Nano-Drug delivery systems for the enhancement of bioavailability and bioactivity

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**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 blood plasma levels. Thus, bioavailability is defined as the rate and extent (amount) of absorption of 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 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, Bioactivity, Nanotechnology, Nanocarriers

1. **Introduction**

A drug which is obtained from plant, animal or any other synthetic source exerts its therapeutic efficacy by delivering its active medicaments to specific site of action to obtain required pharmacological response. Mostly, drugs act by binding with targeted receptor or enzymes and inhibiting or otherwise transforming their pharmacological activities. The therapeutic result of any constituents may obtain 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 sometime simply as bioavailability [1]. 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. In other words, 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 blood plasma levels. Thus, bioavailability is defined as the rate and extent (amount) of absorption of 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 the diseases and save the human being to 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 problem associated with these dosage form like its efficacy, bioavailability, bioactivity, toxicity, biocompatibility, side-effects and inactivity problem are which 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 which 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 in to 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.

1. 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.
2. 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.
3. 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.
4. Fast Excretion- Elimination is an important pharmacokinetic parameter. The removal of drug from the body by excretory organs like kidney is called excretion. Due to fast excretion of drug molecule makes the constituent very less effective therapeutically as required amount of drug molecule is not reached to the specific target organs [7].
5. Fraction of drug required zone: Some of our body organ require a need of accumulation of drug in a specific rate and extent such as in case of tumor cells amount of drug need to be high as compared to normal cells for proper effective treatment. Lack of proper accumulation of drug is directly associated with various chemotherapeutic agents for a curable cancer treatment [8].

Bioactivity is an approach which 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 drugs ability to bind to its receptor or target and initiate the desired physiological response. The bioactivity is associated with drug delivery symptoms refer to the issue of maintaining the therapeutic efficacy of the drug throughout the delivery process [9].

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

1. 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.
2. 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.
3. 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.
4. 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.
5. 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.
6. 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
7. **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 nanoscale, material and devices exhibit some unique properties and symptoms. Since last decade, nanoparticles have gain 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 system. Nanotechnology offers different manipulation over the drug design, drug synthesis and fabrication of drug delivery systems. Drugs stability, solubility, and targeted delivery can be improved by encapsulating that drug within nanocarriers or nanomatrix [11]. The diverse technological benefits of nanoparticles using 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 the treatment with increase bioavailability, reduces the frequency of administration, and promotes targeting of drugs to specific sites. Nanomaterials has 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, development of control release targeted drug delivery includes presence of active drug in the target area of the body such as cancerous cells and sustained release of dosage form in which the drug is released over an extended period of time in a controlled manner from the dosage form [12].

1. **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. But these nano drug delivery systems are designed to improve the efficacy and safety of drug delivery by enhancing the drugs pharmacokinetic properties, reducing side effects, and increasing drugs bioavailability and bioactivity. Nanoparticle-based drug dosage forms have shown high solubility, control release, improved pharmacokinetic and pharmacodynamic properties. Particle size, surface charge and shape play important roles in creating effective nanoparticle delivery systems that function through a variety of mechanisms [13].

* Particle size-Particle size and size distribution are the most important characteristics because these determine the chemical and physical properties of nanomaterials. The hydrodynamic size and size distribution determine the in vivo distribution, biological fate, toxicity, and targeting ability of these nanomaterials for drug delivery systems. They can manipulate drug loading, release, and stability. It has been reported that nanomaterials are advantageous over microscale particles due to their small size and high mobility that makes them capable of higher cellular uptake suitable for a wider range of cellular and intracellular targets [14].
* Surface Charge-Surface charge is usually expressed and measured in terms of the nanomaterials zeta potential which reflects the electrical potential of particles that is influenced by its composition and the medium in which it is dispersed. Zeta potential having a value of ± 30 mV has been reported to be stable in suspension leads to preventing aggregation of particles [15]. The surface charge of nanomaterials is crucial to drug loading. Drugs can be loaded via a number of processes such as covalent conjugation, hydrophobic interaction, charge-charge interaction or encapsulation. Loading of molecules depends upon the nature of the drug as well as nature of target molecule, also alters the surface charge. By changing zeta potential attachment or adsorption of charged molecule can be determined on the surface of nanoparticle [16]
* Drug Loading: Incorporation of a drug on or in nanomaterials is referred to as drug loading. An ideal nanoparticles drug delivery system should have a high drug-loading capacity without aggregation. High drug loading capacity can minimize administration or the number of doses [17]. Dispersibility is needed for smooth and efficient delivery of the drugs. Drug loading can be accomplished in several ways; however, drug loading and entrapment efficiency depend on drug solubility in the nanoparticles, dispersion medium, nanomaterials size and composition, drug molecular weight (MW) and solubility, drug-nanomaterials interaction, and/or the presence of surface functional groups (i.e. carboxyl, amine, ester, etc.) on either the drugs or on the nanomaterials [18].
* Drug Targeting: Targeting of tumors leads to improving chemotherapy by nanomaterials providing a highly specific and versatile platform for cancer treatment. Enhanced permeability and retention enable selective localization in tumors spontaneously due to fenestrated blood vessels as in the case of drug-loaded liposome (doxorubicin-liposome complex). It has been shown to effectively improve selective localization in human tumors in vivo of small-molecule drugs such as doxorubicin as demonstrated by nanosized liposomes target tumors spontaneously because of the fenestrated blood vessels. This is due to enhanced permeability and subsequent drug retention [19]

1. **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]

**Fig 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 sustain 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].

1. **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 outcome.

1. **Presently available nano-drug delivery systems**

Drug delivery nanoparticles typically measure less than 100 nm in at least one dimension and are made of a variety of biodegradable substances, including natural or manufactured polymers, lipids, metals, or both. Since bigger micromolecules are less effectively absorbed by cells than nanoparticles, they could be used as efficient delivery and transport systems. Drugs can either be affixed to the particle surface or integrated into the particle-matrix for therapeutic uses. The fate of a drug, after it enters the biological environment, ought to be under the control of a drug-targeting system. Numerous studies have been conducted on nano systems with various biological characteristics and compositions for applications in medication and gene delivery [29].

Many medication delivery methods have been created in recent years 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. These carriers can be targeted by conjugating them with certain antibodies targeting a particular area of interest. They are sensitive to pH and temperature changes and have a slow rate of degradation. Drug targeting can be divided into two types: passive targeting and aggressive targeting. High solubility, controlled release, and better pharmacokinetic and pharmacodynamic features have all been demonstrated by formulations based on nanoparticles surface charge and particle size, in order to create effective nanoparticle delivery systems, size and shape are crucial factors [30].

**Nano-drug delivery systems:**

* Hydrogel: For the encapsulation and delivery of drugs, therapeutic proteins, or vaccine antigens, hydrogel nanoparticles based on hydrophobic polysaccharides are used. a new system that A promising compound is cholesterol pullulan, an extracellular polysaccharide 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 two immiscible liquids, a surfactant with or without a co-surfactant is used to bring the mixture together and stabilize it. 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: Polymeric micelles often have a restricted distribution to prevent rapid renal elimination, allowing them to accumulate in tumor tissues. They are about 100 nm in size. Additionally, their non-specific interactions with biological components are restricted by the polymeric shell. Since these nanostructure’s internal core structure allows for the assimilation of hydrophobic pharmaceuticals, which increases their stability and bioavailability, they offer significant potential for hydrophobic drug delivery [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 are highly branched macromolecules with a variety of functional groups available for 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 for use as drug delivery systems because of their globular form and the ease 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 their distinctive physical, chemical, and optical features. Silver, gold, iron oxide, and silica nanoparticles are examples of inorganic nanoparticles. Liposomes, dendrimers, and micelles lack specific features like surface plasmon resonance (SPR) that metal nanoparticles like silver and gold do. They demonstrated a number of benefits, including strong biocompatibility and adaptability when it comes to surface functionalization [34].
* Nanocrystal: Pure solid drug particles with a size between 1000 nm are known as nanocrystals. These are entirely drugs, with no carriers attached, and are often stabilized using stabilizers or surfactants made of polymers. They can be utilized for drug encapsulation, controlled drug release, targeted drug delivery, imaging and theragnostic, combination therapies, and biocompatibility and safety [31].
* Nanoparticles Made Of Carbon: Carbon nanotubes (CNTs) and fullerenes are the two primary categories of carbon-based nanoparticles. A form of allotrope is CNTs. Single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs) are two types of carbon with cylindrical frameworks and deepening on the number of sheets in concentric cylinders. The carbon allotrope known as fullerene has a hollow cage structure made up of at least sixty carbon atoms. C-60 has a structure known as Buckminsterfullerene that resembles a hollow shell like a football. These formations contain pentagonal and hexagonal-shaped carbon units. Due of its electrical conductivity, structure, high strength, and electron affinity, they have commercial applications [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 nanocapsules or nanospheres [36].
* Lipid-based nanoparticles: Lipid nanoparticles typically have a spherical shape with a diameter between 10 and 100 nm. It is made out of a sturdy core and is composed up of a matrix of soluble lipophilic molecules and lipids. These nanoparticle’s exterior core is stabilized by emulsifiers and surfactants. These nanoparticles are used in the biomedical industry as medication carriers, delivery systems, and RNA release agents in the treatment of cancer [36].
* Quantum dot: The semiconductor nanocrystals known as quantum dots (QDs) have a diameter range of 2 to 10 nm. Size affects a variety of features, including absorbance and photoluminescence. Due to the QD's emission in the near-infrared region ( less than 650 nm), which is different from conventional organic dyes due to low tissue absorption and reduced light scattering, the QDs has attracted a lot of attention in the field of nanomedicine. Additionally, diverse emission colours over a broad spectrum range can be produced when QDs of various shapes, sizes, and/or compositions are excited by the same light source [37].
* Biopolymeric Nanoparticle: Nanosized biopolymeric nanoparticles are made of biopolymers, which are organic polymers generated from living things. These nanoparticle's biocompatibility, biodegradability, and low toxicity make them suitable for usage in a variety of biomedical and drug delivery applications. 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 utilised. Having a high molecular weight, melting point, or taking the form of salt point preventing the creation of appropriate formulas [38].

1. **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. Through improvements in drug delivery, nanotechnology has had a significant impact on the medical industry over the past ten years. Drug delivery based on nanotechnology aims to target the medication payload to the appropriate location and time, at the proper (ideal) dosage [39].

1. **Targeted Drug Delivery**: A recent review on the creation of nanoparticle delivery systems for focused drug delivery has been reviewed. Targeted delivery may be accomplished actively or passively. Actively the therapeutic agent must be targeted in order to be obtained by conjugation, medicinal substance or delivery method to a tissue-specific or cell-specific ligand. Targeting passively is accomplished via putting the medication within a macromolecule or the target organ is passively reached by a nanoparticle. Nanoparticle-encapsulated medicines or pharmaceuticals attached to macromolecules can be passively targeted using the enhanced permeability and retention (EPR) effect [32].
2. **Stimuli-Responsive Systems**: Nano-drug delivery systems that react to particular stimuli like temperature, pH, light, or enzymes are being developed by scientists. In reaction to the unique circumstances at the target site, these systems can be designed 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].
3. **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 complimentary 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].
4. **Gene Delivery:** The use of nanoparticles as gene therapy carriers is being investigated. In order to rectify genetic diseases or modify gene expression for therapeutic purposes, researchers are looking at the use of nanoparticles to deliver therapeutic genes to target cells. For effective and targeted gene delivery, strategies include the use of viral or non-viral vectors, 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].
5. **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 regimen. To a variety of nanocarriers with different compositions have been created to attain this purpose, surfaces, morphologies, and characteristics. Utilizing the increased permeability and retention (EPR) effect, nanocarriers are made to specifically localize and accumulate in tumours for the purpose of controlling the spatial distribution of drugs [46].
6. **Immunotherapy Enhancement:** In order to increase the efficacy of immunotherapy, which has shown promising results in the treatment 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 tumour microenvironment. Numerous preclinical studies and early clinical results show that nanotechnology can address some of the issues that currently restrict cancer immunotherapy. To increase the bioavailability and stability of therapeutic medicines, nanoparticles can direct them to certain locations in the body by systemic administration, tumour implants, microneedle injection, or tumour homing peptides [47-48].
7. **Nanoscale Imaging Agents:** In order to increase diagnostic capabilities, nanoparticles are being investigated as imaging agents. For application in imaging techniques including computed tomography (CT), magnetic resonance imaging (MRI), and fluorescence imaging, researchers are creating nanoparticles. These imaging tools can help with early illness detection, pinpoint therapy target localization, and treatment response tracking. This option is provided via nanoparticle technology. The majority of popular biomedical imaging techniques, including fluorescence imaging, MRI, CT, US, PET, and SPECT, use nanoparticle-based contrast agents [49].
8. **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].
9. **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. Furthermore, these nanoparticles can carry a tumor-specific therapeutic drug that can deliver the required concentrations of the therapeutic agent using external or molecular impulses [37].
10. **Types of nano-drug delivery systems**

Nanocrystalline, polymeric, nonpolymeric, and lipid-based nanoparticles are the four main classifications for nanoparticles. Nanoparticles made of polymers include micelles, drug conjugates, gels, protein nanoparticles, and dendrimers. Nonpolymeric nanoparticles include nanodiamonds, silica, quantum dots, carbon nanotubes, and metallic nanoparticles. Liposomes and solid lipid nanoparticles (SLNs) are lipid-based nanoparticles. Therapeutic compounds are combined in the crystal state to create crystalline nanoparticles [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].

1. Dendrimers: Highly branching macromolecules resembling trees are called dendrimers. They are excellent for targeted medication administration and imaging applications because they can be synthesised with fine control over their size and surface functionalization [53].
2. 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].
3. 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].
4. Protein nanoparticles: These nanoparticles have good biocompatibility and the possibility for tailored administration since they use proteins or peptides as carriers [55].
5. Nanogels: Colloidal or polymeric gels are nonfluid networks that expand when they come into contact with a fluid. The International Union for Pure and Applied Chemistry (IUPAC) defines nanogels as gel particles with these characteristics, but less than 100 nm in diameter. 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].
6. *Lipid-based nanoparticles:*
7. 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. The liposomes are the most frequently clinical trials nanosystems as drug delivery systems [54].
8. Exosomes: Exosomes are tiny extracellular vesicles that are essential for the movement of different biomolecules and cell-to-cell 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 received a lot of attention in biomedical research and drug delivery due to their involvement in a variety of physiological and pathological processes [57].
9. Solid Lipid nanoparticles: Solid lipid nanoparticles (SLN) were created as a regulated alternative to emulsions, liposomes, and protein nanoparticles (PNPs) as a colloidal drug delivery system. Solid lipids are used to create SLNs, which are then stabilised by one or more surfactants. SLN has more advantages for medication delivery than other methods. Superior tolerability, biodegradability, high bioavailability through the ocular route, and particle carriers a specific effect on the brain [54].
10. *Non polymeric nanoparticles:*
11. Carbon nanotubes: The discovery of carbon nanotubes dates back to 1991. They are carbon-based tubular constructions. These tubes are composed of sealed graphite sheet cylinders. Bucky balls at one or both ends, and range in length between 1 and 100 nm. Single-walled nanotubes SWNTs and Two types of multiwalled nanotubes (MWNTs) have grown in popularity recently, MWNTs Common combinations also contain C60-fullerenes. They arrive in several graphite cylinder arrangements and are hollow and noted for resembling cages and nanotubes fullerenes. They are appropriate for encapsulating drugs due to their size and external characteristics and they have essential physical attributes [58,52].
12. Nanodiamonds: In general, the diameter of nanodiamonds (NDs), which are carbon nanoparticles with a truncated octahedral morphology, ranges from 2 to 8 nm. They have the advantages of nanomaterials, such as tiny size, huge surface areas, chemical stability and extremely high hardness, stiffness, and strength, in addition to exhibiting a number of superior features of diamond like high capacity for adsorption and large surface area. Therefore, the physical and chemical characteristics of NDs are superior over customary materials [50].
13. Metallic nanoparticles: Metallic nanoparticles are made up of metal atoms and are typically between 1 and 100 nanometers in size. 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].
14. Quantum dots: Semiconducting structures that are 2–10 nm in size make up quantum dots (QDs). 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].
15. Silica based nanoparticles: Due to its affordability and flexibility to be used to simulate complicated systems, silica-based nanoparticles have considerable advantages in nanomedicine. 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 increases medicinal agent's adsorption and also their stability [59].
16. *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, often with grain sizes ranging from a few nanometers to a few 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].

1. **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 innovative nano-based systems can either function as therapeutic agents on their own or as carriers for delivering various active pharmaceuticals to particular bodily regions. Nanocrystals, liposomes and lipid nanoparticles, PEGylated (PEG-Polyethylene glycol) polymeric nanodrugs, other polymers, protein-based nanoparticles, nanoparticles based on metals and other nanostructures are examples of nanostructures that are now marketed [62]. When used as nano-carriers, nanoparticles can improve the non-specificity of routinely administered cancer treatments and boost their solubility, stability, specificity, multimodality, and efficacy [53].

1. Types of nanocarriers [62]:
2. Nanocrystals
3. Polymeric nanoparticles
4. Liposomes
5. Magnetic nanoparticles
6. Micelles
7. Dendrimers
8. Mesoporous silica nanoparticles
9. Carbon nanotubes
10. Gold nanoparticles
11. Quantum dots
12. 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. These goods, which come from numerous international businesses, demonstrate the current and (presumably) future effectiveness of nanoparticles as medicinal agents. These categories include protein-based, lipid-based, polymeric (including PEGylated biologics, gels, and emulsions), metallic NPs (Nanoparticles), nanocrystals, liposomes, and lipid-based products [62-64].

1. Nanocrystals:
2. Emend®: The FDA approved aprepitant in its nanocrystalline form as Emend® (Merck & Co., Inc., NJ, USA) in 2003 [65].
3. 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 calcium hydroxyapatite (HA) [Ca10(PO4)6(OH)2] with crystals of 20 nm diameter. The osteoconducting properties of HA are similar to those of natural bone minerals [65].
4. Rapamune®: Sirolimus (rapamycin), also known as Rapamune®, is a medicine with the generic name Sirolimus that was approved by the FDA in 2010 and is manufactured by Wyeth Pharmaceuticals Inc., a division of Pfizer Inc. in Pennsylvania, USA. It is utilised to stop kidney transplant rejection [52].
5. Vitoss®: A popular synthetic bone graft alternative called Vitoss® (Orthovita, Inc. PA, USA) is made of 100 nm β-tricalcium phosphate (β-TCP, Ca3[PO4]2) nanocrystals and was approved by the FDA in 2003 through the 510(k) pathway, a process for approving medical devices [63].
6. 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].
7. TriCor® : In order to lower triglyceride and cholesterol levels to prevent the development of atherosclerosis, TriCor® (Abbott Laboratories; generic name: fenofibrate, IL, USA) was approved in 2004 [65].
8. Lipid-based nano pharmaceuticals and liposomes:
9. Doxil® (Liposomal Doxorubicin): The FDA granted approval to Doxil (Alza, Pakistan), also known as Caelyx®, Evacet®, and Lipodox®, in 1995. It is a form of nanodrug used to treat a variety of tumours, including AIDS-related Kaposi's Sarcoma (KS) and metastatic ovarian cancer [66].
10. DaunoXome® : Another anthracycline anticancer medication that can be used in chemotherapy for malignancies and HIV-associated Kaposi's Sarcoma (KS), liposomal daunorubicin, also known as DaunoXome® (Galen, Craigavon, UK), received FDA approval in 1996 [66].
11. Onivyde® (Irinotecan liposome injection): Irinotecan liposomal nanoformulation Onivyde® (Merrimack Pharmaceuticals, MA, USA), also known as MM-398 or PEP02, was authorised by the FDA in 2015 for the treatment of metastatic pancreatic cancer [66-67].
12. 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].
13. Marqibo® : The FDA approved liposome vincristine sulphate, also known as Marqibo® (Talon Therapeutics, CA, USA), in 2012. Vincristine is a tubulin-binding anticancer alkaloid that prevents cell division [67-68].
14. AmBisome® : The liposomal version of Amphotericin B (AmB) or L-AmB, known as AmBisome®  (NeXstar Pharmaceuticals, CA, USA), is an antifungal drug used to treat a variety of fungal diseases [66].
15. Vyxeos® : In 2017, the FDA approved the medication Vyxeos® (Jazz Pharmaceutics, Dublin, Republic of Ireland) for the treatment of adults with acute myeloid leukaemia brought on by prior therapy or acute myeloid leukaemia with changes associated with myelodysplasia [68].
16. Abelcet® : Abelcet, a different AmB lipid compound, was authorised in 1965 by (Defiante Farmaceutica of Funchal, Portugal) [65].
17. Visudyne®: The liposomal formulation of the photosensitizer (PS), benzoporphyrin derivative mono acid ring A, is called Visudyne® (QLT Phototherapeutics, Vancouver, Canada). It was given FDA approval in 2001 to treat wet age-related macular degeneration, which causes choroidal neovascularization [66].
18. Polymer based nano pharmaceuticals:
19. 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].
20. 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].
21. Neulasta® : The FDA granted approval for Neulasta® (Amgen, Inc., California, USA), a PEGylated version of filgrastim, in 2002 [65].
22. Oncaspar® : The FDA authorised Oncaspar® Enzon Pharmaceuticals Inc., NJ, USA), a PEGylated-Lasparaginase in 1994 under the generic name pegaspargase. Acute lymphoblastic leukaemia and chronic myelogenous leukaemia are both treated with this medication [65].
23. Pegasys® : The FDA authorised Pegasys®, also known as peginterferon alfa-2a, in 2002. It was manufactured by (Genentech USA, Inc. in California) before being marketed under the name (Hoffmann-La Roche Inc.) Recombinant human alfa-2a interferon Pegasys, which is conjugated to branched PEG (40 KDa), is used to treat chronic hepatitis B and hepatitis C [65].
24. Somavert® : The PEGylated analogue of human growth hormone (GH) for the treatment of acromegaly, Somavert® (Pfizer Pharmaceuticals, CT, USA), is known by the generic name pegvisomant (B2036-PEG). It was given FDA approval in 2003 [65].
25. 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].
26. Mircera® : Epoetin β (EPO) conjugated to methoxy-PEG, also known as Mircera®, is a medication formulation used to treat anaemia. Both the FDA and the European Commission approved Mircera in 2007 [65].
27. PEG-INTRON® : PEG interferon alfa-2b was approved by the FDA in 2001 and is now used as a monotherapy or in combination with other medications, such as ribavirin, to treat chronic hepatitis C [65].
28. Krystexxa® : Patients with refractory chronic gout can benefit from Savient Pharmaceuticals' Krystexxa® (also known as Pegloticase, formerly known as Puricase, NJ, USA).FDA approval came in September 2010 [65].
29. Plegridy® : The FDA authorised Plegridy or PEG-IFN-β-1a in 2014 for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) [65].
30. Adynovate® : Clinical trials have demonstrated this medication's security and effectiveness in treating haemophilia [66].
31. Other types of polymer-based nano pharmaceuticals:

Other than pegylated formulations, polymer-based nanopharmaceuticals either contain polymer chains as their own, like Copaxone® and Renagel, or use polymers to disperse drug molecules, like Eligard and Estrasorb [52,63,65-67].

1. Copaxone®
2. Eligard®
3. Renagel®
4. Estrasorb®
5. Zilretta®
6. Protein-based nano pharmaceuticals:
7. Abraxane® : The FDA has approved the drug Abraxane® (Celgene Pharmaceutical Co. Ltd.), also known as ABI-007, for the treatment of metastatic breast cancer in 2005, lung cancer in 2012, and metastatic pancreatic adenocarcinoma in 2013 [68].
8. Ontak® : In 1999, the FDA approved denileukin diftitox, also known as Ontak®  (Eisai, Japan), for the treatment of T-cell lymphoma [65].
9. Rebinyn® : In 2017, the FDA approved the PEGylated Glycoprotein Drug, also known as Rebinyn® (NovoNordisk, Bagsvaerd, Denmark). Patients with factor IX (FIX) deficiency, generally known as haemophilia, use it [65].
10. Metal-based nano pharmaceuticals:

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].

1. Feraheme® : In 2009, the FDA approved the injectable medication formulation ferumoxytol, also marketed as Feraheme® or Rienso® (AMAG Pharmaceuticals, MA, USA), for the treatment of anaemia [52-63].
2. Application of nanoparticles in COVID-19 Vaccines:
3. Pfizer-BioNtech:

On November 9, 2021, the New York-based pharmaceutical company Pfizer and the German company BioNTech made history by announcing that their coronavirus vaccine was over 90% effective. The FDA granted it the first emergency use permission ever granted to a coronavirus vaccine by the United States on December 11, just over a month later [52-69].

1. Moderna Vaccine:

On December 18, a week after the vaccination made by Pfizer and BioNTech, the FDA granted emergency use permission for a vaccine created by Boston-based Moderna. The COVID-19 vaccination Moderna was the second. The FDA has approved a vaccination. Similar to Pfizer and BioNTech, Moderna makes the vaccine using mRNA [52-70].

1. Oxford-AstraZeneca:

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

1. Sinopharm:

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

1. 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].

1. Johnson & Johnson:

Johnson & Johnson has investigated JNJ-78436735, also known as Ad26.COV2, a coronavirus vaccine. Scientific studies have demonstrated that a single dose of the vaccination rate reached 72% in collaboration with the Beth Janssen Pharmaceutical, the Israel Deaconess Medical Centre (a Johnson & Johnson division located in Belgium) produces that shot [52-69].

1. **Bioavailability and Bioactivity**

**A.** 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 enhancing 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].

* 1. **Enhancement of nano drug delivery system on Bioactivity**

Nano drug delivery systems (NDDS) have emerged as a revolutionary approach to improving 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.

* 1. **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.

Advantages of Enhanced Bioavailability:

1. 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.

1. 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.

1. 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].

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.

* 1. **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.

* *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.

* *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.

1. **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 chapter will provide a comprehensive overview of the applications of bioactive loaded nanotechnology in drug delivery.

* *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.

* *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.

* *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.

* *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.

* *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.

* *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 nanomicelles, 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.

1. **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 towards the realization of safer, more efficient, and patient-tailored therapies in modern medicine.

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