



NANOPARTICLES IN THE PHARMACEUTICAL INDUSTRY: APPLICATIONS, CHALLENGES AND FUTURE PERSPECTIVES

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ABSTRACT

Nanotechnology is one of the novel methods being explored in pharmaceutical research and drug development due to its unique physicochemical and biological properties, which are different from the bulk materials. Nanoparticles containing active pharmaceutical ingredients (APIs), such as poorly water-soluble drugs can enhance the dissolution, solubility, bioavailability, stability and delivery of the active ingredients. Pharmaceutical nanoparticles are polymeric nanoparticles, lipid-based systems, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nanocrystals, metallic nanoparticles and other inorganic/hybrid systems depending on their composition and application. The particle size, size distribution, surface properties, morphology, drug loading and stability are all important factors affecting their pharmaceutical performance. The applications of nanoparticles in the fields of controlled and targeted drug delivery, cancer therapy, gene and nucleic-acid delivery, diagnostic applications, antimicrobial therapy, and delivery across biological barriers have been explored. But it is still difficult to shift technology from a laboratory to commercial products because of the problems of formulation stability, reproducibility, scale-up, manufacturing cost, toxicity and regulatory requirements. This review briefly discusses the important pharmaceutical applications, important features, preparation methods, industrial challenges and future prospects of some important pharmaceutical nanoparticle system.

Key Words:

Nanoparticles; nanomedicine; drug delivery; nanocrystals; liposomes; pharmaceutical industry; targeted delivery; nanotechnology

1. INTRODUCTION

Nanotechnology is related to the design and use of materials with a scale range of size that can exhibit unique physical, chemical, optical and biological properties that are dependent on the size. In the medical field, these characteristics have led to the emergence of pharmaceutical science applications that aim at modifying the physicochemical and pharmacokinetic properties of therapeutic agents through the use of nanoparticles for drug delivery. [1] An important pharmaceutical problem overcome by nanotechnology is low aqueous solubility of the drug molecule. Lack of water solubility can result in low dissolution rate and variable absorption/oral bioavailability. One way in which nanodrug formulation reduces the particle size of an API to the nano scale is by increasing the surface area to volume ratio, thus increasing the dissolution and absorption rates of the API. Nanosized versions of a drug are not the only way that nanoparticles can be used as drug carriers. Depending on the

formulation, therapeutic molecules can be incorporated into, attached to polymeric, lipidic, metallic or other nanoscale structures.[2] These systems can be engineered to ensure controlled drug release, increase drug stability and to alter the biodistribution of the drug and to allow targeted delivery to specific tissues/cells. Therefore, the importance of nanotechnology in pharmaceuticals doesn't stop with enhancing solubility. Nanoparticulate systems have been studied for a variety of applications including the possibility of targeted delivery, cancer therapies, gene delivery, diagnostic applications, antimicrobial applications and delivery across biological barriers and across a drug. On the other hand, the pharmaceutical production requires control of the particle size, particle shape, surface characteristics, load parameters, stability and reproducibility. [1,3]

2. CLASSIFICATION OF PHARMACEUTICAL NANOPARTICLES:

Particles of less than 1000 nm can be sorted into different classes according to their chemical and structural composition for use in the pharmaceutical field. Nanoparticles can be categorized as polymeric nanoparticles, lipid-based nanoparticles, nanocrystals, metallic and inorganic nanoparticles, dendrimer-based systems and carbon-based nanomaterials. [4]

2.1 Polymeric nanoparticles

Polymeric nanoparticles are nanoparticles in which the natural or synthetic polymers are used as carrier for the drugs. The drugs can be incorporated into the polymeric matrix or attached to the surface of the particle. They can be tailored to affect the release (and degradation) of the drug, and the interactions with biological tissues. However, in the case of controlled or sustained drug release, polymeric have an increased level of interest. Surface modification can also provide the potential for attachment of targeting molecules. Surface properties of nanoparticles, loading and release of drugs are very important aspects for their performance in the controlled and targeted drug delivery system. [1]

2.2 Lipid-based nanoparticles

The lipid-based nanoparticles are liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs) and other lipidic systems. Their lipid content allows them to be used with a variety of pharmaceutical molecules and may enhance the ability of drugs with poor aqueous solubility to be solubilized and delivered. One of the most studied lipid based nanocarriers is liposomes. They are made of one or more phospholipid bilayers, which enclose an aqueous compartment. Liposomes are amphiphilic, and thus can contain hydrophilic compounds in the aqueous compartment and hydrophobic compounds in the lipid bilayer. [5]

2.3 Liposomes

Liposomes are spherical vesicles made up of phospholipids (and, usually, cholesterol). Their lipid composition, their surface charge density and their preparation and size affect them. Liposomes can either be unilamellar or multilamellar vesicles. Unilamellar vesicles are single lipid bilayers while multilamellar vesicles are made of multiple concentric lipid bilayers. [2] Liposomes have great pharmaceutical potential since they can transport drugs of varied physicochemical properties. However, there is an aqueous core that can be used to trap

hydrophilic drugs, and a lipid bilayer that can be used to bind lipophilic drugs. [2] Surface modification by polyethylene glycol (PEG) may lead to an increase in the circulation time and a decrease in recognition and uptake by the mononuclear phagocytic system (MPS). [2,3] The story of liposome technology taking "cafeteria trips" from the lab to the clinic as a useful drug is one example of a spectacular success with pharmaceutical translation; PEGylated liposomal doxorubicin (DOXIL) [3] is a case in point.

2.4 Solid lipid nanoparticles and nanostructured lipid carriers

The drug is embedded in a solid lipid matrix and the SLNs are lipid-based nanoparticles. The NLCs employ these ideas by incorporating the liquid lipid to the lipid matrix, leading to a less ordered structure and potentially beneficial for drug incorporation and delivery. These systems have been studied in detail for poorly water-soluble drugs and controlled release. [6]

2.5 Nanocrystals and nanosuspensions

An important method is drug nanocrystals, which consist of nanosized crystals of the API, usually stabilizers are used. In contrast to carrier-based nanoparticles, nanocrystals are able to carry a very high content of active pharmaceutical substance. The nanocrystallization process is especially helpful for poorly water-soluble drugs, due to the increase in surface area that occurs, which can improve their dissolution and bioavailability. [7] The synthesis of nanocrystal formulations can be done via top down and bottom-up approaches. Nanoparticles of Metal and Inorganic origin:

2.6 Metallic and inorganic nanoparticles

Examples of metallic and inorganic nanoparticles are those with a gold, silver, iron oxide and other metal and metal-oxide based structure. They possess special physicochemical and surface properties which have been explored for drug delivery, imaging, diagnostic use and antimicrobial activity. [4] However, their biological distribution, degradation and toxicity should be carefully taken into account in their application in pharmaceuticals as the biological action of the nanoparticles can vary from the bulk materials. [4]

2.7 Dendrimers and carbon-based nanoparticles

The use of carbon-based nanoparticles and dendrimers. Dendrimer are macromolecules with multiple functional groups on the surface and a well-defined architecture, in the form of a highly branched three-dimensional structure.

They can be modified or functionalized with pharmaceutical agents and targeting ligands. Nanostructures based on carbon are also of interest for pharmaceutical and biomedical applications, because of the surface properties and their possible use as a vehicle for imaging or delivery. [8]

3. CHARACTERISTICS OF PHARMACEUTICAL NANOPARTICLES

None of the most fundamental properties of the formulation of a nanoparticle for therapeutic use is its physicochemical properties. The size & size distribution of particles. One of the critical properties of a pharmaceutical nano particle is the size of the particle. A smaller particle size of the drugs will provide a larger surface area for dissolution, which may improve the dissolution behaviour of the drugs. The size may also impact the distribution, uptake and clearance of the biological system. Ideally, the particle-size distribution should be narrow, as this will give the formulation a more uniform and reproducible formulation. Hence, it is necessary to control the particle size and size distribution for industrial production. The surface charge and zeta potential are discussed in this section. [1] The surface charge effect on the interactions between nanoparticles, aqueous environment and lipid membrane. A widely used parameter, that reveals information about the surface charge, is Zeta Potential and may help provide information about the colloidal stability. Properties of the surfaces themselves can also influence the interactions of cells and can also reduce aggregation of particles if they are suitable.

3.1 Morphology

The shape and morphology of particles influence surface area, aggregation, dissolution and interactions with biological systems. Therefore, the morphological characterisation is an important aspect of the fabrication of nanoparticles. [1] The loading and encapsulation efficiency of the drug into the PLGA microsphere was calculated. The loading of the drug and the efficiency of drug encapsulation were evaluated. Drug loading and encapsulation efficiency are quantity of drug in the formulation and percentage of drug, respectively, that is incorporated. In the pharmaceutical industry, a high drug loading is of special importance to reduce the amount of carrier and excipients needed. Drug can be loaded in liposomal systems during the process of vesicle formation or after the formation of vesicles. Lipid bilayer can be used to trap hydrophobic drugs and the aqueous compartment can be used to trap water soluble drugs. [2] These studies require the use of a dedicated bioreactor. A special bioreactor is needed to perform these studies. The stability

and drug-release behavior were examined. The stability and drug-release behavior was determined. The physical and chemical stability of pharmaceutical nanoparticles is important. During storage, particles can undergo aggregation, particle growth, sedimentation, etc. During storage, many particles can aggregate, grow, and/or settle, etc. Kumar et al. pointed out that stability, reproducibility and control of particle properties are crucial criteria for industrial nanodrug development [1]. Another important parameter is the release of drugs. Ideally, the formulation should be stable for the storage and administration period and release at the desired site. Liposomal systems [3] is an example of a balance between the stability of a drug and its release at the target site.

4. USE OF NANOPARTICLES IN THE PHARMACEUTICAL INDUSTRY

4.1 Improvement of solubility and bioavailability

The greatest known pharmaceutical use of nanoparticles is the enhancement of poorly water-soluble drugs' dissolution. The surface area of API particles is increased when the particle size is reduced and hence can increase dissolution and absorption. Nanocrystals and nanosuspensions are especially suitable for this application as a small amount of carrier matrix can be used for a high API content in the formulation. The production of controlled and sustained drug delivery systems.[9]

4.2 Controlled and sustained drug delivery

The drug release rate can be controlled by designing the nanoparticles. The release can be affected by the composition of the polymer, the composition of the lipids, the particle size, interaction between the drug and the carrier on the surface of the particles, and others. Controlled release may help to maintain therapeutic levels for extended durations and can lead to a lower number of required doses. As an example, liposomal systems can be manipulated for changes in drug retention and release in response to changes in membrane composition and surface characteristics. [3]

4.3 Targeted drug delivery

The nanoparticles can be used to target therapeutic agents to specific tissues or cells. Targeting can be passive, depending on the physicochemical properties of the carrier and the properties of diseased tissue, or active, by means of ligands (antibodies, receptor-binding molecules, etc.). Barenholz said passive and active targeting were significant strategies in the liposomal drug delivery system. The incorporation of recognition element into the

liposome surface is necessary for active targeting, while passive targeting depends on the interaction between the properties of the liposomes and the microanatomy of the tissues. [10]

4.4 Cancer therapy

Pharmaceutical nanotechnology has been especially significant in the field of cancer, where the systemic toxicity of conventional anticancer drugs, and their lack of specificity for tumor localization can pose problems. Nanoparticle systems have the potential to alter drug distribution and offer opportunities for controlled or targeted delivery. [1,4] An important example of successful pharmaceutical translation is liposomal doxorubicin. PEGylated liposomal systems have the ability to extend circulation and modify drug distribution of encapsulated drugs. [3] The delivery of genes and of nucleic acids. Nanoparticles can be used to protect and deliver nucleic acids into cells. The strategy explored for intracellular delivery is to use lipoplexes, which are complexes of cationic lipids and negatively charged nucleic acids [3]. Other nanocarriers such as polymeric and lipid based can be modified to increase the uptake and intracellular release.

4.6. Brain and CNS delivery

In the CNS, drugs are restricted from entry through biological barriers, namely the blood–brain barrier.

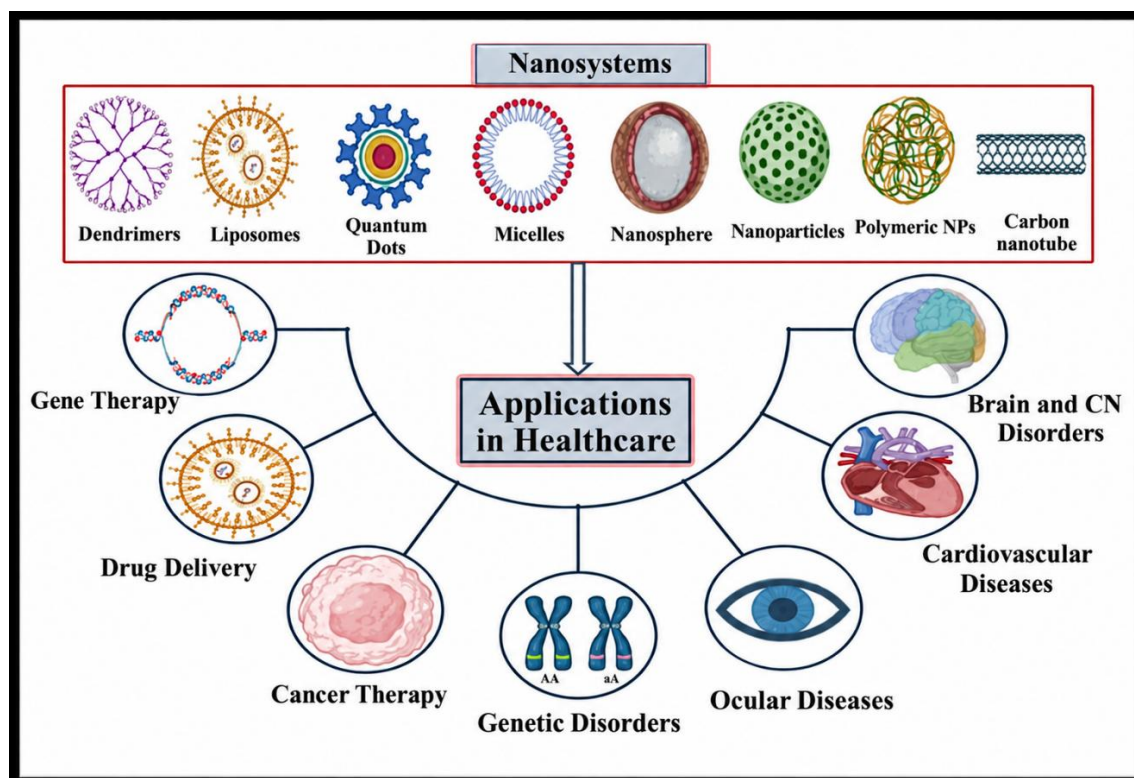
Nanoparticles have been studied as a means to enhance delivery of specific therapeutics to the brain. Nanoparticles have the potential to alter drug distribution and to interact with the biological barriers, thereby becoming an area of interest for CNS drug delivery. But, the long-term safety, biodistribution and fate of such systems must be carefully explored. [1,4]

4.7. Imaging and diagnostic uses of MRI

Nanomaterials may exhibit optical, magnetic or other physicochemical properties that are useful in imaging and diagnostics. For instance, biomedical imaging and diagnostic applications of metallic and inorganic nanoparticles have been studied. The integration of diagnostic and therapeutic functions in a single nanosystem has also been a factor contributing to the interest in the field of multifunctional nanomedicine platforms. [10]

4.8 Antimicrobial applications

Some of the nanoparticles are intrinsically antimicrobial. The antimicrobial properties of metallic nanoparticles, especially those containing silver, have been studied. [4] However, for their pharmaceutical uses, they need to be properly evaluated for toxicity, exposure and dose; since antimicrobial activity does not always translate to biological safety.



5. Preparation and manufacturing processes of pharmaceutical nanoparticles:

Generally, the methods of preparing nanoparticles can be classified into two categories: the top-down and the bottom-up approaches.

5.1 Top-down approaches [11,12]

Top-down processes start with bigger particles of drugs and then the particles get smaller up to the nanoscale. There are two common methods: Milling and High-pressure homogenization.

5.2 Milling:

Milling is a process which applies mechanical energy to decrease the size of particles. Wet media milling is widely studied since nanosized drug particles can be obtained in the presence of stabilizers. While relatively simple, milling can be scaled up for industrial production, but there are potential issues with contamination from the milling media, polymorphic change and amorphization.

5.3 High-pressure homogenization:

High-pressure homogenization is another top-down process that involves forcing the drug dispersion through a special homogenization chamber under high pressure. This process can be scaled up for production in the laboratory and larger scale.

5.4 Bottom-up approaches

The bottom-up methods involve making nanoparticles by assembling them from molecules, precipitation or crystallization from solution. An example of these is the liquid antisolvent precipitation method and supercritical fluid-based methods. [1]

In antisolvent precipitation, a drug solution in a suitable solvent is added to an antisolvent, leading to the nucleation and growth of nanosized particles. Drug concentration, mixing, temperature, the ratio of solvent to antisolvent and stabilizer concentration can affect particle size. [1] Another route to creating nanosized particles with drugs is a supercritical-fluid process that can be beneficial in certain pharmaceutical systems. But they can be affected by the complexity of the process and requirements for equipment in the use in industry.

6. CHALLENGES AND LIMITATIONS

Although there has been a lot of research work on the pharmaceutical nanoparticles, some challenges restrict the commercialization of laboratory developed nanoparticles.

6.1 Biological quality

Due to their high surface area, nanoparticles can be prone to aggregation, particle growth and other instability issues. Additional processing considerations may be required for the use of nanosuspensions, such as the use of stabilizers, or with spray drying or freeze drying, the conversion to dry powders may introduce additional processing considerations. [13]

6.2 Reproducibility

The formulation composition or processing conditions have the potential to alter particle size, morphology and surface characteristics slightly. Therefore, it is crucial that all critical quality attributes are reproducible in pharmaceutical manufacturing. [14]

6.3 Scale-up and manufacturing

An effective laboratory formulation can have different properties when large scale manufactured. Kumar et al. noted that insufficient scale-up techniques, large particle size distributions and problems in controlling the shape of the particles were significant hurdles to industrial implementation. [15] Manufacturing processes are therefore required to be scalable from the outset of their development.

6.4 Toxicity and biological safety

Nanoparticles may have different interactions with biological systems than do their bulk counterparts. Their small size and high surface area might affect cellular uptake, biodistribution and biological responses. The toxicity should instead be evaluated based on the composition, size, surface properties, route and dosage of the nanoparticle. Ahmed et al. stressed the importance of potential adverse effects of some nanomaterials and the need for toxicity assessment for safe use in the pharmaceutical field.[16]

6.5 Cost

The manufacturing process can be costly due to the specialized equipment, high purity raw materials, surface modification and strict quality control. The clinical benefit of a nanoparticle formulation needs to outweigh the extra manufacturing complexity for successful commercialization. [17]

7. REGULATION AND SAFETY PHARMACEUTICAL PRODUCTS

Considerations for Regulation and Safety Pharmaceutical products involving nanoparticles need to be characterized in ways other than traditional pharmaceutical formulations due to the size, surface properties, morphology and composition of the nanoparticles, which may impact on the biological behaviour. The quality attributes that are important are the particle size and distribution, morphology, surface charge, composition, drug loading and release, impurities, and physical and chemical stability. Both Manufacturing processes need to be reproducible and have the appropriate control of critical parameters. [18] Biodistribution, toxicity, degradation, elimination or potential interactions with biological systems should be taken into account for safety evaluation. Special care might be needed for nanoparticles that remain in the tissues and/or consist of material that can not be biodegraded easily. [19] Liposomal products illustrate the significance of controlling the physicochemical parameters during pharmaceutical development. Alterations in lipid composition, particle size and surface modification can alter both circulation and drug retention and release. [20] Regulatory development of nanomedicines thus mandates incorporation of both pharmaceutical quality and nonclinical safety and clinical performance, instead of traditional characterization methods.

8. FUTURE PERSPECTIVES

Nanotechnology in the pharmaceutical industry will continue to be more complex in the future, with more sophisticated systems that are able to incorporate a combination of functions in a single formulation. Now, research has progressed from just nanosized particles of the drugs to multifunctional systems, which are engineered to have improved solubility, controlled release, targeting and biological compatibility. One of the challenges for the future is the need for reproducible, scalable and economically viable manufacturing processes. Industrial translation is possible with optimized nanoparticle production processes and optimized stabilization methods, and a better understanding of the mechanisms of particle formation. Surface engineering also offers potential for engineering nanoparticles for biointeractions. Surface modification by PEGylation, attachment of ligands and other modifications can be used to modify circulation, cellular uptake or tissue localization [20]. An additional key point is the combination of therapy and diagnosis. Imaging and drug delivery with nanoparticles can play a role in personalized and Theranostic approaches. The long-

term safety, manufacturing consistency, and regulatory needs must, however, be carefully evaluated in developing such systems. Therefore, achieving improved laboratory performance is not the only thing that will drive the success of pharmaceutical nanotechnology, but also establishing a clear correlation between specific properties of the nanoparticles, manufacturing processes, biological behaviour and clinical outcome.

9. CONCLUSION

Nanoparticles have attracted significant attention in pharmaceutical research due to the possibilities offered by their nanoscale engineering to modify the solubility, dissolution, stability, release and biological distribution of therapeutic agents. The various nanoparticle classes (e.g., polymeric, lipid-based, metallic, inorganic and drug nanocrystal systems) offer unique opportunities for pharmaceutical development. They are used in various applications including poorly water-soluble drugs, controlled and targeted drug delivery, cancer therapeutics, gene delivery, CNS delivery, antimicrobial and diagnostic imaging. The liposomal formulations show that nanoparticle technology can come from the experimental stage into the field of clinically relevant pharmaceutical products. However, significant challenges such as stability, toxicity, reproducibility, scale-up, cost and regulation evaluation still exist. In the future, therefore, it is important to focus not only on the development of new nanoparticle design but also on the development of robust manufacturing processes, in-depth evaluation of safety aspects, and reproducible control of critical quality attributes.

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