Nano drug delivery system: Key to novel approach

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ABSTRACT

Over the past few years, nanotechnology has had a tremendous impact on the drug delivery system. This technique is significantly changing how innovative medication delivery systems will function in the future (NDDS). One of the NDDS that has numerous uses in the areas of clinical treatment and research is nanoparticles (NPs). Therapeutic medications that are encapsulated in nanoparticle form provide benefits over conventional dosage forms of these drugs, including increased pharmacological efficacy, safety, biodegradability, bioavailability, and therapeutic index. The main focus of the current review article is on various nanoparticulate drug delivery systems, such as nanotubes, solid lipid nanoparticles, superparamagnetic nanoparticles, liposomes, quantum dots, dendrimers, ceramic nanoparticles, and nanoerythrosomes, as well as their usefulness in many fields.

Keywords: Nanotechnology , drug delivery system , nanoparticles, nanosponges , nanoemulsion

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INTRODUCTION

The word "Nano," which meaning "a billionth," is derived from the Greek word "Dwarf". A Nanometer is one billionth of a metre, or 250 millionth of an inch, or around 1/80,000 of the diameter of a human hair or 10 times that of a hydrogen atom [1]. Prof. Norio Taniguchi of Tokyo Science University first used the term "Nanotechnology" in 1974 to refer to the precise fabrication of materials with nanoscale tolerances. Unknowingly, Drexler used the phrase in his 1986 book "Engines of Creation: The Coming Era of Nanotechnology"[2].

ADVANTAGES OF NANOPARTICLES [3]

- ✓ Relatively simple preparation.
- ✓ Specific medication delivery.
- ✓ Nanoparticles' small size permits them to pass through tiny capillaries and be absorbed by cells, which enables effective medication accumulation at the body's target areas.
- ✓ Effective size and size dispersion control.
- ✓ The medicine in the capsule is well protected.
- ✓ Drug retention at the site of action.
- ✓ Extended clearance period.
- ✓ Enhanced therapeutic effectiveness.
- ✓ Enhanced bioavailability and Dose equivalence
- ✓ Drugs in stable dosage forms that either have an unacceptable low bioavailability in non-nanoparticulate dosage forms or are unstable in stable dosage forms.
- ✓ In an aquatic environment, active substances dissolve more quickly with increased surface area.
- ✓ Greater bioavailability is typically correlated with faster dissolution.
- ✓ Tinier drug
- ✓ Less variation between fed and fasting states.
- ✓ Reduced toxicity

Disadvantages of Nanoparticles:

- ✓ Toxicity concerns with the widespread usage of polyvinyl alcohol as a detergent.
- ✓ Limited ability to aim.
- ✓ It is not feasible to stop therapy.
- ✓ Cytoxicity.
- ✓ Pulmonary inflammatory disease and lung cancer risk
- ✓ Inflammation of the alveoli.
- ✓ The interference with autonomic balance caused by nanoparticles, which has an immediate impact on vascular and cardiac function.[3]

CHALLENGES

Low Solubility: One of the main issues when creating a particular medicine formulation is low water solubility. The bioavailability of the dig is impacted by poor solubility[4][5]. As a result, it represents a significant hurdle for any novel chemical entity that researchers and businesses uncover.

Low bioavailability: The percentage of a drug dose that is available for systemic circulation is known as bioavailability. It is a significant aspect of the drug's pharmacokinetics. When given intravenously, a drug's bioavailability is 100%; however, due to partial absorption, when given orally, the drug's bioavailability lowers. Thus, when administering the medicine in a manner other than intravenously, bioavailability must be taken into account[6].

Low efficacy: Efficacy is the highest effect a medicine dose may produce. Drugs need to have high binding affinities to their targets in order to be highly effective. This is referred to as the drug's molecule's affinity[7]. If the drug and target molecule have a poor affinity, the maximum response will be lowered. One of the main issues with medication molecules that causes treatment of serious diseases to take a long period is low efficacy[8].

Quick Excretion: Quick excretion is the process through which excretory organs, such as the kidneys, remove drugs from the body. Fast drug molecule excretion reduces the medicine's effectiveness since the target organs do not receive the intended amount of drug molecule [9].

Fraction of medication necessary zone is not persistent. In some areas of the organ, such as the tumour cells, a high concentration of drug is required in comparison to normal cells to ensure proper and effective therapy. Chemotherapeutic drugs are related to a lack of optimal drug accumulation throughout the course of cancer treatment[10].

Action Mechanism of Nano Drug Delivery Systems:

Nanoparticles can be used to enhance drug delivery because they have advantageous features that can be leveraged to circumvent the body's defence mechanisms. In an effort to improve the effectiveness, safety, and tolerance of ingested medications, several nanoparticle formulations have been used in drug research. High solubility, controlled release, and better pharmacokinetic and pharmacodynamic features have all been demonstrated by formulations based on nanoparticles. Effective nanoparticle delivery systems can be made using a variety of processes, and particle size, surface charge, and shape are crucial factors **[11]**.

1.Particle size: The most crucial aspects of nanomaterials are their particle size and size distribution, which affect their chemical and physical properties. The in vivo distribution, biological destiny, toxicity, and targeting capacity of these nanomaterials for drug delivery systems are determined by their hydrodynamic size and size distribution. They have the ability to control medication loading, release, and stability. According to reports, nanomaterials have an advantage over microscale particles because of their tiny size and high mobility, which allows for greater cellular uptake and makes them appropriate for a variety of cellular and intracellular targets[12]

2.Surface Charge: Surface charge is typically expressed and evaluated in terms of a nanomaterial's zeta potential, which represents the electrical potential of particles and is impacted by both the composition of the particle and the media in which it is disseminated. According to reports, zeta potentials with values below 30 mV are stable in suspension and help keep particles from aggregating[13]. Nanomaterial surface charge is essential for drug loading. Several techniques, including covalent conjugation, hydrophobic contact, charge-charge interaction, and encapsulation, can be used to load drugs. The nature of the medication and the nature of the target molecule both influence how molecules are loaded, which also changes the surface charge. It is possible to identify the attachment or adsorption of charged molecules to a nanoparticle's surface by adjusting the zeta potential[14].

3. Loading drugs

Medication loading is the process of incorporating a drug on or in nanomaterials. The best drug delivery system for nanoparticles should be able to load large amounts of medication without aggregating. High medication loading capacity can reduce dosage or administration[15]. Dispersibility is required for the medications to be delivered smoothly and effectively. Drug loading can be done in a variety of ways, but the effectiveness of drug loading and entrapment depends on the drug's solubility in the nanoparticles, the dispersion medium, the size and composition of the nanomaterials, the drug's molecular weight (MW), its solubility, the interaction between the drug and the nanomaterials, and/or the presence of surface functional groups (such as carboxyl, amine, ester, etc.) on either the drug or the nanomaterial[10][16].

4.Targeting Drug Use

Nanomaterials that target the tumour improve chemotherapy and offer a highly specialised and adaptable platform for cancer treatment. Due to fenestrated blood arteries, enhanced permeability and retention allow for selective localisation in tumours on an as-needed basis, as in the case of drug-loaded liposomes (doxorubicin-liposome complex). There is evidence that Nanosize liposomes target tumours spontaneously because of the fenestrated blood arteries, effectively improving selective localisation of small-molecule medicines like doxorubicin in human malignancies in vivo. Increased permeability and subsequent drug retention are to blame

for this[17]. As opposed to targeting ligand-drug conjugates, targeting nanomaterials as drug delivery vehicles or nanocarriers for site-specific delivery provides a number of benefits.

When a ligand connects with its receptor, a substantial payload of therapeutic agent compared to the number of ligand-binding sites can be delivered to the target cell or tissue by efficient drug loading of high concentrations of drug within the nanocarriers. Through the improvement in the tumour signal to background ratio, this is highly beneficial for imaging tumors[18].

The medicine is loaded without regard to how the ligands are coupled because the nanocarriers are connected to the ligand. Additionally, this avoids pharmacological activity that may be caused by the conjugation of a ligand and a drug or that has been rendered inactive by a potentially harmful coupling event. Depending on the size of the nanomaterials and the size of the medicine, several ligand molecules can be attached to the nanocarriers to boost the likelihood of binding to target cells, particularly for those with low binding affinities[19]

5. Attachment to receptor sites

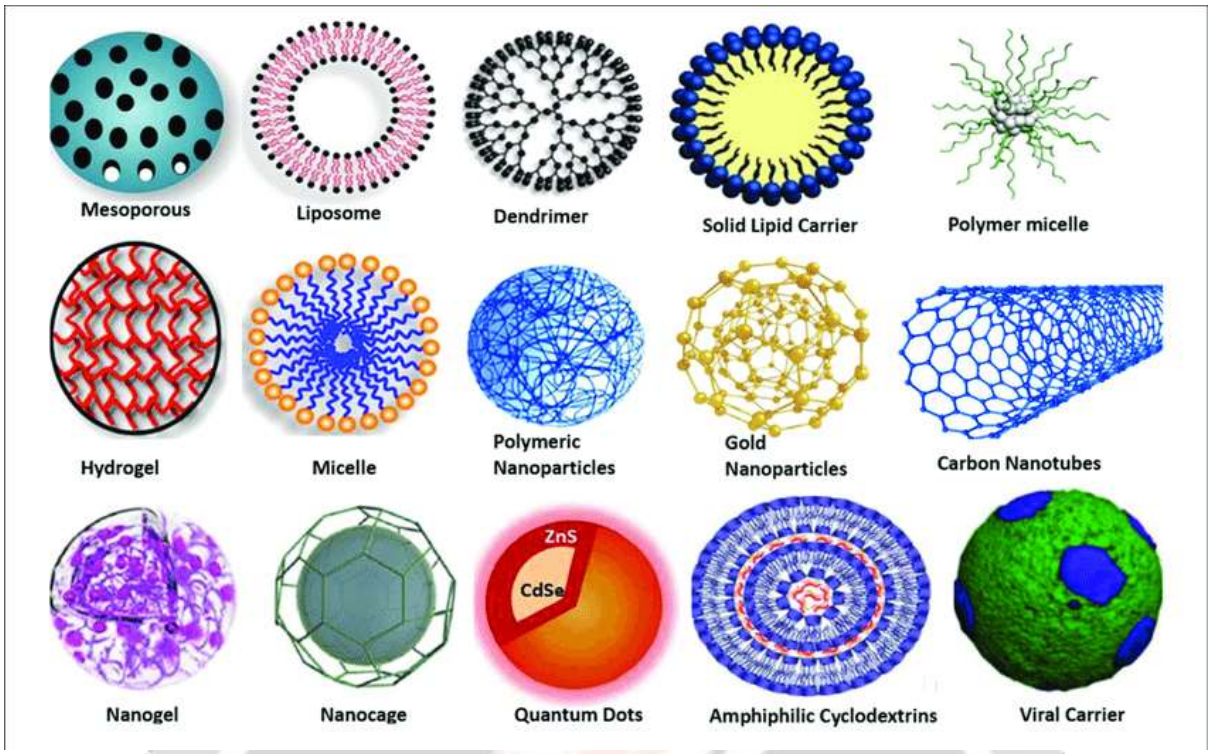
When drugs are given to the MPS (Mono Phagocytic System), which includes the liver, spleen, lungs, and bone marrow, they change the drug distribution profile. However, when injected intravenously, nanoparticles as drug carriers can be detected by the human immune system, which causes phagocytes to remove them from circulation[20]. The amount of blood components (such as opsonins) that bind to a nanoparticle's surface and influence its in vivo fate depends on the nanoparticle's size, surface hydrophobicity, and surface coating functionalities[21]. Preventing opsonization and extending the circulation of nanoparticles in vivo are crucial for improving the odds of medication targeting success. The nanoparticles can do this by utilising nanoparticles with biodegradable hydrophilic copolymers, such as PEG (Polyethylene Glycol), or by pre-coating them with hydrophilic polymers and/or surfactants [22].

The increased permeability and retention (EPR) effect causes extravasation of nanoparticles as they enter tumour tissues. In order to attain longer circulation half-lives by reduced macrophage mononuclear absorption and more effective cellular uptake, medications carried by nanoparticles for delivery or nano-enabled drugs at the lower size range are preferred to the upper submicron and micron sizes [23].

6. Drug Release

Drug release is the process of releasing a drug from a nanoparticle into the body, whereas biodegradation is the collapse of the drug delivery system within the body. When creating a nanoparticle drug delivery system, it's crucial to take into account both drug release and biodegradation. The drug's effectiveness is further influenced by its solubility, diffusion, and particle size in addition to its active ingredients. Due to the small size of the particles, a high surface-to-volume ratio causes a quicker drug release at the surface. Larger particles, on the other hand, have larger cores, allowing for the encapsulation of more medicines per particle and a slower release. Therefore, adjusting drug release rates can be triggered by changing particle size [24].

Nanomaterials' interactions with cells give them an advantage while trying to pass the blood–brain barrier. The blood brain barrier is made up of a layer of endothelial cells that surrounds the brain and blocks the passage of high-molecular weight substances. Nanoparticles' ability to cross the blood–brain barrier is a significant benefit for drug delivery systems for successful therapies[25]. Despite the advancements and innovations in nanotechnology-based medicinal techniques, the efficacy of nanoparticles for the treatment of neurological illnesses, such as brain tumours, strokes, and Alzheimer's disease, has remained mostly limited. The development of neurology-related nanotechnology-based diagnostics and therapies will continue to depend on the targeting of medications to the central nervous system[26].



TYPES OF NANOPARTICLES DRUG DELIVERY

1.Nanosuspension

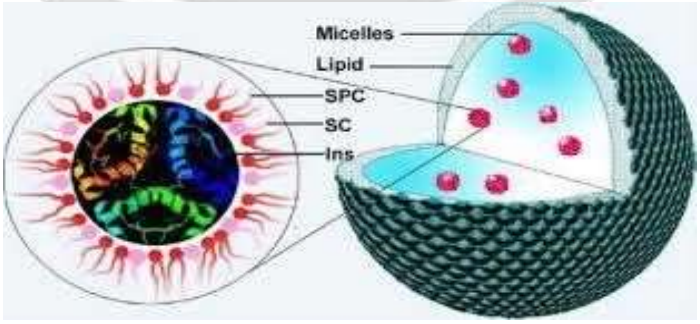
Nanosuspension is the term used to describe the suspension of medication nanoparticles in a liquid. The size of a nanoparticle ranges from 200 to 500 nm, and the compound's improved saturation, solubility, and dissolving rate make nanosuspension stand out. Under 1 mcm in size, the saturation and solubility rise [27]. Nanosuspension also has the ability to alter the crystalline structure of a particle, so increasing its amorphous proportion or even producing entirely amorphous particles. The adhesiveness of nanoparticles and nanosuspensions to tissue is increased [28]. According to reports [29], administering drugs orally in the form of nanosuspension increases their bioavailability and rate of absorption.

Examples of nanosuspension: To increase ocular availability, ibuprofen is produced as a nanosuspension using the emulsion-solvent diffusion process. [30] In contrast, Danazol's nanosuspension is created using nanocrystal technology to increase bioavailability.

2. Solid nanoparticles of lipid (SLN)

The submicron colloidal carriers (50–1,000 nm) that make up the solid lipid nanoparticles are made of physiological lipid and are distributed in water or an aqueous surfactant solution. Liquid lipid was substituted with a solid lipid to address the drawbacks of oil droplets in their liquid state, which eventually resulted in solid lipid nanoparticles [29].

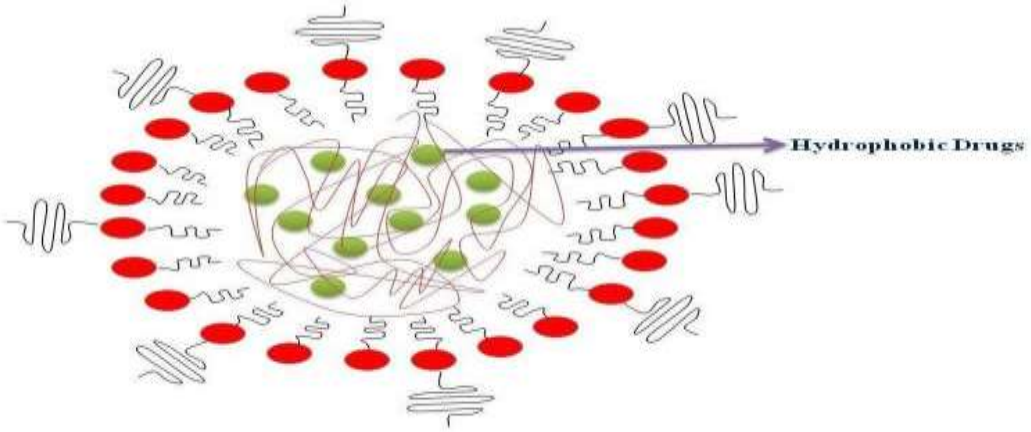
Figure: Solid Lipid Nanoparticles



3. Nanoparticles made of polymers [31]

A nanoparticle matrix is used to dissolve, trap, absorb, adhere, or encapsulate the medication. Depending on the method of preparation, varied qualities and release characteristics for the encapsulated medicinal agent can be obtained in the form of nanoparticles, nanospheres, or nanocapsules. Nanospheres are matrix systems in which the drug is physically and uniformly spread, in contrast to nanoparticles, which are vesicular systems in which the drug is confined to a cavity surrounded by special polymer membranes. The benefits of employing

nanoparticles for medicine delivery come from their two primary fundamental characteristics. Due to their small size, nanoparticles can first enter smaller capillaries and then be ingested by cells, enabling effective drug accumulation at the target areas. Second, the sustained drug release within the target location over a period of days or even weeks is made possible by the use of biodegradable components in nanoparticle synthesis.



Polymeric Nanoparticle

4. polymeric micelles

Numerous studies on polymeric micelles as a medication carrier have been conducted [32]. The low critical micellar concentration of polymeric micelles, which renders them stable and prevents their rapid dissociation in vivo, indicates that polymeric micelles have greater thermodynamic stability in physiological solution.

Micelles are distinguished by their distinctive core-shell design, in which hydrophobic regions are isolated from the aqueous exterior, and have a relatively restricted size distribution in the nanometer range.

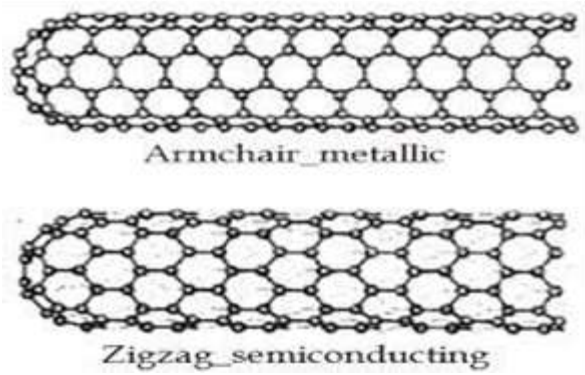
For the systemic distribution of medications that are not water soluble, micellar systems are helpful [33]. From stable dispersion in aqueous media, drugs can be partitioned in the hydrophobic cores of micelles and the outer hydrophilic layer, which can subsequently be delivered intravenously. Following intravenous injection, the distribution of drug-loaded polymeric micelles (less than 100 nm in diameter) has been demonstrated to have a prolonged systemic circulation duration due to their smaller size and hydrophilic shell, which reduces their uptake by the reticuloendothelial system. Medicines that are integrated into polymeric micelles have a restricted distribution in non-targeted locations and may accumulate into tumours to a larger extent than free drugs.

5. Nanoscale magnets

In the world of medicine, magnetic nanoparticles are an effective and adaptable diagnostic tool. Techniques for magnetic immunoassays have been developed in which the magnetically labelled target's primary field is immediately measured by a sensitive magnetometer. Magnetic resonance imaging contrast agents include superparamagnetic nanoparticles. The inorganic iron oxide core of the magnetic nanoparticles is covered with a polymer, such as dextran. After routine dosing, indomethacin concentration was higher in the liver and spleen, where endocytosis and phagocytosis could take place, showing selective targeting by magnetic nanoparticles of 8000 Oe-strength [34].

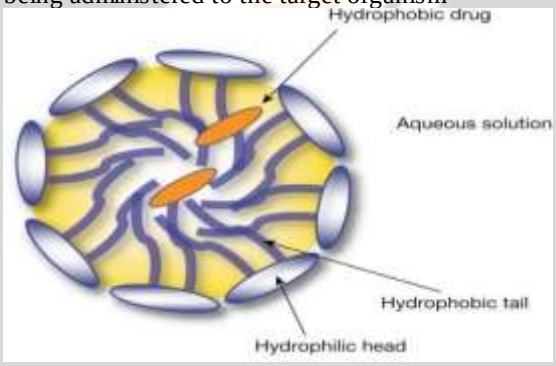
6.Carbon nanotubes

With a diameter as small as 0.7 nm and a length of several millimetres, carbon nanotubes are a novel kind of carbon molecule that are surrounded by a hexagonal network of carbon atoms [35]. A half fullerene molecule can open or close each end. Nanotubes are special materials because of their tiny dimensions and exceptional physical, mechanical, and electrical capabilities. Despite weighing six times less than the best steels, carbon nanotubes have a mechanical strength that is more than sixty times greater. Additionally, they offer three-dimensional structures, have a very large specific surface area, are superior heat conductors, and exhibit special electrical properties. They can absorb molecules at a higher rate [36].



7.Liposomes

A valuable tool in biology, biochemistry, and medicine is the liposome. Liposomes are tiny synthetic vesicles with a spherical form that can be made from cholesterol and naturally occurring, non-toxic phospholipids. Liposomes are a promising drug delivery technology because of their size, hydrophilic and hydrophobic nature, and biocompatibility. Properties of liposomes are greatly influenced by lipid composition, size, surface charge, and production technique. Due to their size and quantity of bilayers, they are divided into three classes. Small unilamellar vesicles (SUV) are 25–50 nm in diameter, enclosed by a single lipid layer. SUV-like heterogeneous groups of vesicles known as large unilamellar vesicles (LUV) are encased in a single lipid layer. The lipids in multilamellar vesicles (MLV) are split into different groups by a layer of liquid water between them. In comparison to medications in solution, pharmaceuticals coupled with liposomes have significantly different pharmacokinetic features. They work well in lowering systemic toxicity and preventing the encapsulated drug from degrading too soon after being administered to the target organism [37].



Fig; Liposomes

8. Gold-coated nanoshells

The newly developed composite nanoparticles known as gold nanoshells have the distinct biocompatibility of gold colloid and infrared optical activity. Concentric sphere nanoparticles known as metal nanoshells have a dielectric (usually silica or gold sulphide) core and a metal (gold) shell. The plasmon-derived optical resonance of gold can be considerably altered in wavelength from the visible area of maximal physiological transmissivity by altering the relative thickness of the core and shell layers. The gold nanoshell's absolute size can be changed [34], and It is possible to make it either selectively absorb incident light (for particle diameter 75 nm) or disperse it. The surface characteristics of gold nanoshells are nearly identical to those of gold colloid because the gold shell layer is produced using the same chemical process utilised to create gold colloid. Breast cancer cells can be destroyed using gold nanoshells.

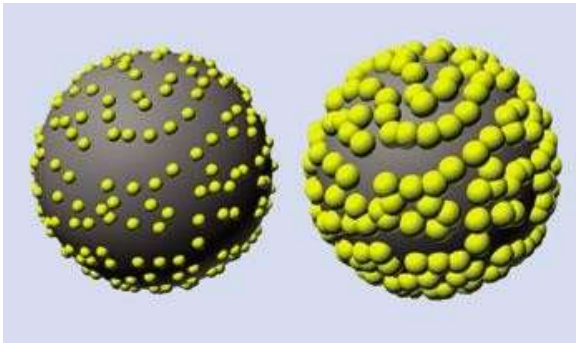


Figure ; Nanoshells

9.Ceramic nanoparticles

The recently discovered field of encapsulating biomolecules in inorganic (ceramic) particles has potential applications in a number of cutting-edge areas of contemporary materials science, including medication delivery systems. Ceramic nanoparticle benefits include straightforward preparation with desired size, shape, and porosity, as well as no impact on swelling or porosity with no pH change.

10.Nanopores

Due to their exceptional qualities in terms of thermal insulation, controllable material separation and release, and their suitability as templates or fillers for chemistry and catalysis, materials with defined pore-sizes in the nanometer range are of particular interest for a wide range of industrial applications [38]. Aerogel is a type of nanoporous material that is created using the sol-gel chemical process.

11.Nanowires

Nanowires are conductive or semi-conductive particles with a high length/diameter ratio and a crystalline structure of a few dozen nm. Nanowires based on silicon, cobalt, gold, or copper have already been created [35]. In nanoelectronics, they are used to transport electrons and can be made of different metals, including oxides, sulphides, and nitrites.

PREPARATION OF NANOPARTICLES FROM PREFORMED POLYMERS

Method for evaporating emulsion solution

It involves two steps. The polymer solution is turned into an aqueous phase in the first stage, and then the solvent for the polymer is evaporated in the second step, precipitating the polymer as nanoparticles that are then collected by ultracentrifugation, cleaned with distilled water, and lyophilized for storage [39]

Method using two emulsions and evaporation

To create an emulsion-free mixture, the aqueous drug solution is added to the organic polymer solution while being vigorously stirred. The second aqueous phase is then added, and continuous stirring is used to create the w/o/w emulsion. High-speed centrifugation is used to separate the nanoparticles, while evaporation removes the solvent from the emulsion [40]. For the encapsulation of hydrophilic drugs, the double emulsion approach is used [41].

salting-out technique

A salting-out phenomenon is used to separate the water-miscible solvent from the aqueous solution [42]. Heat-sensitive materials can use this procedure because it doesn't require a temperature increase [43].

Method of emulsions in diffusion

The encapsulating polymer is saturated with water after being dissolved in a fairly water-miscible solvent. Then, a stabiliser containing an aqueous solution emulsifies the polymer-water saturated solvent phase. Either filtering or evaporation are used to remove the solvent. The technique reduces scale up, requires no homogenization, and is highly reproducible [44].

Method of solvent precipitation

The premade polymer is precipitated from an organic solution using this approach, and the organic solvent is diffused in the aqueous medium whether surfactants are present or not [45].

Dialysis

A dialysis tube is filled with the appropriate molecular weight cutoff polymer that has been dissolved in an organic solvent. Dialysis is carried out. Following the displacement of the solvent inside the membrane, the polymer aggregates and a homogenous suspension of nanoparticles is created and method use of supercritical fluids

Supercritical fluids are a kind to the environment and have the ability to create highly pure polymer nanoparticles [46]. It provides a useful and efficient method of particle synthesis while avoiding the disadvantages of conventional techniques [47].

PREPARATION OF NANOPARTICLES BY MONOMER POLYMERIZATION

Polymerization of emulsions

Due to the use of hazardous chemical solvents, one of the earliest techniques for producing nanoparticles has lost some of its significance [48]

Polymerization of a mini-emulsion

A high-shear instrument (ultrasound) and a low-molecular-mass chemical are used in mini-emulsion polymerization [49].

Polymerization of microemulsions

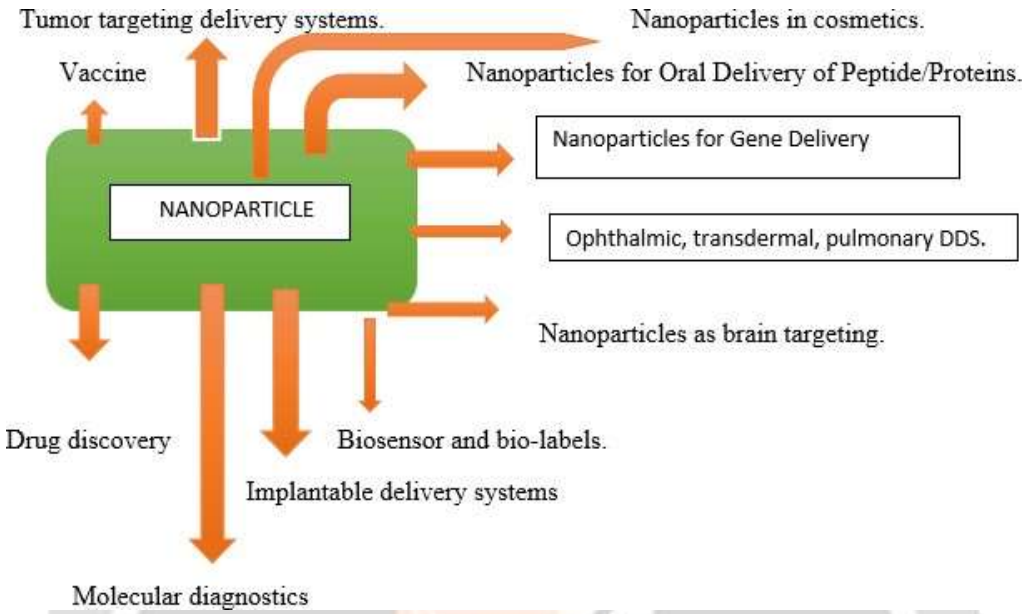
The aqueous phase of a microemulsion containing thermodynamically stable swelling micelles receives the water-soluble initiator. A surfactant that has interfacial tension almost 0 at the oil/water contact totally covers the particles [50].

Multi-layer polymerization

This kind of step-growth polymerization takes place at the boundary between an organic solution containing a second monomer and an aqueous solution that contains one monomer [51]

NANOPARTICLE PHYSICOCHEMICAL CHARACTERIZATION

Using sophisticated microscopic techniques including scanning electron microscopy, transmission electron microscopy, dynamic light scattering, and atomic force microscopy, the transfection efficiency of nanoparticles is assessed by their particle size, shape, and surface charge [52]. Particle diameter, size distribution, and surface charge all have an impact on the physical stability and distribution of nanoparticles [53]



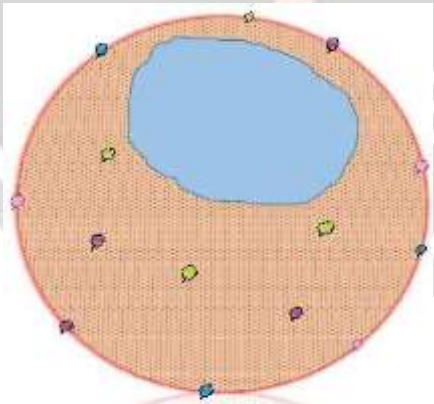
Application of nanoparticles in pharmaceutical field

NANOSPONGES

Introduction

Although the first Nanosponge drug delivery system was solely intended for topical use, they are now also available for oral and intravenous (IV) administration [54].

A contemporary type of material known as a "nanosponge" is composed of minute particles with a small, nanometer-wide hollow. Different kinds of materials can be used to fill these little cavities. These tiny particles have the potential to carry both hydrophilic and lipophilic therapeutic substances, which increases the stability



of molecules or medication substances that are weakly water-soluble [55].

Fig. 1: Structure of a nanosponge showing a cavity for drug loading

Advantages of nanosponges

1.Increase the drug's low water solubility in aqueous solution.
2.Nanosponges have the ability to release medication molecules in a controlled manner.
3.The nanosponges function as a self-sterilizer since bacteria cannot pass through their minuscule (0.25 m) pore size.
4.Nanosponges are a non-irritating, non-mutagenic, and non-toxic drug delivery mechanism.
5.Nanosponges aid in the removal of poisonous and venomous material from the body.

6.Drug administration by nanosponges minimises negative effects.
7.Boost the formulation's flexibility and stability.
8.Lower the dosage frequency.
9.Better adherence from the patient.
10.Nanosponges complexes are stable at temperatures of 130 °C and a wide range of pH (i.e. 1- 11) [56]

Disadvantages of nanosponges

1.Dose dumping may occasionally occur with nanosponges since they can only encapsulate small chemicals and are not suited for bigger compounds [57]

Methods of preparation

Solvent method

Nano sponges are made via the solvent approach by combining the polymer with polar aprotic solvents like dimethyl sulfoxide (DMSO) and dimethylformamide (DMF). Then, a crosslinker is added to this mixture at a 1:4 ratio. The aforementioned reaction needs to be carried out at a temperature of 10 °C to reflux the solvent's temperature for a duration of 1 to 48 h. The solution is cooled to room temperature when the reaction is finished, and the resultant product is then added to bi-distilled water. Under vacuum, the product is filtered, refined by soxhlet extraction with ethanol, and then dried to recover the product.

Emulsion solvent diffusion method

This approach creates nanosponges by mixing ethyl cellulose and polyvinyl alcohol in various ratios or amounts. This approach employs both dispersed and continuous phases. Ethyl cellulose and the medication form the dispersed phase, which is then combined with 20 ml of dichloromethane and some polyvinyl alcohol (PVA) to create the continuous phase (aqueous). The mixture is then agitated for around two hours at a speed of 1000 rpm. By filtration, the finished product, or nanosponges, are obtained. At a final temperature of 400 °C, the product is innoven dried [58].

Characterization of nanosponges

The following is a list of the characterisation techniques for the drug/nanosponges complex:

studies on solubility

It is possible to assess the drug's solubility and bioavailability using inclusion complexes. This method is the one that is used the most frequently to analyse the inclusion complexes of nanosponges. The plot of a project can be used to determine its level of completion phase sluggishness Studies on drug solubility are carried out to determine the medication's pH, solubilization profile, and to assess the factors influencing drug solubility [59].

Microscopic study

Scanning and transmission electron microscopes can be used to study drugs and nanosponges at the microscopic level. The discrepancy between the crystallisation state and the final product visible under an electron microscope indicates inclusion complex development.

Zeta potential determination

Zeta potential is the differential in potential between two layers of fluid that are imprisoned with scattered particles (the dispersion medium and immobile layer). The primary indicator for the stability of the colloidal dispersion is zeta potential. The zeta potential can be determined by adding an additional electrode to particle size analysis equipment or a zeta seizer. The stability of a colloidal dispersion increases with zeta potential value.

Thermodynamical method

The thermo-chemical approach can be used to assess whether drug molecules or particle alterations take place before the thermal destruction of nanosponges. Melting, evaporation, oxidation, breakdown, and polymeric modifications are only a few of the possible drug particle alterations. The drug molecules' alterations show that a strong complex has formed.

Particle size and polydispersity

Using the 90Plus particle size determining programme, the dynamic light scattering technique is used to determine the size of the particles. The definition of dynamic light scattering (DLS) as a method for determining the size distribution profile of nanoparticles. Finally, the poly-dispersity index (PDI) and particle diameter can be determined.

Thin layer chromatography (TLC)

TLC can be characterised as a method for separating non-volatile or evaporative mixtures. If a certain drug molecule's Rf value falls within the allowed range in this approach, it can be useful in identifying the development of a complex between the drug and the nanosponges.

Infrared spectroscopy

Infrared spectroscopy can be used to analyse how the medicine interacts with nanosponges in the solid state. As complexes develop, nanosponge bands can somewhat alter. Less than 25% of complexes have guest molecules attached, and the medication The spectrum of nanosponges makes it simple to conceal spectrum. The method is ineffective for identifying the inclusion complex when compared to other methods [60].

Loading efficiency

By measuring the amount of drug loaded into a nanosponge using a UV spectrophotometer and high-performance liquid chromatography for nanosponges, one may calculate the loading efficiency of a given nanosponge particle. The following equation can be used to determine the loading effectiveness of nanosponges.

Application of nanosponges

Because of their biocompatibility and adaptability, nanosponges have a wide range of applications in the pharmaceutical industry. Nanosponges can be utilised as an excipient in the pharmaceutical industry to create

$$LE = \frac{\text{Actual drug content in nanosponges}}{\text{Theoretical drug content}} X\,100$$

topical dosage forms as well as tablets, capsules, granules, pallets, suspensions, and solid dispersions. Both lipophilic and hydrophilic drug molecules, or more specifically those chemicals that fall within the biopharmaceutical classification system (BCS-class II) as well as the poorly water-soluble medication, can be accommodated by nanosponges [61].

Nanosponges for drug delivery

Because of their minuscule porosity structure, nanosponges can transport the medicine that is insoluble in water. Solubility and permeability of drug nanosponges complexes play a significant effect in accelerating the rate of dissolution. According to reports, nanosponges made of -cyclodextrine are three to five times more effective at delivering the medication to the desired location. Nanosponges can be manufactured for oral, parenteral, topical, or inhalation dose forms and are typically solid in nature. The nanosponges complexes are dissolved in a suitable excipient, such as lubricants, diluents, and anti-cracking agents, to prepare tablets or capsules for oral delivery.

Nanosponges for cancer therapy

The delivery of anticancer drugs is currently one of the most difficult tasks in the pharmaceutical industry because of their poor solubility. According to one report, direct injection is three times less effective than nanosponge's complex at slowing tumour growth. The complex of the nanosponge loads a drug and exposes a tightly-attached targeting peptide

having an upper layer of radiation-induced cells on the tumour receptor. When nanosponges come into contact with a tumour cell, they adhere to its surface and begin to release medication molecules. Targeting drug delivery has the benefit of achieving a more potent therapeutic impact at a lower dose and with fewer adverse effects [62].

Nanosponges for delivery of protein

Bovine serum albumin (BSA) was employed as a model protein to examine the ability of -cyclodextrin-based nanosponges to encapsulate substances. Because the protein solution for bovine serum albumin (BSA) is unstable, it is kept in lyophilized form for storage. When proteins are lyophilized from their natural structures, they might become denatured. The key challenge in creating and developing proteins is preserving their natural structure for long-term storage both before and after processing. Nanosponges can improve the protein stability when delivering proteins containing cyclodextrine bases, such as bovine serum albumin (BSA). Additionally, protein encapsulation, controlled administration, stabilisation, and enzyme immobilisation have all been accomplished using nanosponges [63].

Role of nanosponges for treatment of fungal infections

One of the most serious diseases in the world is a fungus infection of the skin [64]. Due to a number of benefits, including the ability to target medications to the site of infection directly and a decrease in systemic adverse effects, topical therapy is a popular option for the treatment of conjunctivitis. A pharmaceutical fungicide known as imidazole, sometimes known as econazole nitrate, is used topically to treat vaginal thrush, jock itch, tinea capitis, ringworm, and athlete's foot. Cream, ointment, lotion, and solution are the econazole nitrate items that are currently on the market. A high concentration of active ingredients must be mixed in order for econazole nitrate to be effectively absorbed when administered topically. Due to this, econazole nitrate nanosponges were created using the emulsion solvent method and put in a hydrogel as a topical administration system for the drug's prolonged release [65–66].

Itraconazole, another antifungal medication, is classified as a class II biopharmaceutical product and has a slow disintegration rate and low bioavailability. Therefore, the goal of this work was to make itraconazole more soluble in order to address the bioavailability issue. Itraconazole's solubility can be improved in these nanosponges by using -cyclodextrine that has been cross-linked with carbonate bonds and loaded with itraconazole.

Nanosponges, which are absorbent in treating poison in blood, can remove the harmful poison from our blood by absorbing the poison. By injecting nanosponges into the circulation, we can use them to absorb poisons rather than antidotes.

The nanosponge imitates a red blood cell in the bloodstream where it deceives toxins into attacking it before absorbing it. Each nanosponge has a different capacity for absorbing toxic compounds [67].

NANOEMULSION

Introduction

Oil-in-water (o/w) emulsions with mean droplet diameters between 50 and 1000 nm are known as nanoemulsions. The phrases sub-micron emulsion (SME) and mini-emulsion are sometimes used interchangeably because the typical droplet size is between 100 and 500 nm. Since the first nanoemulsion was created in the 1940s, there are three different types of nanoemulsions: oil-in-water (O/W), water-in-oil (W/O), and bi-continuous. By changing the components of the emulsions, these three varieties can be converted between one another. [68]

Advantage of Nanoemulsion[69]

1.reduce the unpredictability of the absorption
2.improving the solubility of compounds that are lipophilic
3.use to cover up a bad taste
4.Use for medication delivery via many routes, including as topical, oral, and intravenous.
5.facilitated effective and quick medication absorption through the skin and GIT.

Disadvantage of Nanoemulsion[70]

1.Surfactant and co-surfactant, which are crucial for stability, have to be used at high concentrations.
2.Temperature and pH levels in the environment have an impact on the stability of nanoemulsions.
3.The applied surfactant and co-surfactant should not be harmful.
4.Low solubility capacity for compounds with high melting points

Nanoemulsion types[71]

Nanoemulsions are divided into three categories based on their oil and water phases:

• Water and oil (o/w) In this system, an oil droplet from the internal phase is disseminated in an aqueous phase outside of it.

• In a water-in-oil (w/o) nanoemulsion, water droplets from the internal phase are disseminated across the external oil phase.

• Bi-continuous Nanoemulsion In this system, water and oil droplets are sporadically distributed throughout.

The stability of these three types of Nanoemulsions was achieved by adding an adequate amount of compatible co-surfactant. The co-surfactant could be anionic, cationic, or nonionic.

Component of Nanoemulsion

- Oil
- Surfactant
- Co- Surfactant
- Aqueous phase

Oil

Since the medicine will be integrated as a droplet in the oily phase that disperses in the aqueous phase, the choice of oil utilised in the formulation of the nanoemulsion is regarded as a crucial element. Therefore, the oil chosen must be able to dissolve the ingredients used in dosage forms to obtain a larger percentage of drug-loaded, and it also needs to be compatible with other Nanoemulsion components. Nanoemulsion uses natural, synthetic, or semi-synthetic oils. [72]

Surfactant (surface-active agent)

Surfactants are chemicals that reduce the surface tension or interfacial tension that exists between a solid and a liquid. Depending on the hydrophilic-lipophilic balance (HLB) ratio, surfactants can serve as detergents, dispersants, wetting agents, foaming agents, emulsifiers, and wetting agents. Surfactant is used in the creation of nanoemulsions to stabilise the system, and the choice of surfactant depends on the type of nanoemulsion being created. For o/w nanoemulsion, hydrophilic surfactants with HLB values more than 10 are utilised, whereas hydrophobic surfactants with HLB values lower than 10 are used for w/o nanoemulsion. Utilizing surfactant mixtures with low and high HLB values causes a stable nanoemulsion to form after water dilution. [73]

Co- Surfactant

When the surfactant failed to reduce the interfacial tension between oil and water, these components were added to the formulation of nanoemulsions. As a co-surfactant, propylene glycol, poly glyceryl oleate, or PEG 400, it penetrated a monolayer of surfactant and disrupted its crystalline liquid phase, hence reducing the interfacial tension of the surfactant when it has a high stiffness. [74]

Aqueous phase

Since deionized water has a pH of 7 and no electrolytes, it is employed as the aqueous phase in the formulation of nanoemulsions. Ionic content, electrolytes, and pH are examples of aqueous phases whose composition might affect an emulsion's stability and droplet size. Due to a fall in zeta potential and a pH change in the formulation, the electrolyte reduces the repulsion force between droplets, causing droplet flocculation in the formulation .[75]

Methods of Nanoemulsion preparation

High–energy emulsification method

Since nanoemulsions cannot form spontaneously, they are thought of as non-equilibrium systems that require chemical or mechanical energy to create. Ultrasound generators, high-pressure homogenizers, and high-shear stirring are used to provide mechanical energy input during the preparation of nanoemulsions using the high-energy approach. [76] Strong forces encourage the formation of nanoemulsion by these mechanical devices, which break the phases of the water and oil. In order to create homogeneously small droplets under high pressure and in the shortest amount of time, homogenizers are frequently used in the production of nanoemulsions. The cost-effectiveness of an ultrasonic generator comes from the requirement for less surfactant. [77]

Low–energy emulsification method

By utilising the system's physicochemical characteristics, this approach produced droplets that were smaller and more uniform .[78] This approach has several restrictions on the sorts of oils and emulsifiers it can use, including proteins and polysaccharides. Synthetic surfactants are utilised in high concentrations along with low-energy methods to overcome this issue, but this is limiting the range of applications, particularly for food processing. [79]

Spontaneous Nanoemulsion

It makes use of the chemical energy generated during dilution procedures with a continuous phase that maintains a consistent temperature throughout the emulsification process without causing the system to shift into a different phase. [80] This process creates Nanoemulsion at ambient temperature without the use of any extra equipment. Oil droplets spontaneously formed in this system when an oil phase containing a hydrophilic ingredient was combined with water. This mechanism depends on water-dispersible material moving from the oil to the water phase as indicated by the red arrows. [79]

Phase inversion temperature (PIT)

This approach involves a constant composition and a change in temperature. The solubility of nonionic surfactants like poly ethoxylated is temperature dependent. As a result, the emulsifications happened by changing the affinities of surfactants to oil and water in relation to temperature. The PIT approach results in the smallest droplet size and interfacial tension. emulsifications by taking use of the low interfacial tension at HLB temperature. [81]

Phase inversion composition (PIC)

This method involves a steady temperature change in the composition temperature. The addition of a single component to the emulsion is simpler than causing a change in temperature, hence the (PIC) method is employed for large-scale production rather than (PIT). By continuously adding oil or water to a mixture of water and surfactant or oil and surfactant, nanoemulsion is created. [80]

Evaluation of Nanoemulsion:

Transmission electron microscopy, nanoemulsion droplet size analysis, viscosity estimation, refractive index, in vitro skin[82], permeation studies, skin irritation test, in vivo efficacy study, thermodynamic stability studies, and surface characteristics are some of the various characterization parameters for nanoemulsion. Nanoemulsion droplets were in the size range of 25–40 nm, with some particle aggregates in the range of 100–150 nm, and their surface charges had a significant impact on the stability of the emulsion system and the disposition of the droplet in vivo[82.]

Nanoemulsion Droplet Size Analysis: The diffusion method was used to measure droplet size distribution using a light-scattering particle size analyzer Coulter LS-230. Droplet size distribution is one of the significant physicochemical properties of a nano-emulsion. It utilises the scattering of laser light by particles to determine the size distribution. The PIDS assembly, which includes an incandescent light source, polarising filters, a PIDS sample cell, and an additional seven photodiode detectors, measures the polarisation intensity differential scattering. It is used to measure the distribution of droplet sizes, such as when 0.5 ml of emulsion was added to the measurement compartment (125 ml of water). The volume distribution of the results was displayed.

Two more methods that have been developed to assess the droplet size of nanoemulsions—laser light scattering (LLS) and energy filtering transmission electron microscopy—are of interest in this article (EFTEM). They are naturally stable against creaming, sedimentation, flocculation, and coalescence because to the small droplet size. Additionally, it enables the efficient delivery of active substances to the skin. [83-84-85.]

Polydispersity Index: Using photon correlation spectroscopy, the average diameters and polydispersity index of the samples were calculated. A He-Ne laser was used to do the tests at 25 °C.

Viscosity Assessment: A Brookfield DV III ultra V6.0 RV cone and plate rheometer with a spindle was used to assess the viscosity of the formulations without dilution. [84-85.]

Refractive Index: The ratio of a wave's phase speed (vp) to its speed (c) in a reference medium is known as the refractive index (n) of that medium. Examples of such waves include sound and light.

$n=c/vp$

It was calculated at 25 0.5°C using an Abbes type refractrometer (Nirmal International).

pH: A pH metre was used to determine the apparent pH of the formulation [84-85]

Transmission electron microscopy (TEM): Transmission electron microscopy was used to examine the nanoemulsion's morphology and structure. The shape and size of the nanoemulsion droplets were revealed using a combination of diffraction modes and bright field imaging at escalating magnification. The observations were carried out by dropping a drop of the nanoemulsion directly onto the grid of holes in the holey film and watching it dry.
Drug Content: Reverse phase HPLC was used to analyse the drug content using a C18 column [86.]

Zeta Potential: Zeta potential is a method for assessing the surface charge characteristics and long-term physical stability of nanoemulsions. ZetaPALS is the device used to evaluate surface charge.
The experiments were made using dilute nanoemulsion formulations, and the values were calculated using the oil droplets' electrophoretic mobility. Zeta potentials with a minimum of 20mv are preferred.[87]

Percentage Transmittance: The produced nanoemulsion formulations' percentage transmittance was assessed spectrophotometrically using a UV-VIS Spectrophotometer [88.]

Applications of Nanoemulsion:

1.Cosmetics using nanoemulsions[89]
2.Nanoemulsions that fight microbes.
3.precautionary in a bioterrorism attack.
4.Mucosal vaccines using nanoemulsions
5.Non-Toxic Disinfectant Cleaner: Nanoemulsion.
6. The technology of nanoemulsions in cell culture.
7. Improved oral administration of poorly soluble drugs using nanoemulsion formulations [90.]
8.Drug delivery methods that self-nanoemulsify are number 8[91-92-93].
9. Transdermal distribution using nanoemulsions[94-95].
10. The use of nanoemulsion in the treatment of numerous other illness conditions, such as the osteoarthritis therapy diclofenac cream.
11. Solid self-nanoemulsifying delivery systems as a base technology for poorly soluble drug formulation.

CONCLUSION

Drug delivery made possible by nanotechnology has a promising future in pharmaceutics. The drug delivery industry is significantly impacted by the development of nanotechnology, with effects on nearly all routes of administration, including oral and injectable. The current pharmaceutical industry is frequently characterised by inadequate bio-availability, which all too frequently leads to greater patient expenses and ineffective therapy, but more critically, increased risks of toxicity. Since nanotechnology concentrates on the extremely small, it is ideally suited to develop systems that can more effectively deliver medications to the body's tiniest regions. Drugs delivered via nanotechnology can also pass through cell membranes, which is crucial for the anticipated expansion of genetic medicine over the coming years. Nanotechnology-enabled medication delivery could result in decreased drug toxicity, lower treatment costs, higher bioavailability, and an extension of the commercial life of unique drugs for both doctors and patients.

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