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FROM DESIGN TO CLINICAL TRANSLATION: PHYSICOCHEMICAL PROPERTIES GOVERNING PHARMACEUTICAL NANOPARTICLES IN MODERN DRUG DELIVERY

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ABSTRACT

Pharmaceutical sciences have undergone a revolution thanks to nanotechnology, which has solved issues with traditional drug delivery methods such poor solubility and targeting. The physicochemical characteristics that control nanoparticle biodistribution, cellular uptake, and efficacy—such as size, shape, surface chemistry, and charge—are examined in this review. Top-down and bottom-up preparation methods, characterisation methods (DLS, TEM, zeta potential), and applications in neurological illnesses, cancer, and vaccines are all covered. Precision medicine is promised by stimuli-responsive and AI- optimized nanocarriers, however scalability and safety issues still exist. Clinical translation potential is highlighted by recent developments, such as LNP-mRNA vaccines.

KEYWORDS: Physicochemical characteristics, targeted therapy, drug delivery, nanomedicine, nanoparticles, and characterisation methods.

INTRODUCTION

The interdisciplinary discipline of nanomedicine was born out of the quick development of nanotechnology from a specialised field of study to a key component of contemporary pharmaceutical innovation.[1] Working in the 1–100 nm range makes it possible to create nanostructured systems with special physicochemical characteristics, such as large surface area, adjustable surface chemistry, and designed reactivity to biological stimuli, that are not possible with traditional bulk formulations.[2,3] Conventional dose forms are often characterised by unsatisfactory patient adherence, off-target toxicity, restricted bioavailability, and poor solubility, all of which result in reduced therapeutic outcomes.[4] On the other hand, well-thought-out nanocarriers can improve the pharmacokinetic and pharmacodynamic profiles of a variety of medications by increasing solubility, extending circulation duration, enabling regulated or stimuli-responsive release, and achieving tissue- or cell-specific delivery. Clinically proven nanomedicines like lipid nanoparticle (LNP)-based mRNA vaccines against COVID-19, Abraxane (albumin-bound paclitaxel), and Doxil (PEGylated liposomal doxorubicin) have already shown how nanoscale engineering can fundamentally alter both preventive and therapeutic medicine.[5,6] These goods are prime examples of how platforms enabled by nanotechnology can reduce dose-limiting toxicities, get beyond biological obstacles, and open up new treatment options, such as nucleic acid delivery.[7,8] A distinct transition from "first-generation" carriers to multifunctional, stimuli-responsive, and AI- assisted nanomedicines intended for precision therapy and real-time treatment response monitoring is also highlighted in

recent publications.[9,10] With a focus on nanocarrier classes, structure-function relationships, preparation and characterization techniques, therapeutic applications, translational bottlenecks, and emerging directions, the current review summarizes recent developments in pharmaceutical nanotechnology.[11,12,13,14]

Examples of Pharmaceutical Nanocarrier Classes The major types of nanocarriers used in pharmaceutical applications are described below.

Liposomes and Lipid Nanoparticles (LNPs)

With one or more phospholipid bilayers encasing an aqueous core that can hold both hydrophilic and hydrophobic medications, liposomes continue to be one of the most well- established nanocarrier platforms.[15,16,17] Liposomes are given "stealth" qualities and targeting capabilities via PEGylation and ligand functionalization, which prolong circulation half-life and decrease mononuclear phagocyte system (MPS) uptake.[18,19] LNPs, a more recent development of lipid systems, have become the mainstay for the delivery of mRNA and other nucleic acids because they facilitate effective cytosolic release, improve endosomal escape, and shield labile cargo from enzyme degradation. Iterative optimization of ionizable lipids, helper lipids, cholesterol content and PEG‑lipids has turned LNPs into a modular platform now being rapidly translated to vaccines for influenza, RSV, HIV and personalized cancer immunotherapy, as well as gene‑editing therapies for rare diseases.[20,21,22]

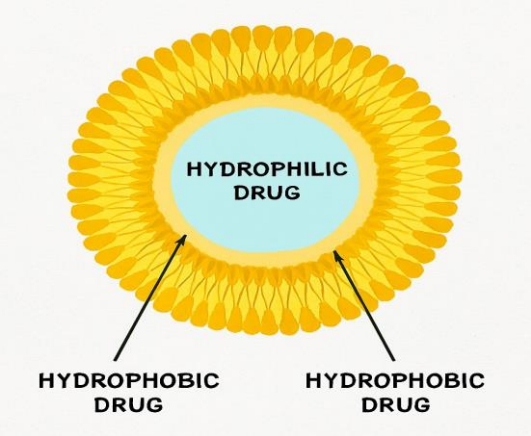

Fig. 1: Structure of Liposomes.

Lipid nanoparticles (LNPs) represent a more recent evolution of lipid-based carriers. They have gained global recognition for their pivotal role in delivering nucleic acid therapeutics, most notably in the mRNA-based COVID-19 vaccines.[23,24,25] LNPs protect labile nucleic acids from enzymatic degradation, facilitate endosomal escape and enable efficient intracellular delivery. Their modular composition, typically involving ionizable lipids, cholesterol, helper lipids and PEG-lipids allows fine tuning of biocompatibility and pharmacokinetics.[26,27,28,29]

Polymeric Nanoparticles (PNPs)

Polymeric nanoparticles are solid colloidal systems synthesized from biocompatible and biodegradable polymers such as poly (lactic-co-glycolic acid) (PLGA), chitosan, alginate, and other natural or synthetic materials.[30,31,32,33] These nanoparticles can exist as nanospheres in which the drug is uniformly dispersed throughout the polymer matrix or as nanocapsules which contain a distinct core surrounded by a polymeric shell.[34,35,36,37,38] PNPs are well suited for sustained and controlled drug delivery due to their tunable degradation profiles and ability to modulate release kinetics. In order to enable active targeting to tumor cells, inflammatory tissues, or particular receptors at barrier points like the blood–brain barrier (BBB), these systems can be created as nanospheres or nanocapsules and have their surfaces functionalized by antibodies, peptides, or small molecules.[39,40,41,42] Recent research has focused on immunomodulatory payloads, multi-drug loading, and responsive polymers that alter their solubility or structure in response to temperature, pH, or redox gradients. This allows for the coupling of disease-specific microenvironments with spatiotemporal regulation of release.[43,44,45,46]

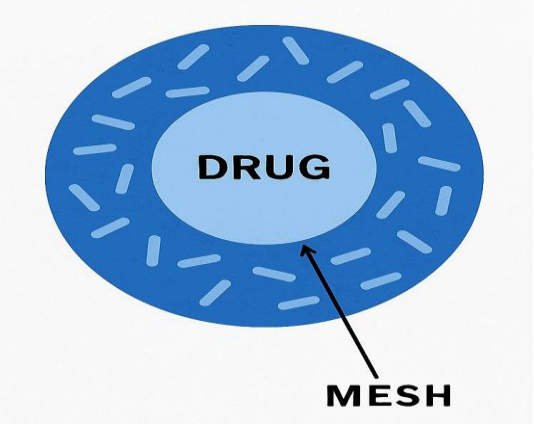

Fig No:2. Structure of Polymeric Nanoparticle.

Inorganic Nanocarriers and dendrimers

Inorganic nanoparticles including gold nanoparticles (AuNPs), silver nanoparticles (AgNPs) and mesoporous silica nanoparticles (MSNs) offer unique physicochemical properties that differ fundamentally from organic nanocarriers. To combine efficacy with long-term biocompatibility and clearance, careful control of size, shape, and surface chemistry is necessary.[47,48,49,50] Their surface can be densely functionalized with medicines, targeting ligands, and stealth coatings, enabling very modular designs. Dendrimers are appealing platforms for gene delivery, antiviral therapy, and imaging probes where high loading and regulated presentation of ligands are crucial because of their multivalent surface and monodisperse, tree-like topology, which provide fine control over size and functionality.[51,52,53,54]

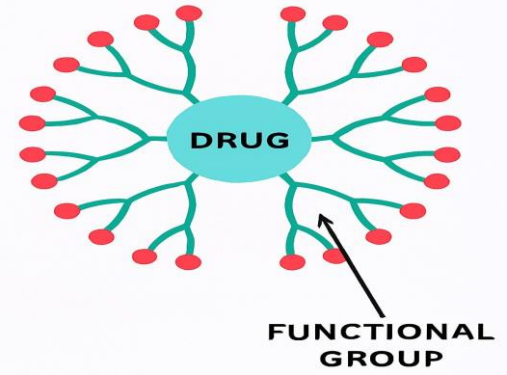

Fig No:3. Structure of Dendrimer.

Polymeric Micelles and Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) and polymeric micelles are especially effective at solubilizing hydrophobic medications and enhancing their oral or parenteral bioavailability. While stimuli- responsive chemistries can be added to initiate release in acidic or enzyme-rich environments, their tiny size and "soft" surfaces aid in extended circulation and tumor penetration.[55,56,57,58] The advantages of several material classes are being combined in hybrid organic–inorganic structures and core–shell architectures, which are attracting interest because they allow for things like simultaneous imaging, triggered release, and mechanical strengthening of scaffolds for regenerative medicine.[59,60,61,62]

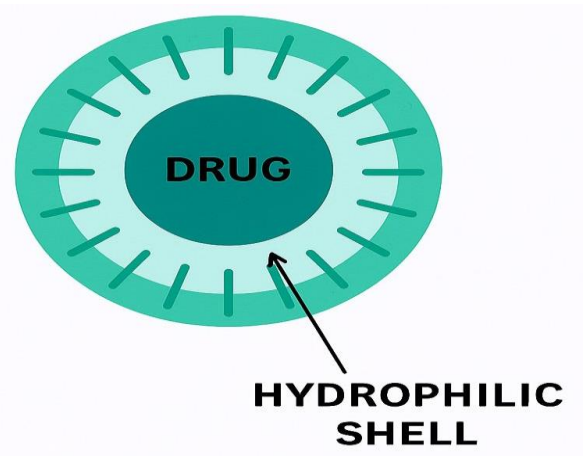

Fig No. 4: Structure of SLNs.

Solid lipid nanoparticles (SLNs) composed of solid lipids stabilized by surfactants provide an alternative lipid-based delivery platform with advantages such as high physical stability, low toxicity and protection of labile drugs from degradation.[63,64,65,66] SLNs are particularly useful for enhancing the oral bioavailability of poorly soluble compounds and supporting controlled drug release profiles. Research on nanomedicine in the post-pandemic age has shifted its focus to multifunctional and intelligent nanocarriers that can integrate with immunotherapy, gene-editing tools, and therapy and diagnosis at the same time. Numerous second-generation nano formulations are currently advancing into advanced clinical trials, and recent thorough studies demonstrate how nanomedicine is quickly extending beyond oncology into cardiovascular, neurological, infectious, and regenerative diseases.[67,68,69,70]

Methods of Preparation

The development of pharmaceutical nanoparticles requires reliable, scalable, and reproducible preparation methods that enable precise control over essential quality attributes such as particle size, morphology, surface chemistry, and stability. Broadly, nanoparticle fabrication strategies are categorized as top-down or bottom-up approaches. Top-down techniques rely on size reduction of bulk materials, whereas bottom-up methods promote the assembly of particles from molecular precursors. The choice of method depends on the physicochemical characteristics of the drug, intended delivery route, and desired nanocarrier properties.[71,72,73]

i) Top-Down Methods

Top-down processes are primarily employed to produce nanocrystals or to reduce the size of existing microparticles. These methods utilize mechanical forces to fragment larger structures into nanoscale entities.

➢ Wet Bead Milling

Wet bead milling is a widely adopted size-reduction technique in which the drug is dispersed in an aqueous medium containing stabilizers and mixed with high-density milling beads. Mechanical shear and collisions generated during agitation progressively reduce the particle size to the nanometer range. Critical parameters include bead size, milling duration, agitation intensity, and stabilizer concentration. Temperature control during milling allows processing of thermolabile drugs. This robust method has been applied in the production of FDA-approved nanodrug formulations such as fenofibrate (Tricor®).[74,75,76]

➢ High-Pressure Homogenization (HPH)

High-pressure homogenization forces a coarse drug suspension through a narrow orifice at extremely high pressures, generating intense shear forces, turbulence, and cavitation. These forces effectively break down particles and yield nanosized dispersions with narrow size distribution. HPH minimizes the risk of contamination as it does not involve grinding media and is suitable for aqueous and non-aqueous systems. Its scalability makes it apreferred technique in industrial manufacturing, with applications in products such as AmBisome® and Visudyne®.[77,78]

➢ Sonication

Sonication employs high-frequency ultrasonic waves to induce acoustic cavitation, resulting in the fragmentation of larger particles or vesicles. It is commonly used to convert multilamellar vesicles (MLVs) into small unilamellar vesicles (SUVs) in liposomal systems. While sonication is simple and effective at laboratory scale, challenges include potential metal contamination from

probes and degradation of sensitive compounds upon prolonged exposure.[79,80]

ii) Bottom-Up Methods

Bottom-up methods create nanoparticles through controlled nucleation and growth from molecular or ionic precursors. These approaches offer superior control over particle morphology, composition, and surface properties.

➢ **Nanoprecipitation (Solvent Displacement Method)**

Nanoprecipitation involves dissolving a polymer and drug in a water-miscible organic solvent followed by rapid mixing with an aqueous non-solvent. The sudden reduction in solvent polarity induces polymer precipitation, leading to spontaneous formation of nanoparticles. This method is simple, fast, and reproducible, yielding uniform particles without the need for high shear or complex equipment.[81,82,83]

➢ **Emulsion–Solvent Evaporation/Diffusion**

This versatile technique involves emulsifying an organic phase containing drug and polymer into an aqueous surfactant solution.

- **Single Emulsion (O/W):** Primarily used for hydrophobic drugs. After emulsification, the volatile organic solvent is evaporated, resulting in hardened polymeric nanospheres.[84]
- **Double Emulsion (W/O/W):** Preferred for hydrophilic drugs, peptides, and proteins. A primary water-in-oil emulsion is created, which is subsequently emulsified in a second aqueous phase. Removal of organic solvent results in nanocapsules encapsulating the hydrophilic payload.[85]

These methods allow tailored drug loading and controlled release profiles.

➢ **Thin-Film Hydration (Bangham Method)**

Thin-film hydration is a classical technique for liposome fabrication. Lipids are first dissolved in an organic solvent mixture, which is then evaporated to form a thin lipid film on the flask surface. Upon hydration with an aqueous buffer above the lipid's phase transition temperature, multilamellar vesicles form spontaneously. Vesicle size and lamellarity can be further refined using extrusion, ultrasonication, or homogenization.[86]

➢ **Ionic Gelation / Polyelectrolyte Complexation**

Ionic gelation is particularly suited for hydrophilic polymers such as chitosan. The method involves mixing a positively charged polymer solution with a multivalent anionic cross- linker such as sodium tripolyphosphate (TPP). Electrostatic interactions result in instantaneous formation of nanoparticles under mild, solvent-free conditions, making the method suitable for encapsulating sensitive biomolecules.[87,88]

➢ **Green Synthesis**

Green synthesis utilizes biological agents—plant extracts, microbes, or enzymes—as natural reducing and stabilizing agents to produce metal nanoparticles such as silver and gold. This eco-friendly, non-toxic approach avoids harsh chemicals, enhances biocompatibility, and is particularly attractive for biomedical applications including imaging and antimicrobial therapy.[89,90]

iii) Advanced and Hybrid Techniques

To overcome limitations of traditional methods, modern nanoparticle production incorporates innovative and combined strategies.

➢ **Supercritical Fluid Technology**

Supercritical fluids, especially supercritical CO_2, act as solvents or anti-solvents to precipitate nanoparticles with narrow size distribution and high purity. Techniques such as Rapid Expansion of Supercritical Solutions (RESS) and Supercritical Anti-solvent (SAS) processing minimize residual solvents and promote environmentally sustainable manufacturing. However, the requirement for specialized equipment and operational complexity limits widespread adoption.[91,92,93,94]

➢ **Combinative/Hybrid Technologies**

Hybrid approaches merge the benefits of multiple methods—for example, NanoEdge™ technology combines precipitation with high-pressure homogenization to improve size uniformity and stability. These integrative strategies enhance formulation efficiency and are increasingly used in industrial nanoparticle development.[95,96,97,98]

Characterization Techniques

Comprehensive characterization is an essential component of pharmaceutical nanoparticle development, ensuring that the physicochemical and biological properties of the system align with the intended therapeutic objectives. Accurate assessment of parameters such as particle size, surface charge, morphology, drug loading, and biological performance is crucial for predicting in vivo behaviour, ensuring stability, and meeting regulatory standards. Thus, a multidisciplinary suite of analytical techniques is employed to achieve a rigorous evaluation of nanomedicine platforms.[109-115]

i) Size and Zeta Potential Measurement

Particle size and surface charge are fundamental determinants of nanoparticle stability, biodistribution, cellular uptake, and therapeutic performance.

➢ **Dynamic Light Scattering (DLS)**

DLS is the most widely used technique for determining the hydrodynamic diameter and size distribution (polydispersity index, PDI) of nanoparticles in colloidal suspension. The method analyses fluctuations in scattered light caused by Brownian motion. Its rapid measurement time, minimal sample preparation, and non-destructive nature make it indispensable for routine quality control. A PDI value below 0.3 generally

indicates a monodisperse and homogeneous nanoparticle population, consistent with optimal formulation stability.[116]

➢ **Zeta Potential Analysis**

Zeta potential provides a quantitative measure of nanoparticle surface charge by assessing electrophoretic mobility under an applied electric field. Strongly positive (greater than +30 mV) or strongly negative (less than –30 mV) zeta potential values typically correlate with high colloidal stability due to electrostatic repulsion that minimizes aggregation. This parameter is particularly critical for predicting long-term storage stability and in vivo circulation behaviour.[117-118]

ii) Morphology and Structural Analysis

Morphological characterization provides structural confirmation of nanoparticle shape, size, and internal architecture, complementing data obtained from DLS.

➢ **Transmission Electron Microscopy (TEM)**

TEM offers high-resolution, two-dimensional imaging and is considered the gold standard for direct visualization of nanoparticles. Contrast is typically enhanced using negative staining agents such as uranyl acetate. TEM enables precise determination of core particle size, morphology (e.g., spherical, rod-shaped), and internal structural features such as liposomal bilayers or micellar core–shell organization.[119-120]

➢ **Scanning Electron Microscopy (SEM)**

SEM provides detailed, three-dimensional surface topography of nanoparticles, usually under dry sample conditions. It is especially useful for characterizing solid lipid nanoparticles, polymeric systems, and particles where surface morphology influences drug release or interactions with biological membranes.[121-122]

➢ **Atomic Force Microscopy (AFM)**

AFM employs a nanoscale probe to scan and map the surface of nanoparticles, generating precise three-dimensional topographical images. Beyond imaging, AFM can measure mechanical properties—including stiffness, elasticity, and adhesion forces—providing insights into nanoparticle robustness and interaction with biological environments.[123- 125]

iii) Drug Loading and Release Analysis

Quantification of drug incorporation efficiency and assessment of release dynamics are critical for confirming therapeutic viability.

➢ **Encapsulation Efficiency (EE) and Drug Loading Capacity (DLC)**

These parameters are determined by separating free (unencapsulated) drug from nanoparticle-associated drug through methods such as centrifugation, ultrafiltration, or dialysis. Quantification of drug content is typically performed using analytical techniques such as High-Performance Liquid Chromatography (HPLC), UV-Visible spectroscopy, or Mass Spectrometry (MS). EE and DLC values provide essential information regarding formulation optimization, dosing accuracy, and therapeutic potential.[126-128]

➢ **In Vitro Drug Release Studies**

Drug release profiling is conducted under simulated physiological conditions—such as varying pH, temperature, or enzymatic environments—to predict in vivo behaviour.

Methods including dialysis membranes, sample-and-separate techniques, and flow- through cells are employed to assess release kinetics. These studies confirm whether the nanocarrier design supports sustained, controlled, or stimuli-responsive drug release.[129-130]

iv) In Vitro and In Vivo Biological Characterization

Biological evaluation is essential to validate the safety and functional performance of nanoparticles before clinical translation.

➢ **Cytotoxicity and Biocompatibility Assays**

In vitro assays, including MTT, MTS, and LDH release tests, assess cell viability and toxicity following nanoparticle exposure. These evaluations ensure that the carrier material and any surface modifications are biocompatible and non-toxic at therapeutic concentrations.[131-132]

➢ **Cellular Uptake and Intracellular Trafficking**

Techniques such as flow cytometry and confocal laser scanning microscopy are used to quantify and visualize nanoparticle internalization by cells. Fluorescently labeled nanoparticles allow real-time monitoring of their transport pathways, confirming the efficiency of targeting ligands or surface-engineered systems.[133]

➢ **In Vivo Pharmacokinetics (PK) and Biodistribution**

Animal models are employed to study nanoparticle absorption, distribution, metabolism, and excretion (ADME) profiles. Imaging modalities—such as fluorescence imaging, positron emission tomography (PET), or computed tomography (CT)—enable real-time tracking of labeled nanoparticles in biological systems. PK and biodistribution studies provide critical insights into circulation time, organ targeting, and overall therapeutic potential.[134]

RESULTS AND DISCUSSION

A review on pharmaceutical nanoparticles' physicochemical traits, detailing synthesis approaches (top-down such as bead milling and homogenization; bottom-up including nanoprecipitation and gelation), analytical tools (DLS for size/PDI <0.3 monodispersity, zeta >±30 mV stability, TEM/SEM/AFM morphology), and impacts on performance (10-200 nm size ideal for circulation/EPR, charge influencing uptake).Notable

outcomes show 10-200 nm particles achieve extended blood retention, lower MPS uptake, and superior tumor accumulation through EPR, with ~50 nm optimal for endocytosis-based cell entry. Standards verify stability (low PDI to high) and triggered release (e.g., pH-responsive), matching needs in approved therapies like Tricor® and AmBisome®.Such features address conventional delivery flaws like poor solubility/targeting, yet issues like corona formation and production scale-up remain, stressing modifications like PEG for better distribution.

CONCLUSION

The analysis affirms customized nanoparticle properties—dimensions, form, charge, stability—boost drug delivery outcomes, supporting targeted therapies in oncology, vaccines, and neural disorders. Different Prospects involve smart, AI-enhanced carriers to tackle barriers in toxicity and manufacturing, expanding nanomedicine's reach across diseases.

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