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REVIEW ARTICLE

Nano-based drug delivery systems: A comprehensive review of design, mechanisms and applications

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ABSTRACT

Nano-based drug delivery systems (NDDS) have emerged as a transformative approach in modern medicine, offering enhanced therapeutic efficacy, targeted delivery, and reduced systemic toxicity. This comprehensive review explores the fundamental design principles of NDDS, including material selection, surface functionalization, and payload encapsulation strategies. Various delivery mechanisms—such as passive and active targeting, stimuli-responsive release, and cellular uptake pathways—are examined to highlight their roles in optimizing drug bioavailability and therapeutic outcomes. The review further delves into current and emerging applications of nanocarriers across oncology, infectious diseases, neurological disorders, and gene therapy. Additionally, it addresses the challenges related to biocompatibility, large-scale production, regulatory hurdles, and clinical translation. By integrating recent advancements and interdisciplinary insights, this paper provides a holistic overview of the field and identifies promising directions for future research and development in nanomedicine.

INTRODUCTION

The use of nanoscale materials to improve the effectiveness and specificity of medicinal agents is what makes nano-based drug delivery systems (DDS) a ground-breaking medical strategy. These systems are made to enhance medication solubility, bioavailability, and targeted administration by utilizing the special physicochemical characteristics of nanomaterials. These factors are essential for the treatment of complicated illnesses like cancer and viral infections. The integration of nanotechnology into drug delivery has led to significant advancements in therapeutic outcomes, allowing for more precise treatment options with reduced side effects compared to conventional methods [1-3]. The prominence of nano-based DDS has been particularly notable in oncology, where traditional therapies often suffer from limitations related to drug distribution and rapid clearance from the body. Nanocarriers such as liposomes, polymeric nanoparticles, and dendrimers have demonstrated enhanced capabilities for encapsulating chemotherapeutic agents, thereby improving their stability and controlled release profiles [4-6]

Additionally, the creation of stimuli-responsive drug release mechanisms makes it possible for targeted therapies to deliver medications exactly where they are needed, increasing their efficacy while lowering systemic exposure[7-9]. Although nano-based DDS have many benefits, they also have significant drawbacks, such as problems with the drug's stability, toxicity, and biocompatibility within the nanocarriers. The possible negative health consequences of several nanoparticles have been questioned, highlighting the necessity of careful testing and control of these systems prior to their broad clinical use.[9-10]. Effective drug distribution is also severely hampered by the complexity of biological barriers like the blood-brain barrier, underscoring the constant need for creative solutions to get beyond these restrictions[11-12]. The investigation of novel nanomaterials and delivery methods continues to be a dynamic and

quickly changing topic as nanomedicine research progresses. In a number of medical applications, including as gene-based therapeutics and the treatment of infectious diseases, the incorporation of these technologies into clinical practice has the potential to revolutionize therapeutic techniques and ultimately improve patient outcomes [13-15].

HISTORICAL BACKGROUND

The development of drug delivery systems has undergone significant transformation over the years, culminating in the contemporary focus on nano-based technologies. Early drug delivery methods primarily relied on conventional systems, which often faced limitations regarding drug stability and targeted delivery. However, advancements in nanotechnology over the past few decades have provided innovative solutions, leveraging unique physicochemical properties of nanomaterials to enhance drug delivery efficacy [1-2]. The integration of nanotechnology into drug delivery began gaining traction in the early 2000s, when researchers recognized the potential of nanoscale materials to improve pharmacokinetic and pharmacodynamic properties of drugs [3-4]. This era marked a shift towards the development of targeted drug delivery systems capable of delivering therapeutic agents more precisely to affected tissues, thereby minimizing side effects and enhancing therapeutic outcomes[2,5]. Research into nano-drug delivery systems has particularly emphasized their advantages in cancer treatment, where traditional therapies often yield suboptimal results due to non-specific distribution and rapid clearance from the body[7,8]. The introduction of nano-carriers, such as liposomes, polymeric nanoparticles, and dendrimers, has provided platforms for the encapsulation of chemotherapeutic agents like paclitaxel, improving their stability and release profiles [2, 7, 9]. These innovations represent a significant milestone in the evolution of drug delivery systems, highlighting the promising role of nanotechnology in modern medicine[10,11]. As research progresses, the exploration of new nanomaterials continues to inspire innovative drug delivery strategies, making it a dynamic and rapidly evolving field. Current investigations are focused on optimizing the design and function of nano-carriers to further enhance targeted delivery and reduce toxicity, solidifying their place as a cornerstone of contemporary therapeutic approaches [11-13].

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DESIGN OF NANO-BASED DRUG DELIVERY SYSTEMS

Polymer Nanoparticles

Polymer nanoparticles serve as a significant category of carriers for drug delivery and can be divided into two main classes: non-biodegradable and biodegradable materials [1, 14]. Poly(lactic-co-glycolic acid) (PLGA), polyvinyl imine (PEI), polycaprolactone (PCL), and polyvinyl alcohol (PVA) are prominent examples of synthetic polymers. Due to their biocompatibility, non-toxicity, and lack of teratogenic effects, these synthetic polymers can live steadily with the majority of medications because their breakdown products do not harm cells [14, 15]. In contrast, polysaccharides, peptides, cholesterol (Chol), and cyclodextrin inclusion complexes are examples of natural polymers [13, 15]. Amphiphilic block copolymers usually self-assemble to produce polymer nanoparticles, which guarantees stability in their core and allows them to efficiently encapsulate insoluble medications [14, 16-18].

Macromolecular Carriers

Synthetic and frequently branching macromolecules are essential to nano-drug delivery systems. Because of their spherical shape, which permits monodisperse arrangements, they can be used as nano-carriers to administer and solubilize specific insoluble medications. In addition to maintaining monodispersity and having the ability to adjust their molecular weight, dendritic macromolecules' distinctive branched architectures improve their efficacy as drug delivery vehicles [19, 20]. These macromolecules are great options for drug delivery applications because they offer a large number of surface functional groups and produce a hydrophobic environment that facilitates drug encapsulation [19]. Despite their advantageous properties, the presence of surface cationic charges can limit their clinical utility [1, 20, 21-28].

Composite Nanomaterials

The development of composite nanomaterials—which combine many features for improved functionality—is being investigated more and more. This includes creating multifunctional nano-drug delivery systems (NDDSs) that can hold both therapeutic and contrast agents by incorporating metal or inorganic non-metallic nanoparticles into polymer or lipid-based systems [20, 29]. By modifying the inorganic materials organically, these hybrid systems seek

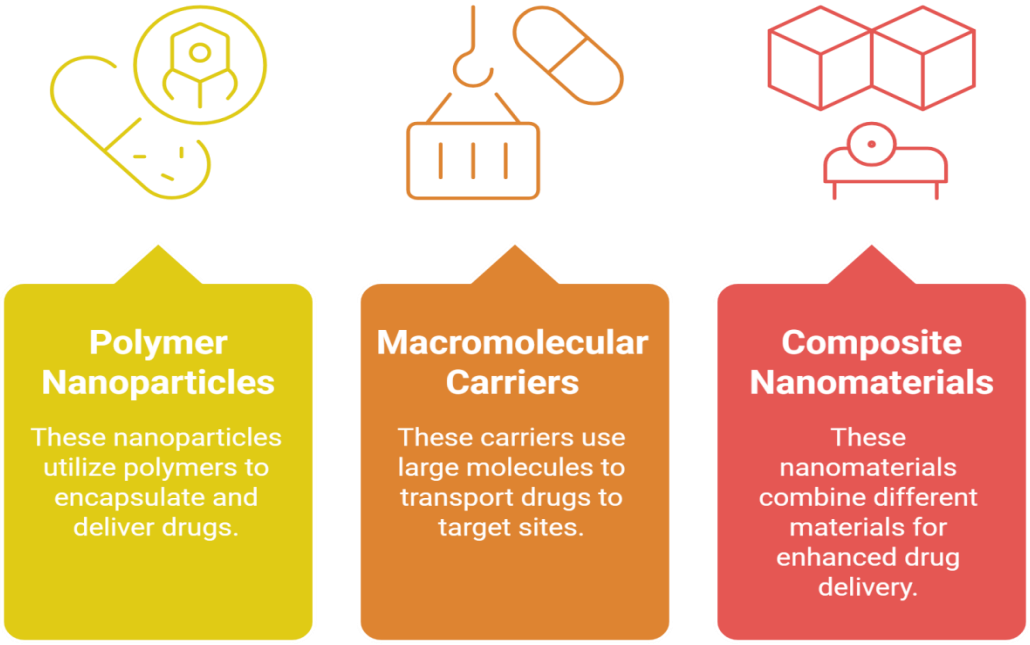

Figure 1: Types of of nano-based drug delivery systems

to enhance their physical and chemical characteristics, in vivo kinetics, and biocompatibility [30]. NDDSs with customized architectures and a variety of functions can be created by combining different metals and inorganic components [29, 31, 32].

RELEASE MECHANISMS FOR DRUGS

In nano-based drug delivery systems (DDS), drug release mechanisms are essential for guaranteeing the efficient and precise administration of medicinal drugs. In order to regulate and enhance medication release profiles, which can be roughly divided into passive and active release mechanisms, several strategies have been devised.

Mechanisms of Stimulus-Responsive Release

The regulated release of therapeutic medicines in response to particular stimuli, such as pH shifts, temperature changes, or the presence of particular biomolecules, is made possible by stimuli-responsive drug release mechanisms. This method can increase therapeutic efficacy while reducing negative effects by triggering the release of medications at the targeted site. For instance, controlled release studies have looked at the possibility of pH-sensitive linkages like hydrazone and imine, showing that drug release may be adjusted depending on the local pH environment [1, 33].

Mechanisms of Passive Release

The intrinsic qualities of the drug and the surrounding environment are used by passive drug release mechanisms to promote release. The size of the nanoparticles plays a crucial role in this mechanism since it affects their capacity to pass through biological barriers and arrive at their target locations. Nanoparticles with a size of less than 10 nanometers can readily cross capillary walls, while those ranging from 10 to 100 nanometers may undergo passive diffusion through inter-endothelial junctions, thereby entering lymphatic vessels and enhancing medication delivery to specific regions in the body [12, 34, 35].

Self-Assembly in Drug Delivery

One important factor in the development of nano-drug delivery devices is self-assembly. Self-assembled nanoparticles (NPs) derived from natural products have demonstrated encouraging outcomes in terms of loading and delivering medicinal substances. For example, under some circumstances, licorice protein has been shown to self-assemble into NPs that can encapsulate a significant quantity of aconitine,

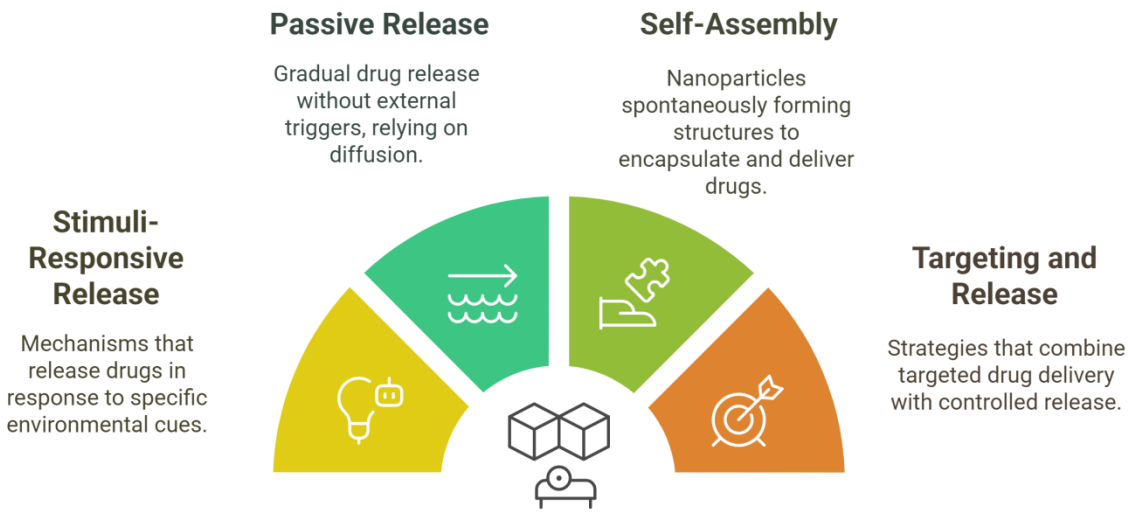

Figure 2: Drug release mechanisms in nano-based drug delivery systems

enhancing the drug's pharmacokinetics and bioavailability [1, 36]. This technique provides for tailored action at the site of interest in addition to improving medication stability and solubility.

Combining Targeting and Release Mechanisms

The effectiveness of targeted drug delivery systems relies on the integration of various mechanisms to ensure that therapeutic agents accumulate at the desired site and are released in a controlled manner. Achieving high targeting efficacy involves the retention of DDS in the physiological system long enough to target specific cells and tissues while avoiding premature degradation by the immune system [10, 11]. The combination of passive targeting through the lymphatic system and active release strategies can significantly enhance the therapeutic impact of drug delivery systems, making them a vital area of research in nanomedicine.

APPLICATIONS IN MEDICINE

Cancer Therapy

In oncology, nanoparticles have been instrumental in enhancing the delivery of chemotherapeutic agents. Various formulations, such as gold nanoparticles combined with traditional chemotherapeutics, have shown increased tumor targeting and improved therapeutic outcomes [37]. For instance, studies have demonstrated that lipid-based nanoparticles containing small interfering RNA (siRNA) targeting tau mRNA significantly reduce tau protein levels in animal models, offering a novel therapeutic strategy for tauopathies associated with neurodegenerative diseases [10]. Additionally, combining nanoparticles with heat therapy has exhibited a synergistic effect, enhancing the efficacy of both chemotherapy and radiotherapy [10, 38-40].

Overview of Nano-Based Drug Delivery Systems

With their increased effectiveness and decreased side effects compared to traditional medications, nano-based drug delivery systems (DDS) have become a revolutionary method in medical therapy. These systems are very helpful in treating complicated illnesses like cancer and viral infections since they are made to enhance the targeting and controlled release of medicinal drugs. Smart delivery carriers that can react to particular physiological triggers have been made possible by recent developments in nanocarrier technology, which optimizes medication release patterns and reduces systemic exposure [36,41].

Infectious Disease Management

Nano DDS are also being explored for treating viral and bacterial infections. Injectable nanoparticles that encapsulate antiretroviral drugs present a novel approach to delivering medication to HIV patients, thereby reducing dosing frequency and potentially serving as a preventative measure against infection [7, 36]. This method streamlines treatment regimens, increasing patient adherence and improving health outcomes [42-52].

Gene-Based Therapies

Gene delivery poses unique challenges due to biological barriers and the susceptibility of genetic material to degradation. Nanoparticles, including lipid and polymeric carriers, have

proven effective in incorporating plasmid DNA, mRNA, and siRNA for gene-based therapies. Their ability to protect and deliver genetic materials allows for innovative vaccine development and personalized medicine applications, marking a significant step forward in treating genetic disorders and enhancing immune responses [10, 53].

ADVANTAGES OF DRUG DELIVERY SYSTEMS BASED ON NANOTECHNOLOGY

Numerous benefits provided by nano-based drug delivery systems (DDS) improve the efficacy and security of medicinal substances. These advantages result from the special qualities of nanostructures, which allow them to get around a lot of restrictions related to traditional drug delivery techniques.

Enhanced Bioavailability and Solubility

One of the primary advantages of nano-DDS is their ability to significantly improve the solubility and bioavailability of poorly soluble drugs. Nanotechnology allows for the reduction of particle size, which increases the surface area and facilitates higher absorption rates in biological systems [54, 55]. This enhancement in solubility can lead to a more efficient therapeutic response, especially for drugs that typically face bioavailability challenges [56, 57-64].

Targeted Delivery

Drugs can be selectively accumulated at particular locations within the body by using nano-carriers that are designed for targeted delivery. This focused strategy reduces adverse effects linked to systemic distribution while simultaneously optimizing the drug's therapeutic impact [19, 62]. To improve the accuracy of medication administration, some ligands that bind to receptors that are overexpressed in sick tissues can be incorporated into the design of nanocarriers [66, 67].

Controlled Release Mechanisms

The use of regulated release methods is another important benefit. In order to sustain drug levels for extended periods of time, nano-DDS can be engineered to release their payloads in response to specified physiological variables, such as pH shifts or enzyme activity [14, 68]. This capability can help mitigate issues related to drug stability and side effects, as it allows for a steady release rather than a rapid bolus [1, 69, 70-72].

Biocompatibility and Biodegradability

Many nano-carriers exhibit favorable biocompatibility and biodegradability, which are crucial for reducing potential toxicity and adverse reactions in patients [8, 69]. Natural product-based nano-DDS, in particular, benefit from low-cost and environmentally friendly synthesis processes that contribute to their appeal in clinical applications [10, 41].

Prolonged Drug Retention

Nano-DDS also contribute to prolonged retention times of drugs within the bloodstream or targeted tissues. This results in a longer duration of therapeutic action and can potentially reduce the frequency of dosing [13, 54]. By extending the half-life of injectable medications, these systems can improve patient compliance and overall treatment outcomes [73].

Versatility in Applications

The versatility of nano-based drug delivery systems extends to various fields, including cancer therapy, vaccine delivery, and the treatment of chronic diseases. By optimizing the physicochemical properties of the carriers, researchers can tailor nano-DDS to meet specific clinical needs, thus broadening the scope of therapeutic interventions available [11, 74-76].

CHALLENGES AND LIMITATIONS

The efficacy and safety of nano-based drug delivery systems in clinical settings are impacted by a number of obstacles and restrictions. These restrictions fall into three general categories: delivery efficiency, stability, and biocompatibility.

Drug Stability and Release

One of the primary challenges is drug instability, which can lead to a risk of displacement and uncontrolled release of the therapeutic agents from the nanoparticles [10]. These factors can compromise the intended therapeutic outcomes, as they may affect the concentration and bioavailability of the drug at the target site. Furthermore, the release profiles of nanoparticles can be inconsistent, contributing to unpredictable pharmacokinetics and pharmacodynamics [77].

Biocompatibility and Toxicity

One major issue with using nanoparticles for medicine delivery is still biocompatibility. The ability of a biomaterial to carry out its intended function in a medical application while evoking the most suitable positive reaction in the receiver, without generating undesirable local or systemic changes, is known as biocompatibility [2].

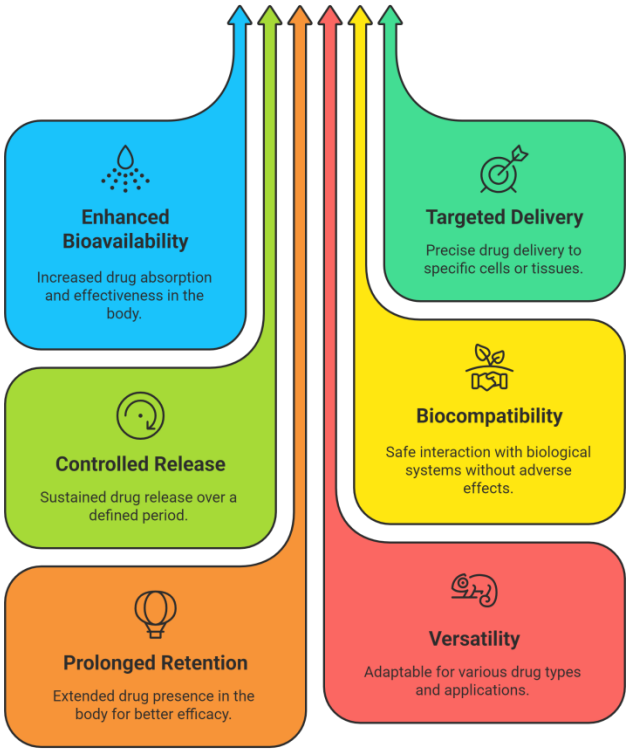

Figure 3: Advantages of nano-based drug delivery systems

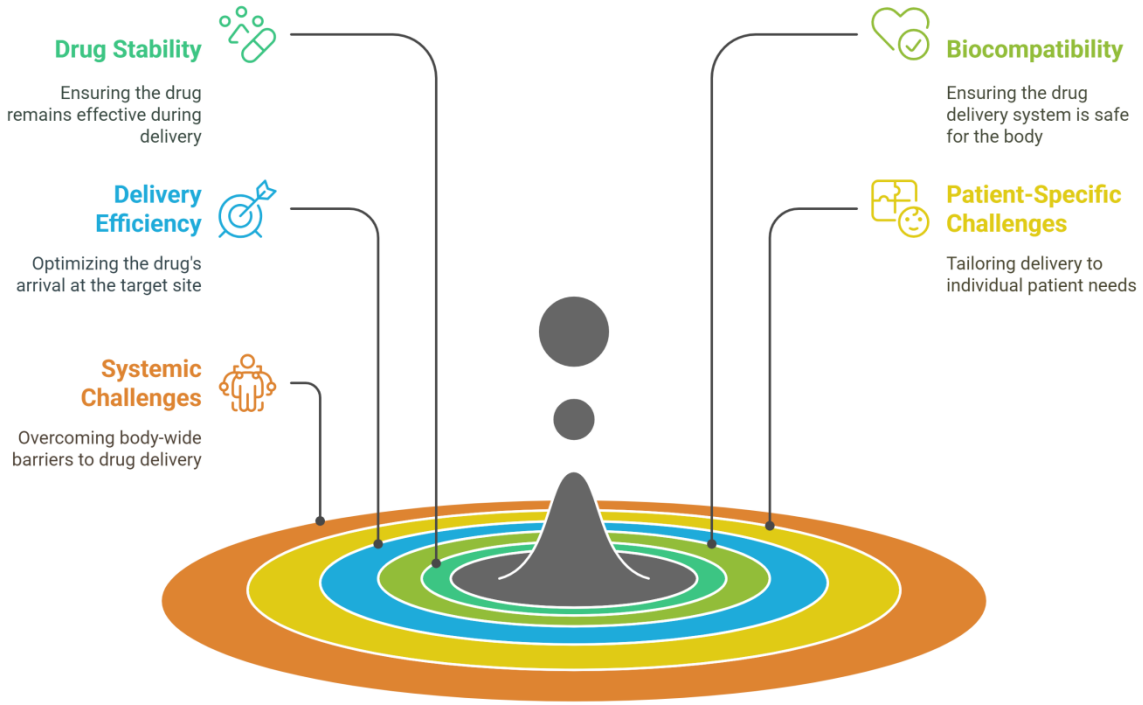

Figure 4: Challenges and limitations of nano-based drug delivery systems

The toxicity of nanoparticles can adversely affect the normal structure and physiological state of tissues and organs [3]. Studies have demonstrated size-dependent toxicity of metal oxide particles, suggesting that smaller nanoparticles may pose greater risks to cellular health compared to their larger counterparts [1, 11]. For instance, intranasal delivery of copper oxide nanoparticles has been shown to induce pulmonary toxicity and fibrosis in experimental models [1, 78].

Delivery Efficiency

The distribution of medications intended for the central nervous system is significantly hampered by the selective permeability of biological barriers, such as the blood-brain barrier (B-BB) and the blood-cerebrospinal fluid barrier (B-CSFB). These barriers can prevent nanoparticles from reaching their intended sites of action, thereby limiting their therapeutic efficacy [77]. Furthermore, problems including poor oral solubility and stability can make clinical use of nano-drug delivery systems even more challenging, possibly resulting in brief periods of efficacy and frequent dosing [79, 80].

Patient-Specific and Systemic Challenges

Systemic healthcare concerns, clinical skills, and patient-specific problems can all complicate the diagnostic journey for patients in need of nanotechnology-based therapy [11]. Variations in patient outcomes and treatment delays can be caused by any of these reasons. For nano-based drug delivery systems to be successfully incorporated into standard clinical practice, several obstacles must be removed.

CONCLUSION

Therapeutic development has advanced significantly with the advent of nano-based drug delivery technologies, which provide accurate, effective, and adaptable methods of drug administration. Utilizing the distinct physicochemical characteristics of nanomaterials, these systems have shown improved drug solubility, controlled release, targeted administration, and fewer adverse effects. The diverse design approaches, underlying mechanisms, and wide variety of biomedical applications that characterize this quickly developing discipline have all been examined in this study. Even with impressive advancements, issues including clinical translation, long-term safety, large-scale manufacture, and regulatory compliance still exist. Unlocking the full potential of nanomedicine will require addressing these obstacles through interdisciplinary cooperation and ongoing innovation. Nano-based drug delivery systems are expected to be crucial to the development of customized and precision medicine in the future as research continues to close the gap between laboratory discoveries and clinical solutions.

REFERENCES

[1] Sultana A, Zare M, Thomas V, Kumar TS, Ramakrishna S. Nano-based drug delivery systems: Conventional drug delivery routes, recent developments and future prospects. Medicine in Drug Discovery. 2022 Sep 1;15:100134.

[2] Prakash S. Nano-based drug delivery system for therapeutics: A comprehensive review. Biomedical Physics & Engineering Express. 2023 Aug 17;9(5):052002.

[3] Ezike TC, Okpala US, Onoja UL, Nwike CP, Ezeako EC, Okpara OJ, Okoroafor CC, Eze SC, Kalu OL, Odoh EC, Nwadike UG. Advances in drug delivery systems, challenges and future directions. Heliyon. 2023 Jun 1;9(6).

[4] Afzal O, Altamimi AS, Nadeem MS, Alzarea SI, Almalki WH, Tariq A, Mubeen B, Murtaza BN, Iftikhar S, Riaz N, Kazmi I. Nanoparticles in drug delivery: From history to therapeutic applications. Nanomaterials. 2022 Dec 19;12(24):4494.

[5] Sahu T, Ratre YK, Chauhan S, Bhaskar LV, Nair MP, Verma HK. Nanotechnology based drug delivery system: Current strategies and emerging therapeutic potential for medical science. Journal of Drug Delivery Science and Technology. 2021 Jun 1;63:102487.

[6] Dnyaneshwari Mahadev Shingate, Jameel Ahmed S Mulla. Exploring Liposomes: Comprehensive Classification, Preparation Techniques, and Composition Insights. Indian Journal of Novel Drug Delivery. 2024;16(2): 80-90.

[7] Vinothini K, Rajan M. Mechanism for the nano-based drug delivery system. InCharacterization and biology of nanomaterials for drug delivery 2019 Jan 1 (pp. 219-263). Elsevier.

[8] Elumalai K, Srinivasan S, Shanmugam A. Review of the efficacy of nanoparticle-based drug delivery systems for cancer treatment. Biomedical Technology. 2024 Mar 1;5:109-22.

[9] Patra JK, Das G, Fraceto LF, Campos EV, Rodriguez-Torres MD, Acosta-Torres LS, Diaz-Torres LA, Grillo R, Swamy MK, Sharma S, Habtemariam S. Nano based drug delivery systems: recent developments and future prospects. Journal of nanobiotechnology. 2018 Dec;16:1-33.

[10] Egwu CO, Aloke C, Onwe KT, Umoke CI, Nwafor J, Eyo RA, Chukwu JA, Ufebe GO,

Ladokun J, Audu DT, Agwu AO. Nanomaterials in drug delivery: strengths and opportunities in medicine. Molecules. 2024 May 31;29(11):2584.

[11] Hamid R, Manzoor I. Nanomedicines: Nano based Drug Delivery Systems Challenges and. Alternative Medicine: Update. 2021 Oct 27:59.

[12] Cheng X, Xie Q, Sun Y. Advances in nanomaterial-based targeted drug delivery systems. Frontiers in bioengineering and biotechnology. 2023 Apr 13;11:1177151.

[13] Haleem A, Javaid M, Singh RP, Rab S, Suman R. Applications of nanotechnology in medical field: a brief review. Global Health Journal. 2023 Jun 1;7(2):70-7.

[14] Suri SS, Fenniri H, Singh B. Nanotechnology-based drug delivery systems. Journal of occupational medicine and toxicology. 2007 Dec;2:1-6.

[15] Pathak C, Vaidya FU, Pandey SM. Mechanism for development of nanobased drug delivery system. Applications of targeted nano drugs and delivery systems. 2019 Jan 1:35-67.

[16] Crintea A, Dutu AG, Sovrea A, Constantin AM, Samasca G, Masalar AL, Ifju B, Linga E, Neamti L, Tranca RA, Fekete Z. Nanocarriers for drug delivery: an overview with emphasis on vitamin D and K transportation. Nanomaterials. 2022 Apr 17;12(8):1376.

[17] Vidya Ashok Kheradkar, Jameel Ahmed S. Mulla. Nanosuspension: A Novel Technology for Drug Delivery. Asian Journal of Research in Pharmaceutical Sciences. 2023; 13(2):106-110.

[18] Chejara DR, Mabrouk M, Badhe RV, Mulla JA, Kumar P, Choonara YE, du Toit LC, Pillay V. A bio-injectable algin-aminocaproic acid thixogel with tri-stimuli responsiveness. Carbohydrate polymers. 2016 Jan 1;135:324-33.

[19] Alshawwa SZ, Kassem AA, Farid RM, Mostafa SK, Labib GS. Nanocarrier drug delivery systems: characterization, limitations, future perspectives and implementation of artificial intelligence. Pharmaceutics. 2022 Apr 18;14(4):883.

[20] Abed SN, Deb PK, Surchi HS, Kokaz SF, Jamal SM, Bandopadhyay S, Tekade RK. Nanocarriers in different preclinical and clinical stages. In Basic fundamentals of drug delivery 2019 Jan 1 (pp. 685-731). Academic Press.

[21] Patil SM, Mulla JAS. Cubosomes Uncovered: Insights into Their Types, Preparation Techniques, Evaluation Methods and Emerging Applications. Indian Journal of Novel Drug Delivery. 2024;16(2):104 -112.

[22] Rane KA, Mulla JAS. Hyaluronic Acid-Coated Niosomes: A Promising Drug Delivery System with Potential Applications. Indian Journal of Novel Drug Delivery. 2024;16(1):11-19.

[23] Shewale SS, Mulla JA. Non-Ionic Surfactant Vesicle (Niosome): A Novel Drug Delivery System. Indian Journal of Novel Drug Delivery. 2022;14(3):129-37.

[24] Patil KS, Mulla JAS. A Review on Microemulsion Based Hydrogel for Topical Drug Delivery. World Journal of Molecular Pharmaceutics. 2023; 1(1): 22-33.

[25] Mulla JAS, Karande BS. Microemulsion based hydrogel formulation for topical drug delivery - A concise review. Indian Journal of Novel Drug Delivery. 2021;13(2): 63-69.

[26] Jameel S. Mulla, Payal Pujari, Onkar S. Sangar. An Overview of the Transdermal Drug Delivery System. International Journal of Creative Research Thoughts. 2022; 10(5): a497-a507.

[27] Jadhav VU, Jamakandi VG, Mulla JA, Borkar SN, Karpe P, Suresh R, Dama GY, Sanap GS, Chatap VK. Reservoir Type Nicorandil Transdermal Delivery System By Using Permeation Enhancers. Indian Drugs 2009; 46(9): 23-31.

[28] Jamakandi V.G., Mulla J.S., Vinay B.L., Shivakumar H.N. Formulation, characterization and evaluation of matrix type trandermal patches of model antihypertensive drug. Asian Journal of Pharmaceutics 2009;3:59-65.

[29] Kim M, Shin M, Zhao Y, Ghosh M, Son YO. Transformative Impact of Nanocarrier-Mediated Drug Delivery: Overcoming Biological Barriers and Expanding Therapeutic Horizons. Small Science. 2024 Nov;4(11):2400280.

[30] Kumarasamy RV, Natarajan PM, Umapathy VR, Roy JR, Mironescu M, Palanisamy CP. Clinical applications and therapeutic potentials of advanced nanoparticles: A comprehensive review on completed human clinical trials. Frontiers in Nanotechnology. 2024 Oct 21;6:1479993.

[31] Chavhan R. Nanosuspensions: Enhancing drug bioavailability through nanonization.

InAnnales Pharmaceutiques Françaises 2024 Jun 28. Elsevier Masson.

[32] Mulla JA, Mabrouk M, Choonara YE, Kumar P, Chejara DR, du Toit LC, Pillay V. Development of respirable rifampicin-loaded nano-lipomer composites by microemulsion-spray drying for pulmonary delivery. Journal of Drug Delivery Science and Technology. 2017 Oct 1;41:13-19.

[33] Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. Nature reviews drug discovery. 2021 Feb;20(2):101-24.

[34] Cheng X, Xie Q, Sun Y. Advances in nanomaterial-based targeted drug delivery systems. Front Bioeng Biotechnol. 2023; 11: 1177151. Proyección de los nanomateriales en la medicina del futuro Antonio Jesús Salinas Sánchez.

[35] Wilczewska AZ, Niemirowicz K, Markiewicz KH, Car H. Nanoparticles as drug delivery systems. Pharmacological reports. 2012 Sep 1;64(5):1020-37.

[36] Din FU, Aman W, Ullah I, Qureshi OS, Mustapha O, Shafique S, Zeb A. Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. International journal of nanomedicine. 2017 Oct 5:7291-309.

[37] Saleem K, Khursheed Z, Hano C, Anjum I, Anjum S. Applications of nanomaterials in leishmaniasis: A focus on recent advances and challenges. Nanomaterials. 2019 Dec 9;9(12):1749.

[38] Mulla JA, Suresh S, Khazi IA. Formulation, characterization and in vitro evaluation of methotrexate solid lipid nanoparticles. Research J. Pharm. and Tech. 2009;2(4):685-9.

[39] Maiti D, Naseeruddin Inamdar M, Almuqbil M, Suresh S, Mohammed Basheeruddin Asdaq S, Alshehri S, Ali Al Arfaj S, Musharraf Alamri A, Meshary Aldohyan M, Theeb Alqahtani M, Mohammed Alosaimi T, Haran Alenazi S, Almadani ME, Ahmed S Mulla J, Imam Rabbani S. Evaluation of solid-lipid nanoparticles formulation of methotrexate for anti-psoriatic activity. Saudi Pharm J. 2023;31(6):834-844. doi: 10.1016/j.jsps.2023.04.007.

[40] Mulla JA. Drug Delivery and Therapeutic Approaches to Prostate Cancer. Indian Journal of Novel Drug Delivery. 2018;10(3):98-109.

[41] Lamberti M, Zappavigna S, Sannolo N, Porto S, Caraglia M. Advantages and risks of nanotechnologies in cancer patients and occupationally exposed workers. Expert opinion on drug delivery. 2014 Jul 1;11(7):1087-101.

[42] Panchamukhi SI, Mulla JA, Shetty NS, Khazi MI, Khan AY, Kalashetti MB, Khazi IA. Benzothieno [3, 2-e][1, 2, 4] triazolo [4, 3-c] pyrimidines: Synthesis, Characterization, Antimicrobial Activity, and Incorporation into Solid Lipid Nanoparticles. Archiv der Pharmazie. 2011;344(6):358-65.

[43] Mulla JAS, Khazi MIA, Khan AY, Gong YD, Khazi IAM. Design, Characterization and In vitro Evaluation of Imidazo[2,1-b][1,3,4]thiadiazole Derivative Loaded Solid Lipid Nanoparticles. Drug Invention Today. 2012;4(8): 420-423.

[44] Gosavi AA, Thorat PA, Mulla JAS. Formulation and Evaluation of Acyclovir Loaded Transferosomal Gel for Transdermal Drug Delivery. J. Drug Delivery Ther. 2024;14(9):122-30.

[45] Mulla JA, Palkar MB, Maddi VS, Khazi IA. Rational design of antibacterial thienopyrimidines by 2D-QSAR study. J. Drug Delivery Ther. 2012;2(2):55-66.

[46] Mulla JAS, Palkar MB, Maddi VS, Khazi IAM. 2D-QSAR study of thienopyrimidine derivatives: An approach to design effective anti-bacterial agents. International Journal of Drug Design and Discovery. 2012;3:784-797.

[47] Nalawade SN, Mulla JAS, Kapse MV. Formulation and characterization of a topical Murraya koenigii gel for antibacterial activity. World Journal of Molecular Pharmaceutics. 2023;1(1): 34-40.

[48] Mulla JAS, Khazi MIA, Panchamukhi SI, Gong YD, Khazi IAM. Synthesis and pharmacological evaluation of novel thienopyrimidine and triazolothienopyrimidine derivatives. Medicinal Chemistry Research. 2014;23:3235-3243.

[49] Mulla JS, Khan AY, Panchamukhi SI, Khazi MA, Kalashetti MB, Khazi IM. Synthesis and Antitubercular Activity of Mannich bases of imidazo[2,1-b][1,3,4]thiadiazoles. Indian Journal of Novel Drug delivery. 2011;3(4):289-295.

[50] Badiger NP, Mulla JS, Khazi I, Khazi IM. Synthesis and antimicrobial activity of

sulfide and sulfone derivatives of 4-(2-chloro-4-fluorophenyl)-1, 3-thiazol-2-amine/acetamide. Pharmaceutical Chemistry Journal. 2013;46:667-671.

[51] Ashok B, Kumar Naik KH, Mulla JAS, Naik N. An agile synthesis of 5-phenyl-1, 2, 3-selenadiazoles by using dabco as an efficient catalyst and their analgesic and anti-inflammatory activity. Indo American Journal of Pharmaceutical Research. 2015;5(4): 1404-1410.

[52] Kumar Naik KH, Ashok B, Naik N, Mulla JAS, Prakasha A. DNA binding, anti-inflammatory and analgesic evaluation of metal complexes of N/S/O donor ligands; Synthesis, spectral characterization. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2015;141:88-93.

[53] Mulla JAS, Shetty NS, Panchamukhi SI, Khazi IAM. Formulation, Characterization and *in vitro* Evaluation of Novel Thienopyrimidines and Triazolothienopyrimidines Loaded Solid Lipid Nanoparticles. International Journal of Research in Ayurveda & Pharmacy. 2010; 1(1): 192-200.

[54] Gunasekaran T, Haile T, Nigusse T, Dhanaraju MD. Nanotechnology: an effective tool for enhancing bioavailability and bioactivity of phytomedicine. Asian Pacific journal of tropical biomedicine. 2014 May 1;4:S1-7.

[55] Grifoni L, Vanti G, Donato R, Sacco C, Bilia AR. Promising nanocarriers to enhance solubility and bioavailability of cannabidiol for a plethora of therapeutic opportunities. Molecules. 2022 Sep 17;27(18):6070.

[56] Liu Y, Liang Y, Yuhong J, Xin P, Han JL, Du Y, Yu X, Zhu R, Zhang M, Chen W, Ma Y. Advances in nanotechnology for enhancing the solubility and bioavailability of poorly soluble drugs. Drug Design, Development and Therapy. 2024 Dec 31:1469-95.

[57] Mulla JAS, Chalke PM, Londhe SP, Patil MA, Nalawade SN, Sawant RR. Design and Optimization of Nanosponges of Poorly Soluble Voriconazole Using Central Composite Design. Indian Journal of Novel Drug Delivery. 2023;15(4): 189-199.

[58] Mhoprekar JD, Mulla JA. Nanosponges drug delivery: A concise review. World Journal of Nanoparticle Research. 2023;1(1):17-28.

[59] Mabrouk M, Chejara DR, Mulla JA, Badhe RV, Choonara YE, Kumar P, Du Toit LC, Pillay V. Design of a novel crosslinked HEC-PAA porous hydrogel composite for dissolution rate and solubility enhancement of efavirenz. International journal of pharmaceutics. 2015 Jul 25;490(1-2):429-37.

[60] Hogale AB, Mulla JAS. Formulation and Characterization of rapidly dissolving buccal films of montelukast sodium. Indian Journal of Novel Drug Delivery. 2021; 13(3): 144-148.

[61] Nikam GG, Mulla JAS. Design, Development and Characterization of Fast Dissolving Oral Film of Clonazepam. Indian Journal of Novel Drug Delivery. 2020Jan-Mar; 12(1): 48-54.

[62] Mulla JS, Khazi IM. Influence of Process Variables on Particle Size of Solid Lipid Nanoparticles. Indian Journal of Novel Drug Delivery. 2009; 1(1): 47-49.

[63] Mulla JAS, Hajare SC, Doijad RC. Particle Size and It's Importance in Industrial Pharmacy: A Review. Indian Journal of Novel Drug delivery. 2016;8(4):191-198.

[64] Mulla JS, Sharma NK, Khazi IM. Solid lipid nanoparticles: Measures of characterization. Indian Journal of Novel Drug delivery. 2011;3(2): 258-263.

[65] Dunuweera SP, Rajapakse RM, Rajapakshe RB, Wijekoon SH, Nirodha Thilakarathna MG, Rajapakse RM. Review on targeted drug delivery carriers used in nanobiomedical applications. Current Nanoscience. 2019 Aug 1;15(4):382-97.

[66] Lv Y, Li W, Liao W, Jiang H, Liu Y, Cao J, Lu W, Feng Y. Nano-drug delivery systems based on natural products. International Journal of Nanomedicine. 2024 Dec 31:541-69..

[67] Mabrouk M, Mulla JA, Kumar P, Chejara DR, Badhe RV, Choonara YE, du Toit LC, Pillay V. Intestinal targeting of ganciclovir release employing a novel HEC-PAA blended lyomatrix. AAPS PharmScitech. 2016 Oct;17(5):1120-30.

[68] De Jong WH, Borm PJ. Drug delivery and nanoparticles: applications and hazards. International journal of nanomedicine. 2008 Dec 1;3(2):133-49.

[69] Hami Z. A brief review on advantages of nano-based drug delivery systems. Annals of Military and Health Sciences Research. 2021 Jan 1;19(1).

[70] Mulla JAS, Aralelimath VR, Tipugade O, Shinde SS, Tetgure NG, Mulla AA, Gavali DD. Formulation and Evaluation of Teneligliptin-Loaded Mucoadhesive

Microspheres. Indian Journal of Novel Drug Delivery. 2020;12(4): 222-227.

[71] Naikawadi AN, Mulla JAS. Review on classification and factors influencing the design of sustained release formulations. World Journal of Drug Delivery 1(1), Jan-Mar, 2023, 28-33.

[72] Chakorkar SS, Mulla JAS. Cubosome-based Corticosteroidal Drug Delivery System for Sustained Ocular Delivery: A Pharmacokinetic Investigation. Ind. J. Pharm. Edu. Res. 2024;28(2s): s502-s514.

[73] Mabrouk M, Bijukumar D, Mulla JA, Chejara DR, Badhe RV, Choonara YE, Kumar P, du Toit LC, Pillay V. Enhancement of the biomineralization and cellular adhesivity of polycaprolactone-based hollow porous microspheres via dopamine bio-activation for tissue engineering applications. Materials Letters. 2015 Dec 15;161:503-7.

[74] Singh R, Lillard Jr JW. Nanoparticle-based targeted drug delivery. Experimental and molecular pathology. 2009 Jun 1;86(3):215-23.

[75] Mukesh Vinod Kapse and Jameel Ahmed S. Mulla. Unlocking the potential of phytosomes: a review of formulation techniques, evaluation methods, and emerging applications. Acta Materia Medica. 2024;3(4):509-520

[76] Vidya A Kheradkar, Jameel Ahmed S Mulla. Phytosomes: An advanced drug delivery system. World Journal of Pharmacognosy & Phytochemistry. 2023; 1(1): 1-8

[77] Lv Y, Li W, Liao W, Jiang H, Liu Y, Cao J, Lu W, Feng Y. Nano-drug delivery systems based on natural products. International Journal of Nanomedicine. 2024 Dec 31:541-69.

[78] Shirke SN, Mulla JAS. Intranasal nanoemulsion for brain targeting: A review. Indian Journal of Novel Drug Delivery. 2023;15(1): 1-11.

[79] Suri SS, Fenniri H, Singh B. Nanotechnology-based drug delivery systems. Journal of occupational medicine and toxicology. 2007 Dec;2:1-6.

[80] Dubal R B, Mulla J A S, Kapse M V, Design, development and characterization of ketorolac tromethamine-loaded transdermal patches. J Pharm Biol Sci. 2024;12(2):144-150.