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# INNOVATIONS IN NANOPARTICULATE DRUG DELIVERY SYSTEMS: MANUFACTURING AND EVALUATION PERSPECTIVES

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**ABSTRACT**

Background:

Nanoparticulate drug delivery systems (NDDS) have revolutionized the field of medicine, offering precise, targeted, and efficient delivery of therapeutic agents. These systems enhance drug solubility, stability, bioavailability, and controlled release. This study explores recent innovations in NDDS, focusing on advancements in manufacturing techniques and evaluation methodologies.

Objective:

To review recent trends in nanoparticulate drug delivery systems, emphasizing novel manufacturing approaches and the evaluation parameters critical for their clinical success.

Methods:

An extensive review of current literature was conducted to analyze the latest developments in NDDS manufacturing, including techniques like nanoprecipitation, emulsion-solvent evaporation, and microfluidics. Evaluation parameters such as particle size, drug encapsulation efficiency, surface morphology, release kinetics, and stability were also studied. Insights were drawn from preclinical and clinical studies to understand the practical applications and challenges in NDDS development.

Results:

Innovative manufacturing techniques, such as microfluidics and 3D printing, have enabled precise control over particle size, drug loading, and scalability. Evaluation parameters have evolved to incorporate advanced analytical tools, including dynamic light scattering, scanning electron microscopy, and in vitro/in vivo correlation studies. Key challenges include ensuring reproducibility, scalability, and regulatory compliance. However, NDDS demonstrates significant potential in treating chronic diseases, including cancer, neurodegenerative disorders, and infectious diseases.

Conclusion:

Nanoparticulate drug delivery systems represent a transformative approach in pharmaceutical sciences. Advances in manufacturing techniques and comprehensive evaluation frameworks are critical for their successful development and clinical translation. Future research should address scalability, cost-effectiveness, and regulatory hurdles to fully realize the potential of NDDS in improving therapeutic outcomes.

**Keywords:** Nanoparticulate drug delivery systems, manufacturing techniques, evaluation parameters, drug encapsulation, controlled release..

## I. INTRODUCTION

The intentional engineering and manipulation of particulate matter into a physical state between 1 and 100 nm is known as nanotechnology. This material may then be rearranged or reassembled into nano-systems with enhanced functionality [1]. More and more research is being done on the possible use of nanoparticles and nanomaterials in medicine. One particularly interesting and potential application area is medication delivery. One such ground-breaking innovation that uses nanotechnology to increase therapeutic effectiveness, reduce side effects, and enhance medication delivery efficiency is the nano drug delivery system [2].

"A formulation or a device that enables the introduction of a therapeutic substance into the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body" [3] is the definition of a drug delivery system (DDS). By increasing drug solubility and stability, these systems maximise therapeutic effectiveness and provide increased drug bioavailability. Systemic toxicity is decreased and off-target effects are minimised by their capacity to deliver drugs to certain tissues, cells, or subcellular compartments [4].

According to Grand View Research, the worldwide market for nano drug delivery is expected to increase at a 14.1% compound annual growth rate (CAGR) between 2021 and 2026, reaching an impressive $126.8 billion by that time [5]. This exponential growth may be attributed to the several advantages that nano drug delivery methods provide, including enhanced bioavailability, extended drug release, targeted administration to specific cells or tissues, and the ability to get past biological barriers [6].

Longer therapeutic action, fewer doses, and better patient compliance are all made possible by nano drug delivery systems, which greatly aid in regulated and sustained drug release. Another significant benefit is that it enables medications to reach previously unreachable locations by overcoming biological barriers like the blood-brain barrier [7]. Furthermore, combination therapy—in which many medications or therapeutic agents are contained inside a single nanoparticle—is made possible by nano drug delivery systems, encouraging synergistic effects and individualised treatment plans [8]. All things considered, using nano drug delivery methods has a lot of potential to improve treatment results, reduce side effects, and advance precision medicine [9].

Both organic and inorganic nanocarriers are used in nanodrug delivery systems. Organic nanocarriers include solid liquid nanoparticles, liposomes, dendrimers, polymeric nanoparticles, polymeric micelles, and virus-based nanoparticles. Inorganic nanoparticles include mesoporous silica nanoparticles and carbon nanotubes. One kind of nano drug delivery technology that has been well studied is liposomes [10]. Doxil, a liposomal version of doxorubicin, was approved for the treatment of ovarian cancer and Kaposi's sarcoma associated with AIDS because it demonstrated better effectiveness and less cardiotoxicity than the free drug [11].

Notwithstanding their promise, there are significant obstacles that must be overcome before nano drug delivery systems may be successfully used in clinical settings [12]. Additional difficulties arise with nano medicine delivery systems' stability and storage. One of the biggest challenges in guaranteeing constant quality, repeatability, and scalability of nanoparticles is the intricate production and scale-up procedures required [13]. Facilitating regulatory clearance and market access requires the establishment of uniform standards for evaluating safety, effectiveness, and quality. Finally, the exorbitant cost of nano medicine delivery devices prevents them from being widely used. Improving accessibility requires addressing economic feasibility and creating cost-effective production methods [14].

## II. TYPES OF THE NDDSS

The many morphologies of nanoparticles include liposomes, dendrimers, carbon nanomaterials, fullerenes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers, nanoshells, quantum dots, superparamagnetic nanoparticles, and others [15]. The following describes these many nanoparticle morphologies, their significance, and their difficulties as drug delivery systems:

### 2.1. Lipsomes

Liposomes are colloidal particles made of amphiphilic phospholipids that self-assemble to create lipid bilayers. They are often used in drug

delivery, specifically targeting cancer cells, and range in size from 25 nm to 200 nm. Since their discovery in 1965, liposomes have been used as medication delivery vehicles since 1971 [16]. The creation of their bilayer structure is driven by the hydrophobic effect. When PEG is added to the surface of liposomes, they may avoid being opsonised by the reticuloendothelial system. The first FDA-approved nanotechnology product for cancer therapy was the liposomal drug Doxil. One benefit of liposomes is that they may transport smaller molecules as well as biological macromolecules like DNA [17].

**2.1.1. Types of liposomes**

The pharmaceutical and cosmetics industries make extensive use of liposomes as medication delivery vehicles. They have benefits such enhanced biodistribution, drug stability, membrane-like structure, and compatibility with both hydrophilic and hydrophobic medications [18]. Liposomes fall into four categories:

1) Conventional liposomes consist of an aqueous core and a lipid bilayer that may include phospholipids and neutral, cationic, or anionic cholesterol. In this instance, either hydrophobic or hydrophilic materials may be used to fill the lipid bilayer and the aqueous gap.

2) PEGylated types: To establish steric equilibrium, polyethylene glycol (PEG) is applied to the liposome's surface.

3) Ligand-targeted type: Ligands are joined to the liposome's surface or to the end of already joined PEG chains. Peptides, carbohydrates, and antibodies are examples of ligands.

4) A theragnostic liposome, which combines the first three liposome kinds, is the fourth type. In addition to a medicinal, imaging, and targeting component, it often comprises a nanoparticle [19].

Thin layer hydration, mechanical agitation, solvent evaporation, solvent injection, and surfactant solubilisation are all part of the standard manufacturing process [20].

**2.1.2. Liposome as drug delivery systems**

Liposomes' remarkable properties have led to extensive study on their use in the delivery of medications to tumour and malignant tissues using two primary techniques: passive targeting and active targeting, as seen in Figure 1[21].

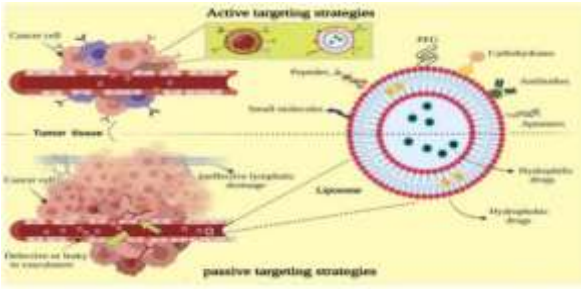


Figure 1. Passive targeting and active targeting.

Targeting ligands including antibodies, peptides, proteins, carbohydrates, Aptamer, and other small molecules may be used to surface functionalise liposomes for stealth via PEGylation and to enhance receptor-mediated endocytosis. In vivo, PEGylation extends the half-life of liposomal circulation. Drug types may be coupled to the liposome surface, encapsulated into the aqueous lumen, or integrated into the lipid bilayer according to their hydrophobic or hydrophilic nature [22].

The physical characteristics of the tumour and the size of the nanoparticles determine passive targeting. Vascular endothelial growth factor (VEGF) is overexpressed in cancer cells, leading to an excessive amount of angiogenesis. When liposomes are the right size, they may stay in the circulation longer and enable the anti-tumor medication nanosystem to focus on the tumour tissue. Vascular holes in tumour tissue are larger than those in healthy tissue [23].

Anomalies in the lymphatic system cause nanoparticle retention durations to increase when a drug delivery system reaches malignant tissue, which is impossible for small drug molecules [24].

By protecting lipsomes from opsonisation, the biocompatible PEG polymer is used to further coat the nanoparticle, allowing it to bypass the reticuloendothelial (RES) system and extending

the time blood circulates in the circulatory system [25].

Light is used in photodynamic therapy (PDT) to activate photosensitising medications, which release singlet oxygen or reactive oxygen species (ROS) that kill tumours. PDT has been studied for use in different malignancies after being first used for bladder cancer [26]. Nanocarriers may boost PDT by encapsulating photosensitisers and enhancing their stability and bioavailability. However, PDT only works on surface tumours because of the low light penetration. Nanocarriers can overcome limitations such limited bioavailability, hydrophobic side effects, large dose needs, and self-aggregation in aqueous conditions. They have the potential to increase the efficacy of PDT [27].

Because of their amphiphilic and non-ionic nature, liposomes are effective drug carriers that can carry both lipid-soluble and water-soluble medications [28]. To develop long-lasting and precise drug delivery systems, researchers may adjust their permeability, stiffness, size, and surface functionalisation [29]. medication oxidation is avoided and biodegradable medication delivery is addressed by liposomal delivery [30].

Liposome-based structures are useful, but they have limitations that keep them from being widely used in clinical settings. The main issues include their limited solubility in aqueous solutions, short half-life in the body, high manufacturing costs, physical and chemical stability, and allergic responses to certain liposomal compounds [31].

**2.2. Carbon nanomaterials**

All life on Earth originated from carbon, the fundamental building component of DNA. It exists in several different forms because of its distinct electron configuration (1s2, 2s2, and 2p)[32]. It has several technological applications, including as the transportation of synthetic chemicals and medications, because of its ability to bind itself and almost any element [33].

Based on structural variations, CBNs are classified as graphene, mesoporous carbon, carbon nanotubes, nanodiamonds, and fullerenes. These materials exhibit improved immunogenicity, biocompatibility, and drug-loading capability [34]. Functionalised CBNs have made it feasible to develop biocompatible scaffolds and nanomedicines. They have been studied for cancer treatment because of their excellent supramolecular stacking, high adsorption capacity, and photothermal conversion capability [35]. Combining chemical functionalisation with adaptive properties may enhance therapy.

**2.3. Carbon nanotubes**

Carbon nanotubes (CNTs) are cylinders or tubes that possess a unique combination of strength, elasticity, and stiffness. Sp2 hybridisation produced the elongated enfolded graphene sheets known as single-walled nanotubes (SWCNTs), which feature cylindrical and hollow one-dimensional shapes. These carbon nanotubes may expand to hundreds of times their initial length and have a diameter of around 1 nm [36].

Multiple graphene sheet layers make up multi-walled carbon nanotubes (MWCNTs), which have more intricate electrical characteristics. These nanotubes come in sizes ranging from 5 nm to 50 nm [37].

When tagged with functional groups or medicinal compounds, functionalised carbon nanotubes (f-CNTs) exhibit enhanced solubility, biocompatibility, and decreased toxicity [38]. Mechanical strength may be impacted by the covalent and non-covalent changes applied to change CNT surfaces [39].

Among the many forms of carbon nanotubes, SWCNTs have garnered interest because to their prospective advantages in metal nanoparticles, including bulk drug loading, structural flexibility, intrinsic stability, improved

circulation time, and bioavailability [40]. The capacity of functionalised SWCNTs to entrap low molecular weight compounds and antibodies allows for higher drug loading. Additionally, this makes it possible for biological molecules to conjugate without triggering an immune reaction.

Although doxorubicin (DOX) is often used in chemotherapy, it has drawbacks such as permanent toxicity, limited barrier crossing capacity, and adverse effects. Because of their great surface area, stability, and capacity to penetrate cell membranes, carbon nanotubes (CNTs) can transport DOX efficiently while minimising adverse effects. When paired with hyaluronic acid (HA), amino-functionalized single-walled carbon nanotubes (NH2-SWCNTs) demonstrated accelerated release of DOX in the tumour cell environment during the therapy of breast cancer. The structure of doxorubicin (DOX) is shown in Figure 2[41], and SWCNTs-DOX-HA improved the therapy of breast cancer by reducing tumour cell proliferation and inducing apoptosis more successfully than SWCNTsDOX alone.

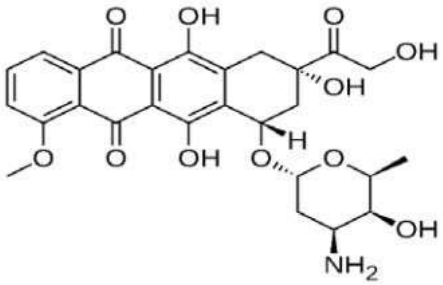


Figure 2. Structure of doxorubicin (DOX)

pH-sensitive SWCNT-folic acid (FA) conjugates reduced DOX adverse effects while exhibiting increased drug loading and anticancer effects. FA-EDA-MWCNTs-DOX demonstrated cytotoxicity and pH-dependent release against breast cancer cells [42].

**2.4. Graphene**

A single sheet of carbon with partly full sp2 orbits, graphene has a high surface area, excellent mechanical strength, optical clarity, and outstanding thermal conductivity. It functions as a semiconductor, interacting with electrons to produce new quasi-particles. Ballistic transport without scattering is made possible by graphene nanoribbons and quantum dots [43].

Graphene is less soluble and has strong electrical conductivity. Changes like graphene oxide and layered graphene-oxide are made possible via sol-gel chemistry. With polymer surface modification improving biocompatibility, graphene and its derivatives offer a wide range of uses in medicine and drug delivery [44]. In response to stimuli, graphene nanoparticles control medication release according to external and internal inputs, enhancing absorption, removing obstacles, and reducing adverse effects [45].

Among graphene nanomaterials, GOs have garnered a lot of interest because to the functional groups found on their side walls. Using π-π stacking and hydrophobic contact, graphene was able to trap DOX and camptothecin. It is simpler for GOs to bind to the hydroxyl and amino groups of DOX when they have hydroxyl and carboxyl groups on their surface [46].

According to a research conducted using 4T1 cancer cell lines, the electrochemical approach effectively demonstrated both cellular and carrier capacity. 5-fluorouracil loaded GO was developed based on pH-stimuli drug delivery, and Figure 3[47] displays the structure of 5-fluorouracil.

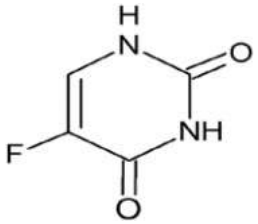


Figure 3. Chemical structure of 5-fluorouracil.

In the acidic pH of the tumour environment (5.8), this formulation regulated the release of the anticancer drug; however, in the

physiological pH of 7.4, the release was significantly diminished.

## III. MULTIFUNCTIONAL NANOPARTICLES AS NDDSS

As a result of their direct targeting of the damaged organs, metal nanoparticles allow drug delivery systems to minimize adverse effects.

### 3.1. Silver nanoparticles

Silver, the precious metal with the greatest profit-orientedness due to its antiviral, antifungal, and antioxidant qualities, is used in the production of NPs and nanoparticles. These are well-known for their antibacterial, antiviral, antifungal, and antioxidant activities, as well as their physicochemical qualities that are remarkably enhanced in comparison to the bulk material. These include optical, thermal, electrical, and catalytic capabilities [48]. It has been shown that a range of cell types are vulnerable to the cytotoxicity that silver nanoparticles generate via necrosis and apoptosis. They also exhibit results against the negative effects of traditional treatments, including suppression of stem cell development, increased lactate dehydrogenase (LDH) leakage, reactive oxygen species (ROS) formation, and DNA damage [49].

### 3.2. Gold nanoparticles

Gold nanoparticles, or AuNPs, are strong radiosensitizers that are used in medical procedures including cancer therapy and medication delivery [50]. Strong radiosensitizers used in medication delivery and cancer therapy are gold nanoparticles, or AuNPs. Because Au NPs may control medication release by internal biological triggers or external light activation, they can transport a wide range of medicinal substances, recombinant proteins, vaccines, or nucleotides into their targets. AuNP-based medication delivery has garnered a lot of interest due to its remarkable efficacy [51].

## IV. TARGETING STRATEGY OF THE NDDSS

Active targeting and passive targeting are the two ways that nanocarriers may deliver nanodrugs to their intended targets. Active targeting focusses on certain markers that are only present in diseased cells and not in healthy ones. Molecules that interact with the overexpressed folate receptors in diseased cells are one example. One biomarker that is overexpressed in ovarian cancer and that can be actively targeted is CA-125 [52].

The size of polymers matters in passive targeting. At the location of sick cells, larger polymers may accumulate more. This occurs as a result of the polymers' ability to enter the ill region via leaky blood vessel junctions. It's similar to exploiting blood channel holes to get medications to the right place [53].

Figure 4 shows how to target nanoparticles (NPs) passively and actively to increase the therapeutic effectiveness of anticancer medications. Utilising the enhanced permeability and retention (EPR) effect, Figure 4A passively targets NPs; Figure 4B actively targets ligand-attached NPs to improve NP accumulation and cellular uptake through receptor-facilitated endocytosis [54].

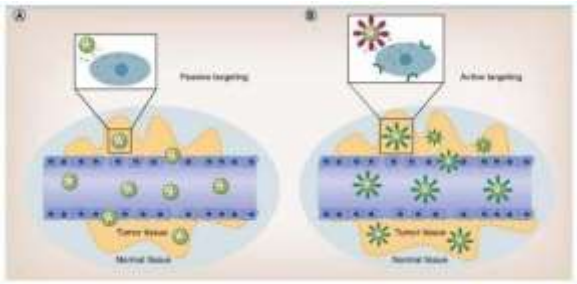

Figure 4. Passive and active targeting of nanoparticles (NPs) as a drug delivery system.

## V. APPLICATION OF NDDSS

There are several uses for nano drug delivery devices in the medical industry. Here are a few:

### 5.1. AuNPs in cancer therapy

Understanding how gold nanoparticles are biodistributed and accumulate in biological systems is crucial for their potential application as treatments. Only with precise nanomaterial characterisation, a trustworthy animal model, a

large sample, and robust statistical analysis can this be possible. AuNPs reduce the chance of negative consequences and control harm to healthy cells [55]. Aggregation [56] and a size-dependent deadly impact on different cancer cells [57] are characteristics of AuNPs, a new component in cancer treatment. AuNP's anti-cancer properties are complex and poorly understood. Although AuNPs have positive charges, they are absorbed and internalised by negatively charged molecules such lipids found in both healthy and malignant cell membranes [58]. Tiny AuNPs build up within HeLa cells as a consequence of endocytosis, another way that AuNPs enter cells [59].

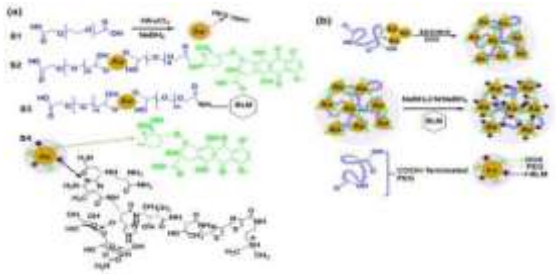

Figure 5. Synthesis of PEG-AuNPs NPs (a) the chemical composition of DOX and BLM and the procedures involved in conjugating them to the surface of S1; (b) a schematic depicting the production of S2, S3, and S4 NPs.

We concentrated on creating the following drug delivery systems using gold nanoparticles: AuNPs coated in PEG with carboxylic groups, PEG-AuNPs associated with DOX, PEG-AuNPs associated with BLM, and, lastly, PEG-AuNPs associated with both DOX and BLM (designated as S1, S2, S3, and S4, respectively), as shown in Figure 5[59].

**5.2. AgNPs as anti-viral agents**

The emergence of resistance by many viral infections to anti-viral medications is a major issue for the biotechnological, pharmaceutical, and medical sectors [60]. AgNPs are well known to inhibit viruses due to their effective interactions with sulfhydra, amino, carboxyl, phosphate, and imidazole groups.

AgNPs have lately acquired appeal as anti-viral medications because of their effectiveness in inhibiting a wide range of viruses, such as hepatitis, coronavirus, influenza, herpes, recombinant respiratory syncytial virus, and human immunodeficiency virus [61]. As shown in Figure 6[62], AgNPs were used to develop a nanoscale delivery system for the antiviral medication zanamivir. Additionally, AgNPs were surface-enriched with amantadine to inhibit H1N1 virus resistance.

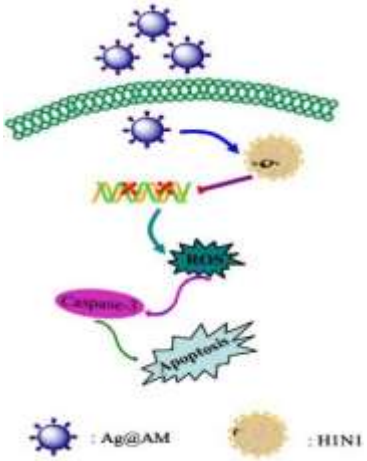


Figure 6. The reversal of H1N1 influenza virus-induced apoptosis by silver nanoparticles.

## VI. CONCLUSION AND FUTURE PERSPECTIVES

The growth and development of nanotechnology for therapeutic and medical applications during the last two to three decades has offered previously unheard-of opportunities to produce medical diagnoses and treatments for human diseases. The enhanced solubility of a range of cargoes, disease-fighting ability, controlled transmission, improved strength, increased biodistribution inside the organism, modula table (adjust to a certain proportion) means of transport across tissues and cells, and controlled delivery to the target location are all examples of the nanomaterials' high degree of control over the desired properties. Higher sensitivity picture components and detectors for analysis and identification might be made using these kinds

of methods. Before this research may result in therapeutically effective drugs, there are still issues that need to be addressed. A significant barrier to the commercialisation of this technology is the development and assessment of innovative methods to control the interactions of nanoparticles with the body. It is necessary to find a way to distribute nanomaterials to specific body parts without letting organs like the liver and spleen capture them. Nanoscale manipulation of material characteristics has made it feasible to improve and alter current technology. Therefore, given enough time and research, the promise of drugs based on nanotechnology may come to fruition.

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