ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/25nov1105

Nanoparticulate Drug Delivery as Versatile Platform for Enhanced Drug Delivery: Mechanisms, Challenges, and Future Perspectives

Sushmita P. Sawant[1]; Madan D. Pomaje[2]; Dr. Ashwini Patil[3]

[1,2,3]Department of Pharmaceutics, Govindrao Nikam College of Pharmacy, Sawarde, University of Mumbai, Ratnagiri -415606, Maharashtra, India

Publication Date: 2025/11/28

Abstract: Conventional drug delivery systems such as tablets, capsules, and injections often suffer from limitations including poor solubility, low bioavailability, rapid clearance, and lack of site-specific targeting, which reduce therapeutic efficiency and increase systemic side effects. In recent years, nanotechnology has become a promising strategy for addressing these issues. Nanoparticles generally measure between 10 and 1000 nm, exhibit distinctive physicochemical properties, such as a large surface area and adjustable surface features, allowing for enhanced drug solubility, controlled release, and precise delivery. Nanoparticulate drug delivery systems (NDDS) offer several advantages, including enhanced bioavailability, reduced dosing frequency, and the ability to cross biological barriers like the blood–brain barrier. Several nanoparticle-based formulations, such as Doxil® and Abraxane®, have already received regulatory approval, highlighting their clinical potential. This review aims to provide an overview of nanoparticulate drug delivery systems, with an emphasis on the types of nanoparticles, methods of preparation, characterization, applications, regulatory considerations, and future perspectives.

Keywords: *Nanoparticles, Drug Delivery, Targeted Delivery, Nanotechnology, Bioavailability.*

How to Cite: Sushmita P. Sawant; Madan D. Pomaje; Dr. Ashwini Patil (2025). Nanoparticulate Drug Delivery as Versatile Platform for Enhanced Drug Delivery: Mechanisms, Challenges, and Future Perspectives. *International Journal of Innovative Science and Research Technology*, 10(11), 1724-1734. https://doi.org/10.38124/ijisrt/25nov1105

I. INTRODUCTION

Nanoparticulate drug delivery systems (NDDS) are state-of-the-art therapeutic platforms that leverage nanoparticles, typically measuring between 10 and 1000 nm, to optimize the delivery and effectiveness of pharmaceutical agents. These nanoscale carriers are characterized by a high surface-to-volume ratio and adaptable physicochemical properties, which enable them to proficiently encapsulate drugs, safeguard them from degradation, and ensure their controlled release at the target site. Depending on the formulation, nanoparticles can be polymeric, lipid-based, inorganic, or hybrid in nature, offering flexibility in design and application.[1]

One of the major advantages of NDDS is their ability to enhance the solubility and bioavailability of poorly water-soluble drugs, thereby improving therapeutic outcomes. They also enable controlled and sustained release profiles, reducing dosing frequency and improving patient compliance. Nanoparticles can achieve both passive and active targeting, passive targeting occurs through the enhanced permeation and retention (EPR) effect in tumors, while active targeting is achieved by surface functionalization with ligands, antibodies, or peptides that recognize specific receptors. Moreover, nanoparticles can cross complex biological barriers such as the intestinal epithelium and the blood–brain barrier, expanding their utility to a wide range of therapeutic areas.[2]

While NDDS present numerous advantages, they also face significant hurdles. Problems such as insufficient physical stability, the risk of drug leakage, and variations from one batch to another can restrict their overall performance. Large-scale manufacturing remains complex and costly, while concerns about long-term toxicity, immunogenicity, and clearance pathways persist. Furthermore, regulatory frameworks for nanoparticle-based formulations are still evolving, which complicates clinical translation. Thus, while NDDS present a transformative approach to modern drug delivery, their optimization and standardization remain areas of active research.

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/25nov1105

II. TYPES OF NANOPARTICLES IN DRUG DELIVERY

Nanoparticulate drug delivery systems can be broadly classified into several categories depending on their composition, structural properties, and applications. Different types of nanoparticles possess distinct benefits and drawbacks, which make them appropriate for various therapeutic applications.

➢ *Polymeric Nanoparticles*

Polymeric nanoparticles are solid colloidal entities crafted from either natural or synthetic polymers, with dimensions generally spanning from 10 to 1000 nm. These particles can encapsulate drugs within the polymer matrix or have them adsorbed or attached to their surface. Commonly utilized natural polymers include albumin, chitosan, and gelatin, while synthetic options often involve polylactic acid (PLA), poly (lactic-co-glycolic acid) (PLGA), and polycaprolactone (PCL). They offer excellent biocompatibility, controlled drug release, and protection of drugs from degradation. Albumin nanoparticles, for example, are utilized in Abraxane®, an FDA-approved formulation for cancer therapy.[3], [4]

Dendrimers are polymers characterized by their extensively branched, tree-like architecture, which includes numerous terminal functional groups. These structures can be tailored for specific uses in drug delivery, targeting, and gene transfer. Their monodisperse structure and tunable surface chemistry make them versatile nanocarriers. Polymeric micelles, on the other hand, are self-assembled nanostructures formed from amphiphilic block copolymers. They possess a hydrophobic core that encapsulates poorly soluble drugs and a hydrophilic shell that enhances stability and circulation time. Both dendrimers and micelles are particularly effective in improving the solubility of hydrophobic drugs and facilitating targeted delivery.[5]

➢ *Lipid-Based Nanoparticles*

Lipid-based nanoparticles represent some of the most thoroughly investigated and clinically utilized systems. This group includes liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs). Liposomes are vesicular formations made up of phospholipid bilayers, which can encapsulate both hydrophilic and lipophilic drugs. They were the first nanocarriers to gain clinical approval, exemplified by Doxil, which is used for delivering doxorubicin. SLNs are composed of solid lipids stabilized by surfactants and provide advantages such as controlled release and drug stability. NLCs are second-generation lipid nanoparticles that combine solid and liquid lipids, offering improved drug loading and reduced crystallization. These lipid-based carriers are especially useful for oral, topical, and parenteral delivery.[6], [7], [8]

➢ *Metal Oxide or Inorganic Nanoparticles*

Metallic nanoparticles are made of gold, silver, and iron oxide, have garnered considerable interest due to their distinct optical, magnetic, and surface characteristics. Gold nanoparticles are extensively utilized in drug delivery, medical imaging, and photothermal therapy. In contrast, silver nanoparticles are well-known for their potent antimicrobial properties. Iron oxide nanoparticles are applied in targeted drug delivery and serve as contrast agents in magnetic resonance imaging (MRI). Quantum dots, another subclass of inorganic nanoparticles, possess unique optical properties and are being explored for bioimaging and targeted therapy. However, concerns regarding their long-term toxicity and biodegradability remain a challenge for clinical applications.[9]

III. METHODS OF PREPARATION

➢ *Top-Down and Bottom-Up Approaches*

The methods of nanoparticle preparation are generally categorized into top-down and bottom-up approaches, each with distinct principles, advantages, and limitations. In the top-down approach, nanoparticles are produced by breaking down bulk materials into smaller nanosized structures using physical forces. Common techniques include high-pressure homogenization, where intense mechanical shear forces reduce particle size; milling methods such as ball milling, which grind materials into nanoscale powders; and laser ablation, where high-energy lasers fragment bulk material into nanoparticles. The top-down approach is relatively simple and scalable, making it suitable for industrial production. However, it often results in a broad particle size distribution, surface imperfections, and potential contamination due to mechanical processes.[10]

The bottom-up strategy involves forming nanoparticles by assembling them from molecular or atomic building blocks, typically through chemical or physicochemical reactions. Techniques under this category include nanoprecipitation, where a solvent containing drug and polymer diffuses into a non-solvent to form nanoparticles; sol-gel processing, which converts molecular precursors into solid nanostructures; emulsion techniques, where solvent evaporation or diffusion leads to particle formation; and self-assembly methods, in which amphiphilic molecules organize into nanostructures such as micelles or liposomes. Bottom-up approaches often offer enhanced control over the size, shape, and surface properties of particles, resulting in nanoparticles that are highly uniform and stable. However, they may require stringent processing conditions, expensive solvents, or sophisticated equipment, and scaling up can be challenging.[11]

➢ *Polymerization-Based Method*

The polymerization-based method is a bottom-up approach used for the preparation of polymeric nanoparticles, In this approach, nanoparticles are formed directly from monomers through different types of polymerization reactions. Depending on the process, drugs can either be dissolved in the monomer solution before polymerization or adsorbed/entrapped in the polymer matrix after particle formation. This technique allows for controlled particle size, narrow distribution, and versatile drug loading, making it highly relevant for drug delivery systems.[12]

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/25nov1105

➢ *Principle*

In this method, suitable monomers (e.g., alkyl cyanoacrylates, acrylamides, or methacrylates) are polymerized in an aqueous or non-aqueous medium using chemical initiators, heat, or radiation. During polymerization, the drug can be incorporated either by entrapment within the growing polymer network or by adsorption onto the preformed nanoparticles. Surfactants or stabilizers (such as PVA, poloxamers, or SDS) are often used to prevent aggregation and control particle size.

- *Emulsion Polymerization*

In the process of emulsion polymerization, monomers are dispersed in a water-based solution that contains surfactants and initiators. The drug can be incorporated either by dissolving it in the monomer phase or by adsorption after polymerization. The process typically results in uniform, small-sized nanoparticles with high stability. However, residual surfactants or initiators may require removal due to potential toxicity.[13]

- *Interfacial Polymerization*

In interfacial polymerization, polymer formation occurs at the interface between two immiscible phases (commonly water and oil). The drug is either dissolved in one of the phases or entrapped as the polymer shell forms at the interface, creating nanocapsules with a distinct core–shell structure. This approach is especially effective for encapsulating lipophilic drugs, achieving both high levels of entrapment and a controlled release mechanism.[14]

- *Dispersion Polymerization*

Dispersion polymerization takes place in a continuous medium where the polymer that forms is not soluble, leading to the spontaneous generation of nanoparticles. Stabilizers are usually added to maintain particle dispersion and prevent aggregation. This technique is suitable for producing monodisperse particles and is often applied in the preparation of nanoparticles.

➢ *Advantages and Limitations*

Polymerization techniques provide several benefits, such as the production of nanoparticles that are uniform in size, exhibit high stability, and possess specifically designed surface features. They also allow flexibility in designing nanospheres (solid matrix with drug dispersed) or nanocapsules (core–shell with drug confined in the core). However, limitations include the possible presence of toxic residual monomers, surfactants, or initiators, which necessitates purification before biomedical application.[15]

➢ *Nanoprecipitation*

Nanoprecipitation often referred to as the solvent displacement method, is recognized as one of the most straightforward and commonly employed techniques for creating polymeric nanoparticles. In this bottom-up method, a polymer forms a precipitate once a solvent that mixes with water is displaced. In this technique, the polymer and the drug are initially dissolved in an organic solvent that is compatible with water., such as acetone, ethanol, or acetonitrile. This organic phase is then slowly added to an aqueous phase containing a stabilizer or surfactant under continuous stirring. Upon contact, rapid diffusion of the organic solvent into the aqueous medium leads to supersaturation of the polymer, resulting in spontaneous precipitation and the formation of nanoparticles.[16]

The approach provides numerous advantages, such as its ease of use, reliability, and the ability to create nanoparticles with a consistently narrow size distribution without the need for high shear forces or complex equipment. It is particularly suitable for encapsulating hydrophobic drugs, as they can be efficiently entrapped within the polymeric matrix during the precipitation process. Furthermore, the mild processing conditions make this method compatible with thermosensitive drugs such as peptides and proteins.[17]

➢ *Solvent Evaporation Method*

The method of solvent evaporation is widely utilized for the production of polymeric nanoparticles., especially nanospheres and nanocapsules. This method is based on emulsification of a polymer–drug solution in an organic solvent followed by removal of the solvent, leading to the precipitation of nanoparticles.

In this process, the drug and polymer are first dissolved in a water-immiscible organic solvent such as dichloromethane, chloroform, or ethyl acetate. This organic phase is then emulsified into an aqueous phase containing a surfactant or stabilizer (such as polyvinyl alcohol or polysorbates) using mechanical stirring, sonication, or high-shear homogenization, forming an oil-in-water (O/W) emulsion. Once the emulsion is formed, the organic solvent is gradually evaporated either under reduced pressure or by continuous stirring at room temperature. As the solvent evaporates, the polymer begins to precipitate, capturing the drug and forming solid nanoparticles that are distributed throughout the aqueous phase.[18]

➢ *Sol-Gel Method*

The sol–gel method is a bottom-up approach that involves the chemical transformation of small molecular precursors into a solid network of nanoparticles through hydrolysis and condensation reactions. This technique is particularly used for the preparation of inorganic nanoparticles such as silica, titanium dioxide, and other metal oxides, which can serve as effective carriers in drug delivery systems.

In this process, metal alkoxides (for example, tetraethyl orthosilicate – TEOS for silica nanoparticles) or metal salts are dissolved in a suitable solvent, usually an alcohol. Hydrolysis of these precursors is initiated by adding water under acidic or basic conditions. This results in the formation of hydroxyl groups, which undergo condensation reactions to produce a three-dimensional sol network. As the reaction proceeds, the sol gradually evolves into a gel-like structure. Following the drying and stabilization processes, nanoparticles are developed with precise control over their size, porosity, and surface characteristics.[19]

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/25nov1105

➢ *Coacervation / Phase Separation Method*

The coacervation or phase separation method is a widely used technique for preparing polymeric nanoparticles, especially for encapsulating sensitive bioactive molecules such as proteins, peptides, and nucleic acids. This approach involves the separation of a solution into two distinct phases: one that is rich in polymers, known as the coacervate, and another that is deficient in polymers. This separation facilitates the trapping of drug molecules within the polymeric framework.

In this process, the drug is initially dissolved or distributed within a polymer solution that has been formulated using a suitable solvent. A non-solvent or a coacervating agent (such as salts, organic solvents, or changes in pH/temperature) is then added, which reduces the solubility of the polymer in the continuous phase. As a result, the polymer precipitates out and forms a separate, concentrated phase around the drug molecules, leading to nanoparticle formation. The nanoparticles are then hardened by cross-linking agents (e.g., glutaraldehyde) or by solvent evaporation, followed by purification steps such as centrifugation or filtration.[20]

IV. CHARACTERIZATION OF NANOPARTICLES

➢ *Particle Size and its Distribution*

These are essential attributes that affect how nanoparticles are distributed in the body, their uptake by cells, their duration in circulation, and the routes through which they are cleared. Size is most commonly measured as hydrodynamic diameter by dynamic light scattering (DLS) (reports the particle in its solvated state) and can be complemented with nanoparticle tracking analysis (NTA) or differential centrifugal sedimentation for number-based distributions; electron microscopy (TEM) yields the dry/true physical size and internal structure.[21]

➢ *The Polydispersity Index*

It obtained from DLS, quantifies size uniformity—values <0.1 indicate very narrow (monodisperse) populations, values ≈0.1–0.2 are usually acceptable for pharmaceutical formulations, and values >0.3 imply broad distributions that may affect reproducibility and performance.[21], [22]

➢ *Zeta Potential*

It measures the surface electrostatic potential (electrophoretic mobility) and predicts colloidal stability: high absolute values (commonly > |30| mV) suggest strong electrostatic repulsion and good suspension stability, whereas values near zero favor aggregation; note that measured zeta depends strongly on medium composition and pH.[23]

➢ *Morphology*

Shape, surface texture and presence of pores is visualized by SEM (surface topography), TEM (internal structure, core–shell architecture) and AFM (3D surface topography in air or liquid). It is critical to report both hydrodynamic and dry sizes, PDI, zeta potential (including measurement medium/pH), and representative micrographs because these physical attributes directly affect in-vitro behavior and in-vivo fate.[24]

➢ *Drug Loading and Entrapment/Encapsulation Efficiency*

Drug loading and entrapment efficiency (EE) quantify how much active pharmaceutical ingredient (API) is actually associated with the carrier and therefore determine dose, formulation mass and cost. The calculations involves following formulae-

$$\textit{Drug loading}\ (\%) = \frac{\textit{quantity of drug in nanoparticles}}{\textit{quantity of nanoparticles}} \times 100$$

$$\textit{Entrapment efficiency}\ (\%) = \frac{\textit{amount of entraped drug in nanoparticles}}{\textit{total amount of drug used in formulation}} \times 100$$

Practically free (unentrapped) drug is separated from nanoparticle-bound drug by ultracentrifugation, ultrafiltration, size-exclusion chromatography or dialysis; the separated fractions are assayed by validated analytical methods (HPLC, LC–MS, or UV-Vis) to compute loading and EE.[3]

- *In-vitro release profile*

This testing assesses the kinetics and mechanism of drug release: typical setups include dialysis-bag or sample-and-separate methods under sink conditions, with controlled temperature and agitation; release media should mimic biological fluids (with surfactants if solubility is limiting). Release profiles often display an initial spike due to drugs adsorbed on the surface, which is then followed by a gradual release from the matrix. By fitting the release data to models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas, one can determine whether the primary mechanism is diffusion, erosion, or anomalous transport. High loading with controlled release is desirable, but excessive loading can lead to drug crystallization, leakage and unstable kinetics-therefore optimization and robust analytical quantification are essential.[25]

- *Stability Studies*

Stability evaluation addresses whether the nanoparticle formulation retains its intended attributes (size, PDI, zeta potential, drug content, activity) under storage and handling conditions. Stability testing includes physical stability (aggregation, sedimentation, changes in size/PDI and morphology), chemical stability (API degradation, polymer hydrolysis, oxidation), and functional stability (loss of targeting ligand activity). Standard assessments are: periodic DLS/ζ measurements and microscopy to detect aggregation; HPLC/LC–MS to quantify drug potency and degradation products; DSC/TGA and XRD to monitor crystallinity

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/25nov1105

changes; turbidity and visual inspection for macroscopic changes; and microbial/endotoxin testing where appropriate. Stress studies—freeze–thaw cycles, accelerated temperature/humidity, light exposure, and shear/sterilization simulations—identify failure modes. For biologics, serum stability and proteolytic degradation studies (incubation in plasma/serum) are crucial because protein adsorption (protein corona) can rapidly alter particle behavior. If lyophilization is used for storage, optimization of cryo/lyoprotectants and post-reconstitution characterization (size, EE, activity) must be reported. Stability data guide selection of storage conditions, shelf-life estimates, and formulation improvements for clinical translation.[26]

- *Surface Chemistry and Functionalization*

Surface composition and modifications dictate nanoparticle interactions with biological systems, circulation time, cell uptake, targeting ability and immunogenicity. Common surface strategies include stealth coatings (PEGylation or zwitterionic polymers) to reduce opsonization and prolong blood residence; covalent or non-covalent attachment of targeting ligands (antibodies, peptides, aptamers, small molecules) for active targeting; charged moieties or pH-sensitive linkers for stimuli-responsive behavior; and surface crosslinking for stability. Characterization of surface chemistry uses complementary techniques: Fourier-transform infrared spectroscopy (FTIR) and nuclear magnetic resonance (NMR) for functional group identification, X-ray photoelectron spectroscopy (XPS) for elemental surface composition, thermogravimetric analysis (TGA) to estimate grafting density, and contact angle measurements for surface hydrophilicity.[27], [28]

V. FACTORS AFFECTING ON NANOPARTICLES

- The choice of polymer or lipid concentration directly affects particle size; higher polymer concentrations usually produce larger particles due to increased viscosity and slower diffusion.
- Drug-to-polymer ratio influences the size: higher drug content often leads to larger particles because of limited encapsulation sites.
- Solvent type and miscibility are also important; solvents with high diffusion rates (e.g., acetone) promote smaller particles in nanoprecipitation, whereas less miscible solvents yield larger aggregates.
- Stirring speed and homogenization pressure are major process variables; higher energy input breaks droplets more effectively, resulting in smaller nanoparticles. the use of surfactants or stabilizers reduces interfacial tension and prevents coalescence, thereby producing finer and more uniform particles.
- The zeta potential indicates the surface charge of nanoparticles and plays a crucial role in determining their stability when suspended. A higher absolute zeta potential (e.g., > ±30 mV) generally indicates strong electrostatic repulsion, reducing aggregation and enhancing colloidal stability. Factors such as the type and concentration of stabilizers or surfactants play a role in determining the zeta potential. For example, ionic surfactants like sodium dodecyl sulfate impart a negative charge, while cationic polymers such as chitosan provide positive charge.[7], [29]
- pH of the medium strongly affects surface ionization; nanoparticles containing carboxyl groups show higher negative charges at alkaline pH due to deprotonation.
- Ionic strength of the medium can shield surface charges, reducing zeta potential and promoting aggregation.
- polymer composition and functional groups (amine, hydroxyl, carboxyl) define the inherent charge of nanoparticles and thus their interactions with biological membranes.[30]
- The drug-to-carrier ratio: increasing drug content up to the saturation point enhances loading, but excessive drug may crystallize outside the nanoparticles.
- Drug solubility in the chosen solvent also matters; hydrophobic drugs have higher encapsulation efficiency in lipid-based or polymeric systems, whereas hydrophilic drugs often require double emulsion or coacervation methods.[31]
- The polymer–drug interaction plays a vital role; stronger hydrophobic, hydrogen bonding, or electrostatic interactions lead to improved entrapment.
- Preparation method also affects drug loading: techniques like nanoprecipitation may result in lower loading for hydrophilic drugs, while emulsion-based methods often give higher efficiency. Finally, process parameters such as solvent evaporation rate, stirring speed, and surfactant type influence encapsulation efficiency by affecting drug partitioning between aqueous and organic phases.[32], [33]

VI. ROUTES OF ADMINISTRATION

Nanoparticulate drug delivery systems can be delivered by many routes; choosing the route determines the design constraints (size, surface chemistry, release kinetics) because each administration pathway presents unique anatomic and physiologic barriers.

- *Oral Delivery*

It protects labile drugs from enzymatic degradation, improve apparent solubility of poorly water-soluble compounds, and can be engineered for mucoadhesion or receptor-mediated uptake (e.g., M-cell transcytosis in Peyer's patches) to enhance uptake. Lipid-based nanoparticles can promote lymphatic transport and partially bypass first-pass clearance, while surface modification (chitosan, lectins, PEG) can increase residence time and permeation. Challenges include maintaining stability in the gastric environment, avoiding premature release/aggregation, variable absorption between patients (food effect, GI motility), potential interaction with efflux transporters (P-gp), and scaling reproducible, cost-effective oral nanoparticle formulations. For oral NDDS, careful optimization of particle composition, mucoadhesive properties, and in-vitro/in-vivo correlation studies are essential.[34]

- *Parenteral Delivery (IV / IM / SC)*

Parenteral administration (especially intravenous) provides immediate systemic availability and is the preferred

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/25nov1105

route for targeted or fast-acting therapies. Nanoparticles, such as liposomes, polymeric NPs, albumin NPs, and nanocrystals, can utilize the enhanced permeation and retention (EPR) effect to accumulate in tumors or be modified with ligands for targeted delivery. Key advantages are precise dose delivery, avoidance of GI degradation and first-pass metabolism, and possibility for controlled-release depots via IM/SC injection. Major challenges are immune recognition and rapid clearance by the mononuclear phagocyte system (MPS)/Kupffer cells, complement activation or infusion reactions, stringent sterility/endotoxin requirements, and aggregation risk; these are addressed by PEGylation/stealth coatings, surface charge control, and strict manufacturing controls. Size and surface chemistry must be tuned (commonly ~10–200 nm) to balance renal clearance, extravasation, and MPS uptake.[35]

➢ *Pulmonary Delivery*

Nanoparticles can be delivered as nebulized suspensions, aerosols, or as "Trojan" microparticles that contain nanoparticles and have aerodynamic diameters (≈1–5 μm) optimized for deep lung deposition. Advantages include rapid onset, high local drug concentrations for lung pathologies, and potential systemic uptake via the alveoli. Challenges include achieving suitable aerodynamic properties (nanoparticles often need to be formulated into inhalable carriers), stability during aerosolization, mucociliary clearance and macrophage phagocytosis, and the risk of pulmonary inflammation or toxicity.[36]

➢ *Ocular Delivery*

Nanoparticles (liposomes, polymeric NPs, nanoemulsions, in-situ gelling systems) can increase precorneal residence time (via mucoadhesive coatings), enhance corneal penetration, and provide sustained release to reduce dosing frequency. For posterior segment diseases, intravitreal injection of biodegradable nanoparticles allows prolonged drug exposure while avoiding systemic exposure. Key challenges are small administration volumes, ocular irritation or toxicity, maintaining optical clarity, sterilization without altering particle properties, and invasive procedures.[37]

➢ *Transdermal / Topical Delivery*

Lipid nanoparticles (SLNs, NLCs), ethosomes, transfersomes, nanoemulsions, and nanoparticle-loaded patches improve drug solubilization, drug partitioning into the stratum corneum, and controlled release for local therapy. Microneedles and iontophoresis are frequently combined with nanoparticles to transiently bypass the stratum corneum and enable systemic delivery or vaccine administration. Challenges include limited permeation of large or hydrophilic molecules without physical enhancement, potential for skin irritation or sensitization, dose limitations, and ensuring consistent dosing across variable skin types.[7]

➢ *Nasal Delivery*

Nanoparticles for nasal delivery (mucoadhesive polymeric NPs, nanoemulsions, in-situ gelling systems) increase residence time, protect drugs from nasal enzymes, and can be engineered for uptake by the olfactory epithelium. Advantages are rapid onset, avoidance of hepatic first-pass, and potential direct central nervous system access. Primary challenges are rapid mucociliary clearance, limited administration volume, enzymatic degradation in the nasal cavity, and local irritation; formulations must balance mucoadhesion and diffusion.[38]

➢ *Mucosal Routes*

Buccal, rectal, vaginal, intrathecal, intra-tumoral routes are used when local action or specific biodistribution is desired. Buccal and sublingual nanoparticle formulations bypass first-pass metabolism and allow rapid systemic uptake but are constrained by limited surface area and salivary washout. Rectal and vaginal NDDS enable local therapy and partial avoidance of first-pass metabolism; formulation must contend with mucus barriers and variable retention. Intrathecal or intra-tumoral nanoparticle administration achieves direct CNS or tumor exposure but requires stringent sterility, biocompatibility, and invasiveness considerations.[39]

VII. MECHANISM OF NANOPARTICULATE DRUG DELIVERY SYSTEMS

The therapeutic success of nanoparticulate drug delivery systems (NDDS) relies on their ability to overcome physiological barriers and deliver drugs precisely to the intended site of action. The mechanisms governing their drug delivery can be broadly categorized into cellular uptake pathways, targeting strategies, and controlled/stimuli-responsive release mechanisms.

➢ *Cellular Uptake Mechanisms*

Nanoparticles interact with biological membranes and enter cells mainly through endocytosis. Depending on particle size, surface charge, and surface modifications, different uptake pathways may predominate:

- Clathrin-mediated endocytosis: Small nanoparticles (50–200 nm) can be internalized via clathrin-coated pits, leading to intracellular trafficking and possible lysosomal degradation.[40]
- Macropinocytosis and phagocytosis: Larger nanoparticles (>500 nm) or those recognized by immune cells are taken up via macropinocytosis or phagocytosis. Surface modifications (e.g., PEGylation or ligand attachment) can influence the specific route of internalization and thus determine drug fate inside the cell.

➢ *Passive and Active Targeting [41]*

- Passive targeting: Nanoparticles take advantage of physiological traits like the enhanced permeability and retention (EPR) effect found in tumors. Because of the presence of leaky blood vessels and inadequate lymphatic drainage, these nanoparticles tend to gather more in tumor tissues.
- Active targeting: Functionalizing the surface of nanoparticles with ligands like antibodies, peptides, aptamers, or small molecules allows them to specifically attach to receptors that are overexpressed on target cells,

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/25nov1105

such as folate receptors on cancer cells. This approach enhances selectivity, minimizes off-target effects, and boosts therapeutic effectiveness.

➢ *Controlled and Stimuli-Responsive Release*

Nanoparticles are designed to deliver their drug payload in a controlled or stimulus-responsive way, ensuring site-specific action and reducing systemic toxicity:[42], [43], [44]

- pH-sensitive release: Useful for tumor tissues (acidic extracellular environment) or intracellular compartments like endosomes/lysosomes. Polymers that degrade or swell in acidic conditions trigger drug release.
- Temperature-sensitive release: Thermosensitive liposomes and polymeric nanoparticles release drugs upon exposure to hyperthermia (40–42°C), often applied in localized cancer therapy.
- Enzyme-responsive release: Nanoparticles functionalized with enzyme-cleavable linkages release drugs in response to overexpressed enzymes.
- Redox-sensitive release: Disulfide-bonded nanoparticles release their cargo in response to the high glutathione levels inside cells compared to the extracellular environment.

VIII. APPLICATIONS OF NANOPARTICULATE DRUG DELIVERY SYSTEMS

➢ *Cancer Therapy*

Nanoparticles have revolutionized oncologic drug delivery by improving tumor accumulation, enhancing intracellular delivery, and enabling multimodal therapy. The enhanced permeability and retention (EPR) effect enables the passive concentration of various nanoparticles in tumor regions, while active targeting—through surface ligands (antibodies, peptides, folate, transferrin, etc.) increases uptake by cancer cells that overexpress specific receptors. Nanocarriers permit co-delivery of chemotherapeutics with chemosensitizers, siRNA or immunomodulators to overcome multidrug resistance and heterogeneous tumor microenvironments; they also support stimuli-responsive release (pH, enzymes, redox, heat) that triggers drug liberation selectively in tumor tissue.[45]

➢ *Neurological Disorders*

The blood–brain barrier (BBB) tightly regulates CNS entry and severely limits many drugs; nanoparticles offer multiple strategies to bypass or traverse this barrier. Surface functionalization with ligands for receptor-mediated transcytosis (transferrin, insulin, low-density lipoprotein receptors, or ApoE-mimetic peptides) enables transport across brain endothelium, while intranasal formulations can provide a direct nose-to-brain route that partially avoids systemic clearance. Nanoparticles stabilize fragile neurotherapeutics (peptides, proteins, siRNA, small molecules), enable controlled release to reduce dosing frequency, and can target specific cell types (neurons, microglia) to modulate disease pathways in Alzheimer's, Parkinson's, gliomas and stroke.[35]

➢ *Cardiovascular Diseases*

In cardiovascular medicine, nanoparticles are employed to improve delivery of anti-inflammatory, anti-thrombotic, and regenerative agents to diseased vasculature or myocardium. Strategies include targeted nanoparticles that home to atherosclerotic plaques (binding to VCAM-1, scavenger receptors or modified LDL), redox- or shear-responsive carriers that release payload at sites of vascular stress, and nanoparticle-based thrombolytics that concentrate fibrinolytic agents at clot sites to reduce systemic bleeding risk. For myocardial repair, nanoparticles can deliver cardioprotective drugs, growth factors, or gene-editing cargos to ischemic tissue and are being investigated as vehicles to enhance cell therapy or stimulate angiogenesis.[46]

➢ *Infectious Diseases & Vaccines*

Nanoparticles serve both therapeutic and prophylactic roles against infectious agents. As drug carriers they improve delivery of antimicrobials to intracellular reservoirs (e.g., macrophage-harbored tuberculosis), reduce systemic toxicity by localizing high drug concentrations, and enable combination therapies to limit resistance. For vaccines, nanoparticle platforms (lipid nanoparticles, polymeric particles, virus-like particles, and inorganic carriers) protect antigens or nucleic acids, enhance uptake by antigen-presenting cells, and act as adjuvants to shape immune responses (humoral and cellular). The success of mRNA lipid-nanoparticle vaccines in the COVID-19 pandemic exemplifies rapid antigen delivery and potent immunogenicity.[47]

➢ *Gene and Protein Delivery*

Nonviral nanoparticle vectors have become indispensable for delivering nucleic acids (siRNA, mRNA, plasmid DNA) and therapeutic proteins, offering lower immunogenicity and greater payload flexibility than viral systems. The primary design objectives include safeguarding the cargo from extracellular nucleases and proteases, ensuring effective cellular uptake, and facilitating endosomal escape to deliver the cargo into the cytosol or nucleus as needed. Lipid nanoparticles (LNPs) excel at mRNA delivery by promoting endosomal release, while polymeric carriers and peptide-based systems offer tunable biodegradability and targeting. Nanoparticle delivery enables applications from transient expression (vaccination, protein replacement) to durable gene editing (CRISPR/Cas systems) when combined with targeting and controlled-release strategies.[17], [48]

IX. REGULATORY AND SAFETY ASPECTS OF NANOPARTICULATE DRUG DELIVERY SYSTEMS

➢ *Biocompatibility and Toxicity Concerns*

Nanoparticles may elicit immune reactions, cytotoxicity, hemolysis, complement activation, or inflammation, depending on their composition, size, surface charge, and aggregation state. Biocompatible materials such as biodegradable polymers (PLGA, PLA), lipids (liposomes, solid lipid nanoparticles), and albumin are preferred to minimize toxicity. Key toxicity concerns include:[43], [49]

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/25nov1105

- Cellular toxicity: Excessive positive charge or reactive surfaces can damage cell membranes.
- Organ accumulation: Non-biodegradable nanoparticles may accumulate in the liver, spleen, lungs, or kidneys.
- Oxidative stress and inflammation: Surface chemistry or residual solvents can trigger reactive oxygen species (ROS) production.
- Immunogenicity: Surface proteins or contaminants may induce complement activation or cytokine release.

Toxicity is typically assessed through in vitro cytotoxicity assays, hemocompatibility studies, and in vivo pharmacokinetic, biodistribution, and safety studies in animal models. Optimizing size, surface chemistry, and degradability is crucial to balance efficacy and safety.

➢ *FDA and EMA Approved Nanoparticulate Formulations*

Several NDDS have successfully transitioned from research to clinical use, demonstrating regulatory feasibility. These examples mention in (table no.1), that demonstrate that biodegradability, safety, reproducible manufacturing, and validated analytical methods are key criteria for regulatory approval.[8], [46], [49], [50]

Table 1 Nanoproducts with Their Therapeutic Uses

Product	Type of Nanoparticle	Therapeutic Use	Highlights
Doxil®	PEGylated liposomal doxorubicin	Cancer	Prolonged circulation, reduced cardiotoxicity, EPR-based tumor targeting.
Abraxane®	Albumin-bound paclitaxel nanoparticles	Breast, lung, pancreatic cancers	Solvent-free formulation, enhanced tumor uptake via albumin transport pathways.
Onivyde®	Liposomal irinotecan	Pancreatic cancer	Controlled release, improved pharmacokinetics.
Feraheme®	Iron oxide nanoparticles	Iron deficiency anemia	Superparamagnetic iron oxide, biocompatible coating.
COVID-19 mRNA vaccines (Pfizer-BioNTech, Moderna)	Lipid nanoparticles	SARS-CoV-2	Protects mRNA, enables intracellular delivery, elicits potent immune response.

➢ *Guidelines for Clinical Translation [51]*

Organizations like the U.S. FDA, EMA, and ICH establish comprehensive frameworks for assessing NDDS.

- Characterization requirements: Particle size, zeta potential, polydispersity, surface chemistry, drug loading, release profile, and stability.
- Preclinical safety: Extensive in vitro and in vivo analyses encompassing cytotoxicity, immunogenicity, genotoxicity, and biodistribution.
- Manufacturing considerations: Good Manufacturing Practice (GMP) compliance, scalable and reproducible processes, sterile production for parenteral products.
- Clinical evaluation: Phase I–III trials assessing pharmacokinetics, pharmacodynamics, safety, efficacy, and immunogenicity if relevant.
- Post-marketing surveillance: Monitoring for long-term toxicity, rare adverse effects, and immunogenicity.

X. CHALLENGES AND FUTURE PERSPECTIVES [52], [53]

Nanoparticulate drug delivery systems (NDDS) offer significant potential to enhance therapeutic effectiveness, minimize adverse effects, and facilitate targeted or controlled drug release. However, their translation from bench to bedside is still constrained by several challenges. Addressing these challenges is critical to fully realize the potential of nanoparticle-based therapies.

➢ *Scale-Up and Manufacturing Challenges*

While laboratory-scale synthesis of nanoparticles is well established, large-scale, reproducible manufacturing remains a major hurdle. Key challenges include:

- Complexity of fabrication methods: Techniques such as nanoprecipitation, emulsion-solvent evaporation, or microfluidic-assisted synthesis require precise control of process parameters. Scaling these methods while maintaining particle uniformity is technically demanding.
- Sterility and regulatory compliance: Parenteral and ocular nanoparticles must be produced under strict Good Manufacturing Practice (GMP) conditions. Maintaining sterility without altering particle properties adds further complexity.
- Stability and storage: Nanoparticles can aggregate or undergo chemical degradation over time. Formulating stable, long-shelf-life products suitable for commercial distribution is challenging.

➢ *Long-Term Toxicity and Immunogenicity Issues*

Nanoparticles can interact with biological systems in unpredictable ways, raising concerns about long-term safety:

- Organ accumulation and persistence: Non-biodegradable or poorly cleared nanoparticles may accumulate in organs such as the liver, lungs, kidneys, or spleen potentially causing chronic toxicity.
- Genotoxicity and oxidative stress: Some nanoparticles induce reactive oxygen species (ROS), inflammation, or DNA damage depending on size, surface chemistry, or residual solvents.
- Biodegradability optimization: Designing nanoparticles with controlled biodegradation rates and biocompatible materials is essential to reduce long-term adverse effects.

➢ *Cost-Effectiveness*

The development and commercialization of NDDS can be expensive due to:

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/25nov1105

- High costs of raw materials (e.g., lipids, polymers, targeting ligands).
- Sophisticated manufacturing technologies and quality control requirements.
- Extensive preclinical and clinical testing to meet regulatory standards.

➢ *Emerging Trends: Smart Nanoparticles, Personalized Nanomedicine, and Theranostics [54]*

Despite these challenges, the future of NDDS is promising due to emerging technologies:

- Smart nanoparticles: Stimuli-responsive systems are engineered to release drugs selectively when they detect changes in pH, temperature, enzyme activity, or redox conditions. This strategy boosts the effectiveness of the drugs while reducing the risk of affecting unintended targets.[55]
- Targeted and personalized nanomedicine: Ligand-functionalized nanoparticles can target specific receptors expressed in individual patients' tissues, supporting precision medicine approaches.
- Theranostics: Nanoparticles can combine therapeutic and diagnostic capabilities (e.g., imaging agents with chemotherapy), enabling real-time monitoring of drug delivery, tumor progression, or therapeutic response.
- Integration with advanced technologies: Researchers are investigating the use of microfluidics, artificial intelligence, and machine learning to enhance the design of nanoparticles, forecast biological interactions, and boost clinical results.

XI. CONCLUSION

While NDDS face significant manufacturing, safety, and economic challenges, the field is rapidly advancing. Emerging developments in smart, targeted, and multifunctional nanoparticles are set to overcome existing barriers, facilitating the creation of personalized, safer, and more effective therapeutic options. The future of NDDS lies in integrating engineering, materials science, and molecular medicine to develop next-generation nanomedicines with both therapeutic and diagnostic capabilities.

REFERENCES

[1]. A. Yusuf, A. R. Z. Almotairy, H. Henidi, O. Y. Alshehri, and M. S. Aldughaim, "Nanoparticles as Drug Delivery Systems: A Review of the Implication of Nanoparticles' Physicochemical Properties on Responses in Biological Systems," *Polymers (Basel)*, vol. 15, no. 7, p. 1596, Mar. 2023, doi: 10.3390/polym15071596.

[2]. K. Attri, M. Yadav, and S. Shrivastav, "Nanoparticles: A Novel Approach for Targeted Delivery of Medicines," *Journal of Drug Delivery and Therapeutics*, vol. 9, no. 3, pp. 734–739, May 2019, doi: 10.22270/jddt. v9i3.2721.

[3]. M. Geszke-Moritz and M. Moritz, "Biodegradable Polymeric Nanoparticle-Based Drug Delivery Systems: Comprehensive Overview, Perspectives and Challenges," *Polymers (Basel)*, vol. 16, no. 17, p. 2536, Sep. 2024, doi: 10.3390/polym16172536.

[4]. A. O. Elzoghby, W. M. Samy, and N. A. Elgindy, "Albumin-based nanoparticles as potential controlled release drug delivery systems," *Journal of Controlled Release*, vol. 157, no. 2, pp. 168–182, Jan. 2012, doi: 10.1016/j.jconrel.2011.07.031.

[5]. M. Zenze, A. Daniels, and M. Singh, "Dendrimers as Modifiers of Inorganic Nanoparticles for Therapeutic Delivery in Cancer," *Pharmaceutics*, vol. 15, no. 2, p. 398, Jan. 2023, doi: 10.3390/pharmaceutics15020398.

[6]. S. Priya, V. M. Desai, and G. Singhvi, "Surface Modification of Lipid-Based Nanocarriers: A Potential Approach to Enhance Targeted Drug Delivery," *ACS Omega*, vol. 8, no. 1, pp. 74–86, Jan. 2023, doi: 10.1021/acsomega.2c05976.

[7]. I. Chauhan, M. Yasir, M. Verma, and A. P. Singh, "Nanostructured Lipid Carriers: A Groundbreaking Approach for Transdermal Drug Delivery," *Adv Pharm Bull*, vol. 10, no. 2, pp. 150–165, Feb. 2020, doi: 10.34172/apb.2020.021.

[8]. M. S. Aldughaim, M. Muthana, F. Alsaffar, and M. D. Barker, "Specific Targeting of PEGylated Liposomal Doxorubicin (Doxil®) to Tumour Cells Using a Novel TIMP3 Peptide," *Molecules*, vol. 26, no. 1, p. 100, Dec. 2020, doi: 10.3390/molecules26010100.

[9]. Y. Chen and X. Feng, "Gold nanoparticles for skin drug delivery," *Int J Pharm*, vol. 625, p. 122122, Sep. 2022, doi: 10.1016/j.ijpharm.2022.122122.

[10]. N.-D. Jaji, H. L. Lee, M. H. Hussin, H. M. Akil, M. R. Zakaria, and M. B. H. Othman, "Advanced nickel nanoparticles technology: From synthesis to applications," *Nanotechnol Rev*, vol. 9, no. 1, pp. 1456–1480, Dec. 2020, doi: 10.1515/ntrev-2020-0109.

[11]. S. S. Low *et al.*, "Sonoproduction of nanobiomaterials – A critical review," *Ultrason Sonochem*, vol. 82, p. 105887, Jan. 2022, doi: 10.1016/j.ultsonch.2021.105887.

[12]. J. P. Rao and K. E. Geckeler, "Polymer nanoparticles: Preparation techniques and size-control parameters," *Prog Polym Sci*, vol. 36, no. 7, pp. 887–913, Jul. 2011, doi: 10.1016/j.progpolymsci.2011.01.001.

[13]. A. Honciuc and O.-I. Negru, "Role of Surface Energy of Nanoparticle Stabilizers in the Synthesis of Microspheres via Pickering Emulsion Polymerization," *Nanomaterials*, vol. 12, no. 6, p. 995, Mar. 2022, doi: 10.3390/nano12060995.

[14]. Q. Shen, "Advances in unusual interfacial polymerization techniques," *Polymer (Guildf)*, vol. 270, p. 125788, Mar. 2023, doi: 10.1016/j.polymer.2023.125788.

[15]. F. Zhong and C. Pan, "Dispersion Polymerization versus Emulsifier-Free Emulsion Polymerization for Nano-Object Fabrication: A Comprehensive Comparison," *Macromol Rapid Commun*, vol. 43, no. 3, Feb. 2022, doi: 10.1002/marc.202100566.

[16]. J. Loureiro, S. P. Miguel, I. J. Seabra, M. P. Ribeiro, and P. Coutinho, "Single-Step Self-Assembly of Zein–Honey–Chitosan Nanoparticles for Hydrophilic Drug Incorporation by Flash Nanoprecipitation,"

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/25nov1105

Pharmaceutics, vol. 14, no. 5, p. 920, Apr. 2022, doi: 10.3390/pharmaceutics14050920.

[17]. M. Tarhini *et al.*, "Protein-based nanoparticle preparation via nanoprecipitation method," *Materials*, vol. 11, no. 3, Mar. 2018, doi: 10.3390/ma11030394.

[18]. G. Li *et al.*, "An improved solvent evaporation method to produce poly (lactic acid) microspheres via foam-transfer," *Int J Biol Macromol*, vol. 172, pp. 114–123, Mar. 2021, doi: 10.1016/j.ijbiomac.2021.01.031.

[19]. D. Bokov *et al.*, "Nanomaterial by Sol-Gel Method: Synthesis and Application," *Advances in Materials Science and Engineering*, vol. 2021, no. 1, Jan. 2021, doi: 10.1155/2021/5102014.

[20]. L. Shu, Y. Gong, M. Lin, J. Sun, and X. Chen, "Advanced coacervation-driven nanoscale polymeric assemblies for biomedical applications," *Appl Phys Rev*, vol. 11, no. 2, Jun. 2024, doi: 10.1063/5.0197742.

[21]. S. L. Yupanqui-Mendoza and V. Arantes, "An enzymatic hydrolysis-based platform technology for the efficient high-yield production of cellulose nanospheres," *Int J Biol Macromol*, vol. 278, p. 134602, Oct. 2024, doi: 10.1016/j.ijbiomac.2024.134602.

[22]. Y. Alhamhoom, G. Ravi, R. A. M. Osmani, U. Hani, and G. M. Prakash, "Formulation, Characterization, and Evaluation of Eudragit-Coated Saxagliptin Nanoparticles Using 3 Factorial Design Modules," *Molecules*, vol. 27, no. 21, Nov. 2022, doi: 10.3390/molecules27217510.

[23]. M. Mabrouk, D. B. Das, Z. A. Salem, and H. H. Beherei, "Nanomaterials for Biomedical Applications: Production, Characterisations, Recent Trends and Difficulties," *Molecules*, vol. 26, no. 4, p. 1077, Feb. 2021, doi: 10.3390/molecules26041077.

[24]. Y. Song, K. Fang, M. N. Bukhari, K. Zhang, Z. Tang, and R. Wang, "Disperse dye/poly (styrene-methacrylic acid) nanospheres with high coloration performance for textiles," *J Clean Prod*, vol. 263, p. 121538, Aug. 2020, doi: 10.1016/j.jclepro.2020.121538.

[25]. J. Weng, H. H. Y. Tong, and S. F. Chow, "In Vitro Release Study of the Polymeric Drug Nanoparticles: Development and Validation of a Novel Method," *Pharmaceutics*, vol. 12, no. 8, p. 732, Aug. 2020, doi: 10.3390/pharmaceutics12080732.

[26]. A. N. Payzullaev, B. A. Allaev, S. Z. Mirzaev, J. M. Abdiev, J. Urinov, and A. Parkash, "The Impact of Silicon Dioxide Nanoparticle Size on the Viscosity and Stability of Nanofluids: A Comprehensive Study," *ECS Advances*, vol. 2, no. 3, p. 031001, Sep. 2023, doi: 10.1149/2754-2734/ace121.

[27]. J. Krishnan, P. Poomalai, A. Ravichandran, A. Reddy, and R. Sureshkumar, "A Concise Review on Effect of PEGylation on the Properties of Lipid-Based Nanoparticles," *Assay Drug Dev Technol*, vol. 22, no. 5, pp. 246–264, Jul. 2024, doi: 10.1089/adt.2024.015.

[28]. Y. Wang *et al.*, "Enhanced dispersion stability of gold nanoparticles by the physisorption of cyclic poly (ethylene glycol)," *Nat Commun*, vol. 11, no. 1, p. 6089, Nov. 2020, doi: 10.1038/s41467-020-19947-8.

[29]. M. Chorny, I. Fishbein, H. D. Danenberg, and G. Golomb, "Lipophilic drug loaded nanospheres prepared by nanoprecipitation: effect of formulation variables on size, drug recovery and release kinetics," *Journal of Controlled Release*, vol. 83, no. 3, pp. 389–400, Oct. 2002, doi: 10.1016/S0168-3659(02)00211-0.

[30]. R. Sridhar and S. Ramakrishna, "Electrosprayed nanoparticles for drug delivery and pharmaceutical applications," *Biomatter*, vol. 3, no. 3, Jul. 2013, doi: 10.4161/biom.24281.

[31]. N. Dhiman, R. Awasthi, B. Sharma, H. Kharkwal, and G. T. Kulkarni, "Lipid Nanoparticles as Carriers for Bioactive Delivery," *Front Chem*, vol. 9, Apr. 2021, doi: 10.3389/fchem.2021.580118.

[32]. H. Nazlı, B. Mesut, and Y. Özsoy, "In Vitro Evaluation of a Solid Supersaturated Self Nanoemulsifying Drug Delivery System (Super-SNEDDS) of Aprepitant for Enhanced Solubility," *Pharmaceuticals*, vol. 14, no. 11, p. 1089, Oct. 2021, doi: 10.3390/ph14111089.

[33]. R. Kesharwani, P. Jaiswal, D. K. Patel, and P. K. Yadav, "Lipid-Based Drug Delivery System (LBDDS): An Emerging Paradigm to Enhance Oral Bioavailability of Poorly Soluble Drugs," *Biomedical Materials & Devices*, vol. 1, no. 2, pp. 648–663, Sep. 2023, doi: 10.1007/s44174-022-00041-0.

[34]. S. Bertoni, N. Passerini, and B. Albertini, "Nanomaterials for oral drug administration," in *Nanotechnology for Oral Drug Delivery*, Elsevier, 2020, pp. 27–76. doi: 10.1016/B978-0-12-818038-9.00004-1.

[35]. R. Maher, A. Moreno-Borrallo, D. Jindal, B. T. Mai, E. Ruiz-Hernandez, and A. Harkin, "Intranasal Polymeric and Lipid-Based Nanocarriers for CNS Drug Delivery," *Pharmaceutics*, vol. 15, no. 3, p. 746, Feb. 2023, doi: 10.3390/pharmaceutics15030746.

[36]. J. Kim *et al.*, "Microfluidic Platform Enables Shearless Aerosolization of Lipid Nanoparticles for mRNA Inhalation," *ACS Nano*, vol. 18, no. 17, pp. 11335–11348, Apr. 2024, doi: 10.1021/acsnano.4c00768.

[37]. D. Khiev *et al.*, "Emerging Nano-Formulations and Nanomedicines Applications for Ocular Drug Delivery," *Nanomaterials*, vol. 11, no. 1, p. 173, Jan. 2021, doi: 10.3390/nano11010173.

[38]. T. Jamshidnejad-Tosaramandani, S. Kashanian, I. Karimi, and H. B. Schiöth, "Synthesis of an insulin-loaded mucoadhesive nanoparticle designed for intranasal administration: focus on new diffusion media," *Front Pharmacol*, vol. 14, Aug. 2023, doi: 10.3389/fphar.2023.1227423.

[39]. K. Bahrami, E. Lee, B. Morse, O. L. Lanier, and N. A. Peppas, "Design of nanoparticle-based systems for the systemic delivery of chemotherapeutics: Alternative potential routes via sublingual and buccal administration for systemic drug delivery," *Drug Deliv Transl Res*, vol. 14, no. 5, pp. 1173–1188, May 2024, doi: 10.1007/s13346-023-01493-7.

[40]. X. Cheng, Q. Xie, and Y. Sun, "Advances in nanomaterial-based targeted drug delivery systems," *Front Bioeng Biotechnol*, vol. 11, Apr. 2023, doi: 10.3389/fbioe.2023.1177151.

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/25nov1105

[41]. S. Dahiya, R. Dahiya, and E. Hernández, "Nanocarriers for Anticancer Drug Targeting: Recent Trends and Challenges," *Crit Rev Ther Drug Carrier Syst*, vol. 38, no. 6, pp. 49–103, 2021, doi: 10.1615/CritRevTherDrugCarrierSyst.2021035650.

[42]. Y. Choi, J. Kim, S. Yu, and S. Hong, "pH- and temperature-responsive radially porous silica nanoparticles with high-capacity drug loading for controlled drug delivery," *Nanotechnology*, vol. 31, no. 33, p. 335103, Aug. 2020, doi: 10.1088/1361-6528/ab9043.

[43]. J. C. Munyemana, H. He, C. Fu, Y. Fan, X. Sun, and J. Xiao, "Recombinant Collagen-Templated Biomineralized Synthesis of Biocompatible pH-Responsive Porous Calcium Carbonate Nanospheres," *ACS Omega*, vol. 8, no. 34, pp. 30879–30887, Aug. 2023, doi: 10.1021/acsomega.3c01467.

[44]. N. Van Bavel, A.-M. Lewrenz, T. Issler, L. Pang, M. Anikovskiy, and E. J. Prenner, "Synthesis of Alginate Nanoparticles Using Hydrolyzed and Enzyme-Digested Alginate Using the Ionic Gelation and Water-in-Oil Emulsion Method," *Polymers (Basel)*, vol. 15, no. 5, p. 1319, Mar. 2023, doi: 10.3390/polym15051319.

[45]. N. Wang, L. Chen, W. Huang, Z. Gao, and M. Jin, "Current Advances of Nanomaterial-Based Oral Drug Delivery for Colorectal Cancer Treatment," *Nanomaterials*, vol. 14, no. 7, p. 557, Mar. 2024, doi: 10.3390/nano14070557.

[46]. T. Matoba, J. Koga, K. Nakano, K. Egashira, and H. Tsutsui, "Nanoparticle-mediated drug delivery system for atherosclerotic cardiovascular disease," *J Cardiol*, vol. 70, no. 3, pp. 206–211, Sep. 2017, doi: 10.1016/j.jjcc.2017.03.005.

[47]. B. Brar, S. Marwaha, A. K. Poonia, B. Koul, S. Kajla, and V. D. Rajput, "Nanotechnology: a contemporary therapeutic approach in combating infections from multidrug-resistant bacteria," *Arch Microbiol*, vol. 205, no. 2, p. 62, Feb. 2023, doi: 10.1007/s00203-023-03404-3.

[48]. H. Peng *et al.*, "Challenges and opportunities in delivering oral peptides and proteins," *Expert Opin Drug Deliv*, vol. 20, no. 10, pp. 1349–1369, Oct. 2023, doi: 10.1080/17425247.2023.2237408.

[49]. N. Kimura, M. Maeki, A. Ishida, H. Tani, and M. Tokeshi, "One-Step Production Using a Microfluidic Device of Highly Biocompatible Size-Controlled Noncationic Exosome-like Nanoparticles for RNA Delivery," *ACS Appl Bio Mater*, vol. 4, no. 2, pp. 1783–1793, Feb. 2021, doi: 10.1021/acsabm.0c01519.

[50]. A. O. Elzoghby, W. M. Samy, and N. A. Elgindy, "Albumin-based nanoparticles as potential controlled release drug delivery systems," *Journal of Controlled Release*, vol. 157, no. 2, pp. 168–182, Jan. 2012, doi: 10.1016/j.jconrel.2011.07.031.

[51]. A. Simões, F. Veiga, and C. Vitorino, "Question-based review for pharmaceutical development: An enhanced quality approach," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 195, p. 114174, Feb. 2024, doi: 10.1016/j.ejpb.2023.114174.

[52]. Yash gupta vishal rai, "NANOTECHNOLOGY BASED DRUG DELIVERY SYSTEM CURRENT STATUS AND FUTURE PROSPECTS," *International Research Journal of Modernization in Engineering Technology and Science*, May 2023, doi: 10.56726/IRJMETS39424.

[53]. S. Adepu and S. Ramakrishna, "Controlled Drug Delivery Systems: Current Status and Future Directions," *Molecules*, vol. 26, no. 19, p. 5905, Sep. 2021, doi: 10.3390/molecules26195905.

[54]. S. H. Boppana *et al.*, "Current approaches in smart nano-inspired drug delivery: A narrative review," *Health Sci Rep*, vol. 7, no. 4, Apr. 2024, doi: 10.1002/hsr2.2065.

[55]. D. Marabada, J. Li, S. Wei, Q. Huang, and Z. Wang, "Cyclodextrin based nanoparticles for smart drug delivery in colorectal cancer," *Chem Biol Drug Des*, vol. 102, no. 6, pp. 1618–1631, Dec. 2023, doi: 10.1111/cbdd.14344.