Review Article

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Current Novel Nanocarriers in Drug Delivery: A Review

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ABSTRACT

Nanotechnology's applicability in medicine, specifically drug delivery, is expected to grow substantially. Because of their ability to overcome drug transportation constraints, nanotechnology in drug transport systems could be a possible technique for overcoming traditional drug delivery. A targeted Drug Delivery system can enhance the transport and nearby awareness of drugs. Targeted transport processes for most cancer therapeutics have proven a steep upward push over the beyond few decades. However, in comparison to the plethora of hit pre-scientific studies, the best passively centered Nanocarriers (NCs) had been accredited for scientific use and none of the actively centered NCs have superior beyond scientific trials. Herein, we overview the principles at the back of centered transport processes to decide the ability motives for restrained scientific translation and success. We advocate standards and concerns that ought to be taken into account for the improvement of novel actively centered NCs. We additionally spotlight the possible instructions for the improvement of a hit tumor and concentrated on strategies.

Keywords: Nanocarrier, Nanotechnology, Drug, Target, Tumor, Therapeutic.

1. Introduction

Drug delivery refers to the strategies, plans, innovations, and processes associated with transporting a drug substance in the body to accomplish the ideal remedial effect. From the traditional era, various methodologies were incorporated for drug administration in humans and animals to achieve therapeutic efficacy against the desired ailment [1]. Ongoing time, the drug delivery system has been advanced and significant research is still going to develop a new drug for existing drugs, the prime focus has been on the fabrication of smart Drug delivery systems, which can be managed, targeted, and provide desired drug release. The headway of novel Novel Drug delivery systems (NDDSs) has drawn in articulated consideration and is a developing field in drug science [2]. There are five ages of Drug delivery systems (DDSs), in which significant advancement has been made from conventional drug delivery to gene therapy and nanorobotics [3].

In the course of the most recent couple of many years, creating supported or controlled DDSs has been a concentration, to sustain and control drug release, with minimum side effects and better therapeutic efficacy [4]. With the advancement in the drug delivery system, the emergence of 4th and 5th generation drug delivery lays a better emphasis on drug targeting for specific diseases, such as cancer, neurological, and brain drug targeting. This generation of drug delivery system has specific merits, such as better stability with biocompatibility, increased permeability and retention effect, and close targeting [5].

The beginning of nanotechnology holds fantastic promise for advances in biomedical research. Nanotechnology touches every edge of life starting from nanoscale devices to drug delivery frameworks [6]. Observing nanotechnology for drug transportation appears a smart approach for site-specific transport of drug molecules due to the fact nanocarriers can defend a medicine from degradation with the aid of using eluding the reticuloendothelial framework [7]. The introduction of a targeted drug delivery system for cancers is one more potential development that can be accomplished with a nanotechnology-based delivery system. Utilization of Nanoparticle (NP)-based Drug delivery brings a chance for controlled release of medications, permitting adequate time for medications to act with raised therapeutic effect activity and react to specific stimuli, like pH, light, heat, or enzymes [8,9].

The excessive blood flow profile empowers delivery thru biological obstructions and increases the accessibility of drugs in the steady intracellular compartment. In view, focused transport of therapeutics in most cancers usually entails systemic management of drug administration packaged in nanocarriers (NC) or localized transport of therapeutics to the diseased tissue [10]. The confinement of therapeutic molecules in nanocarriers can enhance their solubility and bioavailability, adjust their biodistribution, and also can facilitate access to the target cell [11]. A nanocarrier distributes drugs to the disease site either actively or passively. In the previous case, peptides and antibodies coupled to the DDS are anchored with the receptor or the lipids or antigens at the designated site by direct chemical conjugation [12]. While passive drug delivery includes transportation of the drug by self-assembled nanostructured material and delivery of the encapsulated drug to the target. The review aims to provide current updates about nanocarriers and the mechanism of drug targeting in cancerous tissue [13].

1.1 Drug Targeting

The primary precept behind drug targeting is turning in a high concentration of drug to the targeted site while minimizing its drug concentration to the nontargeted region and this helps in decreasing the side effects due to, higher doses, nontarget, and multitarget interactions concentrations [14]. Targeting additionally ameliorates undesirable interactions of the drug with bioenvironmental elements that affect drug access to targeted sites in the body, as it incorporates coordinated drug behavior, focused on the target site and pharmaceutical carrier [15]. The word target denotes a cell or group of cells, a specific organ suffering from acute or chronic conditions and demanding treatment [16]. In drug targeting, the drug is loaded in a carrier (specially engineered molecule or system) that delivers the drug to preselected sites. Preferably, a drug targeting complex is relied upon to be nontoxic, nonimmunogenic, biochemically latent, biodegradable, biocompatible, and physiochemically stable *in vivo* and *in vitro* and expected to be readily and easily eliminated from the body with minimum leakage [17]. In request to guarantee the satisfaction of these ideal qualities, designated target drug products should be formulated while taking into consideration about properties of the target cell, type of carrier, and its ability to transport the drug to a specific receptor [18].

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These considerable variables include the concentration of the drug, location of the target organ or cell, nature, and surface morphology of the carrier to transport the drug to a specific target [19]. For effective targeting of desired cells or tissue, physiological variables such as blood flow for intravenous drug delivery and tissue architecture, as well as physicochemical parameters such as carrier geometry, avidity, composition, and functionalization, should be managed [20]. Furthermore, the clinical enhanced permeability and retention (EPR) effect, extravasation, intertumoral distribution, and tumor heterogeneity are all factors to consider. Traits of overexpression and overexpression characteristics are crucial elements to consider [21].

If the ideal properties are very much met and definition factors all-around considered, TDD can be applied successfully in imaginative nanomedicine and therapeutics. However, TDD can be utilized to treat numerous persistent and irresistible sicknesses, its most significant application is in treating carcinogenic growths, because of its better microphage entrance and improved focus at the disease site [22]. Promising applications and reasons for TDD incorporate malignant growth treatment, immunization adjuvant, visual and cerebrum conveyance, DNA and oligonucleotide conveyance, intracellular and foundational focusing on, oral and transdermal conveyance, catalyst immunoassays, and radio imaging [23, 24]. By and large, results revealed with these applications incorporate, reduced toxicity, upgraded take-up, enhanced bioavailability, and immune response by improved drug effect, better drug absorption, and permeation, and improve drug retention [25].

1.2. Types of Targeted Drug delivery system

Passive targeting is a type of DD that focuses on the circulatory system. Drug targeting occurs in this strategy as a result of the body's natural response to physicochemical features of the drug or drug-delivery system [26]. This is predicated on the drug(s) accumulating in locations that target the target site, such as in tumor tissue. In passive targeting, NP is used as a carrier system and aim to enter in blood vessels further in a disease state, which gives a chance for, marked drug accumulation in the target region [27].

This process is helped by moderate lymphatic drainage - the EPR effect (Enhanced Permeability and Retention).

On the other hand, active targeting is a specific ligand-receptor–type interaction that happens after blood circulation and extravasation. It chiefly depends on the biological interface between target cells and the ligands joined to NPs [28]. Different kinds of ligands have been utilized for this purpose, including proteins, polysaccharides, nucleic acids, peptides, and small particles [29]. Tumors are characterized by the aid of using particularly defective vessel structure and severe lymphatic drainage, according to the EPR impact. Small nanocarriers are believed to be applicable for passive concentration anticancer drugs, at exceptionally smaller dimensions than ordinary blood-vessel gaps, and might without difficulty attain and selectively localize in tumors [30]. However, current research has tested that interendothelial gaps on tumors aren't chargeable for NP transport and accumulation into solid tumors without difficulty attain and selectively localize tumors [31]. Active transport mechanisms are expected to be higher for uptake of centered NPs from the bloodstream into the tumor micro surroundings than greater passive transport mechanisms just like the EPR impact [32].

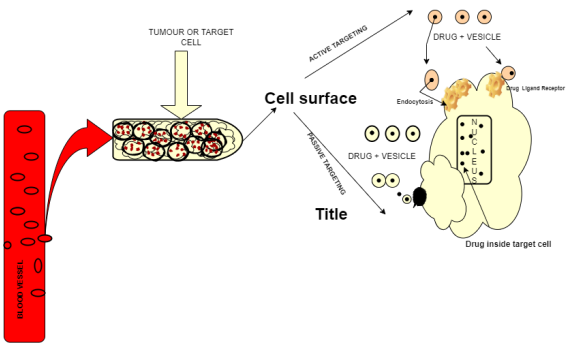

Figure 1. Schematic Diagram depicting Active VS Passive Targeting

Though the development of NPs for targeting brings many promising advantages, the efficacy of current nanodrugs is not significantly better than the original drug treatments, especially in cancer chemotherapy. This is because of poor and incomplete nano-drug penetration into tumor tissue, due to the complex features associated with a nano-drug size and tumor pathology [33]. Remodeling the microenvironment of tumor tissues, carrier charge inversion, dimensional change, and surface modification are among the demonstrated strategies for promoting tumor

penetration of nano drugs. Even with promising penetration-enhancing strategies, the effective application of targeting tumors is far from complete, and cancer chemotherapy still has many difficulties and challenges. As such, DD and targeting systems of a more bioresponsive nature, reduced side effects, and better treatment efficacy are required [34]. Though the improvement of NPs for targeting brings many promising advantages, the efficacy of cutting-edge nano drugs isn't substantially higher than the unique drug treatments, mainly in most cancer chemotherapy [35]. This is due to incomplete nano-drug penetration into tumor tissue, because of the complicated functions related to nano-drug length and tumor pathology. Remodeling the microenvironment of tumor tissues, vehicle rate inversion, dimensional change, and surface amendment are some of the tested techniques for promoting tumor penetration of nano drugs. Even with favorable penetration-improving techniques, the powerful application of targeting tumors is a long way from complete, and most cancer chemotherapy nonetheless has many problems and challenges. As such, DD and targeting structures of a greater bioresponsive nature decreased side effects, and higher deal with treatment efficacy [36].

1.2.1. First, Second, Third, and Fourth Order Targeting:

Drug targeting can in addition be categorized into three (or four) unique orders of targeting. First-order targeting refers to the limited distribution of the drug carrier systems to the capillary bed of a predetermined goal site, organ, or tissue. It comprises compartmental targeting in, the peritoneal cavity, lymphatics, plural cavity, eyes, joints, cerebral ventricles, etc**.** Second-order targeting selective delivery of drugs to particular molecular types including tumor cells and not to the normal cells [37]. When Nanoparticles are mainly engulfed by Kupffer cells in the liver, the level of NPs acting on other liver cells is reduced. Therefore, the selective delivery of NPs to the targeted specific cells is one of the most important issues in drug targeting [38]. Third-order targeting is defined as drug delivery, especially to the intracellular site of centered cells. An example encompasses receptor primarily based ligand-mediated access of a drug complex into a molecular through endocytosis and fourth-order targeting is nominated for drugs targeting macromolecules, such as DNA and proteins [39].

1.2.2. Local and Systemic targeting

The Local Target System is a non-invasive targeting strategy whose primary purpose is to deliver drugs to local sites to treat local medical conditions. With systemic targeting, such a treatment system is delivered via an invasive route, such as intravenous administration of a nanotechnology system [37]. Such a system delivers the drug through the systemic circulation after being distributed into the body. The main limitation of such a system is due to the side effects of the drug in certain tissues [40].

1.2.3. Physical, chemical, and biological targeting

Physical targeting represents a system that localizes the active ingredient to the target region based on size, composition, or other properties that do not specifically target biological receptors [41]. Chemical targeting involves the localization of the drug in the target area through the use of site-specific prodrugs. The drug can also be directed to the region through the use of enzymatic or chemical reactions that result in targeting the action of the vehicle or sustained release of active ingredient [42]. By biological targeting, using antibodies (Abs), peptides, proteins, or other biomolecules that have an affinity with the receptor, site, or another biological target in a particular manner, Localized drugs can target the region. Gene expression can also be localized to the target region by using a cell, tissue, or other-specific promoter in the vector system [43].

1.2.4. Reverse, Dual, Double, and Combined targeting

When the normal activity of the reticuloendothelial system is inhibited by an empty colloidal carrier to minimize its passive drug uptake, the system becomes saturated by suppressing its defense mechanism [44]. This is an approach known as reverse targeting. Double targeting is the delivery of the carrier molecule with its therapeutic activity and is, therefore, an increase in the (synergistic) therapeutic effect of the drug. In dual targeting, temporal and spatial methods are combined, i.e., spatial placement at a particular location. Combination targeting is a method of targeted delivery with direct access to the target using a carrier, polymer, and homer with molecular specificity [45].

1.2.5. Location and disease targeting

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TDD with specific site-based strategies targeted the delivery of specific cells, organs, and organelles. Intracellular targeting, gastrointestinal targeting (GIT), brain targeting, and airway targeting are some examples of location-based targeting [46]. The intracellular administration of pharmaceutical agents such as proteins, Abs, and drug-loaded nanocarriers ensures that therapeutic activity is delivered specifically to the nucleus of specific organelles. Floating DD is a tissue model for this type of targeting, where antiviral, antifungal, and antibiotic agents are absorbed from very specific regions of the GIT. Various specific oral controlled-release systems have been developed to target the stomach/duodenum, small intestine, lymph nodes, and colon [47]. Polymer-based DDSs such as dopamine-liposome conjugates show effective brain targeting with reduced degradation during circulation, whereas disease-based target distribution is site-specific therapies targeting tumors and other targetable infectious diseases. Infection control with nano DDS could be a practical alternative to antibiotic therapy [48]. Designing nano vaccines to achieve enhanced targeting and improve cellular responses is a new perspective. Specific and specific approaches to target several pathogens important for cell survival are under development. This covers the function of NPs with antibacterial agents [49].

2. Types of nanocarriers of Drug Delivery

Progressed nanomaterial Therapeutic systems hold specific benefits over the regular conventional therapeutic system. Most regularly sped-up removal of drugs by scavenger cells can be constrained by balancing the size of nanocarriers. A kind of nanocarrier is used for drug transport applications [50]. The previously mentioned resources of Nanocarriers fulfill the conditions to improve chemotherapy for malignant growth, in which it is vital to keep the ideal drug levels in cancer tissue and to debilitate the drug concern for healthy tissues. Nanocarriers of ideal size can travel through the Capillary vascular walls which aid assist in passive tumor targeting [51]. The ability to capsulize and transport insufficiently water-solvent medications offers agreed potency for pharmaceutical applications. Lipid-primarily based nanocarriers are usually round in form comprising of a lipid bilayer that compartmentalizes an aqueous section and constitutes liposome, lipid NPs, and emulsions. Polymeric nanocarriers include dendrimers, polymer micelles, etc. Inorganic NPs regarding metals may be used as nanocarriers for DDS primarily based totally on their specific utility and suitability for clinical imaging [52]. Nanocarriers may be designed in modular shapes from lots of substances in one-of-a-kind styles and sizes for intracellular DDS. Effective DDS controllably launches therapeutics amid transportation. Adjustment of movement and successive clearance of the drug from the frame enhance drug healing viability. The principal cause of the usage of nanobiotechnology in drug transport is to grow attention and lifelong of drug withinside the diseased site and reduce its attention in ordinary cells for reinforcing the curing effect [53, 54]. Pan et al. developed DOX-Mesoporous silica NPs-TAT peptide conjugates that showed promise in combating multidrug resistance in most cancer cells by boosting therapeutic adequacy and lowering side effects. This will reduce unfavorable outcomes and eliminating multidrug resistance in most cancer cells by boosting therapeutic adequacy [55] (Table 1, Table 2).

2.1 Polymeric nanoparticles:

Biodegradable polymeric NPs have attracted impressive consideration in drug delivery attributable to their pharmacokinetic control and simplicity of change through different ligands. Also, they give a supported delivery design from the lattice to the objective site and have incredible steadiness [56]. Throughout the long term, polymeric NPs of various morphologies have been incorporated according to the prerequisite of their transportation to the infected site and conveyed medication [57]. Polymer nanoparticles (NPs) have received a great deal of attention in recent years due to their small size and their properties. Advantages of macromolecular NPs as drug carriers include the potential use of controlled release, the ability to protect bioactive drugs and other molecules from the environment, their bioavailability, and their therapeutic index [58].

The various biodegradable polymers commonly used in the fabrication of polymeric nanoparticles include poly(lactide) (PLA), poly(lactide-co-glycolide) (PLGA) copolymers, poly (ε-caprolactone) (PCL), and poly (amino acids) and also some natural polymers like alginate, chitosan, gelatin, and albumin [59].

Different methods for producing polymeric NPs can be utilized depending on the type of medicine to be

Table 1. Advantages and Disadvantages of Drug Delivery system

Advantages	Disadvantages
Increasing the duration of action, minimizing the frequency of dose, and ensuring medications bioavailability.	Toxicity of the drug delivery mechanism is a possibility.
Drugs' harmful side effects are minimized.	Surgical intervention is required, either for system installation or removal.
Defending the medication from deterioration	There's a chance that dangerous degradation products will emerge.
Increasing patient adherence	Patients' dissatisfaction with the DDS device
Increasing drug use by reducing drug concentration variations in the blood	The high cost of DSS and its use [55, 34]

Table 2. Types of Cancer and Proposed Drug delivery system

S.no	Type of cancer	Challenges	Formulations
1	Eye Cancer	Accessing Posterior Segment of Eye and Increasing Intra-Viteral Half-Life	Topical delivery Implant Local injections [32]
2	Breast Cancer	Nonspecific Distribution of Drug and Systemic Toxicity	Polymeric Micelles Carbon Nanotubes Nanorod Liposomes [33]
3	Brain Cancer	Non-Uniform Drug Distribution and Low Diffusion	Biodegradable Implants/Reservoirs Convection - Enhanced Delivery Intranasal Delivery [34]
4	Lung Cancer	Pulmonary Compatibility of Particles	Aerosol (Liposomes, Polymeric Particles, Porous Nanoparticles, Aggregates Particles, Inorganic Particles) [23]
5	Skin Cancer (Melanoma)	Minimizing Systemic Absorption Through the Skin	Topical Gels/Films/Particles Microneedles Barrier Disruption (Ultrasound) [24]
6	Bladder Cancer	Drug Penetration for Deeply Embedded Tumors	Intravesical Delivery Indwelling Devices [36]
7	Ovarian Cancer	Sustained Release of Drug to Prevent Non-Specific Toxic Effect While Maintaining Therapeutic Dose in Peritoneum	Implants/ Reservoirs [37]
8	Colorectal Cancer	Drug Penetration for Deeply Embedded Tumors	Polymeric Micelles Vesicular Drug Delivery [38]

placed in them and their requirements for a specific administration route. The dispersion of prefabricated polymers or the polymerization of monomers is the two basic techniques used in general [60]. Organic solvents are often employed in the first phase of most procedures that require the usage of prefabricated polymers to dissolve the polymer. These solvents have the potential to cause toxicity and environmental damage. Solvent residues must also be eliminated from the finished product. Techniques based on the polymerization of monomers can be used to load chemicals into polymeric NPs with improved efficiency and in a single reaction step [61]. The products are commonly obtained as aqueous colloidal suspensions, regardless of the mode of preparation used.

PLGA NPs have been broadly utilized for the embodiment of various limited enemies of disease medications, for example, estradiol, haloperidol, cisplatin, doxorubicin, 9-nitrocamptothecin, and paclitaxel [62]. The clinically utilized antitumor DOX experiences harmfulness, cardiomyopathies, and congestive cardiovascular breakdown issue. Notwithstanding, the epitome of DOX into PEGylation-PLGA nanoparticles has further developed its hostile to cancer properties [55, 63]. In addition, PLGA NPs can adequately transport ineffectively water-soluble drug med curcumin (CUR) to ovarian carcinoma cells. Essentially, PLGA NPs have additionally been accounted for to diminish the poisonousness of cisplatin [64, 65]. Pan et al. used a nanoprecipitation

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process to create plumbagin-loaded PSMA aptamer-targeted poly D,L-lactic-co-glycolic acid-b-polyethylene glycol (PLGA-PEG) nanoparticles (NPs) and investigated their impact on prostate cancer cells *in vitro*. The nanoparticles measured 189.4 nm in diameter and had a zeta potential of 17.1 mV. At 0.5 hours, cellular absorption of both targeted and nontargeted NPs was around 90%. Targeted and nontargeted NPs both had IC_{50} values of 32.59 and 39.02mM, respectively. As a result, plumbagin-loaded PSMA aptamer-targeted NPs could be a viable prostate cancer targeted therapy [66]. Physical characteristics such as composition and concentration, as well as size, shape, surface properties, crystallinity, and dispersion state, can all affect polymeric NPs. These features are frequently evaluated using a variety of methodologies to fully characterize the NPs [67]. Electron microscopy, dynamic light scattering (DLS) or photon correlation spectroscopy (PCS), near-infrared spectroscopy, electrophoresis, and chromatography are just a few of the most widely utilized techniques. Characterization of polymeric NPS is critical not only for their applicability but also for determining concerns such as nanotoxicology and workplace exposure evaluation, which are necessary for assessing health and safety risks and controlling manufacturing processes [68, 69].

2.2. Magnetic nanoparticles (MNPs):

The industrial demand of magnetic nanoparticles encloses a wide range of magnetic recording media used in biomedical applications, such as magnetic resonance contrast agents used as therapeutic methods in cancer treatment. The ability of magnetic nanoparticle application requires having exclusive properties [70]. For biomedical applications, the use of particles that exhibit superparamagnetic behavior at room temperature is recommended. In addition, therapeutic, biological, and medical diagnostic applications require magnetic particles to be stable in water and physiological environments at pH 7 [71]. The colloidal stability of this liquid depends on the charge and surface chemistries that lead to both steric and Coulomb repulsion, and the size of the particles must be small enough to avoid gravitational precipitation. Extra limitations to the potential particles could be utilized for biomedical applications (*in vivo* or *in vitro* applications) [72]. For in vivo applications, the magnetic nanoparticles should be embodied with a biocompatible polymer during or after the preparation procedure to keep changes from the native structure, the development of substantial aggregates, and biodegradation when exhibited to the natural biological system. The nanoparticle covered with polymer will likewise permit restricting of drugs by entanglement on the particles, adsorption, or covalent connection [73]. The central point, which decides the toxicity and the biocompatibility of these materials, are the properties of the magnetically responsive component, like iron, magnetite, cobalt, and nickel, and the concluding size of the particles, their core, and the coatings [74]. Iron oxide nanoparticles like magnetite (Fe3O4) or its oxidized structure maghemite (γ-Fe2O3) are by a wide margin the most generally utilized nanoparticles for biomedical applications. Exceptionally magnetic materials, for example, cobalt and nickel are prone to oxidation and are harmful; consequently, they are of slight interest. Besides, the significant benefit of utilizing particles of sizes less than 100 nm is their higher powerful surface regions, lower sedimentation rates, and improved tissular dispersion [75].

Magnetic nanoparticles' biomedical applications can be categorized based on whether they are used inside or outside the body (*in vivo*, *in vitro*) [76]. *In vitro,* the principal applications are diagnostic separation, selection, and magneto relaxometry, whereas, in vivo, it can be further divided into therapeutic (hyperthermia and drug-targeting) and diagnostic applications (nuclear magnetic resonance [NMR] imaging) [77, 78].

2.3 Gold nanoparticles (AuNPs):

If versatile and generally nontoxic material, have drawn far-reaching interest for helpful applications in humans [79]. Gold nanoparticles (AuNPs), have become profoundly achievable materials for treating malignant cancers owing to their interesting quenching efficiencies, biocompatibility, and huge surface modifiability. For instance, Astra Zeneca an organization with CytImmune visioned AuNPs-based nanomedicine in malignant growth treatment. The PEGylated (polyethylene glycol) colloid gold particles-based product, Aurimune (CYT-6091)11 whose nontoxicity has been pronounced being under ongoing clinical trial. It can productively convey the tumor necrosis factor-alpha (TNFα) to cancer sites [80]. Additionally, numerous other AuNPs-based chemotherapy mediators such as Auroshell are striving for success in clinical trials. AuNPs have promis-

ing biocompatibility along with modulated physicochemical properties that are very attractive for the design of advanced systems for cancer treatment. AuNPs due to their easy surface modification has been widely studied as drug delivery vehicles and for targeting specific cells or tissues [81].

Researchers have developed modified drug delivery systems based on AuNPs with enhanced in vivo stability and bioavailability. Biopolymer-conjugated AuNPs are used in the delivery system, biosensing, delivery systems, diagnostic, and biomarker detection [82].

Also, Colloidal AuNPs don't gather in the liver, bringing about no hepatic damage *in vivo*/*in vitro* models. Besides, AuNPs are safeguarded from phagocyte take-up using covering with a PEG brush progressively clear from the body and can be reduced inside the cells [83]. As multifunctional specialists, AuNPs can be used for combined treatment and diagnostics such as for *in vivo/in vitro* real-time imaging, radiation sensitizers, and thermal ablation of tumors [84].

2.4. Mesoporous silica nanoparticles (MSNPs)

In the mid-2000s, MSNPs were generally utilized as drug delivery devices. The shape-and size-controllable pores of MSNPs can amass pharmaceutical medication and arrest their inappropriate release and depravement before accomplishing their allocated target [85]. It has been exhibited that silica can store and deliver therapeutics, like anti-microbial, in a maintained and controlled manner. Wei et al., in a theranostic review, showed that levofloxacin hydrochloride (LFH)- stacked mesoporous silica (MS) microspheres, immobilized on a nanohydroxyapatite/polyurethane bioactive composite surface, could cause a controlled medication discharge profile, in which LFH was let out of the framework for 42 days [86]. Additionally, silica can expand the biocompatibility of some DDSs, for example, attractive NPs biopolymers, and micelles. Mesoporous silica NPs have different applications (in, e.g., tissue engineering), and are broadly utilized as controlled DDSs because of their alluring properties, for example, tunable pore size and volume just as simple surface functionalization. MSNPs have arisen as new inorganic materials for biomedical applications [87,88]. MSNPs, with a molecule size of 30-200 nm, are suitable repositories and can be stacked with different remedial/symptomatic specialists, attributable to their enormous explicit surface region (up to 1000 m2/g) and pore volume (> 0.9 cm3/g) just as high biocompatibility [89]. They can hinder the untimely arrival of their cargoes, and thus, undesirable debasement in the stomach and digestion tracts before arriving at the objective sites [90]. They have slight poisonousness, minimal expense, flexible pore size, and a basic combination process. MSNPs are synthetically and thermally stable and have optically straightforward properties. They likewise have consistently organized pores (size scope of 2- 50 nm) with decent width, and their surface can be effectively functionalized to improve their phone uptake. MSNPs, contrasted with natural transporters, like micelle, gel, and liposome, have higher stacking capacity, and because of their high medication embodiment productivity, they fundamentally influence nanobiotechnology research exercises [91]. They have been effectively utilized as a transporter for the oral conveyance of hydrophobic medications, subsequently, impressively incrementing their disintegration rate and bioavailability contrasted with the standard medications [92]. Table 3 covers the type of nanocarriers, and Table 4 depicts the current status of the nanocarrier.

3. Therapeutic applications of Nanocarrier

Nanotechnologies are gaining traction in medicine, particularly in the development of new medication delivery methods. Drugs can reach specific diseased locations with the help of nano-sized carriers, extending therapeutic efficacy while reducing unwanted side effects [93]. Furthermore, recent nanotechnological breakthroughs, such as surface stabilisation and stimuli-responsive functionalization, have considerably increased the nanocarrier assisted drug delivery system's targeting ability and therapeutic efficacy [94]. The following nanocarriers are associated with following therapeutic applications:

3.1 Polymeric Nanocarrier

Polymeric nanoparticles have risen to prominence in the field of drug delivery research. Their use in nanomedicine can boost bioavailability, pharmacokinetics, and thus the efficacy of different medicines or contrast agents [95]. Many experiments have been conducted to produce new polymeric nanocarriers, however their clinical use is limited. New polymeric nanocarriers as novel diagnostic and therapeutic sys-

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tems. Their multifunctionality, which arises from the polymers' unique chemical and biological properties, provides better drug delivery and a controlled, sequential release of a different therapeutics to diseased tissue [96].

3.1.1 In Bioimaging, Drug Delivery, Diagnosis

Polymer nanoparticles, out of all the nanomaterials accessible, have attracted scientists' curiosity for medical applications because of some intriguing features, such as biodegradability, biocompatibility, and low cytotoxicity. Researchers were able to analyse drug distribution and release at the target region in real time by mixing an imaging agent with the encapsulated drug within a polymeric nanoparticle [97]. The real-time monitoring of drug distribution aids in the prediction of drug response and makes it easier to personalise treatment regimens to each individual.

In comparison to the free agent, MRI contrast agents such as semicrystalline polyurea nanocarriers containing Gadobutrol (commercial contrast agent of gadolinium (III) complex) provide greater tissue contrast. PEGylated nanocarriers containing cubic cobalt ferrite nanocubes were also detected in tumour tissue using MRI following intratumoral injection [98]. Anti-VEGFR2 (vascular endothelial growth factor receptor type 2 overexpressed on tumor surrounding vascular endothelial cells) and anti-p53 antibodies are functionalized on gold nanoshelled PLGA nanocarriers for precise ultrasound molecular imaging of breast cancer [97, 98].

Dual-targeted nanocarriers accumulate in the tumor (orthotopic mice breast cancer) around two times more than non-targeted nanocarriers, ensuring accurate breast cancer detection, according to the authors [99].

3.1.2 Stimuli-Responsive Drug Delivery System

The most commonly studied nanocarriers are polymer-based nanocarriers, which include synthetic and

Table 3. Type of Nanocarriers and Characterization

Nanocarrier	Properties	Methods of Preparation	Characterization
Polymeric nanocarrier	Active drugs can be encapsulated within or surface-adsorbed onto the polymeric core of particles ranging in size from 1 to 1000 nm.	Nanoprecipitation. Emulsification/reverse salting-out Emulsification/solvent diffusion Solvent Evaporation	Morphology: Important factor in the design of nanocarriers due to its impact on behavior such as cell uptake, drug release kinetics, and diffusion in complex biological media Particle Size Distribution Chemical Composition and Crystal Structure Surface Area and Chemistry Zeta Potential: measure of the effective electric charge on the nanoparticle's surface, quantifying the charges Determination of the Drug Association Pharmaceutical *In Vitro* Release Kinetics [68, 69]
Magnetic nanoparticles (MNPs):	Magnetic nanoparticles are a type of nanoparticle that can be controlled by applying magnetic fields to them.	Solution Precipitation Thermal Decomposition Polyol Method Hydrothermal or Solvothermal	Size determination (small-angle neutron scattering (SANS): to determine the particle shape or their size distribution Chemical Characterization Magnetism: to depict motion of electric charges [70, 71]
Gold nanoparticles	Gold nanoparticles (aunts) are small gold particles with diameters ranging from 1 to 100 nm and shapes varying from spherical to rod-like to cage-like.	Chemical, Electrochemical, Irradiation, Sonochemical, Solvothermal, Photochemical Laser ablation.	Morphology Particle Size Distribution Chemical Composition and Crystal Structure Surface Area and Chemistry: precisely control and tailor the surface properties of gold nanoparticles to meet the needs of applications Zeta Potential *In Vitro* Release Kinetics [80]
Mesoporous silica nanoparticles	Mesoporous nanoparticles have a porous structure and a vast surface area, allowing multiple functional groups to be attached to target the drug moiety to a specific site.	Sol-gel process Microwave technique Chemical etching method templating method	Shape, size, and pore size *In Vitro* Release Kinetics: Centrifugal Ultrafiltration or High Performance Liquid Chromatography (HPLC) [77]

natural polymers. Chitosan, alginate, and hyaluronic acid are among common natural polymers utilised for this purpose [100, 101]. Zhao et al., for example, used the conventional self-assembly approach to create a graphene oxide-based drug delivery system with chitosan as an exterior shell. The inclusion of the chitosan shell prevented the premature release of therapeutic agents in normal extracellular media, while the release of therapeutic agents was subsequently increased in acidic media due to the detachment of the chitosan shell [102].

Targeted polymeric NPs can be used to deliver chemotherapies to tumour cells with more adequacy and less damage to healthy tissues in the case of malignant growth [103]. When only sparingly water-dissolvable drugs are used, the medication may be released directly from the NPs by dispersion, or it may occur in conjunction with the decomposition of the NPs into monomeric atoms. pH-switchable NPs are made from polymeric molecules with amphoteric functionalities that help the NPs coordinate the pH conditions they may encounter in the human body [104].

3.1.3 Bioimaging

Conjugated Polymer nanoparticles (CPNs), which have gained prominence in bioimaging, are made by combining polymer NP with a variety of semiconducting nanoparticles and have shown promising outcomes in clinical imaging. The particles can be used to reimage cells and tissue for fluorescence-based imaging techniques including microscopy and tomography [84]. CPN is a new photoacoustic-based crossover imaging material that has demonstrated its utility in high-resolution molecular imaging with incredible penetration depth [105].

Dual encapsulation of chemotherapeutic and inorganic nanoparticles has also been attempted. Jeon and coworkers created paclitaxel-loaded nanocarriers with crosslinked gold nanoparticles and poly(amidoamine) dendrimers. In a mouse tumor model, the combination's therapeutic efficacy was validated. Magnetic targeting can also be done with superparamagnetic iron oxide nanoparticles (SPIONs). After local exposure to the magnetic field, PLGA-PEG nanocarriers containing SPION and docetaxel showed faster and stronger accumulation, as well as improved tumour growth suppression. PLGA-PEG nanocarriers were used as a magnetically-targeted triple-modal imaging agents since encapsulated inorganic chemicals are commonly used as contrast agents. SPIONs and indocyanine green (a fluorescent near-infrared dye) were enclosed in the hydrophobic core this time, and diethylene triamine penta acetic acid was attached to PLGA-PEG to chelate Indium-111 (radioisotope). After intravenous injection, this method was evaluated on mice and allowed for successful tumour visualisation using fluorescence, MRI, and nuclear imaging [106].

3.2 Magnetic Nanoparticles

Due to their unique physico-chemical properties, magnetic resonance imaging (MRI) contrast, accessible synthesis, easy surface coatings, low toxicity, and good biodegradability, magnetic nanoparticles (MNPs) have gotten a lot of attention for cancer theranostics applications [107]. Due to their enhanced magnetization upon application of an outside magnetic field and excellent T2/T2* relaxation abilities, MNPs operate as capable (MRI) agents. As a result, MNPs are widely used in MRI imaging, biosensors, theranostics, delivery, magnetic hyperthermia, photodynamic therapy, and photothermal ablation therapy, among other cancer theranostics applications [108].

3.2.1 Drug Delivery

MNPs, when used in conjunction with an external magnetic field and/or magnetizable implants, allow particles to be delivered to the appropriate target area, fixed at the local site while the drug is delivered, and acted locally (magnetic drug targeting) [109]. Biotherapeutics and chemotherapeutics both aim to stop tumours from growing by disrupting or inhibiting cell functions such DNA replication, protein production, cell division, or anti-apoptotic pathways. The administration of physiologically active molecules such as peptides, proteins, DNA, or small interfering RNA (siRNA) is referred to as biotherapeutics. The transfer of DNA or siRNA is also referred to as gene therapy [110]. Chemotherapeutics, on the other hand, refers to the administration of small molecule medications like paclitaxel and 5-fluorouracil, as well as temozolomide (TMZ) and doxorubicin. MNPs have recently been used in biotherapeutic and chemotherapeutic applications by a number of researchers [111].

Nanoparticles are now being studied for their potential use in delivering radionuclides, both α and β emitters, and/or radiosensitizers to tumour cells

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in order to cause DNA damage through the formation of free radicals or ionic radiation. Nanoparticles outperform conventional radiation procedures by decreasing off-target tissue damage caused by the treatment's non-specific nature through passive and active targeting [1]12]. Additionally, nanoparticles are used in combination therapies such as chemotherapy and gene therapy. Munaweera et al. showed that magnetic nanoparticles containing both platinum-based chemotherapeutics and neutron-activated holmium-166 might be used as a chemo-radiotherapeutic for non-small cell lung cancer treatment [113].

3.2.2 Diagnostic Applications

The need for a new class of pharmaceuticals, known as magneto-pharmaceuticals, has arisen as a result of the development of NMR imaging for clinical diagnosis. These medications must be given to a patient to improve imaging contrast between healthy and diseased tissue and/or reveal organ function or blood flow. In addition, Magnetic nanoparticles has been utilized in diagnosis of genetic disorders [114]. Su et al. described a rolling circle amplification (RCA)-based electrochemiluminescence (ECL) test for detecting point mutations. An allelediscriminating padlock probe was designed for targeting the p53 oncogene locus sequence in the test. The magnetic bead-based ECL platform was used to examine the resulting elongated hybridised products [115].

3.2.3 Bioseparation

DNA analysis is now an important part of molecular biology. Finding an appropriate DNA isolation system is critical to the experiment's success. DNA isolation is a common practise for collecting DNA for molecular investigation [116]. Separation of certain biological entities (e.g., DNAs, proteins, and cells) from their native habitat is frequently required for examination in biomedical studies. Because of their on-off nature of magnetization with and without an external magnetic field, superparamagnetic colloids are perfect for this application, allowing the movement of biomaterials with a magnetic field [117].

Shan et al. revealed a new method for isolating pDNA from E. coli cultures. They proposed employing multifunctional magnetic nanoparticles to bioseparate pDNA (MNPs). Multifunctional bioadsorbents made of carboxyl-modified superparamagnetic nanoparticles. These nanoparticles were utilised to trap cells and then remove the genomic DNA/protein complex after lysis. This was accomplished by utilising nanoparticle features like as bio-affinity and magnetic guiding via a high magnetic field. Furthermore, the yield and purity of pDNA extracted using MNPs is comparable to that obtained with organic solvents or commercial kits [118]. Furthermore, the use of multifunctional MNPs has proven to be a time- and cost-effective pDNA preparation process that does not require centrifugation or the use of toxic organic solvents.

3.2.4 Magnetic Resonance Imaging (MRI)

Because of its high soft tissue contrast, no penetration limit, and spatial resolution, magnetic resonance imaging (MRI) is a noninvasive technology commonly used to identify diseases. MRI produces detailed images of organs, tissues, bones, and other internal body structures using a high magnetic field and radio frequency pulses [119]. It provides information about the size, shape, and location of various lesions while inflicting no harm. MRI uses Superparamagnetic iron oxide NPs are proven to be a class of new probes suitable for in vitro and in vivo cellular and molecular imaging at the intersection of nanomaterials and medical diagnostics. In comparison to paramagnetic contrast agents, superparamagnetic contrast agents produce more proton relaxation in magnetic resonance imaging [MRI] [114].

3.3 Gold Nanoparticles

Gold nanoparticles, which have unique optical and Surface Plasmon Resonance (SPR) capabilities among diverse organic and inorganic nanoparticles, have become the top choice for researchers, notably in the biological and pharmaceutical fields. Gold nanoparticles are used in ultrasensitive detection and imaging-based therapy approaches for the treatment of lethal diseases such as cancer because of their optical qualities [120].

3.3.1 Diagnostic Applications

There has been no significant advancement in clinical X-ray contrast agents over the previous three decades. Despite major disadvantages in medical imaging, such as short imaging time, the requirement for catheterization in many cases, infrequent renal toxicity, and low contrast in large patients, the iodine-based chemical platform has not been replaced [121]. To overcome this constraint, gold nanoparticles (AuNPs) have been developed. High osmolal-

ity causes the negative effects of numerous iodine agents: Iodine agents only have three (monomer) or six (dimer) iodine atoms per molecule. 1.9 nm diameter spherical AuNPs, on the other hand, contain about 250 Au atoms. As a result, AuNPs have a negligible osmolality of 7.2 mM, which can be increased by adding more saline to obtain iso-osmolality. Another advantage of AuNP solutions for intravenous injections is their low viscosity [122-123]. When used in various biofluids, Au has amazing advantages as an excellent X-ray contrast agent. Because Au has a higher absorption coefficient than iodine and is less affected by bone and tissue interference, it provides better contrast at lower doses. NPs can stay in the bloodstream longer than low-molecular-weight iodine solutions, allowing for longer imaging times [124].

3.3.2 Antimicrobial Activity

NPs prevent bacteria from forming biofilms. Biofilms have a structure that makes bacteria extremely resistant to external substances. Previous research has shown that AuNPs can disrupt biofilm integrity by interacting with EPSs. Due to their high cell affinity, AuNPs are quickly taken up by immune cells, allowing for precision distribution to the diseased area, aiding microbial pathogen inhibition and damage [125]. Modified gold nanoparticles can be an excellent medium for photothermal treatments to kill bacteria since they have photothermal effects.

3.3.3 Drug Carriers

Antitumor agents and antibiotics are the most commonly delivered drugs. Antibiotics and other antibacterial agents are also examples of items that gold nanoparticles can convey. The ability to make a stable vancomycin-colloid gold complex and its efficiency against diverse enteropathogenic strains of E. coli, Enterococcus faecium and Enterococcus faecalis (including vancomycin-resistant strains) have also been proven [122].

3.4 Mesoporous Silica Nanoparticles (MSNPs)

Because of their unique intrinsic properties, such as high surface area, large pore size, good biocompatibility and biodegradability, and stable aqueous dispersion, mesoporous silica nanoparticles (MSNs) have gotten a lot of attention in recent decades as a promising platform in the biomedicine field. Pore sizes range from 2 to 50 nm, making these porous materials ideal candidates for a variety of biomedical applications. They've been employed in a variety of applications mentioned below:

3.4.1 Drug Delivery

It is well understood that an effective delivery system must be capable of transporting the desired guest molecules without loss before reaching at the desired location. When the system arrives at its destination, it must be able to discharge the cargo in a regulated manner. Any early release of guest molecules is a difficult challenge to solve [126]. Many toxic anticancer medicines, for example, require "zero release" before reaching the targeted cells or tissues. However, many current biodegradable polymer-based drug delivery systems rely on hydrolysis-induced carrier structural disintegration for release [127]. When these composites are dispersed in water, matrix contained chemicals are released very instantly. Furthermore, such systems often necessitate the use of organic solvents for drug loading, which can result in undesired changes to the structure and/or function of the encapsulated molecules, such as protein denaturation and aggregation [128]. Surface functionalized mesoporous silica materials, on the other hand, have several distinct advantages, including stable mesoporous structures, large surface areas, tunable pore sizes and volumes, and well-defined surface properties for site-specific delivery and hosting molecules of various sizes, shapes, and functionalities, as previously mentioned.

2.3.2 Theranostic

Therapeutic and diagnostic agents are combined in theranostic nanomedicines to monitor and treat diseases at the same time. Optical imaging, computed tomography (CT), radionuclide imaging, and magnetic resonance imaging (MRI) can all be utilized to diagnose theranostic nanomedicine with contrast agents or molecular probes. MSPs have gotten a lot of attention as a theranostic agents because of their capacity to carry several payloads at the same time, as well as their inherent optical and photochemical properties [129].

2.3.3. Biosensors

MSNPs have demonstrated potential benefits in biosensor applications such as enzyme immobilization for catalytic activity in this regard. They can improve the stability of enzyme catalytic activity and has a wide surface area, allowing them to immobilize

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sensing molecules and optical transparency for optical detection through the material matrix layers due to its very porous structure. Micro and mesoporous silica, in contrast to other solid nanoparticle biosensors, has two distinct advantages:

1) High Porosity. Large surface areas and pore volumes allow large amounts of sensing molecules to be encapsulated/immobilized per particle, resulting in quick response times and low detection limits. 2) Optical transparency.

2) Optical transparency. This unique property allows optical detection through material layers. Because of these benefits, many porous-silica-based materials have been used to construct biosensors.

Glucose biosensors have gotten a lot of press since they can be used to monitor and treat diabetes [128, 130].

4. Conclusion

Nanomedicines are capable drug delivery systems which could yield progression in therapeutic efficacy. They have numerous figures of advantages over conventional DDS that be afflicted by the sudden release of the drugs [131]. The encapsulation of the drug into nanocarriers can stable a drug from environmental and biological degradation, lowering drug dosing and accelerating healing process via controlling drug release. They could enhance solubility of drugs, permeability, and bioavailability which might be commonly difficult to target the diseased site [132].

The distinguished properties of NPs, like, flexible synthesis, controlled size, Optimal drug release, biocompatibility and response to environmental surroundings of cancerous cells have been acknowledged and it has been used in an intensive form of

Table 4. Current Status of Nanocarrier in the Market

Trade Name	API	Indication	Type	Benefit
Zilretta (Flexion Therapeutics)	Triamcinolone acetonide	Osteoarthritis knee pain	Polymeric	Extended-release
Cimzia (UCB)	Certolizumab pegol	Crohn's disease, psoriatic arthritis, ankylosing spondylitis	Polymeric	Longer circulation time, greater stability in vivo
Macugen (Bausch and Lomb)	Pegaptanib	Neovascular AMD	Polymeric	Greater aptamer stability
Eligard (Tolmar)	Leuprolide acetate and polymer	Prostate cancer	Polymeric	Longer circulation time, controlled payload delivery
Rebinyn (Novo Nordisk) (available in 2018)	Coagulation factor IX (recombinant), glycopegylated	Hemophilia B	Polymeric	Longer half-life, greater drug levels between infusions
Nanotherm	Iron Oxide Nanoparticle	AC magnetic heating, Solid tumor Hyperthermia	Magnetic nanoparticle	Precise Drug Delivery
Clariscan™	Iron Oxide Nanoparticles	Enhanced MRI contrast Approved	Magnetic nanoparticle	Accurate diagnostic.
Ferumoxtran-10 Combidex Sinerem (AMAG)	Iron dextran colloid	Imaging lymph node metastases	Magnetic nanoparticle	Accurate diagnostic
Resovist (Bayer Schering Pharma) Cliavist	Iron carboxydextran colloid	Imaging of liver lesions	Magnetic nanoparticle	Accurate diagnostic
Auroshell	Gold Nanoshell	IR laser heating	Gold nanoparticle	In Phase 1 Study

Trade Name	API	Indication	Type	Benefit
Aurimmune	Gold	Cancer therapy	Gold nanoparticle	In Phase 2 Study
Auritol (CYT21001)	PEGylated Colloidal Gold Nanoparticle	Solid tumors	Gold nanoparticle	In Preclinical study
BIND-014	Polymeric Nanoparticle formulation of Decetaxel	Various Cancers	Polymeric Nanoparticle	In Phase 1 study
BioVant	Calcium Phosphate Nanoparticles	Vaccine adjuvant		In Phase 1 study
Doxil Caelyx (Janssen)	Liposomal doxorubicin (PEGylated)	Ovarian cancer HIV□associated Kaposi's sarcoma	Liposomes	Longer circulation time, controlled payload delivery
DaunoXome (Galen)	Liposomal daunorubicin (non□PEGylated)	HIV□associated Kaposi's sarcoma (primary)	Liposomes	Various leukemias
NPI 32101	Silver Nanoparticles	Atopic Dermatitis	Silver Nanoparticles	In the Phase 2 study
Panzem NCD 2	Methoxyestradiol/ Nanocrystal	Glioblastoma	Nanocrystal	In the Phase 2 study
CRLX101	Cyclodextrin nanoparticles/ Camptothecin	Various Cancers	Nanoparticles	In the Phase 2 study
AS15	Liposome	Metastatic breast cancer	Liposome	In the Phase 2 study
Aurimune	Liposome Tf Antibody/ p53 gene	Solid tumors	Liposome	In the Phase 2 study
K-012	Polymeric Micelle of SN-38	Various Cancers	Polymeric Nanoparticle	In the Phase 2 study
OSI-211	Iron Oxide Nanoparticles	Imaging of Cancers	Magnetic Nanoparticle	In the Phase 2 study

applications. Numerous advancements have been progressing with time in the modification of surface attributes of nanocarriers to perform unique binding with ligand and releasing drugs at the target site [133]. Enhancement of those techniques mixed with the vast development made withinside the subject of Nanocarriers as an advanced comprehension. The apparent improvement in commercial products shows significant results *In vivo*, predicting the efficacy and safety of nanocarriers in ailments like cancer, Alzheimer's disease and many other disorders [134].

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Conflict of Interest

The authors declare that they have no conflict of interest.

Statement of Contribution of Researchers

Niharika Lal has designed the layout, study conception and design of manuscript, Praveen Kumar Gaur and Sameer Rastogi has collected the data and draft the manuscript preparation. Kanak Lata has reviewed the final version of manuscript.

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