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Review Article

A Brief Review on Nanomedicine Used for Targeted Drug Delivery

Dipanshu Suryawanshi*, Saloni Chimankare, Rohit Kumbhar

Research Scholar, METs Institute of Pharmacy, Adgaon, Nashik, Maharashtra.

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ABSTRACT

Nanomedicine has emerged as a transformative strategy for drug delivery, characterized by its ability to precisely target affected areas, enhance drug availability in the body, and decrease overall toxicity. The use of nanocarriers, including liposomes, dendrimers, polymeric nanoparticles, and lipid-based nanostructures, allows for the direct administration of pharmaceuticals to diseased tissues, thereby reducing adverse effects and improving therapeutic effectiveness. In contrast, active targeting enhances the delivery process by equipping nanoparticles with specific ligands, such as antibodies, peptides, or aptamers, which selectively bind to receptors that are overexpressed on cancerous cells, thereby facilitating accurate drug localization. The scope of nanomedicine encompasses various fields such as oncology, neurology, infectious diseases, and gene therapy, indicating its ability to transform contemporary medical practices.

INTRODUCTION

Nanoparticle-based drug delivery systems have been the subject of investigation for over four decades, representing one of the most dynamic interdisciplinary research domains currently [1-2]. Ideally, such systems would facilitate the delivery of medications precisely where and when they are required, in the necessary quantities. In recent years, there has been a growing focus on the development of targeted and stimulus-responsive nanomaterials to meet these objectives. Targeted nanoparticles are characterized by their ability to preferentially concentrate in specific tissues compared to non-targeted areas. Stimulus-responsive drug delivery systems initiate drug release or targeted delivery contingent upon a specific trigger. Some of these systems utilize natural environmental factors, including pH levels, hypoxia, or enzyme activity, as stimuli for drug release[3-4]; these are commonly categorized as "passive" systems. Conversely, other systems rely on external stimuli, such as light, ultrasound, or chemical triggers, to activate drug delivery processes[5].The targeting of specific tissues can

***Corresponding Author:** Dipanshu Suryawanshi
Address: Research Scholar, METs Institute of Pharmacy, Adgaon, Nashik, Maharashtra.
Email ✉: deepanshu.suryawanshi007@gmail.com
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also be accomplished by attaching a particular ligand to the surface of nanoparticles [6]. Systems that do not depend solely on general tissue characteristics are typically categorized as "active." The primary objective is to enhance the therapeutic effect of a drug by maximizing the amount of free drug that accumulates (targeting) or is released (triggering) at the designated site of action, thereby improving efficacy while reducing toxicity. Although there is a substantial body of experimental evidence indicating that these methods may be effective, a number of nanoencapsulated drugs have received FDA approval or have progressed to clinical trials[7].Activation by an external stimulus can enhance the delivery to or release at targeted sites, potentially even when tissue characteristics that typically induce such responses are lacking, thereby facilitating targeted approaches without needing a specific ligand. One strategy involves modifying a nanoparticle with a ligand that interacts broadly with various cell membranes, such as derivatives of arginine-glycine-aspartate (RGD) or cell-penetrating peptides. The introduction of a photosensitive component can inactivate the ligand, making it responsive to light, which allows for the localized accumulation of the nanoparticle upon irradiation [8].

Drug delivery systems and its generations:

Drug delivery (DD) encompasses the various methods, formulations, technologies, and processes used to transport pharmaceutical substances within the body to achieve intended therapeutic outcomes [9-10]. This field includes strategies for administering medications to both humans and animals to ensure optimal therapeutic effects. Recent advancements in drug delivery systems (DDSs) have increasingly emphasized the development of smart DD, which aims for precise administration of drugs concerning timing, dosage, and site of delivery while prioritizing safety and efficacy [11]. The rise of novel drug delivery systems (NDDSs) has garnered significant interest, as these systems improve the therapeutic potential of both new and established medications through targeted, controlled, and sustained release mechanisms that align with actual drug demands [10]. The realm of DD is evolving rapidly within pharmaceutical sciences, with five distinct generations of DDSs, where targeted delivery is categorized as part of the fourth generation [12]. Figure 1 depicts the evolution of drug delivery systems (DDSs). In recent decades, the development of sustained or controlled DDSs has gained significant attention, aiming to regulate and/or prolong drug release, minimize dosing frequency, or enhance drug effectiveness relative to traditional delivery methods. An example of a novel drug delivery system (NDDS) is bilayer tablets, which utilize modifications to standard drug preparation and administration techniques. These tablets consist of either two doses of the same medication or different medications combined in a single dosage form, enabling sequential release of the drugs or providing both sustained and immediate release of a singular drug, serving one part as a loading dose and the other as a maintenance dose [13].

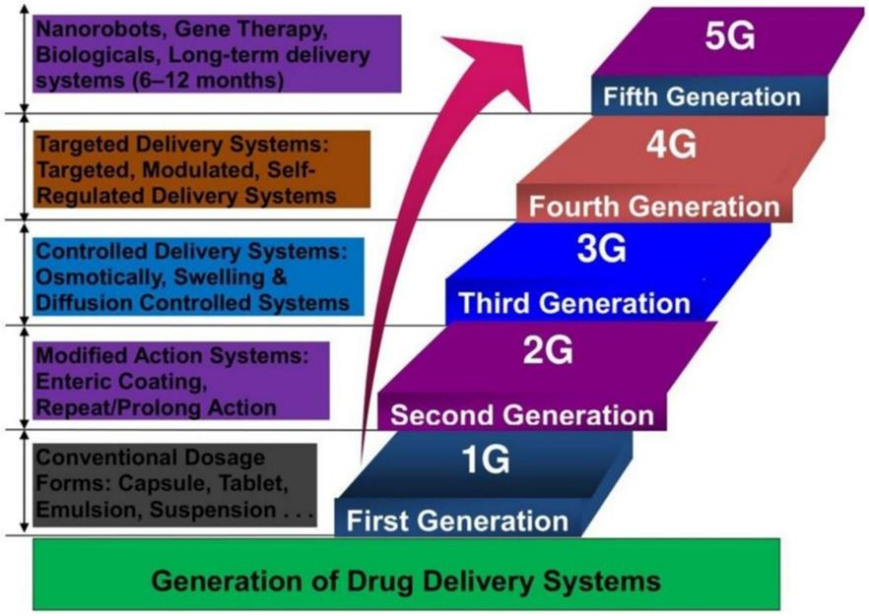

Figure1.Generation of Drug-Delivery Systems

Modifications in traditional drug delivery systems (DDS) signify notable progress; however, certain DDS types require further refinement. These include the delivery of poorly soluble drug formulations, protein delivery, self-regulated insulin delivery, and targeted drug delivery systems (TDDSs). One significant advancement that nanotechnology can enable is the targeted delivery of therapeutics to tumors. TDDSs specifically deliver drugs to designated sites rather than dispersing them throughout the entire body or organ, integrating various scientific disciplines such as polymer science, pharmacology, bioconjugate chemistry, and molecular biology. The objective of TDDS is to manage and regulate pharmacokinetics, pharmacodynamics, off-target toxicity, immunogenicity, and biorecognition of therapeutics[14].Additionally, nanoparticle (NP)-based drug delivery offers the potential for controlled drug release, providing adequate time for drugs to exert their therapeutic effects while responding to specific stimuli, including pH changes, light, heat, or enzymes[15]. Targeted Drug Delivery Systems (TDDSs) focus on delivering medication to specific sites within the body, rather than dispersing it throughout the entire system or targeting a whole organ. These systems integrate various scientific disciplines, including polymer science, pharmacology, bioconjugate chemistry, and molecular biology. The primary objective of TDDS is to manage and control parameters such as pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, and biorecognition of therapeutic agents[16]. Ultimately, this approach aims to enhance the efficacy of treatments while minimizing adverse effects. Unlike traditional Drug Delivery Systems (DDSs), which rely on the general absorption of drugs through biological membranes, TDDSs facilitate a targeted and site-specific release of drugs from their dosage forms[17].

Nano based drug delivery systems:

As nanomedicine continues to advance, significant progress in drug discovery and delivery systems has led to numerous therapeutic strategies and an examination of traditional clinical diagnostic techniques aimed at enhancing drug specificity and diagnostic precision. For example, novel methods of drug administration are currently being

investigated, emphasizing their targeted efficacy in specific areas to minimize toxicity and enhance bioavailability within biological systems [18-19]. In this framework, drug design emerges as a critical element in the development of new lead compounds, informed by an understanding of biological targets. The evolution of computer science, alongside improvements in experimental methodologies for the identification and purification of proteins, peptides, and biological targets, is vital for the advancement of this field [20-21]. Numerous studies and reviews have documented the rational design of various molecules, highlighting the significance of exploring different drug release mechanisms [22]. Furthermore, natural products offer promising solutions to the challenges of drug design and can inspire the discovery of compounds with desired physicochemical attributes [23-25]. Notably, each drug delivery system possesses distinct chemical, physical, and morphological properties, which can affect their interaction with drugs of varying polarities through both chemical and physical interactions, including covalent bonds, hydrogen bonds, electrostatic interactions, and van der Waals forces[26]. The composition of nanocarriers—whether organic, inorganic, or hybrid—and the method by which drugs are integrated, such as core-shell or matrix systems, are crucial for understanding their delivery profiles[27-28]. Collectively, research into the release mechanisms of drugs from nanocarriers has identified various processes, including diffusion, solvent interactions, chemical reactions, and stimuli-controlled release, each of which is critical for elucidating drug release dynamics within these systems are shown in Fig 2. [29-30].

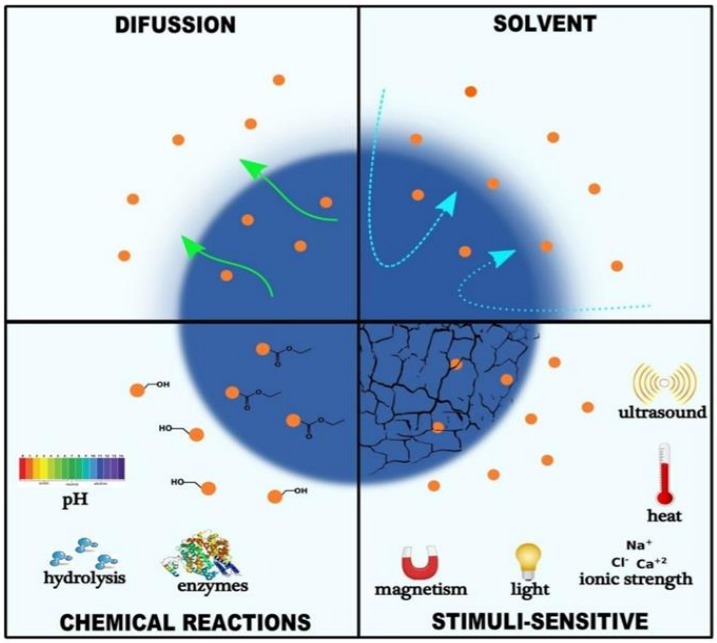

Figure 2. Mechanisms For Controlled Release of Drugs Using Different Types of Nanocarriers

Multifunctional nanoparticles:

Gao et al. [31] and Choi et al. [32] have detailed the application of a multifunctional nanoparticle, which integrates biomolecules with quantum dots (QDs), for the purposes of targeting cancer and facilitating drug delivery. To achieve the targeting of malignant cells, they attached A10 RNA—a specific aptamer that identifies prostate-specific membrane antigen (PSMA)—to the QD. The chemotherapeutic agent doxorubicin (DOX), known for its anthracycline properties and

fluorescence, was incorporated into this conjugate. This innovative conjugate provides an advanced approach for imaging cancer cells. The presence of intercalated DOX within the A10 RNA-QD conjugate suppresses the fluorescence of both DOX and the quantum dot. Upon encountering the designated cancer biomarker, the QD-aptamer (DOX) conjugate is internalized by the cancer cell through endocytosis. Following the release of DOX from the conjugate, both entities regain their fluorescent characteristics, enabling imaging capabilities. This design strategy for the multifunctional nanoparticle ensures the precise detection of cancer biomarkers while simultaneously delivering the drug into the cancer cell, thereby achieving a high degree of specificity.

Nanomedicine in cancer therapy:

In recent decades, significant resources have been allocated to improving the administration of nanotherapeutics for the treatment of solid tumors. Matsumura and Maeda were the first to illustrate, in 1986, that macromolecules within a specific molecular weight range show a tendency to preferentially accumulate in solid tumors through a mechanism known as the enhanced permeability and retention (EPR) effect. This discovery has facilitated the targeted delivery of macromolecular drugs and nanomedicines to tumor tissues[34]. However, it has become increasingly evident that the EPR effect is more intricate than initially understood. It exhibits considerable variability not only across different patients but also among various tumor types, attributed to the intrinsic heterogeneities in tumor genetic profiles, tumor microenvironments, and the physicochemical characteristics of nanoparticles[35-36]. Although supplementary methods have been proposed to mitigate the heterogeneity associated with the EPR effect and enhance tumor targeting, many patients still experience tumors characterized by non-permeable blood vessels, which limit the effectiveness of EPR-mediated delivery of nanomedicines. Consequently, a range of alternative strategies, including tumor vascular targeting, cell-mediated tumor targeting, iRGD-mediated tumor targeting, and locoregional delivery, have been suggested for achieving EPR-independent tumor targeting(fig.3)[37-39].

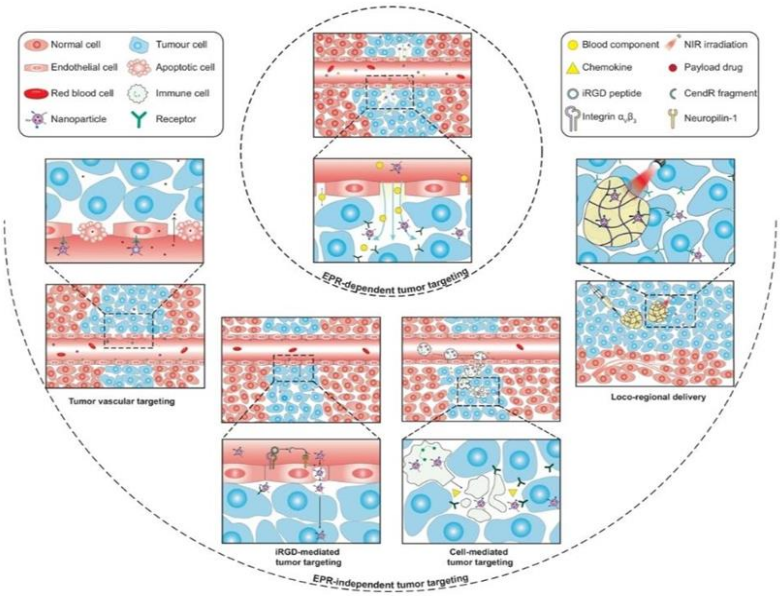

Figure 3: Schematic illustration of EPR-dependent and -independent strategies for tumor tissue-targeted nanoparticle delivery

Recent advancements in cancer research have led to the identification of several critical hallmarks associated with neoplastic diseases, which aid in elucidating their underlying mechanisms. Investigations into the molecular features of cancer pathogenesis have paved the way for the development of mechanism-based targeted therapies aimed at treating human cancers [41]. By concentrating on the primary mediators involved in the molecular proceses of cancer development, researchers have engineered multi-functional nanomedicine specifically for targeted cancer therapy. (Fig 4)

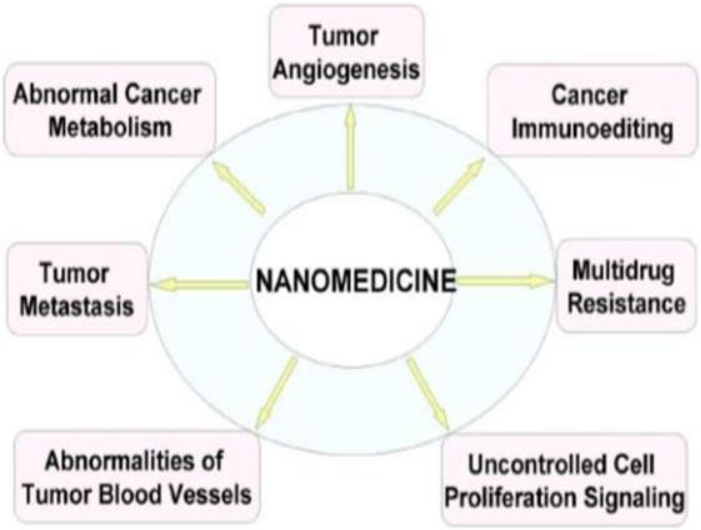

Figure 4: The application of nanotechnology for selective targeting the emerging hallmarks of cancer

Nanosystems in inflammation:

Over the last twenty years, numerous cell adhesion molecules have been identified. These glycoproteins, located on the cell surface, function as receptors facilitating both cell-to-cell and cell-to-extracellular matrix adhesion [42-44]. Cell adhesion molecules are categorized into four primary classes: integrins, cadherins, selectins, and the immunoglobulin superfamily. They are essential for the effective migration of inflammatory cells like neutrophils and monocytes into inflamed tissues and for orchestrating the host's response to infections. Nevertheless, substantial evidence indicates that excessive neutrophil migration in inflamed lungs can result in significant tissue injury and increased mortality. Hence, ongoing research is focused on optimizing neutrophil migration into affected organs. Advancements in the understanding of cell adhesion molecules have influenced the design and development of therapeutic agents (including peptides and proteins) for potential treatments of cancer, cardiovascular, and autoimmune diseases [45-47]. These molecules play crucial roles in various conditions, including cancer [48-49], thrombosis [50-51], and autoimmune disorders such as type-1 diabetes [52-54]. RGD peptides have been employed to specifically target integrins αvβ3 and αvβ5, while peptides derived from intercellular adhesion molecule-1 (ICAM-1) are used to target the αvβ2 integrin. Additionally, peptides originating from αvβ2 can interact with ICAM-1 expressing cells. Cyclic RGD peptides have been conjugated with paclitaxel (PTX-RGD) and doxorubicin (Dox-RGD4C) to enhance the targeted delivery of these drugs to tumor cells. In experiments involving mice harboring human breast carcinoma cells (e.g., MDA-MB-435),

those treated with Dox-RGD4C showed survival, whereas all control mice that did not receive treatment succumbed to the disease [55]. This conjugate effectively targets αvβ3 and αvβ5 integrins present on the tumor vasculature during the process of angiogenesis.

CONCLUSION:

Nanomedicine has transformed the landscape of targeted drug delivery by significantly improving therapeutic efficacy while reducing adverse effects. Utilizing nanocarriers like liposomes, dendrimers, polymeric nanoparticles, and lipid-based nanoparticles enables the targeted administration of drugs directly to diseased cells, thereby enhancing bioavailability and lowering systemic toxicity. However, despite its significant promise, several challenges persist, including issues related to scalability, stability, immune responses, and the regulatory approval process. Future developments in nanotechnology, particularly personalized nanomedicine and stimuli-responsive nanocarriers, hold the potential to optimize drug delivery systems further. Ongoing research and collaboration among scientists, healthcare professionals, and regulatory agencies are crucial to maximize the clinical benefits of nanomedicine.

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