STRATEGIES IN THE DESIGN OF NANOPARTICLES FOR THERAPEUTIC APPLICATION

Nishant R. Bisen, Roshni D.Agrawal, Dr. Tulsidas P.Nimbekar

Abstract
nanoparticles are tiny structures under 100 nm with a high surface-to-volume ratio, making them highly versatile for various applications. their performance is primarily driven by their synthesis method, size, shape, and especially the base materials used. these materials categorize nps into organic, inorganic, and carbon-based groups, including polymers, lipids, and metal ions. each material offers unique chemical attributes that determine how effectively the np functions in a specific field. because efficiency and safety are paramount, certain materials are preferred for their high performance and low toxicity. this review examines these classifications and maps specific materials to their ideal practical uses. by understanding these base components, researchers can better predict the activity and safety of nps in therapeutic and industrial settings. ultimately, the choice of material is the most critical factor in successful nanoparticle design. this study provides a concise overview of how these classifications guide modern nanotechnology research. it serves as a roadmap for selecting the right nanoparticle for the right application.
Key word :
Introduction ,classification of nanoparticals platforms,targeted drug dilevary statergies ,nano based drug delivery system,biomimeti drug delivery system, extracorporeal device , application ,references

1.Introduction:-

Feynman was the first physicist to propose the idea of nanotechnology in 1959 in the "There's Plenty of room at the Bottom" lecture. This idea started outstanding advancements in the field of nanotechnology[1]. Since then, nanotechnology has developed quickly and is now regarded as one of the 21st century's most revolutionary scientific discoveries, particularly in the area of medicine. The potential of nanotechnology to transform healthcare has drawn more attention in recent decades, leading to substantial investment and research worldwide. Because governments and organizations see nanotechnology as a driver of innovation, economic growth, and societal well-being, they have increased funding initiatives[2].

Nanoparticles (NPs) are defined as materials with dimensions smaller than 100 nm and presenting various shapes, i.e., spheres, rods, dendritic shapes, etc. . This definition is accepted by the European Union Commission[3]. Research in the multidisciplinary field of nanotechnology encompasses chemistry, biology, engineering, andmedicine, and it holds enormous promise for early symptom diagnosis and clinical treatment and studies on the environment. Recently,In the biological sciences, nanoparticles (NPs), primarily metal NPs such as gold,silver, copper[4], iron[5],metal oxide[6] etc. have grown to beutilized for both therapeutic and diagnostic purposes. That expansion in the applications and usage ofNPs can be explained by their unusually small size and massive surface area.stability at high temperatures, high responsiveness to living tissues, and to-volume ratio,and the transport of cells[7]. Nanotechnology has gained popularity recently and had a beneficial impact on preclinical shipping in the new field of nanomedicine and medical

advancement in medicine. Today,Drug delivery to the target site is facilitated by nanomaterials, which create nano-systems and nanocarriers. According to how nanoparticles (NPs) are used and applied at the nanoscale, there are numerous advantages and uses, such as medication delivery and bioimaging[8].Nanoparticles (NPs)have the precise delivery of therapeutic agents to targeted tissues, which reduces total dosage and potential toxic effects, the improved stability and bioavailability of active pharmaceutical ingredients post-administration, the ability to exhibit superior safety and efficacy profiles, the ability to release drugs in controlled timeframes, the ability to facilitate passive targeting and drug accumulation in malignant tumors and other pathological sites via the enhanced permeability and retention (EPR) effect, and the potential for nanopharmaceutical products to be more cost-effective than their traditional counterparts are just a few of the many benefits of using nanoparticles (NPs) in drug manufacturing[9]. However, NPs face various biological barriers upon administration, depending on the route of administration (e.g., i.m., s.c., i.v., oral, intravitreal, pulmonary, nasal).Oral delivery is difficult due to the acidic stomach environment and the mucus layer in the gastrointestinal (GI) tract, which can trap and remove the NPs. Pulmonary delivery (inhalation) is challenged by respiratory barriers like mucus, ciliated cells, and clearance by macrophages [10].

Pharmacology has changed as a result of nanomaterials' introduction of innovative drug delivery and therapeutic intervention platforms. They are great options for tackling issues in targeted therapy, controlled release, and biocompatibility because of their unique physicochemical characteristics, which include high surface-to-volume ratios, tuneable sizes, and functionalizable surfaces. These nanomaterials' interactions with biological systems, including pharmacokinetics, biodistribution, and cellular uptake, are controlled by their biophysical chemistry[11]. An outline of the different kinds of nanomaterials utilized in pharmacological application is provided below, with an emphasis on their biophysical chemisty (fig.1).

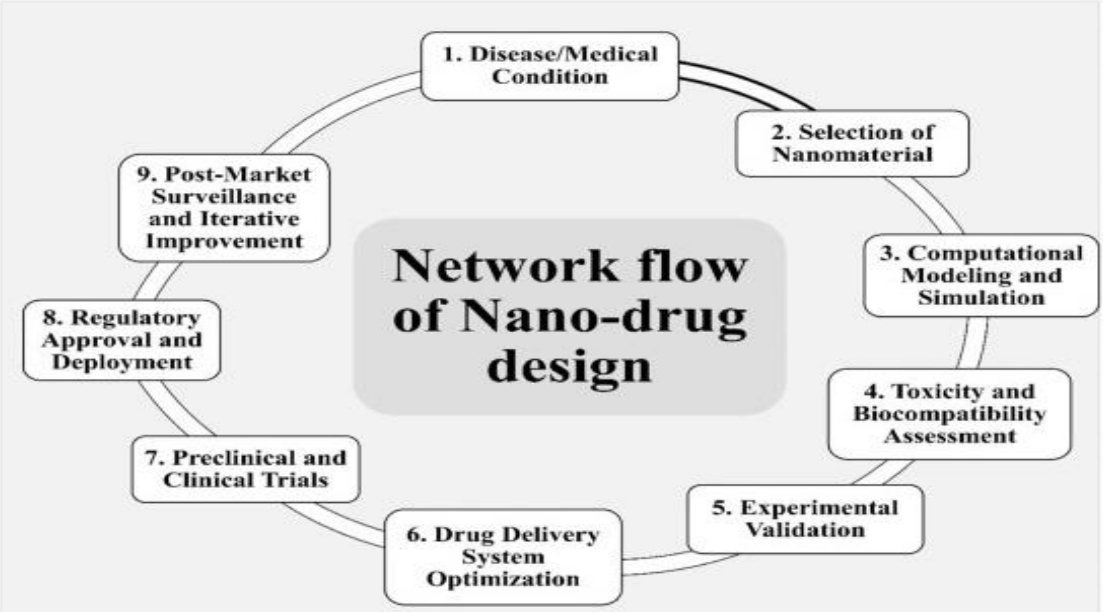

Fig . Network flow of interdisciplinary collaboration of nano-drug design.

2 Classification of nanoparticles platform :

The synthesis methods, shape, and size of the NPs can significantly change the efficiency and activity of the particle. Considering all these factors, the chosen material is also a primary variable that determines the role, and especially the type, of NP. Based on the material, NPs are classified into three main types—inorganic, carbon-based, and organic—and subdivided into different kinds such as metallic,ceramic, polymeric, and lipid-based due to their distinct characteristics, size, and shape[12] (fig.2).

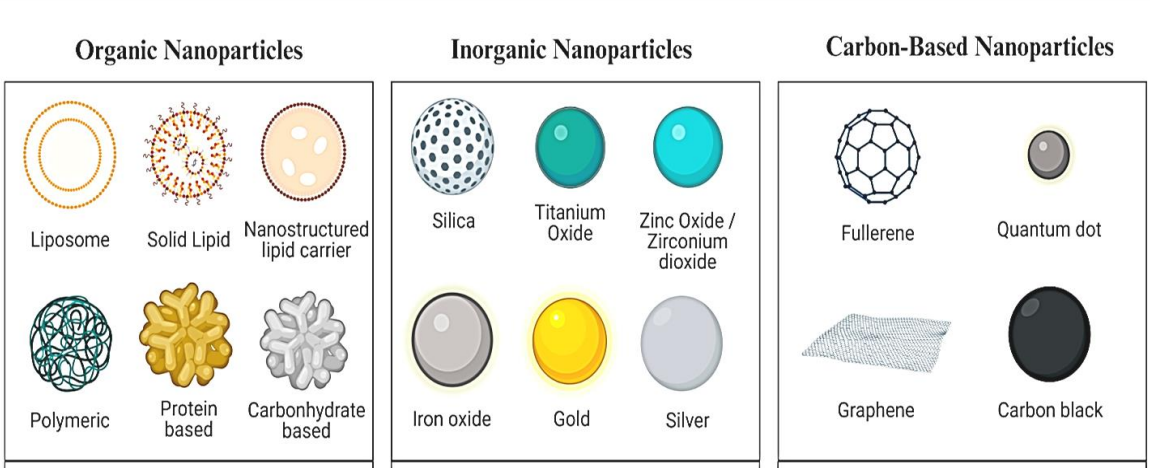

fig .2Classification of Nanoparticles

Organic nanoparticles (NPs), including micelles, liposomes, and dendrimers, are excellent drug delivery systems due to their biodegradable and non-toxic nature. Key types, such as nanocapsules and nanospheres, are often labeled as polymeric nanoparticles. Some, like micelles and liposomes, have a hollow sphere for drug encapsulation, while matrix particles have a solid core that adsorbs molecules on its surface. Their properties make them ideal for targeted pharmaceutical transportation[13].Inorganic nanoparticles lack carbon, are non-toxic, biocompatible, hydrophilic, and highly stable compared to organic types. They're classified into metal and metal oxide nanoparticles. Metal nanoparticles (e.g., gold, silver, iron) are synthesized from metal precursors, exhibiting unique optoelectrical properties due to plasma resonance. Their properties are size-dependent (10−100 nm), involving surface area, charge, and shape.Metal oxide nanoparticles (e.g., zinc oxide, iron oxide) are made to increase reactivity and efficiency compared to their pure metal counterparts.Ceramic nanoparticles (nonmetallic solids) are synthesized via heating/cooling and used in applications like photocatalysis and imaging.[14]Carbon-based nanomaterials have seen a rise in new materials and synthesis methods. They are typically classified by their spatial dimensions (0D, 1D, 2D) [7]. A more concise classification divides them into carbon nanotubes, carbon nanofibers (both 1D), and carbon nanospheres (0D), based on physical and chemical properties. Other 0D materials include carbon dots. This chapter will use this latter, simpler classification, also detailing the synthesis methods and discussing specific stimuli-responsive nanomaterials relevant to cutting-edge research.[15]

3.Targeted Drug Delivery Strategies:

Drug Delivery Systems (DDS) are advanced technologies designed for controlled and targeted drug release to specific tissues. Recent innovations include nanoparticles, molecularly imprinted polymers, and 3D printing. DDS significantly enhances drug stability, optimizes distribution, and allows for precise localization and timing of release, even across barriers like the blood–brain barrier. This approach decreases required therapeutic dosage and reduces toxicity, thereby elevating the therapeutic index. The core functions of DDS are drug targeting, controlled release, enhanced absorption, and improved stability, meeting critical clinical demands and improving patient. The primary need for Targeted Drug Delivery (TDD) over conventional systems (DSs) is the poor performance of traditional methods across pharmacodynamic, pharmacokinetic, pharmaceutical, and pharmacotherapeutic features.TDD is vital to enhance therapeutic effectiveness and reduce toxicity by precisely directing drugs, overcoming the inherent flaws of conventional methods like the invasiveness of parenteral delivery, the limitation of oral routes for certain drugs, and the localized scope of topical applications.Drug effectiveness is compromised unless delivered to the site of action at an optimal dosage and rate to maximize benefits while minimizing side effects.Ultimately, drug targeting improves outcomes through increased efficacy, modulated pharmacokinetics, controlled biodistribution, increased specificity of localization, decreased toxicity, reduced dose, and improved patient compliance.[16]

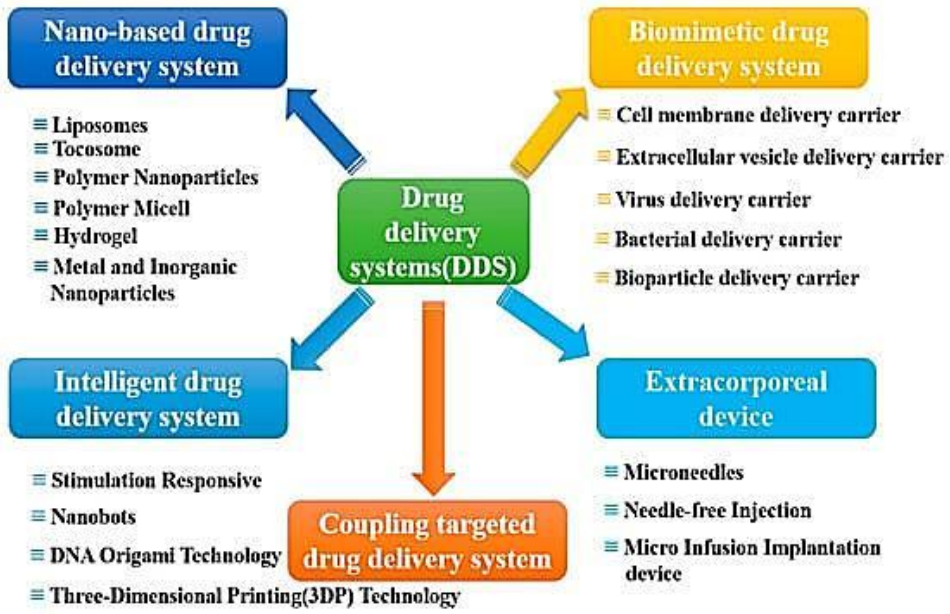

Fig .3 Types of drug delivery system

3.1.Nanobased drug delivery system:

Nanotechnology, proposed in 1959, is rapidly advancing the life sciences by integrating with biotechnology, IT, and cognitive science.It creates nanoformulations with unique physical, chemical, and biological properties for vast biomedical applications.In Nanodrug Delivery Systems (NDDSs), it enhances drug solubility, stability, and tumor targeting.This application also helps to mitigate toxic side effects of drugs.Common materials for NDDSs include liposomes, nanodrugs, polymer micelles, hydrogels, and inorganic systems.[17]

3.1.1.Liposomes:

Liposomes are enclosed vesicles (20–1000 nm) formed by ordered lipid bilayers, featuring a hydrophobic shell and a hydrophilic core.Their unique composition offers excellent biocompatibility and normal metabolism.This structure allows liposomes to enhance drug solubility and mitigate drug toxicity.Crucially, liposomes can encapsulate both hydrophilic and hydrophobic drugs .By encapsulating drugs, liposomes protect them from degradation and prevent off-target accumulation in tissues and organs.The integration of liposome drug delivery systems into clinical practice took nearly fifty years.This nanotechnology-based advancement has significantly propelled the development of new treatments.Liposome systems have enabled a "quantum leap" for anti-tumor, anti-bacterial infection drugs, and vaccines.For example, using solid lipid nanoparticles (a type of liposome system) to deliver the anticancer agent resveratrol was highly effective.It led to significantly higher brain concentration and high penetration into brain tumors in Wistar rats, while showing minimal systemic toxicity [18].

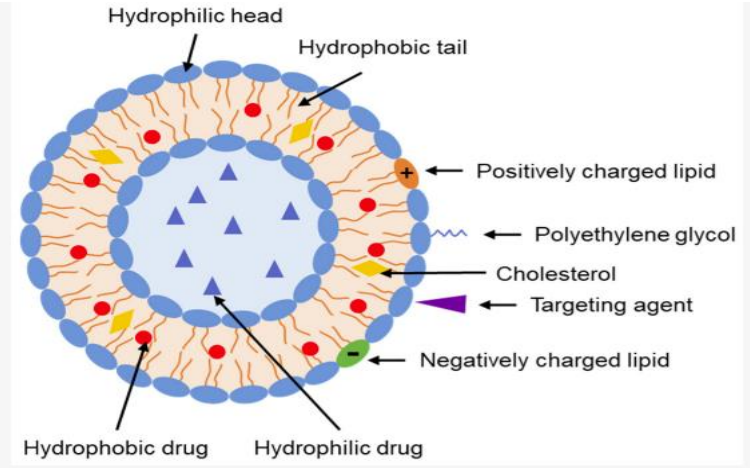

Fig. hydrophilic and hydrophobic structure of liposome drug delivery system

Liposomes are vital in tumor therapy by augmenting X-ray radiationand promoting immunotherapy (e.g., ACSL capturing TAAs to boost T cell response). They significantly reduce the cardiotoxicity and side effects (like alopecia and nausea) of anticancer drugs like doxorubicin .Liposomes also improve treatment for infections, shown by the augmented anticoccidial activity of DQNLs , and the enhanced antibacterial effect of lichenin liposomes + rifampicin for drug-resistant tuberculosis .Liposomes facilitate drug transport across the blood-brain barrier (e.g., transferrin-modified liposomes for glioma regression) and improve

antifungal efficacy (e.g., AmB targeting DC-SIGN receptor) .Lipid Nanoparticles (LNPs) are a specialized, pivotal technology, forming multilayer cores to safeguard and deliver oligonucleotidesfor gene therapy.Innovative LNP strategies include Selective Organ Targeting (SORT) for precise delivery to extrahepatic tissues and the use of iPLNPs with novel phospholipids for organ-selective delivery .Recent LNP successes include restoring cardiac function in heart failure mice and delivering mRNA to the placenta without crossing into the fetus for pregnancy complications.LNPs are the delivery vector for COVID-19 mRNA vaccines and are used in advanced cancer therapy to create CAR T cells by delivering the CAR gene into the nucleus. Nanoprimer technology enhances LNP bioavailability by reducing uptake by the reticuloendothelial system (RES) .Liposomes are also used in microbiota transplantation, with Lipid Membrane-Coated Bacteria (LCB) enhancing microbial survival and therapeutic efficacy in colitis models .Despite their success, liposomes suffer from low drug loading, poor stability, and high production costs.The future of LNP systems focuses on enhancing targeting and responsiveness to stimuli (temperature, enzymes) for precise treatment[19] .

3.1.2. Tocosomes:

Tocosomes are sophisticated, vesicular bioactive carrier systems composed predominantly of alpha-tocopherol phosphate (TP), a biologically active derivative of Vitamin E. Similar to liposomes, they are made of amphiphilic molecules forming bilayer colloidal structures, which gives them analogous drug delivery and release characteristics. TP's unique properties, including narrow particle size distribution, high encapsulation efficiency, exceptional biocompatibility, and low immunogenicity, contribute to its prolonged stability and make it highly adaptable for drug delivery engineering. Clinically, TP is recognized for its health benefits, such as cardioprotection, anti-inflammatory effects, and inhibition of tumor metastasis.[20]In drug delivery, Tocopherol formulations (TP, phospholipids, cholesterol) are used for the controlled release of anticancer agents like 5-fluorouracil. For targeted therapy, a temperature-sensitive coated tocosome (blending Chitosan and poly(N-isopropylacrylamide)) was developed for metastatic kidney cancer drugs, sunitinib malate and sorafenib tosylate, demonstrating enhanced stability and scalabilit. Furthermore, the FDA-approved Vitamin E polymer, Tocophersolan (TPGS), is utilized to overcome drug resistance. Modified TPGS (TPGS-CHMC) delivered docetaxel (DTX), significantly enhancing the antitumor efficacyand reducing toxicity against paclitaxel-resistant ovarian cancer in mouse models .Tocopherols, known for their exceptional antioxidant properties and biocompatibility, are highly suitable for developing nanocarriers like tocosomes for the nutraceutical and pharmaceutical sectors. The main advantages of using tocosomes are two-fold: they enhance the therapeutic effects of encapsulated agents by directly delivering them to cells, which allows for reduced dosages and minimizes potential side-effects. Additionally, tocosomes benefit from being manufacturable using safe ingredients obtained from natural sources [21].

3.1.3 Polymer nanoparticles:

Polymer nanoparticles (PNPs) are colloidal drug carriers (10–1000 nm) that can more readily traverse biological barriers (like the blood-brain barrier) than larger liposomes. PNPs use materials ranging from synthetic polymers (e.g., PLGA) to natural polymers (e.g., chitosan, gelatin). These systems are biodegradable and offer several advantages: reducing systemic toxicity, delaying drug degradation, improving release kinetics, and enhancing overall safety and efficacy .Surface PEGylation extends circulation and enhances the EPR effect; one sophisticated strategy uses NIR light-triggered dePEGylation to achieve synergistic photothermal chemotherapy, resulting in pulsated drug release [47].For example, PLGA-based PNPs have shown a good safety profile and antifungal effects with minimal hemolytic toxicity in vitro[22].The small size of PNPs makes them a vital strategy for overcoming the blood-brain barrier (BBB), a key challenge in drug delivery for brain disorders.Dendrimers are tree-like macromolecules shown to cross the blood-brain barrier (BBB).Hydroxy polyamidoamine (PAMAM) dendrimers effectively deliver small drugs to injured brain tissue by crossing both the BBB and blood-cerebrospinal fluid barriers. Size is a factor: 6.7 nm PAMAM dendrimers show longer blood circulation and greater brain accumulation than 4.3 nm versions.Additionally, dendrimers with cationic surface properties can cross the BBB and localize specifically in neurons and glial cells.This makes dendrimers promising carriers for drug delivery to the brain[23].

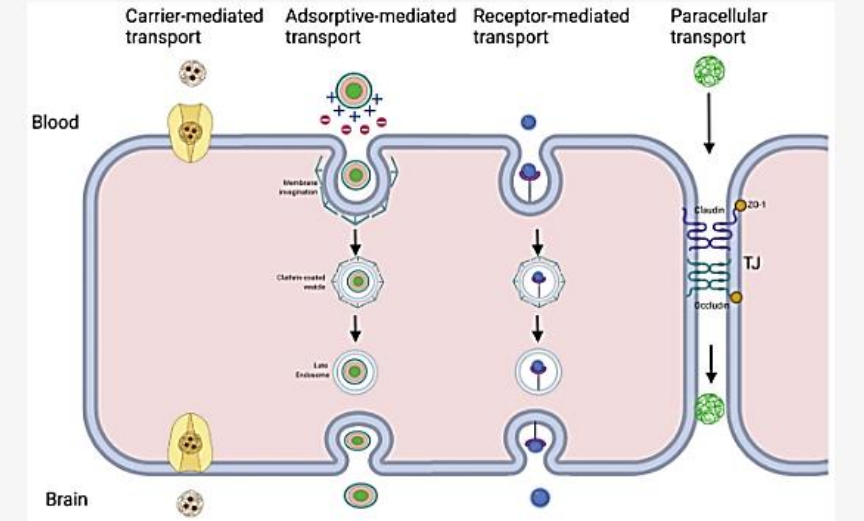

Fig. Nanomedicine crossing blood brain barrier

Fucoidan-Based Nanocarriers have been developed to target endothelial P-selectin, allowing them to penetrate the challenging blood-brain barrier (BBB) . This strategy effectively delivered the anti-tumor agent vismodegib to brain tumors via P-selectin-mediated transport, leading to a significant enhancement of therapeutic efficacy.Molecularly Imprinted Polymers (MIPs), known as "synthetic antibodies," use molecular imprinting technology (MIT) to create binding cavities that precisely match a template molecule in size and affinity, enabling sustained drug release . A specific type, the Magnetic MIP (MMIP) nanogel, was synthesized to address the poor bioavailability of the anticancer agent Quercetin (QC). This MMIP is biocompatible and specifically recognizes QC, making MIPs promising for both rapid drug separation and

delivery[24].Polysaccharide Nanoparticles (PNPs) have shown advancements in their mechanisms and composite material development, but research is incomplete regarding their potential toxicity, polymer stability, and precise drug delivery mechanisms . Therefore, future research must focus on a meticulous analysis of the pharmacokinetics, safety profiles, and immunogenicity of these polymer nanodrug delivery systems to bridge the existing gaps [25].

3.1.4. polymer micelle:

Polymer micelles (PMs) are widely used colloidal aggregates (10-100 nm) formed by amphiphilic block copolymers in water.Their small size allows them to evade the immune system (RES), thus extending systemic circulation time .The hydrophilic shell prevents drug loss and resists complement system activation, overcoming common drug clearance issues .PMs are extensively used as carriers for highly potent, toxic, and poorly soluble small molecule drugs. They show promise in antifungal therapy (acid-base responsive micelles for itraconazole) and can be loaded with multiple agents for targeted tumor delivery, improving patient survival and quality of life .Structurally, PMs feature a hydrophobic core for drug encapsulation and a hydrophilic core for structural stability in aqueous environments.Specific ligands on the corona enable them to traverse the blood-brain barrier (BBB) via transcytosis for effective brain delivery . For instance, PLA-PEG micelles modified with t-Lyp1 ligand inhibited glioma progression in animal models.Advanced wormlike micelles (e.g., mPEG-b-PDPA) can be engineered to degrade in response to the brain tumor microenvironment for targeted drug release .They are also used to precisely control particle size and release kinetics for compounds in traditional Chinese medicine (e.g., curcumin, paclitaxel). Despite some limitations in long-term safety data, PMs are a key focus for future development and broad application in delivering hydrophobic drugs, with some formulations already authorized internationally[26].

3.1.5. Hydrogel :

Hydrogels are polymer networks that swell in water, offering biocompatibility, biodegradability, and low toxicity for sustained and targeted drug release .Innovative designs include anear-infrared light-activated hydrogel nanomotor that penetrates tumors to release drugs and immune adjuvants, achieving a synergistic phototherapy, chemotherapy, and immunotherapy effect .Hydrogels are excellent for tissue repair; for instance, anti-swelling nanofiber hydrogels accelerate fibroblast migration and angiogenesis for wound healing .A novel system uses hydrogels to carry ligands that competitively bind tumor-released ATP, promoting the release of immune adjuvants to enhance the synergistic therapeutic effect of oxaliplatin or X-ray irradiation .In veterinary medicine, thermosensitive gel vaccines (e.g., for Newcastle disease) provide sustained release, eliciting a robust and prolonged humoral and cellular immune response[17].Recently, an antimicrobial peptide-loaded supramolecular nanofiber hydrogel (Hydrogel RL) showed sustained release, biocompatibility, and potent antibacterial activity against MRSA, promising a solution for chronic wound infections .Hydrogels can resist gastrointestinal degradation, like calcium alginate beads, which remain intact in the stomach and are released in the intestine, benefiting from strong mucosal adhesion.

However,oral hydrogel systems face the clinical challenge of rapid disintegration upon contact with large intestinal fluids, which requires future focus .Despite advantages in modulating release kinetics and enabling remote/controlled targeting, clinical application is limited by the challenge of assessing their response characteristics after in vivo implantation .Future research must focus on achieving more precise control over the carrier properties and release kinetics under various internal and external trigger conditions[27].

3.1.6 Metal and inorganic nanoparticles:

Metal and inorganic nanoparticles (NPs) form a promising and diverse category in nanomedicine, valued for their high specific surface area, enhanced bioavailability, and low toxicity, leading to extensive use in combined tumor treatments. Significant carriers include gold, copper, mesoporous silica, and carbon-based nanomaterials. In therapy, NPs like copper ions in oxidative stress amplifiers are used to sensitize immunotherapy and reverse the tumor microenvironment [80], while a phosphorus/nitrogen-doped hollow carbon quantum dot enhances the intranuclear delivery of DOX. Multifunctional CuS nanocomposites combine drug delivery with photothermal/photodynamic therapies to promote T-cell infiltration. In the veterinary field, gold NPs treat canine cancer , and nanosilver NPs (AgNPs) exhibit enhanced antibacterial effects by disrupting bacterial components; additionally, nanoscale zero-valent iron (nZVI) is used to mitigate antibiotic resistance genes in manure [. To address the NPs' reactivity, surface modification is necessary, with gold nanoparticles being the most utilized due to their high biocompatibility and ability to cross the blood-brain barrier (BBB) via cleavable bonds. Advanced systems include transferrin/RVG-peptide-conjugated liposomes (RVG-Tf) for efficient BBB transport, and transferrin-modified liposomes (Tf-PL) that successfully target liver cancer. A convertible liquid metal system has even been engineered to release doxorubicin in acidic endosomes, enhancing chemotherapy. While inorganic NPs are highly tailorable, a complete understanding of their toxicity, biodistribution, and clearance in vivo is lacking, making the investigation of drug retention and the enhancement of clearance processes critical for future clinical application organic nanoparticles[28].

3.2 Intelligent drug delivery system:

3.2.1 Stimulation responsive:

Targeted and controlled drug release is key to maximizing therapeutic efficiency and minimizing side effects.Controlled release nanoplatforms allow loaded drugs to act "smart."Research into stimuli-responsive polymeric gels was boosted after Tanaka's observation of polyacrylamide gel phase transition in 1978.Around the same time, thermal-sensitive liposomes were first reported for drug delivery.This led to the wide development and use of various stimuli-responsive biomaterials for controlled drug delivery systems (DDSs).The advancement of nanotechnology now allows drugs to be conjugated with nanoparticles.With their superior size and surface properties, nanomaterials are now considered highly promising smart DDSs."Smart DDSs" (Drug Delivery Systems) are defined as nanoplatforms that prevent drug release until

they reach the target site, where drugs are released at a proper rate.This primarily focuses on nanotechnology-based smart DDSs designed to carry drug molecules.The smart nanoplatforms ensure drugs do not freely leak during circulation but release only upon accumulation at targets via active or passive targeting.These systems are stimuli-responsive, triggered by endogenous or exogenous. (as illustrated in Figure). Endogenous triggers relate to disease pathology (e.g., pH, enzymes, redox gradient).Exogenous triggers include external stimuli (e.g., temperature, magnetic field, light, ultrasound, electric pulse) used to initiate or enhance drug release[29].

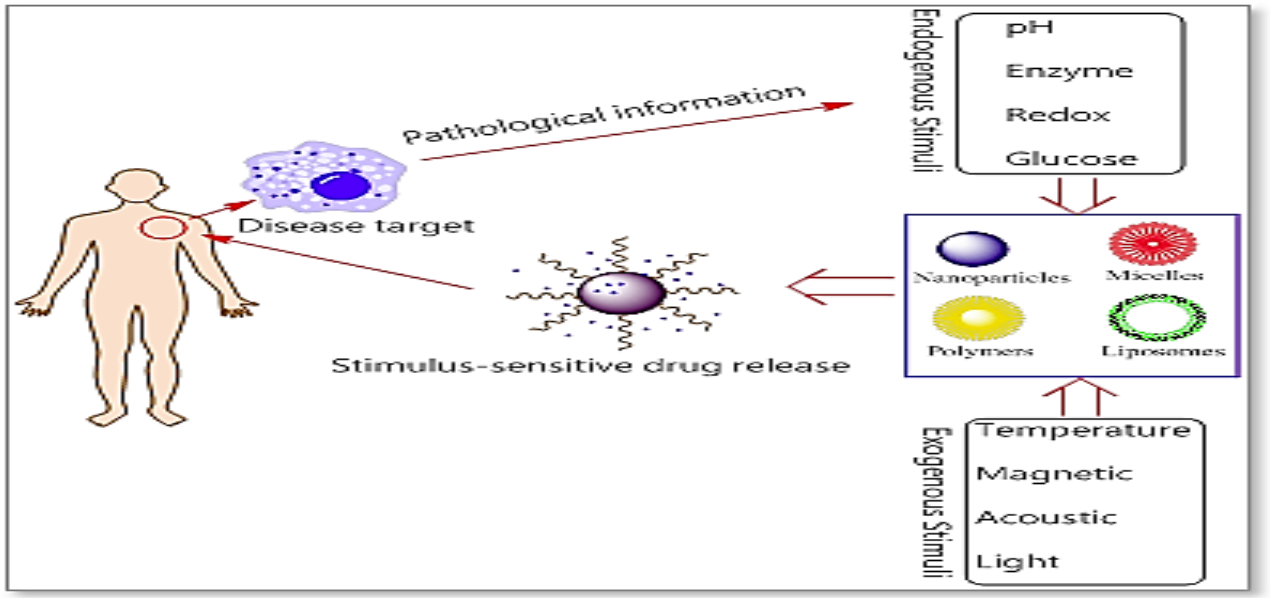

Fig. show the stimuli-responsive DDSs

3.2.2 Nanobots :

Nanobots are minuscule robots, just several nanometers wide, designed to execute a specific function, particularly in drug delivery. Traditionally, drugs circulate throughout the body, but nanobots can target a precise location, making treatment much more effective and reducing side-effects. Advocates believe this could revolutionize medicine, using devices like Computational Genes to repair or detect damages and infections (nanomedicine).According to Robert Freitas, typical medical nanorobots in the bloodstream would be 0.5-3 micrometers in size, constrained by the need to pass through capillaries. They would be primarily constructed from carbon (diamond/fullerene composites) due to its strength, fabricated in specialized desktop nanofactories. Doctors could monitor the nanodevices inside the body using MRI, especially if they were built with the isotope (which has a nonzero nuclear magnetic moment) instead of the natural . After injection, the nanobots would travel to a specific organ or tissue mass. The doctor would track their progress and scan the body to visually confirm that the nanodevices have successfully congregated around the target (e.g., a tumor mass), ensuring the procedure's success [30].

1.2.3. DNA Origami Technology

The controlled delivery of pharmaceuticals to targeted diseased tissues or cells is a significant medical challenge. While no carrier can improve a subpar drug, a well-designed drug delivery system is crucial to amplify the effectiveness and precision of a high-quality drug, aiming to maximize therapeutic benefits while minimizing harmful off-target side effects.Nanocarriers offer key advantages by aiding the

administration of hydrophobic or insoluble pharmaceuticals, improving drug stability, enabling selective delivery routes, increasing drug safety, enhancing drug transport across biological barriers, and improving the bioavailability and pharmacokinetics of medications.[17]A fascinating advancement is the use of DNA origami, which leverages the molecular recognition capabilities of programmed DNA hybridization to construct precise nanostructures. This technique fabricates homogeneous nanostructures (50 to 400 nm) suitable for delivery to tumor regions benefiting from the Enhanced Permeability and Retention (EPR) effect. The addressable nature of DNA origami allows it to act as a "drawing board" to precisely localize multiple functional moieties (like therapeutic agents and tumor-targeting ligands). These structures can also serve as 3D containers with internal docking sites to protect their molecular cargo. Furthermore, their ability to undergo stimuli-triggered reconfiguration allows for the precise control of drug release at specific sites.In gene editing, the CRISPR/Cas9 system relies on the Cas9 protein and a single-guide RNA (sgRNA)to recognize target DNA via a protospacer-adjacent motif (PAM). However, the large size of the Cas9 protein complicates effective delivery. To solve this, Ding et al. developed a DNA origami-based CRISPR/Cas9 gene editing system for in vivo therapy. They created a PAM-rich structure called DOPAM via a one-pot assembly to easily load the sgRNA/Cas9 complex. The loaded complex, DOPAMRC, was compacted (L-DOPAMRC) with a disulfide bond and enhanced with a DNA aptamer and a hyaluronic acid (HA) peptide for targeted delivery and endosomal escape. Once escaped, the structure is opened by a glutathione (GSH) reduction process, triggering the release of the complex upon Rasa H-induced cleavage. This innovative platform successfully edited tumor-associated genes (e.g., PLK1) in invivo gene therapy, showing promise for editing and repairing multiple genes[31].

3.2.4 Three-dimensional printing technology:

Three-dimensional (3D) printing is a fabrication technique that uses a layer-by-layer deposition method, and the techniques used in smart drug delivery devices are classified into three main categories based on how the material is deposited: extrusion-based, droplet-based, and vat-based printing.In extrusion-based 3D printing, material is forced out through a nozzle using mechanical force (like pneumatics, screws, or pistons). Materials that exhibit shear thinning properties are preferred, as their viscosity decreases under the high shear forces at the nozzle for easy extrusion, but then immediately increases after leaving the nozzle to retain the printed shape. Alternatively, heat can be applied at the nozzle to soften the material, which then hardens as the heat is removed.Droplet-based printing jets micro-droplets of the printing or binding material onto a substrate or powder bed. This includes techniques like microvalve, acoustic wave jetting, thermal, and piezoelectric inkjet. In binder-based droplet printing, a binding material is dropped onto a powder bed of the desired final material. In material-based droplet printing, the material droplets are deposited and then subsequently crosslinked, either by being deposited into a crosslinking pool or through UV light, which allows for higher resolution designs. However, this method requires a lower viscosity, limiting the types of materials that can be used and resulting in a lower initial mechanical strength, making immediate crosslinking necessary to hold the shape.Vat-based 3D printing involves the selective curing of a vat of

liquid crosslinkable material. A printing platform is repeatedly lowered into the vat, and light (lasers or patterned light) is shone onto the surface to crosslink and solidify the material layer by layer. Examples include stereolithography, digital light processing, and two-photon polymerization (TPP). TPP achieves nanometer-scale resolution by curing material only at the focal point of a high-power pulse laser, though this process is not easily scalable for larger objects. The final product's quality in vat-based methods is sensitive to the optical properties of the material, which dictates the interaction with the lasers and the degree of crosslinking.These methods are primarily used to fabricate the non-electronic parts of smart drug delivery devices; the techniques for 3D-printed electronics are distinct and will be described separately[32].

3.3 Biomimetic drug delivery system:

3.3.1Cell membrane delivery carrier:

Cell membrane biomimetic nanomedicine delivery systems represent a new approach to overcome challenges in drug delivery by leveraging the distinct and remarkable abilities of natural cells. Cells such as Red Blood Cells (RBCs), which circulate for extended periods, platelets, which adhere to matrices and play a role in coagulation, and cancer cells, which possess homologous targeting abilities, retain their specific functions through biomacromolecules present on their membranes. The concept was pioneered by Zhang et al. in 2011, who developed the first system by coating polymer cores with RBC membranes. This camouflage allowed the nanoparticles to exploit the RBC's prolonged circulation capabilities and ability to avoid clearance by macrophages in the bloodstream, resulting in the nanoparticles remaining in circulation for approximately 40 hours and achieving remarkable therapeutic effects. The success of this erythrocyte membrane system has spurred the development of biomimetic delivery systems using membranes from a variety of other cells, including platelets, leukocytes, cancer cells, and stem cells. Significant ongoing research is focused on utilizing these carriers, as well as developing genetically engineered and hybrid membranes, to further enhance their biocompatibility and tumor-targeting for improved cancer therapy efficacy[33].

3.3.2Extracellular vesicle delivery carrier:

Extracellular Vesicles (EVs) are lipid-bilayer enclosed nanovesicles released by virtually all cell types and found throughout the body's biofluids (including blood, saliva, and cerebrospinal fluid), encompassing three main subtypes: exosomes, microvesicles, and apoptotic bodies. As effective drug delivery carriers, EVs exhibit high stability in the circulation and can traverse significant biological barriers. Their function is uniquely biomimetic: they naturally protect their enclosed cargo and deliver it to target cells via ligand–receptor interactions. Proteins on the EV surface are crucial for this process, notably by enhancing membrane fusion with target cells and preventing their premature removal by the immune system through the inhibition of CD47-mediated phagocytic clearance (the "don't eat me" signal), thereby prolonging their circulatory half-life. Cellular entry often depends on surface ligands, such as heparin sulfate proteoglycans

(HSPGs), or recipient cell receptors like scavenger receptor class B, type 1 (SR-B1). Furthermore, recent research suggests that EVs possess an intrinsic tropism (predisposition) for certain organs, a characteristic that can be finely tuned and utilized for the highly efficient, targeted deliver of therapeutic agents.The clinical translation of Extracellular Vesicles (EVs) is progressing rapidly, driven by their potential as targeted therapeutic carriers, biomarkers, and immunological modulators. Key advantages supporting this progress include the EVs' natural ability to cross biological barriers, their reduced immunogenicity compared to synthetic nanoparticles, and the opportunity to engineer their surface for improved tissue-specific delivery. However, significant hurdles remain, notably scalable production, variability in isolation, batch-to-batch reproducibility, and establishing a clear regulatory categorization. Addressing these challenges has become a primary focus for global biotech and academic innovators, particularly in Far East countries like Japan, South Korea (e.g., Eutilex, Curocell, focusing on immunotherapies), Singapore (e.g., Paragraf Therapeutics, focusing on diagnostics), and China (investing in scalable production). Beyond drug delivery, EVs are integral to numerous biological processes, including tumorigenesis, inflammation, and tissue repair. Their composition reflects the parental cell status, making them excellent candidates for liquid biopsies in disease monitoring. Furthermore, stem cell-derived EVs are considered a potentially safer alternative to cell transplantation in regenerative medicine, as they overcome limitations like immune rejection and tumorigenic potential. These intrinsic characteristics-high cellular selectivity, protection of cargo, and potential for use as a theranostic platform (combining therapy and diagnostics)—highlight the translational readiness of EVs for next-generation medicine, an application being thoroughly validated in ongoing preclinical and clinical studies[34].

3.3.3 Virus delivery carrier:

Conventional drug carriers, developed over the past three decades from materials like lipids, polymers, and proteins, must be biocompatible, biodegradable, and efficient for clinical viability, with protein-based nanomaterials showing particular promise. Among these, Virus-Like Particles (VLPs) stand out as non-infectious, self-assembling, virus-derived structures that mimic the shape and size of a virus but lack the genetic material for host cell invasion. These attractive properties stem from their ability to self-assemble into specific, spatially stable configurations, with responsive amino acid sidechains that enable the conjugation of therapeutic molecules. VLPs are highly valued in preventive medicine, demonstrating significant success in the creation of highly immunogenic VLP-based vaccines (including candidates for SARS-CoV-2) that elicit both antibody- and cell-mediated immune responses. Beyond vaccines, Viral Nanoparticles (VNPs) and VLPs are rapidly advancing in nanomedicine, with promising applications in selective drug delivery and gene therapy. The use of plant viruses as a source for VLPs minimizes potential safety risks, making them especially attractive. Production can be scaled up using molecular farming or fermentation, resulting in biocompatible and biodegradable products suitable for carrying diverse payloads in cancer therapies, immunotherapies, and theranostics. Furthermore, VLPs can serve as nanoscale container for templated inorganic synthesis (like iron oxide in the ferritin cage) or polymerization, and their

modifiable internal and external surfaces allow for increased payload efficiency, where a single nanoparticle can deliver numerous drug molecules to a target cell. This ability to be genetically and chemically modified, combined with their natural tropism, is crucial for future development toward tissue-specific targeting and extended circulation half-lives [35].

3.4 Extracorporeal device :

3.4.1 Microneedles

Polymeric Microneedles (PMNs) as a preferred type of extracorporeal device for drug delivery, often in conjunction with nanocarriers. PMNs, which are micron-sized (25–1500 µm) needles organized on a tiny patch, are favored due to their low cost, flexibility, efficient skin permeability, and biocompatibility. They function by creating reversible, transient microchannels that bypass the stratum corneum (SC) and deposit the drug into the dermal microcirculation without causing the pain associated with deeper hypodermic needles. Research indicates that the penetration depth is directly correlated with needle length, and that using sharp tips (e.g., 5 µm diameter) and certain shapes (triangular and square) is essential for proper, controlled insertion. While their self-dissolving nature eliminates biohazardous sharp waste, PMNs have limitations, including a struggle in loading capacity for lipophilic drugs and an unmanageable rate of drug release. The emerging strategy of integrating nanocarriers with PMNs aims to overcome these drawbacks, opening new horizons for therapeutic and diagnostic applications by mediating enhanced transdermal drug delivery, with future research focusing on optimization of formulation, sterilization, and stability.[36]

3.4.2 Needle free injection:

Needle-free jet injection systems (NFJISs) are vital for effective drug delivery, especially to the dermis, where dendritic and Langerhans cells boost immune response with small vaccine doses. This need for small, variable, and repeatable doses for subcutaneous/transdermal delivery drove the development of a novel hybrid NFJIS.This system combines compressed air and spring force to achieve variable injection volumes with high repeatability. A key feature is its movability, designed for the mass immunization of animal herds or field use. The NFJIS is specifically engineered to deliver doses in the 0.2 to 0.5 mL range for young farm animals and humans. It primarily targets the subcutaneous layer at relatively low pressures. Higher pressures allow for the flexibility of reaching the intramuscular layer when required for deeper penetration. The inlet compressed air pressure is identified as the key determining parameter to control injection depth and intensification. The paper details the design, fabrication, and experimental evaluation of this small-volume NFJIS.The developed Needle-Free Jet Injection System (NFJIS) was designed to deliver an injection volume of 0.1–0.6 mL (targeting 0.2–0.5 mL ± 0.1 mL safety margin) using an inlet compressed air pressure of 0.20–0.50 MPa. The system features a piston-plunger assembly where a low-pressure piston, driven by pneumatic pressure, is mechanically linked to the high-pressureplunger in contact with the drug. This setup creates a pressure intensification ratio of approximately 90 times, due to the cross-sectional area ratio

between the piston and plunger.The drug delivery capability and injection volume control of the final NFJIS were successfully validated through ex vivo experiments on porcine tissue[37].

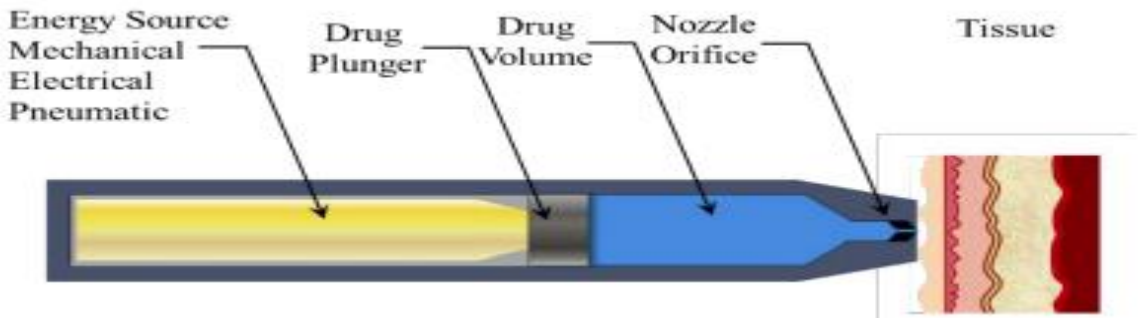

Fig.Model of a needle free jet injector

3.5 Coupling targeted drug delivery system :

3.5.1Site directed coupling of the cysteine:

Opening the interchain disulfide bonds of an antibody using a reducing agent (like TCEP or DTT) yields reactive cysteine residues. The reduced antibody can then be coupled with small molecule toxins linked to disulfonates or dibromobimane for site-specific Antibody-Drug Conjugate (ADC) coupling. Alternatively, phage display is used to introduce reactive cysteine mutations (e.g., LC-V110, HC-A114 in Trastuzumab) on the Fab surface. The interchain bonds are first selectively reduced and restored (using CuSO4), leaving only the mutated free thiols. These specific free thiols then react with drug linkers to achieve precise, site-specific ADC conjugation.[38,39]

3.5.2 Site specific coupling of non–natural amino acid:

Non-natural amino acids (NNAAs) offer a site-specific coupling approach for Antibody-Drug Conjugates (ADCs), surpassing the limited reactivity of natural lysine and cysteine. This method uses modified tRNA/aminoacyl-tRNA synthetase pairs to integrate NNAAs (like acetyl phenylalanine) into recombinant antibodies during ribosomal protein synthesis. The NNAAs introduce specific functional groups: ketone groups form stable oxime bonds with hydroxylamines, while azide groups react with alkynes (via copper-catalyzed or copper-free cycloaddition). This strategy ensures site-specific, quantitative coupling, resulting in ADCs with uniform Drug-to-Antibody Ratio (DAR), enhancing efficacy and safety[38, 40].

3.5.3 Site specific coupling of glycosyl :

Antibody glycan chains in the Fc region can be modified for site-specific conjugation. Enzymes like Gal T and Sial T transfer sugar residues, which are then oxidized with (NaIO4) to introduce aldehyde groups. These aldehydes react with molecules containing hydrazine or primary amine functionalities, creating Antibody-Drug Conjugates (ADCs) with uniform DAR. Alternatively, sugar transferases can introduce azide groups that react with cyclooctyne (a copper-free click chemistry) to form stable ADCs[38,41].

3.5.4 Site specific coupling of enzyme:

Enzymatic coupling using Transglutaminase (TGase) achieves site-specific ADC conjugation by catalyzing a reaction with the glutamine residues on the antibody. TGase can target either a natural residue, a mutated deglycosylated site, or a strategically inserted glutamine-tagged peptide sequence (like LLQGA). Once internalized via receptor-mediated endocytosis, cleavable ADCs release their cytotoxic payload through mechanisms like hydrolysis or reduction in endosomes. Non-cleavable ADCs require lysosomal degradation. The released drug induces cell apoptosis and can also trigger a bystander-killing effect on adjacent cells, depending on its hydrophobicity [38,42].

4.Targeted delivery therapeutic application of nanoparticles :

Targeted delivery involves successfully directing and accumulating a therapeutic agent at a desired site. For efficiency, the agent-loaded system must be retained in the body, evade the immune system, target specific cells/tissue, and release the payload. Nanoparticles are a major focus, especially for cancer treatment (over 20% of clinical therapeutic nanoparticles), with research also extending to conditions like neurodegenerative, infectious, and autoimmune diseases. The subsequent section provides the application of therapeutic nanoparticles as targeted drug delivery system .[43]

4.1 cancer :

Current cancer therapies are hindered by nonspecific drug distribution and low tumor concentrations, which causes complications like multidrug resistance.The primary goals are to achieve better targeting and delivery efficiency in tumors, moving beyond the limited efficacy of conventional drug conjugates like monoclonal antibodies.Nanotechnology (nanoparticles from 5−200 nm) offers a solution by enabling materials that can self-assemble, encapsulate drugs, and selectively interact with cancer at a molecular level.This approach enhances both drug delivery and noninvasive imaging (CT, MRI, PET), promising a future for personalized oncology.[44]

4.2 Iinfectious disease:

The critical rise in multidrug resistance is driving the development of nanoantibiotics and the reformulation of existing drugs using nano-based delivery platforms. Nanoparticle therapeutics fall into two main categories: those with intrinsic antimicrobial activity (like AgNPs), and those that act as biodegradable carriers (like liposomes and nanosuspensions) to deliver antimicrobials effectively.[45]

4.3 Autoimmune disease:

Autoimmune diseases arise from the chronic loss of immune tolerance to self-antigens, leading to tissue damage (e.g., MS, SLE). The ideal treatment seeks to restore tolerance by specifically eliminating the autoantigen-specific response. Nanocarrier technology is a promising platform for this goal, as it enhances

drug delivery and stability. Nanovaccines, in particular, can be engineered by adjusting their properties (size, surface) to improve APC uptake, enhance targeting, and induce the desired immune modulation needed to restore tolerance[46].

4.4 Cardiovascular disease:

Nanoscience is advancing disease management by using nanoparticles (1–100nm) as versatile drug carriers to improve targeting, drug deposition, and reduce toxicity. While early systems like liposomes face challenges, newer polymeric and inorganic materials (like magnetic iron oxide) offer better solutions for drug delivery and imaging. This technology is crucial for treating Cardiovascular Disease (CVD)—a leading cause of death—by addressing issues like inadequate drug accumulation and difficult plaque localization through improved diagnosis, treatment, and drug delivery methods.[47]

4.5 Neurodegenerative disease:

Nanotechnology is crucial for developing new therapies for Neurodegenerative Disorders (NDs) like AD and PD, which are currently limited by symptomatic treatments and the major hurdle of the Blood-Brain Barrier (BBB). Nanoparticles (1–100 nm) offer a solution by providing targeted drug delivery and enhancing efficacy across the BBB. The most successful in vivo example is PBCA nanoparticles, which are thought to cross the barrier via receptor-mediated endocytosis, paving the way for safer and more effective CNS treatments [48].

CONCLUSION:

The design of nanoparticles (NPs) is a revolutionary strategy in medicine, offering significant advantages like targeted delivery, enhanced drug stability, and reduced toxicity compared to conventional systems. These materials, classified by composition (organic, inorganic, carbon-based), are crucial as drug carriers in diverse systems like Nanodrug Delivery Systems (NDDSs) and intelligent formulations. Development of nanoparticle-based therapeutic agents has been extensively studied, and nano-delivery systems are the area of prime importance for specifically targeting the desired area in the treatment of many diseases. Although nanoparticle-based delivery systems contribute significantly to the targeted therapy.This nanoscale technology will be incorporated in the medical system to diagnose, transport therapeutic drugs, and detect cancer growth, according to the National Cancer Institute.Nanomedicine will be the future of medicine, and nanoparticle-based therapeutics lies at the heart of it. However, a long ground should be gained before prosperity. Most importantly, long-term safety/toxicity of the nanoparticles should be investigated. Meanwhile, the discoveries on disease mechanisms and new drugs will lead to ways of placing more efficient and safer nanoparticle-based therapeutics in treatment regimens.

REFERENCES :

1) Obaid Afzal 1,Abdulmalik S. A. Altamimi 1,Muhammad Shahid Nadeem 2,Sami I. Alzarea 3,Waleed Hassan Almalki 4, aqsa tariq 5, bismillah mubeen 5, saima iftikha7, naeem riaz8, and imran kazmi 2, A review on Nanoparticles in Drug Delivery: From History to Therapeutic Applications. Nanomaterials 2022, 12(24), 4494; https://doi.org/10.3390/nano12244494.
2) Raisa Nazir Ahmed Kazi 1,Ibrahim W. Hasani 2,Doaa S. R. Khafaga 3,Samer Kabba 4,Mohd Farhan 5,Mohammad Aatif 6,Ghazala Muteeb 7, and ystri a. fahim 8. Nanomedicine: The Effective Role of Nanomaterials in Healthcare from Diagnosis to TherapyPharmaceutics 2025, 17(8), 987; https://doi.org/10.3390/pharmaceutics17080987.
3) Magdalena Raszewska-Famielec 1 and Jolanta Flieger2. Nanoparticles for Topical Application in the Treatment of Skin Dysfunctions—An Overview of Dermo-Cosmetic and Dermatological Products. Int. J. Mol. Sci. 2022, 23,15980. https://doi.org/10.3390/ijms232415980.
4) Akash Kumar 1,2, Nabojit Das 1,2 and Raja Gopal Rayavarapu 1,2,*. Role of Tunable Gold Nanostructures in Cancer Nanotheranostics: Implications on Synthesis, Toxicity, Clinical Applications and Their Associated Opportunities and Challenges. Nanotheranostics 2023, 4, 1–34.https://doi.org/10.3390/jnt4010001.
5) Denisa-Maria Radulescu 1, Vasile-Adrian Surdu 1, Anton Ficai 1,2 , Denisa Ficai 1, Alexandru-Mihai Grumezescu 1,2,3 and Ecaterina Andronescu 1,*. Green Synthesis of Metal and Metal Oxide Nanoparticles: A Review of the Principles and Biomedical Applications. Int. J. Mol. Sci. 2023, 24,15397. https://doi.org/10.3390/ijms242015397.
6) Ali Al-Samydai1, Maha N. Abu Hajleh2, Farah Al-Sahlawi3, Hamdi Nsairat1 ,Arwa Al Khatib1, Moath Alqaraleh4 and Alia K. Ibrahim 5. Advancements of metallic nanoparticles: A promising frontier in cancer treatment.2024. 10.1177/00368504241274967.journals.sagepub.com/home/sci.
7) Faheem Ahmad 1,* , Mounir M. Salem-Bekhit 2,3,*, Farmyard Khan 1, Sultan Alshehri 2, Amir Khan 1, Mohammed M. Ghoneim 4, Hui-Fen Wu 5,6, Ehab I. Taha 2 and Ibrahim Elbagory 7. Unique Properties of Surface-Functionalized Nanoparticles for Bio-Application: Functionalization Mechanisms and Importance in Application. Nanomaterials 2022, 12, 1333. https://doi.org/10.3390/nano12081333.
8) Ankesh Kumar 1, SK Shahvej 2, Pankaj Yadav 1, Unnati Modi 1, Amit K. Yadav 1, Raghu Solanki 1* and Dhiraj Bhatia 1*. A review on Nanoparticles in Drug Delivery: From History to Therapeutic Applications. Nanomaterials 2025, doi:10.20944/preprints202502.1400.v1.
9) Sanja Petrovic1, Bogdan Bita 2, and Marcela-Elisabeta Barbinta-Patrascu 2*.Nanoformulations in Pharmaceutical and Biomedical Applications: Green Perspectives. Int. J. Mol. Sci. 2024, 25(11), 5842; https://doi.org/10.3390/ijms25115842.
10) Melanie Bresinsky and Achim Goepferich. Control of biomedical nanoparticle distribution and drug release in vivo by complex particle design strategies. https://doi.org/10.1016/j.ejpb.2025.114634.
11) Nagarjuna Prakash Dalbanjan a, Karuna Korgaonkar b c, Manjunath P. Eelager d e, Basavaraj Neelappa Gonal f, Arihant Jayawant Kadapure a, Suresh B. Arakera f,Praveen Kumar S.K. In-silico strategies in nano-drug design: Bridging nanomaterials and pharmacological applications.https://doi.org/10.1016/j.ntm..100091
12) Furkan Eker 1, Hatice Duman 1, Emir Akda¸sçi 1, Ecem Bolat 1, Sümeyye Sarıta¸s 1, Sercan Karav 1* and Anna Maria Witkowska 2*.A review on Nanoparticles in Drug Delivery: From History to Therapeutic Applications.. 2024, 29, 3482. https://doi.org/10.3390/molecules29153482.
13) Basmah H. Alshammari† a, Maha M. A. Lashinb, Muhammad Adil Mahmood† *c, Fahad S. Al-Mubaddelde, Nasir Ilyasf, Nasir Rahman , Mohammad Sohailc, Aurangzeb Khan g, Sherzod Shukhratovich Abdullaev and Rajwali Khan .Organic and inorganic nanomaterials: fabrication, properties and applications. DOI: 10.1039/D3RA01421E.
14) Irfan Ijaz ,Ezaz Gilani, Ammara Nazir &Aysha Bukhari. Detail review on chemical, physical and green synthesis, classification, characterizations and applications of nanoparticles. https://doi.org/10.1080/17518253.2020.1802517.
15) CHEN ZHAO, JUN KANG, YUWEN LI, YAN WANG, XIAOYING TANG, AND ZHENQI JIAN. Carbon-Based Stimuli-Responsive Nanomaterials: Classification and Application. DOI: 10.34133/cbsystems.0022.

16) Qian Chen 1,†, Zhen Yang 1,†, Haoyu Liu 1, Jingyuan Man 1, Ayodele Olaolu Oladejo 1,2, Sally Ibrahim 1,3,Shengyi Wang 1,* and Baocheng Hao 1. Novel Drug Delivery Systems: An Important Direction for Drug Innovation Research and Development. https://doi.org/10.3390/pharmaceutics16050674.
17) Huang, P.; Wang, X.; Liang, X.; Yang, J.; Zhang, C.N.; Kong, D.L.; Wang, W.W. Nano-, micro-, and macroscale drug delivery systems for cancer immunotherapy.https://doi.org/10.1016/j.actbio.2018.12.028.
18) Rouba D. Al Bostami 1,Waad H. Abuwatfa 1,2 andGhaleb A. Husseini 1,2. Recent Advances in Nanoparticle-Based Co-Delivery Systems for Cancer Therapy. https://doi.org/10.3390/nano12152672.
19) Rurik, J.G.; Tombácz, I.; Yadegari, A.; Fernández, P.O.M.; Shewale, S.V.; Kimura, T.; Soliman, O.Y.; Papp, T.E.; Tam, Y.K.; Mui, B.L.; et al. Car T cells produced in vivo to treat cardiac injury.DOI: 10.1126/science.abm0594.
20) Yasukazu, S.; Atsushi, Y.; Nobuhiko, M. Alpha-tocopheryl phosphate suppresses tumor invasion concurrently with dynamic morphological changes and delocalization of cortactin from invadopodia.https://doi.org/10.3892/ijo_00000445
21) Qi, Z.W.; Shi, J.; Song, Y.Z.; Deng, Y.H. A novel micellar carrier to reverse multidrug resistance of tumours: TPGS derivatives with end-grafted cholesterol.DOI: 10.1080/1061186X.2023.2205614.
22) Van de Ven, H.; Paulussen, C.; Feijens, P.B.; Matheeussen, A.; Rombaut, P.; Kayaert, P.; Van den Mooter, G.; Weyenberg, W.; Cos, P.; Maes, L.; et al. PLGA nanoparticles and nanosuspensions with amphotericin B: Potent in vitro and in vivo alternatives to Fungizone and AmBisome. https://doi.org/10.1016/j.jconrel.2012.05.037.
23) Srinageshwar, B.; Peruzzaro, S.; Andrews, M.; Johnson, K.; Hietpas, A.; Clark, B.; McGuire, C.; Petersen, E.; Kippe, J.; Stewart, A.; et al. PAMAM Dendrimers Cross the Blood-Brain Barrier When Administered through the Carotid Artery in C57BL/6J Mice.DOI: 10.3390/ijms18030628.
24) He, S.; Zhang, L.; Bai, S.; Yang, H.; Cui, Z.; Zhang, X.; Li, Y. Advances of molecularly imprinted polymers (MIP) and the application in drug delivery.https://doi.org/10.1016/j.eurpolymj.2020.110179.
25) Kim, K.S.; Suzuki, K.; Cho, H.; Youn, Y.S.; Bae, Y.H. Oral nanoparticles exhibit specific high-efficiency intestinal uptake and lymphatic transport. DOI: 10.1021/acsnano.8b04315.
26) Owens, E.; Peppasn, A. Opsonization, biodistribution, and pharmacokinetics of polymeric nanoparticles.DOI: 10.1016/j.ijpharm.2005.10.010.
27) Shang, L.; Liu, J.; Wu, Y.T.; Wang, M.; Fei, C.Z.; Liu, Y.C.; Xue, F.Q.; Zhang, L.F.; Gu, F. Peptide supramolecular hydrogels with sustained Release Ability for Combating Multidrug-Resistant Bacteria.DOI: 10.1021/acsami.3c01453.
28) V. Chandrakala, Valmiki Aruna & Gangadhara Angajala. Review on metal nanoparticles as nanocarriers: current challenges and perspectives in drug delivery systems.
29) Dong Liu, Fang Yang , Fei Xiong , Ning Gu.The Smart Drug Delivery System and Its Clinical Potential.doi: 10.7150/thno.14858.
30) Sachin S.Salunkhe1, Neela M.Bhatia1, Sachin S.Mali2, Jyoti D.Thorat2, Amita A.Ahir1Ashok A.Hajare2.Nanorobots: novel emerging technology in the development of pharmaceuticals for drug deliveryapplications.
31) Ruipeng Chen, Xuexia Jia, Wei Pang, Yingao Yang, Huanying Zhou & Zhixian Gao. Applications of DNA origami in biomedicine: advances, challenges, and prospects.https://doi.org/10.1007/s42114-025-01457-0.
32) Wai Cheung Ma 1,*, Guo Liang Goh 1, Balasankar Meera Priyadarshini 1, Wai Yee Yeong 1. 3D printing and 3D-printed electronics: Applications and future trends in smart drug delivery devices. doi: 10.18063/ijb.725.
33) Zhenxing Xia 1,2,†,Weiwei Mu 1,2,†,Shijun Yuan 1,2,Shunli Fu 1,2,Yongjun Liu 1,2,* andNa Zhang 1,2,*.Cell Membrane Biomimetic Nano-Delivery Systems for Cancer Therapy. https://doi.org/10.3390/pharmaceutics15122770.
34) Viswanathan Sundaram, Santosh Aryal. Emerging Biomimetic Drug Delivery Nanoparticles Inspired by Extracellular Vesicles. https://doi.org/10.1002/wnan.70025.
35) Alaa AA Aljabal Icon,Sk Sarif Hassan,Ritesh M Pabari,Seyed H Shahcheraghi,Vijay Mishra5,Nitin B Charbe. The Viral Capsid As Novel Nanomaterials for Drug Delivery. https://doi.org/10.2144/fsoa-2021-0031.

36) Salwa Naga, Thirumalesh Chevala,Srinivas Reddy Jitta,Shirleen Miriam Marques,Vanessa Marcia Vaz, Lalit Kumar.Polymeric microneedles for transdermal delivery of nanoparticles: Frontiers of formulation, sterility and stability aspects. https://doi.org/10.1016/j.jddst.2021.102711.
37) Mojiz Abbas Trimzi 1 and Young-Bog Ham 2. A Needle-Free Jet Injection System for Controlled Release and Repeated Biopharmaceutical Delivery. https://doi.org/10.3390/pharmaceutics13111770.
38) Meng Li, Tiantian Wang, Dan Tan, Mengqi Wang, Changhai Lei, Yuqing Wang, Shi Hu. Research progress of antibody coupling technique in targeted drug delivery. https://doi.org/10.1002/INMD.20240108.
39) Jagath R Junutula 1, Helga Raab, Suzanna Clark, Sunil Bhakta, Douglas D Leipold, Sylvia Weir. Site-specific conjugation of a cytotoxic drug to an antibody improves the therapeutic index. DOI: 10.1038/nbt.1480.
40) Trevor J Hallam 1, Vaughn V Smider.Unnatural amino acids in novel antibody conjugates. DOI: 10.4155/fmc.14.79.
41) Xiuru Li 1, Tao Fang, Geert-Jan Boons. Preparation of well-defined antibody-drug conjugates through glycan remodeling and strain-promoted azide-alkyne cycloadditions. DOI: 10.1002/anie.201402606.
42) Patrick Dennler 1, Aristeidis Chiotellis, Eliane Fischer, Delphine Brégeon, Christian Belmant, Laurent Gauthier, Florence Lhospice, François Romagne, Roger Schibli. Transglutaminase-based chemo-enzymatic conjugation approach yields homogeneous antibody-drug conjugates. DOI: 10.1021/bc400574z.
43) 43Abuzer Alp Yetisgin 1,Sibel Cetinel 2, Merve Zuvin 3, Ali Kosar 3,4and Ozlem Kutlu 2,4. Therapeutic Nanoparticles and Their Targeted Delivery Applications. https://doi.org/10.3390/molecules25092193.
44) Dr. Xu Wang PhD, Dr. Lily Yang MD, Dr. Zhuo (Georgia) Chen PhD, Dr. Dong M. Shin MD.Application of Nanotechnology in Cancer Therapy and Imaging. **https://doi.org/10.3322/CA.2007.0003**
45) Ellis Tobin, Sara Brenner. Nanotechnology Fundamentals Applied to Clinical Infectious Diseases and Public Health. https://doi.org/10.1093/ofid/ofab583
46) Yuhong Tang and Lili Li.The Application of Nanovaccines in Autoimmune Diseaseshttps://doi.org/10.2147/IJN.S440612
47) Chuanyun Tang, Kexun Zhou, Di Wu Icon &Hong Zhu. Nanoparticles as a Novel Platform for Cardiovascular Disease Diagnosis and Therapy. https://doi.org/10.2147/IJN.S474888.
48) Girish Modi a, Viness Pillay b, Yahya E. Choonara b, Valence M.K. Ndesendo b,Lisa C. du Toit b,Dinesh Naidoo.Nanotechnological applications for the treatment of neurodegenerative disorders.https://doi.org/10.1016/j.pneurobio.2009.05.002.