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Review Paper

Nanospheres In Modern Pharmaceutics: Design, Preparation, Characterization, Therapeutic Applications, And Future Perspectives

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ABSTRACT

Nanospheres are described as monolithic structures that are of a matrix type with dimensions of between 10 to 1000 nm in which the active pharmaceutical ingredient is either physically or uniformly dispersed, dissolved, or adsorbed across the entire particle. This review summarizes nanospheres as the next-generation drug delivery systems intended to obtain site-specific targeting and regulated release of drugs. A range of different materials can be used to produce nanospheres, such as synthetic biodegradable polymers (e.g., PLA, PLGA), natural biopolymers (e.g., chitosan, albumin, gelatin) as well as inorganic materials such as silica. It outlines different methods of preparation i.e. nanoprecipitation (solvent displacement), solvent evaporation, along with emulsion polymerization and critical characterisation i.e. Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), Dynamic Light Scattering (DLS) to measure the size and zeta potential of particles. Critical pharmaceutical properties such as drug entrapment efficiency (EE%), drug loading, and in vitro release kinetics are also analyzed. In addition, Nanospheres have been widely applied in oncology, neurological diseases, and oral macromolecule delivery with the special capacity of overcoming relatively complicated biological barriers, such as the blood-brain barrier. Although nanospheres have been proposed to possess some important advantages such as improved bioavailability and less systemic toxicity, challenges associated with manufacturing scalability, particle aggregation, and regulatory issues are also still persistent. Lastly, recent progress in the area of smart stimuli-responsive systems and the future of nanospheres in personalized medicine and theranostics.

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INTRODUCTION

Nanotechnology has become a central area in the pharmaceutical sciences, and has provided an attractive platform to overcome the limitations of the traditional drug delivery systems, including low solubility, non-specific biodistribution, and systemic toxicity.^{4,18,38,39,40,41} In this area, the nanoparticles can also be termed as solid colloidal structures with the sizes of “10-1000 nm” and are usually divided into two different families, namely nanospheres and nanocapsules.^{2,9,14,42,43,44,45}

Nanospheres refer to matrix type, monolithic systems in which the entire structure is solid and homogeneous in the entire particle.^{2,8,33} The active pharmaceutical ingredient in such systems is dispersed, dissolved or adsorbed onto the polymeric matrix or onto the surface of the polymeric matrix.^{2,14,18,46} This structural design sets them apart to nanocapsules which follow the system of a reservoir holding the drug in the form of a central core (liquid or solid) with a clear polymer membrane around it.^{3,8,14,47,48}

The ultimate aim of nanospheres as drug delivery vehicles development is to create site targeting and controlled release of drugs at a therapeutically optimal rate and dose schedule.^{2,14,18,49} They are able to overcome biological barriers including the blood-brain barrier, which is frequently closed to larger particulate formations, due to their ultra-miniscule volume and distinctive physicochemical characteristics, including a high surface area-to-volume ratio.^{9,23,34,50,51} Moreover, it is possible to fabricate nanospheres of a very broad range of materials such as synthetic or natural polymers, proteins, and inorganic materials to protect drugs against enzyme destruction and enhance bioavailability of molecules which are poorly soluble in water.^{1,18,52} Nanospheres are also capable of greatly improving the therapeutic effect of the medication and reducing unnecessary side effects by concentrating the drug into the area of

interest and decreasing its concentration in the normal tissues.^{5,18,53,54}

NANOSPHERES CHARACTERISATION

Characterisation of Nanospheres is a critical step in the pharmaceutical development process to guarantee their reproducibility, stability, and pharmacological activities.^{4,18} Comprehensive analysis is the analysis of the physicochemical characteristics, structural integrity, and drug-related parameters through a sophisticated method of analysis.^{2,4,8}

Particle Size and Size Distribution: The most important parameter is arguably the size because it directly determines the drug release, biodistribution, cellular uptake, and physical stability.^{2,16,30} Dynamic Light Scattering (DLS), also known as Photon Correlation Spectroscopy (PCS), is the most common way of measuring the hydrodynamic diameter and Polydispersity Index (PDI).^{2,36,55,56} Other methods include Nanoparticle Tracking Analysis (NTA) and Fraunhofer diffraction.^{8,18}

Surface Morphology and Shape: The shape and smoothness of the surface of the nanospheres can be observed with the help of Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) that help to see the spherical nature, smoothness of the surface, and possible aggregation.^{2,26,60,61} Atomic Force Microscopy (AFM) can be used to visualize high-resolution 3D surface profiles and measure roughness of the surface and mechanical properties such as stiffness.^{4,17,18,57,58,59}

Surface Charge (Zeta Potential): The electrokinetic potential of the particle is a primary indicator of colloidal stability, which is reflected by the magnitude of the absolute zeta potential (greater than ± 30 mV); a high value results in strong repulsion between particles and prevents aggregation and sedimentation.^{2,17,18,62,63} Cellular internalization is also influenced by the surface



charge, so that cationic nanospheres tend to be more effective at interacting with negatively charged cell membranes, leading to a higher uptake rate.^{16,22,64,65}

Drug Loading and Entrapment Efficiency: Two parameters are commonly used to determine the number of active pharmaceutical ingredient (API) molecules successfully loaded into the system; **Entrapment Efficiency (EE%)**: The percentage of the total drug added that is actually loaded into the nanospheres.^{2,16} **Drug Loading (DL%)**: The ratio of the weight of the drug loaded to the total weight of the nanospheres.^{2,30} These are usually measured by High-Performance Liquid Chromatography (HPLC) or UV-Vis spectroscopy following the removal of unencapsulated drug using ultracentrifugation or gel filtration.^{2,16,20}

Physical State and Crystallinity: Crystalline or amorphous physical form of the drug in the polymeric matrix is a key determinant of solubility and release kinetics.^{2,32} Differential Scanning Calorimetry (DSC) and X-ray Diffraction (XRD) are used to identify the absence or presence of crystalline drug peaks.^{2,4,8,27} Often, drugs are in the amorphous form or molecular dispersion in nanospheres which greatly increases the solubility and release kinetics of poorly water-soluble molecules.^{2,6,66,67}

Chemical Composition and Interactions: It is crucial to confirm that the drug remains unchanged and to determine the interaction between the drug and the excipients.^{2,4} Fourier Transform Infrared (FT-IR) Spectroscopy can be used to detect functional groups and to confirm the formation of inter-molecular hydrogen bonds or other covalent/non-covalent bonding.^{2,18,68,69,70} X-ray Photoelectron Spectroscopy (XPS) or Nuclear Magnetic Resonance (NMR) can be used for surface elemental analysis and to investigate the internal structure.^{3,8,12,71,72}

Stability and Swelling: Stability testing is done to study how the size of the particles, PDI, and drug

delivery change with time (e.g. 6 months) at varying conditions such as temperature and humidity.^{2,4,73} In the case of pH-sensitive systems, pulsatile swelling tests evaluate the behaviour of the matrix to shrink or expand in line with changes in environmental pH, which induces release of the cargo.^{21,27}

CLASSIFICATION OF NANOSPHERES

Nanospheres can be classified systematically in terms of their biodegradability, materials they are built with and their ability to target their functions.

1. Based on Biodegradability

Biodegradable Nanospheres: These are the most frequent in the modern medicine since they are broken down into non-toxic metabolites and they can be readily eliminated from the body.^{9,36} Examples include:

Natural polymers: Albumin, gelatin, modified starch, chitosan, and dextran.^{9,31}

Artificial polymers: Polylactic acid (PLA), polyglycolic acid (PGA), poly(lactide-co-glycolide) (PLGA) and polycaprolactone (PCL).^{31,36}

Non-biodegradable Nanospheres: The first nanospheres that were developed were using non-degradable polymers like polyacrylamide, polymethyl methacrylate (PMMA) and polystyrene.¹⁴ Although stable, their use in systemic circulation is restricted by their potential for long-term toxicity and tissue accumulation.¹⁴

2. According to Material Composition.

Polymeric Nanospheres: These are solid colloidal particles of the matrix type in which the drug is physically dispersed or adsorbed.^{14,15} These are the most common nanospheres that are studied in drug delivery because they are versatile and stable.^{36,37}

Inorganic Nanospheres: These are well structured particles that are not easily destabilized.¹



Metallic Nanospheres: Gold (AuNPs) and silver (AgNPs) are applied due to their individual optical, electronic and antimicrobial features.^{4,35}

Ceramic and Silica Nanospheres: A recent example is mesoporous silica nanoparticles (MSNs), which provide high surface area to high drug payloads and excellent chemical/biological stability.⁴

Carbon-Based Nanospheres: This is mainly typified by Fullerenes (buckyballs) which are hollow spheres of carbon atoms that can be functionalized by attaching hydrophilic moieties in order to deliver drugs to the target locations such as the brain.^{1,34}

Lipid-Based Nanospheres: Although a large number of lipid systems are vesicular (i.e. liposomes), Solid Lipid Nanoparticles (SLNs) may be treated as matrix-type nanoparticles in which drugs are incorporated within a solid hydrophobic lipid core.^{4,36}

3. According to Functional Targeting.

Magnetic Nanospheres: These are those particles which have magnetic material, normally iron oxides, which are responsive to an external magnetic field.^{4,9} They are applied in physical guided drug targeting and contrasting in Magnetic Resonance Imaging (MRI).^{1,11}

Immune Nanospheres: These are formed by the surface of the particles being coated with antibodies or antigens and permit the specific ligand-receptor targeting of a given cell or tumor.⁹

Immuno-magnetic Nanospheres: This is a hybrid category, which encompasses both immune competence and magnetic response in order to enhance site-specific targeting to a large extent.⁹

pH-Sensitive Nanospheres: They are prepared specifically with polymers (such as some Eudragit-copolymers) which swell or dissolve at distinct pH levels to release themselves in a controlled manner in the gastrointestinal tract or tumor microenvironment.²¹

Enzyme-Responsive Nanospheres: These systems are based on the use of polymer backbones, side chains or cross-linkers that contain moieties that can be selectively degraded by specific enzymes. The enzymatic reaction results in the degradation of the nanosphere or the alteration of its permeability causing the "on-demand" delivery of the drug.^{10,22}

MATERIALS INVOLVED IN THE PREPARATION OF NANOSPHERE

The choice of materials used in the preparation of nanosphere is a sensitive factor that dictates their biological performance, drug loading capacity and release kinetics.^{1,18} Such substances usually fall into the following categories; synthetic polymers, natural polymers (proteins and polysaccharides), and inorganic substances.^{1,5}

1. Synthetic Polymers: Pharmaceutical research has taken synthetic polymers because of their adjustable properties of physicochemical characteristics and reproducible production.^{18,37}

Polyesters: Polylactic acid (PLA), polyglycolic acid (PGA), and their copolymer poly (lactide-co-glycolide) (PLGA) are the most prominent synthetic materials.^{1,36,37} They are approved by FDA to have a variety of medical applications since they break down through hydrolysis to lactic and glycolic acid metabolites that are non-toxic.^{16,18,36}

Polycaprolactone (PCL): This is a hydrophobic polymer, which degrades slower than PLA, hence good in the production of long-term implantable drug delivery devices.^{16,22}

Other Synthetic Polymers: these are polycyanoacrylates (e.g., poly-n-butyl-cyanoacrylate), poly anhydride, poly vinyl alcohol (PVA), poly acrylic acid, and poly(methyl methacrylate) (PMMA).^{8,26,36,37}



2. Natural Polymers: Proteins

Proteins are interesting in the production of nanosphere, since they are biodegradable, biocompatible and have various functional groups, which can be modified.^{1,4,24}

Albumin: Human serum albumin (HSA) and bovine serum albumin (BSA) are both widely applied.^{1,30} They do not cause toxicity, immunity, or tend to accumulate in tumor and inflammatory tissues.^{1,22,30}

Gelatin: Gelatin is an animal-derived protein that is a by-product of collagen hydrolysis, and the FDA has classified it as a generally recognized as safe (GRAS) substance.^{1,4,36}

Plant and Other Proteins: Zein (corn), gliadin (wheat), soy protein isolate (SPI) and silk proteins (fibroin and sericin) are investigated due to low immunogenicity and sustainability.^{1,4,30} Milk proteins (casein and whey Proteins (-lactoglobulin and -lactalbumin)) are also investigated in oral delivery of drugs.^{1,4}

3. Natural Polymers: Gums and Polysaccharides

Polysaccharides have good biocompatibility and are frequently endowed with special biological characteristics such as mucoadhesion.^{1,22}

Chitosan: It is a natural carbohydrate polymer that has been modified to have cationic properties and mucoadhesive properties that aid in the absorption of drugs across the cellular membranes.^{1,5,36}

Alginate: Alginate is a polysaccharide extracted out of brown seaweed and is known to form stable gels and is usually utilized in the controlled release of proteins and peptides.^{18,28,36}

Other Carbohydrates: They are starch, dextran, cellulose (and its derivatives such as ethyl cellulose) and cyclodextrins.^{1,22,24,32}

Natural Gums: Gum arabic, guar gum and xanthan gum are plant exudates that are used to form biodegradable nanospheres in the delivery of targeted and sustained delivery.¹⁸

4. Surface Modifiers and Excipients:

There are different additives that are added to enhance stability and targeting ability of the nanospheres.^{4,37}

Polyethylene Glycol (PEG): PEGylation (surface modification with PEG) is the gold standard in the generation of so-called stealth nanospheres that avoid immune system recognition and prolong their circulation in the blood.^{4,22,26,35}

Surfactants and Stabilizers: Poloxamers (Pluronic), polysorbates (Tween 80), and lecithins are employed to regulate the particle size and prevent aggregation during the synthesis process.^{3,4,20,37}

pH-Sensitive Polymers: Copolymers such as Eudragit (L100, S100) are usually incorporated into the nanosphere matrix to be stable in the stomach and only to release their cargo in the specific pH of the intestine or colon.^{20,21,30}

PREPARATION OF NANOSPHERES

Nanospheres are prepared using two main conceptual strategies, which are the dispersion of pre-existing polymers and the polymerization of monomers.^{3,33} Both methodologies are chosen depending on the properties of the material, the drug that is to be introduced and the release profile that is desired.⁵

1. Preparation by Preformed Polymers:

This method finds extensive application in pharmaceutical research because of the existence of biocompatible and FDA-approved polymers such as PLA and PLGA.^{3,18,37}

Solvent Evaporation: A polymer and drug are dissolved with an organic solvent (e.g., dichloromethane or ethyl acetate) and emulsified in an aqueous phase that includes a stabilizer to create an oil-in-water (o/w) emulsion.^{3,8,18,22} The solvent is organic and is eliminated via evaporation (either by stirring, heating or pressure)



which causes the polymer to flake into matrix-type nanospheres.^{3,9,22}

Nanoprecipitation (Solvent Displacement): This is a one-step method, and entails dissolution of polymer and drug in a solvent that is miscible with water (such as acetone or methanol) and dropwise addition to an aqueous phase.^{6,8,22} The fast diffusion of the organic solvent into the water causes the spontaneous precipitation of the polymer and the formation of small, uniform nanospheres by the so-called Ouzo effect.^{9,19,22,24}

Emulsification/Solvent Diffusion: This is a variation of the solvent evaporation technique and in this case a slightly soluble solvent is employed.^{3,6,8,16} With the introduction of any superfluous water into the emulsion, the solvent dissolves into the continuous phase and the polymer is solidified and nanosphere is generated.^{4,8,33}

Salting Out: This procedure involves the miscibility of a water-miscible solvent (such as acetone) with water being inhibited by the high-concentration inclusion of a salting-out agent (such as magnesium chloride) to the aqueous phase.^{3,8,16} Further dilution with water leads to the diffusion of the solvent, which leads to the formation of nanosphere.^{8,22}

Dialysis: The polymer and the drug are dissolved in an organic solvent and put in a dialysis tube.^{8,22} A gradual diffusion of the solvent into a non-solvent medium (water) causes gradual aggregation of the polymer, and a homogeneous suspension of the nanospheres.^{8,22,24}

2. Preparation through Monomer Polymerization.

Emulsion Polymerization: This is a process where monomers are emulsified in an aqueous solution and polymerized through heat, light or chemical initiators.^{9,18,22} This technique is generally applied on synthetic materials such as

polyalkylcyanoacrylates (PACA) and polymethylmethacrylate (PMMA).^{3,9,33}

Interfacial Polymerization: Polymerization is done at an interface between two phases (immiscible, monomer droplets and aqueous phase) and is commonly used to form reservoir-like structures but can also be applied to some nanosphere matrices.^{4,9,22}

3. Polymers Special Techniques: Biological activity is usually preserved with milder processing conditions with natural polymers.

Ionic Gelation (Ionotropic Gelation): It is applied to hydrophilic polymers such as chitosan, alginate and gelatin.^{3,6,18} It consists of an electrostatic cross-linking of a polyelectrolyte (e.g. cationic chitosan) with a multivalent counter-ion (e.g. anionic sodium tripolyphosphate) to create a highly cross-linked gel of nanoparticles.^{6,15,22}

Coacervation/Desolvation: This method is particularly preferred with protein-based nanospheres (e.g. albumin or gelatin) whereby changes in solvent conditions (pH, electrolytes, or addition of a non-solvent like ethanol) are used to induce phase separation and particle nucleation.^{4,9,16,37}

4. Inorganic Nanosphere Preparation.

Sol-Gel Process: Sol-gel is mostly applied to silica nanoparticles (SiNPs) and mesoporous silica nanoparticles (MSNs).^{4,11,13} It is the hydrolysis and condensation of silicone precursors (such as TEOS) in controlled pH and thermal conditions to create silica network.^{11,13,31}

Chemical Reduction: It is the most typical process of the metallic nanospheres (Gold, Silver), whereby, the metal ions are reduced to atoms by the action of chemical agents (such as sodium borohydride or citrate) and then nucleation and growth occurs.^{4,17,36}



5. High-technology and Scale-up Technologies.

Supercritical Fluid Technology: Techniques such as Rapid Expansion of Supercritical Solution (RESS) and Supercritical Anti-Solvent (SAS) have used supercritical to isolate polymers into small particles.^{8,35} This is a non-toxic organic solvent technique and is applicable to high-purity applications.^{3,6,8}

Microfluidic Techniques: These work in channels of micrometers to enable the handling of fluids accurately and quick mixing of fluids.^{19,22} This gives excellent control of particle size, polydispersity, and reproducibility than the traditional bulk techniques.^{4,19,22}

Spray Drying and Nano-Spray Drying: It is a mechanical process where a fluid is atomized into small droplets onto which hot gas is used to dry to create solid particles.^{22,31} Nano-spray drying is tailored to manufacture sub-micron sized nanospheres to be used in oral/respiratory delivery.²²

MECHANISM OF DRUG RELEASE FROM NANOSPHERE

The physicochemical properties of the matrix and its interaction with the surrounding environment are the main factors that control the mechanism of drug release of nanospheres, which are solid, monolithic matrix-type systems, in which the drug is physically and uniformly distributed throughout the polymer.^{2,3,8,15} As explained in the sources, the basic mechanisms and kinetics of drug release are the following:

1. Primary Release Mechanisms

Extraction of a matrix-type nanosphere is generally subject to five possible routes.^{3,4,32}

Desorption: This is when the drug molecules that are weakly adsorbed or bound to the huge surface area of the nanosphere are rapidly shed off.^{3,16,30} This may lead to an initial burst release that can

prove helpful in the attainment of an immediate therapeutic concentration.^{5,16,32}

Diffusion: The drug molecules can either travel through the polymer network or water filled pores in the matrix.³² When the diffusion of drugs is higher than the breakdown of the polymer, then the diffusive pathway takes over the release mechanism.^{3,16,30}

Matrix Erosion: Drug is released from polymer matrix undergoes erosion or disintegrates.^{4,16}

-Surface Erosion: This is common to hydrophobic polymers (e.g., polyanhydrides) in which the drug is dispersed at the surface during the degradation of the polymer at a constant rate.³²

-Bulk Erosion: This is characteristic of polymers such as PLA and PLGA and water is permeated through the entire matrix, leading the polymer to decompose all along.³²

Combined Erosion-Diffusion: The vast majority of bio-degradable systems involve a dual process in which the drug is diffused away as the matrix is eroded over time.^{3,16,30}

Swelling: In nanospheres made of hydrogel, when water is introduced into the hydrogel, it pushes the hydrogel into an expanded rubbery phase where drug molecules are scattered out.²⁴

2. Stimuli-Responsive (Smart) Release

Nanospheres can nowadays be designed to release upon a certain biological or external signal:²²

pH-Triggered Release: Systems in polymers, such as Eudragit S100, are stable on the low pH of the stomach but dissolve or swell in the elevated pH of the colon (pH > 7), permitting site-specific delivery.^{2,20,21}

Redox-Responsive Release: Nanospheres with disulphide bonds can break apart and release their contents when they come into contact with high levels of glutathione inside cells, which is common in tumour environments.^{19,22,31}

Enzymatic Degradation: Some polymers are designed to be broken down by certain enzymes



that are overproduced at disease sites, like proteases or cathepsins, which makes it possible to release them "on demand".^{10,22}

Exogenous Stimuli: External stimuli can be triggered by active release in case of magnetic fields (heat generation), ultrasound, or near-infrared (NIR) light.^{15,19,22,28}

3. Dispersal Dynamics and Modeling.

The mathematical models to the data are used to quantify and predict release:^{2,4}

Zero-Order Kinetics: This occurs when the drug is emitted at an unvarying intensity with time, regardless of its concentration.³²

First-Order Kinetics: The rate of release is a factor that is based on the concentration of the drug in the remaining matrix.^{3,32}

Korsmeyer-Peppas Model: This works with a release exponent (n) to determine the transport mechanism. For spherical samples.^{24,27}

- $n \approx 0.43$: Fickian diffusion.
- $0.43 < n < 1.0$: Non-Fickian anomalous transport.
- n : Known as Super Case II release, which entails diffusion that happens simultaneously, swelling (polymer unfreezing) and erosion of the matrix.²

4. Release rates are influenced by factors.

Particle Size: Smaller nanospheres connote greater surface area to volume ratio which in most cases results in increased drug fluxes and initial burst relative to larger particles.³²

Polymer Molecular Weight: Polymer Molecular weight is reverse correlated with release rate; the higher the molecular weight the slower the degradation and the longer the release.^{16,32}

Copolymer Composition: Within a copolymer, the total rate of release can be enhanced by incorporating more of a more quickly degradable

monomer (or by adding more monomers of both types).³²

Drug Distribution: The release of drugs which are localized around the surface occurs quickly whereas uniformly dispersed drugs that are deep in the core are known to give a plateau or stable release phase.^{5,32}

ADVANTAGES OF NANOSPHERES

There are numerous benefits of nanospheres in pharmaceutical and medical processes which can primarily be traced back to the structural design, submicron size and the ability to compose the nanospheres out of a wide variety of materials. Being systems of a matrix nature, they offer a strong platform in the current drug delivery.^{2,7,8,33}

1. Site-Specific Targeting and Improved Tissues penetration.

Active and Passive Targeting: Nanospheres have the potential to target diseased tissues, i.e. tumours, by active and passive targeting via the so-called enhanced permeability and retention (EPR) effect.^{9,18,32,33} Moreover, their surface can be functionalized with selected ligands, antibodies or peptides in order to attain active targeting of cellular receptors.^{9,18,19,34}

Crossing Biological Barriers: They have a very small size and can traverse even the tiniest capillary tubes and access deep-target organs such as the liver, spleen, and lungs.^{9,28,32} They work especially well when targeting the brain, with surface-modified nanospheres (e.g. coated with Polysorbate 80) being able to circumvent the blood-brain barrier (BBB) through receptor-mediated endocytosis.^{3,9,18,26,35}

Prolonged Circulation: Smaller particles (less than 200 nm) have a high radius of curvature, which inhibits opsonin binding, and thus they have a longer half-life in the bloodstream.^{9,32,33}



2. Controlled and Sustained Drug Release.

Optimized Dose regimens: Nanospheres release their drug load by either diffusion of a matrix or by erosion or by stimuli-responsive responses.^{10,32}

This enables the drug levels to be maintained in the therapeutic range over longer durations lessening administration rate (e.g. daily doses to once a month).^{10,13,32}

Adjustable Release Profiles: The researchers can make the release constant, pulsatile or even triggered by the environmental conditions, such as pH or temperature by choosing a particular polymer or controlling the molecular weight.^{9,22,32,33}

3. Active Ingredients Protection and Stabilization.

Shielding against Degradation: The solid polymeric matrix is a mechanical barrier that helps to shield drugs, particularly sensitive proteins, peptides and nucleic acids, against enzymatic and chemical breakdown in unfavorable biological fluids.^{9,32,33}

Improved Shell Life: In the case of pharmacologically active agents, which are otherwise unstable, encapsulation into nanospheres maintains the structure and bioactivity of the agent during storage and in the circulatory system.^{3,16,18,35}

4. Bioavailability and Solubility Improvement.

Solubilization of Hydrophobic Drugs: Nanospheres are an excellent delivery system of poorly water-soluble drugs (BCS Class II and IV), which are dispersed at the molecule scale within a hydrophobic matrix, which can be used to enhance saturation solubility and dissolution rate of hydrophobic drugs by many orders of magnitude.^{3,16,19,32,33}

Mucoadhesion and Absorption: The use of natural polymers such as chitosan gives the system

mucoadhesive effect, which prolongs the residence time of the system on biological membranes (i.e. GI or nasal mucosa) and open tight junctions to aid drug absorption.^{5,18,19,35}

5. Decreased Toxicity and Respondent Patient compliance.

Targeted Delivery: The nanospheres reduce the toxicity and unwanted off-target effects within the body because they can deliver the drug to the target location and minimize its exposure to healthy tissues.^{8,9,10,12,18,24,32}

Safe Metabolism: A variety of nanospheres are prepared using biodegradable polymers (such as PLA and PLGA) approved by the FDA that disintegrate under hydrolysis to non-toxic metabolites (e.g. lactic acid) which are excreted through Krebs cycle.^{10,14,18,34,37}

Ease of Administration: They are small and spherical, which allows the formulation into injectable suspensions that do not obstruct blood vessels, oral, pulmonary, and topical delivery systems; hence, enhancing patient acceptance and adherence.^{8,9,18,32,33,36}

6. High Functional Power

High Loading and Reactivity: Nanospheres are very high in stability with respect to surface area-to-volume ratio, which results in high drug loading efficiency and prompt reaction to external/internal stimuli when compared to traditional micro-scale systems.^{12,28,31,32,35}

The ability to co-deliver therapeutic agents and imaging agents (such as quantum dots or iron oxide) makes nanospheres promising theranostic platforms that can be used to simultaneously track drug distribution and therapeutic response in one platform.^{6,10,19,22,34}



LIMITATIONS

Although nanospheres have enormous therapeutic capabilities, they also have a number of severe constraints in terms of their physical characteristics, biological behavior, and production protocols.

1. Consideration of Limitations on the Physical and Handling.

Particle Aggregation Nanospheres of this size are highly repulsive with a low surface energy, leading to a significant aggregation or clumping behavior due to their small size.^{8,9,32}

Difficulties: Nanospheres are challenging to handle physically both in dry and liquid states.⁹

Stability Issues: They are metastable in nature and less stable than bulk materials, and they need surface alterations such as PEGylation to be effective under normal conditions.^{4,10}

2. Pharmacokinetic Problems of Loading and Release.

Reduced Loading Capacity: Nanospheres with limited size and great surface area size can counter-intuitively lead to reduced or incomplete loading of drugs.^{8,9}

Features commonly found in burst release A well known disadvantage is the burst release effect, in which much of the drug loosely adsorbed to the surface is released quickly in a burst and cannot be controlled upon administration.^{8,9,19,32}

Inactivation during Fabrication: The bioactive molecules trapped especially proteins can be inactivated or denatured by the hostile conditions involved in some production processes.^{32,37}

3. Biological and Toxicological Concerns.

Reactive Oxygen Species (ROS) Generation: No matter what material is employed, high surface area-to-volume ratio of nanospheres may result in

the generation of ROS, which causes oxidative stress, DNA damage and cell death.^{1,23}

Organ Accumulation and Chronic Toxicity: Nanospheres are more likely to get accumulated in the gastrointestinal tract, liver, and the spleen.^{9,30} The non-biodegradable particles have the risks of long term tissue retention and chronic systemic toxicity.^{10,14}

Material-Specific Toxicity:

-**Inorganic/Metallic:** Silver and gold nanospheres have the potential to cause genotoxicity and inflammation at increasing medicine doses.^{1,17}

-**Carbon-Based:** These are able to stimulate the inflammation of the respiratory and cardiovascular systems.¹

-**Synthetic Polymers:** Polymers such as PLGA release acidic degradation products that have the potential to induce inflammatory reactions in tissues.²⁸

-**Proteins:** There is the possibility of the causation of autoimmune reactions particularly when repeated administered.³⁷

4. Clearance and Biodistribution Problems.

Rapid RES Clearance: Hydrophobic nanospheres are extremely vulnerable to opsonization, which is the layer of plasma proteins on the surfaces, enabling the reticuloendothelial system (RES) to swiftly be able to locate and eliminate them in the blood.^{9,16,33}

Non-selective Distribution: Nanospheres have no functionalized surfaces, so it can disseminate all over healthy tissues potentially causing off-target toxicities.⁷

5. Production and Regulation barriers.

Scalability and Cost: A shift in the technology of small-scale laboratory synthesis to the large scale industrial production is difficult on the technical side and expensive.^{4,18} Consistency of batch to

batch that relates to size, charge and loading is a significant challenge.^{10,22}

Absence of Standardization: There are at present no international regulatory guidelines that are harmonized or a standardized way of in vitro testing of nanopharmaceuticals that makes it difficult to approve.⁴

Residual Solvents: A lot of preparation techniques are based on organic solvents (such as chloroform or acetone) and the fact that these solvents need to be removed absolutely in the end product is an annoying but essential safety measure.^{4,6}

6. Environmental Impact

Persistence and Bioaccumulation: Nanospheres may remain longer in the environment than conventional drugs due to their distinctive chemical properties and as a result, persist, bioaccumulate, and cause an ecological disturbance.⁴

EVALUATION OF NANOSPHERES

Nanospheres are thoroughly evaluated in nanomorphological, nanochemical, nanopharmacological, and nanobiological methods to guarantee the safety and effectiveness of these nanoparticles in medicine.

a. Morphological and body Characterisation.

Scanning Electron Microscopy (SEM): Scanning electron microscopy is applied to measure the morphology of the nanospheres, surface texture, and form of the nanospheres.^{2,17,18,20,27} It gives 3D topographical images to reveal the distribution of particles and the possible aggregation.^{4,12,17,18}

Transmission Electron Microscopy (TEM): TEM can be used to visualize the internal structure of the nanoparticles and is needed in distinguishing a solid nanoparticle and hollow nanocapsule.^{2,4,12,17,18,26,29}

Atomic Force Microscopy (AFM): This technique is used to scan the surface so that the roughness and topography of the surface can be measured at the nanoscale.^{4,12,17,18}

Particle Size and Size Distribution: Generally, such a size is determined by the use of Dynamic Light Scattering (DLS) or Photon Correlation Spectroscopy (PCS), which can identify the hydrodynamic diameter.^{2,4,12,17,18,20,33}

Polydispersity Index (PDI): This is a dimensionless parameter which determines how homogenous the population of the particles is with a PDI of less than 0.5 suggesting a small and stable population (of the particle).^{2,17,18,20,36}

Zeta Potential Analysis: This is used to measure the surface charge which is a primary indication of colloidal stability.^{2,3,4,12,17,18} When the absolute zeta potential is high (usually above $\pm 30\text{mV}$), the particles will repel, which prevents clumping and aggregation.^{2,3,17,18}

2. Chemical and Structural Analysis.

Fourier Transform Infrared Spectroscopy (FTIR): FTIR plays a crucial role in the determination of chemical integrity and the character of intermolecular interaction (interaction between the drug and the polymer matrix), e.g., hydrogen bonding.^{2,4,8,18}

Differential Scanning Calorimetry (DSC): This method identifies the physical condition of the drug within the nanosphere matrix.^{2,4,8,12,18,27} As an example, the melting peak of a drug does not exist, meaning that the substance is an amorphous and not a crystalline form, which tends to increase solubility.^{4,6,11,27}

X-ray Diffraction (XRD): XRD will be used to identify the crystalline or amorphous nature of the nanospheres and general composition.^{4,8,17,27}

X-ray Photoelectron Spectroscopy (XPS): This is also referred to the ESCA, and it gives a surface elemental analysis that is applicable in sampling



the efficacy of surface coating or the presence of targeting ligands.^{3,8,12,15}

3. Drug Loading and Release Performance.

Entrapment Efficiency (EE%) and Drug Loading (DL%): These are measured by HPLC or UV-Vis spectrophotometry.^{2,5,18,20,27} EE% is determined as the percentage ratio of drug that was successfully bound or entrapped to the amount of drug utilized in the process of preparation.^{2,16,20}

In Vitro Release Studies: Release can be studied by either dialysis bag diffusion technique or sample and separate in simulated biological fluids.^{2,3,4,18,20,27}

Release Kinetics: The data is modeled based on mathematical models such as Zero-order, Higuchi, or Korsmeyer-Peppas to determine whether the drug is being released through diffusion or matrix erosion or swelling.^{2,16,18,24,27}

4. Biological and Functional assessment.

In Vitro Cytotoxicity: Cell viability or the IC₅₀ (concentration needed to kill 50% of the cell growth) are measured with assays such as Sulphorhodamine-B (SRB) or MTT to determine efficacy and safety on a particular cell line.^{2,15,18}

Pharmacokinetics (PK): The parameters that are investigated by in vivo studies in animal models include (maximum plasma concentration), (time to reach peak concentration) and AUC (area under the curve) in order to establish systemic bioavailability.^{4,20,27}

The biodistribution: This follows the accumulation of the nanospheres in the body, it typically concentrates at high levels in the liver and the spleen because it gets taken up by the reticuloendothelial system (RES).^{4,9,11,15,37}

Stability Studies: Selected formulations are kept at room temperature and refrigeration temperature over several months (e.g., 6 months) to test

whether there are any changes in particle size, zeta potential, or drug retention.^{2,4,18,36}

APPLICATIONS OF NANOSPHERES

Nanospheres have transformed the therapeutic arena, offering complex drug delivery systems that enhance solubility, stability and site-specificity in medicine in different fields.¹⁸ They have a special monolithic matrix structure that enables release of active pharmaceutical compound by diffusion or polymer erosion to be controlled.^{2,7,18}

1. Oncology (Cancer Treatment)

Among the most notable uses of nanospheres is in the field of oncology where they counter address the drawbacks of systemic toxicity and non-specific localization with related to the conventional chemotherapy.¹⁸

Passive Targeting: Nanospheres selectively deliver their cargo to tumor tissue by the enhanced permeability and retention (EPR) effect that utilizes the leaky vasculature in tumors.^{9,17,18}

Active Targeting: With the functionalization of the nanospheres surface with ligands, antibodies, or peptides, they can be designed to target receptors that are overexpressed on cancer cells, increasing their internalization in the cells.^{9,18,19}

Case Studies: Nanospheres made of PLGA loaded with paclitaxel have also shown a remarkable decrease in tumor growth in the preclinical models with little harm to normal tissues.¹⁸

2. The second one is Neurological Disorders and brain targeting.

The blood-brain barrier (BBB) prevents the delivery of medications to the central nervous system, but nanospheres provide one way to overcome it.^{9,18,30}

BBB Penetration: Nanoparticle surface-modified with Polysorbate 80 can be used to cross the BBB



through a receptor-mediated endocytosis process.^{9,26}

Neurodegenerative Diseases PEGylated nanospheres are used in order to deliver anti-Alzheimer and anti-Parkinson drugs, which provide sustained release and lessen the dose frequency.¹⁸

Diagnostics Polymeric nanospheres are under study as early warning annexes of Alzheimer disease because they are capable of locating particular mutant proteins in the brain.²⁶

3. Oral and Systemic Drug Delivery.

Nanospheres enhance the uptake of the labile drugs or drugs that are not well dissolved in water via different systemic pathways.^{8,21}

Oral Delivery of Biomacromolecules: To prevent the bioavailability of peptides and proteins (e.g., insulin) oral delivery to the gastrointestinal tract, they are encapsulated in biodegradable nanospheres.^{9,18,21}

Colon-Specific Delivery: pH-sensitive nanospheres that are Eudragit® copolymer-based have been developed to deliver drugs specifically to the colon, which is effective in treating inflammatory bowel disease and ulcerative colitis.^{20,21}

Cardiovascular Health: Nanospheres carrying statins (such as atorvastatin) or anti-thrombotic drugs increase the time and efficacy of drugs in the process of hyperlipidemia and atherosclerosis treatment.¹⁸

4. Local Deliveries (Ocular, Pulmonary and Vaginal)

Ocular Delivery: Nanospheres improve the residence time and uptake of the drugs into the eye, by overcoming the barriers such as tear film to treat diseases such as glaucoma and age-related macular degeneration.¹⁸

Pulmonary Delivery: Inhaled corticosteroids that are administered as nanospheres have a higher lung retention rate and can provide topical therapy to asthma and COPD with fewer side effects to the system.¹⁸

Vaginal Delivery: pH-responsive polymeric nanospheres have been used to deliver drugs under semen stimulation, as microbicides in preventing HIV and other sexually transmitted diseases.²¹

5. Advanced Medical Technologies

Tissue Engineering: Nanospheres can be used as injectable gels, as porogens to enhance porosity of scaffolds to allow tissue infiltration and bone regeneration.²⁸

Blood Cleansing: Biodegradable Nanospheres: It is possible to biodegrade magnetic nanospheres to carry certain toxins in the blood; and then to take them out in another magnetic separator in a shunt, which could help in curing biological or radiological toxin exposures.¹⁵

Gene and Vaccine Delivery: Nanospheres are effective vectors to deliver DNA, RNA, and antisense oligonucleotides and ensure cellular uptake of gene therapy or mucosal immunization cargo.^{9,18,30}

6. Commercial and Promoted Goods.

Some nanosphere-based formulations have either made it to the market or to clinical trials stage. Indicatively, an example of polymeric nanosphere formulation used in the treatment of hypertension is Verelan PM.⁴

RECENT ADVANCES IN NANOSPHERES

The latest advancement of nanosphere technology has seen the advancement of less advanced drug carriers into multi-advanced, smart and multifunctional carriers. These breakthroughs combine materials science, biotechnology, and



artificial intelligence to break through biological barriers that have been present for a long time.

1. The concept of Smart and Stimuli-Responsive Systems: The contemporary nanospheres are meant to be stimuli-sensitive, i.e. they are only able to release their cargo upon the body in response to certain stimuli.^{10,19}

pH-Responsive Nanospheres: These types of systems utilise the acidic tumour or inflammatory microenvironment.^{2,21,74,75}

Indicatively, biodegradable polymers are used together with Eudragit polymers to form nanospheres which could be stable in the stomach but leak drugs particularly in the colon or tumor tissues.^{2,21,76}

Dual and Multi-Responsive Systems: Developed designs are now operating on several triggers at once, e.g. a near-infrared (NIR) light signal and a pH signal, with high-precision, on-demand, drug release.^{11,22}

Redox and Enzyme Sensitivity: Nanospheres that have redox-cleavable disulfide linkers are designed to disperse and release drugs only upon exposing them to the large concentrations of glutathione present in cells.^{19,31}

2. Hybrid and Biomimetic Architectures.

The tendency among researchers is to mix various classes of materials in order to generate hybrid systems with a better property.

Another type of next-generation nanoparticles is Lipid-Polymer Hybrid Nanoparticles (LPHNPs): This nanoparticle combines the sustained release and mechanical stability of a polymeric core with the high biocompatibility and ease of targeting of a lipid shell.¹⁹

Biomimetic Coating: One of the major advances is to coat synthetic cores of nanosphere with cell-derived membranes (e.g. red blood cells, white blood cells, or platelets).⁴ This enables the particles to get the innate functionality of the

source cell as in the capability to avoid the immune system or to attack certain inflamed tissues.⁴

Polymer-Caged Nanobins: This is a novel subclass of the liposomes that have pH-responsive polymer layers on the surface to increase the structural integrity and allow targeted release in the acid tumor environments.¹⁹

3. Dental Nanotechnology.

Combining the therapeutic and diagnostic capabilities into one nanosphere named theranostic is one of the notable fields of development.^{6,22}

Mesoporous Silica Nanospheres (MSNs): these have a superior structural tunability as well as huge surface area (greater than 1000) to load drugs.^{4,11} Recent developments involve MSNs that have caps made of gold nanoparticles to release on light activation or they have been functionalized with quantum dots to provide real-time fluorescence imaging.¹¹

Inorganic-Organic Hybrids: Hybrid nanospheres comprising of iron oxide cores are applied in the magnetic drug targeting as well as high-contrast agents in MRI so that clinicians can monitor the distribution of drugs in real-time.^{1,22,29}

Carbon-Based Spheres: Fullerenes (C60) are also under consideration as radical sponges due to their antioxidant qualities/functionalized with hydrophilic groups to serve as vectors to penetrate the blood-brain barrier.^{1,34}

4. Synthesis and design syntactic technological advancements.

Recent manufacturing and computing devices have enhanced scalability and precision of production of nanosphere.

Microfluidics and Continuous Flow Synthesis: These are methods that are realized in channels of micrometer range, enabling accurate manipulation of fluids, and fast mixing.^{4,19} This gives high



uniformity in nanospheres with high control in particle size and drug encapsulation efficiency than the traditional batch methods.^{4,22}

Flash Nanoprecipitation: This is a type of nanoprecipitation in which the turbulent flow is used to create naturally supersaturated regions leading to the precipitation of particles suddenly with a high loading of hydrophobic drugs in an extremely reproducible way.²²

AI and Machine Learning: The AI is currently utilized to design and optimize nanosphere formulations faster by anticipating its physicochemical characteristics and modeling its distributions in the body.⁴

Green Nanotechnology: The movement is towards an emphasis on the concept of the so-called ecofriendly synthesis techniques, where microorganisms or plant extracts are used in place of toxic chemical reagents, minimizing environmental footprint and costs of manufacturing.^{11,17}

5. Novel Clinical Applications

The nanotechnological product was introduced as **Nanosphere Blood Cleansing:** This is based on a radical design where nanospheres that are biodegradable are injected into the blood and the particles bind with certain toxins (e.g., biological or radiological attack); the particles are then filtered out by a special magnetic separator that is placed over a special shunt.¹⁵

Anisotropic (Non-Spherical) Designs: The designs are traditionally spherical, and following recent studies, rod, worm, and disk-like designs are studied.²² Such varying shapes have the potential to vastly change the cellular uptake and circulation time, whereby certain types of the rod-shaped particles have been found to have excellent tumor penetration compared to their spherical counterparts.²²

FUTURE ASPECTS OF NANOSPHERES

The future of nanosphere technology in pharmacy and medicine is defined by a transition of the simple carriers to the autonomous, so-called intelligent systems, which will be able to move in the complex biological environments.^{1,34} Current research and development are aimed at addressing the existing translational challenges with the help of multidisciplinary teamwork and sophisticated computing technologies.^{10,11}

1. Personalized (Individualized) Nanomedicine and Precision Stratification.

Personalized Therapy: Future directions will be to personalize treatment plans according to genetic, proteomic and metabolic profile of a patient.⁴

Biomarker Integration: Scientists are trying to pinpoint particular categories of patients who respond better to certain nanoformulations in accordance with their immune responses or in particular tumor microenvironment.⁴

Real-Time Monitoring: Future systems will probably also include real-time patient feedback and adaptive dosing to maximize the therapeutic effect and minimize individual toxicity.⁴

2. Digital Twin Technologies and Artificial Intelligence (AI).

Computational Optimization: AI and machine learning models are being applied more frequently to model the physicochemical behavior and toxicological consequences of nanospheres, making the design process much faster.⁴

Digital twins: Digital twins will be created to formulate nanosphere formulations in silico by developing computational models of individual patients, eliminating the need to use empirical trial-and-error approaches.⁴



3. High-tech Smart and Stimuli-Responsive Designs.

Self-Immolative Systems: Future nanospheres will incorporate self-immolative systems and multi-stage-responsive systems, which are capable of detecting extremely small variations in biological conditions to release drugs with high-precision.²²

Autonomous Navigation: The long-term objective involves the autonomous nano-DDS which could be transported on the blood, search and identify the location of the disease, and automatically perform the releases or repairs procedures.³⁴

Theranostic Versatility: The next generation systems will be more integration-friendly to achieve the goals of imaging, diagnostics and therapy in a single multifunctional device and allow concomitant treatment and real-time tracking of drug delivery.^{10,19}

4. Complex Biomacromolecules Expansion.

Next-Generation Cargo: With the transition to larger biomolecules, nanospheres will gain importance in the delivery of peptides, proteins, monoclonal antibodies, and nucleic acids (DNA/RNA), which are vulnerable to enzymatic degradation.^{22,30}

Gene Editing: A combination of nanospheres and advanced gene-editing systems such as CRISPR-Cas9 has a great potential of treating incurable genetic diseases in the past.^{4,10}

5. Clinical and Technological Revolutionary Paradigms.

Nanosphere Blood Cleansing: in this case, biodegradable magnetic nanospheres can be used to adsorb and eliminate particular toxins in the blood stream through external magnetic separators, as a potential future use case in the treatment of biological or radiological exposures.¹⁵

Multi-Platform Integration: Future studies will investigate the combination of nanospheres with

other platforms of drug delivery, including implantable devices and injectable hydrogels, to provide sustained localised therapy.^{18,28}

Organ-on-a-Chip Evaluation: It will be possible to apply body-on-a-chip systems to assess the inter-organ crosstalk and long-term biodistribution of nanospheres, which are more accurate in simulating human physiology than the existing animal models.⁴

6. Evolution of Regulatory and Manufacturing.

Adaptive Frameworks: There is an urgent call to have adaptive and harmonized international regulatory standards specifically on nanopharmaceuticals to simplify the process of laboratory to clinic.⁴

Green Nanotechnology: The sector is shifting towards ecologically-friendly production processes, which employ natural extracts or microorganisms in an attempt to reduce environmental impact and reduce the cost of production.¹¹

Scalable Accuracy: The innovation of continuous flow production and microfluidics will establish a new benchmark of mass-produced, reductable manufacture of nanomedicines with homogeneous attributes.^{4,11}

CONCLUSION

Conclusively, nanospheres constitute a ground-breaking frontier in the pharmaceutical sciences, which provide a strong and multifaceted platform of delivering a variety of therapeutic agents. These sub-micron sized particles are monolithic by nature and have been shown to transduce poor water-solubility, poor-absorption and labile bioactive molecules into performance/deliverable drugs. Nanospheres offer an essential protective layer that shields therapeutic cargo by dispersing or adsorbing drugs into their solid core thereby preventing enzymatic and chemical degradation in



the hostile biological environments. The main clinical benefit of the nanosphere technology is that the latter leads to site-specific targeting and controlled release. These systems have the advantage of concentrating disease-specific tissues - such as tumours or inflamed foci - with medication through the use of a variety of mechanisms such as the enhanced permeability and retention (EPR) effect or functionalization of surfaces with specific ligands, to achieve the greatest therapeutic effect and the lowest systemic toxicity. They can also be used to penetrate complicated biological barriers such as the blood-brain barrier because of their ultra-tiny volume which provides new opportunities to treat neurological disorders into which traditional methods could not reach. Although they have great potential, a number of challenges still have to be overcome to be used on a large scale in clinical use. The problems of scalability in manufacturing, reproducibility of batches to batches and aggregation of particles need to be narrowed down to achieve pharmaceutical grade consistency. Moreover, the absence of harmonised international regulatory standards directly designed to suit nanomedicines is also a major challenge of next-generation formulations approval and commercialisation. In the future, the trend in nanosphere technology is toward intelligent and stimuli-responsive and theranostic systems. A combination of artificial intelligence, adaptive stratification of biomarkers, and biomimetic surfaces will ensure that in the near future autonomous nano-devices can be used to search, identify, and cure diseases more precisely than ever before. Finally, with research to close the gap between laboratory innovation and clinical practice, nanospheres will transform the healthcare landscape, greatly enhancing patient outcomes and quality of life in a wide range of human illnesses.

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