Nano and Medical Materials 2023, 3(1), 121.
https://doi.org/10.59400/nmm.v3i1.121

Review

Recent advances and future challenges of nano-based drug delivery systems

Nazish Jahan*, Noor Ul Huda, Arooj Fatima, Huma Shamshad

Department of Chemistry, University of Agriculture, Faisalabad 38000, Pakistan
*** Corresponding author:** Nazish Jahan, nazishjahan@uaf.edu.pk

CITATION

Jahan N, Huda NU, Fatima A, Shamshad H. Recent advances and future challenges of nano-based drug delivery systems. Nano and Medical Materials. 2023; 3(1): 121. https://doi.org/10.59400/nmm.v3i1.121

ARTICLE INFO

Received: 11 July 2023
Accepted: 8 September 2023
Available online: 17 September 2023

Abstract: Nanomedicine and nano-delivery systems constitute an emerging and swiftly progressing discipline, employing nanoscale materials for diagnostic tools and targeted, controlled administration of therapeutic agents. Nanotechnology offers substantial advantages for treating chronic ailments, facilitating precise, site-specific delivery of therapeutic agents. Recent applications encompass a diverse array of nanomedicine implementations, including chemotherapeutic, biological, and immunotherapeutic agents, for treating diverse medical conditions. This comprehensive review provides an updated summary of recent strides in the realm of nanomedicines and nano-based drug delivery systems. It critically examines the utilization of nanomaterials to enhance the effectiveness of both novel and established drugs (e.g., natural products) and to enable selective disease diagnosis through the identification of disease marker molecules. The review also addresses the prospects and challenges associated with the transition of nanomedicines from synthetic or natural origins to their practical clinical deployment. Furthermore, the document offers insights into prevailing trends and future prospects within the domain of nanomedicine.

Keywords: nanotechnology; nano drug delivery systems (NDDSs); nanomedicines; targeting strategy of NDDSs

1. Introduction

Nanotechnology is the deliberate engineering and manipulation of particulate matter into a physical state that is between 1 nm and 100 nm, which may then be reorganized or reassembled into nano-systems with increased function [1]. The potential uses of nanoparticles and nanomaterials in medicine are being investigated more and more. The field of drug delivery stands out as a highly captivating and promising area of application. The nano drug delivery system is one such ground-breaking invention that makes use of nanotechnology to boost treatment efficacy, decrease adverse effects, and improve drug delivery efficiency [2].

A drug delivery system (DDS) is defined as "a formulation or a device that enables the introduction of a therapeutic substance into the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body" [3]. These systems offer enhanced drug bioavailability by improving drug solubility and stability, thereby maximizing therapeutic efficacy. Their ability to achieve targeted drug delivery to specific tissues, cells, or subcellular compartments minimizes off-target effects and reduces systemic toxicity [4].

The global market for nano drug delivery is anticipated to reach a remarkable $126.8 billion by 2026, growing at a 14.1% compound annual growth rate (CAGR) between 2021 and 2026, per Grand View Research [5]. The many benefits that nano drug delivery systems provide, such as improved bioavailability, prolonged drug

release, targeted administration to particular cells or tissues, and the capacity to overcome biological barriers, may be credited for this exponential expansion [6].

Nano drug delivery systems help a lot in sustained and controlled drug release, enabling prolonged therapeutic activity, reduced dosing frequency, and improved patient compliance. Overcoming biological barriers, such as the blood-brain barrier, is another noteworthy advantage, as it allows drugs to reach previously inaccessible sites [7]. Additionally, nano drug delivery systems present opportunities for combination therapy, where multiple drugs or therapeutic agents can be encapsulated within a single nanoparticle, promoting synergistic effects and personalized treatment strategies [8]. Overall, the utilization of nano drug delivery systems holds great promise in enhancing therapeutic outcomes, mitigating adverse effects, and advancing the field of precision medicine [9].

Nano drug delivery systems have both organic and inorganic nanocarriers. Solid liquid nanoparticles, liposomes, dendrimers, polymeric nanoparticles, polymeric micelles, and virus-based nanoparticles are examples of organic nanocarriers. Carbon nanotubes and mesoporous silica nanoparticles are examples of inorganic nanoparticles. For instance, liposomes, a type of nano drug delivery system, have been extensively explored [10]. Doxil, a liposomal formulation of doxorubicin, showed improved efficacy and reduced cardiotoxicity compared to the free drug, leading to its approval for the treatment of ovarian cancer and AIDS-related Kaposi's sarcoma [11].

Despite their potential, nano drug delivery systems face certain challenges that need to be addressed for their successful translation into clinical applications [12]. The stability and storage of nano drug delivery systems present additional challenges. The complex manufacturing and scale-up processes involved in ensuring consistent quality, reproducibility, and scalability of nanoparticles pose a significant challenge [13]. Establishing standardized guidelines for assessing safety, efficacy, and quality is essential for facilitating regulatory approval and market entry. Lastly, the high cost associated with nano drug delivery systems limits their widespread adoption. Developing cost-effective manufacturing processes and addressing economic feasibility are necessary to improve accessibility [14].

2. Types of the NDDSs

Liposomes, dendrimers, carbon nanomaterials, fullerenes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers, nano shells, quantum dots, superparamagnetic nanoparticles, and others are examples of the many morphologies of nanoparticles [15]. The description, importance, and challenges of these different morphologies of nanoparticles as drug delivery systems are given below:

2.1. Lipsomes

Liposomes are colloidal particles enclosed by lipid bilayers, formed by self-assembly of amphiphilic phospholipids. They have sizes ranging from 25 nm to 200 nm and are often used in drug delivery, particularly targeting cancer cells. Liposomes were discovered in 1965 and have been utilized as drug delivery systems since 1971 [16]. The hydrophobic effect drives their bilayer structure formation.

Liposomes can evade opsonization by the reticuloendothelial system when PEG is added to their surface. Doxil, a liposomal medication, was the first FDA-approved nanotechnology product for cancer treatment. Liposomes have the advantage of delivering both biological macromolecules like DNA and smaller molecules [17].

2.1.1. Types of liposomes

Liposomes are widely used in pharmaceutical and cosmetic industries as carriers for drug delivery. They offer advantages such as membrane-like structure, drug stability, improved biodistribution, and compatibility with hydrophilic and hydrophobic drugs [18]. There are four categories for liposomes:

1) Traditional liposomes are composed of an aqueous core and a lipid bilayer that may contain neutral, cationic, or anionic cholesterol and phospholipids. In this case, the lipid bilayer and the aqueous space can be filled with either hydrophobic or hydrophilic substances.
2) PEGylated types: The surface of the liposome is coated with polyethylene glycol (PEG) to create steric equilibrium.
3) Ligand-targeted type: Ligands are connected to the surface of the liposome or to the end of PEG chains that have previously been attached. Ligands include peptides, sugars, and antibodies.
4) The fourth liposome type is known as a theragnostic liposome and incorporates the first three liposome types. It frequently contains a nanoparticle as well as a therapeutic, imaging, and targeting component [19].

The normal production process includes thin layer hydration, mechanical agitation, solvent evaporation, solvent injection, and surfactant solubilization [20].

2.1.2. Liposome as drug delivery systems

Due to their exceptional qualities, liposomes have been widely researched for their use in medicine delivery to malignant and tumor tissues using two main methods: passive targeting and active targeting as shown in **Figure 1** [21].

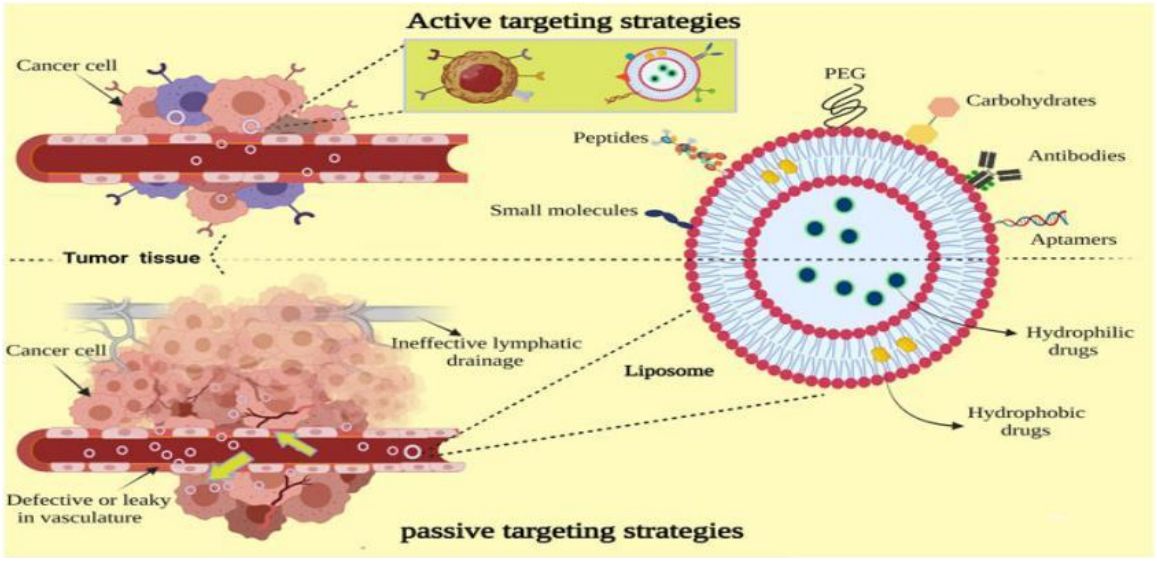

Figure 1. Passive targeting and active targeting.

Liposomes can be surface functionalized to dedicate stealth through PEGylation and to meliorate receptor mediated endocytosis by utilizing targeting ligands such as antibodies, peptides, proteins, carbohydrates, Aptamer, and various other small molecules. PEGylation prolongs liposomal circulation half-life in vivo. Types of drugs based on whether they are hydrophobic or hydrophilic can be encapsulated into the aqueous lumen, incorporated into the lipid bilayer, or conjugated to the liposome surface [22].

Passive targeting is based on the physical features of the tumor and the magnitude of the nanomaterials. Cancer cells overexpress vascular endothelial growth factor (VEGF), which causes an excessive amount of angiogenesis. The proper size of liposomes may flow in the bloodstream for a longer duration, allowing the anti-tumor drug nano system to concentrate on the tumor tissue. Tumor tissue has bigger vascular holes than normal ones [23].

When a drug delivery system accesses malignant tissue, nanoparticle retention durations rise due to anomalies in the lymphatic system, which is not conceivable for tiny drug molecule [24].

This process involves further coating the nanoparticle with a biocompatible PEG polymer, which allows it to escape the reticuloendothelial (RES) system as well as prolongs the duration blood circulates in the circulatory system; PEG has this effect by shielding lipsomes from opsonization [25].

In photodynamic treatment (PDT), light is used to activate photosensitizing drugs, producing reactive oxygen species (ROS) or singlet oxygen which destroy tumors. PDT was first employed for bladder cancer and has since been researched for usage in other cancers [26]. By encapsulating photosensitizers, nanocarriers can increase PDT by increasing the bioavailability and stability of the photosensitizers. However, due to the limited light penetration, PDT is only effective on surface tumors. Limitations such as low bioavailability, hydrophobic adverse effects, high dosage requirements, and self-aggregation in aqueous media are addressed by nanocarriers. They show promise for raising PDT effectiveness [27].

Liposomes are versatile carriers for drugs, being able to transport both water and lipid-soluble drugs due to their amphiphilic and non-ionic structure [28]. Researchers can manipulate their permeability, stiffness, size, and surface functionalization to create sustained and targeted drug delivery systems [29]. Liposomal delivery addresses the need for biodegradable drug delivery and prevents drug oxidation [30].

Despite their benefits, liposome-based structures have drawbacks that prevent widespread clinical application. Their physical and chemical stability, low solubility in aqueous solutions, short half-life in the body, high production costs, and allergic reactions to specific liposomal chemicals are the key challenges [31].

2.2. Carbon nanomaterials

DNA's basic building block, carbon, is responsible for the creation of all life on earth. Due to its unique electron configuration ($1s^2$, $2s^2$, 2p), it can be found in a variety of forms [32]. Due to its capacity to bind itself and practically all elements, it

has a wide range of technical uses, including the transport of pharmaceuticals and synthetic materials [33].

CBNs are divided into carbon nanotubes, graphene, mesoporous carbon, nanodiamonds, and fullerenes based on their structural differences. These materials have enhanced drug-loading capacity, biocompatibility, and immunogenicity [34]. It has been possible to create biocompatible scaffolds and nanomedicines using functionalized CBNs. Due to their superior supramolecular stacking, high adsorption capacity, and photothermal conversion capacity, they have been investigated for cancer therapy [35]. Therapy can be improved by combining chemical functionalization with adaptive characteristics.

2.3. Carbon nanotubes

Carbon nanotubes (CNTs) are tubes or cylinders with a special blend of stiffness, elasticity, and strength. Single-walled nanotubes (SWCNTs) are elongated enfolded graphene sheets that were created through sp^2 hybridization and have one-dimensional hollow and cylindrical forms. These CNTs have a diameter of roughly 1 nm and can grow to hundreds of times their original length [36].

Multi-walled carbon nanotubes (MWCNTs) are composed of many graphene sheet layers and have more complicated electrical properties. Sizes of this type of nanotubes range from 5 nm to 50 nm [37].

Functionalized CNTs (f-CNTs) have improved solubility, biocompatibility, and reduced toxicity when tagged with functional groups or therapeutic molecules [38]. Covalent and non-covalent modifications are used to alter CNT surfaces, but they may affect mechanical strength [39].

The potential benefits of SWCNTs in metal nanoparticles, such as bulk medication loading, structural adaptability, inherent stability, enhanced circulation time, and bioavailability, have drawn attention among the many types of carbon nanotubes [40]. Higher drug loading is possible thanks to the ability of functionalized SWCNTs to entrap low molecular weight substances and antibodies. This also enables the conjugation of biological molecules without inducing an immunological response.

Doxorubicin (DOX) is commonly used in chemotherapy, but it has limitations, including side effects, low barrier crossing ability, and irreversible toxicity. Carbon nanotubes (CNTs) can effectively transport DOX, reducing side effects due to their high surface area, stability, and cell membrane penetration. In breast cancer treatment, amino-functionalized single-walled CNTs (NH_2-SWCNTs) combined with hyaluronic acid (HA) showed faster DOX release in the tumor cell environment. SWCNTs-DOX-HA reduced tumor cell growth and induced apoptosis more effectively than SWCNTs-DOX alone, enhancing breast cancer treatment and the structure of doxorubicin (DOX) is shown in **Figure 2** [41].

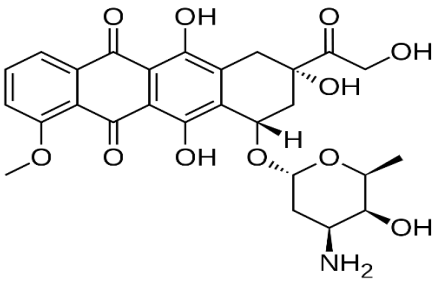

Figure 2. Structure of doxorubicin (DOX).

pH-responsive SWCNT-folic acid (FA) conjugates demonstrated higher drug loading and anti-tumor effects, reducing DOX side effects. FA-EDA-MWCNTs-DOX showed pH-dependent release and cytotoxicity against breast cancer cells [42].

2.4. Graphene

Graphene, a single layer of carbon with partially filled sp^2-orbits, possesses large surface area, superior thermal conductivity, optical clarity, and strong mechanical strength. It acts as a semiconductor, forming new quasi-particles upon interaction with electrons. Quantum dots and graphene nanoribbons enable ballistic transport without scattering [43].

Graphene exhibits good electrical conductivity and reduced solubility. Sol-gel chemistry allows for alterations like graphene oxide and layered graphene-oxide. Graphene and its derivatives have diverse applications in medicine and drug delivery, with polymer surface modification enhancing biocompatibility [44]. Graphene nanomaterials respond to stimuli, regulating drug release based on internal and environmental inputs, improving absorption, overcoming barriers, and minimizing side effects [45].

Because of the functional groups that are present on the side walls, GOs have attracted a lot of attention among graphene nanomaterials. DOX and camptothecin were captured by graphene through hydrophobic interaction and π-π stacking. The presence of hydroxyl and carboxyl groups on the surface of GOs makes it easier for them to attach to the hydroxyl and amino groups of DOX [46].

A study using the 4T1 cancer cell lines showed that the electrochemical method successfully exhibited carrier capacity and cellular capacity. Based on pH-stimuli drug delivery, 5-fluorouracil loaded GO was created and the structure of 5-fluorouracil is shown in **Figure 3** [47].

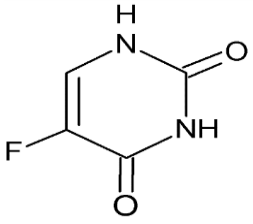

Figure 3. Chemical structure of 5-fluorouracil.

This formulation controlled the release of the anticancer agent in the tumors environment's acidic pH of 5.8, however the release was dramatically reduced in the physiological pH of 7.4.

3. Multifunctional nanoparticles as NDDSs

As a result of their direct targeting of the damaged organs, metal nanoparticles allow drug delivery systems to minimize adverse effects.

3.1. Silver nanoparticles

The manufacture of NPs and nanoparticles uses silver, which is the precious metal with the highest profit-orientedness because of its antiviral, antifungal, and antioxidant properties. These are well-known due to their unusually improved physicochemical properties relative to the bulk material, such as optical, thermal, electrical, and catalytic capabilities, as well as their anti-bacterial, anti-viral, anti-fungal, and antioxidant activities [48]. A variety of different cell types have been shown to be susceptible to cytotoxicity caused by silver nanoparticles via apoptosis and necrosis. Additionally, they show results against side effects of conventional therapies such DNA damage, the production of reactive oxygen species (ROS), an increase in lactate dehydrogenase (LDH) leakage, and inhibition of stem cell differentiation [49].

3.2. Gold nanoparticles

AuNPs, also known as gold nanoparticles, are potent radiosensitizers used in medical operations such drug administration and cancer treatment [50]. Gold nanoparticles, or AuNPs, are potent radiosensitizers utilized in cancer treatment and drug administration. Au NPs are able to deliver a variety of pharmaceutical compounds, recombinant proteins, vaccines, or nucleotides into their targets thanks to their capacity to govern drug release via internal biological triggers or external light activation. Given its impressive effectiveness, AuNP-based drug delivery has drawn a lot of attention [51].

4. Targeting strategy of the NDDSs

There are two mechanisms by which nanocarriers can deliver to target nano-drugs: active targeting and passive targeting. In active targeting, we focus on specific markers found only in sick cells, not healthy ones. For example, we can use molecules that interact with the overexpressed folate receptors in sick cells. CA-125 is an example of a biomarker overexpressed in ovarian cancer that can be actively targeted [52].

In passive targeting, the size of polymers is important. Larger polymers can accumulate more at the site of diseased cells. This happens because the polymers can pass through leaky blood vessel junctions and reach the sick area. It's like taking advantage of the openings in the blood vessels to deliver the drugs where they are needed [53].

In **Figure 4**, the illustration of passive and active targeting of nanoparticles (NPs) for enhancing the therapeutic efficacy of anticancer drugs **Figure 4A**: passive

targeting of NPs taking advantage of the enhanced permeability and retention (EPR) effect; **Figure 4B**: active targeting of NPs attached with ligands to enhance accumulation and cellular uptake of NPs via receptor-facilitated endocytosis [54].

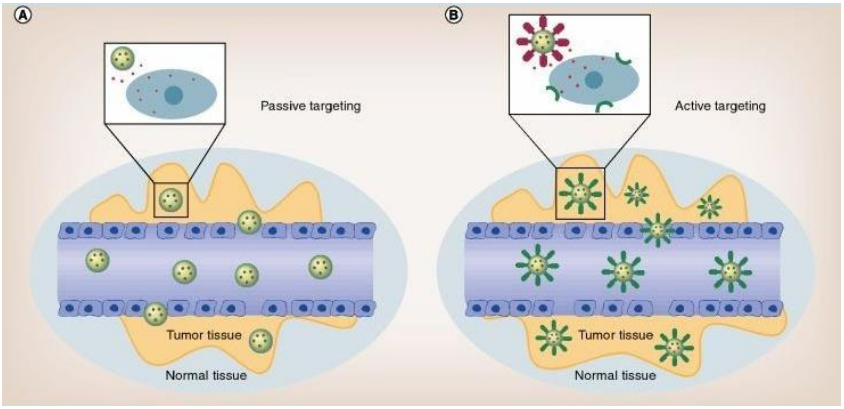

Figure 4. Passive and active targeting of nanoparticles (NPs) as a drug delivery system.

5. Application of NDDSs

Nano drug delivery systems have various applications in medical field. Some are given below:

5.1. AuNPs in cancer therapy

For gold nanoparticles to be used as therapeutics, it is essential to comprehend how they are biodistributed and accumulate in living systems. This can only be done with accurate characterization of the nanomaterials, a reliable animal model, a sizeable sample, and strong statistical analyses. AuNPs regulate damage to healthy cells and lessen the likelihood of adverse outcomes [55]. AuNPs are a novel component in cancer therapy that display aggregation and a size-dependent lethal effect on various cancer cells [56,57]. The anti-cancer action of AuNP is complicated and poorly understood. The positive charges are on AuNPs, but cancerous and healthy cell membranes include molecules that are negatively charged, such as lipids, which cause AuNPs to be absorbed and internalized [58]. Another mechanism by which AuNPs enter cells is endocytosis, which results in the accumulation of tiny AuNPs inside HeLa cells [59].

We focused on the development of the following gold nanoparticles-based drug delivery systems: AuNPs covered by PEG carrying carboxylic groups, PEG-AuNPs linked to DOX, PEG-AuNPs linked to BLM, and, finally PEG-AuNPs linked to both DOX and BLM (referred to as S1, S2, S3 and S4, correspondingly) as illustrated in **Figure 5** [59].

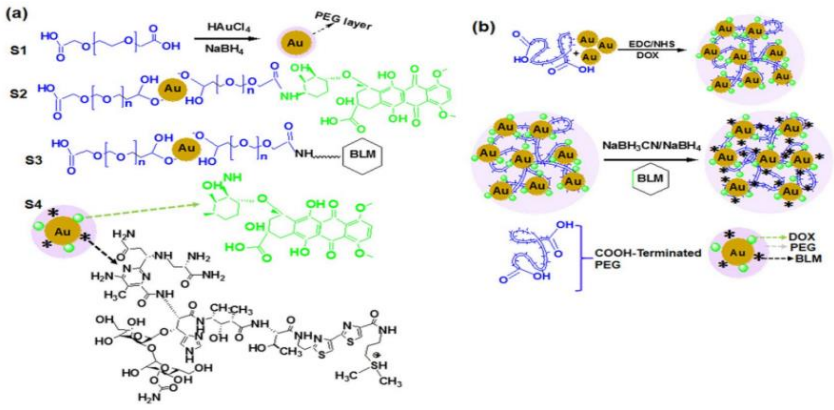

Figure 5. Synthesis of PEG-AuNPs NPs **(a)** the chemical composition of DOX and BLM and the procedures involved in conjugating them to the surface of S1; **(b)** a schematic depicting the production of S2, S3, and S4 NPs.

5.2. AgNPs as anti-viral agents

A significant problem for the pharmaceutical, medical, and biotechnological industries is the development of resistance by different viral pathogens against anti-viral drugs [60]. Because of their successful interactions with sulfhydra, amino, carboxyl, phosphate, and imidazole groups, AgNPs are well acknowledged to suppress viruses.

Due to their inhibitory efficiency against a variety of viruses, including hepatitis, coronavirus, influenza, herpes, recombinant respiratory syncytial virus, and human immunodeficiency virus, AgNPs have recently gained popularity as anti-viral medicines [61]. AgNPs were employed to create a nanoscale delivery system for the antiviral drug zanamivir, and surface-enriching AgNPs with amantadine to prevent H1N1 virus resistance as demonstrated in **Figure 6** [62].

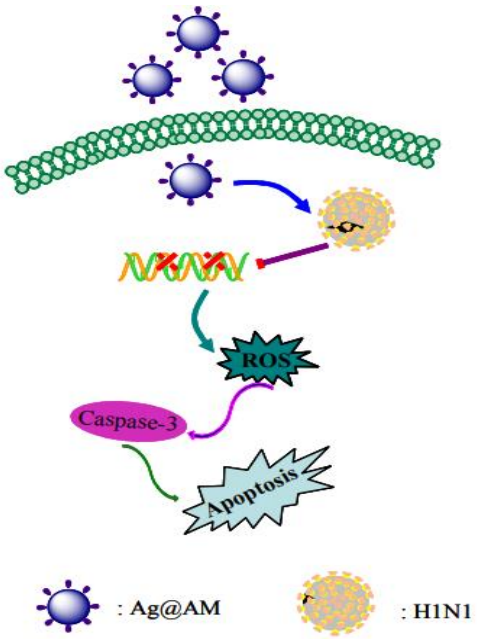

Figure 6. The reversal of H1N1 influenza virus-induced apoptosis by silver nanoparticles.

6. Conclusion and future perspectives

Incomparable opportunities to develop medical diagnoses and treatments for human ailments have been made possible by the development and growth of nanotechnology for therapeutic and medical-related purposes over the previous two to three decades. As shown by their enhanced solubility of a variety of cargoes, disease-fighting capacity, controlled transmission, improved strength, increased biodistribution inside the organism, Modula table (adjust to certain proportion) means of transport across tissues and cells, and controlled delivery to the target location, the nanomaterials exhibit a high degree of control over the desired properties. These kinds of methods are available to make detectors and imaging components that have improved identification and analysis sensitivity. Before this research can offer clinically effective medicines, there are still many challenges to be solved. The development and testing of cutting-edge methods for controlling how nanoparticles interact with the body is one of the main challenges to turn this technology into medicines. It is necessary to find a solution to the problem of delivering nanomaterials to specific body regions while preventing entrapment by organs like the liver and spleen. By modifying material qualities at the nanoscale, there has been enough room to improve and change current technologies. Therefore, with enough time and research, the promise of nanotechnology-based drugs may become a reality.

Conflict of interest: The authors declare no conflict of interest.

References

1. Nasrollahzadeh M, Saiadi SM, Sajjadi M, Issaabadi Z. An introduction to nanotechnology. In: Interface Science and Technology. Elsevier; 2019.
2. Doran J, Ryan G. Does nanotechnology research generate an innovation premium over other types of research? Evidence from Ireland. Technology in Society 2019; 59: 101183. doi: 10.1016/j.techsoc.2019.101183
3. Qiao L, Yang H, Gao S, et al. Research progress on self-assembled nanodrug delivery systems. Journal of Materials Chemistry B 2022; 10(12): 1908–1922. doi: 10.1039/D1TB02470A
4. Osman N, Devnarain N, Omolo CA, et al. Surface modification of nano-drug delivery systems for enhancing antibiotic delivery and activity. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology 2022; 14(1): e1758. doi: 10.1002/wnan.1758
5. Jain KK. An overview of drug delivery systems. In: Jain KK (editor). Drug Delivery Systems. Humana; 2019. Volume 2059, pp. 1–54.
6. Wang Y, Sun T, Jiang C. Nanodrug delivery systems for ferroptosis-based cancer therapy. Journal of Controlled Release 2022; 344: 289–301. doi: 10.1016/j.jconrel.2022.01.034
7. Wang C, Li F, Zhang T, et al. Recent advances in anti-multidrug resistance for nano-drug delivery system. Drug Delivery 2022; 29(1): 1684–1697. doi: 10.1080/10717544.2022.2079771
8. Li R, Chen Z, Li J, et al. Nano-drug delivery systems for T cell-based immunotherapy. Nano Today 2022; 46: 101621. doi: 10.1016/j.nantod.2022.101621
9. Ma Z, Li B, Peng J, Guo D. Recent development of drug delivery systems through microfluidics: From synthesis to evaluation. Pharmaceutics 2022; 14(2): 434. doi: 10.3390/pharmaceutics14020434
10. Tian C, Zheng S, Liu X, Kamei K. Tumor-on-a-chip model for advancement of anti-cancer nano drug delivery system. Journal of Nanobiotechnology 2022; 20(1): 1–16. doi: 10.1186/s12951-022-01552-0
11. Liu W, Ma Z, Wang Y, Yang J. Multiple nano-drug delivery systems for intervertebral disc degeneration: Current status and future perspectives. Bioactive Materials 2022; 23: 274–299. doi: 10.1016/j.bioactmat.2022.11.006

12. Qin J, Wang X, Fan G, et al. Recent advances in nanodrug delivery system for tumor combination treatment based on photothermal therapy. Advanced Therapeutics 2023; 6(3): 2200218. doi: 10.1002/adtp.202200218
13. Chavda VP, Patel AB, Mistry KJ, et al. Nano-drug delivery systems entrapping natural bioactive compounds for cancer: Recent progress and future challenges. Frontiers in Oncology 2022; 12: 867655. doi: 10.3389/fonc.2022.867655
14. Jain A, Jain SK. In vitro release kinetics model fitting of liposomes: An insight. Chemistry and Physics of Lipids 2016; 201: 28–40. doi: 10.1016/j.chemphyslip.2016.10.005
15. Babu A, Templeton AK, Munshi A, et al. Nanodrug delivery systems: A promising technology for detection, diagnosis, and treatment of cancer. AAPS PharmSciTech 2014; 15(3): 709–721. doi: 10.1208/s12249-014-0089-8
16. Wang J, Guo J, Wei Z. Strategies for liposome drug delivery systems to improve tumor treatment efficacy. AAPS PharmSciTech 2021; 23(1): 27. doi: 10.1208/s12249-021-02179-4
17. Dimov N, Kastner E, Hussain M, et al. Formation and purification of tailored liposomes for drug delivery using a module-based micro continuous-flow system. Scientific Reports 2017; 7(1): 12045. doi: 10.1038/s41598-017-11533-1
18. Bozzuto G, Molinari A. Liposomes as nanomedical devices. International Journal of Nanomedicine 2015; 10: 975–999. doi: 10.2147/IJN.S68861
19. Sercombe L, Veerati T, Moheimani F, et al. Advances and challenges of liposome assisted drug delivery. Frontiers in Pharmacology 2015; 6: 286. doi: 10.3389/fphar.2015.00286
20. Kotla NG, Chandrasekar B, Rooney P, et al. Biomimetic lipid-based nanosystems for enhanced dermal delivery of drugs and bioactive agents. ACS Biomaterials Science & Engineering 2017; 3(7): 1262–1272. doi: 10.1021/acsbiomaterials.6b00681
21. Nakhaei P, Margiana R, Bokov DO, et al. Liposomes: Structure, biomedical applications, and stability parameters with emphasis on cholesterol. Frontiers in Bioengineering and Biotechnology 2021; 9: 705886. doi: 10.3389/fbioe.2021.705886
22. Sakurai Y, Kajimoto K, Hatakeyama H, Harashima H. Advances in an active and passive targeting to tumor and adipose tissues. Expert Opinion on Drug Delivery 2015; 12(1): 41–52. doi: 10.1517/17425247.2015.955847
23. Liu Y, Bravo KMC, Liu J. Targeted liposomal drug delivery: A nanoscience and biophysical perspective. Nanoscale Horizons 2021; 6(2): 78–94. doi: 10.1039/D0NH00605J
24. Attia MF, Anton A, Wallyn J, et al. An overview of active and passive targeting strategies to improve the nanocarriers efficiency to tumour sites. Journal of Pharmacy and Pharmacology 2019; 71(8): 1185–1198. doi: 10.1111/jphp.13098
25. Nunes SS, Fernandes RS, Cavalcante CH, et al. Influence of PEG coating on the biodistribution and tumor accumulation of pH-sensitive liposomes. Drug Delivery and Translational Research 2019; 9(1): 123–130. doi: 10.1007/s13346-018-0583-8
26. Kashkooli FM, Soltani M, Souri M. Controlled anti-cancer drug release through advanced nano-drug delivery systems: Static and dynamic targeting strategies. Journal of Controlled Release 2020; 327: 316–349. doi: 10.1016/j.jconrel.2020.08.012
27. Moghassemi S, Dadashzadeh A, Azevedo RB, et al. Photodynamic cancer therapy using liposomes as an advanced vesicular photosensitizer delivery system. Journal of Controlled Release 2021; 339: 75–90. doi: 10.1016/j.jconrel.2021.09.024
28. Joshi S, Hussain MT, Roces CB, et al. Microfluidics based manufacture of liposomes simultaneously entrapping hydrophilic and lipophilic drugs. International Journal of Pharmaceutics 2016; 514(1): 160–168. doi: 10.1016/j.ijpharm.2016.09.027
29. Jain A, Jain SK. In vitro release kinetics model fitting of liposomes: An insight. Chemistry and Physics of Lipids 2016; 201: 28–40. doi: 10.1016/j.chemphyslip.2016.10.005
30. Manconi M, Marongiu F, Castangia I, et al. Polymer-associated liposomes for the oral delivery of grape pomace extract. Colloids and Surfaces B: Biointerfaces 2016; 146: 910–917. doi: 10.1016/j.colsurfb.2016.07.043
31. Li M, Du C, Guo N, et al. Composition design and medical application of liposomes. European Journal of Medicinal Chemistry 2019; 164: 640–653. doi: 10.1016/j.ejmech.2019.01.007
32. Wang J, Guo J, Wei Z. Strategies for liposome drug delivery systems to improve tumor treatment efficacy. AAPS PharmSciTech 2021; 23(1): 27. doi: 10.1208/s12249-021-02179-4
33. Rauti R, Musto M, Bosi S, et al. Properties and behavior of carbon nanomaterials when interfacing neuronal cells: How far have we come? Carbon 2019; 143: 430–446. doi: 10.1016/j.carbon.2018.11.026
34. Mohajeri M, Behnam B, Sahebkar A. Biomedical applications of carbon nanomaterials: Drug and gene delivery potentials. Journal of Cellular Physiology 2018; 234(1): 298–319. doi: 10.1002/jcp.26899
35. Wang SY, Hu HZ, Qing XC, et al. Recent advances of drug delivery nanocarriers in osteosarcoma treatment. Journal of Cancer 2020; 11(1): 69–82. doi: 10.7150/jca.36588
36. Bepete G, Coleman KS. Carbon nanotubes: Electronic structure and spectroscopy. In: Comprehensive Nanoscience and Nanotechnology, 2nd ed. Academic Press; 2019. pp. 205–218.

37. Ganji DD, Kachapi SHH. Semi nonlinear analysis in carbon nanotube. In: Application of Nonlinear Systems in Nanomechanics and Nanofluids, 1st ed. William Andrew Publishing; 2015. pp. 13–70.
38. Beg S, Rahman M, Jain A, et al. Emergence in the functionalized carbon nanotubes as smart nanocarriers for drug delivery applications. In: Grumezescu AM (editor). Fullerens, Graphenes and Nanotubes: A Pharmaceutical Approach. William Andrew; 2018. pp. 105–133.
39. Merum S, Babu VJ, Ramakrishna S. Functionalized carbon nanotubes in bio-world: Applications, limitations and future directions. Materials Science and Engineering: B 2017; 223: 43–63. doi: 10.1016/j.mseb.2017.06.002
40. Kushwaha SKS, Ghoshal S, Rai AK, Singh S. Carbon nanotubes as a novel drug delivery system for anticancer therapy: A review. Brazilian Journal of Pharmaceutical Sciences 2013; 49(4): 629–643. doi: 10.1590/S1984-82502013000400002
41. Liu D, Zhang Q, Wang J, et al. Hyaluronic acid-coated single-walled carbon nanotubes loaded with doxorubicin for the treatment of breast cancer. Pharmazie 2019; 74(2): 83–90. doi: 10.1691/ph.2019.8152
42. Uttekar PS, Lakade SH, Beldar VK, Harde MT. Facile synthesis of multi-walled carbon nanotube via folic acid grafted nanoparticle for precise delivery of doxorubicin. IET Nanobiotechnology 2019; 13(7): 688–696. doi: 10.1049/iet-nbt.2018.5421
43. Garcia CD, Crevillen AG, Escarpa A. Carbon-based Nanomaterials in Analytical Chemistry. Royal Society of Chemistry; 2018.
44. Bai RG, Husseini GA. Graphene-based drug delivery systems. In: Unnithan AR, Kurup Sasikala AR, Park CH, et al. (editors). Biomimetic Nanoengineered Materials for Advanced Drug Delivery. Elsevier; 2019; pp. 149–168.
45. Yang Y, Liu J, Sun X, et al. Near-infrared light-activated cancer cell targeting and drug delivery with aptamer-modified nanostructures. Nano Research 2016; 9: 139–148. doi: 10.1007/s12274-015-0898-4
46. Pattnaik S, Surendra Y, Rao JV, Swain K. 18—Carbon family nanomaterials for drug delivery applications. In: Mozafari M (editor). Nanoengineered Biomaterials for Advanced Drug Delivery. Elsevier; 2020; pp. 421–445.
47. Aliabadi M, Yunessnia lehi A, Shagholani H, Gerayeli A. Planar polymer-graphene oxide nanohybrid as a 5-fluorouacil carrier in pH-responsive controlled release. Journal of Drug Delivery Science and Technology 2018; 43: 103–106. doi: 10.1016/j.jddst.2017.09.020
48. Le Ouay B, Stellacci F. Antibacterial activity of silver nanoparticles: A surface science insight. Nano Today 2015; 10(3): 339–354. doi: 10.1016/j.nantod.2015.04.002
49. Praphakar RA, Jeyaraj M, Ahmed M, et al. Silver nanoparticle functionalized CS-g-(CA-MA-PZA) carrier for sustainable anti-tuberculosis drug delivery. International Journal of Biological Macromolecules 2018; 118: 1627–1638. doi: 10.1016/j.ijbiomac.2018.07.008
50. Jain S, Hirst DG, O'Sullivan JM. Gold nanoparticles as novel agents for cancer therapy. The British Journal of Radiology 2012; 85(1010): 101–113. doi: 10.1259/bjr/59448833
51. Chow EKH, Ho D. Cancer nanomedicine: From drug delivery to imaging. Science Translational Medicine 2013; 5(216): 216rv4. doi: 10.1126/scitranslmed.3005872
52. LiSunita Kumbhat NK. Carbon-based nanomaterials. In: Essentials in Nanoscience and Nanotechnology, 1st ed. Wiley; 2016. pp. 189–236.
53. Shah A, Aftab S, Nisar J, et al. Nanocarriers for targeted drug delivery. Journal of Drug Delivery Science and Technology 2021; 62: 102426. doi: 10.1016/j.jddst.2021.102426
54. Hirsjarvi S, Passirani C, Benoit JP. Passive and active tumour targeting with nanocarriers. Current Drug Discovery Technologies 2011; 8(3): 188–196. doi: 10.2174/157016311796798991
55. Tiloke C, Phulukdaree A, Anand K, et al. Moringa oleifera gold nanoparticles modulate oncogenes, tumor suppressor genes, and caspase-9 splice variants in A549 cells. Journal of Cellular Biochemistry 2016; 117(10): 2302–2314. doi: 10.1002/jcb.25528
56. Cui W, Li J, Zhang Y, et al. Effects of aggregation and the surface properties of gold nanoparticles on cytotoxicity and cell growth. Nanomedicine: Nanotechnology, Biology and Medicine 2012; 8(1): 46–53. doi: 10.1016/j.nano.2011.05.005
57. Gong N, Chen S, Jin S, et al. Effects of the physicochemical properties of gold nanostructures on cellular internalization. Regenerative Biomaterials 2015; 2(4): 273–280. doi: 10.1093/rb/rbv024
58. Albanese A, Tang PS, Chan WCW. The effect of nanoparticle size, shape, and surface chemistry on biological systems. Annual Review of Biomedical Engineering 2012; 14: 1–16. doi: 10.1146/annurev-bioeng-071811-150124

59. Farooq MU, Novosad V, Rozhkova EA, et al. Retracted article: Gold nanoparticles-enabled efficient dual delivery of anticancer therapeutics to HeLa cells. Scientific Reports 2018; 8(1): 2907. doi: 10.1038/s41598-018-21331-y
60. Gurunathan S, Qasim M, Choi Y, et al. Antiviral potential of nanoparticles—Can nanoparticles fight against coronaviruses? Nanomaterials 2020; 10(9): 1645. doi: 10.3390/nano10091645
61. Yuan YG, Zhang S, Hwang JY, Kong IK. Silver nanoparticles potentiates cytotoxicity and apoptotic potential of camptothecin in human cervical cancer cells. Oxidative Medicine and Cellular Longevity 2018; 2018: 6121328. doi: 10.1155/2018/6121328
62. Li Y, Lin Z, Zhao M, et al. Reversal of H1N1 influenza virus-induced apoptosis by silver nanoparticles functionalized with amantadine. RSC Advances 2016; 6(92): 89679–89686. doi: 10.1039/C6RA18493F