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# Nanoparticles

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**ABSTARCT**

The synthesis and application of materials whose constituents exist at the nanoscale typically, up to 100 nm in size—is referred to as nanotechnology. Nanotechnology investigates molecule and sub molecular structure behavior in addition to electrical, optical, and magnetic activity. The use of particle delivery systems as carriers for both small and big molecules in medicine delivery has garnered significant research interest during the past few decades. Nanoparticles and other particulate systems have been utilized as a physical method to modify and enhance the pharmacokinetic and pharmacodynamic characteristics of different kinds of pharmaceutical compounds. They have been employed in vivo to safeguard the drug entity in the bloodstream, limit drug access to specific locations, and administer the medication to the site of action at a steady and regulated rate. It has the potential to revolutionize a series of medical and biotechnology tools and procedures so that they are portable, cheaper, safer, and easier to administer. Nanoparticles are being used for diverse purposes, from medical treatments, using in various branches of industry production such as solar and oxide fuel batteries for energy storage, to wide incorporation into diverse materials of everyday use such as cosmetics or clothes, optical devices, catalytic, bactericidal, electronic, sensor technology, biological labelling and treatment of some cancers.

**KEYWORDS:** nanoparticles, drug delivery, targeting, drug release.

## INTRODUCTION

Particulate dispersions or solid particles with a size range of 10–1000 nm is referred to as nanoparticles. The medication dissolves, confined, enclosed, or affixed to a matrix of nanoparticles. One can obtain nanoparticles, nanospheres, or nano capsules depending on the preparation technique used. Whereas nanospheres are matrix systems where the drug is uniformly and physically distributed, Nano capsules are systems where the drug is contained within a specific polymer membrane-enclosed cavity. Biodegradable polymeric nanoparticles have been used as possible drug delivery vehicles in recent years. These particles, known as long-circulating particles and coated with hydrophilic polymers like poly (ethylene glycol) (PEG), can circulate for a long time and target a specific organ. They can also be used as carriers of DNA in gene therapy.1-4

Controlling particle size, surface characteristics, and release of are the main objectives of creating nanoparticles as a delivery method. pharmacologically active substances to ensure that the medication acts at the desired place at the best possible rate and dosage. Although liposomes have been explored as potential carriers with special benefits such as preventing drug degradation, directing medication to the site of action, and lowering toxicity or side effects, their uses are constrained by innate issues like low encapsulation efficiency, rapid drug leakage in the presence of blood components, and poor storage stability. Conversely, there are a few unique benefits that polymeric nanoparticles have over liposomes. For example, they have beneficial controlled release capabilities and aid in increasing the stability of medications and proteins.5-6

Nanoparticles are employed in many different fields of industry production, including solar and oxide fuel batteries for energy, as well as in medical treatments. storage, to widespread integration into a variety of products

used on a daily basis, like clothing or makeup 7. Multi-functionalization is the main characteristics of nanoparticles. Nanoparticles can be integrated with ligands, imaging labels, therapeutic agents and other functionalities for specific drug delivery and cellular uptake. Doxorubicin, an anticancer drug can conjugate with gold nanoparticles.8

## PREPARATION OF NANOPARTICLES

Nanoparticles can be made from various materials such as proteins, polysaccharides and synthetic polymers. The choice of matrix materials depends on many factors, including [7]: (a) the size of the nanoparticles required; b) internal properties of the medicine, e.g., solubility and stability in water; (c) surface properties such as charge and permeability; (d) degree of biodegradability, biocompatibility and toxicity; (e). Desired drug release profile; and f) antigenicity of the final product. Nanoparticles were most often produced by three methods: (1) dispersion of preformed polymers; (2) polymerization of monomers; and (3) ionic gelation or coacervation of hydrophilic polymers. However, other methods such as supercritical fluid technology[8] andparticle reproduction in non-wetting models (PRINT) [9] have been described in the nanoparticle production literature. It has been claimed that the latter has complete control over particle size, shape and composition, which could serve as a model for mass production of nanoparticles in industry. Preformed polymer dispersion: Preformed polymer dispersion is a common method used to prepare biodegradable nanoparticles from poly (lactic acid) (PLA); poly (D, L-glycolide),PLG; poly(D,L-lactide-co-glycolide) (PLGA) and poly(cyanoacrylate) (PCA), [10-12]. This technique can be used in different ways as described below. Solvent evaporation method: In this method, the polymer is dissolved in an organic solvent such as dichloromethane, chloroform or ethyl acetate, which is also used as a solvent to dissolve the hydrophobic drug. The mixture of polymer and drug solution is then emulsified into an aqueous solution containing a surfactant or emulsifier, resulting in an oil-in-water (o/w) emulsion. After the formation of a stable emulsion, the organic solvent is evaporated either by reducing the pressure or by continuous stirring. Particle size was affected by stabilizer type and concentrations, homogenizer speed and polymer content[13].Rapid homogenization or sonication can often be used to obtain small particles[14].Spontaneous emulsification or solvent dispersion method: This is a modified version of the solvent evaporation [15] method. In this method, a water-miscible solvent is used as the oil phase along with a small amount of water-immiscible organic solvent. Spontaneous diffusion of solvents creates turbulence at interfaces.

## POLYMERIZATION METHOD

In this method, monomers are polymerized to form nanoparticles in an aqueous solution. The drug is added either by dissolving it in the polymerization medium or by adsorption on the nanoparticles after the polymerization is complete. The nanoparticle suspension is then purified to remove the various stabilizers and surfactants used for polymerization by ultracentrifugation and resuspension of the particles in an isotonic surfactant. This technique has been described for the preparation of polybutylcyanoacrylate or poly (alkyl cyanoacrylate) nanoparticles[16;17]. The formation of nano capsules and their particle size depends on the concentration of surfactants and stabilizers [18].

## COACERVATION OR ICONIC GELATION METHOD

Much research has focused on the preparation of particles using biodegradable hydrophilic polymers such as chitosan, gelatin and sodium alginate. Calvo and co-workers developed a method to prepare hydrophilic chitosan nanoparticles by ionic gelation [19, 20]. The method involves a mixture of two aqueous phases, one of which is the polymeric chitosan, di-block. copolymer ethylene oxide or propylene oxide (PEO-PPO) and the other is the polyanion sodium tripolyphosphate. In this method, the positively charged amino group of chitosan interacts with the negatively charged tripolyphosphate to form coacervates in the nanometer range. Coacervates are formed by electrostatic interactions between two aqueous phases, while ionic gelation involves the transition of a material from a liquid to a gel due to ion interaction conditions at room temp...

**Production of nanoparticles using supercritical fluid technology**

Traditional methods such as solvent extraction-evaporation, solvent dispersion and organic phase separation methods require the use of organic solvents that are dangerous for the environment and physiological systems. Therefore, supercritical fluid has been investigated as an alternative for the production of biodegradable micro and nanoparticles because supercritical fluids are environmentally safe 21. Supercritical fluid can generally be defined as a solvent whose temperature is above the critical temperature at which the liquid remains as one phase regardless of pressure 21. SupercriticalCO2 (SC CO2) is the most commonly used supercritical liquid due to mild critical conditions (Tc = 31.1 °C, Pc = 73.8 bar), non-toxic, non-flammable and cheap. The most common processing methods for supercritical fluids are supercritical antisolvent (SAS) and rapid critical solvent expansion (RESS). The SAS process uses a liquid solvent, such as methanol, which is completely miscible with the supercritical fluid (SC CO2) to dissolve the micronized solute; In process conditions, since the solute does not dissolve in the supercritical fluid, extraction of the liquid solvent with the supercritical fluid leads to the time precipitation of the solute, resulting in the formation of nanoparticles 8. Thoteand Gupta (2005) reported the use of a modifieds AS method to form hydrophilic drug dexamethasone phosphate drug nanoparticles for microencapsulation purposes 22. RESS differs from the SAS process in that the \ n solute is dissolved in a supercritical fluid (like supercritical to methanol) and then the solution rapidly expands through a small nozzle to a lower pressure 21 , So the resolving power of supercritical fluids decreases dramatically and the solute eventually precipitates. This technique is clean because the precipitate is essentially insoluble. RESS and its amendments. the process has been used to produce polymer nanoparticles 23. Supercritical fluid technology technology, while environmentally friendly and suitable for mass production, requires specially designed equipment and is more expensive.

**Effect of Characteristics of Nanoparticles on Drug Delivery**

***PARTICAL SIZE***

Particle size and size distribution are the most important properties of nanoparticle systems. They determine the in vivo distribution, biological fate, toxicity and targeting of nanoparticle systems. In addition, they can also affect drug loading, drug release and nanoparticle stability. Many studies have shown that small nanoparticles have several advantages over microparticles as a drug delivery system. 24. In general, nanoparticles have relatively higher intracellular uptake compared to microparticles and are accessible to a wider range of biological targets due to their small size and relative mobility. Desai et al found that uptake of 100 nm nanoparticles was 2.5 times higher than 1 µm microparticles and 6 times higher than 10 µm microparticles in the Caco-2 cell line25.In a subsequent study, 26 nanoparticles penetrated the submucosa in situ in a rat intestinal model, while microparticles were found mainly in the epithelial lining. It has also been reported that \particle can cross the blood-brain barrier after hyperosmotic mannitol opened tight junctions, which can provide sustained delivery of therapeutic agents in hard-to-treat diseases, brain. tumors 27. Among 80-coatednanoparticles have been shown to cross the blood-brain barrier 28. In some cell lines, only submicron nanoparticles can be efficiently taken up, but not larger microparticles29. Particle size affects drug release. Smaller particles have a larger surface area, so most of the drug is on or near the surface of the particle, resulting in rapid drug release. Larger particles have large cores, which allow more drug to be slowly encapsulated. Disperse 30. Smaller particles also have a greater risk of particle aggregation during storage and transport of nanoparticle dispersions. It is always a challenge to make nanoparticles with the smallest possible size but as stable as possible. Particle size can also affect polymer degradation. For example, the degradation rate of PLGA polymer was found to increase with increasing particle size in vitro 31. It was thought that PLGA degradation products formed in smaller particles could easily diffuse out of the particles, while degradation production large particles are more likely to remain in the polymer matrix longer. causes autocatalytic degradation of the polymeric material. Therefore, larger particles were expected to promote faster polymer degradation and drug release. However, Panyam et al prepared PLGA particles of different size classes and found that the in vitro degradation rates of the polymer were not significantly different for different particle sizes32.Currently, the fastest and most. a routine method for particle size determination is photon correlation spectroscopy or dynamic light scattering. Photon correlation spectroscopy requires knowledge of the medium viscosity and determines particle diameters based on Brownian motion and light scattering properties33. Results

obtained by photon correlation spectroscopy are usually checked with a scanning or transmission electron microscope (SEM or TEM).

**Surface properties of nanoparticles**

When nanoparticles are administered intravenously, they are easily recognized by the body's immune system and phagocytes remove them from the bloodstream 34. In addition to the size of the nanoparticles, their number is determined by their hydrophobicity. surface. Adsorbed blood components, mainly proteins(opsonin's). This in turn affects the fate of nanoparticles 34, 35in vivo. Binding of these opsonin's to the nanoparticle surface, called opsonization, acts as a bridge between the nanoparticle and the phagocyte. Combining a drug with conventional carriers results in a change in the biodistribution profile of the drug because it is primarily transported to the mononuclear phagocytic system (MPS), such as the liver, spleen, lungs and bone. marrow. Indeed, after entering the blood, unmodified surface nanoparticles (conventional nanoparticles) are rapidly opsonized and massively cleared by macrophages from MPS-rich organs. n is used for foreign substances, especially to recognize foreign macromolecules. Therefore, to increase the probability of successful drug targeting of nanoparticles, it is necessary to minimize opsonization and prolong the circulation of nanoparticles in vivo. This can be achieved by (a) coating nanoparticles with hydrophilic polymers/surfactants; (b) Preparation of nanoparticles with biodegradable copolymers with hydrophilic segments such as polyethylene glycol (PEG), polyethylene oxide, polyoxamer, poloxamer and polysorbate 80(Tween 80). Studies show that the shape of PEG on the particle surface is extremely important for the opsonin-repellent function of the PEG layer. PEG surfaces in brush-like and intermediate configurations reduced phagocytosis and complement activation, while sponge-like PEG surfaces were strong complement activators and promoted phagocytosis 2, 37. Nanoparticle Zeta Potential Nanoparticles are usually used to characterize the surface charge properties38. It reflects the electric potential of the particles and is affected by the composition of the particle and the medium in which it is dispersed. Nanoparticles with a zeta potential above (+/-) 30 mV are stable in suspension because the surface charge prevents particle aggregation. Zeta potential can also be used to determine whether the charged active material is encapsulated in the center of the nano capsule or adsorbed at the mouth.

***Drug Loading***

Ideally, a successful nanoparticulate system should have a high drug loading capacity, which reduces the number of matrix materials required for delivery. The loading of drugs can be done by two methods:• addition during nanoparticle production (incorporation method)• absorption of drugs after formation of nanoparticles by incubating the carrier with a concentrated drug solution (adsorption) ./absorption technique).Drug loading and entrapment efficiency are highly dependent on solid state drug solubility in the matrix material or polymer (solid solubility or dispersion), which is related to polymer composition, molecular weight, drug polymer interactions , and ends functional groups (ester or carboxyl) performance when charged at or near its isoelectric point when it has minimum solubility and maximum adsorption. a very effective way to increase drug load 43, 44. Drug release to develop a successful nanoparticle system, both drug release and polymer biodegradation are important factors to consider. In general, the rate of release of a drug depends on: (1) the solubility of the drug; (2) desorption of surface-bound/adsorbed drug; (3) diffusion of drugs through the nanoparticle matrix; (4) nanoparticle matrix erosion/degradation; and (5) a combination of erosion/diffusion process. Thus, the release process is governed by solubility, diffusion and matrix biodegradation. In nanospheres where the drug is uniformly distributed, release occurs by matrix diffusion or erosion under immersion conditions. If drug diffusion is faster than matrix erosion, the release mechanism is largely driven by the diffusion process. The rapid initial release or "burst" is mainly due to the weakly bound or adsorbed drug on the large surface area of the nanoparticles 45. It is obvious that the method of adding has an effect on the release profile. When the drug is loaded by the incorporation method, the system has a relatively small explosive effect and better sustained release properties 46. When the nanoparticles are covered with a polymer, the release is controlled by diffusion of the drug from the core through the polymer film. The film coating acts as a release barrier, so drug solubility and diffusion into the polymer film becomes a determining factor in drug release. In addition, the release rate can also be influenced by the ionic interaction between the drug and the addition of excipients. If the drug interacts with excipients forming a complex that is less soluble in water, the release of the drug can be very slow, an almost non-existent ejection effect 43; during the

addition of excipients such as ethylene oxide-propylene oxide block polymer(PEO-PPO) to chitosan, the model drug together with bovine serum albumin (BSA)reduces the matrix material (chitosan) due to the competitive electrostatic interaction of PEO -PPO with chitosan, in which an increase in drug release can be observed20.Different methods can be used to study drug release in vitro: (1) diffusion cells juxtaposed with artificial or biological membranes; (2) dialysis bag diffusion technique;(3) reverse dialysis bag technique; (4) mixing followed by ultracentrifugation/centrifugation; (5)Techniques of ultrafiltration or centrifugal ultrafiltration. Usually, the release study is performed by controlled mixing followed by centrifugation. Since the separation of nanoparticles from the release agents is time consuming and technical difficulties, the dialysis technique is usually preferred.

**Applications of Nanoparticulate Delivery Systems**

Tumor targeting using nanoparticulate delivery systems the rationale of using nanoparticles for tumor targeting is based on 1) nanoparticles will be proximity to tumor targets due to increased permeability and retention effect or active targeting of ligands on the nanoparticle surface; 2) nanoparticles reduce the exposure of healthy tissues to drugs, limiting the distribution of the drug to the target organ. Verdun et al showed that mice treated with doxorubicin incorporated in poly(isohexylcyanoacrylate) nanoparticles showed higher concentrations of doxorubicin in liver, spleen and lungs than mice treated with free doxorubicin. nanoparticle composition, such as polymer type, hydrophobicity and biodegradation profile and related drug molecular weight, its location within the nanospheres and attachment method by adsorption or incorporation, have a great impact on drug distribution. patterning life. The exact underlying mechanism is not fully understood, but nanoparticle biodistribution is rapid, from ½ hour to 3 hours and likely involves MPS and endocytosis/phagocytosis 48. Bibby et al recently reported that cyclic RGD -- Biodistribution and pharmacokinetics (PK) of a nanoparticle formulation of doxorubicin in tumor-bearing mice 49. Their biodistribution studies showed a decrease in drug concentration over time in the heart, lung, kidney, and plasma, and an accumulation of drug concentrations in the liver, spleen, and tumors. Most of the injected dose appeared in the liver (56%) and only 1.6%in the tumor 48 hours after injection, confirming that the nanoparticles have a high propensity to take up the liver. This indicates that a major challenge in using nanoparticles for tumor targeting is to avoid particle uptake by the mononuclear phagocyte system (MPS) in the liver and spleen. This tendency of MPS towards nanoparticle endocytosis/phagocytosis offers the opportunity to effectively deliver therapeutic agents into these cells. This biodistribution can be useful in the chemotherapy treatment of tumors localized to MPS-rich organs/tissues, such as hepato-carcinoma, liver metastases from gastrointestinal cancers or gynecological cancers, bronchopulmonary tumors, primitive tumors. tumors and metastases, small cell tumors, myeloma and leukemia. The use of conventional doxorubicin-loaded nanoparticles has been shown to be effective against a liver metastasis modeling mouse. It was found that the incidence of metastases decreased more than the free drug. The increased therapeutic efficacy of the preparation was based on the transfer of doxorubicin from healthy tissues, which acts as a drug depot, to malignant tissues 50. Histological examination showed significant nanoparticles in the lysosomal vesicles of Kupffer cells, while nanoparticles could not be clearly detected in tumor cells 50. Thus, Kupffer cells could induce mass release by phagocytosis after uptake of nanoparticles. of doxorubicin, leading to a drug concentration gradient favorable for long-term diffusion of free and still active drug into adjacent metastatic cells50.If conventional nanoparticles are used as carriers in chemotherapy, some cytotoxicity to Kupffer cells can be expected, which would lead to Kupffer cell deficiency and would naturally lead to reduced liver uptake and reduced therapeutic effects. effectless than 2 weeks apart 51. In addition, conventional nanoparticles can also target the bone marrow (MPS tissue), an important but unfavorable site of action for most cancer drugs, because chemotherapy with such carriers may increase the myelosuppressive effect. Therefore, the ability of conventional nanoparticles to improve the efficacy of anticancer drugs is limited to tumor targeting at the level of MPS-rich organs. Targeting nanoparticles containing cancer drugs to other tumor sites is also not possible if the nanoparticles are quickly removed.

**Long circulating nanoparticles**

To be successful as a drug delivery system, nanoparticles must be able to target tumors which are localized outside MPS-rich organs. In the past decade, a great deal of work has been devoted to developing so-called “stealth” particles or PEGylated nanoparticles that are invisible to macrophages or phagocytes 52. An important

breakthrough in the field occurred when the use of hydrophilic polymers (such as polyethylene glycol, polo amine, poloxamer, and polysaccharides) was effective in coating. conventional nanoparticles within an opposite effect on the absorption of MPS 52, 53. These coatings provide a dynamic "cloud" of hydrophilic and neutral chains on the surface of the particle, which repel plasma proteins 54 55. As a result, the coated nanoparticles become invisible to MPS, so they remain.in the bloodstream for a longer time. Hydrophilic polymers can be added to the surface in two ways, either by adsorption of surfactants or by block or branched copolymers to make nanoparticles 51, 52. Studies show that PEG-coated nanoparticles not only have a longer half-life in the blood, but are also able to selectively extravasate to pathological sites, such as tumors or inflamed areas with bleeding vasculature 51. As a result, such long-circulating nanoparticles have an increased potential to directly target tumors outside MPS-rich regions 51. The size of colloidal carriers and their surface properties are critical to the biological fate. of nanoparticles. A size below 100 nm and a hydrophilic surface are required to reduce opsonization reactions and subsequent clearance by macrophages. 52. Coating of Standard Nanoparticles with Surfactants or PEG to Produce a Long-Lasting Agent. circulating carriers now used as a standard strategy to target drugs in vivo. Great efforts have been made to achieve "active targeting" of nanoparticles to deliver drugs to the right targets based on molecular recognition processes such as ligand-receptor or antigen-antibody interactions. Considering that folate receptors are overexpressed on the surface of malignant cells in some people, and cell adhesion molecules such as selectins and integrins are involved in metastatic events, nanoparticles with specific ligands such as folate may be involved. used to target ovarian cancer, while specific peptides or carbohydrates can be used to target integrin sands elect ins 56. Oyewumi et al showed that the benefits of folate ligand coating facilitate the internalization and retention of tumor cells. \. n Gd nanoparticles in tumor tissue 57. Targeting with small ligands seems to be more likely because they are easier to handle and to produce. In addition, it can be useful if active targeting ligands are used in combination with long-circulating nanoparticles to maximize the likelihood of successful active targeting of the nanoparticles.

**Reversion of multidrug resistance in tumour cells**

Although anticancer drugs reside in the tumor interstitial, their effectiveness against many solid tumor types can be limited, because cancer cells are able to develop resistance mechanisms 58. These mechanisms allow tumors to evade chemotherapy. Multidrug resistance (MDR) is one of the most important problems in chemotherapy. MDR is mainly caused by the overexpression of plasma membrane p-glycoprotein (Pg.), which is able to extract various positively charged xenobiotics, including some anticancer drugs, de cells 58. restores tumor cell sensitivity to anticancer drugs by avoiding Pgp-mediated MDR, several strategies have been implemented, including the use of colloidal \carriers. The conjugation of drugs to colloidal carriers such as nanoparticles to combat drug resistance is due to the fact that Pgp probably recognizes drug efflux from tumor cells only when the drug is in the plasma membrane and not when it is in the cytoplasm or in lysosomes after endocytosis 59 60.

**Nanoparticles for oral delivery of peptides and proteins**

Significant advances in biotechnology and biochemistry have led to the discovery of a large number of bioactive molecules and vaccines based on peptides and proteins. Development of suitable carriers remains a challenge due to the fact that the bioavailability of these molecules is limited by the epithelial barriers of the gastrointestinal tract and their susceptibility to digestion degradation by digestive enzymes of the gastrointestinal tract. Polymeric nanoparticles enable bioactive molecules to be encapsulated and protected against enzymatic and hydrolytic degradation. For example, \insulin-loaded nanoparticles have been found to maintain insulin activity and produce a decrease in blood glucose levels in diabetic rats for up to 14 days after oral administration 61. The surface area of man. mucosa is200 times that of the skin 62. The gastrointestinal tract provides various physiological and morphological barriers to protein or peptide passage, e.g. (a) proteolytic enzymes in the intestinal lumen, such as pepsin, trypsin and chymotrypsin.; (b)proteolytic enzymes at the brush edge membrane (endopeptidases); c) intestinal bacterial flora; and (d) the mucus layer and the epithelial cell covering itself 63 . The histological architecture of the mucosa is designed to effectively prevent absorption of particles from the environment. One important strategy to cross the gastrointestinal barrier is drug delivery in a colloid carrier system, such as nanoparticles, which is able to improve the drug delivery system and interaction mechanisms. epithelial cells in the digestive tract.

**Targeting of nanoparticles to epithelial cells in the GI tract using ligands**

Targeting strategies that improve the interaction of particles with adsorptive enterocytes and Peyer's patch M cells in the gastrointestinal tract can be classified into those using specific binding to ligands or receptors and those based on a non-specific adsorption mechanism. On the surface of enterocytes and M cells there are cell-specific carbohydrates that can be binding sites for colloidal drug carriers containing suitable ligands. Certain glycoproteins and lectins bind selectively to this type of surface structure through a specific receptor-mediated mechanism. Various lectins, such as papule tin and tomato lectin, have been studied to improve the absorption of oral peptides. The ability of various peptides (e.g., granulocyte colony-stimulating factor, erythropoietin) and particles to increase oral bioavailability by covalently binding to vitamin B-12 has been studied 66, 67. This intrinsic process requires a mucoprotein produced by gastric mucosa and which specifically binds to cobalamin. Mucoprotein reaches all the way to the ileum, where resorption is mediated by specific receptors. Enhancement of absorption by non-specific interactions in general, absorption of macromolecules and particles from the gastrointestinal tract involves either a cell-mediated or an endocytic pathway. The paracellular absorption pathway of nanoparticles uses less than 1% of the mucosal surface area. Using polymers such as chitosan68, starch 69 or poly(acrylate) 70, the paracellular permeability of macromolecules can be increased. The endocytosis pathway for nanoparticle uptake is via either receptor-mediated endocytosis, i.e., active targeting, or adsorptive endocytosis, which does not require ligands. This process is initiated by the non-specific physical adsorption of the material on the cell surface due to electrostatic forces such as hydrogen bonds or hydrophobic interactions. 71. Adsorptive endocytosis depends mainly on the size of the material and surface properties. If the surface charge of the nanoparticle is positive or uncharged, it provides an affinity for adsorptive enterocytes, although hydrophobic, while it is negatively charged and hydrophilic, it shows a higher affinity for adsorptive enterocytes and M-cells. This indicates that a combination of size, surface charge and hydrophilicity play an important role in affinity. This is demonstrated with poly(styrene) nanoparticles and when carbonylated 72.

**Nanoparticles for gene delivery**

Polynucleotide vaccines deliver the genes encoding relevant antigens into host cells, where they are expressed, producing an antigenic protein in the vicinity of professional antigen-presenting cells to initiate an immune response. Such vaccines produce both.

humoral and cell-mediated immunity, because intracellular production of protein, as opposed to extracellular storage, stimulates both arms of the immune system 73.DNA, the main ingredient of polynucleotide vaccines, can be produced cheaply and has much better storage and handling properties than the ingredients of most protein-based vaccines. Therefore, polynucleotide vaccines are poised to replace many conventional vaccines, especially immunotherapy. However, polynucleotide delivery has several problems that limit their use. These problems include the efficient delivery of the polynucleotide to the target cell population and its localization to the nucleus of those cells, as well as ensuring that the integrity of the polynucleotide is preserved during its delivery to the target website Plasmid DNA-loaded nanoparticles can also act as an efficient long-acting gene delivery system because they can pass from the rapidly degrading end lysosomal compartment to the cytoplasmic compartment 74. Hedley et al. 75reported that after intracellular uptake and end lysosomal escape, nanoparticles could release DNA at a constant rate, resulting in sustained gene expression. This gene delivery strategy can be applied to facilitate bone healing using PLGA nanoparticles containing therapeutic genes such as bone morphogenic protein.

**Nanoparticles for drug delivery into the brain**

The blood-brain barrier (BBB) is an important factor limiting the development of new CNS drugs. The BBB is characterized by relatively impermeable endothelial cells with tight junctions, enzymatic activity, and active efflux transport systems. Ineffectively prevents the movement of water-soluble molecules from the bloodstream to the central nervous system and can also reduce the concentration of fat-soluble molecules in the brain by enzymes or efflux pumps. Consequently, the BBB only allows selective transport of molecules necessary for brain function. Strategies to target nanoparticles to the brain are based on the presence of specific receptor-mediated transport systems and interaction at the BBB. For example, polysorbate 80/LDL, transferrin receptor-binding antibody (such as OX26), lactoferrin, cell permeable peptides and melanotransferrin are capable of non-self-transport. drugs to

the brain. by a chimeric construct that can undergo receptor-mediated transcytosis 77-81. It was reported that poly (butyl cyanoacrylate) nanoparticles could deliver the hexapeptide dalargine, doxorubicin, and other agents into the brain, which is important because drugs have difficulty crossing the BBB 77. report success with polysorbate 80-coated NPs, this system has many disadvantages, including desorption of the polysorbate coating, rapid NP degradation, and toxicity due to high concentrations of polysorbate 80.37. OX26 Mabas (anti-transferrin receptor MAb), the most studied BBB-targeting antibody, have been used to improve the BBB penetration of liposomes82. However, recently Ji et al. showed that brain uptake of lactoferrin, an iron-binding glycoprotein belonging to the transferrin (Tf) family, is twofold compared to OX26 and transferrin in vivo 79. We may soon see these BBBs specific molecules. used to target nanoparticles to the brain.

## CONCLUSION

The foregoing show that nanoparticulate systems have great potentials, being able to convert poorly soluble, poorly absorbed and labile biologically active substance into promising deliverable drugs. The core of this system can enclose a variety of drugs, enzymes, genes and is characterized by a long circulation time due to the hydrophilic shell which prevents recognition by the reticular-endothelial system. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and particle engineering, is still required. Further advances are needed in order to turn the concept of nanoparticle technology into a realistic practical application as the next generation of drug delivery system. References

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