Journal of Composites and Compounds 7(2025) 1-7

Available Online at www.jourcc.com

Journal homepage: www.JOURCC.com

Journal of Composites and Compounds

The immunological implications of nanocomposite drug delivery systems

Mehrasa Nikandish [a], Bahram Rezazadeh Moghaddam [b]*, Melika Chinaveh [c], Aynaz Ziaeijazi [d], Leila Akhvlediani [e], Ana Gujabidze [f,g]

[a] *King's College London, Faculty of Life Science and Medicine King's College London, London, UK*

[b] *School of Health Sciences, University of Georgia,Tbilisi, Georgia*

[c] *School of Science and Health, The University of Georgia, Tbilisi, Georgia*

[d] *School of Allied Medical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran*

[e] *School of Medicine & Health Sciences, BAU International University Batumi, 6010, Batumi, Georgia*

[f] *Pharmaceutical Company LTD Davati, Chief Microbiology, Tbilisi, Georgia*

[g] *Invited Lecturer in Biochemistry and Microbiology, University of Georgia, Tbilisi, Georgia*

ABSTRACT

This review discusses recent advances in nanocomposite applications, with a particular concentrate on their progress as drug delivery systems. It explores the intrinsic properties of nanocomposites that effect their interaction with the immune system and potential in vivo toxicity. It also includes the immune system's interaction with nanomaterials, immunological responses provoked by nanocomposite systems, and the factors that impact immune reactions such as size, shape, surface properties, composition, and biodegradability. The review also discusses surface modifications and targeting ligands that can optimize nanocomposite performance. Through understanding nano-bio interfaces technology, researchers can design bio-effective nanomaterials that open new possibilities for biomedical applications, especially as targeted and safe drug delivery platforms.

ARTICLE INFORMATION

Article History:
Received 13 March 2025
Received in revised form 15 May 2025
Accepted 18 May 2025

Keywords:
Controlled release
Drug delivery systems
Nanocomposites
Immunology
Targeted drug delivery

Table of Contents

1. Introduction 2
2. Overview of nanocomposite drug delivery systems 2
2.1. Definition and classification of nanocomposites 2
2.2. Definition and classification of drug delivery system 2
2.3. Advantages of nanocomposites over conventional delivery systems 2
2.4. Current applications in drug delivery 2
3. The immune system and its interaction with nanomaterials 3
4. Immunological responses to nanocomposite systems 4
5. Factors influencing immune reactions to nanocomposites 4
5.1. Size, shape, and surface properties 4
5.2. Composition and biodegradability 4
5.3. Surface modifications and targeting ligands 5
6. Conclusion 5
7. References 5

* *Corresponding author: Bahram Rezazadeh Moghaddam, Email: Bahram.std@ug.edu.ge*

https://doi.org/10.61882/jcc.7.2.3

1. Introduction

The rapid growth of scientific and technological advancement has driven nanotechnology and nanocomposites to the forefront of modern research [1, 2]. As integral components of nanoscience, these materials have attracted substantial interest across different fields such as biomedicine, electronics, energy, and environmental science, driven by their unique properties and special performance at the nanoscale [3, 4]. Over the past few decades, nanotechnology has revolutionized everyday life such as enhancing intracellular drug delivery, improving food preservation, and increasing the efficiency of targeted therapeutics, especially in cancer treatment [1, 3, 5, 6]. Such progresses have not only raised up global living standards but also greatly affected the economy [3].

In drug delivery systems, nanocomposites are now concentrated on reaching precise targeting, higher drug loading capacities, controlled release, and enhanced cellular uptake. Among the evolving approaches are biomimetic nanocarriers such as hydrogels, micelles, liposomes, dendrimers, and polymeric nanostructures that mimic natural cell functions. These biomimetic strategies have presented promising potential for boosting therapeutic efficiency and specificity [7].

Moreover, advancements in nanomaterials including quantum dots, nanowires, nanotubes, layered nanostructures, graphene derivatives, and MXenes have extended the horizon of material science [8]. Due to their high surface-to-volume ratio, aspect ratio, and customizable shapes, new functionalities have appeared, enabling stronger, lighter, and more versatile materials [9-11]. However, the increased use of nanoparticles also rises concerns about possible toxicity and biological interactions [5, 8, 12].

This review discusses the immunological implications of nanocomposite drug delivery systems, emphasizing how their exceptional properties impact immune responses either positively, by promoting targeted therapy, or negatively, through immune toxicity. Hence, understanding these interactions is crucial for designing safer, more effective nanomedicines that influence the full potential of nanoparticles and nanocomposites in healthcare.

2. Overview of nanocomposite drug delivery systems

2.1. Definition and classification of nanocomposites

Nanocomposites are advanced materials containing a matrix such as metal, ceramic, or polymer reinforced with nanoscale fillers, usually less than 100 nm in size. They can be classified based on the number of dimensions in the nanoscale, including 0D (nanoparticles), 1D (nanorods, nanowires), 2D (nanofibers, nanotubes), and 3D (nanogranules, nanoclays) [13].

Nanocomposites can be polymer-based, ceramic-based, or metal-based. Polymer nanocomposites, widely used in biomedical applications, often include polymers like polyurethane, epoxy, and chitosan, combined with nanomaterials such as graphene, nanotubes, or metal oxides [5, 13-15]. These materials exhibit unique properties like enhanced mechanical strength, thermal stability, and chemical resistance, as a result of their high surface area and nanoscale structures [12, 16, 17]. They can also play a crucial role in advancing drug delivery systems through improved stability, targeting, and controlled release capabilities [18]. Their tailored properties have increased applications across numerous areas [8].

Nanocomposites comprising polymers or inorganic nanoparticles such as silica, zinc oxide, and iron oxide are used to improve antigen stability, processing, and sustained release in vaccine development. Zinc oxide nanocomposites are particularly capable owing to their biocompatibility and ability to modulate immune responses, making them suitable as vaccine adjuvants and in cancer immunotherapy. However, they can also induce inflammation and toxicity by generating reactive oxygen species (ROS) and cytokines, demonstrating the necessity for careful design and efficient safety evaluation [18].

2.2. Definition and classification of drug delivery system

A drug delivery system (DDS) is a formulation or device, with regulatory oversight depending on its purpose that presents a therapeutic agent into the body. It can perform as an interface between the patient and the drug. The aim of DDS is controlling the release rate, timing, and site of action of therapeutic agents to improve efficiency and safety [19]. Over recent decades, research has developed several DDS technologies, including microparticles, nanoparticles, transdermal patches, inhalers, implants, and antibody–drug conjugates, significantly affecting the treatment of diseases like cancer, diabetes, and cardiovascular conditions. The development and clinical translation of these systems continue to drive growth and innovation in the field [20].

2.3. Advantages of nanocomposites over conventional delivery systems

Nanocomposites offer significant enhancements over conventional drug delivery systems by enabling targeted, controlled, and sustained release of therapeutics [8]. Unlike traditional methods such as oral, injectable, or topical routes, nanocarriers like nanoparticles, liposomes, and micelles improve drug stability, enhance tissue targeting, and reduce side effects and toxicity [21, 22]. They also allow for precise delivery to specific cells or tissues, increasing therapeutic efficacy [23]. Additionally, nanocomposites facilitate innovative approaches like personalized medicine, smart stimuli-responsive systems, and advanced manufacturing techniques such as 3D printing, further optimizing drug management [22, 24]. Overall, these advantages lead to improved patient adherence, minimized adverse effects, and the potential to treat complex conditions more effectively [24].

2.4. Current applications in drug delivery

Nanocomposites are extensively used in drug delivery, especially for oral administration, enhancing targeting, solubility, and bioavailability. They assist to overcome challenges such as stability and biological obstacles by allowing site-specific and controlled release [25]. For example, in cancer therapy, nanocarriers can increase drug efficacy and decrease side effects, often by means of activating the immune system to target tumor cells. These cutting-edge systems hold promise for personalized and efficient treatments across various diseases [26].

Nanocomposites, such as layered double hydroxide (LDH) [27] and clay-based systems [28], are increasingly used for targeted drug delivery due to their flexibility, surface modification, and wide distribution potential. Coatings can reduce toxicity and direct drugs to specific sites, especially for oral, systemic, or localized treatments. In Inflammatory bowel disease, nanocarriers loaded with monoclonal antibodies like infliximab have demonstrated enhanced efficacy and reduced systemic side effects [29]. Kim et al. [29] developed nanocomposite carriers loaded with infliximab (IFX) that demonstrated high encapsulation efficiency and a narrow size distribution. These carriers provided colon-specific

anti-inflammatory effects without disrupting systemic balance. Specifically, EAC-L showed promise for non-cytotoxic oral delivery of large molecules, stimulating immune cells and enhancing anti-inflammatory responses in the gut. Both AC-IFX-L and EAC-IFX-L significantly improved colitis symptoms and reduced TNF-α levels in a mouse model, indicating their potential as effective oral therapies for Inflammatory bowel disease. Fig. 1. illustrates fluorescence imaging taken 7 hours after oral administration of Cy7-labeled delivery carriers, showing a strong Cy7 signal in the colon alongside a notably weaker but detectable fluorescence in the small intestine.

Additionally, nasal nanocarriers and hydrogel nanocomposites are advancing non-invasive delivery methods, improving bioavailability and prolonging mucosal contact. These innovations highlight nanocomposites' growing role in efficient, targeted, and minimally invasive therapies [30].

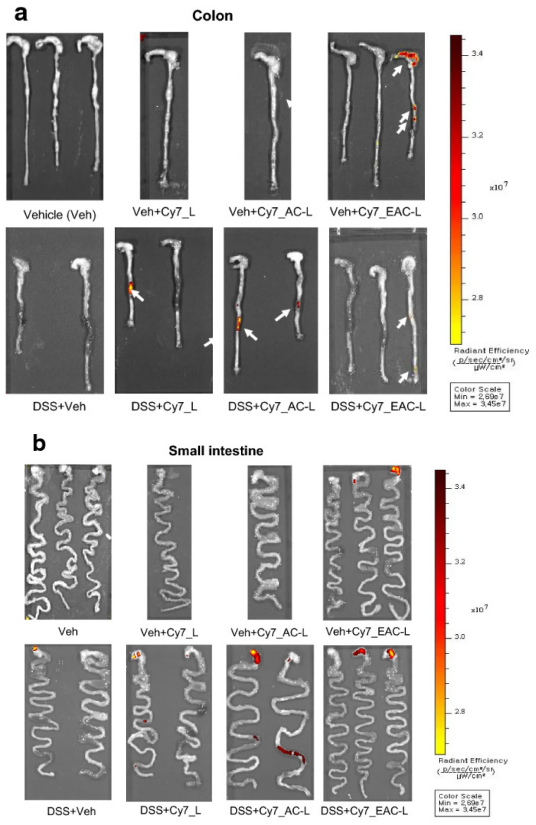

Fig. 1. In vivo drug delivery systems are efficiently targeted to the inflamed colon, minimizing systemic exposure. a) Imaging performed 7 hours after oral administration of Cy7-labeled delivery vehicles using an in vivo imaging system (IVIS) revealed fluorescence signals in the inflamed colon across all treatment groups. The arrows in the images highlight areas of intense fluorescence at the inflammation sites. b) Additionally, fluorescence levels of Cy7 were measured in the inflamed small intestine for the AC-L and EAC-L groups [29].

Chintapula et al. [31] designed a nanocomposite drug delivery system for COVID-19 using Remdesivir (RDV). They synthesized and characterized nanoparticles and nanocomposites, confirming successful drug loading and nanofiber coating. TEM images showed spherical RDV nanoparticles (about 100 nm) and nanofibers, with coatings increasing particle size and shifting surface charge positively. Fluorescence microscopy and MALDI analysis verified the presence and integrity of cell-penetrating peptides in the nanocomposites. This system highlights how nanotechnology can enhance antiviral delivery, with implications for immune response modulation and improved drug targeting.

Fig. 2 shows the characterization of nanoparticles and nanocomposites.

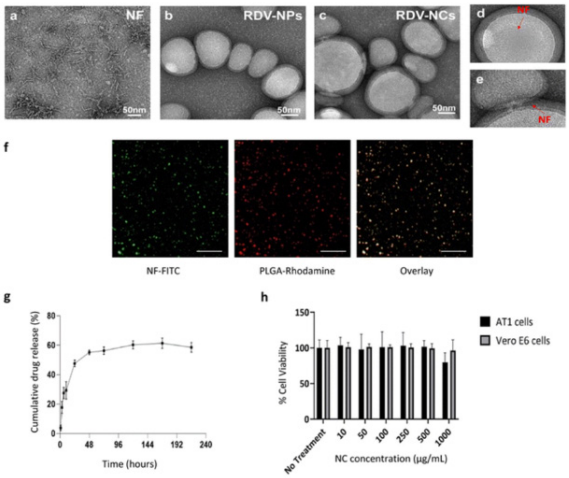

Fig. 2. (a) TEM images of nanofibers, RDV nanoparticles, and nanocomposites; (b-e) enlarged views demonstrating nanofiber presence; (f) FITC-labeled nanofibers adsorbed onto Rhodamine-labeled PLGA nanoparticles, with merged images highlighting co-localization; (g) RDV release from PLGA nanoparticles, showing a burst within 24 hours and over 60% released in 10 days; (h) toxicity tests of the nanocomposites on human lung and Vero E6 cells across various concentrations [31].

3. The immune system and its interaction with nanomaterials

Nanomaterials are recognized by the immune system as foreign entities, similar to pathogens, primarily through innate immune mechanisms targeting chemical patterns. This recognition can trigger immune responses that pose challenges for nanomaterial-based drug and gene delivery [32]. Interactions with immune cells including macrophages, dendritic cells, neutrophils, and lymphocytes can be beneficial or harmful, but the underlying mechanisms are not fully understood [33, 34]. These interactions often involve pattern recognition receptors like toll-like receptors (TLRs) and can activate both innate and adaptive responses, including cytokine production and Th1/Th2 polarization [34]. While nanomaterials can improve immune responses such as boosting vaccine efficacy, they can also lead to adverse immune reactions or toxicity. Therefore, understanding and evaluating these immune interactions, including potential immunotoxicity, are crucial for developing safe and effective nanomedicine applications. Modulating immune engagement may be helpful or undesirable depending on the intended therapeutic use [35]. For example, superparamagnetic iron oxide (SPIO) nanoparticles can activate immune recognition, mostly through their exposed anionic surfaces which are recognized by scavenger receptors on macrophages. Coatings like dextran help improve solubility but do not fully prevent immune interactions. SPIOs can trigger complement pathways, mainly the lectin and classical pathways, leading to rapid clearance and immune reactions such as anaphylactic responses [32].

Nanoparticles can also induce oxidative stress by generating ROS, such as superoxide and hydroxyl radicals, due to their oxidant properties. This ROS production can lead to immune modulation, affecting immunogenicity, antigenicity, clearance, and immune responses, which may cause hypersensitivity, inflammation, or immunosuppression. NPs interact with immune cells like macrophages, B cells, and T cells, either stimulating or suppressing immune functions depending on their design. Smaller

NPs (<10 nm) are rapidly excreted, while larger particles (>100 nm) are cleared by the mononuclear phagocytic system. While immunomodulation by NPs holds promise for treating disorders and improving vaccine efficacy, it also carries risks of adverse reactions. Careful design and understanding of these interactions are essential for safe clinical use [34]. Fig. 3 illustrates the potential interactions between a typical nanomaterial (either polymeric or metal-based, shown as red spheres) and different immune cells [34].

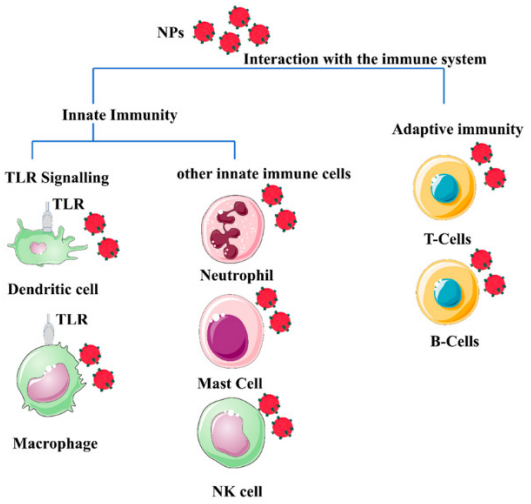

Fig. 3. Diagram showing a typical nanomaterial (either polymeric or metal-based) represented by red spheres, illustrating their possible interactions with various immune cells [34].

4. Immunological responses to nanocomposite systems

NPs can disturb the immune balance via multiple mechanisms, though full understanding remains elusive. One key mechanism is inducing oxidative stress, which contributes to allergy and asthma by damaging cells and disrupting immune regulation. NPs may also damage epithelial barriers in the respiratory tract, increasing susceptibility to allergens, with enzymes like MMP-9 playing a role in tissue remodeling. Additionally, NPs can modulate the adaptive immune response, shifting the Th1/Th2 balance, some NPs promote Th1 cytokines (e.g., INF-γ, TNF-α), boosting anti-tumor activity, while others influence Th2 responses. Nano-induced effects on dendritic cell maturation also impact immune activation and have been exploited in vaccine design. Furthermore, exposure to certain NPs elicits cytokine production patterns indicative of both inflammatory and immune-modulating responses, highlighting their complex role in immunotoxicity [33].

5. Factors influencing immune reactions to nanocomposites

The different properties of NPs properties, such as size, morphology, surface charge, and composition, influence the interaction with immune cells. Most NPs induce an innate immune response [34].

5.1. Size, shape, and surface properties

The size, shape, and surface properties of nanoparticles critically influence immunological responses [6, 36, 37]. Optimal immune activation occurs within a specific size range (10–500 nm), where nanoparticles effectively interact with immune cells; larger sizes (>500 nm) are more readily absorbed by tissue cells, while smaller sizes (<10 nm) quickly enter circulation. Nanoparticles around 80 nm are efficiently endocytosed by dendritic cells (DCs), promoting strong antigen presentation and T cell responses. Shape also impacts uptake and immune activation; for instance, nanorods exhibit higher cellular internalization, but spherical shapes can induce stronger immune responses and cytokine production [6]. Surface properties like charge and hydrophilicity/lipophilicity further modulate these interactions, affecting delivery, retention, and immune stimulation [36]. Surface hydrophobicity is crucial in nanoparticle immunology, as more hydrophobic particles are more readily taken up by phagocytes, leading to stronger immune responses. Studies show that hydrophobic particles promote higher antigen internalization by dendritic cells and stimulate greater cytokine production, enhancing vaccine efficacy. Increasing surface hydrophobicity improves interactions with cell membranes, facilitating antigen delivery and immune activation [38]. Consequently, carefully designing nanoparticles' size, shape, and surface features is vital for optimizing vaccine adjuvants and immunotherapies.

Grunberger et al. [39] studied four types of silica nanoparticles of different sizes and porosities in vitro, highlighting increasing interest in their use for drug delivery and the importance of understanding their immunological safety. They found that at high doses (around 40 mg/kg in humans), these particles could cause immunotoxic effects depending on their properties. However, at lower, clinically relevant doses (≤8 mg/kg), they were not immunotoxic, supporting their potential for systemic delivery and imaging. Fig. 4. shows the effect of NPs on cytokine secretion.

5.2. Composition and biodegradability

Many inorganic nanoparticles (NPs), like gold and silver, used in photothermal therapy are non-biodegradable, leading to organ accumulation, toxicity, and inflammation. This raises safety concerns and limits clinical use [41]. To address this, biodegradable, biocompatible materials are being developed. Combining inorganic NPs with organic or carbon-based nanomaterials offers a promising way to reduce immune-related issues and improve safe, targeted cancer therapy [42]. Many research has shown that biodegradable nanoparticles can effectively deliver antigens, activating both innate and adaptive immunity with minimal doses [40]. Biodegradable polymers like PLGA and PCL, approved by the FDA, are widely used for vaccine and drug delivery due to their safety and versatility [37, 38, 43-47]. However, particle size and surface chemistry require careful optimization to prevent unwanted immune responses [38], such as those seen with PEGylated NPs. Ongoing research is essential to refine these nano-systems for advanced immunotherapies and vaccines [48].

Petrizzo et al. [40] examined the immunological impact of nanoparticle-based vaccine delivery. They developed cationic PLGA/PEI nanoparticles that showed improved uptake by dendritic cells without toxicity. These NPs efficiently delivered ovalbumin, inducing DC maturation and activating naïve CD_4^+ T cells toward a Th1 memory phenotype, promoting strong cytotoxic responses. Although PEI modification enhanced cellular uptake, both PLGA and PLGA/PEI NPs similarly stimulated immune responses, suggesting their potential for cancer vaccines. Further optimization with receptor-targeting ligands could improve antigen presentation.

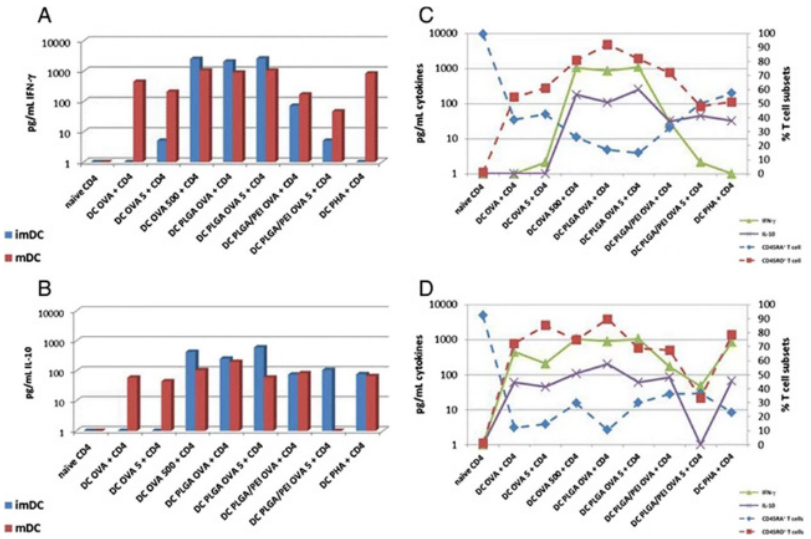

Fig. 4. Effect of NPs on cytokine secretion. IFN-γ (a) and IL-10 (b) production was evaluated after 7 days of T cell co-cultivation with either OVA-imDCs or OVA-mDCs. A correlation analysis between $CD4^+$ T cell subsets and cytokine production was performed in either OVA-imDCs (c) or OVA-mDCs (d) co-culture setting [40].

5.3. Surface modifications and targeting ligands

With rising cancer cases, targeted delivery of anti-cancer drugs has gained focus. Surface modifications with ligands (e.g., antibodies, peptides) enhance nanoparticle targeting to tumor-specific receptors, improving drug efficacy and reducing side effects [49-53]. Ligand-coated nanoparticles can evade the immune system, prolong circulation, and precisely target tumor cells. However, their surface properties also influence immune responses, affecting uptake, cytokine secretion, and clearance. Understanding these immunological effects is essential for designing safer, more effective NP-based therapies [54-57]. Many ligand-conjugated NPs effectively control cellular functions by modulating the spatial arrangement of ligands on their surface, which is crucial for developing therapies with precise ligand-receptor interactions to improve efficacy [58]. Bandyopadhyay et al. showed that the density of anti-DEC-205 antibodies on biodegradable nanoparticles influences immune responses. Higher ligand density increased IL-10 production by DCs and T cells through DEC-205 receptor cross-linking, which also upregulated CD36; blocking CD36 reduced IL-10, highlighting the importance of ligand density in vaccine design [59]. Furthermore, Fakhari et al. [60] studied the effect of ligand density on PLGA nanoparticles affects targeting. Using a cyclic peptide, cLABL, for ICAM-1, they adjusted surface reactive sites by varying Pluronic® mixtures. Higher reactive Pluronic® increased cLABL density, which improved cellular uptake in A549 cells. This highlights the importance of optimizing ligand surface density to enhance nanoparticle targeting effectiveness. Moreover, it was shown that surface-modified lanthanide nanoparticles are promising for cancer therapy due to their unique optical properties, ability to carry therapeutic agents, and customizable targeting ligands. They enable precise, image-guided, and multi-modal treatments like phototherapy, radiotherapy, chemotherapy, and immunotherapy, often responding to tumor microenvironment cues [61]. Optimizing surface chemistry is key for effective, side-effect-free cancer treatments, with ongoing research focusing on enhancing the therapeutic potential of nanoparticle.

6. Conclusion

Understanding immune processes, especially the complement pathway, is vital for designing nanocarriers that evade immune detection and minimize side effects. FDA-approved biodegradable polymers like PCL, PLA, and PLGA have shown promise in vaccine and cancer immunotherapy applications, with particle size influencing immune responses. Careful surface chemistry modification is essential to enhance biocompatibility, reduce immunotoxicity, and improve pharmacokinetics. Continued research on immune interactions will pave the way for safer, more effective nanomedicine strategies.

Author contributions

Mehrasa Nikandish: Investigation, Writing – original draft, Writing – review & editing, **Bahram Rezazadeh Moghaddam:** Conceptualization, Writing – original draft, Writing – review & editing; **Melika Chinaveh:** Writing – original draft, Writing – review & editing; **Aynaz Ziaeijazi:** Writing – original draft, Writing – review & editing; **Leila Akhvlediani:** Writing – original draft, Writing – review & editing; **Ana Gujabidze:** Writing – review & editing.

Funding

No funding was received for this study.

Conflict of interest

The authors declare no conflict of interest.

Data availability

No data is available.

REFERENCES

[1] A. Tariq, S.A. Bhawani, M. Nisar, M.R. Asaruddin, K.M. Alotaibi, Starch-based nanocomposites for gene delivery, Polysaccharide-based nanocomposites for gene delivery and tissue engineering, Woodhead Publishing, (2021) 263.
[2] T.E. Twardowski, Introduction to nanocomposite materials: properties, processing, characterization, DEStech Publications, Inc2007.
[3] A. Yusuf, A.R.Z. Almotairy, H. Henidi, O.Y. Alshehri, M.S. Aldughaim, Nanoparticles as drug delivery systems: a review of the implication of nanoparticles' physicochemical properties on responses in biological systems, Polymers 15(7) (2023) 1596.

[4] G. Armstrong, An introduction to polymer nanocomposites, European Journal of Physics 36(6) (2015) 063001.
[5] N.H. Al-Mutairi, A.H. Mehdi, B.J. Kadhim, Nanocomposites materials definitions, types and some of their applications: A review, European Journal of Research Development and Sustainability 3(2) (2022) 102-108.
[6] M. Hao, B. Chen, X. Zhao, N. Zhao, F.-J. Xu, Organic/inorganic nanocomposites for cancer immunotherapy, Materials Chemistry Frontiers 4(9) (2020) 2571-2609.
[7] M. Sheikhpour, L. Barani, A. Kasaeian, Biomimetics in drug delivery systems: A critical review, Journal of Controlled Release 253 (2017) 97-109.
[8] J. Njuguna, F. Ansari, S. Sachse, V.M. Rodriguez, S. Siqqique, H. Zhu, Nanomaterials, nanofillers, and nanocomposites: types and properties, Health and environmental safety of nanomaterials, Elsevier2021, pp. 3-37.
[9] J. Requejo-Isidro, R. Del Coso, J. Solis, J. Gonzalo, C.N. Afonso, Role of surface-to-volume ratio of metal nanoparticles in optical properties of Cu: Al2O3 nanocomposite films, Applied physics letters 86(19) (2005).
[10] M. Shahbaz, H. Naeem, S. Murtaza, N. Ul-Huda, M. Tayyab, A. Hamza, U. Momal, Application of starch as an active ingredient for the fabrication of nanocomposite in food packaging, Starch Based Nanomaterials for Food Packaging, Elsevier2024, pp. 161-208.
[11] M.D. Malyshev, D.V. Guseva, V.V. Vasilevskaya, P.V. Komarov, Effect of Nanoparticles Surface Bonding and Aspect Ratio on Mechanical Properties of Highly Cross-Linked Epoxy Nanocomposites: Mesoscopic Simulations, Materials 14(21) (2021) 6637.
[12] C.C. Okpala, The benefits and applications of nanocomposites, Int. J. Adv. Eng. Tech 12 (2014) 18.
[13] W.S. Khan, N.N. Hamadneh, W.A. Khan, Polymer nanocomposites–synthesis techniques, classification and properties, Science and applications of Tailored Nanostructures 50 (2016).
[14] V. Kodolov, V. Trineeva, Fundamental definitions for domain of nanostructures and metal/carbon nanocomposites, Nanostructure, Nanosystems and Nanostructured Materials: Theory, Production and Development (2013) 1-42.
[15] L. Chen, Classification of Nanofillers, Nano-Objects, Nanomaterials, and Polymer Nanocomposites Based on Chemical Nature and Identity, Chemical Physics of Polymer Nanocomposites: Processing, Morphology, Structure, Thermodynamics, Rheology 1 (2024) 1-14.
[16] C.C. Okpala, Nanocomposites–an overview, Int. J. Eng. Res. Dev 8(11) (2013) 17.
[17] P.I. Dolez, Nanomaterials definitions, classifications, and applications, Nanoengineering, Elsevier2015, pp. 3-40.
[18] P. Sharma, N.-Y. Jang, J.-W. Lee, B.C. Park, Y.K. Kim, N.-H. Cho, Application of ZnO-based nanocomposites for vaccines and cancer immunotherapy, Pharmaceutics 11(10) (2019) 493.
[19] K.K. Jain, An overview of drug delivery systems, Drug delivery systems (2019) 1-54.
[20] A.C. Anselmo, S. Mitragotri, An overview of clinical and commercial impact of drug delivery systems, Journal of Controlled Release 190 (2014) 15-28.
[21] A.C. Berkowitz, D.M. Goddard, Novel drug delivery systems: future directions, Journal of Neuroscience Nursing 41(2) (2009) 115-120.
[22] A. Sultana, M. Zare, V. Thomas, T.S. Kumar, S. Ramakrishna, Nano-based drug delivery systems: Conventional drug delivery routes, recent developments and future prospects, Medicine in Drug Discovery 15 (2022) 100134.
[23] O. Kayser, A. Lemke, N. Hernandez-Trejo, The impact of nanobiotechnology on the development of new drug delivery systems, Current pharmaceutical biotechnology 6(1) (2005) 3-5.
[24] M.S. Alam, A. Akhtar, I. Ahsan, S. Shafiq-un-Nabi, Pharmaceutical product development exploiting 3D printing technology: conventional to novel drug delivery system, Current pharmaceutical design 24(42) (2018) 5029-5038.
[25] V. Andretto, A. Rosso, S. Briançon, G. Lollo, Nanocomposite systems for precise oral delivery of drugs and biologics, Drug delivery and translational research 11 (2021) 445-470.
[26] G.C. Lôbo, K.L. Paiva, A.L.G. Silva, M.M. Simões, M.A. Radicchi, S.N. Báo, Nanocarriers used in drug delivery to enhance immune system in cancer therapy, Pharmaceutics 13(8) (2021) 1167.
[27] A.U. Kura, M.Z. Hussein, S. Fakurazi, P. Arulselvan, Layered double hydroxide nanocomposite for drug delivery systems; bio-distribution, toxicity and drug activity enhancement, Chemistry Central Journal 8(1) (2014) 47.
[28] M. Jafarbeglou, M. Abdouss, A.M. Shoushtari, M. Jafarbeglou, Clay nanocomposites as engineered drug delivery systems, RSC advances 6(55) (2016) 50002-50016.
[29] J.M. Kim, D.H. Kim, H.J. Park, H.W. Ma, I.S. Park, M. Son, S.Y. Ro, S. Hong, H.K. Han, S.J. Lim, Nanocomposites-based targeted oral drug delivery systems with infliximab in a murine colitis model, Journal of nanobiotechnology 18 (2020) 1-13.
[30] S. Salatin, J. Barar, M. Barzegar-Jalali, K. Adibkia, M.A. Milani, M. Jelvehgari, Hydrogel nanoparticles and nanocomposites for nasal drug/vaccine delivery, Archives of pharmacal research 39 (2016) 1181-1192.
[31] U. Chintapula, S.-U. Karim, P.R. Iyer, H. Asokan-Sheeja, B. Neupane, F. Nazneen, H. Dong, F. Bai, K.T. Nguyen, A novel nanocomposite drug delivery system for SARS-CoV-2 infections, Nanoscale Advances 6(15) (2024) 3747-3758.
[32] D. Simberg, Iron oxide nanoparticles and the mechanisms of immune recognition of nanomedicines, Taylor & Francis, 2016, pp. 741-743.
[33] S. Hussain, J.A. Vanoirbeek, P.H. Hoet, Interactions of nanomaterials with the immune system, Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology 4(2) (2012) 169-183.
[34] A.A. Aljabali, M.A. Obeid, R.M. Bashatwah, Á. Serrano-Aroca, V. Mishra, Y. Mishra, M. El-Tanani, A. Hromić-Jahjefendić, D.N. Kapoor, R. Goyal, Nanomaterials and their impact on the immune system, International journal of molecular sciences 24(3) (2023) 2008.
[35] B. Fadeel, Hide and seek: nanomaterial interactions with the immune system, Frontiers in immunology 10 (2019) 133.
[36] S. Yan, W. Gu, Z.P. Xu, Re-considering how particle size and other properties of antigen–adjuvant complexes impact on the immune responses, Journal of colloid and interface science 395 (2013) 1-10.
[37] J.M. Silva, M. Videira, R. Gaspar, V. Préat, H.F. Florindo, Immune system targeting by biodegradable nanoparticles for cancer vaccines, Journal of controlled release 168(2) (2013) 179-199.
[38] E. Vega, J.M. Burgos, E.B. Souto, M.L. García, M. Pujol, E. Sánchez-López, Biodegradable nanoplatforms for antigen delivery: part I–state of the art review of polymeric nanoparticles for cancer immunotherapy, Expert Opinion on Drug Delivery 21(8) (2024) 1251-1262.
[39] J.W. Grunberger, M.A. Dobrovolskaia, H. Ghandehari, Immunological properties of silica nanoparticles: a structure–activity relationship study, Nanotoxicology 18(6) (2024) 542-564.
[40] A. Petrizzo, C. Conte, M. Tagliamonte, M. Napolitano, K. Bifulco, V. Carriero, A. De Stradis, M. Tornesello, F. Buonaguro, F. Quaglia, Functional characterization of biodegradable nanoparticles as antigen delivery system, Journal of Experimental & Clinical Cancer Research 34 (2015) 1-13.
[41] N. Beniwal, A. Verma, C.L. Putta, A.K. Rengan, Recent trends in bio-nanomaterials and non-invasive combinatorial approaches of photothermal therapy against cancer, Nanotheranostics 8(2) (2024) 219.
[42] X. Yu, Q. Zhang, L. Wang, Y. Zhang, L. Zhu, Engineered nanoparticles for imaging and targeted drug delivery in hepatocellular carcinoma, Experimental Hematology & Oncology 14(1) (2025) 62.
[43] E. Marin, M.I. Briceño, C. Caballero-George, Critical evaluation of biodegradable polymers used in nanodrugs, International journal of nanomedicine (2013) 3071-3091.
[44] T. Akagi, M. Baba, M. Akashi, Biodegradable nanoparticles as vaccine adjuvants and delivery systems: regulation of immune responses by nanoparticle-based vaccine, Polymers in nanomedicine (2012) 31-64.
[45] G. Herrera, S. Paudel, S. Lupini, C. Astete, C. Sabliov, D. Rodrigues, Biodegradable nanoparticles aid the gut microbial community in delaying antibiotic resistance emergence, Environmental Science: Nano 11(11) (2024) 4501-4512.
[46] S.A. Arabiyat, Prospectus and Concerns of Immunomodulatory Nanotechnologies and Nanoparticles Biocompatibility and Toxicity, Nanotechnology Based Microbicides and Immune Stimulators, Springer2025, pp. 165-189.
[47] J.M. Burgos, E. Vega, M.L. García, M. Pujol, E. Sánchez-López, E.B. Souto, Biodegradable nanoplatforms for antigen delivery: part II–nanoparticles, hydrogels, and microneedles for cancer immunotherapy, Expert Opinion on Drug Delivery 21(9) (2024) 1385-1394.
[48] A. Pisani, G. Bardi, Immunology of biodegradable nanoparticles: A brief overview on a wide growing field, Exploration of Immunology 1(1) (2021) 48-60.
[49] N. Ying, X. Lin, M. Xie, D. Zeng, Effect of surface ligand modification on the properties of anti-tumor nanocarrier, Colloids and Surfaces B: Biointerfaces 220 (2022) 112944.
[50] A. Abdelkawi, A. Slim, Z. Zinoune, Y. Pathak, Surface Modification of Metallic Nanoparticles for Targeting Drugs, Coatings 13(9) (2023) 1660.
[51] P. Huang, C. Wang, H. Deng, Y. Zhou, X. Chen, Surface engineering of nanoparticles toward cancer theranostics, Accounts of Chemical Research 56(13) (2023) 1766-1779.
[52] T. Thomsen, H.-A. Klok, Chemical cell surface modification and analysis of nanoparticle-modified living cells, ACS applied bio materials 4(3) (2021) 2293-2306.
[53] F. Sabir, M. Qindeel, M. Zeeshan, Q. Ul Ain, A. Rahdar, M. Barani, E. González, M.A. Aboudzadeh, Onco-Receptors Targeting in Lung Cancer via Application of Surface-Modified and Hybrid Nanoparticles: A Cross-Disciplinary Review, Processes 9(4) (2021) 621.
[54] D.F. Moyano, Y. Liu, D. Peer, V.M. Rotello, Modulation of immune response using engineered nanoparticle surfaces, Small 12(1) (2016) 76-82.
[55] G. Moku, V.R. Gopalsamuthiram, T.R. Hoye, J. Panyam, Surface modification of nanoparticles: methods and applications, Surface modification of polymers: Methods and applications (2019) 317-346.
[56] S.M. Honmane, M.S. Charde, S.S. Salunkhe, P.B. Choudhari, S.N. Nangare, Polydopamine surface-modified nanocarriers for improved anticancer activity: Current progress and future prospects, OpenNano 7 (2022) 100059.
[57] N.H. Abd Ellah, S.A. Abouelmagd, Surface functionalization of polymeric nanoparticles for tumor drug delivery: approaches and challenges, Expert opinion on drug delivery 14(2) (2017) 201-214.
[58] Y. Choi, B.K. Cho, S.H. Seok, C. Kim, J.H. Ryu, I.C. Kwon, Controlled spatial characteristics of ligands on nanoparticles: determinant of cellular functions, Journal of Controlled Release 360 (2023) 672-686.

[59] A. Bandyopadhyay, R.L. Fine, S. Demento, L.K. Bockenstedt, T.M. Fahmy, The impact of nanoparticle ligand density on dendritic-cell targeted vaccines, Biomaterials 32(11) (2011) 3094-3105.
[60] A. Fakhari, A. Baoum, T.J. Siahaan, K.B. Le, C. Berkland, Controlling ligand surface density optimizes nanoparticle binding to ICAM-1, Journal of pharmaceutical sciences 100(3) (2011) 1045-1056.
[61] Z. Luo, Z. Yi, X. Liu, Surface engineering of lanthanide nanoparticles for oncotherapy, Accounts of Chemical Research 56(4) (2023) 425-439.