Texila International Journal of Public Health
ISSN: 2520-3134
DOI: 10.21522/TIJPH.2013.12.03.Art006

Transformative Nano-Drug Delivery Strategies: Addressing Challenges in Modern Therapeutics

M. N. Anusha[1], Rishab Rampradeep[2], N. Aravindha Babu[1], K. M. K. Masthan[1], Archana Behera[3], and Mukesh Kumar Dharmalingam Jothinathan[3]*

[1]*Department of Oral Pathology and Microbiology, Sree Balaji Dental College and Hospital, Bharath Institute of Higher Education and Research (BIHER), Bharath University, Chennai, Tamil Nadu, India*

[2]*Department of Respiratory Medicine, Saveetha Medical College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai, India*

[3]*Centre for Global Health Research, Saveetha Medical College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai, India*

Abstract

The conventional methods of drug delivery, primarily oral and injectable routes, have encountered limitations in effectively administering new drugs. These limitations arise particularly with drugs such as proteins and nucleic acids, where traditional routes may not be optimal for therapeutic efficacy. Novel biological medications necessitate innovative delivery strategies to mitigate adverse effects and enhance patient compliance. Nanometer-sized drug particles present unique characteristics that offer potential improvements in various dosage formats. Within this size range, particles exhibit resistance to settling, increased saturation solubility, rapid dissolution, and enhanced adherence to biological surfaces. Consequently, these properties facilitate a quicker onset of therapeutic action and improved bioavailability. The emergence of nanotechnology provides scientists with a versatile tool to address both traditional and innovative drug delivery challenges. By leveraging nanotechnology, researchers explore new avenues for drug delivery, striving to optimize therapeutic outcomes while minimizing adverse effects. This review underscores the transformative potential of nano-drug delivery systems in advancing pharmaceutical sciences and enhancing patient care.

Keywords: *Drug delivery, Nanodrug, Nanotechnology, Nanoparticles.*

Introduction

The study of the unique properties of small materials, ranging in size from 1 to 100 nm, is known as nanoscience. Nanotechnology is using these materials to create or alter new objects [1].

A potential remedy is using drug-targeted delivery systems built on nanomaterials and nanotechnology. When compared to free pharmaceuticals, nano-drug delivery systems (NDDS) using nanoparticles (NPs) as drug carriers can maximise drug solubility and stability, allow for targeted distribution and controlled release, concentrate therapeutics at tumour sites, and reduce systemic side effects [2].

To maintain the biological activity of the source cells without compromising the physicochemical characteristics and drug-carrying ability of the NPs, a novel intelligent biomimetic nano-drug delivery system (BNDDS) was built by encasing NPs in biologically generated cell membranes (CMs) [3].

In the last two decades, scientists have investigated biomimetic membrane-

Received: 11.06.2024 ***Accepted: 31.07.2024*** ***Published on: 30.09.2024***

****Corresponding Author: itsmemukesh@gmail.com***

camouflaged nanocarriers, which provide characteristics like immune evasion, biological barrier crossing, pharmacokinetics, and pharmacodynamic control for targeted and customised tumour therapy. Bibliometric tools Pajek and VOS Viewer were used to visualise assessments of term co-occurrence from 2018 to 2023 [4].

Nanotechnology is lifting the bar by enabling innovative techniques in drug delivery, tissue regeneration, medical device manufacture, and many other fascinating evolutions. Drug delivery methods are designed to precisely release drugs at the right location. Nanotechnology has enhanced its function in each of these areas.

This page provides an overview of the fundamentals and development of nanotechnology, as well as information on the many kinds of nanoparticles and how they are made, nano diagnostics, drug delivery technologies, obstacles to drug delivery, and the risks associated with the field.

Evolution of Nanotechnology

Humans have employed nanoparticles and structures for a long time; the Romans did so as early as the fourth century AD. This exhibits one of the most fascinating instances of nanotechnology in recorded history. The British Museum's Lycurgus cup is a superb illustration of ancient glassmaking techniques. The earliest known example of a glass type that can reflect many colours of light selectively is dichroic glass. Dichroic glass refers to two distinct varieties of glass that exhibit colour changes under specific lighting conditions. In 1990, the researchers examined the cup under a transmission electron microscope (TEM) to interpret the dichroism occurrence. The existence of nanoparticles with a diameter of 50–100 nm is responsible for the observed dichroism (two colours). An X-ray study of the nanoparticles revealed that they are composed of a 7:3 ratio of silver to gold. They also include roughly 10% copper [5].

Light absorption gives the Au nanoparticles their red colour. The green colour results from light being scattered by smaller silver nanoparticle (AgNPs) particles, whereas the reddish-purple hue is caused by the dye absorbing bigger particles. One famous example of an old synthetic nanomaterial is the Lycurgus Cup. In mediaeval church windows, the fusing of Au and AgNPs produces a reddish-yellow light, demonstrating the action of nanoparticles in glass.

Branches of Nanotechnology

Nano Engineering

It is a category of nanotechnology applied to the nanometer scale.

Green Nanotechnology

It is the area of nanotechnology that makes processes more environmentally sustainable. It comprises developing environmentally friendly nanoproducts and applying them to long-term sustainability.

Wet Nanotechnology

Bioscience and drugs are included in this. The process of building up from small to huge quantities is known as "wet nanotechnology."

Manufacturing Nanoparticles

Two methods are used to synthesise the nanoparticles: the top-down method and the bottom-up method.

Top-Down Approach

By using modern technologies like precision engineering, the majority of the material is broken down into nanoparticles in this method. This method uses a numerical system in conjunction with sensors and either diamond or cubic boron nitride for size management. The top-down method also makes use of lithography technology, which involves subjecting the surface to light, ions, or electrons and then depositing material on top of it to create the desired material.

Bottom-Up Approach

It describes the assembly of atomic-level nanostructures using a variety of physical and chemical techniques. Chemical synthesis is a method for producing raw materials that can be used directly in products in their bulk-disordered form or as building blocks for more complex ordered materials. Self-assembly is a bottom-up approach where molecules or atoms organise themselves into ordered nanostructures through chemical-physical interactions. The only technique that enables individual positioning of single atoms, molecules, or clusters is positional assembly.

Milling

The process of turning a large amount of material into nanoparticles has been used for years. Energy transfer and mechanical grinding are used to accomplish this. It should be emphasised that the nanoparticles produced by these techniques are polydisperse, and because of the high energy input, additional surfactants and solvents are often required to stop agglomeration as well as extreme temperature rises. The process's lengthier grinding times, which are required to produce particles as small as 10–100 nm and produce impurities that are challenging to separate from the product, are another drawback.

High-Pressure Homogenisation

Multiple homogenization cycles are required to produce smaller and narrower particle size distributions since high-pressure homogenization is an energy-intensive process. The use of an organic solvent is not necessary for this procedure because huge batch sizes can now be accommodated by commercially available high-pressure homogenizers, and scaling up is widely accepted as a feasible option.

Ultrasonication

This method employs less shear stress during manufacture. Nevertheless, there is a chance of metal contamination with the equipment, and the produced nanoparticles have a broader particle size distribution [6].

Nanoprecipitation

Nanoprecipitation is based on the spontaneous generation of nanoparticles when mixing an aqueous phase with a water-miscible organic solvent. Nanoparticles naturally form when the chemical's organic solvent diffuses into the aqueous medium where it is insoluble. The most common organic solvents are non-toxic, the nanoprecipitation process is highly efficient at the laboratory scale, and it doesn't require sonication, extremely high temperatures, or energy input. However, control over the polydispersity index and particle size drastically decreases with scale-up. Moreover, long downstream processing times are required for the purification step, which eliminates both the free active component and the organic solvent. Reports state that steps like nanoprecipitation have been added to homogenization under high pressure and wet milling processes to produce smaller particles with small sizes.

Salting Out

This method works very well for creating polymeric nanoparticles. A polymer dissolved in a water-miscible organic solvent is mixed with an aqueous phase containing high concentrations of salts or electrolytes. Scaling up the salting-out approach is easy and efficient. However, the extensive washing needed for purification demands time-consuming downstream processing.

Supercritical Fluid Technology

Among the most popular methods for producing nanoparticle pharmaceuticals is supercritical fluid (SCF) technology. Advantages over other procedures include the use of mild temperature conditions and the lack of an organic solvent requirement. Commercially available setups can be used to achieve large-scale results. Carbon dioxide has

the drawback of being an unreliable solvent in terms of cost.

Solvent Evaporation

The solvent evaporation method, in which the medication and polymer are mixed in a common volatile organic solvent, is widely employed to create polymeric nanoparticles. A non-solvent aqueous system, often containing surfactants, emulsifies this solvent system. After emulsification, the organic solvent is evaporated by swirling, vacuuming, or high temperatures. The process of solvent evaporation results in the production of small, evenly distributed particles. Relatively little thermal stress is applied to the nanoparticles because of the low boiling temperatures of the solvents used in the manufacturing process. One significant drawback of this technology is the solvents used in the production process require explosion-proof rooms and equipment.

Nano Diagnostics

Nanotechnology is used in clinical diagnostics as a method to detect diseases sooner. Because of its extreme accuracy, it can identify even the smallest change in a cell that could result in cancer. The following resources are utilised in methods of diagnosis [Figure 1].

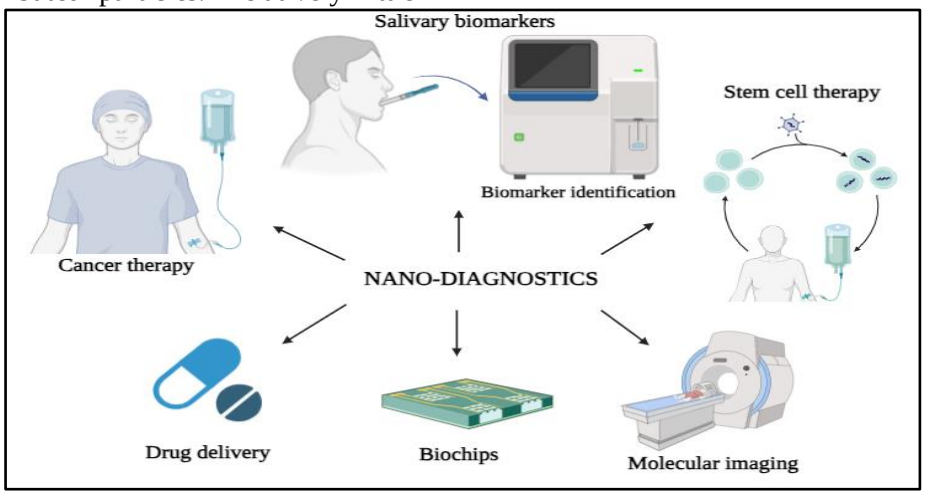

Figure 1. Types of Nano Diagnosis

Nanoscale Cantilevers: Attaches chemicals related to cancer using elastic beams.

Cantilever Array Sensors: They are extremely sensitive and utilised for mass detection.

Nanopores: Enhances DNA sequencing by allowing strands of DNA to pass through microscopic holes in it.

Nanotubes: Used to identify and find the impacted gene. The main material for these rods is carbon.

Quantum Dots: To pinpoint the tumour's location, they bind to proteins in cancerous cells. Under UV light, they can glow brightly.

Multiplexing Modality: The capacity to simultaneously feel a range of big macromolecules.

The primary contribution of nanotechnology to dentistry is its ability to diagnose oral squamous cell cancer. The ability to image these lesions is crucial for managing cancer generally. Clinical imaging modalities such as computer tomography (CT), magnetic resonance imaging (MRI), and ultrasound are examples of structural imaging approaches. Thus, endogenous contrast can be used to provide basic information on the location, size, and spread of tumours as well as to aid in the detection of anatomical patterns. However, when cancers and metastases are smaller than 5 mm, these imaging modalities lose some of

their ability to accurately differentiate between benign and malignant tumours. AuNPs, or gold nanoparticles, act as a contrast agent.

Two methods can be used to create AuNPs: the Turkevich method's citrate reduction of aqueous $HAuCl_4$ and the Brust-Schifrin two-phase synthesis. $NaBH_4$ is used in these procedures as both a reducing agent and a binding agent that contains mercapto. The targeting ligand is either directly modified with a thiol to boost the potency of the nanoparticles or a targeting ligand is attached to modified GNPs with a coating material like lipid, DNA, or polymer [7].

Nanoparticles as Biochips and Salivary Biomarkers

Biochips are an emerging technology that follows the development of nanotechnology. Biochips are tiny devices that have microarrays—a miniature version of test sites—arranged on them. The National Institute of Dental and Facial Sciences in the United States started conducting cooperative research activities in the field of saliva diagnostics in 2002, which marked the beginning of early research in this area related to dental diagnosis. To find technically viable methods and help them move towards commercialization, the National Institute of Dental and Craniofacial Research develops microfluidic and microelectromechanical systems (MEMS) for saliva diagnosis. Saliva diagnostic methods utilising MEMS and nanoelectromechanical system biosensors have been developed as a result of this work. Excellent sensitivity and specificity are demonstrated by these instruments in the detection of analytes at the single-molecule level. A different biochip project is based on Weigum et al.'s research. Studies are being conducted to create cytology-on-a-chip technology that can identify premalignant and cancerous cells extremely accurately. Creating a sensor for OSCC diagnostics was their goal. The oral cytology sample is initially driven to the sensor on an integrated microfluidic platform by a pressure-controlled flow, and the cells that are relatively larger than the membrane pore are kept on the surface. To differentiate between the cytoplasm and the nucleus, the collected cells are labelled with an immunological reagent and a fluorescent dye. Also, the aggressive phenotypes of OSCC were studied by the use of cancer biomarkers such as the epidermal growth factor. Lastly, a 3D fluorescence microscopy scan of the membrane surface is performed on the labelled cells. Automatic picture analysis utilising open-source software comes next. The speed at which the diagnosis can be completed is an advantage of this method.

Nano-Based Molecular Imaging

Magnetic Resonance Imaging

Different kinds of nanoparticles have been used as targeted MRI contrast agents for cancer screening since the development of nanotechnology. These nano-contrast agents can identify cell surface markers, which can result in improved MRI contrast. Superparamagnetic iron oxide (SPIO) and ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles are the two types of nanoparticles that are most frequently investigated [8].

Optical Coherence Tomography

Through the direct modelling of ultrasound, optical coherence tomography (OCT) generates cross-sectional pictures of subsurface tissues. This can be used to search for dysplastic alterations and diagnose oral cancer early. One promising OCT contrast agent is gold nanoparticles. They can produce resonances that aid in preventing major tissue absorption, are easily synthesised, and are biocompatible [9].

Nanotechnology in Biomarker Detection

Examining tumour markers, including interleukin 6 (IL 6), VEGF, TNF-α, and EGF,

could be a potential approach to early cancer diagnosis and detection in the future. To identify oral cancer, a single biomarker detection technique has also been included. A study that was conducted has shown that the gold protein chip approach uses total internal reflection fluorescence microscopy (TIRFM) to detect TNF-α [10].

Cancer Therapy

A laser is used to produce atomic oxygen, which is used in cancer therapy to kill tumour cells. Because of its high cytotoxicity, molecular oxygen efficiently kills cancer cells. Cancer cells occupy the dye required to create atomic oxygen, and it only kills tumour cells that come into direct contact with laser light. Normal cells are unaffected. Hydrophobic dye molecules are encapsulated in porous nanoparticles to prevent them from spreading to other parts of the body and causing harm to normal cells [11].

Stem Cells and Nano-Engineering

A vast foundation in nanotechnology is provided for regenerative medicine. Nanomaterials and nanofibers are utilised to create the tissue that will be modified and to transfer DNA molecules in a regulated manner to the desired location. The field of regenerative medicine is being revolutionised by stem cells. and they play a huge part in cancer therapy. It is possible to biosynthesize mesenchymal, embryonic, and hematopoietic stem cells using current nanotechnological approaches.

Mesenchymal stem cells (MSCs) hold promise for cancer treatment due to their low immunogenicity and tumor-trophic migratory properties. Genetic engineering enhances MSCs' therapeutic potential by enabling the targeted delivery of tumor suppressor agents and nanoparticle drugs. MSC-derived exosomes facilitate intercellular communication and cargo transfer to tumour cells. Clinical trials are underway, supported by promising preclinical findings, underscoring the potential of engineered MSCs in tumor-targeted therapy [12].

Titanium dioxide nanotubes have been shown in studies to be responsible for stem cell induction, differentiation, and migration on the surface of rat mesenchymal stem cells. Treatment for several anomalies and illnesses has been discovered to benefit from the biosynthesis of stem cells in conjunction with imaging methods. Nanomaterials are used in organ transplantation, gene transfer, cellular differentiation, and stem cell labelling.

Table 1. List of Nano Drug Delivery Technologies

Technologies	**Materials**	**Forms**
Biologic	Peptides, lipids, vesicles, nanotube, rings	Nucleic acids, nanoparticles
Polymeric	Poly (lactic acid), poly (glycolic acid), poly (alkyl cyanoacrylate), poly (3-hydroxybutanoic acid), poly (organophosphazene), poly (ethylene glycol), poly(caprolactone), poly (ethylene oxide), poly (amidoamine), poly (l-glutamic acid), poly (ethyleneimine), poly (propylene imine	Vesicles, spheres, nanoparticles, micelles, dendrimers
Silicon-Based	Silicon, silicon dioxide	Porous, nanoparticles nanoneedles

Carbon-based Metallic	Carbon, gold, silver, palladium, platinum	Nanotubes, fullerenes nanoparticles, nanoshells

Drug Delivery Technologies [Table 1]

Types of Nanoparticles & their Role in Drug Delivery

Micelles

Micelles are composed of amphiphilic and amphipathic molecules and are amphipathic surface-active molecules. Its characteristic increases the solubility of hydrophobic medicines, improving their availability within the tissue. Its diameter is between 10-100 nm. They serve as medicinal agents, imaging agents, contrast agents, and drug delivery agents.

There are numerous possible uses for polymeric micelles in biomedicine. For example, polymeric micelles have been suggested for use in intra-parenteral drug administration, especially in the case of medications with low water solubility or as carriers for protein/peptide treatments. The physical entrapment of sparingly soluble drugs by micelle particles has several benefits as drug carriers. These include the ability to transport medications to the desired site of action at concentrations higher than their intrinsic water solubility, which increases bioavailability. Adding micelles also increases the drug's stability [13].

Liposomes

These formations are spherical and range in size from 30 nm to several microns. They are bilayers of lipids. They are employed to introduce therapeutic compounds that are hydrophilic into the aqueous phase. Because of their versatility, they can be modified with polymers, antibodies, and/or proteins, which makes it easier to include macromolecular medications into liposomes, such as crystalline metals and nucleic acids [14].

Dendrimers

These are macromolecules with repeating branches that have functional groups on the outside. The functional groups may have neutral positive or negative charges. These can also be used to change a material's composition and characteristics. As a result, they provide potential platforms for drug delivery, imaging, and biological applications. Drug delivery, site characterization, disease diagnosis (including cell death), disease detection, and therapy reporting are only a few of the multitasking abilities of dendrimers conveying different compounds and their branches [15].

Drugs, antibodies, sugar moieties, lipids, and other physiologically active substances have all been connected to dendrimer functional groups. Prodrugs, or dendrimer-drug conjugates, are compounds in which the drug is covalently bound to the dendrimer, either directly or by the use of a spacer or linker. A drug is released from a prodrug by an enzymatic or chemical cleavage of a hydrolytically labile link. Numerous studies have looked into drug conjugation to Polyamido amines (PAMAM) dendrimers as drug delivery methods. drug conjugation to Polyamidoamines (PAMAM) dendrimers for use in drug delivery mechanisms.

Nanotubes

When attached to peptides, surface-functionalized carbon nanotubes (CNTs) can be absorbed by mammalian cells and utilised as a vaccine delivery mechanism. Calcium carbonate or other sacrificial nanoscale templates are used to create a suspension of porous hollow silica nanoparticles, or PHSNPs. Porous silicon that has been implanted with platinum exhibits anticancer properties and is

being investigated as a potential therapy for silicon-based delivery systems.

Although they appear cylindrical, carbon nanotubes are made of a single layer of carbon atoms wrapped up into a sheet. They are made up of several nanotubes that are concentrically connected. They are employed as medication carriers because of their large surface area and high loading capabilities. Because of their special optical, mechanical, and electrical qualities, they are also utilised as biological sensors and imaging contrast agents.

A novel type of carbon nanostructures known as carbon dots (C-dots) was identified in 2004 and measured at least 10 nm. Low toxicity and other characteristics make C-dots suitable for medication delivery, bioimaging, and biosensors [16].

Metallic Nanoparticles

Metallic nanoparticles include, for example, iron oxide and gold nanoparticles. Iron oxide nanoparticles are composed of hydrophilic polymers like PEG or dextran and a magnetic core. In contrast, gold nanoparticles consist of a core of gold atoms encircled by negatively reactive groups on their surface, which can be functionalized through the addition of a monolayer of surface moieties acting as ligands. Metallic nanoparticles have found use in optical biosensors, laser-based therapy, imaging, and drug administration [17].

Quantum Dots

Quantum dots, also known as QDs, are fluorescent semiconductor nanocrystals that range in diameter from 1 to 100 nm. They have demonstrated potential in several biomedical applications, such as cellular imaging and drug delivery.

Nano-capsules

Nanospheres feature a solid polymeric matrix through which the medication can be dispersed, while nano-capsules have a polymeric wall with a liquid inner core that contains the drug [18].

Hydrogels

A hydrogel is a concoction of water and hydrophilic polymeric chains that can stretch, allowing drugs to pass through the gaps in the mesh to dissolve and disintegrate. Hydrogels are attractive for oral delivery because their polymeric chains can engage closely with saliva glycoproteins, producing a muco-adhesion phenomenon.

Liquid Crystals (LC)

Liquid Crystals (LC): By modifying the drug's release profile and lowering toxicity, liquid crystal systems improve therapeutic efficacy. LCs have the potential to treat cancer, particularly oral cancer.

Lipid Nanoparticles and Solid Polymeric Nanoparticles

Solid polymeric nanoparticles and lipid nanoparticles are nanoscale solid structures composed of proteins, high-melting-point lipids, or natural or manufactured polymers. Medications could be attached to the matrix's surface or incorporated inside it.

Self-Emulsifying Drug Delivery Systems and Nanoemulsions (Sedds)

Drug delivery systems and nanoemulsions that self-emulsify (SEDDS): Two immiscible liquids combine to form nanoemulsions, with one of the liquids dispersing as droplets in the other. In an O/W emulsion, the aqueous phase disperses the oil and surfactants. SEDDS are composed of pharmaceuticals that are dissolved in oils and stabilised by surfactants, which, when exposed to water, create o/w micro- or nano-emulsions in situ.

Microspheres

Microspheres: Made of polymers, lipids, or proteins, microspheres are spherical particles with a few micrometres in diameter.

Organic Nanocarriers

Organic nanocarriers: It is claimed that organic nanocarriers can integrate a variety of

hydrophilic and hydrophobic medications and can adjust in shape. They have a greater capacity for loading medications and are biocompatible. Hydrogels have a strong affinity for water, which makes them widely employed in applications involving the delivery of medications. These hydrogel systems react to chemical or physical stimuli and might be neutral or ionic. Polymers, both synthetic and natural, can be used to make them [19].

Inorganic Nanocarriers

Used for drug conjugation of biomacromolecules. The inorganic nanocarriers are categorized as follows:

1. Carbon nanotubes (CNTs)
2. Noble metal NPs
3. Silver-based NPs
4. Gold-based NPs
5. Magnetic NPs (Fe_3O_4 NPs)
6. ZnO NPs
7. Copper oxide NPs (CuO NPs)

Chronic myeloid leukemia, characterized by the breakpoint cluster region/ accidental bowel leakage (BCR/ABL fusion gene), is treated primarily with tyrosine kinase inhibitors like imatinib. Emerging nanomedicine explores inorganic nanoparticles as potential therapeutic agents, addressing drug resistance and enhancing treatment efficacy [20] [Figure 2].

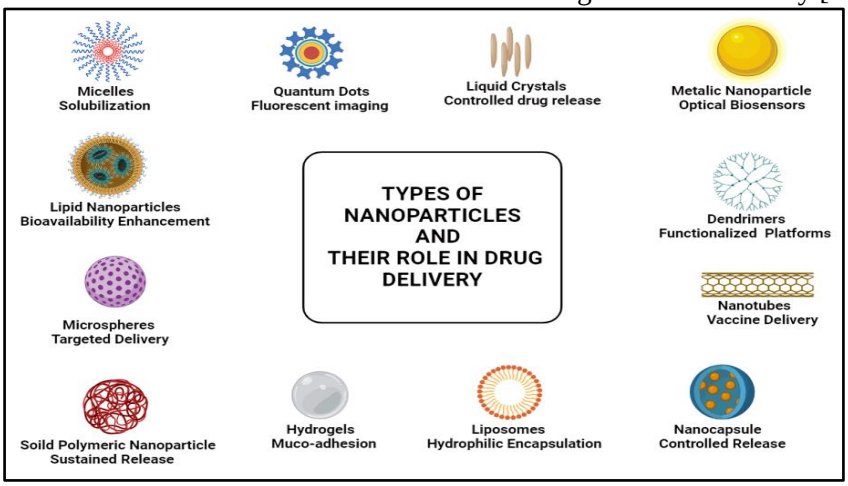

Figure 2. Types of Different Nanoparticles and their Role in Drug Delivery

Microdevices in Drug Delivery [13]

For many years, formulas for the oral administration of medications, including tablets, emulsions, solutions, and capsules, have been developed. Long-standing applications of polymers and nanotechnology have led to the creation of carriers for targeted and regulated drug delivery. Numerous novel drug delivery advancements, including the use of liposomes and enhanced polymeric nanoparticles, have been made possible by this technique. Even so, the majority of the application of pH-responsive carriers has been in research. The medication is safeguarded in the stomach and then delivered into the intestine in a controlled manner for absorption. These formulation techniques produce polydispersity even though they are frequently successful in producing particles for the delivery of oral medications. Additionally, they don't always provide sufficient oral bioavailability and aren't always sufficient for drug protection in the GI system. The oral delivery of different drugs still raises several unanswered questions. Moreover, it is sometimes difficult to achieve adequate oral bioavailability for proteins and peptides utilising the previously outlined formulation approaches. Consequently, there has been a lot of interest in better medication delivery systems that make use of 3D printing and microfabrication methods, for instance [21].

Design of the Device

The devices used for drug delivery can be divided into three main classes:

1. Microneedle patches,
2. Microwells and
3. Microcontainers

The concept behind them all is the same: build a structure that has a drug implanted or enclosed inside of it. The ability to manufacture microdevices depends on the microfabrication techniques that are accessible, and 3D printing is increasingly one of such approaches.

Microneedle Patches

Micro patches served as the model for transdermal patches. They have a low aspect ratio, are flat, and have a small drug reservoir measured in micrometres. Devices that are disc-shaped, thin, and flat have been demonstrated to have the highest surface area in touch with the GI tract. Compared to typical medication formulations, micro patches can have a longer contact time with the intestinal membrane in the continuous flow of the gut, enabling the medicine to be given over a longer period [22].

Microwells and Microcontainers

The microwells and micro containers have substantially greater aspect ratios than the patches, although they are similar in size (100–300 m) and architecture. The micro containers are built on top of the surface layer, whilst the wells are attached to it. This is how they differ from each other. The microwells can be used to assess new drug-loading techniques and have been employed as a proof-of-concept design for testing innovative fabrication processes in novel materials. Numerous intriguing in vivo investigations are employing micro containers. Because of their mucoadhesive nature and longer retention period, the medication can be kept in the device until it reaches the intestine. The devices' design permits unidirectional medication release, which avoids luminal drug loss [23].

Drug Delivery Alternatives

Beyond the common oral and injectable routes, there are other ways to administer drugs, such as transdermal, transmucosal, ocular, pulmonary, and implantation. To provide alternative pharmaceutical delivery, biologics, polymers, silicon-based materials, carbon-based materials, and metals are frequently used. These materials have structures at the micro and, more recently, nanoscales.

Barriers to Oral Drug Delivery

The severe acidic pH of the stomach (pH 1-2) and the enzymes pepsin and other digestive juices that break down and eliminate some active pharmaceutical ingredients are the first biological barriers that drugs encounter after being taken orally. Therefore, it is essential to protect kids from these unfavourable situations. The literature has documented the use of a variety of pH-sensitive hydrogels to address acidic and enzymatic environments (e.g., pH-sensitive hydrogel for insulin delivery). The duodenum and small intestine have different pHs, thus it's important to regulate the delivery system's pKa to prevent the active component from accidentally releasing. It has been demonstrated that carboxymethyl chitosan (CMC), polyacrylamide-grafted-guar gum (PAAm-g-GG) co-polymer particles, and poly(lactic-co-glycolic) acid (PLGA) nanoparticles can all stop unwanted drug release after oral delivery.

Oral administration strategies need to overcome the extracellular biological barrier of strong connections between epithelial cells. The delivery systems' capacity to cross this barrier is greatly influenced by their size, form, and chemical makeup. Hydrophobic pharmaceuticals are mainly taken via the transcellular route, while those that are hydrophilic are primarily taken via the paracellular route. Another mechanism linked to intestinal drug transport is receptor-mediated endocytosis. Drug diffusion may be delayed, for example, if intestinal membrane lectin binds

to different drug-loaded polymeric matrices. Moreover, a great deal of research has discovered a connection between size-dependent receptor-mediated phagocytosis and endocytosis. It is reported that phagocytosis internalises particles bigger than one millimetre. It is reported that phagocytosis internalises particles bigger than one millimetre. Conversely, pinocytosis is associated with fluid internalisation, a process whereby receptor-mediated mechanisms absorb minuscule particles.

The next barrier is the mucus layer, which keeps the cargo from interacting with the epithelial layer. Mucus, mostly composed of mucins (e.g., MUC1, MUC2, MUC13, MUC16), is secreted by goblet cells. Under homeostatic circumstances, the stomach's mucus layer is thick and serves as a physical barrier to shield the epithelium from damage, which may set off innate and adaptive immune reactions. Hydrophilic medications are absorbed via the paracellular route, while hydrophobic pharmaceuticals are absorbed through the transcellular route [24-26].

Among the others is the disruption in bioavailability brought on by pH variations. When compared to other methods of overcoming the physiological barrier, nanotechnology stands out for its ability to fully address the difficulties associated with administering drugs orally.

Surface Properties of Nanoparticles

The surface chemical features of the nanoparticles affect their water dispersibility, drug entrapment, and even their interaction with biological systems. As mentioned before, the stability and dispersibility of nanoparticles are greatly influenced by the way their surface charges interact with one another. Moreover, the biocompatibility, biodistribution, and clearance of nanoparticles are all influenced by their surface chemistry, which also affects how well they interact with biological systems. In certain investigations, these interventions have been altered due to chemical modifications made to the surface properties of nanoparticles, including the type of the particles, molecular weight, and polarity.

Potential Risks of Nanotechnology

Host Mechanism

Several routes exist for nanoparticles to enter the body, including injection during surgery, ingestion, absorption through the skin, and inhalation. Because of their high mobility, nanoparticles may be able to pass through the blood-brain barrier after entering the body. By stimulating phagocytes to hyperactivity, nanoparticles appear to activate the immune system. The body may experience stress reactions and inflammation, which will erode its defences against more dangers. Due to their large surface area, they have the potential to adsorb onto the surface of cells or fluids they come into touch with, disrupting biological and physiological processes in the body, such as enzyme regulatory mechanisms.

Effect on Nature

High energy needs for the production of nanoparticles may have an impact on the environment by releasing persistent and hazardous nanoparticles. Low rates of recovery and limited possibility for recycling. There aren't any strong indications of any other environmental repercussions.

Marketing

These cutting-edge innovations may eventually be absorbed by corporations thanks to nanotechnologies. Big companies are controlling the market by securing patents on inventions at the nanoscale. To date, more than 3,500 patents about nanotechnology have been granted, and the total is rising yearly.

Conclusion

Nanotechnology is revolutionizing drug delivery, promising breakthroughs in pharmaceuticals. The next phase of nano drug

delivery systems hinges on large-scale production of nano or micro materials, requiring collaboration between nanoengineering and drug delivery science while considering prevailing hazards. Nanotechnology paves the way for innovative drug delivery systems. In conclusion, nano-drug delivery systems represent a significant advancement in pharmaceutical sciences, overcoming the limitations of conventional methods. By leveraging nanometer-sized drug particles, researchers optimize therapeutic outcomes with enhanced solubility, rapid dissolution, and improved adherence to biological surfaces. The transformative potential of nanotechnology in drug delivery addresses both traditional and innovative challenges, shaping the future of medicine. As scientists further explore nanotechnology's applications, nano drug delivery systems are poised to revolutionize treatments, offering safer and more effective options for diverse diseases and conditions.

Reference

[1]. Sim, S., & Wong, N. K., 2021. Nanotechnology and its use in Imaging and Drug Delivery (Review). *Biomedical Reports*, 14(5), 1–9. https://doi.org/10.3892/BR.2021.1418/HTML

[2]. Mitchell, M. J., Billingsley, M. M., Haley, R. M., Wechsler, M. E., Peppas, N. A., & Langer, R., 2021. Engineering Precision Nanoparticles for Drug Delivery. *Nature Reviews. Drug Discovery*, 20(2), 101–124. https://doi.org/10.1038/S41573-020-0090-8

[3]. Wang, X., Xia, Z., Wang, H., Wang, D., Sun, T., Hossain, E., Pang, X., & Liu, Y., 2023. Cell-Membrane-Coated Nanoparticles for the Fight Against Pathogenic Bacteria, Toxins, and Inflammatory Cytokines Associated with Sepsis. *Theranostics*, 13(10), 3224–3244. https://doi.org/10.7150/THNO.81520

[4]. Han, X., Gong, C., Yang, Q., Zheng, K., Wang, Z., & Zhang, W., 2024. Biomimetic Nano-Drug Delivery System: An Emerging Platform for Promoting Tumor Treatment. *International Journal of Nanomedicine*, 19, 571–608. https://doi.org/10.2147/IJN.S442877

[5]. Bayda, S., Adeel, M., Tuccinardi, T., Cordani, M., & Rizzolio, F., 2020. The History of Nanoscience and Nanotechnology: From Chemical–Physical Applications to Nanomedicine. *Molecules*, 25(1), 112. https://doi.org/10.3390/molecules25010112

[6]. Günday Türeli, N., & Türeli, A. E., 2020. Industrial Perspectives and Future of Oral Drug Delivery. *Nanotechnology for Oral Drug Delivery: From Concept to Applications*, 483–502. https://doi.org/10.1016/B978-0-12-818038-9.00016-8

[7]. Neel, E. A. A., Bozec, L., Perez, R. A., Kim, H. W., & Knowles, J. C., 2015. Nanotechnology in Dentistry: Prevention, Diagnosis, and Therapy. *International Journal of Nanomedicine*, 10, 6371–6394. https://doi.org/10.2147/IJN.S86033

[8]. Xue, S., Qiao, J., Pu, F., Cameron, M., & Yang, J. J., 2013. Design of a Novel Class of Protein-Based

Acknowledgement

We would like to express our sincere gratitude to the Centre for Global Health Research, Saveetha Medical College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai, India, for providing support for this research work. Finally, we thank all those who contributed to this work, directly or indirectly, and helped make this research possible.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

The authors have no relevant financial or non-financial interests to disclose.

Magnetic Resonance Imaging Contrast Agents for the Molecular Imaging of Cancer Biomarkers. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, 5(2), 163–179. https://doi.org/10.1002/WNAN.1205

[9]. Pandarathodiyil, A. K., 2020 Nanotechnology Based Imaging Modalities in Oral Cancer: A Brief Review. *Nanotechnology*. 7(17). https://doi.org/10.31838/jcr.07.17.406

[10]. Chen, X. J., Zhang, X. Q., Liu, Q., Zhang, J., & Zhou, G., 2018. Nanotechnology: A Promising Method for Oral Cancer Detection and Diagnosis. *Journal of Nanobiotechnology*, 16:1, 16(1), 1–17. https://doi.org/10.1186/s12951-018-0378-6

[11]. Zaib, S., Iqbal, J., 2019. Nanotechnology: Applications, Techniques, Approaches, & the Advancement in Toxicology and Environmental Impact of Engineered Nanomaterials. *Importance & Applications of Nanotechnology*. 8. Nanotechnology: Applications, Techniques, Approaches, & The Advancement in Toxicology and Environmental Impact of Engineered Nanomaterials (meddocsonline.org)

[12]. Shams, F., Pourjabbar, B., Hashemi, N., Farahmandian, N., Golchin, A., Nuoroozi, G., & Rahimpour, A., 2023. Current Progress in Engineered and Nano-Engineered Mesenchymal Stem Cells for Cancer: From Mechanisms to Therapy. *Biomedicine & Pharmacotherapy*, 167, 115505. https://doi.org/10.1016/j.biopha.2023.115505

[13]. Ghezzi, M., Pescina, S., Padula, C., Santi, P., Del Favero, E., Cantù, L., & Nicoli, S., 2021. Polymeric Micelles in Drug Delivery: An Insight of the Techniques for their Characterization and Assessment in Biorelevant Conditions. *Journal of Controlled Release*, 332, 312–336. https://doi.org/10.1016/J.JCONREL.2021.02.031

[14]. Patel, R. J., Patel, A. A., Trivedi, N., Pandya, V., Alexander, A., Patel, V., Prajapati, B. G., & Parejiya, P. B., 2024. Liposomes as Carrier for Drug Delivery in Alzheimer's Disease. *Alzheimer's Disease and Advanced Drug Delivery Strategies*, 153–179. https://doi.org/10.1016/B978-0-443-13205-6.00008-X

[15]. Rastogi, V., Yadav, P., Porwal, M., Sur, S., & Verma, A. 2024. Dendrimer as Nanocarrier for Drug Delivery and Drug Targeting Therapeutics: A Fundamental to Advanced Systematic Review. *International Journal of Polymeric Materials and Polymeric Biomaterials*. https://doi.org/10.1080/00914037.2022.2158334

[16]. Santhosh, H., Treasa Sabu, S., Dharan, S. S., & Info, A., 2021. Carbon Nanotubes: A Promising Novel Drug Delivery System. *International Journal of Research in Pharmaceutical Sciences and Technology*, 2(3), 67–72. https://doi.org/10.33974/ijrpst.v2i3.256

[17]. Neha Desai, Momin, M., Khan, T., Gharat, S., Ningthoujam, R. S., & Omri, A., 2021. Metallic Nanoparticles as Drug Delivery System for the Treatment of Cancer. *Expert Opinion on Drug Delivery*, 18(9), 1261–1290. https://doi.org/10.1080/17425247.2021.1912008

[18]. Marto, J., Ribeiro, H. M., & Almeida, A. J., 2020. Starch-Based Nanocapsules as Drug Carriers for Topical Drug Delivery. *Smart Nanocontainers: Micro and Nano Technologies*, 287–294. https://doi.org/10.1016/B978-0-12-816770-0.00017-4

[19]. Hussein Kamareddine, M., Ghosn, Y., Tawk, A., Elia, C., Alam, W., Makdessi, J., & Farhat, S., 2019. Organic Nanoparticles as Drug Delivery Systems and their Potential Role in the Treatment of Chronic Myeloid Leukemia. 18. https://doi.org/10.1177/1533033819879902

[20]. Ghosn, Y., Kamareddine, M. H., Tawk, A., Elia, C., El Mahmoud, A., Terro, K., El Harake, N., El-Baba, B., Makdessi, J., & Farhat, S., 2019. Inorganic Nanoparticles as Drug Delivery Systems and their Potential Role in the Treatment of Chronic Myelogenous Leukaemia. *Technology in cancer research & treatment.* 18:1533033819853241. https://doi.org/10.1177/1533033819853241

[21]. Zeng, Q., Li, G., & Chen, W., 2023. Ultrasound-Activatable and Skin-Associated Minimally Invasive Microdevices for Smart Drug Delivery and Diagnosis. *Advanced Drug Delivery Reviews*, 203, 115133. https://doi.org/10.1016/J.ADDR.2023.115133

[22]. Rad, Z. F., Prewett, P. D., & Davies, G. J., 2021. An Overview of Microneedle Applications, Materials, and Fabrication Methods. *Beilstein Journal of Nanotechnology*, 12:77, 12(1), 1034–1046. https://doi.org/10.3762/BJNANO.12.77

[23]. Mazzoni, C., & Nielsen, L. H., 2020. Microdevices to Successfully Deliver Orally Administered Drugs. Nanotechnology for Oral Drug Delivery: From Concept to Applications, 285–315. https://doi.org/10.1016/B978-0-12-818038-9.00012-0

[24]. Rewatkar, P., Kumeria, T., & Popat, A., 2020. Size, Shape and Surface Charge Considerations of Orally Delivered Nanomedicines. Nanotechnology for Oral Drug Delivery: From Concept to Applications, 143–176. https://doi.org/10.1016/B978-0-12-818038-9.00005-3

[25]. De Rubis, G., Paudel, K. R., Corrie, L., Mehndiratta, S., Patel, V. K., Kumbhar, P. S., Manjappa, A. S., Disouza, J., Patravale, V., Gupta, G., Manandhar, B., 2024. Applications and Advancements of Nanoparticle-Based Drug Delivery in Alleviating Lung Cancer and Chronic Obstructive Pulmonary disease. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 397(5), 2793-833. https://doi.org/10.1007/s00210-023-02830-w

[26]. Mohammadzadeh, M., Zarei, M., Abbasi, H., Webster, T. J., Beheshtizadeh, N., 2024. Promoting Osteogenesis and Bone Regeneration Employing Icariin-Loaded Nanoplatforms. *Journal of Biological Engineering*, 18(1), p.29. https://doi.org/10.1186/s13036-024-00425-4