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NANOPARTICLES IN DRUG DELIVERY

*Chandramani Charasiya, Vishal Singh

Student Suyash Institute of Pharmacy, Hakka bad, Gorakhpur.

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***Corresponding Author: Chandramani Charasiya**
Student Suyash Institute of Pharmacy, Hakka bad, Gorakhpur.

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ABSTRACT

Recent research on engineered nanoparticles in drug delivery systems (DDSs) has led to the development of a variety of innovative nanocarriers. This review examines both traditional and modern drug carriage systems. Because of the limitations of conventional DDSs, nanocarriers have attracted significant attention. These include polymeric nanoparticles, mesoporous nanoparticles, nanomaterials, carbon nanotubes, dendrimers, liposomes, metallic nanoparticles, nanomedicine, and engineered nanomaterials, which are designed to deliver drugs specifically to targeted sites within the body.

Nanomedicine has advanced rapidly and is being applied to treat conditions such as brain cancer, lung cancer, breast cancer, cardiovascular diseases, and others. These systems offer several advantages, including improved drug bioavailability, faster absorption, controlled release, prevention of drug aggregation, and enhanced solubility in the bloodstream. Nanomedicine represents a transformative advancement in drug delivery, optimizing the therapeutic potential of active pharmaceutical ingredients encapsulated in nanoparticles.

This review compiles key insights on engineered nanoparticles and their applications in targeted drug delivery for various diseases. Most of these nanocarriers have undergone both in vitro and in vivo testing. Looking ahead, further integration of advanced techniques into nanomedicine is expected to enhance the effectiveness of drug delivery systems, thereby improving human health significantly.

KEYWORDS: drug delivery, nanomedicine, therapeutics, nanoparticles, personalized medicine.

INTRODUCTION

Drug delivery systems (DDSs) have long been used to treat a variety of diseases. All medications depend on pharmacologically active compounds (drugs) to produce therapeutic

effects [1]. Some drugs are administered as inactive precursors that only become active after being metabolized within the body [2]. The success of these drugs largely depends on their route of administration. In conventional drug delivery systems (CDDSs), drugs were commonly administered orally, nasally, by inhalation, through mucosal routes, or via injection [3]. However, such methods often resulted in poor absorption, random distribution, unintended damage to healthy tissues, premature elimination from the body, and prolonged treatment periods [4]. Their effectiveness was limited by factors such as enzymatic degradation, variations in pH, mucosal barriers, lack of precise targeting, and the rapid release of drugs, which could increase toxicity in the bloodstream [5]. Nanotechnology is the intentional engineering and manipulation of particulate matter into a physical state of between 1 nm and 100 nm that can be rearranged or reassembled into nano-systems with improved function [6]. The emergence of nanotechnology and its application have put Ireland for instance, at the forefront of scientific research in the last decade [2]. Nanoparticles are the ultimate result of the technological modification of matter, and depending on their sizes, they are a few degrees larger than an atom consequence of the molecular processing of matter. As they possess enhanced characteristics such as auto-reactive stability and self-reassembly, they are easily adaptable and can be modified to achieve a specific characteristic or intended properties such as high surface area when compared to conventional substances [3,4].

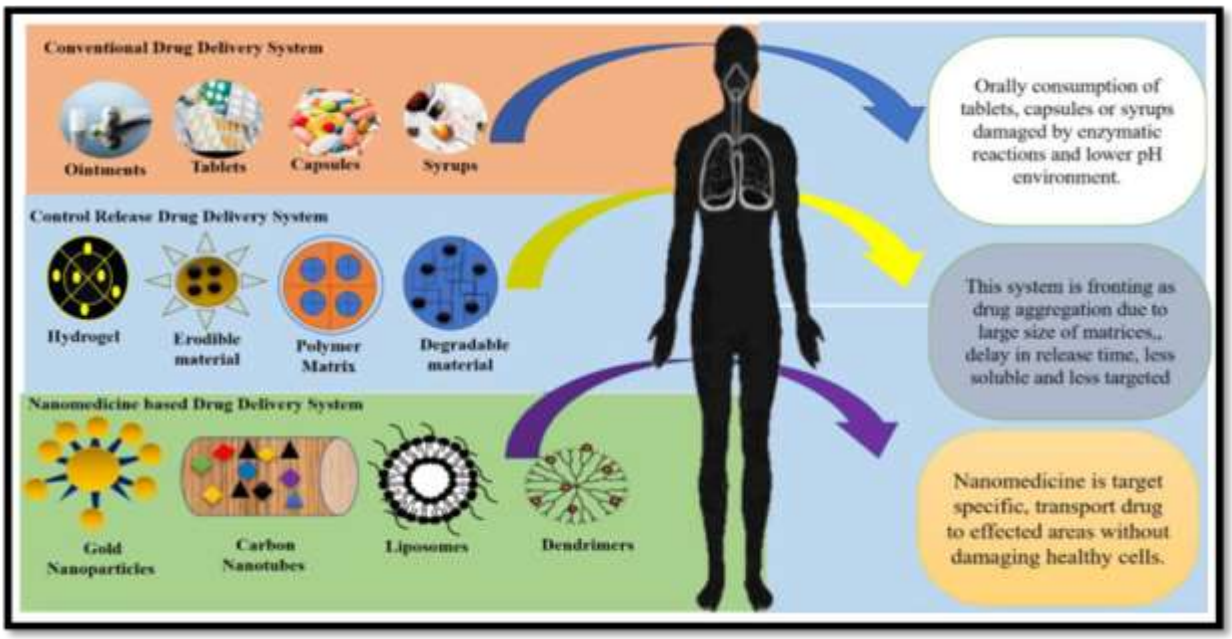

Fig. 1 Illustration of how traditional medications were administered without the use of nanocarriers and harm was done to healthy organs or cells. In contrast, modern procedures use nanomedicines to transport medications to specific parts of the body.

In 1959, physicist Richard Feynman introduced the concept of nanotechnology in his lecture "There's Plenty of Room at the Bottom", sparking significant advancements in the field [15]. Nanotechnology involves the study and manipulation of extremely small structures and lies at the intersection of multiple scientific disciplines, including physics, chemistry, biology, engineering, information technology, electronics, and materials science [16]. At the nanoscale, structures typically range from 1–100 nm [17]. Due to their submicroscopic size, nanoparticles exhibit unique material properties and have diverse applications in engineering, drug delivery, nanomedicine, environmental remediation, catalysis, and the treatment of diseases such as melanoma, cardiovascular diseases (CVD), skin disorders, liver diseases, and more [18].

Integrating nanotechnology with medicine has the potential to improve drug efficiency and bioavailability [19]. The connection between nanoparticles and biomedicine was recognized in the late 1970s, leading to over 10,000 publications referencing nanomedicine, with around thirty appearing by 2005 [20]. By 2015, the *Web of Science* had published over 1,000 articles on nanomedicine, most focusing on biomedical applications of nanoparticles [21]. Advanced forms of nanocarriers include dendrimers, liposomes, peptide-based nanoparticles, carbon nanotubes, quantum dots, polymer-based nanoparticles, inorganic vectors, lipid-based nanoparticles, hybrid nanoparticles, and metallic nanoparticles [22]. These nanocarriers are increasingly used in drug delivery, microfluidics, biosensors, microarrays, and tissue engineering for targeted disease treatment [23–25].

Nanoparticles can selectively target and destroy cancer cells, offering promising cancer therapies [26]. For example, in 2015, the FDA approved clinical trials for Onivyde, a nanomedicine used in cancer treatment [27]. Nanocarriers possess specific physicochemical properties that enhance drug solubility, stability, targeting, degradation control, clearance, theragnostic, and combination therapies [28]. Protein-based nanomedicines have also been explored, in which various protein subunits assemble to deliver drugs directly to tumors [29]. These protein-based nanocarriers include nanoparticles, hydrogels, films, microspheres, nanorods, and Mini pellets, constructed from proteins such as ferritin cages, small heat shock proteins (sHsp), plant-derived viral capsids, albumin, soy and whey proteins, collagen, and gelatine [30,31].

Nanomedicine represents a new era in drug delivery, enabling the design of targeted structures that carry multifunctional payloads with improved pharmacokinetics, specificity,

efficacy, and safety (Figure 2) [32,33]. Failures in traditional chemotherapy have increased the risk of disease recurrence, further complicating the treatment of life-threatening conditions [34].

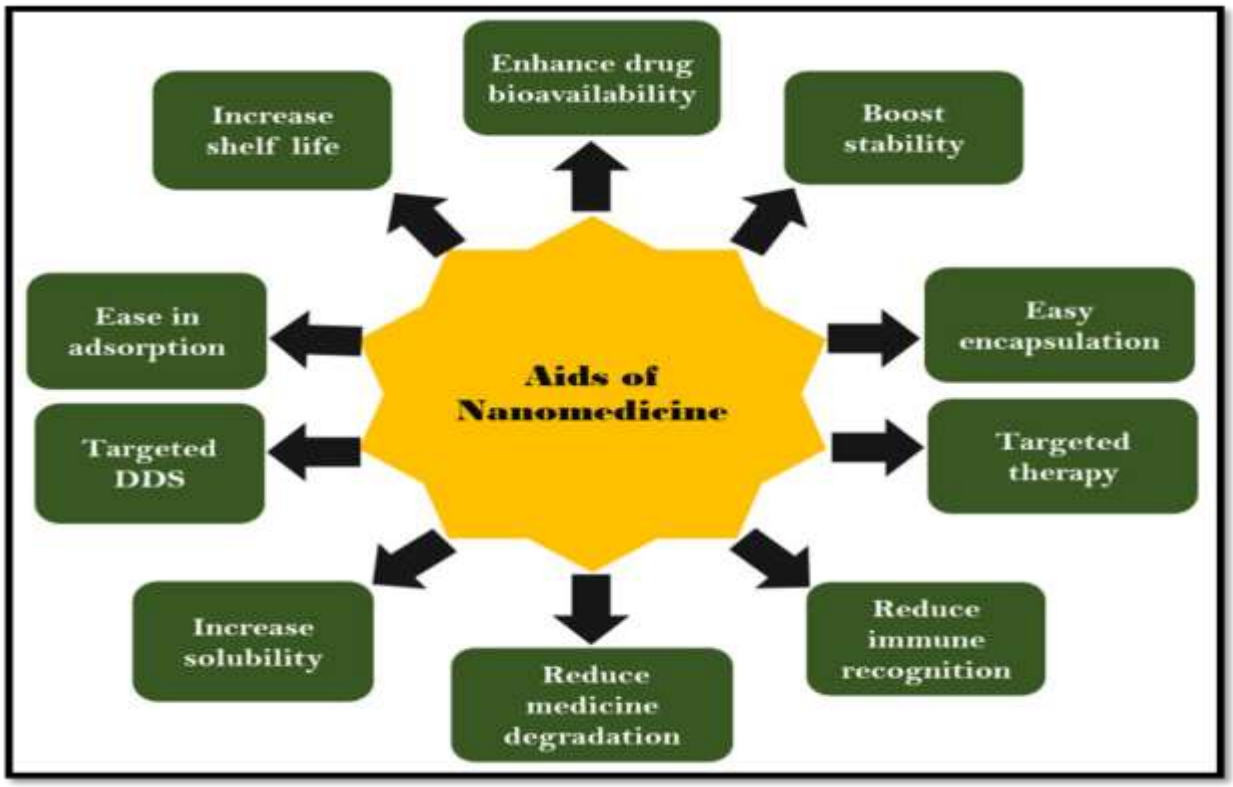

Fig.2 Aids of using nanomedicine platform for delivering drugs to the tumor complex.

History.

Petros and his colleague reviewed historical developments in nanotechnology dating back to the mid-20th century. They noted several key milestones: in 1955, polymers were first conjugated with drugs [35]; the first controlled-release polymer device was introduced in 1964; liposomes were discovered by Bangham in 1965; albumin-based nanoparticles emerged in 1972; liposome-based drugs were developed in 1973; the first micelle formulation was created and approved in 1983; the FDA approved the first controlled-release formulation in 1989; and the first polyethylene glycol (PEG)–protein conjugate reached the market in 1990 [36]. Subsequent research has produced highly promising outcomes for the treatment of various diseases, as summarized .

Over the past three decades, various types of nanoparticles (NPs) have been developed as drug delivery systems, each with unique approaches, disease targets, applications, characterization methods, and reported studies. In 1991, poly-alkyl-cyanoacrylate

nanoparticles were introduced as carriers for site-specific drug delivery in cancer therapy, particularly for chemotherapy and intracellular antibiotherapy, characterized by scanning electron microscopy [37,38]. In 1992, calcium hydroxyapatite ceramic (CHC) was used to load gentamicin in porous blocks for treating chronic osteomyelitis in animal models, retaining bactericidal activity despite the absence of in vivo experiments [39,40]. By 1993, micro- and nanoparticles were explored for oral immunization, with mechanisms such as self-diffusion and pulsed drug release, evaluated through in vitro experiments [41,42]. In 1994, acrylic acid copolymer nanoparticles were applied to enhance opsonin targeting and the reticuloendothelial system, analysed by small-angle X-ray scattering [43,44].

In 1995, poly-alkyl-cyanoacrylate (PECA) nanoparticles entrapping ofloxacin and perfloxacin improved antimicrobial activity for bacterial infections, characterized by freeze-fracture electron microscopy [45,46]. Protein and peptide-based nanoparticles were applied in 1996 for Alzheimer's disease, delivering monoclonal antibodies and recombinant proteins across the blood–brain barrier (BBB) via chimeric peptide approaches, although physiological characterization was not performed [47,48]. In 1997, nanoparticles were utilized in intra-arterial catheter-based delivery for restenosis, showing high biocompatibility without injury [49,50]. By 1998, deblock copolymer nanoparticles in micelles and nanospheres were developed to sustain drug release, enhance solubility, and improve circulation time, though no in vivo characterization was reported [51,52].

In 1999, chitosan nanoparticles enhanced insulin absorption through the nasal cavity for diabetes management, characterized by zeta potential and photon correlation spectroscopy [53,54]. In 2000, liposomes combined with hyperthermia improved targeted drug delivery for ovarian carcinoma, demonstrating effective results in experiments [55,56]. PEGylated poly-cyano-acrylate nanoparticles introduced in 2001 extended drug circulation for prion diseases, with higher brain and spleen uptake in scrapie-infected models [57,58]. Transferrin-mediated receptor endocytosis in 2002 enabled targeted drug and gene delivery to cancer and brain diseases by exploiting transferrin receptor pathways, though characterization was limited [59,60].

By 2003, L-nanoparticles demonstrated targeted delivery to hepatocytes for Hepatitis B, hepatocellular carcinoma, and haemophilia, showing specificity in xenograft mouse models [61,62]. Colloidal gold nanoparticles in 2004 served as vectors for tumor necrosis factor delivery in carcinoma models, analysed by TEM and light scattering [63,64]. In 2005, folate-

conjugated liposomes carrying chemotherapeutics and DNA enabled targeted gene transfer in nasopharyngeal and prostate cancer cells [65,66], while folate-conjugated starch nanoparticles in 2006 targeted liver cancer with doxorubicin, reducing toxicity and enhancing targeting [67,68]. Gold nanoparticles in 2007 facilitated drug and gene delivery in carcinoma cells with reduced toxicity and high transfection efficiency [69,70], and PEGylated gold nanoparticles in 2008 improved in vivo photodynamic cancer therapy with targeted tumor delivery [71,72].

Alginate/chitosan nanoparticles developed in 2009 optimized size and loading parameters for drug delivery via zeta potential and FTIR analysis [73,74], while mesoporous silica nanoparticles in 2010 achieved targeted methotrexate delivery to tumor cells with high cell specificity and low cytotoxicity [75,76]. Nano-diamonds in 2011 delivered small interfering RNA into cancer cells efficiently without structural damage, as confirmed by FTIR and zeta potential analysis [77,78]. Silver nanoparticles emerged in 2012–2014 as vectors for antimicrobial and photo-activated gene silencing, synthesized through green methods and characterized by UV-visible spectroscopy, TEM, and FTIR, showing applications in malaria, dengue, and vector control [79–84].

Polyamidoamine nanoparticles in 2015 served as carriers for anti-malarial drugs, improving solubility, circulation time, and targeting with reduced toxicity [85,86]. Solid lipid nanoparticles in 2016 enabled delivery of photosensitizers and flavonoid derivatives for colon cancer treatment, evaluated by confocal microscopy and DLS [87,88]. In 2017, filamentous bacteriophage-based nanoparticles facilitated targeted drug and gene delivery for bacterial and viral diseases, representing a unique virus-based system [89,90]. Mesoporous silica nanoparticles in 2018 were engineered for siRNA delivery through electrostatic absorption, offering a cost-effective non-viral vector solution [91,92]. Chitosan nanoparticles in 2019 proved versatile for ocular, nasal, pulmonary, buccal, and mucosal drug delivery, including vaccine delivery and cancer treatment [93,94].

In 2020, folic-acid-functionalized mesoporous silica nanoparticles were developed as pH-sensitive systems for targeted cancer therapy, offering prolonged drug release characterized by XRD, TEM, HNMR, SEM, and TGA [95,96]. In 2021, novel silver nanoparticles were applied for mRNA and DNA delivery to stimulate immune responses against SARS-CoV-2, while lipid-based, metal, and resveratrol–zinc nanoparticles demonstrated roles in COVID-19 prevention and therapy, including vaccines and immune sensors [97–100]. In 2022, iridium

oxide and chitosan nanoparticles were synthesized as biocompatible nanoprobes for in vivo cancer therapy and neural regeneration, combining photothermal and drug delivery capabilities without immunogenicity [101,102].

Recent Approaches in Drug Delivery Systems for Various Diseases

Brain Drug Delivery Systems and Their Types

In numerous pathological conditions — including strokes, seizures, multiple sclerosis, AIDS, diabetes, glioma, Alzheimer's disease, and Parkinson's disease — the blood–brain barrier (BBB) becomes compromised [103]. This breakdown is largely due to structural remodeling of protein complexes at endothelial junctions under such pathological states [104]. Under normal conditions, the BBB functions to preserve brain homeostasis by restricting the entry of macromolecules and small molecules from the bloodstream [105]. However, if a drug does cross the BBB, it often results in reduced accumulation within brain tissue and diminished bioavailability, limiting effective treatment of brain disorders [106].

To overcome this challenge, advanced drug delivery systems (DDS) such as cell membrane-based DDS, virus-mediated DDS, or exosome-based DDS are engineered to possess BBB penetration ability, lesion targeting, and safety [107]. Among these, nanocarrier-assisted intranasal delivery has become a prominent method for brain therapy [108]. At an advanced stage, drugs with poor brain distribution can be loaded into nanocarriers that interact with endothelial microvessel cells of the BBB and nasal mucosa, increasing drug residence time and enabling direct nose-to-brain delivery via olfactory nerve pathways [109]. This process improves drug absorption into brain parenchyma through a secondary nose-to-blood-to-brain pathway [110].

Current strategies for brain drug delivery include viral vectors, nanoparticles, exosomes, BBB permeability enhancers, active transporter-based delivery across the BBB, alternative administration routes, nanoparticles specifically designed for brain delivery, and advanced imaging/diagnostic systems under pathological conditions [111].

Role of Nanocarriers in Alzheimer's Disease

Alzheimer's disease (AD) is one of the fastest-growing neurodegenerative disorders in the elderly, characterized by memory loss, diminished verbal abilities, and impaired spatial reasoning [112]. A hallmark of AD is the accumulation of amyloid β (Aβ) plaques, which contribute to cognitive dysfunction [113]. Nanotechnology-based drug delivery approaches

have proven useful in treating such conditions [114]. In AD, delivery systems such as polymeric nanoparticles, liposomes, solid lipid nanoparticles, nanoemulsions, microemulsions, and liquid crystals are employed.

Polymeric Nanoparticles:

1. Tacrine-loaded polymeric nanoparticles administered intravenously enhance brain concentration of the drug while reducing the total dose required [115].
2. Rivastigmine-loaded polymeric nanoparticles administered intravenously improve learning and memory [116].

SLNPs:

SLNPs improve drug retention in the brain and enhance BBB permeability [117]. Examples include:Piperine-loaded SLNPs administered intraperitoneally reduce plaques and masses while enhancing acetylcholinesterase (AChE) activity [118].

1. Huperzine A-loaded SLNPs improve cognitive functions without significant irritation in rat skin studies [119].
2. Coating SLNPs with surfactants like polysorbate improves bioavailability [120,121]. Examples include:
3. Clozapine in a Dynasan 116 lipid matrix coated with Poloxamer 188 and Epikuron 200 for safe brain delivery [122,123].
4. Vitamin A in Glyceryl behenate lipid matrix coated with hydroxypropyl distarch [124,125].
5. Diminazine in stearic acid matrix coated with polysorbate 80 for targeted delivery [126,127].
6. Doxorubicin in stearic acid SLNPs coated with Taurodeoxycholate for effective drug delivery without loss of potency [128,129].

LIPOSOMES:

Liposomes are promising carriers for brain-targeted drug delivery due to their capacity to encapsulate large amounts of drug and their ability to be functionalized with ligands [130–132]. Examples:

1. Curcumin–PEG-loaded liposomes showed high binding affinity to senile plaques and inhibited Aβ aggregation in ex vivo studies, with BBB uptake demonstrated in rats [133].
2. Folic acid-loaded liposomes administered intranasally enhanced drug absorption through the nasal cavity [134].

Nano emulsions:

Beta-Asarone loaded in nano emulsions and administered intranasally improved bioavailability [130].

Microemulsions:

Tacrine-loaded microemulsions administered intranasally enhanced memory performance [135].

Liquid Crystals:

T. divaricate-loaded liquid crystals delivered trans dermally prolonged drug retention and improved skin penetration [136].

Role of Nanocarriers in Parkinson's Disease (PD)

Parkinson's disease (PD) is the second most common neurodegenerative disorder and presents significant challenges in effective drug delivery and diagnosis [137]. Levodopa, the conventional treatment, suffers from poor bioavailability and limited brain penetration [138]. Nanotechnology offers promising strategies to overcome these limitations, employing metal nanoparticles, quantum dots, cerium oxide nanoparticles, organic nanoparticles, liposomes, and gene therapy to enable drugs to cross the BBB [139,140].

For example, Bhatta Misra et al. demonstrated that retigabine-loaded chitosan nanoparticles delivered via the intranasal route in a rat PD model achieved better brain delivery, as confirmed by pharmacokinetic studies [125].

Ropinirole (RP):

RP-loaded solid lipid nanoparticles (RP-SLNs) and nanostructured lipid carriers (RP-NLCs) in hydrogel formulations improved oral and topical drug delivery [141]. These formulations proved to be effective carriers for delivering RP to the brain for PD treatment [142,143].

Mechanism of Nanoparticles in Brain Drug Delivery (Across BBB)

Nanoparticles are typically administered through intranasal, intraventricular, or intraparenchymal routes, enabling them to cross the BBB due to their small size. Upon reaching the BBB, nanoparticles use mechanisms such as receptor-mediated transport, active transport, or passive diffusion to enter the brain. Their small size facilitates passive diffusion across endothelial cells, and their surface properties allow interaction with brain receptors and ligands to enhance targeted delivery (Figure 3) [144].

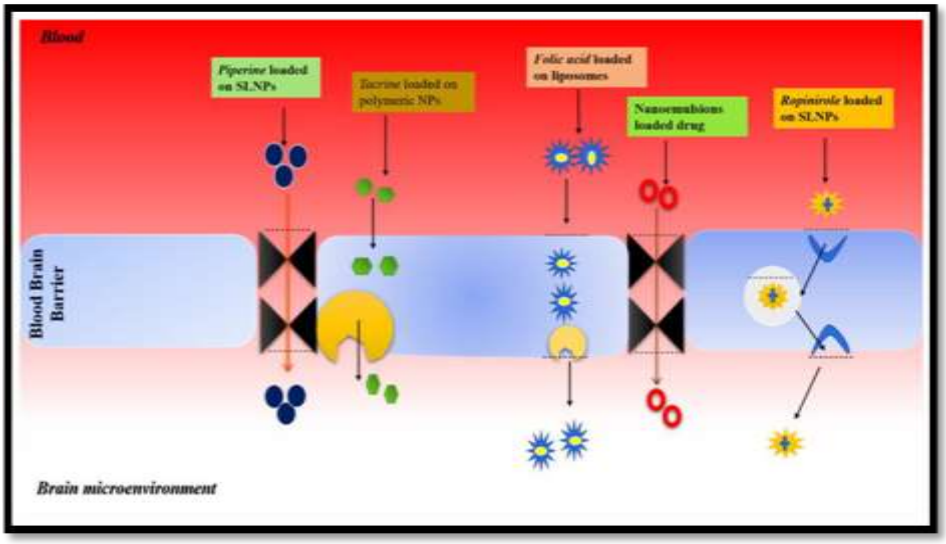

Fig.3 Diagram showing the mechanism of targeted drug delivery across BBB in brain icroenvironment.

Tacrine-loaded polymeric nanoparticles (NPs)

Advantages:

1. Prolonged retention in the brain
2. High biocompatibility
3. Low cost of production
4. Controlled drug release
5. Ability for targeted delivery via ligand conjugation

Disadvantages:

1. Slow biodegradation
2. Potential uncertainty in toxicity[145]

Rivastigmine-loaded polymeric NPs

Advantages:

6. Increased drug concentration in the brain
7. Avoidance of phagocytosis by the reticuloendothelial system (RES)

Disadvantages:

1. Possible increase in oxidative stress
2. Potential toxicity concerns[146]

Piperine-loaded solid lipid nanoparticles (SLNPs)

Advantages:

8. Extensively studied for drug delivery
9. Reduced side effects compared to free drugs
10. Enhanced therapeutic efficacy
11. Improved drug solubility

Disadvantages:

1. Low drug-loading capacity
2. Rapid clearance by the reticuloendothelial system[147]

Folic-acid-loadedliposomes

Advantages:

12. Excellent biocompatibility and biodegradability
13. High stability and bioavailability
14. Active surface targeting possible

Disadvantages:

1. Difficulty in lipid binding
2. Lower stability and reduced drug carriage efficiency [148]

Role of Nanocarriers in Major Cancers

Brain Cancer

Brain cancer is among the most challenging diseases to treat effectively [150]. The difficulty largely arises from the restrictive nature of the blood–brain barrier (BBB), which limits the delivery of therapeutic agents to the brain [151]. The BBB is formed by the brain's microvascular endothelium, creating a selective barrier that separates the blood from neural tissues [152]. This barrier plays a vital role in protecting the brain by preventing harmful toxins, xenobiotics, and other metabolic substances from entering [153]. Common forms of brain cancer include glioma and glioblastoma, both of which are highly aggressive and lethal [154]. These cancers occur at a rate of approximately 5.26 cases per 100,000 individuals, equating to around 17,000 new diagnoses annually. Standard treatments typically involve surgery, radiation, and chemotherapy, often combined with temozolomide (TMZ) [155]. Nanoparticles offer significant promise in brain cancer therapy due to their nanoscale size, ability to specifically target tissues, and capability to cross

In recent years, a variety of nanoparticles (NPs) have been explored treatment due to their ability to improve drug delivery across the blood–brain barrier for brain cancer and enhance therapeutic outcomes. Gold nanoparticles (DOX-SL-GG AuNPs) loaded with doxorubicin have shown increased cytotoxic activity through endocytosis in glioma and glioma stem cell lines, particularly in LN-229 and HNGC-2 cells [157,158]. Albumin-bound nanoparticles carrying lapatinib have been effective in constraining migration, invasion, and adhesion of high brain-metastatic cells in murine models [159,160]. Similarly, lipoprotein-like nanoparticles loaded with lapatinib significantly inhibited tumor growth in U87 glioma xenografts in vivo [161,162]. Gold–iron oxide nanocomposites conjugated with curcumin–lipoic acid exhibited greater cytotoxicity against U87MG brain cancer cells compared to normal astrocytes [163,164]. Tocopherol polyethylene glycol chitosan nanoparticles, loaded with docetaxel, enhanced cellular uptake and cytotoxicity in brain melanoma cells due to synergistic bioadhesive effects [165,166]. Methotrexate-loaded chitosan and glycol chitosan nanoparticles demonstrated cytotoxic effects against C6 glioma cells and overcame multidrug resistance in MDCKII-MDR1 cell lines [167,168]. Furthermore, lipid–drug-conjugated nanoparticles carrying fluorouracil (5-FU) improved the efficacy of chemotherapy for glioma cells both in vitro and in vivo [169,170]. These advances highlight the critical role of nanoparticle-based systems in developing targeted and effective brain cancer therapies.

Breast cancer is one of the leading causes of cancer-related deaths worldwide, with tumors spreading through uncontrolled cell proliferation and invasion via the lymphatic system when malignant [171,172]. According to the World Health Organization (WHO), cancer accounts for approximately 13% of global deaths, resulting in around 8.2 million fatalities annually [173]. Among cancers affecting women, breast cancer is the most prevalent and causes higher mortality rates than even lung cancer [174]. In 2012, there were an estimated 1.7 million new cases of female breast cancer, accounting for 25% of cancer deaths globally [175]. The *Global Cancer Statistics 2020: GLOBOCAN* report, which analyzes cancer incidence and mortality across 36 cancer types in 185 countries, updated these figures, estimating 19.3 million new cancer cases (18.1 million excluding non-melanoma skin cancer) and nearly 10 million cancer-related deaths (9.9 million excluding non-melanoma skin cancer) in 2020 [176]. Notably, female breast cancer surpassed lung cancer as the most commonly diagnosed cancer, with around 2.3 million new cases (11.7%), followed by lung (11.4%), colorectal (10%), prostate (7.3%), and stomach (5.6%) cancers [177].

Treatment for breast cancer typically involves surgery, chemotherapy, radiation therapy, hormonal therapy, and targeted therapy [178]. Recently, nanotechnology has emerged as a promising approach in breast cancer treatment, with both organic and inorganic nanocarriers being utilized for targeted drug delivery [179]. Nanocarriers improve the solubility of hydrophobic anticancer drugs and ensure precise drug targeting [180]. Organic nanocarriers include polymeric nanoparticles, liposomes, and solid lipid nanoparticles, while inorganic types include magnetic nanoparticles, quantum dots, and carbon nanotubes (CNTs), all demonstrating significant potential in advancing breast cancer therapy [181].

Organic Nanomaterials in Breast Cancer Treatment

Several organic nanomaterials have been explored for targeted drug delivery in breast cancer therapy. Solid lipid nanoparticles (SLNPs) targeted to folic-acid receptors have been loaded with letrozole (LTZ) and folic acid. Tested in vitro on MCF-7 breast cancer cell lines, these nanoparticles demonstrated significant cell membrane damage via lactate dehydrogenase (LDH) and MTT assays. Apoptosis induction was further confirmed through Caspase-3 activity and TUNEL assays [182,183].

Curcumin-loaded SLNPs (CURC-SLNs) combined with doxorubicin (DOX) were studied for their effect against triple-negative breast cancer. In vitro results showed CURC-SLNs enhanced curcumin's cytotoxicity by 5–10 times compared to its free form, effectively increasing toxicity in P-glycoprotein-expressing cancer cells [184,185].

Copolymer–magnetite nanoparticles composed of doxorubicin–core-shell chitosan conjugates were tested against HER2-overexpressing breast cancer cells. These anti-HER2-conjugated chitosan graft pluronic F127 nanoparticles proved effective as drug carriers for targeted anticancer therapy [186,187].

PEGylated ε-poly-l-lysine polymeric nanoparticles carrying both doxorubicin and lapatinib were evaluated on MCF-7 breast cancer cell models. This combination therapy delivered via DMMA-P-DOX/LAP nanoparticles significantly reduced or completely eliminated solid tumors in the tested models [188,189].

Inorganic Nanomaterials in Breast Cancer Treatment

Inorganic nanomaterials such as colloidal gold and magnetic nanoparticles have also been applied in breast cancer drug delivery. Gemcitabine-hydrochloride (GEM) loaded onto

colloidal gold nanoparticles, prepared using gum acacia as a polysaccharide-based carrier, was tested in vitro on the MDA-MB-231 breast cancer cell line. These nanoparticles provided targeted delivery of the chemotherapeutic drug to human breast adenocarcinoma cells [190,191].

L-carnosine-coated magnetic nanoparticles (CCMNPs) were evaluated both in vitro and in vivo for their therapeutic effects. These nanoparticles showed high precision in targeting breast cancer cells, leading to a significant reduction in tumor mass without causing systemic toxicity [192,193].

Lung Cancer and Nanocarrier-Based Treatment

The lungs, essential for respiration, consist of airways that channel air in and out, and alveoli that serve as gas exchange sites [194,195]. While the airways form a robust barrier to particle entry, the alveolar wall and capillaries in the gas exchange region are comparatively fragile [196]. This extensive alveolar surface area and efficient blood-air exchange make the lungs more vulnerable to environmental damage, which can contribute to pulmonary diseases such as lung cancer [197]. To overcome the limitations of conventional therapies, various nanoparticles are being developed for respiratory applications. These nanocarriers facilitate treatment for lung disorders including asthma, tuberculosis, emphysema, cystic fibrosis, and cancer [198,199].

Recent advancements in nanoparticle-based lung cancer treatment include:

1. **Poly (L-aspartic acid co lactic acid)/DPPE copolymer nanoparticles** administered via intraperitoneal injection in mouse xenograft models. These nanoparticles, loaded with doxorubicin (DOX), have been applied to treat lung melanoma [200,201].
2. **Poly (β-amino ester) nanoparticles (PBAE)** delivered through intratumoral injection in mouse xenograft models. These self-assembling PBAE polymers complexed with DNA have been tested for transfection efficiency in p53 mutant H446 small cell lung cancer (SCLC) cells [202,203].
3. **Lipid–polymeric nanoparticles** administered intraperitoneally in mice, co-designed with epidermal growth factor (EGF) and loaded with cisplatin and doxorubicin to target lung carcinoma [204].
4. **Co-loaded doxorubicin and cisplatin nanoparticles** delivered via pulmonary administration in mouse models. Methoxy poly-(ethylenimine)-poly(l-glutamate)

copolymers were developed to facilitate codelivery of DOX and CDDP for treating metastatic lung melanoma [205,206].

5. **Redox-responsive and pH-sensitive nanoparticles**, prepared through emulsification and solvent evaporation, loaded with Erlotinib (ETB) and modified with PAA-ss-OA. These were administered subcutaneously in mouse xenograft models targeting non-small cell lung cancer (NSCLC) [207].
6. **Nanoparticle–mesenchymal stem cell (MSC) systems**, where MSCs were loaded with nanoparticles carrying anticancer drugs and administered in rabbits, mice, and monkeys. MSCs demonstrated superior drug uptake compared to fibroblasts, effectively targeting lung melanoma [208,209].
7. **Hyaluronic-acid-based lipid nanoparticles** studied in vitro using dialysis techniques to enhance the efficacy of apigenin (APG) as an Nrf2 inhibitor in combination with docetaxel for NSCLC treatment [210].
8. **MAGE-A3 near-infrared (NIR) luminescent nanoparticles**, applied in vitro and in vivo (mouse models). These hybrid theranostic nanomaterials, coupled with Afatinib, were developed for in situ treatment of lung adenocarcinoma [211].
9. **Hyaluronic-acid-based nanoparticles** tested in vitro and in vivo for targeted delivery of paclitaxel to carcinoma cells. These nanoparticles were shown to overcome drug resistance and effectively inhibit cancer cell growth [212].

Drug Delivery Approaches in Heart Diseases

Cardiovascular diseases encompass a wide range of conditions, including myocardial infarction (MI) [213], ischemic injury, coronary artery disease (CAD), heart arrhythmias, pericardial disease, cardiomyopathy, and congenital heart defects [214,215]. These conditions are among the leading causes of death and disability worldwide [216]. Heart diseases often involve abnormalities in heart structure, impaired function, and damage to cardiac muscle tissue, along with ongoing remodeling and fibrosis [217,218]. Nearly half of MI patients die within five years, highlighting the urgent need for effective therapeutic strategies [216].

This demand has driven advancements in targeted drug delivery to the heart [219], aiming to prevent heart failure following MI [220]. Various nanocarriers have been explored for this purpose, including liposomes, silica nanoparticles, dendrimers, cerium oxide nanoparticles, micelles, titanium dioxide (TiO_2) nanoparticles, stents with nanocoatings, microbubbles, and polymer–drug conjugates. Among these, **magnetic nanoparticles** such as magnetoliposomes

(MLs), which combine liposomes with magnetic nanoparticles, have emerged as promising tools for magnetically targeted drug delivery [221]. PEGylation of MLs prolongs their circulation time in blood, while conjugation with antibodies enhances active targeting to specific sites [222].

Namdari and colleagues demonstrated the potential of liposome-based carriers in a murine MI model. Modified nanocarriers — including cationic liposomes, perfluorocarbon nanoparticles, polyelectrolyte nanoparticles, and polymeric nanoparticles — have been engineered to improve drug loading and delivery efficiency into cells [223].

Examples of Nanocarrier Applications in Heart Disease

1. **Polymeric (PLGA) nanoparticles** tested in balloon-injured carotid and stented porcine coronary artery models in rats, loaded with AG-1295 and AGL-2043, showed significant inhibition of restenosis [224–230].
2. **Perfluorocarbon nanoparticles** applied in human plasma clots and hyperlipidemic animal models, carrying a3b integrins, surface-bound streptokinase, and other agents, demonstrated fibrinolytic activity in vitro and therapeutic potential in vivo [231–235].
3. **Cationic nanoparticles** examined in clinical trials involving patients with 60–99% arterial narrowing, delivered via catheter, showed notable improvement in myocardial perfusion. These nanoparticles delivered vascular endothelial growth factor (VEGF) through a viral vector [236–241].
4. **VEGF nanoparticles**, tested in murine models of myocardial infarction, successfully promoted angiogenesis and improved myocardial perfusion, aiding heart repair in coronary disease [242–245].

Drug Delivery Approaches in Skin Diseases

Skin diseases can be broadly categorized into follicular and cutaneous disorders. Modern treatments increasingly rely on nanotechnology due to its ability to deliver drugs more effectively with fewer side effects. Traditional formulations such as creams, gels, and ointments often fail to penetrate deeply enough into skin tissues. To overcome this limitation, polymeric, lipid-based, and surfactant nanocarriers have been developed.

Polymeric micelles, for example, improve drug penetration into skin layers and are particularly effective in treating skin cancers. Studies have shown that chitosan polymeric nanoparticles, liposomes, and gold nanoparticles can enhance drug delivery for conditions

such as atopic dermatitis by increasing penetration into both the dermal and epidermal layers [246]. Gold nanoparticles, owing to their extremely small size, penetrate the skin efficiently with minimal toxicity and no damage, making them a highly promising option in nanocarrier-based therapies for skin diseases.

Drug Delivery Approaches in Bone Diseases

Bone diseases arise from various pathological factors, including fractures, trauma, osteoporosis, arthritis, infections, and other conditions. Bone regeneration is a highly complex process, and advances in nanotechnology have enabled the fusion of nanomaterials with biomaterials to enhance bone repair. This combination has significantly improved bone implantation and regeneration through the development of advanced bone bioscaffolds [247].

Mechanism of Drug Delivery[248]:

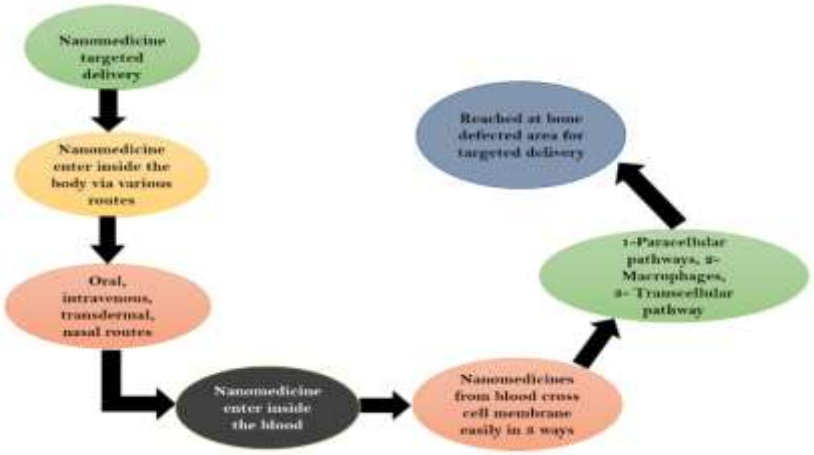

Fig. 4 Mechanism of nanomedicine delivery in bone diseases.

Drug Delivery Approaches in Blood Diseases

Blood disorders encompass a variety of conditions, including hematopoietic disorders, iron deficiency, leukemia, anemia, hemophilia, platelet disorders, and blood cancers. Conventional chemotherapeutic treatments often harm the immune system and carry a high risk of mortality. Bone marrow transplants, while effective for certain conditions, are costly and complex procedures. For instance, thalassemia is treated with the chelating agent deferoxamine to remove excess iron from the bloodstream. Recent research has shown that siRNA-coated nanocomposites possess inhibitory effects on tumor cells in vivo [248]. However, the application of nanomedicine in treating blood disorders remains an area of ongoing research and development.

Future Challenges of Nanomedicine

Nanomedicine holds tremendous promise for transforming clinical care, particularly in treating cancers and reducing mortality and morbidity. Nonetheless, several challenges remain. Integrating nanomedicine into clinical practice involves overcoming regulatory, insurance, and public health barriers. At present, the U.S. Food and Drug Administration (FDA) has not established specific regulations for products containing nanomaterials. Additionally, the absence of standardized protocols for nanomaterials and concerns over their safety have limited funding from agencies such as the Environmental Protection Agency (EPA) and the National Institute for Occupational Safety and Health (NIOSH) [249]. These challenges must be addressed for nanomedicine to achieve its full clinical potential.

CONCLUSIONS

Nanomedicine, as a branch of nanotechnology, is rapidly emerging as a versatile and powerful approach to treat various diseases. Across numerous medical fields, nanoparticle-based drug delivery systems are proving to be effective therapeutic tools. For example, researchers at the University of California are developing techniques to deliver cardiac stem cells directly to injured heart tissue using targeted nanovesicles, enhancing cell retention and repair. Such advances suggest that combining stem cell therapy with nanotechnology will yield significant medical breakthroughs.

Despite the promise, nanomedicine still faces questions related to safety, toxicity, and standardization, which will require future research and regulation. However, the demand for nanoparticle-based targeted drug delivery is growing globally, as these systems have the potential to overcome the limitations of traditional medicine. According to the National Cancer Institute, nanotechnology will likely play a central role in diagnosing diseases, delivering therapeutics, and detecting cancers.

In the context of infectious diseases such as COVID-19, nanoparticles measuring 10–200 nm can be engineered to detect viruses, enable targeted delivery, eliminate pathogens, and enhance immune responses. Nanotechnology holds potential to curb viral spread through nano-based sensors for rapid detection and protective measures for healthcare workers and the public. Furthermore, antiviral nanobiotechnology is being explored to create disinfectants capable of halting virus transmission.

Looking ahead, nanotechnology is poised to develop medicines that are more potent, less toxic, and capable of sustained release to targeted tissues. This progress will make personalized nanomedicine a powerful strategy not only for treating COVID-19 but also for addressing future diseases effectively.

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