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Emerging Nanocarrier Systems in Drug Delivery: From Synthetic Nanotubes to Natural Exosomes.

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Abbreviations :-
CNTs – Carbon Nanotubes
SEDDS – Self-Emulsifying Drug Delivery Systems
NLC – Nanostructured Lipid Carriers
EMA – European Medicines Agency
FDA – Food and Drug Administration
SWCNT – Single Walled Carbon Nanotubes
MWCNT – Multi Walled Carbon Nanotubes

Abstract:

Nanotechnology has recently surged in prominence due to its potential to revolutionize tumor diagnosis and treatment. Nanocarriers address longstanding issues with traditional antitumor drug delivery, such as lack of specificity, harsh side effects, rapid release, and harm to healthy cells. These carriers enhance drug bioavailability, boost therapeutic efficacy, and ensure targeted accumulation. Though numerous nanocarriers exist, only a handful have gained clinical approval for precise antitumor drug delivery.This review explores three key areas: nanocarrier types and their role in anticancer drug delivery, targeting mechanisms and surface modifications, and specific applications in breast, lung, colorectal, and pancreatic tumors. A deeper look into tumor treatment through nanotechnology. Effective nanocarriers for treating selected tumors. Compared to synthetic small-molecule drugs, bioactive peptides offer superior efficiency, selectivity, safety, and tolerability. Yet, hurdles like mucus, digestive enzymes, and epithelial barriers reduce their bioavailability. Researchers are now investigating nanocarrier systems for peptide delivery—liposomes, polymer nanoparticles, polysaccharides, hydrogels, and self-emulsifying systems—each with distinct pros and cons. Recent years have seen growing fascination with nanocarrier systems. They tackle critical challenges: poor solubility, permeability, and GI stability. Improving drug solubility often involves API nanonization or solid lipid formulations. Precision matters. Speed counts. Results speak.

Keywords: Nanocarriers, CNT, SEDDS, Exosomes, Drug Delivery, Nanomedicine.

I. Introduction:

The landscape of drug delivery has undergone a transformative shift in recent years, driven by rapid advancements in nanotechnology and material sciences. Conventional dosage forms though effective often struggle with challenges such as poor bioavailability, limited tissue targeting, rapid drug degradation, and systemic toxicity. To address these limitations, researchers have turned toward nanoscale delivery vehicles capable of transporting therapeutic agents with unprecedented precision and efficiency.[1]

Nanocarrier systems represent a class of engineered platforms typically ranging from1 to 1000 nm, designed to improve the pharmacokinetic and pharmacodynamic profile of drugs. By altering surface chemistry, size, morphology, and composition, nanocarriers are capable of enhancing solubility, prolonging circulation time, improving cellular uptake, and enabling targeted tissue delivery. Beyond mere passive carriers, modern nanosystems are now being designed to respond to biological cues, enabling controlled and stimuli-responsive drug release.

The evolution of nanocarrier technologies has led to the development of diverse systems ranging from **synthetic carbon-based nanotubes** to **lipid-derived nano emulsifying systems**, and more recently, **nature-driven exosomal vesicles**. Each of these categories brings its own advantages and translational potential:

- **Synthetic nanocarriers** such as Carbon Nanotubes (CNTs) offer extreme surface area and tunable chemistry, enabling high payload loading and targeted functionalization.
- **Lipid-based nanocarriers**, including Self-Emulsifying Drug Delivery Systems (SEDDS), provide biocompatibility, enhanced solubility for poorly water-soluble

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drugs, and scalability for industrial production.

- **Natural nanocarriers**, exemplified by exosomes, harness the body's own communication pathways to deliver therapeutic cargo with unmatched biomimetic compatibility and minimal immunogenicity.[2]

As therapeutic molecules become increasingly complex—ranging from hydrophobic APIs to fragile biologics like mRNA and siRNA—the demand for advanced nanocarriers continues to rise. What was once a futuristic concept has now become an active pipeline in pharmaceutical development, with several nanomedicine formulations already achieving clinical approval and many more in preclinical or translational stages.[3]

This review aims to explore and compare three emerging nanocarrier platforms Carbon Nanotubes (CNTs), Self-Emulsifying Drug Delivery Systems (SEDDS), and Exosomeswith a focus on their design principles, mechanisms of drug delivery, current biomedical applications, and translational challenges. By bridging synthetic, lipid-based, and natural nanocarrier approaches, this work provides an integrated perspective on how nanotechnology is reshaping modern therapeutics and paving the way for personalized medicine.

Unlike conventional reviews that discuss nanocarrier systems in isolation, the present review provides an integrative and comparative analysis of synthetic (carbon nanotubes), lipid-based (SEDDS), and natural (exosomes) nanocarriers within a unified translational framework. By examining their structural design, functional capabilities, regulatory positioning, and hybridization potential, this article highlights the convergence of engineered and biomimetic systems toward next-generation precision drug delivery platforms.[4]

II. Synthetic Nanocarriers: Carbon Nanotubes (CNTs)

2.1. Structure and Morphology

The structure of pure SWCNT, which is made entirely of carbon, can be seen as a rolled-up tubular shell of graphene sheet composed of hexagonal rings of carbon atoms of the benzene type. A single atomic layer of crystalline graphite is represented by graphene sheets, which are seamless cylinders formed from a honeycomb lattice. A stack of graphene sheets rolled into concentric cylinders is called a MWCNT. Every nanotube is a single molecule made up of millions of atoms, with diameters as small as 0.7 nm and lengths of tens of micrometres. The SWCNTs typically have a tube thickness of just one atom and only ten atoms around the circumference. MWCNTs are made up of multiple single-walled tubes stacked one inside the other, giving them a larger size. Only MWCNTs are nanostructures with an outer diameter of less than 15 nm; those with an outer diameter greater than that are called carbon nanotubes. Carbon nanotubes are distinct from carbon tubers, which are strands of stacked graphite sheets as opposed to single molecules. In addition to the two fundamental configurations, carbon nanotubes can take three different forms. Chiral, zigzag, and armchair carbon nanotubes are the three types of carbon nanotubes. Several types of carbon nanotubes are created depending on how the graphite is "rolled up" during the manufacturing process. By changing the rolling axis with respect to the hexagonal network of the grapheme sheet and the radius of the closing cylinder, various types of SWCNTs can be generated. The two indices, nn and mm, indicate the number of unit vectors along the two directions in the grapheme honeycomb crystal lattice. When $mmmm$, the nanotube is called "zigzag"; when $nnmmm$, it is called "armchair"; all other conjugations are categorised as chiral.[5]

2.2. Techniques for Carbon Nanotube Synthesis

High-quality nanotube materials are needed for both technological and basic applications. High quality is defined as the absence of structural and chemical defects at a significant length scale (e.g., 1–10 microns) along the tube axes. The number of publications and patents pertaining to carbon nanotube synthesis is rapidly increasing. Many techniques have been developed to produce CNTs and MWNTs with different morphologies and structures in lab quantities. The three most widely used methods for producing CNT are arc discharge, laser ablation, and chemical vapour deposition (CVD). The basic elements required to create nanotubes are a carbon source, a catalyst, and sufficient energy. In order to produce fragments (groups or individual C atoms) that can recombine to form carbon nanotubes, these methods are similar in that they entail adding energy to a carbon source. The energy source could be electricity from an arc discharge, heat from a furnace (roughly 900°C) for CVD, or high-intensity light from a laser (laser ablation).[6]

2.3. Applications of CNT functionalisation methods in medicine

Improving CNTs' surface properties is essential for greater dispersion, solubilisation,

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biocompatibility, and reduced cytotoxicity because they were initially less dispersible and insoluble. CNT surfaces could be altered to make them more soluble in water, serum, and other solvents to enhance their biocompatibility and reduce their cytotoxicity in biological systems for biomedical applications. The biological activities and cytotoxic effects of carbon nanotubes (CNTs) are greatly influenced by their surface chemistry as well as the purification and functionalisation procedures. We have looked at a number of methods for carbon nanotube surface modification and their applications in the sections that follow. Functionalisation of covalents CNTs' solubility and biocompatibility are essential for their successful use in biomedical applications. Covalent functionalisation through a series of acid treatments could be used to purify CNTs, increasing their solubility and reducing their toxicity. A number of purification methods can increase the solubility of CNTs, potentially revealing some charged groups and reducing cytotoxicity. Short, acid-oxidized, carboxylated CNTs with hydrophilic surfaces and high aqueous dispersions were found to be less dangerous and more biocompatible than pure CNTs in mice. When acid-treated, water-soluble SWCNTs were taken up by human monocyte-derived macrophage cells, it was found that P-CNTs were inside the lysosomes and cytoplasm and had no effect on cell viability or structure compared to UP-CNTs. The development of carboxylated SWCNTs for pharmaceutical applications depends on the removal of hazardous impurities associated with carboxylated SWCNTs, as functionalised SWCNTs have also been used to grow mammalian cells.[7]

2.4. Non-covalent functionalisation

Another method for modifying the surface of CNTs is noncovalentfunctionalisation. CNTs are known to interact noncovalently with a wide range of molecules through weak interactions like surface adsorption onto their side walls, π–π stacking, electrostatic interactions, hydrogen bonding, and van der Waals force. These noncovalent methods increase the water miscibility of CNTs, making them less dangerous. CNTs have been noncovalently functionalised with a range of biomolecules, polymers, and surfactants to achieve biocompatibility. Porphyrin derivatives and FITC-terminated PEG chains have also been coated onto the CNT surface due to the π–π interaction between pyrene and the graphitic surface of CNTs, which has reduced toxicity and increased biocompatibility.[8]

2.5. Drug loading mechanisms: classification of π-π interactions

The π-π stacking interaction is a type of noncovalent interaction in chemistry that involves aromatic groups that have π bonds. Based on the geometry of aromatic interactions, three types of π-π interactions can be identified:
(a) T-shaped edge-to-face stacking
(b) offset stacking
(c) face-to-surface stacking.[9]

2.6. The role of π-π interactions in the design of chemical drug delivery systems

Since many clinically used chemical medicines contain aromatic rings, π-π stacking interactions play a major role in the design of chemical drug-delivery systems. During the chemical drug development process, it is believed that the balance between hydrophilicity and lipophilicity is essential for drug absorption and distribution throughout the body. Many medications get their lipophilicity from aromatic ring structures. Pharmaceutical drugs contain aromatic rings.

2.7. The role of π-π interactions in the design of biological drug delivery systems

The need for biological medication delivery systems is growing. The large molecular size, rapid disintegration, and low oral bioavailability of these drugs make the development of suitable delivery systems crucial. Because biological drugs' three-dimensional structure is crucial to their pharmacologic effects, noncovalent loading of biological pharmaceuticals into delivery vehicles is preferred over covalent modification.

The application of π-π interactions in aromatic chemical medications and environment-responsive delivery systems

Because the π-π stacking force is a pH-sensitive force that is weaker than a covalent bond, π-π interaction-based assembly systems can be disassembled in vivo, especially in an acidic environment. This phenomenon has been used to design a pH-driven, reversible assembly mechanism. In this work, single-walled carbon nanotubes were adsorbed onto a gold surface modified with 4,4′-dithiobipyridine using π-π forces in a neutral pH medium.[10]

2.8. Protecting π-π interaction-based drug delivery systems for stability in vivo

A π-π interaction-based delivery system must get past several physiological barriers in order to reach its target site. After systemic delivery,

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circulation proteins and enzymes may bind to or degrade such systems. Nonspecific uptake by reticuloendothelial systems, liver, and lung tissues may also impede delivery system arrival at target tissues. Even within the target tissues, specific delivery to target cells faces physiological challenges. [1112]

2.9. Applications :

a. Nanotubes to deliver drugs and treat cancer

After ten years of intensive research, nanomaterials, particularly carbon nanotubes (CNTs), have developed into potent drug delivery vehicles. CNTs are passively absorbed into tumours without the help of antibodies or other large molecules; this enhanced permeability and retention (EPR) effect has been effectively used to deliver a range of anti-cancer drugs. The ease of functionalisation of CNTs allows for the attachment of several medication Nanotube-based biosensors.

Since the discovery of SWNTs' band-gap fluorescence in the near-infrared (NIR) range, numerous groups have reported fluorescence-based detection, sensing, and imaging using customised SWNTs SWNTs display photoluminescence (PL) between 650 and 1400 nm due to their unique electronic structure, and NIR light between 950 and 1400 nm has a considerable penetration depth in biological tissues. The intensity and wavelength of the fluorescence are also very responsive when using nanotubes as scaffolds for tissue engineering.[11]

Because of their combined chemical, electrical, and mechanical properties, CNTs have been studied for a variety of tissue engineering applications. Recent studies have shown that CNTs increase the number of synaptic connections in cultured hippocampal neurones by 1.6 times, which almost doubles peak post-synaptic current and decreases transient desensitisation

b. Utilising nanotubes for decontamination

The use of CNTs in antimicrobial nanocomposite films has significantly changed over the last ten years. One of the earliest results on protein–nanotube interactions was published by Karajanagi et al. [40], who investigated the effects of the nanoscale environment on the structure and function of proteins.[13]

Despite their remarkable drug-loading efficiency and cellular penetration capabilities, carbon nanotubes remain constrained by unresolved concerns related to long-term biocompatibility and biodistribution. Surface functionalization has significantly reduced toxicity; however, standardized toxicity profiling and scalable purification strategies are still required for clinical advancement. Therefore, while CNTs demonstrate strong potential in targeted and combination therapy, their translational maturity remains moderate compared to lipid-based systems.[14]

III. Lipid-Based Nanocarriers: Self-Emulsifying Drug Delivery Systems (SEDDS) and Their Expanding Role

3.1. Self-Emulsifying Drug Delivery Systems (SEDDS): Composition, Mechanism, and Self-Emulsification

Self-Emulsifying Drug Delivery Systems (SEDDS) are a clever lipid-based nanocarrier strategy intended to get around the inherent drawbacks of medications that are poorly soluble in water. When exposed to aqueous gastrointestinal fluids, these systems—isotropic blends of oils, surfactants, and co-surfactants—have the unusual capacity to spontaneously form fine emulsions. In contrast to traditional emulsions, SEDDS don't need a lot of energy; instead, emulsification happens organically because the formulation's constituent parts create favorable thermodynamic conditions. Surfactants and co-surfactants significantly lower interfacial tension, enabling quick dispersion into micro- or nano-sized droplets, while the oil phase serves as a solubilization reservoir for lipophilic medications. When taken orally, gastrointestinal motility causes a small amount of agitation, which leads to self-emulsification and the formation of a homogenous dispersion with a large surface area. This spontaneous emulsification ensures that the drug remains in a solubilized state throughout its transit in the gastrointestinal tract, preventing precipitation and enabling efficient absorption.

Liquid SEDDS (Oil + Surfactant + Drug)
↓
Contact with GI Fluids
↓
Reduction in Interfacial Tension
↓
Spontaneous Nano Droplet Formation
↓
Large Surface Area & Stable Drug Solubilization
↓
Enhanced Intestinal Absorption[1516]

Fig1 :Composition-Driven Self-Emulsification Process of SEDDS

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3.2. Role of SEDDS in Enhancing Bioavailability of Poorly Soluble Drugs

Poor water solubility remains a major issue in oral drug delivery, particularly with BCS Class II and IV drugs. SEDDS get around this limitation by keeping the drug dissolved from administration until absorption. The enormous interfacial surface area that the nanoscale droplets provide upon dispersion speeds up drug diffusion and absorption across the intestinal membrane.

Beyond solubilization, bile salts and the byproducts of lipid digestion in the gastrointestinal tract combine to form mixed micelles that facilitate drug delivery. Additionally, a number of lipid excipients facilitate lymphatic absorption, which partially avoids hepatic first-pass metabolism. This multifactorial improvement, which includes solubilization, permeability improvement, and metabolic bypass, significantly increases oral bioavailability and stabilizes plasma drug levels.

SEDDS Administration
↓
Drug Solubilization in Lipid Droplets
↓
Mixed Micelle Formation (with Bile Salts)
↓
Enhanced Membrane Permeation
↓
Lymphatic Transport (Partial First-Pass Bypass)
↓
Improved Systemic Bioavailability[1710]

Fig 2 :SEDDS-Mediated Drug Absorption and Systemic Availability Mechanism

3.3. Nanostructured Lipid Carriers (NLCs) vs SEDDS: Comparative Perspective

Although both SEDDS and Nanostructured Lipid Carriers (NLCs) are categorized as lipid-based nanocarriers, their formulation philosophies and in vivo behaviors are very different. NLCs, which are pre-formed particulate systems composed of a mixture of liquid and solid lipids that form an imperfect crystalline lattice, enable higher drug loading and controlled release. Conversely, SEDDS are liquid pre-concentrates that only produce nanodroplets when they come into contact with biological fluids.

SEDDS' rapid solubilization and instant drug availability make them ideal for drugs that require a rapid start of action. On the other hand, NLCs provide better physical stability and longer release patterns. As a result, SEDDS are more appropriate for medications with limited solubility, while NLCs are preferred for prolonged drug administration.[1819]

3.4. Emerging Advances in SEDDS Technology

a. Solid Self-Emulsifying Drug Delivery Systems (S-SEDDS)

One of the most significant advancements in SEDDS technology is the transformation of liquid formulations into solid self-emulsifying systems. While retaining the ability to self-emulsify, solid SEDDS provide improved stability, ease of handling, and compatibility with conventional solid dosage forms. Techniques like spray drying, hot-melt extrusion, and adsorption onto solid carriers are used to produce powders that flow freely. When exposed to aqueous environments, S-SEDDS rapidly re-emulsifies, releasing nanoscale droplets that resemble liquid systems. The gap between formulation performance and industrial viability is closed by this invention.[1520]

b. Hybrid Lipid–Polymer Systems: The Future Direction

Hybrid lipid-polymer nanocarrier systems are a cutting-edge advancement in SEDDS technology. These systems combine the solubilization efficiency of lipids with the structural stability and functional flexibility of polymers. Polymer coatings can enhance stability, control release kinetics, and enable surface modification for targeted drug delivery.

Although SEDDS-based lipid-polymer hybrid systems are still in their early stages of development, they have enormous potential for site-specific delivery, improved therapeutic efficacy, and reduced toxicity, making them crucial for oncology and precision medicine.[2122]

c. Regulatory and Formulation Challenges in SEDDS and Advanced Lipid-Based Nanocarriers

Despite the many therapeutic advantages of SEDDS and recently created hybrid lipid-based nanocarriers, their successful transfer from laboratory research to clinical and commercial use is hampered by a number of formulation and regulatory issues. These challenges stem from the complex multi-component structure of lipid systems, the unpredictable 1099ehaviour of excipients, and the absence of standardized regulatory frameworks created specifically for drug delivery systems based on nanocarriers.[2324]

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1. Formulation Challenges

One of the primary formulation concerns with SEDDS is the careful selection and optimization of lipid excipients. Oils, surfactants, and co-surfactants must exhibit acceptable safety profiles and stability in physiological settings in addition to having a high drug solubilization capability. High surfactant concentrations can be dangerous or irritate the gastrointestinal tract, even though they are often required to ensure successful self-emulsification. Moreover, precipitation of the drug upon dilution in gastrointestinal fluids remains a serious risk, particularly for supersaturated SEDDS formulations.

Scale-up and production repeatability are also major formulation challenges. Modest adjustments to excipient quality, mixing order, or processing conditions can alter drug release behavior, emulsification efficiency, and droplet size distribution.[2420]

2. Regulatory Challenges

Lipid-based nanocarriers fall somewhere between traditional dosage forms and cutting-edge nanomedicines from a regulatory standpoint. Traditional pharmaceutical guidelines, which may not fully capture nano-specific characteristics like droplet size dynamics, in vivo lipid digestion, or lymphatic transport pathways, are frequently used by regulatory bodies to assess SEDDS. Regulatory approval is made more difficult by the absence of standardized characterization techniques for evaluating long-term safety, bioequivalency, and in vivo performance.
The structural complexity and multifunctional design of hybrid lipid-polymer systems make them even more scrutinized. It is necessary to fully address problems with polymer biodegradability, accumulation, and immunogenicity. Furthermore, regulatory requirements for lifecycle management, batch-to-batch consistency, and quality control are constantly changing and necessitate substantial preclinical and clinical documentation.

SEDDS represent one of the most clinically adaptable lipid-based systems due to their simplicity, scalability, and ability to enhance oral bioavailability of poorly water-soluble drugs. However, challenges related to drug precipitation upon dilution, excipient-related toxicity, and limited targeting specificity restrict their application in precision medicine. Future advancements in solid SEDDS and hybrid lipid-polymer systems may overcome these constraints and expand their therapeutic scope beyond conventional oral delivery.[25]

4) Natural Nanocarriers: Exosomes and Their Biomimetic Potential

Exosome biogenesis happens in a number of ways, either constitutively or in response to stimuli. Vesicles with diverse vesicular topologies are produced by the biogenesis of endosomal systems, there are three major subtypes of extracellular vesicles (EVs):

1. Microvesicles, which have a diameter of 50–1000 nm, are released from the cellular membrane through outward blebbing and membrane remodeling.
2. Apoptotic blebs, which are produced by dying cells during late-stage apoptosis, range in size from 100 to 5000 nm.
3. Exosomes are discharged from multivesicular bodies and range in size from 20 to 150 nm, depending on the research group.

When early endosomes develop into late endosomes or multivesicular bodies (MVBs), the process starts. Then, through inward invasion, the endosomal membrane of MVBs creates intraluminal vesicles (ILVs) in the lumen of organelles. Determining the fate of ILVs by lysosomes or exosome production, which involves many sorting processes, is the next critical step. When permitted, the MVBs merge with the cell membrane. Eventually, the process of exocytosis releases ILVs into the extracellular milieu. Exosomes are the name given to these discharged vesicles. They can be released by a variety of healthy cells or, in pathological circumstances, by sick cells. Along with VPS4, VTA1, ALIX, and other related proteins the essential molecules for exosomal genesis the endosomal sorting complex (ESCRT-0, ESCRT-I, ESCRT-II, and ESCRT-III) is crucial central machinery needed for transport. Numerous other endogenous substances, such as GTPase enzymes, have been shown to control vesicle biogenesis and spatiotemporal trafficking.The entire process of exosome vesicle production, from plasma membrane endocytosis to release via exocytosis.[26]

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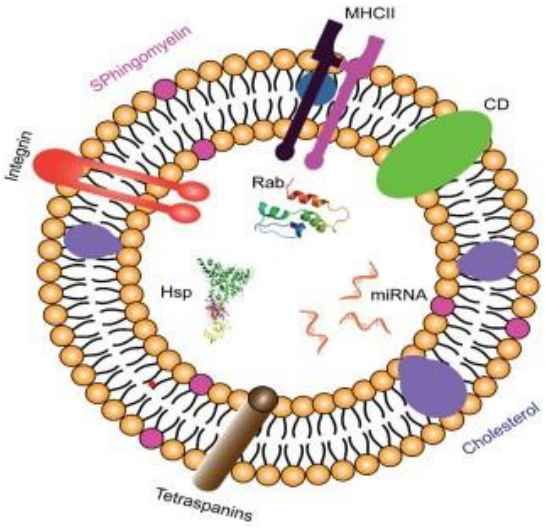

Fig 3 : Representative Structure and Molecular Composition of Exosomes

Isolation and purification

Numerous techniques for isolating exosomes in high purity and quantity have been created as a result of the quick advancements in science and technology. Each technique uses a unique feature of exosomes, such as their density, size, shape, and surface proteins, to make isolation easier. 1 provide a summary of some isolation processes, their isolation mechanism, and the method's advantages and disadvantages. There are no effective techniques for exosome isolation, and the ones that do exist either have the issue of protein and non-exosomal vesicle contamination or are very costly since they require specialized equipment. Although efficiency-based techniques are extremely clean, their high expenses and limited yields have hindered their widespread application in exosome purification. Researchers maintain that the efficiency and purity of the isolated exosomes can be increased by combining two techniques. Due to their scalability and capacity to isolate particular exosome subpopulations, field flow fractionation techniques have drawn particular interest. To be used in therapeutic applications, they must be further improved.

Exosome precipitation, ultrafltration, sucrose density gradient ultracentrifugation, and differential ultracentrifugation are methods for purifying and preparing extracellular vesicles in large quantities. Differential ultracentrifugation and density gradient ultracentrifugation were two techniques utilized to purify large-scale mRNA-loaded exosomes in a study. It was shown that both techniques had comparable rates of mRNA recovery. However, it's possible that the chemicals utilized in the density gradient filtration procedure won't be completely eliminated. Furthermore, using differential ultracentrifugation resulted in more RNAs being condensed in the exosome fractions. Differential ultracentrifugation was therefore determined to be the best technique for exosome purification.[17]

4.1. Engineering approaches (surface modification, loading strategies)

A) Drug loading methods for exosomes

There are still a number of issues with the practical use of exosomes as drug carriers, such as how to effectively transfer medications into exosomes. Exogenous medications, proteins, and nucleic acids have been loaded into exosomes utilizing a variety of techniques, which can be divided into preloading and post-loading techniques. Exosomes that have been extracted or secreted from cells are preloaded with the desired medications and integrated into the parent cells through the use of transfection, activation, etc. As will be covered in detail below, a number of drug loading techniques have been investigated.

Drugs can now be inserted into exosomes using a variety of techniques, including transfection, incubation, saponin-assisted loading, sonication, extrusion, freeze-thaw cycles, electroporation, etc.

The process of loading various compounds, such as medications, therapeutic proteins, or oligonucleotides, into exosomes using chemical or biological agents is known as transfection. A commercial exosome transfection kit called Exo-fect is highly effective in transferring nucleic acids and small compounds directly into exosomes. Transfection can also be mediated by biological agents. For instance, lentivirus can transfer pre-miRNA (LV-miR) precursor molecules. Transfection efficiency can be used to package therapeutic compounds into the exosomal lumen; this method has a higher molecular stability than other loading techniques, but the efficiency is not fixed. Inadequate packaging has occasionally been brought up. In exosomes generated from donor cells, transfection agents may change the expression of certain genes.These could cause loaded nucleic acid agents' biological activity to change. Because some transfection agents have been known to be harmful, this raises severe concerns about the safe use of transfection techniques.

B) The incubation process

There are currently two different kinds of incubation techniques. First, drugs and exosomes are directly incubated, which enables the drug to interact with the

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lipid layer of the exosome membrane. In the second kind, medications are incubated with exosome donor cells before the drug-carrying exosomes are separated. The latter is primarily meant for small molecules or medications with minimal cytotoxicity. Nevertheless, none of the techniques were found to have high loading efficiency. Therapeutic RNA can also be loaded into exosomes using a co-incubation technique in conjunction with hydrophobically modified small interfering RNAs.

C) Saponin-assisted loading

Certain substances can increase the permeability of cell membranes by creating holes or pores through various mechanisms. One of these natural glycosides, saponin, is an effective membrane-penetrating agent that can create holes in exosome membranes and form complexes with membrane cholesterol.

The size distribution and zeta potential, which are typical in extrusion, hypotonic dialysis, and some other loading methods, are unaffected by saponin treatment.

However, the hemolysis effect limits the use of saponins in vivo. Therefore, after being incubated with saponins, exosomes need to go through a purification process.

D) Sonication

Drugs of interest are combined with donor cells or target cell-derived exosomes, which are then sonicated using a homogenizer probe.

Sonication-induced mechanical shear mediates the deformation of exosomal membranes. This enables the medicine to be released at the target spot by the deformed exosomes passing through the comparatively tight lipid layer. The exosomes were incubated to restore the membrane's integrity following ultrasonic therapy. Exosomal aggregation is a possibility. It has been demonstrated that effective drug loading via sonication into macrophage-released exosomes promotes the medication's prolonged release.

Ultrasound has a higher loading efficiency than incubation.

E) Extrusion

This technique, which loads the drug into a lipid extruder with a porous membrane (aperture: 100–400 nm), has the advantage of producing an evenly sized mixture of exosomes and excellent drug loading efficiency. A significant finding was that the extruded exosomes were harmful when porphyrins with varying hydrophobicities were fed into exosomes using a syringe-based mini-extruder fitted with polycarbonate membranes (400 nm pore). However, when the same porphyrin is loaded using other methods, no significant toxicity has been documented or published. This method, known as freeze-thaw cycles, entails incubating exosomes with a specific drug at ambient temperature or at 37 °C for the ideal amount of time that has been empirically determined to support increased drug encapsulation. The combination is then rapidly frozen at a very low temperature (−80 °C) or in liquid nitrogen before being thawed at room temperature once more.

To improve drug encapsulation, freeze-thaw cycles are repeated. The number of repeating cycles, which are controlled by essential exosome components, determines the encapsulation efficiency of loaded cargo. Freeze-thaw cycles have been shown in a few studies to increase exosome aggregation, resulting in a high polydispersity index of the drug-loaded exosomes.

F) The process of electroporation

By using an electric field to disrupt the phospholipid bilayer, electroporation creates tiny holes in the membrane of exosomal vesicles that allow therapeutic payloads to flow through. Large nucleotides, such siRNAs or miRNAs, are best loaded into exosomes using this approach, although caution should be used because it can reduce drug loading efficiency and is susceptible to RNA precipitation or exosome aggregation. An inappropriate electroporation bufer system may cause exosome structural deformation or aggregation. When aggregation is caused by cyto-mix electroporation, a trehalose pulse medium (TPM) can be used to preserve the original exosome size and prevent aggregation.Heavy cargo loading into exosomes, such as SPION5 (superparamagnetic iron oxide nanoparticles), has been made possible by TPM, opening up new possibilities for theranostics research and targeted medicine administration.[272829]

4.2. Exosome surface modification

A number of proteins expressed on the exosome surface are integrated with exosome biodistribution and cell-targeting capabilities. Exosome components can be modified either after they are isolated (post-isolation engineering) or at the cellular level (parenteral cell-based engineering). One method for cellular modification is to create a modified exosome membrane protein through cellular transgene expression by inserting the desired ligand's coding sequence into the signal peptide's sequence frame and the peptide-NH2 termini of a particular membrane protein. The ultimate objective of the

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search for an effective method or appropriate ligand for surface protein modification is to achieve targeting specificity and efficacy to the targeted tissues and cell types.

A) Exosome genetic engineering, peptide modification, and aptamer conjugation

Due to the strong affinity for the overexpressed receptors on the tumor, there was approximately three times more tumor inhibition with aptamer-drug-exosome than with drug-exosome when drug-loaded exosomes with and without surface modifications were examined.

Diacyllipid-aptamer sgc8-decorated doxorubicin-loaded exosomes (produced from immature dendritic cells) have been shown to have similar types of powerful and selective lethal effects in leukemic CEM cells. To maximize the therapeutic benefits of drug candidates, it is essential to target the illness environment.Aptamer-functionalized exosomes administered intravenously were found to be effectively absorbed in the bone marrow of animals suffering from postmenopausal osteoporosis. Additionally, osteogenesis led to an increase in bone mass. In a mouse model of femur fracture, it also quickened the production of callus tissue. Thus, it was discovered to be a promising method for addressing various bone ailments. Attaching an aptamer to an exosome can result in a synergistic improvement of the condition. The coupling of 5′ modified LJM-3064 aptamer to exosomes produced from bone marrow mesenchymal stem cells has demonstrated a synergistic immunomodulatory function and remyelination effect. This implies that exosomes may be a viable option for cutting-edge treatment of neurodegenerative illnesses.

B) Surface coating and complexation of exosomes

Exosomes can be tailored for reactive group functionalization through secondary reactions by coating their surface with an appropriate modifier, such as polydopamine. This opens up new possibilities for innovative applications, such as multidrug therapy or therapeutic approaches. Fusogenic peptide (GALA) and cationic lipid on exosomes electrostatically complexed to boost the cytosolic delivery of dextran, a big molecule with higher ribosome-inactivating protein bioactivity. An intracellular visualization tool could be created by expanding this Even with low blood velocity for an extended length of time, it has been demonstrated that anchoring SPMN (superparamagnetic nanoparticle cluster) to exosomes effectively sustains the delivery of active compounds in the targeted area. Therefore, magnetic nanoparticle technology has strengthened the potential for expansion in biological applications.

C) Surface labeling of exosomes

Exosomes' surface modification by various labeling moieties is particularly important for researching their in vivo fate, the internalization mechanism of exosomes in cancer cells compared to normal healthy cells, and assessing the impact of administration routes on biodistribution. Given the aforementioned biodistribution, it is crucial to remember that exosome surface charges and lipophilicity have a crucial role in the overall kinetic profile, regulating the rate of translocation, hepato-billiary and renal excretion, and specific absorption by certain immune cells. By using in situ biorthogonal click chemistry to label exosomes from human lung adenocarcinoma cells with dye, the inherent tumor-homing activity was preserved.as well as enabled effective exosome tracking in vivo, as confirmed by fluorescence imaging and quantification.

Exosomes offer unmatched biocompatibility and intrinsic targeting capability due to their endogenous origin. Nevertheless, large-scale isolation, purification reproducibility, cargo loading efficiency, and regulatory classification remain significant hurdles. Standardization of manufacturing protocols and clear regulatory guidelines will determine whether exosome-based therapeutics transition from experimental innovation to mainstream clinical application.[3031]

5) Comparative and Integrative Analysis of Nanocarrier Platforms

The advancing landscape of nanomedicine increasingly benefits from comparative assessments across synthetic, lipid-based, and biologically derived nanocarriers. Such comparisons enable a deeper understanding of performance attributes including particle size, surface charge, payload capacity, targeting potential, cytotoxicity, scalability, and regulatory maturity. By placing carbon nanotubes (CNTs), self-emulsifying drug delivery systems (SEDDS), and exosomes in a shared analytical framework, it becomes possible to identify not only strengths and limitations of each platform, but also avenues for technological convergence.

From a dimensional standpoint, exosomes typically range from **30–150 nm**, enabling efficient cellular uptake and endosomal trafficking. CNTs exhibit tunable lengths (from hundreds of nanometers

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to several micrometers) and diameters below 20 nm, which enhance loading capacity but may hinder clearance. By contrast, SEDDS produce nanoemulsions upon aqueous dispersion in the **20–300 nm** size range depending on surfactant–oil ratios. Surface charge also varies: exosomes commonly show mild negative zeta potentials (due to phosphatidylserine-rich membranes), CNT surfaces are highly modifiable via carboxylation or PEGylation, and SEDDS acquire charge indirectly via excipient selection. These shared and divergent physicochemical traits directly influence biodistribution, cellular uptake pathways (clathrin-mediated, caveolin-mediated, macropinocytosis), and immune recognition.

Payload strategies further distinguish these systems. CNTs support **high loading** via π–π stacking and covalent conjugation, making them attractive for hydrophobic anticancer drugs, photosensitizers, and siRNA. SEDDS excel in the **solubilization of poorly water-soluble molecules** by forming isotropic mixtures of oils, surfactants, and co-solvents that spontaneously generate nanoemulsions in gastrointestinal fluids. Exosomes, in contrast, carry endogenous nucleic acids (miRNA, lncRNA, mRNA), lipids, and proteins from donor cells, and can be engineered to encapsulate exogenous drugs with exceptional targeting fidelity and immune tolerance. However, scalability and regulatory compliance remain central bottlenecks for exosome translation, whereas CNTs and SEDDS benefit from more mature manufacturing infrastructures.

From a risk standpoint, CNTs may induce oxidative stress or inflammation depending on length, dispersion quality, and surface chemistry, whereas SEDDS are generally regarded as **low-to-moderate risk** due to GRAS-status excipients. Exosomes exhibit **minimal cytotoxicity**, though immunogenicity varies with cell source and isolation method. Industrial comparability also diverges: SEDDS are already aligned with pharmaceutical regulatory pathways, CNTs face stringent nanotoxicology scrutiny, while exosomes occupy an emerging and largely undefined regulatory category, especially regarding source characterization, purification standards, and batch-to-batch heterogeneity.[3223]

5.1. Cross-Learning: Biological Inspiration for Synthetic Platforms

Biological systems such as exosomes have inspired the nanomedicine field through their innate ability to evade immune clearance, traverse biological barriers, and deliver complex molecular cargo. Synthetic systems can harness this "cell-nature blueprint" by learning from exosomal surface proteins (e.g., integrins, tetraspanins, CD markers) that drive organotropism and tissue-specific docking. Similarly, exosomal lipid composition (cholesterol, sphingomyelin, phosphatidylserine) informs membrane-mimetic lipid formulations that improve endosomal escape and stability. In reverse, the high payload and modularity of CNTs and SEDDS offer design principles to improve exosome engineering, such as integrating synthetic polymers for improved storage stability or enhancing loading efficiency using hydrophobic interactions.

5.2. Hybrid Nanocarrier Systems

The convergence between biological and synthetic nanocarriers has stimulated a new class of **"hybrid systems"**, where material science and cell-derived vesicles interface to create multifunctional platforms. Exosome-mimetic liposomes incorporate phospholipid compositions and surface ligands resembling natural exosomes, improving targeting without relying solely on biological harvesting. Conversely, carbon-exosome composites integrate CNTs within exosomal membranes to enhance mechanical strength, photothermal performance, or loading capacity. These hybrids aim to merge **biocompatibility, targeting precision, and structural robustness**, addressing limitations inherent to single-class carriers.[3334]

5.3. Representative Case Studies

Several recent studies highlight how cross-platform integration yields functional advantages. CNT–lipid hybrids demonstrate enhanced **siRNA loading and membrane fusion**, improving gene silencing efficiency in cancer models. Exosome-inspired SEDDS formulations exploit lipid raft-mimicking compositions to facilitate lymphatic transport and reduce hepatic first-pass metabolism. Meanwhile, exosome-mimetic liposomes have successfully delivered chemotherapeutics with reduced systemic toxicity and improved pharmacokinetics. Collectively, these case studies illustrate how **rational integration** bridges biological compatibility with engineering versatility, moving the field toward more synergistic nanocarrier architectures.[35]

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Feature	CNT	SEDDS	Exosomes
Size Range	<20 nm–µm	20–300 nm	30–150 nm
Drug Type	Hydrophobic, siRNA	Poorly soluble drugs	Proteins, miRNA, drugs
Biocompatibility	Medium–Low	High	Very High
Targeting Ability	Functionalizable	Limited	Intrinsic
Clinical Status	Preclinical	Marketed	Early clinical trials
Limitations	Toxicity, clearance	Surfactant toxicity	Scalability, batch variation

Table 1: Comparison of CNTs, SEDDS, and Exosomes[3637]

6) Translational and Clinical Landscape of Emerging Nanocarrier Systems

The translation of nanocarrier systems from laboratory innovation to clinical application requires alignment between biological performance, manufacturing feasibility, and regulatory acceptance. Among current platforms, carbon nanotubes (CNTs), SEDDS, and exosomes display different levels of clinical readiness.

Preclinical and Clinical Applications:
CNTs remain largely confined to preclinical research, particularly in cancer photothermal therapy, biosensing, and gene delivery, where their high loading capacity and optical properties are advantageous. SEDDS exhibit the highest pharmaceutical maturity, with multiple marketed formulations designed to improve the oral bioavailability of poorly soluble drugs. Exosomes are currently undergoing active evaluation in clinical trials for oncology, regenerative medicine, and neurological indications due to their inherent biocompatibility and cell-derived targeting.

6.1. Regulatory Outlook:
Regulatory frameworks recognize nanocarriers but evaluate them according to composition and intended use rather than as a single class. SEDDS align with established oral dosage form standards since they utilize GRAS excipients and follow conventional bioequivalence pathways. CNTs require extensive biocompatibility and degradation assessments due to persistence and potential inflammatory responses. Exosomes fall under biologic regulations, requiring donor cell characterization, purification control, and immune safety profiling. Both the FDA and EMA are developing guidance on nanomedicine characterization, impurity profiling, and analytical standardization.[38]

6.2. Industrial Scalability and Cost Factors:
Scalability strongly influences clinical adoption. SEDDS benefit from low-cost oils and surfactants, straightforward process scalability, and compatibility with continuous manufacturing. CNTs require specialized synthesis, purification, and functionalization steps that elevate cost and introduce batch variability. Exosomes face the steepest challenges, including low natural yield, complex isolation workflows, cold-chain requirements, and high cost per therapeutic dose. Emerging solutions such as bioreactor-grown vesicles, tangential flow filtration, and chromatography aim to improve scalability and reduce cost barriers.

6.3. Future Trends and Personalized Nanomedicine:
A key trajectory in this field is the development of personalized nanomedicine enabled by hybrid systems. Exosome-inspired liposomal carriers, CNT lipid composites, and bioengineered vesicles offer a path to combine targeting specificity with controlled drug loading and scalable production. These hybrid approaches support a “bench-to-bedside” translation model where platform modularity, regulatory clarity, and digital patient profiling converge to enable tailored therapeutic interventions.[39240]

7) Convergence Toward Intelligent Hybrid Nanocarriers
The future of nanocarrier systems lies not in competition between synthetic and natural platforms, but in their integration. Hybrid nanocarriers that combine the structural robustness of synthetic materials with the biological sophistication of natural vesicles are emerging as

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transformative solutions. Exosome-mimetic liposomes, CNT–lipid composites, and biomembrane-coated nanoparticles represent promising examples of such convergence.These systems aim to achieve enhanced stability, improved targeting accuracy, reduced immunogenicity, and controlled drug release within a single platform. Furthermore, advances in stimuli-responsive materials and surface engineering enable the development of "smart" nanocarriers capable of responding to pH, temperature, enzymatic activity, or redox conditions at diseased sites.Integrating biomimetic strategies with scalable synthetic design may bridge the gap between laboratory innovation and clinical practicality, ultimately reshaping personalized nanomedicine.[41]

8) Challenges:

Insufficient and inconsistent scientific literature: Lack of standardized and reliable studies, especially regarding nanomaterial characterization creates knowledge gaps and slows translational progress.

Discrepancies in Experimental Data: Variability in reported size, charge, toxicity, and pharmacokinetics of nanocarriers prevents clear regulatory and clinical interpretation.

Fragmented Knowledge Base: Scarcity of comprehensive literature undermines pharmaceutical innovation and delays the transition of nanomedicine from laboratory to clinical practice.

Safety and Toxicology Data Gaps:
While therapeutic advantages of nanoparticles are well documented, limited information exists on their:

✓ long-term toxicity
✓off-target interactions
✓organ distribution and accumulation
✓immunological responses

Oversized Carrier Particles:
Larger delivery systems frequently suffer from:
✓poor absorption
✓unstable behavior in vivo
✓low solubility
✓poor tissue targeting
✓adverse physiological reactions
✓Smaller nano-scale architectures mitigate these issues but require advanced fabrication.

Barriers in Precision Targeting: Targeted delivery demands sufficient drug concentration at the site of action, yet systemic delivery often leads to sub-therapeutic accumulation.

a) **Biological Degradation of Sensitive Molecules:**
Example: siRNA is rapidly degraded by enzymes and shows poor cellular uptake due to its negative charge, even at higher doses.

b) **Immune Clearance of Lipid-Based Nanocarriers:**
Micelles and liposomes face biological obstacles such as:
✓ phagocytosis by immune cells
✓ hepatic filtration
✓ potential systemic toxicity
These mechanisms reduce targeting efficiency.

c) **Practical Clinical Barriers:**
Real-world treatment limitations include:
✓ inability of unconscious patients to self-administer
✓ poor permeability at target tissues
✓ food-induced degradation of active compounds
✓ microbial breakdown in the gastrointestinal tract

d) **Toxicity Concerns Across Nanomaterials:**
Some nanocarriers pose significant health risks due to cytotoxicity, inflammatory responses, or long-term bioaccumulation, complicating clinical approval.[42][43]

9) Future perspectives:

Nanomedicine : A Rapidly Evolving Frontier
↓
20+ Years of Research → 1,500 patents + 254 clinical trials
↓
Major Application: Cancer
• Enhanced diagnostic precision
• Improved therapeutic efficacy

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↓

Mechanism:
Nanoparticles → targeted drug delivery → malignant/tumor cells → spare healthy cells

↓

Current Status:
Nanomedicine + Nano-drug delivery = Cutting-edge biomedical research

↓

Future Influence:
Expected to shape medical innovation for decades

↓

Nanoparticle Characteristics:
• Range: nanometer → sub-micrometer (>100 nm)
• Need improvements in:
→ Material uniformity
→ Drug loading & release optimization

↓

Metal-based Nanoparticles:
• Gold, Silver = used in diagnostics
• Dual role: detection + treatment

↓

Example Case:
Gold nanoparticles → strong soft tumor absorption → heat therapy (NIR radiation) → targeted tumor eradication

↓

Current Practical Limitations:
• Limited healthcare integration (especially oncology)
• Field is still young (~20 years)
• Mechanisms & bio-interactions not fully understood

↓

Future Research Directions:
Identify definitive disease markers → achieve pinpoint treatment accuracy → protect normal cells

↓

Research Needs
• Better understanding of molecular pathology
• Link nanoscale materials ↔ subcellular processes

↓

Outcome:
Newer diagnostic & therapeutic strategies → transformative breakthroughs

↓

Expansion Tools
Nanoprobes & nanotheranostic systems → further investigation needed

↓

Technological Innovation Focus:
• Controlled site-specific drug release
• Real-time monitoring of interventions
• Tissue & cell-level drug effect evaluation

↓

Final Goal
Full realization of nanomedicine's revolutionary potential

Fig 4: Future Perspectives in Nanomedicine: A Translational Progression Flow[22 4218]

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Conclusion

The emergence of nanocarrier systems marks a decisive turning point in modern drug delivery, not because they merely improve existing therapies, but because they redefine what is possible within the human body. From the purposeful design of synthetic nanotubes to the naturally strategic behavior of exosomes, nanoscale carriers are gradually closing the gap between therapeutic intention and biological reality. What once depended on chance diffusion and systemic exposure is now moving toward guided transport, selective targeting, and controlled release a shift that reflects maturity in both imagination and engineering.

However, the importance of this field lies beyond performance metrics or clinical endpoints. Nanocarriers introduce a new logic to medicine: one where treatment can be packaged into intelligent structures that sense, respond, and interact with living systems rather than simply passing through them. This conceptual leap positions nanomedicine as more than a technological upgrade it becomes a framework for designing therapies that cooperate with biology instead of fighting against it.

As research continues to push boundaries, it is likely that no single nanocarrier system will dominate the future. Instead, the next generation of breakthroughs will emerge from hybrid strategies, cross-disciplinary thinking, and the blending of synthetic precision with natural elegance. In that sense, the story of nanocarriers is not just about better drugs, but about expanding the language of medicine itself.

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