDSs offer precision in drug delivery, enabling the specific and targeted application of drugs to cancer sites, and minimizing damage to healthy cells.[3,4,5] This approach holds great promise in improving the effectiveness of cancer treatment, potentially reducing side effects and increasing the chances of successful therapy, marking a significant advancement in the battle against cancer.[6,7,8]

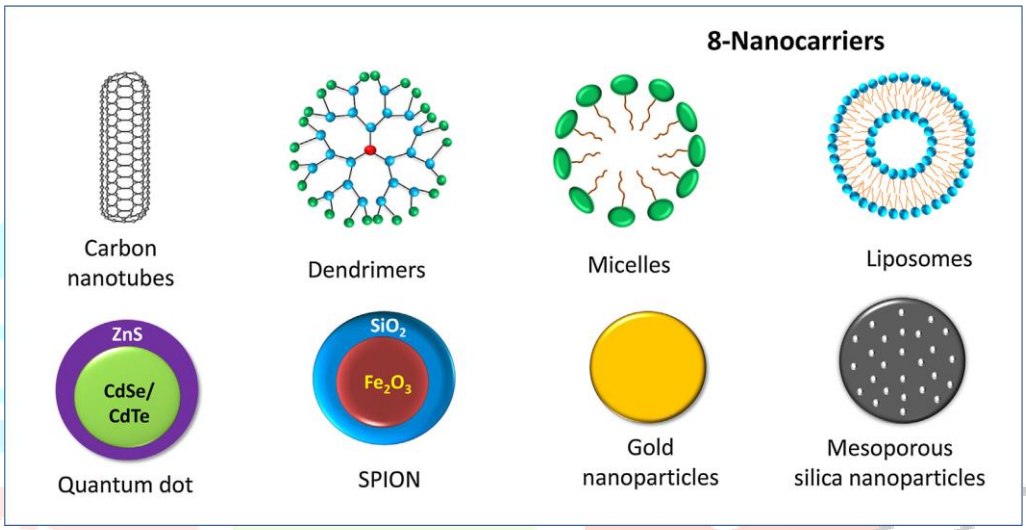

Figure 1. Nanocarriers

Controlled drug delivery systems offer advantages over conventional methods, particularly in cancer treatment where traditional distribution harms healthy and cancer cells alike. Chemotherapeutic agents are delivered to tumors via these carriers, which increase the concentration of drugs in cancerous cells and decrease toxicity in healthy cells, thereby optimizing efficacy and mitigating adverse effects.[9,10]

Controlled drug delivery systems have the added benefit of protecting drugs from degradation and clearance. They are especially valuable for delivering sensitive substances like proteins, gene therapy, and RNA interference agents, preventing enzymatic degradation and enhancing their effectiveness.[11,12] The emergence of nanotechnology has transformed nanoparticles into a potentially effective medium for regulated drug delivery. This is due to their ability to prolong the half-life of drugs, enhance the solubility of hydrophobic drugs, and facilitate sustained and controlled drug release.[13,14] Nanoparticles, which generally have diameters between 10 and 1000 nm, show great potential in optimizing drug delivery and expanding the therapeutic possibilities in various medical fields.[15,16] Stimuli-responsive nanoparticles are instrumental in reducing drug toxicity and managing drug biodistribution. Liposomes, among the first nanoparticle drug delivery systems, were introduced in the 1960s. Over time, a wide range of materials have been developed into nanoparticles for drug delivery.[17,18] Although the FDA has authorized 51 nanoparticles, 77 are still undergoing clinical trials. highlighting their growing importance in healthcare. Approved nanoparticles frequently employ

polymeric and liposomal materials, but researchers are exploring advanced materials like micelles, metallic, and protein-based substances for innovative nanoparticle drug delivery systems.[19,20]

Nanotechnology integrates biological and physical sciences, utilizing nanostructures in fields like Nanomedicine and drug delivery systems founded on nanotechnology.[21,22] Nanomaterials, which commonly vary in size from 1 to 100 nm, are of paramount importance in the progression of nanomedicine. They exert a profound influence on biosensors, microfluidics, drug delivery, microarray tests, and tissue engineering.[23,24] Nanotechnology functions at the nanoscale to produce nanomedicines, which have far-reaching effects on drug delivery, biosensors, biomedicine, and tissue engineering. This influence stems from the revolutionary potential of nanoparticles in the fields of science and healthcare.[25,26]

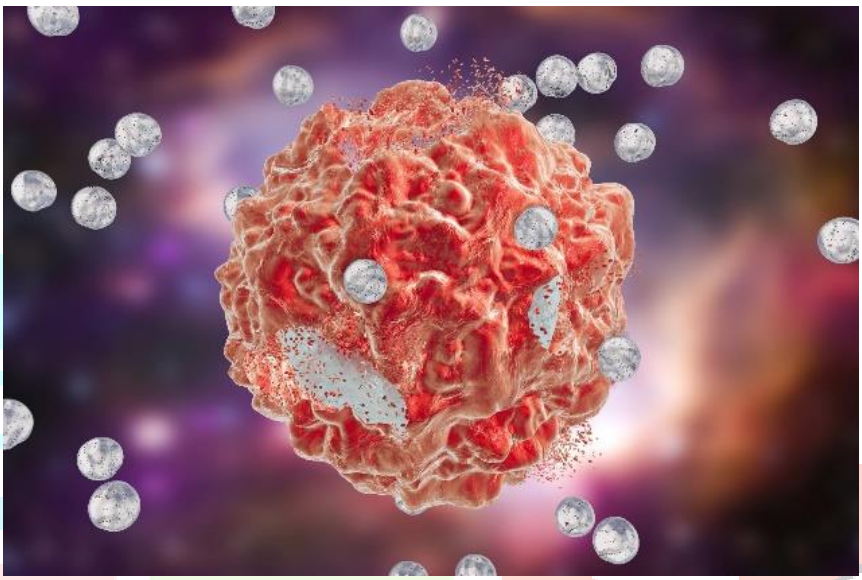

Figure 2. nanomedicine

Nanoparticles, composed of materials with atomic or molecular structures, often take the form of tiny nanospheres, affording them increased mobility in the human body. Their nanoscale size imparts unique biological, mechanical, chemical, electrical, magnetic, and structural properties.[27,28] Leveraging nanostructures as carriers for therapeutic drugs enables precise delivery to target tissues with controlled release, driving the growing recognition of nanomedicines for their potential to enhance drug delivery and therapeutic effectiveness.[29,30]

Nanomedicine is a rapidly developing discipline that employs nanoscience methodologies in the realms of medical biology, prevention of disease, as well as therapeutic interventions. It utilizes nanoscale materials for various applications, such as nanorobots, nanosensors for diagnostics and drug delivery, and cell-activating compounds. Innovative approaches, like nanoparticle-based cancer diagnosis and treatment, have gained momentum.[31,32] The FDA's approval of lipid systems like liposomes and micelles highlights the progress in nanoparticle-based therapies, marking a significant step in advancing medical science.[33]

Nanostructures, due to their prolonged presence in the bloodstream, facilitate controlled and sustained medication release at prescribed doses. Their nanoscale size enables efficient tissue penetration, cellular uptake, precise drug targeting, and reduced plasma fluctuations. Nanostructures, typically 1-10 µm in size, are absorbed by cells at a significantly higher rate compared to larger particles. This property enables them to

collaborate effectively in treating affected cells, yielding enhanced therapeutic outcomes with minimal to no adverse effects.[34,35]

Nanoparticles, pivotal in modern disease assays, excel in collecting information across clinical stages. Their key advantage lies in binding diverse proteins to their surfaces. Gold nanoparticles, for instance, serve as identifiers for tumors and biomarkers in biomolecule detection procedures, illustrating their significance in advancing clinical practices. When selecting nanoparticles for drug delivery, the physicochemical traits of pharmaceuticals are crucial. The combination of bioactive natural substances with nanoscience is gaining traction, particularly in delivering treatments for cancer and various ailments.[36,37]

When determining which nanoparticles to utilize for drug delivery, pharmaceuticals' physicochemical properties are meticulously evaluated. Nanotechnology's incorporation with bioactive natural substances is rapidly expanding, especially in delivering treatments for cancer and various illnesses. This approach offers multiple benefits in harnessing the unique properties of natural chemicals, including the induction of tumor-suppressive autophagy and their role as potent antimicrobial agents. The thorough research on these properties highlights the promising potential of combining nanomaterials with natural compounds for effective disease treatment. Synthetic polymers, including polyvinyl alcohol, poly-l-lactic acid, polyethylene glycol, and poly (lactic-co-glycolic acid), as well as natural polymers such as chitosan and alginate, are widely utilized in the process of nanoparticle nanofabrication for their excellent biocompatibility and biodegradability.[38,39,40]

Nanoparticles made of polymers, such as nanospheres and nanocapsules, serve as potent drug-delivery vehicles. Compact lipid nanostructures like liposomes and micelles, along with phospholipids, are equally valuable for precise and targeted medication administration.[41,42]

Choosing an optimal nano-drug delivery system hinges on the biophysical and biological characteristics of targeted medications. Despite concerns about nanoparticle toxicity in nanomedicine, recent trends emphasize their collaboration with natural compounds to mitigate such issues. Green chemistry, employed in drug-loaded nanoparticle synthesis, minimizes harmful components, reducing drug side effects. Additionally, enhancing bioactivity involves modifying the surface properties, hydrophobicity, size, and shape of these nanomaterials, offering a comprehensive approach to efficient and safe drug delivery systems.[43,44]

Nanotechnology presents numerous advantages in addressing chronic human ailments through precise, site-specific, and target-focused administration of pharmaceuticals. Nevertheless, the insufficiency of knowledge regarding nanostructure toxicity stands as a pivotal concern, necessitating further investigation to enhance efficacy while ensuring heightened safety for the secure practical deployment of these therapeutics.[45,46] Consequently, prudently formulating these nanoparticles holds the potential to mitigate issues linked to their utilization. In light of the aforementioned facts, this review strives to document diverse nanotechnology-driven drug delivery systems, the noteworthy applications of nanomedicines derived from natural compounds, as well as considerations on bioavailability, target control the flow of nano-drugs and their sites. Additionally, the exposition delves into the challenges entwined with nanomaterial utilization in medicinal contexts.[47,48]

The utilization of nanotechnology in medicine delivery systems

In the realm of therapeutic interventions, substantial advancements have transpired in the conveyance of medicinal agents or bioactive compounds derived from natural sources to specific anatomical sites, aiming to

ameliorate diverse maladies. While numerous drug delivery systems have demonstrated efficacy in recent epochs, persistent challenges necessitate resolution. The development of sophisticated technology is imperative to effectively navigate the intricacies of delivering pharmaceutical agents to designated targets. Consequently, scholarly inquiry is presently directed In the context of investigating nano-based drug delivery devices, envisaged to engender a refined paradigm in drug conveyance methodologies.[49,50]

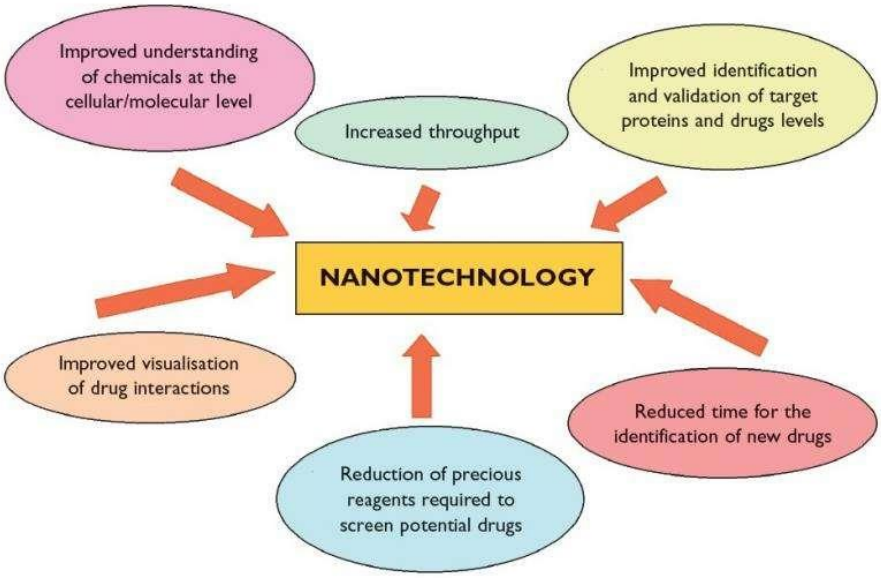

Figure 3. Nanotechnology in medicine delivery systems

Basics of approaches based on nanotechnology for drug design

Nanomedicine constitutes the medical discipline leveraging the principles of nanotechnology for the prevention and treatment of diverse maladies through the utilization of materials at the nanoscale, including biocompatible nanoparticles and nanorobots. Such applications encompass diagnostic, delivery, sensory, and actuation functions within living organisms.[51,52] Drugs characterized by minimal solubility present inherent biopharmaceutical challenges, encompassing restricted bio accessibility post-oral ingestion, diminished diffusion across outer membranes, elevated quantities requisite for intravenous administration, and undesirable antecedent effects preceding conventional vaccination processes. Nonetheless, these constraints can be surmounted through the employment of nanotechnological approaches within drug delivery mechanisms.[53,54]

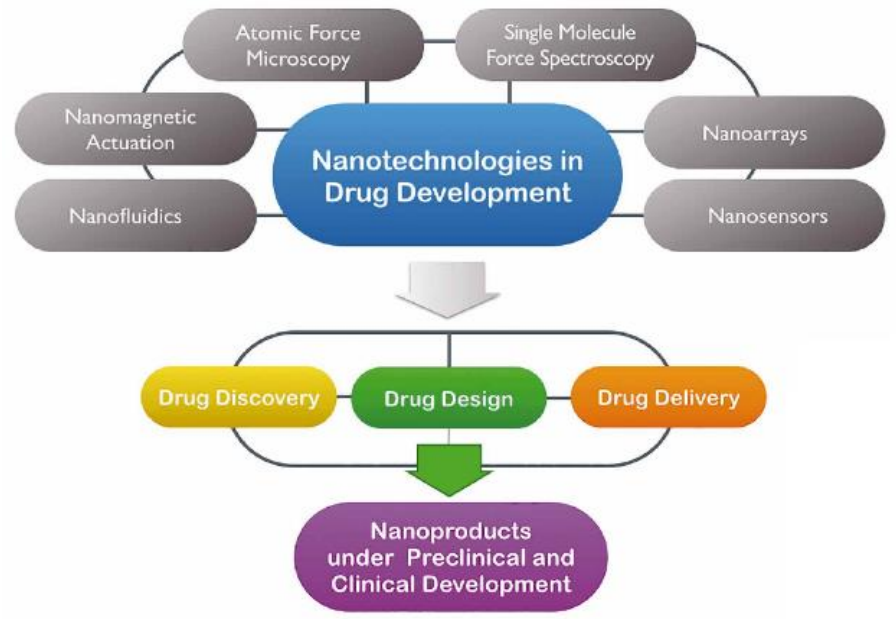

Figure 4. Nanotechnology for drug design

Nanoscale drug design has garnered significant attention in the field of nanoparticle applications because of its potential benefits, including tunable features like diffusivity, immunogenicity, solubility, drug release patterns, and bioavailability.[55] This could lead to improvements in and changes to the methods of administration, as well as decreased toxicity, minimized side effects, optimized biodistribution, and extended drug life cycle. Engineered drug delivery systems are made to release therapeutic compounds under regulated conditions at predetermined areas, or they are directed towards specified locations. They are formed through a process called self-assembly, in which basic building parts spontaneously come together to form well-defined shapes or patterns. These systems also need to overcome obstacles like the mononuclear phagocyte system's opsonization/sequestration.[56,57]

There are two distinct mechanisms by which pharmaceuticals are transported by nanostructures, namely passive delivery and self-delivery. The retention of pharmaceuticals within the inner hollow of the structure mostly arises from the hydrophobic effect. Due to the limited presence of the drug within the hydrophobic milieu, its release is characterized in a gradual and precise manner upon specific localization.[58] In contrast, self-delivery entails the incorporation of medications directly into the carrier nanostructure material, hence facilitating the delivery process. The temporal aspect has significant importance in this context, as the drug's efficacy diminishes when it prematurely dissociates from the carrier, hence impeding its delivery to the intended site. Nanomaterials or nanoformulations have the potential to serve as both active and passive mechanisms for medication delivery. An essential consideration pertains to the precise targeting of pharmaceutical agents.[59,60] To achieve active targeting, specific components of the drug delivery system are linked to the desired target site via binding molecules such as antibodies and peptides. The drug carrier complex exhibits mobility within the bloodstream and exhibits affinity towards the target site due to its inherent characteristics such as pH, temperature, molecular size, and shape.[61,62] Within the cellular framework, the primary focal points encompass receptors situated on cellular membranes, lipids present within cellular membranes, and antigens or proteins located on the surfaces of cells.[63]

Currently, the primary objective of nanotechnology-based medication delivery systems is the treatment of cancer. Nanomedicine has proven to be a significant asset in addressing the challenges associated with cancer treatment.[64]

Drug formulation, drug delivery method, and drug delivery process

The development of nanomedicine in conjunction with advancements in drug delivery technology and drug discovery/design has led to the creation of numerous therapeutic modalities. It has been investigated how well traditional clinical diagnostic methods work to increase medication specificity and diagnostic precision.[65,66] Among the improvements being investigated are novel techniques of administering medications that target specific anatomical regions to decrease toxicity and increase bioavailability within the body.[67]

Figure 5. drug formulation

Given this, the field of drug design seems to have great promise, underpinned by the identification of novel lead drugs informed by biological target knowledge. The intersection of computer sciences and experimental techniques for protein, peptide, and biological target categorization and purification is indispensable for sectoral growth.[68,69] Numerous studies and reviews in this domain underscore the rational design of diverse molecules, emphasizing the imperative examination of distinct drug release mechanisms. Additionally, natural products offer pragmatic solutions to surmount challenges in drug design, serving as inspirational sources for discovering compounds that have the appropriate physicochemical characteristics.[70,71]

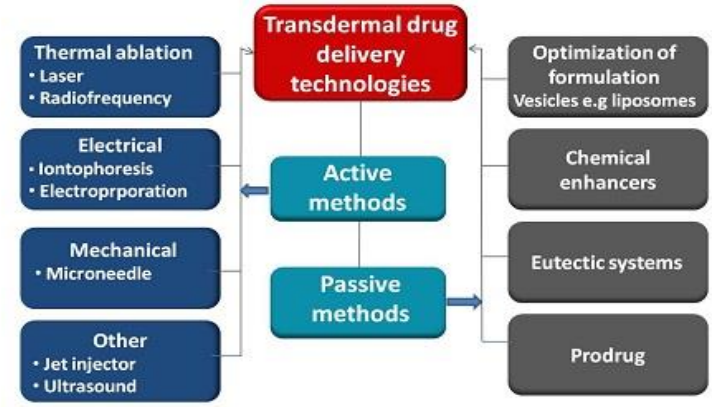

Figure 6. Drug delivery methods

At the same time, medication delivery technologies have become increasingly important in the last few years. These systems are easy to create and help the body release active chemicals in a controlled manner. Notably, nanocarriers designed for imaging and sensory applications have been investigated for their therapeutic effects. A summary of the many uses for nanocarriers in nanomedicine is accompanied by discussions on emerging opportunities and challenges in this sector.[72,73]

Each drug delivery system has unique chemical, physical, and morphological characteristics that lead to different affinities for medications with different polarity. Chemical interactions, such as hydrogen and covalent bonds, as well as physical interactions, like electrostatic and van der Waals interactions, determine these affinities. In a study published in the year, Mattos et al. demonstrated that the release profile of biogenic silica nanoparticles grafted with neem bark extract showed a lower release rate due to chemical interactions than biogenic silica nanoparticles loaded with neem bark extract. A combination of these factors affects the release kinetics of active chemicals within the organism as well as the interactions between nanocarriers and biological systems.[74,75]

Furthermore, Researchers have created lipid shells that are cross-linkable and contain prototypical drugs like docetaxel and wortmannin to control drug discharge kinetics. This meticulous investigation extends to in vitro and in vivo settings, offering a thorough comprehension of the discharge profile. Parameters like nanocarrier composition (organic, inorganic, hybrid materials) and how drugs associate with them (e.g., core–shell or matrix systems) are pivotal in elucidating drug delivery profiles. Several studies have explored release mechanisms Many facets of nanocarriers, including diffusion, solvent impacts, chemical responses, and stimulus-controlled release, are examined in a thorough investigation. Concerning controlled-release systems, this review focuses particularly on polymeric nanocarriers.[76,77,78]

Technologies such as polymers, natural polysaccharides, antibodies, cell membranes, tunable surfactants, and peptides are being used to coat or chemically functionalize nanostructures to increase their selectivity for specified organ areas and decrease their immunogenicity. This is true despite the wide range of nanocarrier

types and drug release characteristics. In some circumstances, such as when a medication has low affinity for a target or crosses barriers like the blood-brain or blood-cerebrospinal fluid barrier, ligand-modified nanocarriers have been employed to breach cell membranes and enable targeted drug administration.[79,80] For example, hyaluronic acid has been shown to have anticancer activity against cells that mimic melanoma stem cells, breast cancer cells, and cells that induce lung adenocarcinoma when added as a ligand to various nanocarriers. Additionally, it has been demonstrated to reduce protein corona immunogenicity and facilitate intravitreal medication administration for retinal gene therapy. However, developing ligand-appended drug delivery systems is a labor-intensive process that necessitates carefully targeted designs that include physiological aspects such as blood flow, disease status, and tissue architecture.[81,82] Only a little amount of research has been done on the relationship between ligand-appended nanocarriers and cell membranes, and the uptake mechanisms are yet unknown. It is commonly recognized that the uptake of nanoparticles occurs via either phagocytic or non-phagocytic mechanisms (such as clathrinid- or caveolae-mediated endocytosis). It has been challenging to standardize the mechanism of action and interactions of these systems in cells, nevertheless, because each of these pathways has unique physicochemical characteristics.[83,84,85]

Stimulus-responsive nanocarriers also show the capacity to modify drug release profiles in reaction to external stimuli. This flexible feature enhances the precision and management of drug delivery systems, paving the way for tailored therapeutic interventions. Numerous extrinsic stimuli, including heat, magnetism, light, pH, and ionic strength, can enhance targeting accuracy and enable accurate dosage management. It's interesting to note that when used in conjunction with lipids or polymeric nanocarriers, superparamagnetic iron oxide nanoparticles can initiate a controlled release system by applying an external magnetic field.[86,87] Ulbrich and colleagues carried out a comprehensive examination of recent advancements in drug delivery systems, particularly those that employ polymeric and magnetic nanoparticles. They also looked at how drugs with or without covalent bonds might affect how cancer is treated. Polymer nanoparticles, synthesized for utilization in Chemo-photothermal treatment triggered by near-infrared (NIR) radiation., represent a notable development.[88,89] Hybrid nanocarriers currently stand as highly promising entities in nanomedicine, amalgamating diverse system properties into a singular framework, thereby ensuring heightened performance for theragnostic systems, which are used for both therapeutic and diagnostic purposes. Nonetheless, the many ways in which drugs function and their toxicity remain relatively elusive, warranting further comprehensive investigations.[90,91] Furthermore, a surge in studies emphasizes the creation of nanocarriers by using microbes and plant extracts in chemical reactions that are safe for the environment, signaling an expanding avenue for exploration.[92]

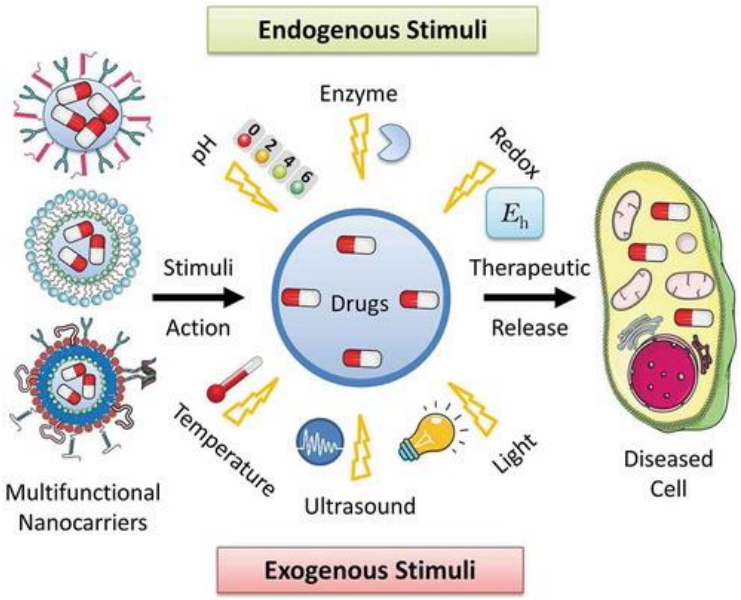

Figure 7. Stimulus-responsive nanocarriers

The future of medication delivery systems and nanoparticles

The field of nanoparticle science currently stands as one of the most captivating domains of research. Cancer emerges as a paradigmatic illustration wherein the use of nonmedical technologies has helped in both diagnosis and therapy. By employing various types of nanoparticles to deliver therapeutically relevant quantities to impacted cells—such as cancer or tumor cells—while maintaining the physiological homeostasis of healthy cells, the field of nanomedicine and nano-drug delivery systems indicates the direction that research and development will follow for many years to come.[93,94]

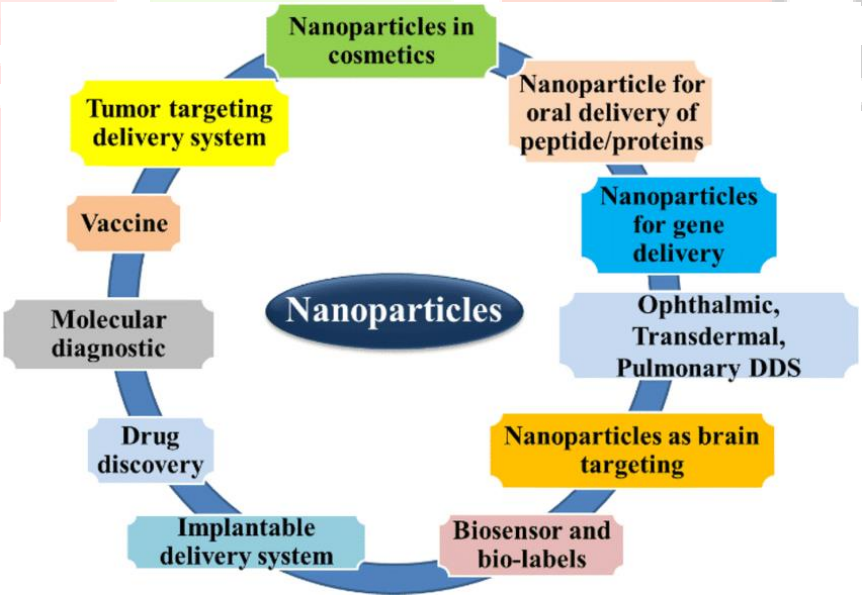

Figure 8. future of nanoparticle

The representative examples of nanoparticles discussed in these letters vary in size; some are truly measured in nanometres, whereas others are measured in sub-micrometres (more than 100 nm). An important area of study to be explored is materials with improved homogeneity combined with improved drug loading and release capabilities.[95,96] Significant progress has been achieved in the application of metal-based nanoparticles for diagnostic purposes, a topic covered in detail in this study. The use of metals—such as gold and silver—

in therapeutic and diagnostic settings is a field of study that seems to have potential for future use of nanoparticles. One notable exuberance in this direction is to gold nanoparticles, which demonstrate significant absorption in soft tumor tissues, rendering tumors susceptible to radiation-induced heat therapy for selective eradication.[97,98]

Although much is known about the potential of nanoparticles and nano-drug delivery systems, there is still very little concrete evidence of their application in healthcare systems, especially in the treatment and diagnosis of cancer. This limitation is because the discipline is still in its infancy, having just produced two decades' worth of substantial study, and there are still many fundamental characteristics that are unknown.[99,100] Finding basic markers in sick tissues—including critical biological markers that enable accurate targeting without interfering with regular cellular functions—will be a focus of future study. In the end, the development of nanoparticle applications will progress in tandem with our growing understanding of diseases at the molecular level, or those that reflect a marker identification that is comparable to the size of a nanomaterial subcellular, thereby providing opportunities for new approaches to diagnosis and treatment.[101,102] Thus, future advancements in nanomedicine applications will be fuelled by a deeper comprehension of molecular disease markers. Beyond the boundaries described in this study, which includes well-known nanoprobes and nano theragnostic products, more research is expected to be of utmost importance for the widespread use of nanoparticles.[103,104]

The idea of releasing certain medications under controlled conditions at disease sites, the technology infrastructure for assessing these occurrences, the effects of pharmaceuticals at the tissue/cellular level, and theoretical mathematical models for forecasting are still not fully developed.[105,106] Many studies in the field of nanoparticles focus on formulation and biomaterials, which are the first steps toward biomedical applications. Multidisciplinary research projects and animal studies will yield valuable data regarding possible uses in drug therapies and diagnostic tests, requiring significant time and resource investments in research. The future of nanomedicine and nano-drug delivery technology is envisioned as being more intelligent and multi-cantered, in line with the worldwide trend towards precision medicine and diagnosis.[107,108]

The idea of developing nanorobots and nanodevices that operate in tissue diagnosis and repair processes with complete external control mechanisms is met with a great deal of enthusiasm. This imagined future, though, is still theoretical and just reflects prospective research projects that humanity may be able to achieve very soon. While nanoparticles are expected to have many advantages, there is also a risk that could affect human health and the environment at large. For this reason, extensive research is needed before using nanoparticles.[109,110] Therefore, a detailed assessment of the potential short- or long-term harmful consequences of new nanomaterials on people and the environment needs to be done. With the increasing prominence of nanoparticles, the cost aspect becomes a new study focus that calls for increased research contributions. Lastly, as previously discussed in the section above, the regulatory framework about nanoparticles will continue to change in tandem with advancements in the uses of these particles.[111,112]

Conclusion

This review encompasses an examination of works about the use of nanoparticles in the fields of drug delivery and diagnostics. A range of nano-scale materials, such as nanorobots and nano sensors, have the potential to be employed in biological systems for purposes such as precise diagnostics, targeted delivery, sensing, or activation. Nanotechnology has been useful in enhancing various aspects of medicine, including solubility, absorption, bioavailability, and controlled release.

Polymeric nano capsules and nanospheres have garnered significant attention due to their production through solvent evaporation, emulsion polymerization, and surfactant-free polymerization. In recent years, there has been a growing interest in theragnostic nanomedicine, a field that combines therapeutic and diagnostic approaches. This interdisciplinary approach has particularly gained attention in the context of cancer research, serving as a model disease for studying the potential applications of theragnostic nanomedicine. Examples of academic research include the utilization of oleic acid-coated iron oxide nanoparticles for near-infrared diagnostics, the application of alginate and folic acid-based chitosan nanoparticles for photodynamic detection of colorectal cancer, the development of fluorogenic peptide probes conjugated to glycol nanoparticles for studying metastatic processes, the use of iron oxide-coated hyaluronic acid as a biopolymeric material in cancer therapy, and the investigation of dextran as a pot.

The prevalence of FDA-approved nanotechnology products and the number of clinical trials conducted have experienced a significant increase since the 1990s. Various types of drug delivery systems are employed in conjunction with pharmaceuticals or biologics, including synthetic polymer particles, liposome formulations, micellar nanoparticles, protein nanoparticles, nanocrystals, and other such entities. The field of nanomedicine has significantly transformed the landscape of biological drug research and delivery, even in the face of ongoing developments in regulatory frameworks and the assessment of safety and toxicity. The field of nanomedicine has made significant advancements in the integration of sickness diagnosis and therapy.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015; 65:5–29.
2. American Cancer Society. Cancer facts and figures 2017. Genes Dev 2017; 21:2525–38.
3. Chabner BA, Roberts TG. Timeline: chemotherapy and the war on cancer. Nat Rev Cancer 2005; 5:65–72.
4. DeVita VT, Chu E. A history of cancer chemotherapy. Cancer Res 2008;68:8643–53.
5. Zhang W, Zhang Z, Zhang Y. The application of carbon nanotubes in target drug delivery systems for cancer therapies. Nanoscale Res Lett 2011; 6:555.
6. Ahmad SS, Reinius MA, Hatcher HM, Ajithkumar TV. Anticancer chemotherapy in teenagers and young adults: managing long term side effects. BMJ 2016;354:i4567.
7. Gillet J, Gottesman MM. In: Multi-drug resistance in cancer. Totowa, NJ: Humana Press; 2010.
8. Alfarouk KO, Stock C-M, Taylor S, Walsh M, Muddathir AK, Verduzco D, et al. Resistance to cancer chemotherapy: failure in drug response from ADME to Pgp. Cancer Cell Int 2015; 15:71.

9. Ahangirian H, Lemraski EG, Webster TJ, Rafiee-Moghaddam R, Abdol- lahi Y. A review of drug delivery systems based on nanotechnology and green chemistry: green nanomedicine. Int J Nanomed. 2017;12:2957.
10. Liu Z, Tabakman S, Welsher K, Dai H. Carbon nanotubes in biology and medicine: in vitro and in vivo detection, imaging and drug delivery. Nano Res. 2009;2:85–120.
11. Orive G, Gascon AR, Hernández RM, Domínguez-Gil A, Pedraz JL. Techniques: new approaches to the delivery of biopharmaceuticals. Trends Pharmacol Sci. 2004;25:382–7.
12. Razzacki SZ, Thwar PK, Yang M, Ugaz VM, Burns MA. Integrated microsystems for controlled drug delivery. Adv Drug Deliv Rev. 2004; 56:185–98.
13. Arayne MS, Sultana N, Qureshi F. nanoparticles in delivery of cardiovascular drugs. Pak J Pharm Sci. 2007; 20:340–8.
14. Patra JK, Baek K-H. Green nanobiotechnology: factors affecting synthesis and characterization techniques. J Nanometre. 2014; 2014:219.
15. Joseph RR, Venkatraman SS. Drug delivery to the eye: what benefits do nanocarriers offer? Nanomedicine. 2017; 12:683–702.
16. Mirza AZ, Siddiqui FA. Nanomedicine and drug delivery: a mini-review. Int Nano Lett. 2014; 4:94.
17. Rudramurthy GR, Swamy MK, Sinniah UR, Ghasemzadeh A. Nanoparticles: alternatives against drug-resistant pathogenic microbes. Molecules. 2016; 21:836.
18. Lam P-L, Wong W-Y, Bian Z, Chui C-H, Gambari R. Recent advances in green nanoparticulate systems for drug delivery: efficient delivery and safety concern. Nanomedicine. 2017; 12:357–85.
19. Haba Y, Kojima C, Harada A, Ura T, Horinaka H, Kono K. Preparation of poly (ethylene glycol) -modified poly (amido amine) dendrimers endcap- simulating gold nanoparticles and their heat-generating ability. Langmuir. 2007;23:5243–6.
20. Shi X, Sun K, Baker JR Jr. Spontaneous formation of functionalized den- drimer-stabilized gold nanoparticles. J Phys Chem C. 2008; 112:8251–8.
21. Park S-H, Oh S-G, Mun J-Y, Han S-S. Loading of gold nanoparticles inside the DPPC bilayers of liposome and their effects on membrane fluidities. Coll Surf B. 2006;48:112–8.
22. de Villiers MM, Aramwit P, Kwon GS. Nanotechnology in drug delivery. New York: Springer; 2008.
23. Kabanov AV, Lemieux P, Vinogradov S, Alakhov V. Pluronic® block copolymers: novel functional molecules for gene therapy. Adv Drug Deliv Rev. 2002; 54:223–33.
24. Wang N, Feng Y. Elaborating the role of natural products-induced autophagy in cancer treatment: achievements and artifacts in the state of the art. BioMed Res Int. 2015;2015:934207.
25. Ouattara B, Simard RE, Holley RA. Piette GJ-P, Bégin A: Antibacterial activity of selected fatty acids and essential oils against six meat spoilage organisms. Int J Food Microbiol. 1997;37:155–62.
26. Sharma G, Raturi K, Dang S, Gupta S, Gabrani R. Combinatorial antimicrobial effect of curcumin with selected phytochemicals on *Staphylococcus epidermidis*. J Asian Nat Prod Res. 2014;16:535–41.

27. Abdelwahab SI, Sheikh BY, Taha MME, How CW, Abdullah R, Yagoub U, El-Sunousi R, Eid EE. Thymoquinone-loaded nanostructured lipid carriers: preparation, gastroprotection, in vitro toxicity, and pharmacokinetic properties after extravascular administration. Int J Nanomed. 2013; 8:2163.
28. Krauel K, Pitaksuteepong T, Davies NM, Rades T. Entrapment of bioactive molecules in poly (alkyl cyanoacrylate) nanoparticles. Am J Drug Deliv. 2004; 2:251–9.
29. Tan Q, Liu W, Guo C, Zhai G. Preparation and evaluation of quercetin-loaded lecithin-chitosan nanoparticles for topical delivery. Int J Nanomed. 2011; 6:1621.
30. Sanna V, Roggio AM, Siliani S, Piccinini M, Marceddu S, Mariani A, Sechi M. Development of novel cationic chitosan-and anionic alginate– coated poly (d, l-lactide-co-glycolide) nanoparticles for controlled release and light protection of resveratrol. Int J Nanomed. 2012; 7:5501.
31. Casettari L, Illum L. Chitosan in nasal delivery systems for therapeutic drugs. J Control Release. 2014; 190:189–200.
32. Obeid MA, Al Qaraghuli MM, Alsaadi M, Alzahrani AR, Niwasabutra K, Ferro VA. Delivering natural products and biotherapeutics to improve drug efficacy. Ther Deliv. 2017; 8:947–56.
33. Miele E, Spinelli GP, Miele E, Di Fabrizio E, Ferretti E, Tomao S, Gulino A. Nanoparticle-based delivery of small interfering RNA: challenges for cancer therapy. Int J Nanomed. 2012; 7:3637.
34. McNamara K, Tofail SA. Nanosystems: the use of nanoalloys, metallic, bimetallic, and magnetic nanoparticles in biomedical applications. Phys Chem Chem Phys. 2015; 17:27981–95.
35. Saadeh Y, Vyas D. Nanorobotic applications in medicine: current proposals and designs. Am J Robot Surg. 2014; 1:4–11.
36. Oliveira ON Jr, Iost RM, Siqueira JR Jr, Crespilho FN, Caseli L. Nanomaterials for diagnosis: challenges and applications in smart devices based on molecular recognition. ACS Appl Mater Interfaces. 2014; 6:14745–66.
37. De Jong WH, Borm PJ. Drug delivery and nanoparticles: applications and hazards. Int J Nanomed. 2008; 3:133.
38. Holzinger M, Le Goff A, Cosnier S. Nanomaterials for biosensing applications: a review. Front Chem. 2014; 2:63.
39. Golovin YI, Gribanovsky SL, Golovin DY, Klyachko NL, Majouga AG, Master AM, Sokolsky M, Kabanov AV. Towards nanomedicines of the future: remote magneto-mechanical actuation of nanomedicines by alternating magnetic fields. J Control Release. 2015; 219:43–60.
40. Lu H, Wang J, Wang T, Zhong J, Bao Y, Hao H. Recent progress on nanostructures for drug delivery applications. J Nanomater. 2016; 2016:20.
41. Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. Nat Biotechnol. 2015; 33:941.
42. Kumari A, Kumar V, Yadav S. Nanotechnology: a tool to enhance therapeutic values of natural plant products. Trends Med Res. 2012; 7:34–42.
43. Chen F, Ehlerding EB, Cai W. Theranostic nanoparticles. J Nucl Med. 2014; 55:1919–22.

44. Swierczewska M, Han H, Kim K, Park J, Lee S. Polysaccharide-based nanoparticles for theragnostic nanomedicine. Adv Drug Deliv Rev. 2016; 99:70–84.
45. Chen K, Chen X. Design and development of molecular imaging probes. Curr Top Med Chem. 2010; 10:1227–36.
46. Yhee JY, Son S, Kim SH, Park K, Choi K, Kwon IC. Self-assembled glycol chitosan nanoparticles for disease-specific theranostics. J Control Release. 2014;193:202–13.
47. Lee C-M, Jang D, Kim J, Cheong S-J, Kim E-M, Jeong M-H, Kim S-H, Kim DW, Lim ST, Sohn M-H, et al. Oleyl-Chitosan nanoparticles based on a dual probe for Optical/MR imaging in vivo. Bioconjug Chem. 2011; 22:186–92.
48. Yang S-J, Lin F-H, Tsai H-M, Lin C-F, Chin H-C, Wong J-M, Shieh M-J. Alginate-folic acid-modified chitosan nanoparticles for photodynamic detection of intestinal neoplasms. Biomaterials. 2011; 32:2174–82.
49. Ryu JH, Na JH, Ko HK, You DG, Park S, Jun E, Yeom HJ, Seo DH, Park JH, Jeong SY. Noninvasive optical imaging of cathepsin B with activatable fluorogenic nanoprobes in various metastatic models. Biomaterials. 2014; 35:2302–11.
50. Lapčík L, Lapcik L, De Smedt S, Demeester J, Chabrecek P. Hyaluro-nan preparation, structure, properties, and applications. Chem Rev. 1998; 98:2663–84.
51. Kim H, Kim Y, Kim I-H, Kim K, Choi Y. ROS-responsive activatable photosensitizing agent for imaging and photodynamic therapy of activated macrophages. Theranostics. 2014;4:1.
52. Choi KY, Chung H, Min KH, Yoon HY, Kim K, Park JH, Kwon IC, Jeong SY. Self-assembled hyaluronic acid nanoparticles for active tumor targeting. Biomaterials. 2010; 31:106–14.
53. Kamat M, El-Boubbou K, Zhu DC, Lansdell T, Lu X, Li W, Huang X. Hyaluronic acid immobilized magnetic nanoparticles for active targeting and imaging of macrophages. Bioconjug Chem. 2010; 21:2128–35.
54. Arpicco S, Lerda C, Dalla Pozza E, Costanzo C, Tsapis N, Stella B, Donadelli M, Dando I, Fattal E, Cattel L. Hyaluronic acid-coated liposomes for active targeting of gemcitabine. Eur J Pharm Biopharm.2013;85:373–80.
55. Wang G, Gao S, Tian R, Miller-Kleinhenz J, Qin Z, Liu T, Li L, Zhang F, Ma Q, Zhu L. Theranostic hyaluronic acid-iron micellar nanoparticles for magnetic field enhanced in vivo cancer chemotherapy. ChemMed- Chem. 2018; 13:78–86.
56. Choi KY, Jeon EJ, Yoon HY, Lee BS, Na JH, Min KH, Kim SY, Myung S-J, Lee S, Chen X. Theranostic nanoparticles based on PEGylated hyaluronic acid for the diagnosis, therapy, and monitoring of colon cancer. Biomaterials. 2012; 33:6186–93.
57. Gombotz WR, Wee S. Protein release from alginate matrices. Adv Drug Deliv Rev. 1998; 31:267–85.
58. Lee KY, Mooney DJ. Alginate: properties and biomedical applications. Prog Polym Sci. 2012; 37:106–26.

59. Baghbani F, Moztarzadeh F, Mohandesi JA, Yazdian F, Mokhtari-Dizaji M. Novel alginate stabilized doxorubicin-loaded nanodroplets for ultrasonic theranostics of breast cancer. Int J Biol Macromol. 2016; 93:512–9.
60. Podgórna K, Szczepanowicz K, Piotrowski M, Gajdosova M, Stepanek F, Warszyński P. Gadolinium alginate nano gels for theragnostic applications. Coll Surf B. 2017; 153:183–9.
61. Moscovici M. Present and future medical applications of microbial exopolysaccharides. Front Microbiol. 1012; 2015:6.
62. Ding Z, Liu P, Hu D, Sheng Z, Yi H, Gao G, Wu Y, Zhang P, Ling S, Cai L. Redox-responsive dextran based theragnostic nanoparticles for near-infrared/magnetic resonance imaging and magnetically targeted photodynamic therapy. Biomater Sci. 2017;5:762–71.
63. Hong S-P, Kang SH, Kim DK, Kang BS. Paramagnetic nanoparticle-based targeting theranostic agent for c6 rat glioma cell. J Nanomater. 2016; 2016:7617894.
64. Mignani S, El Kazzouli S, Bousmina M, Majoral JP. Expand classical drug administration ways by emerging routes using dendrimer drug delivery systems: a concise overview. Adv Drug Deliv Rev. 2013; 65:1316–30.
65. Lounnas V, Ritschel T, Kelder J, McGuire R, Bywater RP, Foloppe N. Current progress in structure-based rational drug design marks a new mindset in drug discovery. Comput Struc Biotechnol J. 2013;5: e201302011.
66. Mavromoustakos T, Durdagi S, Koukoulitsa C, Simcic M, Papadopoulos M, Hodoscek M, Golic Grdadolnik S. Strategies in the rational drug design. Curr Med Chem. 2011; 18:2517–30.
67. Wong PT, Choi SK. Mechanisms of drug release in nanotherapeutic delivery systems. Chem Rev. 2015; 115:3388–432.
68. Prachayasittikul V, Worachartcheewan A, Shoombuatong W, Song tawee N, Simeon S, Prachayasittikul V, Nantasenamat C. Computer-aided drug design of bioactive natural products. Curr Top Med Chem. 2015; 15:1780–800.
69. Chen G, Roy I, Yang C, Prasad PN. Nanochemistry and nanomedicine for nanoparticle-based diagnostics and therapy. Chem Rev. 2016; 116:2826 85.
70. Pelaz B, Alexiou C, Alvarez-Puebla RA, Alves F, Andrews AM, Ashraf S, Balogh LP, Ballerini L, Bestetti A, Brendel C, Bosi S. Diverse applications of nanomedicine. ACS Nano. 2017; 11:2313–81.
71. Mattos BD, Rojas OJ, Magalhaes WLE. Biogenic silica nanoparticles loaded with neem bark extract as a green, slow-release biocide. J Clean Prod. 2017; 142:4206–13.
72. Kinnear C, Moore TL, Rodriguez-Lorenzo L, Rothen-Rutishauser B, Petri- Fink A. Form follows function: nanoparticle shape and its implications for nanomedicine. Chem Rev. 2017; 117:11476–521.
73. Sethi M, Sukumar R, Karve S, Werner ME, Wang EC, Moore DT, Kowalczyk SR, Zhang L, Wang AZ. Effect of drug release kinetics on nanoparticle therapeutic efficacy and toxicity. Nanoscale. 2014; 6:2321–7.

74. Mattos BD, Tardy BL, Magalhaes WLE, Rojas OJ. Controlled release for crop and wood protection: recent progress toward sustainable and safe nanostructured biocidal systems. J Control Release. 2017; 262:139–50.
75. Siepmann F, Herrmann S, Winter G, Siepmann J. A novel mathematical model quantifying drug release from lipid implants. J Control Release. 2008;128:233–40.
76. Ding CZ, Li ZB. A review of drug release mechanisms from nanocarrier systems. Mater Sci Eng. 2017; 76:1440–53.
77. Lee JH, Yeo Y. Controlled drug release from pharmaceutical nanocarriers. Chem Eng Sci. 2015; 125:75–84.
78. Kamaly N, Yameen B, Wu J, Farokhzad OC. Degradable controlled- release polymers and polymeric nanoparticles: mechanisms of controlling drug release. Chem Rev. 2016; 116:2602–63.
79. Torchilin VP. Multifunctional nanocarriers. Adv Drug Deliv Rev. 2012; 64:302–15.
80. Pelaz B, del Pino P, Maffre P, Hartmann R, Gallego M, Rivera-Fernandez S, de la Fuente JM, Nienhaus GU, Parak WJ. Surface functionalization of nanoparticles with polyethylene glycol: effects on protein adsorption and cellular uptake. ACS Nano. 2015; 9:6996–7008.
81. Almalik A, Benabdelkamel H, Masood A, Alanazi IO, Alradwan I, Majrashi MA, Alfadda AA, Alghamdi WM, Alrabiah H, Tirelli N, Alhasan AH. Hyaluronic acid-coated chitosan nanoparticles reduced the immunogenicity of the formed protein corona. Sci Rep. 2017; 7:10542.
82. Martens TF, Remaut K, Deschout H, Engbersen JFJ, Hennink WE, van Steenbergen MJ, Demeester J, De Smedt SC, Braeckmans K. Coating nanocarriers with hyaluronic acid facilitates intravitreal drug delivery for retinal gene therapy. J Control Release. 2015; 202:83–92.
83. Kolhar P, Anselmo AC, Gupta V, Pant K, Prabhakarpandian B, Ruo- Lahti E, Mitragotri S. Using shape effects to target antibody-coated nanoparticles to lung and brain endothelium. Proc Natl Acad Sci USA. 2013; 110:10753–8.
84. Gao WW, Zhang LF. Coating nanoparticles with cell membranes for targeted drug delivery. J Drug Target. 2015; 23:619–26.
85. Muller J, Bauer KN, Propeller D, Simon J, Mailander V, Wurm FR, Winzen S, Landfester K. Coating nanoparticles with tunable surfactants facilitates control over the protein corona. Biomaterials. 2017; 115:1–8.
86. Gao H, Yang Z, Zhang S, Cao S, Shen S, Pang Z, Jiang X. Ligand-modified nanoparticles increase cell uptake, alter endocytosis, and elevate glioma distribution and internalization. Sci Rep. 2013; 3:2534.
87. Jain A, Jain SK. Ligand-appended BBB-targeted nanocarriers (LABTNs). Crit Rev Ther Drug Carrier Syst. 2015; 32:149–80.
88. Shen HX, Shi SJ, Zhang ZR, Gong T, Sun X. Coating solid lipid nano particles with hyaluronic acid enhances antitumor activity against melanoma stem-like cells. Theranostics. 2015; 5:755–71.
89. Gao X, Zhang J, Xu Q, Huang Z, Wang YY, Shen Q. Hyaluronic acid-coated cationic nanostructured lipid carriers for oral vincristine sulfate delivery. Drug Dev Ind Pharm. 2017; 43:661–7.

90. Wang T, Hou JH, Su C, Zhao L, Shi YJ. Hyaluronic acid-coated chitosan nanoparticles induce ROS-mediated tumor cell apoptosis and enhance antitumor efficiency by targeted drug delivery via CD44. J Nanobiotechnology. 2017; 15:7.
91. Muro S. Challenges in design and characterization of ligand-targeted drug delivery systems. J Control Release. 2012; 164:125–37.
92. Kou L, Sun J, Zhai Y, He Z. The endocytosis and intracellular fate of nanomedicines: implication for rational design. Asian J Pharm Sci. 2013; 8:1–10.
93. Li Z, Zhang Y, Zhu D, Li S, Yu X, Zhao Y, Ouyang X, Xie Z, Li L. Transporting carriers for intracellular targeting delivery via nonendocytic uptake pathways. Drug delivery. 2017; 24:45–55.
94. Salatin S, Yari Khosroushahi A. Overviews on the cellular uptake mechanism of polysaccharide colloidal nanoparticles. J Cell Mol Med. 2017; 21:1668–86.
95. Anirudhan TS, Nair AS. Temperature and ultrasound sensitive gatekeepers for the controlled release of chemotherapeutic drugs from mesoporous silica nanoparticles. J Mater Chem B. 2018; 6:428–39.
96. Al-Ahmady Z, Kostarelos K. Chemical components for the design of temperature-responsive vesicles as cancer therapeutics. Chem Rev. 2016; 116:3883–918.
97. Bai Y, Xie FY, Tian W. Controlled self-assembly of thermo-responsive amphiphilic h-shaped polymer for adjustable drug release. Chin J Polym Sci. 2018; 36:406–16.
98. Zhang Z, Zhang D, Wei L, Wang X, Xu YL, Li HW, Ma M, Chen B, Xiao LH. Temperature-responsive fluorescent polymer nanoparticles (TRFNPs) for cellular imaging and controlled release of drugs to living cells. Coll Surf B. 2017; 159:905–12.
99. Guo Y, Zhang Y, Ma J, Li Q, Li Y, Zhou X, Zhao D, Song H, Chen Q, Zhu X. Light/magnetic hyperthermia triggered drug released from multi-functional thermo-sensitive magneto liposomes for precise cancer synergetic theranostics. J Control Release. 2017; 272:145–58.
100. Hervault A, Thanh NT. Magnetic nanoparticle-based therapeutic agents for thermo-chemotherapy treatment of cancer. Nanoscale. 2014; 6:11553–73.
101. Mathiyazhakan M, Wiraja C, Xu CJ: A Concise Review of Gold Nanoparticles-Based Photo-Responsive Liposomes for Controlled Drug Delivery. *Nano-Micro Letters* 2018, 10.
102. Xu L, Qiu LZ, Sheng Y, Sun YX, Deng LH, Li XQ, Bradley M, Zhang R. Biodegradable pH-responsive hydrogels for controlled dual-drug release. J Mater Chem B. 2018; 6:510–7.
103. Ma GL, Lin WF, Yuan ZF, Wu J, Qian HF, Xua LB, Chen SF. Development of ionic strength /pH /enzyme triple-responsive zwitterionic hydrogel of the mixed l-glutamic acid and l-lysine polypeptide for site-specific drug delivery. J Mater Chem B. 2017; 5:935–43.
104. Grillo R, Gallo J, Stroppa DG, Carbo-Argibay E, Lima R, Fraceto LF, Banobre-Lopez M. Sub-micrometer magnetic nanocomposites: insights into the effect of magnetic nanoparticles interactions on the optimization of SAR and MRI performance. Acs Appl Mater Interfaces. 2016; 8:25777–87.
105. Alonso J, Khurshid H, Devkota J, Nemati Z, Khadka NK, Srikanth H, Pan JJ, Phan MH. Superparamagnetic nanoparticles encapsulated in lipid vesicles for advanced magnetic hyperthermia and biodetection. J Appl Phys. 2016; 119:083904.

106. Ulbrich K, Hola K, Subr V, Bakandritsos A, Tucek J, Zboril R. Targeted drug delivery with polymers and magnetic nanoparticles: covalent and noncovalent approaches, release control, and clinical studies. Chem Rev. 2016; 116:5338–431.

107. Chen CW, Syu WJ, Huang TC, Lee YC, Hsiao JK, Huang KY, Yu HP, Liao MY, Lai PS. Encapsulation of Au/Fe3O4 nanoparticles into a polymer nanoarchitecture with combined near-infrared-triggered chemo-photothermal therapy based on intracellular secondary protein understanding. J Mater Chem B. 2017; 5:5774–82.

108. Portero A, Remunan-Lopez C, Criado M, Alonso M. Reacetylated chitosan microspheres for controlled delivery of antimicrobial agents to the gastric mucosa. J Microencapsul. 2002; 19:797–809.

109. Artursson P, Lindmark T, Davis SS, Illum L. Effect of chitosan on the permeability of monolayers of intestinal epithelial cells (Caco-2). Pharm Res. 1994; 11:1358–61.

110. Fernandez-Urrusuno R, Calvo P, Remuan-López C, Vila-Jato JL, Alonso MJ. Enhancement of nasal absorption of insulin using chitosan nanoparticles. Pharm Res. 1999; 16:1576–81.

111. De Campos AM, Sánchez A, Alonso MJ. Chitosan nanoparticles: a new vehicle for the improvement of the delivery of drugs to the ocular surface. Application to cyclosporin A. Int J Pharm. 2001; 224:159–68.

112. Al-Qadi S, Grenha A, Carrión-Recio D, Seijo B, Remunan-Lopez C. Microencapsulated chitosan nanoparticles for pulmonary protein delivery: in vivo evaluation of insulin-loaded formulations. J Control Release. 2012; 157:383–90.