# NANO-DRUG DELIVERY SYSTEMS FOR THE ENHANCEMENT OF BIOAVAILABILITY AND BIOACTIVITY

**Abstract**

Bioavailability refers to the fraction of administered drug that reaches the systemic circulation in an unchanged form and is available to exert its therapeutic effects. It is the rate and extent to which a drug is absorbed from its dosage form and becomes available at the site of action. Bioavailability and bioactivity both the concepts are related to the effectiveness of drugs. The term pharmacological response is directly related to our body's blood plasma levels. Thus, bioavailability is defined as the rate and extent (amount) of absorption of an unchanged drug from its dosage form. An ideal drug must have to live within the body and must not reform the properties of biomolecules apart from target molecules. Nano drug delivery systems, also known as nanocarriers or nanomedicines, refer to a class of pharmaceutical formulations that utilize nanotechnology to deliver drugs or therapeutic agents to specific target sites within the body. Nanotechnology offers precise control over the design and fabrication of drug delivery systems. By encapsulating drugs within nanoparticles or nanocarriers, their stability, solubility, and targeted delivery can be improved. Nanoparticles can protect drugs from degradation, enhance their absorption, and enable controlled release, thus improving bioavailability. Nanoparticles can be engineered to specifically target diseased cells or tissues while sparing healthy ones. Functionalized nanoparticles can be designed to attach to specific molecules or receptors found on cancer cells, for instance. This targeted approach reduces systemic side effects and enhances the bioactivity of therapeutic agents. Bioactive loaded

**Authors**

**Dr. Ratna Jyoti Das**
Institute of Pharmacy, Assam Medical College and Hospital
Dibrugarh, Assam, India.
ratnajyotidas@gmail.com

**Ms. Purabi Das**
Department of Pharmaceutical Sciences
Dibrugarh University
Assam, India.
purabidas998@gmail.com

**Dr. Kalyani Pathak**
Department of Pharmaceutical Sciences
Dibrugarh University
Assam, India.
kalyakster@gmail.com

**Mrs. Parimita Kalita**
School of Pharmacy
The Assam Kaziranga University
Jorhat, Assam, India.
parikalita1991@gmail.com

nanotechnology has emerged as a promising approach for enhancing drug delivery systems. Nanotechnology involves the manipulation and engineering of materials at the nanoscale level to create carriers capable of encapsulating and delivering bioactive compounds. These nanocarriers offer several advantages, including improved drug stability, controlled release, targeted delivery, and enhanced bioavailability. The progress achieved thus far in nano-drug delivery systems offers a glimpse into the future of pharmaceutical sciences, with the potential to revolutionize the treatment landscape and improve patient outcomes across a wide range of medical conditions. Embracing the promise of nano-based drug delivery represents a promising pathway towards the realization of safer, more efficient, and patient-tailored therapies in modern medicine.

**Keywords**: Nano Drug delivery system, Bioavailability, Nanocarriers, Bioactivity, Nanotechnology.

 

## I. INTRODUCTION

A drug which is obtained from plant, animal or any other synthetic sources exerts its therapeutic efficacy by delivering its active medicaments to specific site of action to obtain required pharmacological response. Mostly, drugs acts by binding with targeted receptors or enzymes and inhibiting or otherwise transforming their pharmacological activities. The therapeutic result of any constituents may be obtained from numerous sources which depend upon the criteria to deliver the medicament to its site of action at a specific rate to exert the desired pharmacological response. The ability of the dosage form to elicit its therapeutic response is termed as physiologic availability, biological availability, or sometimes simply as bioavailability [1]. Bioavailability refers to the extent and rate at which a drug or a substance is absorbed into the bloodstream and becomes available at the site of action or metabolism. In other words, it is a critical concept of pharmacology, as it directly influences the pharmacological effectiveness of a drug. Bioavailability and bioactivity both the concepts are both related to the effectiveness of drugs. The term pharmacological response is directly related to our body's blood plasma levels. Thus, bioavailability is defined as the rate and extent (amount) of absorption of an unchanged drug from its dosage form. An ideal drug must have to live within the body and must not reform the properties of biomolecules apart from target molecules [2]. They are wielded to treat almost all diseases and save human beings in fight against numerous infectious diseases and widespread [3]. Modern drug dosage forms have evolved significantly to provide more effective and convenient ways of treating diseases. In spite of all these, some more common problems associated with these dosage forms like their efficacy, bioavailability, bioactivity, toxicity, biocompatibility, side-effects, and inactivity problems are the drug development process [4]. It’s essential to consider these limitations and tailor the choice of dosage form to the specific needs and characteristics of each patient and medication. In recent days, advancement in drug delivery technologies continues to address various highly sophisticated engineered nanoparticles that have been exploited to overcome these problems and enhance overall treatment. A drug-delivery system (DDS) is a formulation or device that allows the introduction of active ingredients into the body in order to improve not only their efficacy but also their safety, by controlling the drug amount, time, and release in the site of action, crossing the biologic membranes to get to the therapeutic target [5]. Different factors influence bioavailability such as route of administration, drug formulation, metabolism, and excretion. Different routes of administration have different bioavailability characteristics. The most common routes of drug administration are oral (swallowing a tablet or capsule) and intravenous administration into the bloodstream which produces 100% bioavailability since the drug is directly administered into the systemic circulation. Oral administration has lower bioavailability due to factors such as incomplete absorption in the gastrointestinal tract and first-pass metabolism in the liver [6].

Bioactivity is concerned with the drug's ability to produce the intended biological response. There are some common attributes that create challenges for DDS related to bioavailability.

- **Poorly Soluble Drugs:** Drugs with low water solubility may have limited dissolution in the gastrointestinal tract, leading to poor absorption and reduced

 

bioavailability. DDS must address strategies to enhance drug solubility or employ alternative routes of administration.

- **First-Pass Metabolism:** Drugs administered orally are subject to first-pass metabolism in the liver before reaching the systemic circulation. This can significantly reduce bioavailability. DDS can aim to bypass first–pass metabolism through alternative routes or develop prodrugs that undergo less metabolism.

- **Gastric Degradation:** Some drugs are susceptible to degradation in the acidic environment of the stomach, reducing their bioavailability. DDS must protect drugs from gastric degradation or use alternative routes of administration.

- **Fast Excretion:** The fast excretion process refers to the rapid removal of waste products and toxins from the body. This is facilitated by organs like the kidneys, which filter blood to remove waste and excess substances, producing urine that is then excreted from the body. The body's efficiency in eliminating waste is crucial for maintaining overall health and preventing the buildup of harmful substances [7].

- **Fraction of Drug Required Zone:** Some specific tumor cells require more amount of drug accumulation in our body, which is high as compared to normal cells for effective cancer treatment [8].

Bioactivity is an approach that refers to the ability of a drug to exert its intended pharmacological or therapeutic effect on the target site of action. In other words, it is the drug's ability to bind to its receptor or target and initiate the desired physiological response. The bioactivity associated with drug delivery symptoms refers to the issue of maintaining the therapeutic efficacy of the drug throughout the delivery process [9].

The current challenges associated with drug development and delivery which pharmaceutical companies are facing related to bioactivity is

- **Targeting Specificity:** The drug should be delivered specifically to the target site to maximize bioactivity and minimize off target effects. Achieving precise targeting is challenging especially when dealing with complex biological barriers and heterogeneous diseases.

- **Drug Stability:** Many drugs are sensitive to environmental conditions, such as temperature, light, and humidity, which can cause degradation and loss of bioactivity. Ensuring the stability of the drug within the DDS during storage and transportation is crucial.

- **Drug Release Kinetics:** Controlling the rate and duration of drug release from the DDS is essential to achieve the desired therapeutic effect. If the drug is released too quickly, it may lead to adverse effects or inadequate treatment, whereas slow release may result in suboptimal bioactivity.

- **Drug Interactions:** The presence of other components within the DDS or the body, such as enzymes or other drugs, may interact with the drug and alter its bioactivity. Drug interactions can lead to reduced effectiveness or unexpected side effects.

- **Biocompatibility and Toxicity:** Some DDS materials or drug formulations may trigger immune responses or exhibit toxicity, compromising the bioactivity of the drug and potentially causing harm to the patient.

- **Patient Variability:** Differences in patient's physiology, metabolism and health conditions can influence the bioactivity of the drug delivered by the DDS. Personalized medicine approaches may be required to account for these variations.

1. **Nanotechnology**: Nanotechnology is a branch of advanced technology that deals with the manipulation and control of matter on an atomic and molecular scale, typically at dimensions between 1 and 100 nanometers. Nanotechnology is the science of the small. Nanotechnology has the ability to observe measure, manipulate, assemble, control, and manufacture particulate at the nanometer scale [10]. Researchers are interested in the nanoscale level due to the numerous advantages of this scale that the properties of materials can be very significantly from those at a larger scale. In the nanoscale, materials, and devices exhibit some unique properties and symptoms. Since the last decade, nanoparticles have gained popularity for applications in biology and medicine. Nanotechnology has the technical ability to retransform the various pharmacokinetic properties, biopharmaceutical properties. Depending upon the morphology, size, composition, and physical-chemical and biological properties of nanoparticles, they played a significant role in the field of drug delivery systems. Nanotechnology offers different manipulations over the drug design, drug synthesis, and fabrication of drug delivery systems. Drug stability, solubility, and targeted delivery can be improved by encapsulating that drug within nanocarriers or nano-matrix [11]. The diverse technological benefits of nanoparticles used as drug carriers are high stability, high carrier capacity, feasibility of incorporation of both hydrophilic and hydrophobic substances, etc. In the context of medicine, nanotechnology has given rise to treatment with increased bioavailability, reduces the frequency of administration, and promotes the targeting of drugs to specific sites. Nanomaterials have wider applications as a revolutionary technology across various industries for genetic tissue engineering, electronics, medical device designing, and the encapsulation and delivery of drugs, energy, and materials science. In the recent context of the drug delivery system, the development of control release targeted drug delivery includes the presence of active drug in the target area of the body such as cancerous cells, and sustained release of the dosage form in which the drug is released over an extended period of time in a controlled manner from the dosage form [12].

2. **Nanodrug Delivery System:** Nano drug delivery systems, also known as nanocarriers or nanomedicines, refer to a class of pharmaceutical formulations that utilize nanotechnology to deliver drugs or therapeutic agents to specific target sites within the body. Nanotechnology in medicine concept was first evolved by Dr. Richard P. Feynman

 

in the year of 1950. One of the most diverse applications of nano in medicine is in drug delivery systems. It is recently hypothesized that most conventional DDS have poor bioavailability and low aqueous solubility limiting their absorption and retention within biological systems. However, these nano-drug delivery systems are designed to improve the efficacy and safety of drug delivery by enhancing the drug's pharmacokinetic properties, reducing side effects, and increasing drug bioavailability and bioactivity. Nano-drug delivery systems (NDDS) are complex and diversified systems. some common features associated with NDDS are specified below [13].

- **Particle Size:** Nanoparticles used in NDDS typically have a size range of 1 to 100 nanometers. This small size helps in vivo distribution, biological profile, toxicity studies, and targeting ability of these nano delivery systems. Moreover, Nanosize immensely promotes drug loading, drug release, and stability profile. It has been reported that nanomaterials due to their small size allows for enhanced permeability and retention effect, enabling them to accumulate in tumor tissues [14].

- **Surface Modification:** Nanoparticles surface charge is usually measured in terms of the nanomaterials zeta potential which reflects the electrical charges of particles [15]. Drug loading also depends on surface charge. Surface charges can be modified with ligands, antibodies, or other molecules to enhance targeting and interaction with specific cells or tissues. This helps improve the selectivity of drug delivery [16].

- **Drug Loading Capacity:** A highly efficient capability of nano drug delivery systems is that they have a high drug-loading capacity without aggregation. High drug loading capacity can be determined by certain factors such as the type of nanoparticle, drug, and manufacturing processes. More drug loading results in decreasing the administration of frequency of doses [17]. Efficient drug loading and high entrapment efficiency directly rely on several factors like drug solubility in the nanoparticles, dispersible medium, drug molecular weight (MW), etc. Surfaces can be modified with ligands antibodies, or other molecules to enhance targeting and interaction with specific cells or tissues. [18].

- **Targeting:** Active Targeting involves attaching ligands or antibodies to the nanoparticle surface that can recognize specific receptors on the target cells, improving chemotherapy by nanomaterials availing a highly specific cancer treatment. Active or passive targeting mechanisms can be incorporated to direct the NDDS to specific cells or tissues. Ligands or antibodies might be used for active targeting [19].

- **Stability:** NDDS should maintain their structure and drug cargo stability during storage and transportation.

- **Biodegradability:** Biodegradable NDDS can be designed in a controlled manner after releasing their payload, minimizing long-term accumulation.

 

- **Release Kinetics:** NDDS can be engineered to release drugs in a controlled manner, which can be tuned based on the nanoparticle material and design. This controlled release can lead to prolonged therapeutic effects and reduced side effects.

3. **Different Nano Drug Delivery Systems:** There are several types of nano-drug delivery systems that have been developed and studied for efficient drug delivery. Here are some commonly used nano-drug delivery systems.

- **Liposomes:** Liposomes are spherical vesicles composed of lipid bilayers. They can encapsulate both hydrophobic and hydrophilic drugs within their core or lipid layers. Liposomes offer excellent biocompatibility, controlled drug release, and the ability to target specific tissues. They have been extensively studied for drug delivery in various applications [20].

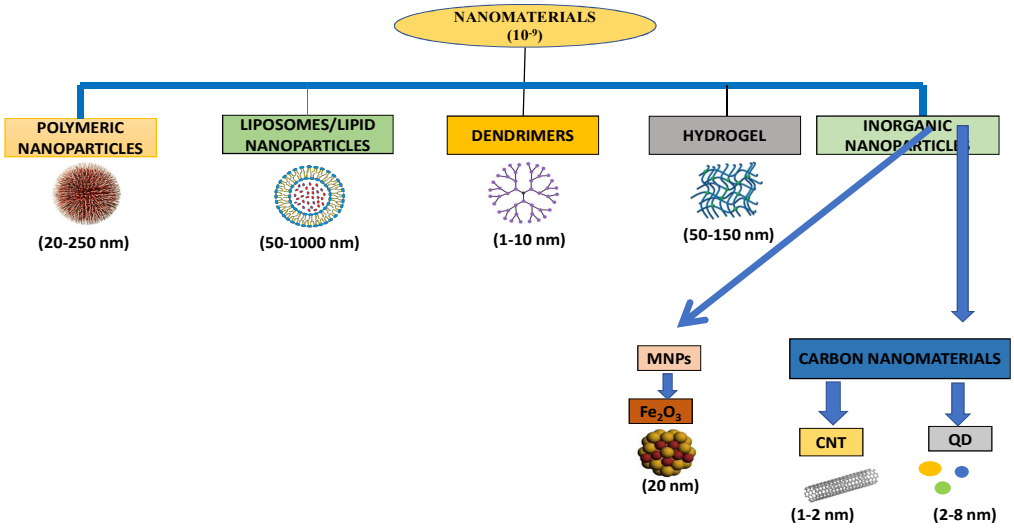


**Figure 1:** Classification of Different Nano Drug Delivery Formulations

- **Polymeric Nanoparticles:** These types of nanoparticles are commonly made up from biodegradable polymers. They have the ability to improve the stability and time of circulation. Synthetic polymers have diverse characteristics like high purity and reproducibility. They have the properties of high drug efficacy and good sustained release. In context of cytotoxicity studies, they are completely biocompatible and biodegradable, suitable for numerous scale-up techniques. Polymeric nanoparticles are composed of biodegradable polymers, such as poly (lactic co glycolic acid) (PLGA) and polyethylene glycol (PEG). Polymeric nanoparticles can encapsulate drugs and provide sustained release over time. They also offer flexibility in particle size, surface modification, and drug loading, making them suitable for different drug delivery applications [21].

- **Nanocrystals:** Nanocrystals are submicron sized crystalline particles composed of drug molecules. They are typically formed using techniques such as precipitations or high –pressure homogenization. Nanocrystals improve drug solubility and dissolution rate, leading to enhanced bioavailability. They are particularly useful for poorly soluble drugs.

- **Carbon Nanotubes:** Carbon nanotubes are cylindrical structures composed of carbon atoms. They have high aspect ratios and unique mechanical and electrical properties. Carbon nanotubes can be functionalized with drugs or used as carriers to deliver therapeutics. They have shown potential in targeted drug delivery and imaging applications [22].

- **Metallic Nanoparticles:** Metallic nanoparticles, such as gold nanoparticles or silver nanoparticles, have been explored for drug delivery applications. They can be functionalized with drugs, antibodies, or other targeting moieties to achieve site-specific delivery. Metallic nanoparticles also have imaging properties that can be utilized for diagnostic purposes [23].

- **Dendrimers:** Dendrimers are highly branched macromolecules with a well-defined structure. Dendrimers are generally found in three-dimensional, nanosized, radially symmetrical molecule forms which are well-defined and homogeneous structure consisting of multiple branches. They have a core-shell architecture that can encapsulate drugs within their interior or conjugate drugs on their surface. Dendrimers offer high drug-loading capacity, precise control over size and surface functionalities, and potential for targeted delivery [24-26].

- **Mesoporous Silica Nanoparticles:** Mesoporous silica nanoparticles have a porous structure with a high surface area. They can be loaded with drugs within their porous framework and release them in a controlled manner. Mesoporous silica nanoparticles offer stability, biocompatibility, and the ability to encapsulate a wide range of drugs [26].

## 4. Impact of Nanodrug Delivery Systems on Bioavailability And Bioactivity

- **Drug Delivery:** Nanotechnology offers precise control over the design and fabrication of drug delivery systems. By encapsulating drugs within nanoparticles or nanocarriers, their stability, solubility, and targeted delivery can be improved. Nanoparticles can protect drugs from degradation, enhance their absorption, and enable controlled release, thus improving bioavailability.

- **Increased Surface Area:** Nanostructured materials possess a high surface-to-volume ratio, which enhances their interaction with biological systems. This increased surface area facilitates better absorption of nutrients, drugs, or therapeutic agents, thereby improving bioavailability [27].

- **Targeted Therapy:** Nanoparticles can be engineered to specifically target diseased cells or tissues while sparing healthy ones. Functionalized nanoparticles can be designed to attach to specific molecules or receptors found on cancer cells, for instance. This targeted approach reduces systemic side effects and enhances the bioactivity of therapeutic agents.

- **Improved Solubility:** Many bioactive compounds have poor solubility, limiting their absorption and effectiveness. Nanotechnology can improve solubility by formulating

 

these compounds into nanoscale structures, such as nanoparticles or nanosuspensions, which increase their surface area and improve their dissolution properties. This, in turn, enhances bioavailability [28].

- **Enhanced Cellular Uptake:** Nanoparticles can facilitate the cellular uptake of bioactive substances by overcoming barriers such as cell membranes. Surface modifications of nanoparticles can improve their interaction with cells, promoting efficient internalization and subsequent bioactivity.

- **Diagnostic Tools:** Nanotechnology-based sensors and imaging agents allow for highly sensitive and specific detection of biological molecules or markers associated with diseases. This enables early diagnosis and monitoring of treatment response, leading to improved bioactivity and better patient outcomes.

## II. PRESENTLY AVAILABLE NANO-DRUG DELIVERY SYSTEMS

Delivery of drugs Nanoparticles are often formed of a range of biodegradable materials, including natural or synthetic polymers, lipids, metals, or both, and are typically smaller than 100 nm in at least one dimension. Larger micromolecules could be used as effective delivery and transport systems because they are less successfully absorbed by cells than nanoparticles. For therapeutic purposes, drugs can either be attached to the particle surface or integrated into the particle matrix. A drug targeting system should have control over a medication's course once it enters the biological environment. Numerous investigations have been done on nano systems with different biological properties and compositions for use in gene delivery and medicine. [29].

Recently, many delivery techniques have been developed by scientists and researchers, and some of them are still being worked on today. Soluble modern drug delivery techniques include polymers, microparticles, Microcapsules, cells, cellular ghosts, lipoproteins, liposomes, micelles, dendrimers, hydrogels, and carbon nanotubes are examples of materials that are used. By conjugating these carriers with specific antibodies that target a specific location of interest, these carriers can be targeted. They are sensitive to pH and temperature changes and have a slow rate of degradation. The two categories of drug targeting are passive targeting and active targeting. Formulations based on nanoparticles have exhibited high solubility, controlled release, and superior pharmacokinetic and pharmacodynamic characteristics, surface charge and particle size, in order to create effective nanoparticle delivery systems size and shape are crucial factors [30].

### 1. Nano-Drug Delivery Systems

- **Hydrogel:** For the medication, therapeutic protein or vaccination antigen encapsulation and delivery, hydrogel nanoparticles based on hydrophobic polysaccharides are used. A new system that a promising compound is an extracellular polymer called cholesterol pullulan is excreted by the fungus *Aureobasidium pullulans* [31].

- **Emulsion:** Oil, water, and a surfactant are combined to form isotropic, thermodynamically stable systems known as emulsions. They include two phases

 

made up of a mixture of a surfactant, with or without a co-surfactant, which is used to emulsify and stabilize a mixture of two immiscible liquids. They might contain droplets with suspensions between 5 and 100 nm. It has been suggested that using microemulsions as medication delivery devices will improve drug penetration across biological membranes. Increased medication solubility and stability, as well as simplicity and affordability of scaling up, are some benefits of microemulsions [32].

- **Micelle:** To avoid quick renal clearance, polymeric micelles frequently have a restricted distribution, which allows them to build up in cancer tissues. They have a size of roughly 100 nm. The polymeric shell also limits their interactions with non-specific biological components. These nanostructures have tremendous promise for hydrophobic drug delivery because their interior core structure enables the assimilation of hydrophobic medicines, increasing their stability and bioavailability [29].

- **Liposome:** Hydrophilic and hydrophobic chemicals completely encapsulate one or more aqueous compartments in liposomes, which are small, spherical vesicles. They might be either one or several bilayers [29].

- **Dendrimer:** These a wide range of functional groups available for heavily branching macromolecules attaching drugs, imaging agents, and targeting molecules, as well as for their absorption. The ADME (absorption, distribution, metabolism, and elimination) profile depends on a number of structural characteristics. Dendrimers are three-dimensional, monodisperse, highly bifurcated structures. These structures are great candidates due of their globular shape and ease of usage as medication delivery systems with which their surface may be functionalized in a regulated manner [33].

- **Inorganic Nanoparticles:** Nanoparticles made of inorganic materials are known as inorganic nanoparticles. They are desirable for a variety of applications, including medication administration, due to distinctive features that are physical, chemical, and visual. Examples of inorganic nanoparticles include silver, gold, iron oxide, and silica particles. Surface plasmon resonance (SPR), which metal nanoparticles like silver and gold have, is one of the distinctive properties that liposomes, dendrimers, and micelles don't have. Strong biocompatibility and versatility in terms of surface functionalization were just a couple of the advantages they showed. [34].

- **Nanocrystal:** Nanocrystals are solid, pure medicine particles with a size between 1000 nm. These are only pharmaceuticals, free of any carriers, and are frequently stabilized with polymer-based stabilizers or surfactants. They can be used for biocompatibility and safety testing, combination therapies, imaging and theranostics, controlled drug release, targeted drug delivery, and drug encapsulation [31].

- **Nanoparticles Made of Carbon:** Two major types of carbon-based nanoparticles are fullerenes and carbon nanotubes (CNTs). CNTs are one kind of allotrope. Depending on the number of sheets in concentric cylinders, single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs) are two different forms of carbon with cylindrical frameworks. At least sixty carbon atoms make up the

 

hollow cage structure of the carbon allotrope known as a fullerene. The Buckminsterfullerene structure of C-60 has the shape of a hollow football. These carbon units are pentagonal and hexagonal in shape. They have practical applications because of their electrical conductivity, structure, high strength, and electron affinity [35].

- **Polymeric Nanoparticles:** Organic-based polymeric nanoparticles have a small size. Depending on the technique used for preparation, these are shaped like structures made of nano capsules or nanospheres [36].

- **Lipid-Based Nanoparticles:** Lipid nanoparticles are typically spherical in shape and range in diameter from 10 to 100 nm. It is made up of a matrix of soluble lipophilic compounds and lipid that surrounds a strong core. Emulsifiers and surfactants help to stabilize the outer core of these nanoparticles. These nanoparticles are utilized in the biomedical field as cancer treatment agents, drug delivery systems, and RNA release agents [36].

- **Quantum Dot:** Quantum dots (QDs), semiconductor nanocrystals, range in diameter from 2 to 10 nm. Size affects a variety of features, including absorbance and photoluminescence. The QDs have received a lot of attention in the field of nanomedicine due to their emission in the near-infrared region (less than 650 nm), which is distinct from standard organic dyes due to minimal tissue absorption and reduced light scattering. Additionally, diverse emission colors over a broad-spectrum range can be produced when QDs of various shapes and the same light source stimulate different shapes, sizes, or compositions. [37].

- **Biopolymeric Nanoparticle:** Nanosized biopolymeric nanoparticles are made of biopolymers, which are organic polymers generated from living things. These nanoparticle biocompatibility, and biodegradability and they are suited for use in a number of biologicals and medication delivery applications due to their versatility, and low toxicity. Drugs, genes and other bioactive compounds can be packaged inside biopolymeric nanoparticles to prevent them from degrading and to enhance their transport to target areas. Several typical biopolymers are employed to create biopolymeric nanoparticles such as chitosan, alginate, gelatin, albumin, starch, and hyaluronic acid [37].

- **Nano suspensions:** They are heterogeneous, surfactant-stabilized drug particle dispersions at the nanoscale. They are effective at binding to receptors. Permit excellent wide surface area which increases their bioavailability and dissolving rate, size, and little area. When medications are ineffective, they can be utilized. Having a high molecular weight, melting point, or taking the form of salt point prevents the creation of appropriate formulas [38].

2. **Ongoing Research on Nano-Drug Delivery Systems:** In order to increase medicine effectiveness, reduce adverse effects, and enable tailored therapeutic delivery, ongoing research on nano drug delivery devices is an important area of interest. Over the past ten years, nanotechnology has significantly impacted the medical industry through

 

advancements in drug delivery. Drug delivery based on nanotechnology aims to target the medication payload to the appropriate location and time at the proper (ideal) dosage [39].

- **Targeted Drug Delivery:** The development of targeted drug delivery systems using nanoparticles has recently been reviewed. Active or passive methods might be used to carry out targeted delivery. To be delivered to a tissue or cell-specific ligand via conjugation, medication or another delivery technique, the therapeutic agent must be actively targeted. Targeting can be done passively by encapsulating the drug in a macromolecule or by having a nanoparticle passively travel to the target organ. The enhanced permeability and retention (EPR) effect can be used to passively target drugs or medications encapsulated in nanoparticles and linked to macromolecules [32].

- **Stimuli-Responsive Systems:** Nanoscale drug delivery techniques that react to particular stimuli like temperature, pH, light or enzymes are being developed by scientists. In reaction to the unique circumstances, these systems can be created at the intended location to release medications under regulated settings. The potential for on-demand drug release and improved treatment efficacy is provided by stimuli-responsive devices. Nanoscale stimulus-responsive devices might be sensitive to particular endogenous stimuli, including reduced interstitial pH, increased glutathione levels or elevated levels of specific enzymes like matrix metalloproteinases [40-41].

- **Combination Therapy:** Research is now being done on the use of numerous therapeutic agents in a single nano drug delivery system. Researchers want to improve treatment outcomes and combat drug resistance by combining various medications with complementary mechanisms of action. Utilizing nanoscale drug delivery devices, combination therapy can increase drug synergy, lower systemic toxicity, and enable the sustained release of numerous medications [42-43].

- **Gene Delivery:** Researchers are looking into using nanoparticles as carriers for gene therapy. In order to rectify genetic diseases or modify gene expression for therapeutic purposes, researchers are looking at the transfer of therapeutic genes to target cells using nanoparticles. For effective and targeted gene delivery, strategies including either viral or non-viral vectors are used, such as lipid nanoparticles or polymeric nanoparticles. Although there are several methods for delivering genes, nano-carrier systems appear to be a great choice for effective gene delivery. One of the most crucial aspects in gene therapy is making the right carrier system selection. Numerous nanocarrier systems including polymeric, liposome, dendrimer, metallic, gelatine, quantum dots, protein, graphene nanocarriers, stimuli response nanocarriers, magnetic nanocarriers and protein nanocarriers have been created effectively [44-45].

- **Controlled Release:** Therapeutic drug's release rate and duration are controlled using controlled release systems in an effort to increase their effectiveness and minimize negative effects. Designing nanocarriers that react to multiple stimuli such as pH, temperature, enzymes or light in order to induce medication release at the desired site and time is a current area of research. By lowering the dose and frequency of administration, nanocarriers that can distribute medications in a spatiotemporally

 

regulated manner may improve therapeutic efficacy, lessen systemic side effects and increase patient adherence to regimens. A variety of nanocarriers with different compositions have been created to attain this purpose, surfaces, morphologies, and characteristics. Nanocarriers are designed to exploit the enhanced permeability and retention (EPR) effect, enabling their targeted accumulation within tumors. This strategy aims to effectively regulate the spatial distribution of medications [46].

- **Immunotherapy Enhancement:** In order to increase the efficacy of immunotherapy, which has demonstrated encouraging outcomes in the management of cancer, researchers are looking into nanoscale drug delivery methods. To enhance immune response and overcome resistance, strategies entail providing immune modulators, such as checkpoint inhibitors or immunostimulatory drugs, directly to the tumor microenvironment. A multitude of preclinical investigations and preliminary clinical findings indicate that the application of nanotechnology has promise in overcoming the existing limitations of cancer immunotherapy. In order to enhance the bioavailability and stability of therapeutic medications, nanoparticles can be employed to facilitate their targeted delivery to specific anatomical sites inside the body. This can be achieved through several means, such as systemic administration, tumor implants, microneedle injection, or the utilization of tumor-homing peptides [47-48].

- **Nanoscale Imaging Agents:** In order to increase diagnostic capabilities, nanoparticle are being investigated as imaging agents. Researchers are currently developing nanoparticles for utilization in imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and fluorescence imaging. These imaging tools can help with early illness detection, pinpoint therapy target localization and treatment response tracking. This option is provided via nanoparticle technology. Nanoparticle-based contrast agents are widely employed in a variety of prominent biomedical imaging techniques such as fluorescence imaging, magnetic resonance imaging (MRI), computed tomography (CT), ultrasound (US), positron emission tomography (PET) and single-photon emission computed tomography (SPECT) [49].

- **Biocompatibility and Safety:** Current research focuses on evaluating the biocompatibility and long-term safety profiles of nano drug delivery devices as they get closer to clinical use. In order to ensure the safety of their use, research is being done to assess potential toxicity, immunological responses, and the elimination of nanocarriers from the body [50-51].

- **Theranostic:** Theranostic treatment, which combines therapy with diagnostics, is widely applied to the treatment of cancer. Theranostic nanoparticles may prove useful to identify the place, describe the condition, and stage of the illness, and provide details on the response to treatment. In addition, nanoparticles have the capability to transport a therapeutic medicine that is particular to a tumor, hence facilitating the targeted delivery of the necessary concentrations of the therapeutic agent through external or molecular stimuli [37].

## III. TYPES OF NANO-DRUG DELIVERY SYSTEMS

The four main subcategories of nanoparticles are lipid-based, polymeric, nonpolymeric, and nanocrystalline. Micelles, drug conjugates, gels, protein nanoparticles, and dendrimers are a few examples of nanoparticles formed of polymers. Nanodiamonds, silica, quantum dots, carbon nanotubes and metallic nanoparticles are examples of nonpolymeric nanoparticles. Lipid-based nanoparticles include liposomes and solid lipid nanoparticles (SLNs). Crystalline nanoparticles are produced by combining therapeutic substances in the crystal form [52]. These are discussed below:

1. **Polymer-Based Nanoparticles:** Nanoparticles made of polymers can be created artificially or naturally. In terms of therapeutic applications, they provide an alternate strategy emphasizing biocompatibility, no immunogenicity, nontoxicity, and biodegradability [52].

    - **Dendrimers:** Highly branching macromolecules resembling trees are called dendrimers. They are excellent for targeted medication administration and imaging applications because they can be synthesized with fine control over their size and surface functionalization [53].

    - **Micelles:** Amphiphilic molecules create self-assembling micelles in an aquatic environment. They have the ability to solubilize hydrophobic medications inside of them, improving drug delivery to targeted areas [54].

    - **Drug Conjugates:** Low-solubility medicinal drugs are most frequently delivered by means of micellar solutions. Micelles collect in the solvent and have a diameter of around 100 m. In a spherical form, the molecules that make up polymeric micelles are organized, with a mantle of the hydrophobic centers surrounded by hydrophilic groups. The great stability of the hydrophilic surface inside physiological systems provides defense against nonspecific absorption by the reticuloendothelial system [52].

    - **Protein Nanoparticles:** These nanoparticles have good biocompatibility and the possibility for tailored administration since they use proteins or peptides as carriers [55].

    - **Nanogels:** Colloidal or polymeric gels are characterized by their nonfluid nature, forming networks that undergo expansion upon interaction with a fluid medium. According to the International Union for Pure and Applied Chemistry (IUPAC), nanogels are gel particles that possess the following attributes: a diameter of less than 100 nm. The capabilities of swelling nanogels are made of naturally occurring or manufactured polymers that have been mechanically or chemically crosslinked, resulting in their flexible scale and high-water concentration [56].

 

## 2. Lipid-Based Nanoparticles

- **Liposomes:** Amphiphilic phospholipids are used to create synthetic liposomes, which self-assemble. They consist of spherical double-layered vesicles that can be as small as 50 nm around an aqueous core domain. General Biological properties of liposomes that are appealing include biocompatibility and biodegradability. Liposomes are widely utilized in clinical studies as medication delivery methods [54].

- **Exosomes:** Exosomes are diminutive extracellular vesicles that play a crucial role in facilitating the transportation of various biomolecules and mediating intercellular communication. Most cell types, including different kinds of body cells like immune cells, stem cells, and cancer cells, release them. They are a sort of nanoscale vesicle that ranges in diameter from 30 to 150 nanometers. Exosomes have garnered significant interest in the field of biomedical research and medication delivery owing to their participation in a diverse range of physiological and pathological mechanisms [57].

- **Solid Lipid Nanoparticles:** Solid lipid nanoparticles (SLN) were developed as a controlled substitute for emulsions, liposomes, and protein nanoparticles (PNPs) in the context of a colloidal drug delivery system. Solid lipids are employed in the production of solid lipid nanoparticles (SLNs), which are subsequently stabilized through the incorporation of one or more surfactants. The use of SLN presents several advantages over alternative approaches for medicine delivery. The ocular route offers notable advantages in terms of superior tolerability, biodegradability, high bioavailability, and the ability of particle carriers to exert specialized effects on the brain [54].

## 3. Nonpolymeric Nanoparticles:

- **Carbon Nanotubes:** The identification of carbon nanotubes may be traced back to the year 1991. These structures are composed of carbon and take the form of tubular shapes. The tubes are comprised of graphite sheet cylinders that have been securely sealed. The buckyballs exhibit the presence of functional groups at either one or both termini, while their length spans a range of 1 to 100 nanometers. In recent times, there has been a surge in the popularity of single-walled nanotubes (SWNTs) and two distinct categories of multi-walled nanotubes (MWNTs). Additionally, it is worth noting that MWNTs are commonly seen in conjunction with C60-fullerenes. They arrive in several graphite cylinder arrangements and are hollow and noted for resembling cages and nanotube fullerenes. They are appropriate for encapsulating drugs due to their size and external characteristics and they have essential physical attributes [58, 52].

- **Nanodiamonds:** Typically, the size of nanodiamonds (NDs), which are carbon nanoparticles characterized by a truncated octahedral structure, falls within the range of 2 to 8 nm. Nanomaterials possess several advantageous characteristics, including their diminutive size, expansive surface areas, chemical stability, and exceptional hardness, stiffness, and strength. Moreover, they demonstrate numerous superior

 

attributes akin to diamond, such as a high capacity for adsorption and a substantial surface area. Therefore, the physical and chemical characteristics of NDs are superior over customary materials [50].

- **Metallic Nanoparticles:** Metallic nanoparticles are made up of metal atoms. Nanoparticles generally exhibit dimensions ranging from 1 to 100 nanometers. They differ from their bulk counterparts in that they have special size-dependent features. These characteristics make them appealing for a variety of applications in numerous disciplines, such as environmental science, materials science, electronics, catalysis, and medicine [58].

- **Quantum Dots:** Quantum dots (QDs) consist of semiconducting structures ranging in size from 2 to 10 nm. They are zinc sulfide-coated organic nanocrystals with a CdSe (Cadmiun selenide) inorganic semiconductor core that are intended to glow under certain lighting conditions and it is of light's influencing nature. The inclusion of a cap enhances QDs' ability to dissolve in aqueous buffers [58].

- **Silica-Based Nanoparticles:** Silica-based nanoparticles possess notable advantages in the field of nanomedicine, mostly attributable to their affordability and versatility in simulating intricate systems. Due to some certain surface characteristics, porosity, and functionalization, they are attractive therapeutic delivery methods where polar silanol units shield the silica nanoparticles' large surface area, making them water-friendly. They increase medicinal agent's adsorption and also their stability [59].

4. **Nanocrystalline:** A substance or material that is "nanocrystalline" is made up of grains or crystals that are smaller than a nanometer. Crystalline materials feature distinct crystalline areas with a distinctive lattice arrangement, and their atomic structure is regular and recurring. These crystallites have special characteristics that set them apart from their bulk counterparts when they are shrunk to nanoscale dimensions. Frequently, the grain sizes typically span from a few nanometers to several hundred nanometers. Due to their improved mechanical, electrical, magnetic, and optical capabilities, nanocrystalline materials have attracted substantial attention in a number of sectors [60-61].

## IV. PRESENTLY AVAILABLE NANO-CARRIERS IN THE MARKET

The fields of nanotechnology and nanomedicine have undergone a revolution. Approved nano-based medicinal compounds have increased dramatically since 1980. These novel nanostructured materials have the capability to operate as therapeutic agents independently or as carriers for the targeted delivery of diverse active medicines to specific anatomical sites. Nanocrystals, liposomes, lipid nanoparticles, PEGylated polymeric nanodrugs (specifically PEG-Polyethylene glycol), various other polymers, protein-based nanoparticles, as well as nanoparticles based on metals and other nanostructures, represent a range of nanostructures that are now being commercially promoted [62]. The utilization of nanoparticles as nano-carriers has the potential to enhance the non-specificity of commonly employed cancer treatments, while also improving their solubility, stability, specificity, multimodality, and efficacy [53].

 

1. **Types of Nanocarriers [**62]
   - Nanocrystals
   - Dendrimers
   - Liposomes
   - Mesoporous silica nanoparticles
   - Micelles
   - Polymeric nanoparticles
   - Carbon nanotubes
   - Quantum dots
   - Magnetic nanoparticles
   - Gold nanoparticles

2. **Available Market Categories of Nano Pharmaceuticals:** Many people use a variety of nano-based medications on a daily basis after they were effectively introduced to the market. The aforementioned products, sourced from a variety of multinational enterprises, provide as evidence for the present and potential future efficacy of nanoparticles in the field of medicine. The aforementioned classifications encompass protein-based, lipid-based, polymeric (including PEGylated biologics, gels, and emulsions), metallic nanoparticles (NPs), nanocrystals, liposomes, and lipid-based products [62-64].

   - **Nanocrystals**

     - **Emend®:**The FDA approved aprepitant in its nanocrystalline form as Emend® (Merck & Company, Inc., New Jersey, USA) in 2003 [65].
     - **Ostim®:** The FDA approved Ostim® (Osartis GmbH & Co. KG, Dieburg, Germany) in 2004 through the 510(k) process (it had previously acquired CE approval in 2002). Ostim® is a nanocrystalline paste of 20 nm-sized crystals of calcium hydroxyapatite (HA) [$Ca_{10}(PO_4)_6(OH)_2$]. The osteo conducting properties of HA are similar to those of natural bone minerals [65].
     - **Rapamune®:** A medication with the generic name Sirolimus, also referred to as Rapamune®, was authorised by the FDA in 2010 and is produced in Pennsylvania, USA, by Wyeth Pharmaceuticals Inc., a branch of Pfizer Inc. It is utilised to stop kidney transplant rejection [52].
     - **Vitoss®:** The FDA approved the popular synthetic bone substitute Vitoss® (Orthovita, Inc. PA, USA) in 2003 under the 510(k) method, a procedure for approving medical devices. It is made of 100 nm β-tricalcium phosphate (β-TCP, $Ca_3$ $[PO_4]_2$) nanocrystals[63].
     - **Ritalin®:** The FDA approved methylphenidate (nanocrystals), better known as Ritalin® (Novartis, Switzerland, Basel), for the treatment of childhood hyperactivity disorders in 1955. Attention deficit hyperactivity disorder (ADHD) is the primary condition that the medication is used to treat [65].
     - **TriCor®: TriCor®** (Abbott Laboratories; generic name: fenofibrate, IL, USA) was authorised in 2004 to decrease triglyceride and cholesterol levels to prevent the onset of atherosclerosis [65].

 

- **Lipid-Based Nanopharmaceuticals and Liposomes**

  - **Doxil® (Liposomal Doxorubicin):** Doxil (Alza, Pakistan), commonly known as Caelyx®, Evacet®, and Lipodox®, received FDA approval in 1995. It is a type of nanodrug used to treat a number of cancers, including metastatic ovarian cancer and Kaposi's sarcoma (KS), which is connected to AIDS [66].
  - **DaunoXome®:** Liposomal daunorubicin (also known as DaunoXome®; Galen, Craigavon, UK), an additional anthracycline anticancer drug that can be used in chemotherapy for cancer and HIV-associated Kaposi's Sarcoma (KS), acquired FDA clearance in 1996 [66].
  - **Onivyde® (Irinotecan Liposome Injection):** The FDA granted approval for the use of the irinotecan liposomal nanoformulationOnivyde® (Merrimack Pharmaceuticals, MA, USA), also known as MM-398 or PEP02, in the treatment of metastatic pancreatic cancer in 2015 [66-67].
  - **DepoCyt® (Liposomal Cytarabine):** The accelerated approval guidelines were used to approve DepoCyt® (Pacira Pharmaceuticals, NJ, USA) in 1999. It is a liposomal version of cytarabine made with the Depofoam® manufacturing process. Additionally, the FDA authorised its use in 2007 to manage the life-threatening condition known as lymphomatous meningitis [65].
  - **Marqibo® :** Liposomal vincristine sulphate, commonly known as Marqibo® (Talon Therapeutics, CA, USA), received FDA approval in 2012. A tubulin-binding anticancer alkaloid called vincristine stops cell division [67-68].
  - **AmBisome®:** AmBisome® (NeXstar Pharmaceuticals, CA, USA), a liposomal form of Amphotericin B (AmB) or L-AmB, is an antifungal medication used to treat a number of fungal illnesses [66].
  - **Vyxeos®:** The drug Vyxeos® (Jazz Pharmaceutics, Dublin, and Republic of Ireland) was approved by the FDA in 2017 for the treatment of adults with acute myeloid leukaemia brought on by prior therapy or acute myeloid leukaemia with alterations related to myelodysplasia [68].
  - **Abelcet®:** Abelcet, a different AmB lipid compound, was authorised in 1965 by (DefianteFarmaceutica of Funchal, Portugal) [65].
  - **Visudyne®:** Visudyne® (QLT Phototherapeutics, Vancouver, Canada) is the brand name of the benzoporphyrin derivative mono acid ring A liposomal formulation of the photosensitizer (PS). To treat wet age-related macular degeneration, which results in choroidal neovascularization, the FDA approved it in 2001 [66].

- **Polymer Based Nanopharmaceuticals**

  - **Cimzia®:** The FDA approved Cimzia® (UCB, Brussels, Belgium), a PEGylated tumour necrosis factor alpha (TNF-α) blocker, in 2008. Its generic name is "certolizumab pegol" (CZP) [65].
  - **Adagen®:** Adagen® (Enzon, Inc., NJ, USA), also known as pegademase bovine, is the first PEGylated designed protein that has been approved by the FDA. It is a PEGylated adenosine deaminase (ADA) [65].
  - **Neulasta®:** The FDA granted approval for Neulasta® (Amgen, Inc., California, USA), a PEGylated version of filgrastim, in 2002 [65].

 

- **Oncaspar®:** In 1994, the FDA approved pegaspargase, the generic name for Oncaspar® Enzon Pharmaceuticals Inc., NJ, USA), a PEGylated-Lasparaginase. This drug is used to treat both chronic myelogenous leukaemia and acute lymphoblastic leukaemia [65].
- **Pegasys®:** The FDA authorisedPegasys®, also known as peginterferon alfa-2a, in 2002. It was manufactured by (Genentech USA, Inc. in California) before being marketed under the name Incorporated by Hoffman-La Roche Chronic hepatitis B and hepatitis C are treated with recombinant human alfa-2a interferon Pegasys, which is conjugated to branched PEG (40 KDa) [65].
- **Somavert®:** Pegvisomant (B2036-PEG) is the generic name for Somavert® (Pfizer Pharmaceuticals, CT, USA), a PEGylated analogue of human growth hormone (GH) used to treat acromegaly. It was given FDA approval in 2003 [65].
- **Macugen®:** EyeTech Pharmaceuticals found the ocular therapeutic drug pegatinib sodium in 2000, and the FDA approved it in 2004. Pegatinib sodium is sold under the trade name Macugen® and was made available to consumers by Pfizer Inc [65].
- **Mircera®:** The medicine Mircera®, also known as epoetin β (EPO) conjugated to methoxy-PEG is used to treat anaemia. In 2007, Mircera was given FDA and European Commission approval [65].
- **PEG-INTRON®:** In order to treat chronic hepatitis C, PEG interferon alfa-2b was given FDA approval in 2001. It is presently used either alone or in conjunction with other drugs, such as ribavirin [65].
- **Krystexxa®:** Patients with refractory chronic gout can benefit from Savient Pharmaceuticals' Krystexxa® (also known as Pegloticase, formerly known as Puricase, NJ, USA). In September 2010, FDA permission was received [65].
- **Plegridy®:** Plegridy, also known as PEG-IFN-β-1a, was approved by the FDA in 2014 for the treatment of adult patients with RRMS. [65].
- **Adynovate®:** Clinical trials have demonstrated this medication's security and effectiveness in treating haemophilia [66].

- **Other Types of Polymer-Based Nanopharmaceuticals:** Other than pegylated formulations, polymer-based nanopharmaceuticals either contain polymer chains as their own, Eligard and Estrasorb use polymers to distribute medication molecules, as do Copaxone® and Renagel [52, 63, 65-67].

  - Copaxone®
  - Eligard®
  - Renagel®
  - Estrasorb®
  - Zilretta®

- **Protein-Based Nanopharmaceuticals**

  - **Abraxane® :** The FDA has approved the drug Abraxane® (Celgene Pharmaceutical Co. Ltd.), also known as ABI-007, for the treatment of lung cancer in 2012, metastatic pancreatic adenocarcinoma in 2013, and metastatic breast cancer in 2005 [68].

 

- **Ontak®:** Denileukindiftitox, also known as Ontak® (Eisai, Japan), was licenced by the FDA in 1999 for the treatment of T-cell lymphoma [65].
- **Rebinyn®:** In 2017, the FDA approved the PEGylated Glycoprotein Rebinyn®-brand drug; manufactured by NovoNordisk in Bagsvaerd, Denmark. It is utilised by individuals with factor IX (FIX) deficiency, often known as haemophilia [65].

- **Metal-Based Nanopharmaceuticals:** A wide range of applications for magnetic-based NP exist today, including medication and gene delivery and diagnosis. As a contrast agent for MRI, Feridex was a brand-named product made from NPs based on iron oxide. Its production was stopped in 2008 as a result of identified negative effects [63].

  - **Feraheme® :** In 2009, the FDA approved the injectable medication formulation ferumoxytol, also marketed for the treatment of anaemia, such as Feraheme® or Rienso® (AMAG Pharmaceuticals, MA, USA) [52-63].

## 3. Application of Nanoparticles in COVID-19 Vaccines

- **Pfizer-BioNtech:** The pharmaceutical giants Pfizer, with headquarters in New York, and BioNTech, with headquarters in Germany, created history on November 9, 2021, when they declared that their coronavirus vaccine was over 90% effective. On December 11, just over a month later, the FDA gave it the first emergency use permission ever given to a coronavirus vaccination by the United States [52-69].

- **Moderna Vaccine:** The FDA authorised the use of a vaccine developed by Boston-based Moderna on December 18, one week after the immunisation produced by Pfizer and BioNTech. The second was the Moderna COVID-19 vaccine. A vaccine has received FDA approval. Moderna produces the vaccine utilising mRNA, just like Pfizer and BioNTech [52-70].

- **Oxford-AstraZeneca:** Together with the British-Swedish Corporation, the University of Oxford developed and validated the coronavirus vaccination AZD1222 or ChAdOx1 nCoV-19. AstraZeneca studies in humans have shown that when two dosages were given 12 weeks apart, the vaccination rate was 82.4%. Effective [52-71].

- **Sinopharm:** The Beijing Institute of Biological Products developed the BBIBP-CorV inactivated coronavirus vaccine before the end of 2020, a state-owned business, Clinical trials were conducted by Sinopharm, which discovered that BBIBPCorV had an efficacy score of 79% [52].

- **Novavax:** The COVID-19 spike protein genetic sequence was used to create antigens using recombinant nanoparticle technology. Preclinical investigations have proven that NVX-CoV2373 binds effectively when used with the exclusive Matrix-MTM adjuvant. Considering that the virus is aiming for human receptors, a crucial and necessary component of vaccination protection [52-72].

 

- **Johnson & Johnson:** Johnson & Johnson has investigated JNJ-78436735, also known as Ad26.COV2, a coronavirus vaccine. According to tests, the immunization rate for a single dosage produced by the Israel Deaconess Medical Centre, a Johnson & Johnson division in Belgium, in partnership with Beth Janssen Pharmaceutical, reached 72% [52-69].

## V. BIOAVAILABILITY AND BIOACTIVITY

1. **Role of Nanocarriers in Bioavailability:** The field of nanotechnology has opened up new possibilities for enhancing the bioavailability of various therapeutic agents, revolutionizing drug delivery and improving patient outcomes. Nanocarriers are nanoscale drug delivery systems designed to encapsulate and protect therapeutic agents, enabling controlled release, targeted delivery, and increased solubility of poorly water-soluble drugs. This chapter explores the critical role of nanocarriers in improving the bioavailability of therapeutic agents, shedding light on their potential applications in medicine and pharmaceuticals [73].

    - **Overcoming Bioavailability Challenges:** Bioavailability refers to the fraction of an administered drug that reaches systemic circulation and is available to exert its pharmacological effect. Several drugs, especially those with low water solubility, face significant bioavailability challenges. Poorly water-soluble drugs often suffer from reduced absorption and limited therapeutic efficacy. Nanocarriers, such as liposomes, micelles, nanoparticles, and nanosuspensions, have been developed to address these issues [74].

    - **Enhanced Solubility:** One of the key roles of nanocarriers is to enhance the solubility of poorly water-soluble drugs. Nanoparticles, for example, can effectively solubilize lipophilic drugs and enhance their bioavailability by increasing their surface area and improving dispersion properties. By encapsulating hydrophobic drugs within their hydrophilic cores, nanocarriers facilitate their transport through the biological barriers, leading to improved absorption and bioavailability [74].

    - **Controlled Release and Targeted Delivery:** Nanocarriers offer the advantage of controlled drug release, allowing sustained and prolonged drug activity, reducing dosing frequency, and minimizing side effects. Furthermore, these carriers can be functionalized with ligands that target specific tissues or cells, enabling site-specific drug delivery. This targeted approach enhances drug accumulation at the desired site, reducing systemic exposure and potential toxicity [75].

    - **Overcoming Biological Barriers:** Biological barriers, such as the blood-brain barrier (BBB) and mucosal barriers, pose significant challenges to drug delivery. Nanocarriers can be engineered to traverse these barriers efficiently. For example, surface modification with specific ligands can facilitate receptor-mediated transcytosis, enabling drugs to cross the BBB and reach the central nervous system [74].

 

- **Nanocarriers in Cancer Therapy:** Nanocarriers have shown tremendous promise in cancer therapy by selectively delivering chemotherapeutic agents to tumor cells, sparing healthy tissues. Liposomes, polymeric nanoparticles, and dendrimers have been extensively studied as anticancer drug carriers due to their biocompatibility and ability to encapsulate both hydrophobic and hydrophilic drugs [75].

- **Clinical Applications:** Several nanocarrier-based drug formulations have already been approved for clinical use. For instance, liposomal doxorubicin (Doxil®) is employed in the treatment of ovarian cancer, breast cancer, and Kaposi's sarcoma. Abraxane®, a nanoparticle albumin-bound paclitaxel formulation, is used in breast, lung, and pancreatic cancer treatment. These examples highlight the clinical potential of nanocarriers in improving bioavailability and therapeutic outcomes. The use of nanocarriers represents a groundbreaking approach to enhance the bioavailability of therapeutic agents. Their ability to improve solubility, achieve controlled release, and facilitate targeted delivery makes them invaluable tools in drug development and personalized medicine. However, continued research is essential to fully understand their safety profile, optimize their design, and unlock their potential for a wider range of therapeutic applications [76].

2. **Enhancement of Nano Drug Delivery System on Bioactivity:** Nano drug delivery systems (NDDS) have emerged as a revolutionary approach to improve the therapeutic efficacy and bioavailability of various drugs. These systems utilize nanoscale carriers, such as liposomes, polymeric nanoparticles, dendrimers, and micelles, to encapsulate and deliver drugs to specific target sites in the body [77]. This precise drug targeting not only reduces systemic toxicity but also enhances the bioactivity of the delivered drug, leading to improved treatment outcomes for various diseases.

    - **Enhanced Drug Stability and Protection:** One significant advantage of NDDS is the ability to protect the encapsulated drug from degradation, leading to increased drug stability [78]. The nano-sized carriers shield the drug molecules from enzymatic degradation and harsh physiological conditions, such as low pH in the stomach or the presence of proteolytic enzymes, allowing the drug to maintain its integrity until reaching the target site.

    - **Improved Pharmacokinetics:** Nanocarriers enable sustained and controlled drug release, which can lead to prolonged drug circulation time and improved pharmacokinetics [79]. This prolonged circulation time enhances drug exposure to the target tissue, increasing the likelihood of effective interactions between the drug and its biological target. Consequently, NDDS can reduce the required dosing frequency and improve patient compliance while maintaining therapeutic efficacy.

    - **Enhanced Cellular Uptake:** Nano drug delivery systems can facilitate cellular uptake of drugs, especially for poorly water-soluble drugs [80]. The nanocarriers can passively accumulate in target tissues through the enhanced permeability and retention (EPR) effect, which exploits the leaky vasculature of tumors, inflamed tissues, or infection sites. Additionally, active targeting strategies, such as ligand-

 

functionalized nanoparticles, can further enhance cellular uptake by binding to specific receptors on the cell surface.

- **Overcoming Biological Barriers:** NDDS can overcome various biological barriers that limit conventional drug delivery. For example, the blood-brain barrier (BBB) prevents many therapeutic agents from reaching the central nervous system. However, nanocarriers can be designed to cross the BBB and deliver drugs to the brain, opening up new possibilities for treating neurological disorders [81].

The enhancement of nano drug delivery systems has significantly impacted the bioactivity of various drugs, improving their therapeutic efficacy and reducing potential side effects. Through improved drug stability, enhanced pharmacokinetics, increased cellular uptake, and the ability to overcome biological barriers, NDDS has shown great promise in revolutionizing drug delivery and expanding treatment options for numerous diseases.

## VI. ADVANTAGES OF ENHANCED BIOAVAILABILITY AND BIOACTIVITY

Enhanced bioavailability and bioactivity play crucial roles in maximizing the therapeutic potential of drugs and pharmaceutical compounds. Bioavailability refers to the proportion of the administered dose of a drug that reaches the systemic circulation, while bioactivity refers to the ability of the drug to elicit a biological response upon reaching its target site. Improving both bioavailability and bioactivity offers several advantages, enhancing the efficacy and safety of medications, as well as reducing treatment costs and potential side effects.

### 1. Advantages of Enhanced Bioavailability:

- **Increased Therapeutic Efficacy:** Enhanced bioavailability ensures that a larger fraction of the administered drug reaches the bloodstream, leading to higher drug concentrations at the target site [82]. This increased exposure improves the drug's ability to interact with its molecular targets, resulting in more robust therapeutic effects. For drugs with narrow therapeutic windows or low potency, improving bioavailability becomes especially critical in achieving the desired clinical outcomes.

- **Reduced Dosage Requirements:** Higher bioavailability allows for reduced dosage requirements to achieve the same therapeutic effect. Lower dosing not only reduces the overall drug burden on the body but also minimizes the potential for adverse effects [83]. Consequently, patient compliance may improve as a result of reduced pill burden, making treatment more manageable and effective.

- **Rapid Onset of Action:** Drugs with enhanced bioavailability often exhibit faster onset of action due to higher and quicker peak concentrations in the bloodstream. This attribute is particularly advantageous for treating acute conditions where rapid symptom relief is essential [84].

 

2. **Advantages of Enhanced Bioactivity:** Enhanced bioactivity ensures that a higher percentage of the drug molecules interact with their intended biological targets [85]. This translates to a more potent and specific pharmacological response, minimizing off-target effects and increasing the drug's therapeutic index. In cases where drug resistance poses a significant challenge, enhancing bioactivity can help overcome this issue. A more potent drug can exert a stronger inhibitory effect on drug-resistant strains or target molecules, improving treatment outcomes [86]. Drugs with improved bioactivity often require smaller doses to achieve the same therapeutic effect. This reduction in dosage can lead to cost savings in drug production and administration, making treatment more affordable and accessible to patients. Enhancing bioavailability and bioactivity of drugs offers multiple advantages, positively impacting the therapeutic efficacy, safety, and overall cost-effectiveness of medications. Increased bioavailability leads to higher drug concentrations at the target site, promoting improved therapeutic outcomes and reduced dosing requirements. On the other hand, enhanced bioactivity ensures greater target engagement, potentially overcoming drug resistance and reducing treatment costs. Together, these advancements contribute to the development of more effective and efficient pharmaceutical interventions.

## VII. PROBABLE DEMERITS OF ENHANCED BIOAVAILABILITY AND BIOACTIVITY

Enhancing the bioavailability and bioactivity of drugs is a desirable goal for improving therapeutic outcomes. However, while these advancements offer several advantages, it is essential to consider the potential drawbacks and challenges associated with increased drug exposure and potency. Understanding these probable demerits can aid in the development of safer and more effective pharmaceutical interventions.

### 1. Probable Demerits of Enhanced Bioavailability

- **Increased Risk of Adverse Effects:** Enhanced bioavailability can lead to higher drug concentrations in the bloodstream, which may increase the risk of adverse effects [87]. Even if the drug is highly effective at its target site, it may also interact with other tissues or receptors, resulting in unintended side effects. This is particularly concerning for drugs with a narrow therapeutic window, as even small fluctuations in plasma concentrations can lead to toxicity.

- **Drug-Drug Interactions:** High bioavailability may increase the potential for drug-drug interactions [88]. When multiple drugs are co-administered, their pharmacokinetics and pharmacodynamics may be affected, leading to unpredictable outcomes. Drug interactions can result in reduced efficacy or enhanced toxicity, necessitating careful consideration of drug combinations.

- **Compliance Issues:** Despite the potential benefits of reduced dosing requirements, enhanced bioavailability can lead to challenges in patient compliance [89]. Patients may find it challenging to adhere to complex dosing schedules or may mistakenly take higher doses than prescribed due to the misconception that "more is better." Non-adherence to treatment regimens can compromise therapeutic outcomes.

 

### 2. Probable Demerits of Enhanced Bioactivity

- **Increased Risk of Target over Activation:** Drugs with enhanced bioactivity may lead to excessive activation of their target receptors or pathways [90]. Overstimulation can trigger adverse biological responses or disrupt the normal physiological balance, potentially exacerbating the disease or causing new health issues.

- **Development of Resistance:** While overcoming drug resistance is one of the advantages of enhanced bioactivity, it can also lead to the development of new forms of resistance over time [91]. High drug potency may exert selective pressure on the target organism, favoring the emergence of resistant strains or altered target sites. This phenomenon can compromise the long-term effectiveness of the drug.

- **Narrow Therapeutic Index Challenges:** Drugs with enhanced bioactivity may possess a narrow therapeutic index, making them more susceptible to dose-related toxicity [92]. Achieving the right balance between therapeutic efficacy and safety becomes challenging, as small deviations from the optimal dosage range can lead to severe adverse effects.

While enhanced bioavailability and bioactivity can significantly improve the efficacy of pharmaceutical interventions, they also carry potential demerits that warrant careful consideration during drug development and clinical use. The risk of increased adverse effects, drug-drug interactions, and compliance issues should be addressed through meticulous dose optimization and patient education. Additionally, the possibility of target overactivation, resistance development, and narrow therapeutic index challenges requires continuous monitoring and research to ensure the safe and effective use of these advanced drug formulations.

## VIII. BIOACTIVE LOADED NANOTECHNOLOGY APPLICATIONS FOR DRUG DELIVERY

Bioactive-loaded nanotechnology has emerged as a promising approach for enhancing drug delivery systems. Nanotechnology involves the manipulation and engineering of materials at the nanoscale level to create carriers capable of encapsulating and delivering bioactive compounds. These nanocarriers offer several advantages, including improved drug stability, controlled release, targeted delivery, and enhanced bioavailability. This article provides a comprehensive overview of the applications of bioactive loaded nanotechnology in drug delivery.

1. **Liposomes:** Liposomes are one of the most widely studied nanocarriers for drug delivery [93]. Composed of phospholipids, liposomes form spherical vesicles that can encapsulate both hydrophilic and hydrophobic drugs within their aqueous core or lipid bilayers. Liposomes protect the encapsulated bioactive compounds from degradation and can be functionalized with targeting ligands to achieve site-specific drug delivery.

 

2. **Polymeric Nanoparticles:** Polymeric nanoparticles are versatile carriers that can be engineered from various biocompatible and biodegradable polymers [94]. They offer excellent stability and control over drug release kinetics. By modifying the nanoparticle's surface, researchers can achieve passive or active targeting to specific tissues, cells, or receptors, enhancing drug accumulation and efficacy at the desired site.

3. **Dendrimers:** Dendrimers are highly branched, tree-like nanostructures that can entrap drugs in their interior or conjugate them on their surface [95]. Their unique architecture allows for precise control over drug loading and release. Additionally, dendrimers can be functionalized with ligands to improve cellular uptake and target specific sites, making them valuable carriers for drug delivery.

4. **Nanomicelles:** Nanomicelles are self-assembled nanostructures formed by amphiphilic molecules in an aqueous environment [96]. They have a hydrophobic core where hydrophobic drugs can be loaded, while their hydrophilic shell stabilizes the structure in biological fluids. Nanomicelles offer advantages such as improved solubility for poorly water-soluble drugs and passive targeting through the EPR effect.

5. **Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs):** SLNs and NLCs are lipid-based nanocarriers that offer advantages in terms of biocompatibility, biodegradability, and controlled release [97]. NLCs, in particular, combine solid lipids with liquid lipids to improve drug loading capacity and prevent drug expulsion during storage. These nanocarriers enhance drug stability and have potential applications in various therapeutic areas.

6. **Nanogels:** Nanogels are three-dimensional networks of cross-linked hydrophilic polymers that can absorb large amounts of water or biological fluids [98]. They offer a unique environment for drug encapsulation, protecting bioactive compounds from degradation while allowing for controlled release. Nanogels are particularly useful for delivering protein-based drugs and therapeutic peptides.Bioactive-loaded nanotechnology has opened up new horizons in drug delivery, offering a myriad of advantages for improved therapeutic outcomes. From liposomes and polymeric nanoparticles to dendrimers and nano micelles, these nanocarriers enable precise drug targeting, enhanced bioavailability, and controlled release. Their potential applications span across various medical fields, including cancer treatment, infectious diseases, inflammatory conditions, and neurological disorders. As nanotechnology continues to advance, we can expect further innovations in drug delivery systems, ultimately leading to more effective and personalized therapies.

## IX. CONCLUSION

Nano-drug delivery systems have emerged as a transformative approach to significantly enhance the bioavailability and bioactivity of various therapeutic agents. This chapter has provided a comprehensive overview of the diverse nano-based technologies utilized for targeted drug delivery, controlled release, and improved therapeutic efficacy. Through the ingenious use of nanoparticles, such as liposomes, polymeric nanoparticles, dendrimers, carbon nanotubes, metallic nanoparticles, solid lipid nanoparticles, and protein-based nanoparticles, researchers have unlocked new avenues to address the limitations of

 

conventional drug delivery methods. By encapsulating drugs within these nanocarriers, it has become possible to protect sensitive drugs from degradation, extend their circulation time, and overcome biological barriers to enable selective targeting of diseased tissues or cells. The ability to achieve sustained and controlled release of drugs from nano-carriers allows for reduced dosing frequency, minimizing adverse effects, and increasing patient compliance. Moreover, the surface functionalization of nanoparticles enables specific ligand-receptor interactions, directing drugs precisely to their intended sites of action, thus optimizing therapeutic outcomes. The potential of nano-drug delivery systems extends beyond their ability to improve drug bioavailability and bioactivity. These platforms have shown promise in combination therapy, co-delivery of multiple drugs, and integration with diagnostic imaging agents, paving the way for personalized medicine and more effective treatment strategies.

As research in the field continues to advance, challenges related to large-scale production, regulatory considerations, and long-term safety profiles must be addressed to accelerate the translation of these technologies from the laboratory to clinical practice. Nevertheless, the progress achieved thus far in nano-drug delivery systems offers a glimpse into the future of pharmaceutical sciences, with the potential to revolutionize the treatment landscape and improve patient outcomes across a wide range of medical conditions. Embracing the promise of nano-based drug delivery represents a promising pathway toward the realization of safer, more efficient, and patient-tailored therapies in modern medicine.

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