

Nano Drug Delivery System and Its Applications: A Novel Review

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Abstract

The most advanced technology for delivering drugs to various sites in the body is nanotechnology. The nanosize of particles possesses a transcellular mechanism in delivering the drug to the target sites. Many diseases can be treated effectively through this delivery using nanocapsules, nanospheres, niosomes, dendrimers, polymeric micelles, liposomes, solid lipid nanoparticles (NPs), carbon nanotubes, fullerenes, polymeric-based NPs, and paramagnetic NPs with a size ranging from 1 nm to 500 nm. The drug is linked with the particles and is used in the treatment of various diseases such as cancer, gene therapy, leishmaniasis, and imaging. Retinal leukostasis, tuberculosis, neovascularization of the choroidal stroma, rejection of the transplant due to an immune response, vaccine delivery, cosmetic and personal care products, insertion across cellular membranes, diagnosis plans, inhalation therapies, presenting optimistic avenues for advancing respiratory medicine and improving patient outcomes, etc. Many researchers are exploring strategies to improve drug loading capacity, such as modifying nanoparticle surfaces or developing novel drug encapsulation techniques. By increasing drug loading, the therapeutic efficacy of these systems can be significantly enhanced. The methods used for the preparation of NPs are the salting-out method, supercritical fluid technology, solvent evaporation method, nano spray drying, double emulsion and evaporation method, and coacervation or ionic gelation method.

Key words: Cosmetic, dendrimers, nanospheres, niosomes, personal care products and supercritical fluid technology, vaccine delivery

INTRODUCTION

Since bigger or larger micro-molecules are significantly less effectively absorbed by cells than nanoparticles, they could be used as an efficient delivery of drugs and therapeutic agents or active ingredients and transport systems. Drugs may either be attached or affixed to the surface of the particle or encapsulated or incorporated into the particle-matrix for therapeutic uses. The outcome of a drug, after

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it enters the specific or target biological environment, ought to be under the direction of a drug-targeting system. Drug delivery nanoparticles typically measure <100 nm in at least one dimension and are made of a variety of biodegradable substances, including natural or manufactured polymers, lipids, and metals. Developing nanoparticles logically based on knowledge of about their interactions with the physiological environment, cell surface population, specific cell receptors, changes in cellular receptors that occur as disease progresses, pathway and location of action of the drug, drug retainment, multiple administration of drugs, molecular pathways, and microbiology of the disorder under considering would be an effective method for achieving effective drug delivery. It is crucial to comprehend the obstacles to medication development, such as the therapeutic agents' stability in a living cell environment.^[1-4]

Depending on the method of preparation, nanoparticles, nanospheres, or nanocapsules can be obtained. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, whereas nanospheres are matrix systems in which the drug is physically and uniformly dispersed. In recent years, biodegradable polymeric nanoparticles, coated with hydrophilic polymers such as poly (ethylene glycol) known as long circulating particles, have been used as potential drug delivery devices because of their ability to circulate for a prolonged period time target a particular organ, act as a carrier of DNA in gene therapy, and their ability to deliver proteins, peptides and genes.^[5]

CHARACTERISTICS OF NANOPARTICLES IN DRUG DELIVERY SYSTEM

Nanomaterials fall into a size range similar to proteins and other macromolecular structures found inside living cells. As such, nanomaterials are poised to take advantage of existing cellular machinery to facilitate the delivery of drugs. Nanoparticles containing encapsulated, dispersed, absorbed, or conjugated drugs have unique characteristics that can lead to enhanced performance in a variety of dosage forms. When formulated correctly, drug particles are resistant to settling and can have higher saturation solubility, rapid dissolution, and enhanced adhesion to biological surfaces, thereby providing a rapid onset of therapeutic action and improved bioavailability. In addition, the vast majority of molecules in a nanostructure reside at the particle surface, which maximizes the loading and delivery of cargos, such as therapeutic drugs, proteins, and polynucleotides, to targeted cells and tissues. Nanoparticle size and surface characteristics can be easily manipulated to achieve both passive and active drug targeting. Site-specific targeting can be achieved by attaching targeting ligands, such as antibodies or aptamers, to the surface of particles, or using guidance in the form of magnetic Nanoparticles. Nanoparticles can also control and sustain the release of a drug during transport at the site of localization, altering drug distribution and subsequent

clearance of the drug in order to improve therapeutic efficacy and reduce side effects [Table 1].^[5,6]

METHODS OF PREPARATION OF NANOPARTICLES^[26-38]

Salting out method

This method has the advantage of lowering the stress on the protein involved in the synthesis of encapsulants, and it produced high efficiency and was simple to scale up. The extraction of water-miscible solvent from such an aqueous solution is what causes the salting-out phenomenon. The first phase involves dissolving the drug as well as the polymer in a vehicle, which would be subsequently emulsified into such an aqueous gel with a salting-out reagent and a colloidal stabilizer. Colloidal stabilizers and salting-out agents, including electrolytes and non-electrolytes, have indeed been employed. Using this method, an oil/water emulsion is created that is then diluted with additional water to improve solvent diffusion inside the aqueous phase and facilitate the production of nanospheres. The manufacture of ethyl cellulose, polylactic acid, and poly-methacrylic acid nanospheres uses the salting-out method.

Supercritical fluid technology

Although supercritical fluid technology is suitable for large-scale production and is ecologically beneficial, it requires specialized, expensive gear. Supercritical fluids are fluids that, even at temperatures higher than their critical temperature, maintain their homogeneity. Due to its moderately critical conditions, non-flammability, high cost, and safety, supercritical CO₂ is the supercritical fluid that receives the most applications.

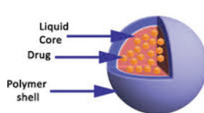
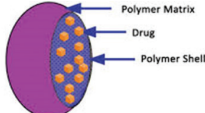
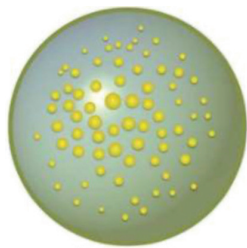
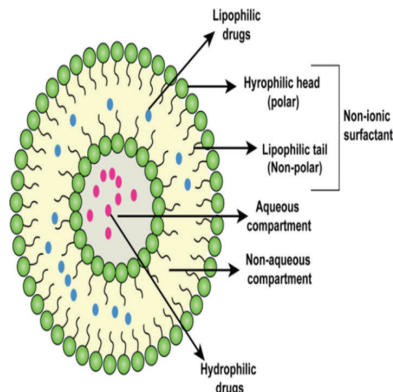
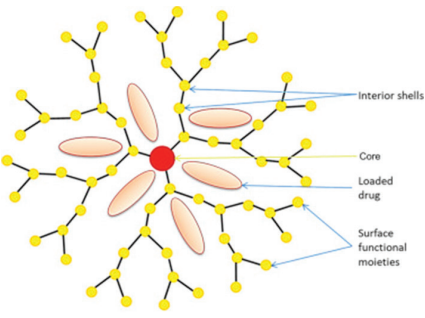
Solvent evaporation method

The first step is the emulsification of a polymer solution in an aqueous phase, which is preceded by the evaporation of the solvent of the polymer, which causes the polymer to precipitate as nanospheres. The drug-polymer mixture is emulsified inside an aqueous solution that includes a surfactant or emulsifying agent to create an oil-in-water emulsion. Once a stable emulsion has been established, the organic solvent is then evaporated either by constant stirring or by lowering the pressure. To create tiny particle sizes, ultrasonication or high-speed homogenization may be utilized. Nanoparticles are gathered by ultracentrifugation, and then any free drugs or stabilizer residue is removed by washing them in distilled water. For preservation, nanoparticles are even further lyophilized.

Nano spray drying

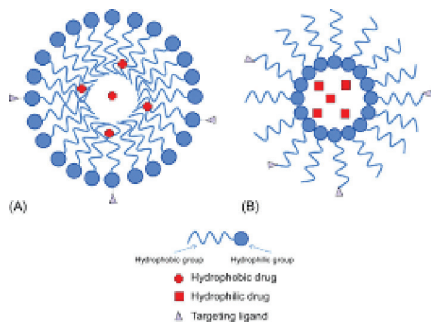
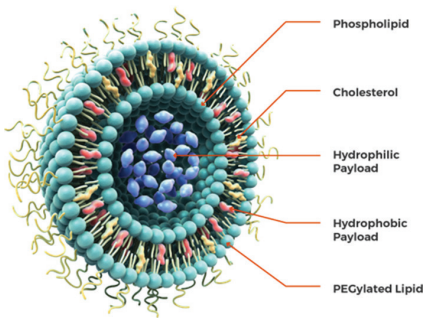
A quick, easy, repeatable, and expandable drying method known as spray drying provides for moderate

Table 1: Types of nanoparticles in various nanoformulations^[7-25]

S. No.	Types of nanoparticles	Characteristics	Benefits/advantages/ applications/uses	Structure
1.	Nanocapsules	The nanocapsules are vesicular systems which are made up of the polymeric membranes in which the inner core is encapsulated at the nanoscale level. The nanocapsules are generally made up of a non-toxic polymer.		 
2.	Nanospheres	Nanospheres are matrix systems in which the drug is physically and uniformly dispersed.		 <p style="text-align: center;">Nanospheres (matrix system)</p>
3.	Niosomes	Niosomes are non-ionic surfactant-grounded vesicles that include non-ionic surfactant and cholesterol as an excipient, employed for medicine delivery to specific spots to achieve asked remedial goods. Structurally, niosomes are analogous to liposomes, as they both correspond to a lipid bilayer.	Niosomes have colorful operations, similar to gene delivery, medicine targeting, antineoplastic treatment, treatment for leishmaniasis, delivery of peptide medicines, studying the vulnerable response, carriers for hemoglobin, transdermal medicine delivery systems, and cosmetics	
4.	Dendrimers	Dendrimers are macromolecules with highly branched polymers with 3-D structures that provide a high degree of surface functionality and versatility. Dendrimers consist of three components: An initiator core, an interior layer composed of repetitive units, and an exterior (terminal functionality) layer attached to the outermost interior layers. To develop dendrimeric systems for delivering drugs, these are prepared from two synthetic iterative approaches: one divergent and another convergent. In the divergent approach, synthesis is initiated from the core and proceeds outward to the exterior through repetition of coupling and activation steps. In contrast, in the convergent approach, synthesis starts from the periphery and proceeds toward the core.	Can be designed to have specific sizes and shapes, have high drug loading capacity, and target specific tissues. Drug delivery, gene therapy, and imaging.	 <p style="text-align: center;">Drug loaded dendrimer</p>

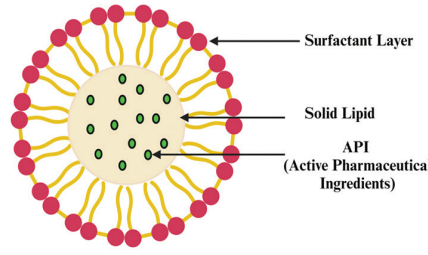
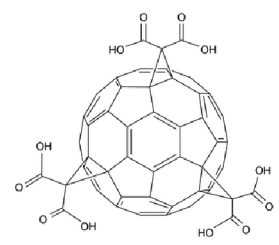
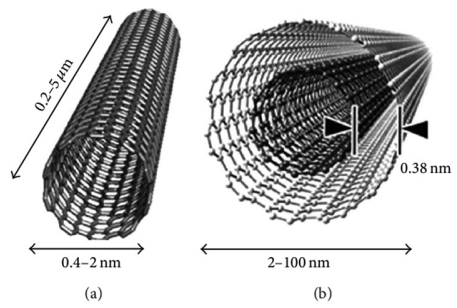
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Table 1: (Continued)

S. No.	Types of nanoparticles	Characteristics	Benefits/advantages/ applications/uses	Structure
5.	Polymeric micelles	Polymeric micelles are other types of polymer-based nanoparticles being studied for clinical use. When amphiphilic block copolymers self-assemble into a core-shell shape with a hydrophobic core and a hydrophilic shell, this makes polymeric micelles. Polymeric micelles have shown promise in delivering hydrophobic drugs to the tumor site, as the hydrophobic core can encapsulate the drug and protect it from degradation. In addition, the hydrophilic shell allows for prolonged circulation time in the bloodstream, enhancing drug delivery efficiency. These unique properties make polymeric micelles a potential solution for improving targeted drug delivery and enhancing patient outcomes.	Delivery of drugs such as fenofibrate and dexamethasone. Brinzolamide, dexamethasone, bevacizumab, triamcinolone, acetamide, everolimus, diclofenac, cyclosporine A, prednisolone, and dexamethasone for the treatment of choroidal neovascularization, retinal dysfunctions, retinal leukostasis, and neovascularization of the choroidal stroma. Rejection of the transplant due to an immune response. Inflammation of the eyes, etc.,	
6.	Liposomes	Liposomes are vesicular structures with an aqueous core surrounded by a hydrophobic lipid bilayer, created by the extrusion of phospholipids. Phospholipids are generally recognized as safe to carry both hydrophilic and hydrophobic molecules through liposomes. The lipid bilayer of liposomes can fuse with other bilayers, such as the cell membrane, which promotes the release of its contents. Liposomes that have vesicles in the range of nanometers are also called nanoliposomes. Liposomes can vary in size, from 15 nm up to several μm , and can have either a single layer (unilamellar) or multiple phospholipid bilayer membranes (multilamellar) structure. Unilamellar vesicles (ULVs) can be further classified into small ULVs (SUVs) and large ULVs (LUVs) depending on their size range.	Can encapsulate hydrophilic and hydrophobic drugs, biodegradable and biocompatible; can target specific tissues. Drug delivery, gene therapy, vaccine delivery, and liposomes can be made to actively target cancer cells by attaching specific targeting molecules, delivering the drug directly to the tumour site, increasing their concentration, and reducing toxicity in healthy tissues.	

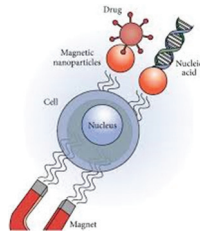
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Table 1: (Continued)

S. No.	Types of nanoparticles	Characteristics	Benefits/advantages/ applications/uses	Structure
7.	Solid lipid nanoparticles (SLNs)	SLNs are formed from solid lipids and have benefits including high drug encapsulation potential, stability, and sustained release. A major advantage of the SLNs is that they are suitable for embedding lipophilic drugs that are, in any case, scarcely soluble in water. These nanoparticles can also be surface functionalized for increased targeting ability and, therefore, can be used to deliver drug molecules across biological barriers like the blood–brain barrier.	Can encapsulate hydrophilic and hydrophobic drugs, biocompatible; can be functionalized with targeting ligands or imaging agents, Drug delivery, cosmetic, and personal care products	 <p>Solid Lipid Nanoparticle (SLN)</p>
8.	Fullerenes	A fullerene is any molecule composed entirely of carbon, in the form of a hollow sphere, ellipsoid, or tube. Spherical fullerenes are also called bucky balls, and cylindrical ones are called carbon nanotubes or bucky tubes. Fullerenes are similar in structure to graphite, which is composed of stacked graphene sheets of linked hexagonal rings; In addition, they may also contain pentagonal (or sometimes heptagonal) rings to give potentially porous molecules.		
9.	Carbon nanotubes	These tubes have a diameter range of 1–100 nm and are composed of graphite sheet cylinders, which are capped at either one or both ends by buckyballs. They are renowned because of being hollow and cage-like, and are available in a number of graphite cylinder forms.	Nanotubes enter cells through endocytosis or insertion from across cellular membranes.	

(Contd...)

Table 1: (Continued)

S. No.	Types of nanoparticles	Characteristics	Benefits/advantages/ applications/uses	Structure
10.	Polymeric-based NPs	Polymeric NPs can be formed as nanospheres, or nanocapsules, depending upon the method of preparation. Nanocapsules are vesicular systems in which the drug is confined to a cavity surrounded by a polymeric membrane, and nanospheres are matrix systems in which the drug is physically and uniformly dispersed. Many synthetic and semi-synthetic, biocompatible, and biodegradable polymers have been used extensively in the clinic for controlled drug release. The most commonly and extensively used polymeric NPs include poly-d, l-lactide-coglycolide, polylactic acid, poly-ε-caprolactone, poly-alkyl-cyanoacrylates, chitosan, and gelatin. Polymeric NPs also possess several remarkable properties, making them a potential drug delivery vehicle.	Arjunglucoside targeted for <i>Leishmania donovani</i> , halofantrine targeted for <i>Plasmodium berghei</i> , rifampicin, and isoniazid, pyrazinamide targeted for <i>Mycobacterium tuberculosis</i> , Beta-lactam/ ciprofloxacin for <i>Staphylococcus aureus</i> , <i>Bacillus anthracis</i> , amphotericin B for <i>Candida albicans</i> , and saquinavir for HIV.	
11.	Paramagnetic nanoparticles	Microscopic magnetic nanoparticles can be manipulated by a magnetic field and have a diameter of <100 nm. These nanoparticle materials are created using magnetic components.	These nanoparticles are used in therapy and diagnosis plans. Targeting of magnetic nanoparticles is useful for identifying particular organs.	

ambient temperatures that are ideal for heat-sensitive biopharmaceutical molecules. In contrast to certain other drying techniques, spray drying is a continual process that turns various liquids into solid particles while providing for alterations in dimension, distribution, structure, porosity, density, and chemical properties. Four steps are involved in spray drying: heating the drying gas, producing droplets, drying the droplets, and collecting the particles.

Emulsions-diffusion method

Excellent encapsulation efficiency, the absence of homogenization, high batch-to-batch repeatability, ease of scaling up, ease, and limited size range are just a few advantages of this method. The encapsulating polymer is saturated with water after being mixed in a solvent that is partially water-miscible. Next, based on the oil-to-polymer proportion, the polymer-water-saturated solvent phase is emulsion in an aqueous solution that contains a stabilizer,

resulting in solvent diffusion to the outer phase as well as the creation of nanospheres or nanocapsules. Based on the solvent's boiling point, the solvent is eliminated in the final phase either through evaporation or filtration.

Double emulsion and evaporation method

Examples of drug nanoformulations created using the double emulsion approach include oleuropein with increased stability and Rose Bengal for the treatment of breast carcinoma.

The double emulsion method is used to load the lipophobic medication. Drug solutions are added to an organic solution that contains the polymer while being stirred constantly to create a w/o emulsion. The second aqueous phase then gradually incorporates the created emulsion. Continue spinning until the w/o/w emulsion forms. After the solvent has evaporated, high-speed centrifugation may be used to separate the nanoparticles.

Polymerization method

Diffusion in the polymerization medium or adsorption onto the nanoparticles after completion of polymerization are the two ways that drugs are introduced during the polymerization. An isotonic medium devoid of surfactants can be utilized to re-disperse the nanoparticle suspension after ultracentrifugation to remove the various stabilizers and surfactants that were employed throughout polymerization.

Coacervation or ionic gelation method

Two distinct aqueous phases have been prepared, one for the polymer and the other for the polyanion sodium tripolyphosphate, and it varies depending on the strong electrostatic attraction between both the positively charged amino group of chitosan and the negatively charged tripolyphosphate to shape coacervates-with-a-magnitude-in-the-nanometer range.

EVALUATION^[5,24,39]

The following are the evaluation parameters for nanoparticles.

Zeta potential

The zeta potential of a nanoparticle is commonly used to characterize the surface charge property of nanoparticles. This reflects the electrical potential of particles and is influenced by the composition of the particle and the medium in which it is dispersed. Nanoparticles with a zeta potential above (\pm) 30 mV have been shown to be stable in suspension, as the surface charge prevents aggregation of the particles.

Particle shape

A scanning electron microscope characterizes the nanosuspension before going for evaluation; the nanosuspension is lyophilized to form solid particles. The solid particles are coated with platinum alloy using a sputter coater.

Particle size

Particle size and size distribution are the most important characteristics of nanoparticle systems. They determine the *in vivo* distribution, biological fate, toxicity, and targeting ability of the nanoparticle system. In addition, they can also influence the drug loading, drug release, and stability of nanoparticles. Currently, the fastest and most routine method of determining particle size is by photon-correlation spectroscopy or dynamic light scattering. The results obtained by photon-correlation spectroscopy are usually verified by scanning or transmission electron microscopy.

Table 2: Various techniques for characterization of nanoparticles

S. No.	Properties of nanoparticles	Method of characterization
1.	Topography (surface)	X-ray diffraction
2.	Electrical	Electrokinetic
3.	Morphology (shape and size)	Atomic force microscopy Dynamic light scattering Electron microscopy
4.	Chemical	Fourier transform infrared spectroscopy Electron dispersive X-ray spectroscopy Ultraviolet -visible spectroscopy
5.	Biological	Microbial colony viability <i>In vivo</i> <i>In vitro</i> cell viability
6.	Optical	Surface plasmon resonance Double photon correlation spectroscopy Microscopy Raman spectroscopy

Drug entrapment efficiency

The nanoparticles were separated from the aqueous medium by ultracentrifugation at 10,000 rpm for 30 min at 50°C. Then the resulting supernatant solution was decanted and dispersed into phosphate buffer saline, pH 7.4. Thus, the procedure was repeated twice to remove the untrapped drug molecules completely. The amount of drug entrapped in the nanoparticles was determined as the difference between the total amount of drug used to prepare the nanoparticles and the amount of drug present in the aqueous medium.

Drug Entrapment efficiency (%) = $\frac{\text{Amount of drug released from the lysed nanoparticle}}{\text{Amount of drug initially taken to prepare the nanoparticles}} \times 100$

Surface hydrophobicity

The measurement of hydrophobicity is an important evolution parameter that provides information about the interaction of the nanoparticles with the biological environment. The generally used methods for the estimation of hydrophobicity: Hydrophobic interaction chromatography, two-phase partition. Contact angle measurement.

In vitro dissolution estimation

In vitro dissolution of the drug was carried out using the dialysis bag method. A dialysis membrane was used for the

release study. The dialysis membrane was soaked in distilled water for 24 h before the release studies. Specific mg equivalent weight of the drug loaded solid lipid nanoparticles (SLNs) was incorporated into the dialysis, which is tied at the two ends. 50 mL of phosphate buffer pH 6.8 was added to a beaker and the dialysis membrane was fixed in it, where the solution was stirred using magnetic stirrer at 50 rpm and the temperature was maintained at $37 \pm 0.5^\circ\text{C}$, at the time intervals of 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 h the sample of 1 mL was taken and same volume was added to the beaker to maintain the sink condition.

Stability study

Stability study for the optimized formulation was carried out according to International Council for Harmonisation guidelines under three conditions: Accelerated temperature ($40 \pm 2^\circ\text{C}/75 \pm 5\%$), room temperature ($25 \pm 2^\circ\text{C}/60 \pm 5\%$ RH), and refrigerated temperature ($4 \pm 2^\circ\text{C}$) for 90 days. There must be no significant change in the particle size, polydispersity index, zeta potential, and entrapment efficiency in the formulation at room and refrigerated temperatures for 90 days. The techniques available for characterization of nanoparticles were listed in table 2.

APPLICATIONS^[40]

Nanoparticles as per-oral drug delivery

Aqueous dispersions or SLN-loaded conventional dosage forms, such as tablets, pellets, or capsules, can be administered orally. The stomach's acidic environment and high ionic strength encourage particle aggregation, so it makes sense that food would significantly affect SLN function.

Nanoparticles for gene delivery

Gene therapy is a method of treating illness that involves either infusing genetic material, or DNA, into the cells to replace a damaged gene or alter its expression. Because of their size, shape, surface, and biological activities, nanoparticles have become the most promising vehicles for clinical gene therapy. Numerous gene-associated human disorders, including cancer, autoimmune diseases, neurodegenerative diseases, hypercholesterolemia, and hemophilia, have garnered considerable interest in gene therapy as a potentially effective treatment approach.

Nanoparticles in ocular delivery systems

A lot of research has been done on using nanoparticles to release drugs to the eye for a long time. The main issue with ophthalmologic formulation is that they are quickly removed

from the eye, which means that the drug is cleared through the nose. It could be demonstrated that nanoparticles have a higher adhesiveness, which leads to higher drug levels at the desired site of action. However, the main issue was that the nanoparticles have limited toxicological acceptance. Gasco demonstrated that SLN has a prolonged retention time at the eye, which was verified using radiolabeled formulations and γ -scintigraphy. The lipids in SLN are easily metabolized, opening up new avenues for ophthalmological drug delivery without affecting vision.

Nanoparticles for targeted imaging

The creation of molecular probes for the visualization of cellular function, characterization, and measurement of molecular processes in living organisms at the cellular and molecular level without disturbing them is known as molecular imaging. Nanoparticles can be effectively used as tumor-specific probes with high specificity when conjugated with tumor-targeting ligands (such as peptides, small organic molecules, antibodies, etc.). As imaging modalities are developed rapidly to aid in disease detection, emerging nanoparticle technologies are joined by the rapid advancement of imaging modalities. For successful transport to the intended target, nanoparticles' charge, size, shape, and hydrophilicity continue to be crucial characteristics. In biological imaging applications, nanomaterials like dendrimers, iron oxide nanoparticles, gold nanoparticles, and quantum dots are frequently utilized. Direct detection of bacterial or viral DNA is feasible when gold nanoparticles are used as ultrasensitive fluorescence probes to identify cancer biomarkers in human blood. Because of their strong X-ray absorption and low toxicity profiles shown in animals over brief periods of time, metallic nanoparticles have enormous potential as X-ray contrast imaging agents.

Nanoparticle delivery to subcellular organelles

The potential area for drug delivery is targeting the drug to the cells or tissue of choice. In delivery systems, targeting refers to the capacity to guide the drug-loaded system to a desired location. Targeted nanoparticles can attach to targets located on the cell surface and enter the cell through endocytosis. This process involves two mechanisms. 1) The preferential accumulation of chemotherapeutic agents in solid tumors is an example of passive targeting, which involves changing the size, shape, and composition of the nanoparticles to target them to a specific organelle. 2) Active targeting enables the surface functionalization of drug carriers with ligands that are selectively recognized by receptors on the surface of the cells of interest. Nanoparticles can be used extensively in targeted drug delivery at the site of disease to improve the drug bioavailability, targeting of drugs to a specific site, and uptake of poorly soluble drugs.

Nanoparticles for drug delivery into the brain

The BBB's presence makes it difficult for medications to enter the brain efficiently, which is one of the most difficult barriers to treating illnesses related to the central nervous system. The brain is shielded against undesirable substances and invasive organisms by the dynamic barrier known as the blood-brain barrier (BBB). By passive diffusion, small hydrophilic molecules with masses under 150 Da and extremely hydrophobic compounds with masses under 400–600 Da can pass through the BBB. The creation of nanoparticles is crucial to achieving this. Nanoparticles ought to be non-inflammatory, non-immunogenic, biodegradable, and biocompatible. Numerous illnesses, such as neurodegeneration (such as amyotrophic lateral sclerosis, Alzheimer's, Parkinson's, Huntington's, and Prion disease), hereditary deficits, and several forms of brain cancer, lack effective treatments. With its prolonged release profile and brain target delivery, nanotechnology has proven to be a valuable tool for bridging the BBB, which is essential for the successful treatment of neurodegenerative diseases.

CONCLUSION

The nanotechnology use in medicine, the preparation of drugs and drug products or formulations, and cosmetics has emerged greatly nowadays. In the future, the efficiency of loading the drug or diagnostic agents should be increased to minimize the usage of the drug and nullify adverse effects.

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