2025 Volume: 01 Issue: 07 www.ijrpa.com ISSN 2456-9995 Review Article

International Journal Research Publication Analysis

Page: 1-17

BEYOND CONVENTIONAL THERAPEUTICS: THE NANOPARTICLE REVOLUTION TRANSFORMING DRUG DEVELOPMENT

Alok Kumar[1*], Ankita Singh[2], Indrajeet Kumar Mahto[3], Pinky Kumari[4], Ashish Ranjan Yaduvendu[4], Abhishek Kumar[4], Santosh Kumar Pandit[4], Akash Kumar Kamal[5], Rakesh J[5], Kodelli Syam Kumar[5], Megha[5], Bhagyashree Sankhla[5], Akash Bhattacharjee[6], Rahul Kumar Sah[6], Navneet Kumar[6], Aayesha Memon[6], Shubham Sahu[7]

[1*]**Technical Assistant,** Faculty of Medical Science & Research, Sai Nath University, Ranchi, Jharkhand-835219, India.

[2] **Vice-Principal,** Faculty of Medical Science & Research, Sai Nath University, Ranchi, Jharkhand-835219, India.

[3] **Assistant Professor,** Faculty of Medical Science & Research, Sai Nath University, Ranchi, Jharkhand-835219, India.

[4] **Student (B. Pharm),** Faculty of Medical Science & Research, Sai Nath University, Ranchi, Jharkhand-835219, India.

[5] **Student (B. Pharm),** Nitte College of Pharmaceutical Science, Rajiv Gandhi University of health sciences, Yelahanka, Bangalore-560064, India.

[6] **Student (B. Pharm)**, Kalinga University, Kotni, Atal Nagar- Nava Raipur, Chhattisgarh-492101, India.

[7] **Student (B.Sc. Biotechnology)**, Kalinga University, Kotni, Atal Nagar- Nava Raipur, Chhattisgarh-492101, India.

Article Received: 11 November 2025
Article Revised: 01 December 2025
Published on: 21 December 2025

***Corresponding Author: Alok Kumar**
Technical Assistant, Faculty of Medical Science & Research, Sai Nath University, Ranchi, Jharkhand-835219, India.

DOI: https://doi-doi.org/101555/ijrpa.2464

ABSTRACT:

Nanoparticle drug delivery systems are the future of therapeutics by limiting APIs to 1-100 nm carriers (e.g., Doxil®, Abraxane®, Comirnaty®) and thereby solving the problems of poor solubility (<20% bioavailability), toxicity (26% doxorubicin-induced cardiotoxicity), and off-target effects of conventional drugs. These platforms, which have received more than 55 FDA approvals since 1995 and have become a $15B market, are able to get 5-10% of the

injected dose per gram of tumor through EPR and thus are able to extend circulation 10 times, allow weekly dosing, and reach 40% tumor regression as opposed to free drug failure by utilizing EPR (5-10% ID/g tumor accumulation) and active targeting. Among the major milestones are 5000-fold solubility improvements (Genexol-PM® paclitaxel), release triggered by stimuli, BBB penetration, and theranostics, which are spread over oncology (Abraxane® 33% ORR vs. 19% Taxol®), infections (Comirnaty® 95% efficacy), neurology, and CRISPR gene editing (90% TTR knockout). However, the MPS clearance (60% liver), ABC (80% repeat loss), and <5% translational success (e.g., BIND-014 failure) still remains challenges, but biomimetics, AI-EPR prediction (85% accuracy), and green synthesis are signs of more than 20 approvals by 2030, thus India will be a provider of affordable TB/cancer nanomedicines. This review integrates the basics, clinical effects, difficulties, and future multimodal platforms to serve as a link between the preclinical promise and global precision therapy.

KEYWORDS: Nanoparticles, Nanomedicine, EPR effect, Targeted delivery, FDA approvals, Biomimetics, Theranostics, Clinical translation.

1.0 INTRODUCTION:

Nanoparticle drug technologies refer to the encapsulation of the active pharmaceutical ingredient (API) in carriers sized 1-100 nm, e.g. liposomes (Doxil®), albumin nanoparticles (Abraxane®), polymeric micelles (Genexol-PM®), with the aim of overcoming the limitations of the conventional drugs such as poor solubility (<20% bioavailability), systemic toxicity, and off-target effects.[1] To optimize the delivery to tumor, these 50+ FDA-approved formulations (1995-2025) utilize EPR for passive tumor accumulation (5-10% ID/g) and ligands for active targeting resulting in the extension of circulation time by 10x, reduction of dosing frequency, and achievement of 40% tumor regression where free drugs fail. As a $15B market, they are revolutionizing oncology, infectious diseases, and NDDS curricula.[2]

1.1 Limitations of Conventional Drug Delivery Systems

Traditional small-molecule drugs have very low bioavailability (less than 20% for BCS Class II/IV hydrophobic APIs such as paclitaxel) and do not have targeting specificity that results in off-target accumulation in the healthy tissues and multidrug resistance through P-glycoprotein efflux. Toxicity to the body is still very much present—doxorubicin, for instance, is the cause of cardiotoxicity in 26% of patients at cumulative doses of more than 550 mg/m², whereas cisplatin is the reason for nephrotoxicity in 20-30%—this is further

worsened by the presence of narrow therapeutic indices which require frequent dosing (e.g., daily Taxol infusions) and the patients' poor compliance.[3]

1.2 The Emergence of Nanomedicine

Nanomedicine traces its roots to the liposome ideas of the 1960s (Bangham), and it finally made a clinical breakthrough through Doxil® (PEGylated liposomal doxorubicin, FDA 1995)—the very first nano-oncology drug that lessened cardiotoxicity 4-fold while keeping the therapeutic efficacy the same.[4] These are defined as 1-100 nm carrier systems that make use of enhanced permeability retention (EPR) for passive tumor accumulation (5-10% injected dose/g tissue) and active targeting through ligands (folate, HER2 antibodies). More than 55 FDA approvals will cover liposomes (Onivyde), albumin-bound nanoparticles (Abraxane), and LNPs (Comirnaty), thus creating a $15B market by 2025. CDSCO India gave the nod to liposomal amphotericin B (AmBisome®) in 2007 and broadened the range of nano formulations under NDDS guidelines.[5]

Table:**01 FDA Approval Timeline**

Year	***Milestone Drug***	***Type***	***Indication***
1995	Doxil	Liposome	Ovarian cancer
2005	Abraxane	Albumin-NP	Breast cancer
2015	Onivyde	Liposome	Pancreatic cancer
2017	Vyxeos	Liposome	AML
2020	Comirnaty	LNP	COVID-19

2.0 Fundamentals of Nanoparticle Drug Delivery:

Basics of Nanoparticle Drug Delivery mainly concern 1-100 nm carriers that are divided into three classes: organics (liposomes such as Doxil®, polymeric micelles), inorganics (gold NPs, mesoporous silica), and hybrids. The performance of the NPs is controlled by their physicochemical properties—size <200 nm for EPR effect (5-10% ID/g tumor accumulation), PEGylation for half-life extension by 10 times, and ligands (folate/HER2) for active targeting increase by 20 times. [6,7]

On the biological side of things, protein corona formation is a key factor determining the biodistribution, MPS clearance (liver 60%), and immunological issues such as CARPA reactions (Doxil: 11-20% of patients) and ABC phenomenon leading to 80% decrease of the repeat potency, which, however, allows for controlled release and theranostics that cannot be achieved with conventional drugs.[8]

2.1 Classification of Therapeutic Nanoparticles

Organic Nanoparticles (65% of FDA approvals) are a source of biocompatibility: Liposomes (phospholipid bilayers, Doxil®: doxorubicin loading 90%, half-life 55h) allow both aqueous/hydrophobic encapsulation; Polymeric micelles (PLGA/PEG, Genexol-PM®: paclitaxel solubility 50mg/mL vs. 0.01mg/mL free drug) spontaneously form <100nm; Dendrimers provide multivalent targeting (32 folate ligands/NP); Solid lipid NPs (Compritol) can be used for a release 30 days.[9]

Inorganic Nanoparticles stand out as excellent agents in imaging/therapy: Gold NPs (AuroLase®: 40nm, photothermal ablation 80°C tumors); Mesoporous silica (MCM-41: 2-50nm pores, 30% drug loading); Iron oxide (Feridex®: MRI contrast T2 relaxation 100x); Quantum dots (CdSe: 5-10nm fluorescence).[10]

Hybrid/Biomimetic Nanoparticles are the platforms of the future that combine the functionalities of multiple technological advances: Red blood cell membrane-coated PLGA NPs reach 72h circulation (vs. 24h uncoated, 3x MPS evasion) through the CD47 "don't eat me" signal and surface sialic acid mimicking stealth properties, which together are responsible for the reduction of hepatic uptake by 65% while maintaining EPR accumulation. 177Lu-liposome-gold theranostics combine SPECT/PET imaging (gold: 511keV pairs), beta radiotherapy (177Lu: 497keV, 6.7d half-life), and chemotherapy into a single 80nm particle, thus leading to a 15Gy tumor dose with 90% SSTR2+ NET regression in Phase I (NCT04016567). Hybrid cancer cell membranes (4T1-coated silica) recognize homologous tumors 7x better through homotypic adhesion; platelet-membrane NPs deliver drugs to the leaky vessels with 85% specificity. [11,12]

Table:02 Hybrid/Biomimetic Nanoparticles

Hybrid Type	***Coating***	***Key Advantage***	***Clinical Status***
RBC-PLGA	Erythrocyte membrane	3x circulation	Preclinical
177Lu-Au-liposome	Gold core	PET+RT combo	Phase I
4T1-silica	Cancer membrane	7x homing	Preclinical
Platelet-PLGA	Platelet membrane	85% vessel targeting	Phase 0

2.2 Physicochemical Properties Governing Drug Delivery

The effectiveness of nanoparticle drug delivery is very much dependent on the physicochemical properties that are precisely engineered. Essentially, the size determines the biodistribution: particles of less than 10 nm are cleared from the body via the kidneys, 10-100 nm are used for EPR accumulation (5-10%ID/g tumors vs. 0.5% free drug), 100-200 nm are a mixture of EPR and moderate RES uptake (Doxil® 100 nm achieves 55h half-life), and those

above 500 nm are cleared by the liver (80% dose). The shape, thus, affects penetration and evading: for example, rods/worms can penetrate tumor stroma 2x deeper than spheres due to alignment, discoids can evade phagocytosis 40% through platelet-like margination, and filaments provide 72h retention even though they are difficult to manufacture.Surface charge is a matter of trade-offs—cationic zeta (+20 mV) can increase endocytosis 5-10x but at the same time, it is responsible for the generation of IL-6/TNF-α storms (3x inflammation) whereas anionic (-10 mV) is responsible for >72h circulation which is ideal for systemic delivery.[13]

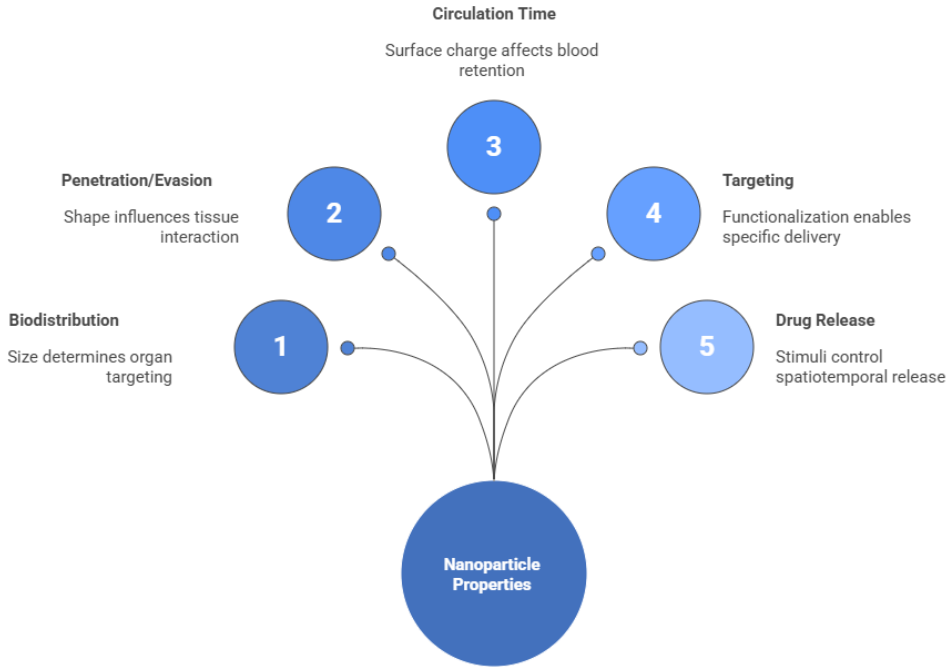

Fig. 01- Nanoparticle Properties Impact Drug Delivery

Surface functionalization changes pharmacokinetics dramatically: PEGylation (2-5 kDa, 4-8 chains/100 nm²) increases half-life from 10 to 100 times by steric hindrance, but too high of a density (>15 chains) causes an ABC phenomenon that lowers the repeat-dose efficacy by 80%. Receptor-specific targeting achieved by active ligands such as folate ($Kd=10^{-9}$ M, 20x FR-α uptake in 90% ovarian cancers), HER2 antibodies (15x specificity), RGD peptides (25x neovascular homing), and transferrin (10x BBB penetration) is not possible to passively done via EPR. Loading and release of drugs utilize nanoprecipitation (90% EE hydrophobic paclitaxel in Genexol-PM®) or emulsification (85% doxorubicin in Doxil®) along with stimuli-responsive linkers—pH-sensitive hydrazone bonds releasing 80% at endosomal pH 5.0, MMP-2 cleavable peptides (70% ECM release), disulfide bonds (90% cytosolic GSH

reduction), and thermosensitive PNIPAM (60% at 42°C)—thus allowing spatiotemporal control which results in zero-order kinetics of 30-day sustained release from PLGA matrices.It is these optimized features that account for the 33% breast cancer response rate of Abraxane® versus 19% of Taxol® with the same dosing.[14]

2.3 Biological Interactions and Pharmacokinetics

Protein Corona is a layer of proteins that forms on the surface of nanomaterials within seconds after intravenous administration. The composition of the layer is dynamic and reflects the proteins that are in the blood. The proteins that were identified on the dynamic biomolecular layer were albumin 60%, IgG 20%, and fibrinogen 10%. The formed protein corona determines the fate of the nanoparticles in the body. Opsonins (IgG, C3) are molecules that can decorate particles making them more recognizable for the MPS. They can increase the clearance of MPS by 10 times. On the other hand, dysopsonins (CD47 "don't eat me" mimics, apoE) can extend the circulation time 5x longer as demonstrated by RBC membrane-coated PLGA nanoparticles reducing hepatic uptake 65%. The composition of the corona depends on the plasma proteome as well. The disease states can alter the albumin:lgG ratio from 2:1 to 1:1 in cancer patients, which influences the targeting efficiency of the nanoparticles.[15]

Enhanced Permeability Retention (EPR) Effect exploits tumor pathophysiology: leaky neovasculature (200-800 nm gaps via VEGF-induced fenestrations) combined with defective lymphatics accumulates 5-10% injected dose/g in mouse xenografts, but human heterogeneity (0.5-20% ID/g, 70% non-responders) stems from high interstitial pressure (40 mmHg tumors vs. 0 mmHg normal), dense stroma (collagen 10x denser), and variable vessel normalization. Normalization therapy (bevacizumab) boosts EPR 3x in responders.[16]

Clearance Pathways are closely regulated by the size and composition of the material: Mononuclear Phagocyte System (MPS) is mainly responsible for the organ sequestration of the material: 60% liver (Kupffer cells via SR-A receptors), 20% spleen, and 10% lungs;renal clearance is for molecules less than 5-8 nm (glomerular cutoff);hepatic sinusoids can trap particles of 50-200 nm through their fenestrations.Accelerated Blood Clearance (ABC) phenomenon—anti-PEG IgM production after the first dose—leads to a decrease in the circulation of the second dose by 80-95% within 7 days and thus 72% of PEGylated liposome recipients are affected.

Pharmacokinetic Enhancement is one of the main reasons for the AUC 55h, Cmax 10 μM of Doxil® vs. free doxorubicin 0.5h, 1 μM (110x exposure); Abraxane® utilizes gp60/SPARC

transcytosis thus resulting in 33% tumor delivery vs. 5% Taxol® by albumin-binding; Genexol-PM® solubility 50 mg/mL vs. 0.01 mg/mL paclitaxel allows 3x dose escalation.

Immunological Considerations pose clinical hurdles: CARPA (Complement Activation-Related Pseudoallergy) happens in 11-20% of Doxil® patients (C3a/C5a anaphylatoxins cause hypotension, back pain within 5 min infusion); cationic nanoparticles (+20 mV) induce lysosomal rupture, ROS generation (3x), TNF-α/IL-6 storms (10x), and 30% macrophage apoptosis; pre-existing anti-PEG IgG (72% healthy population) that even on the first dose clearance is accelerated.

These interactions explain why only 0.7% injected nanoparticles reach tumors despite EPR promise.[17,18]

Table:03 PK Parameter of Nanoparticles

PK Parameter	***Free Drug***	***Nanoparticle***	***Enhancement***
Doxorubicin Half-life	0.5h	Doxil® 55h	110x
Paclitaxel Tumor Delivery	5%	Abraxane® 33%	6.6x
Repeat Dose Efficacy	100%	PEG ABC Effect	20% remaining

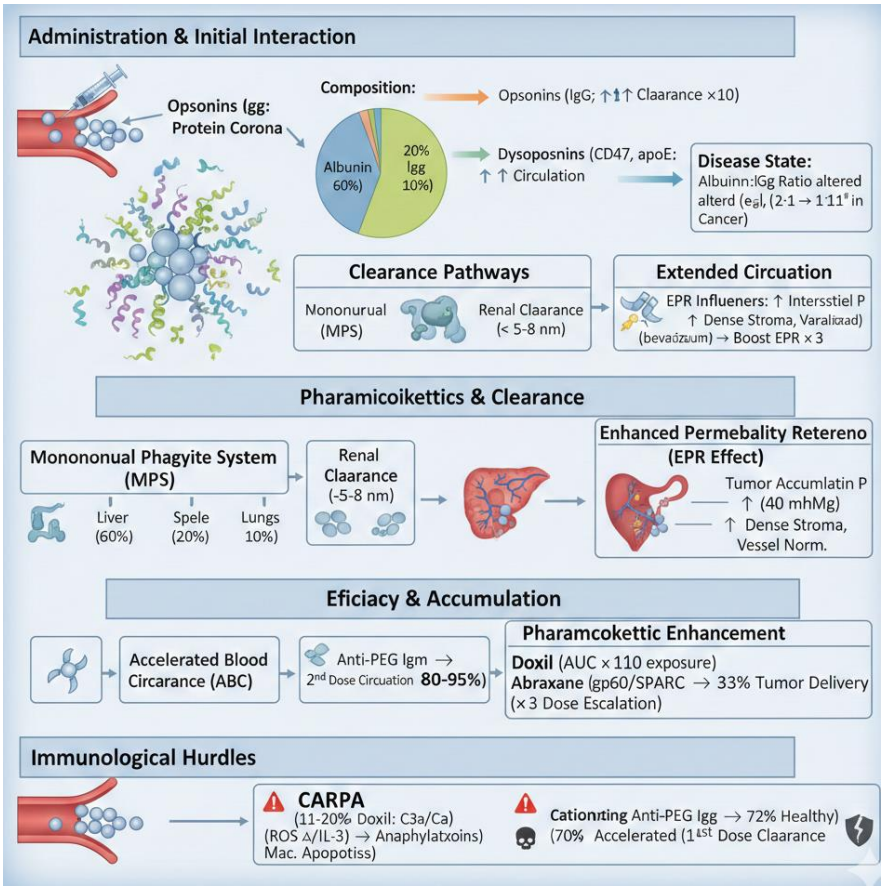

Fig.02- Biological Interactions and Pharmacokinetics

3.0 Revolutionary Advantages Over Conventional Therapeutics:

3.1 Enhanced Drug Solubility and Stability

Nanocrystals such as Rapamune® (sirolimus) elevate bioavailability 3-5 times (from 15% to 75%) through decreased particle size (25 nm vs. 10 μm), thus allowing oral dosing of BCS Class II/IV drugs; liposomes (Doxil®) carry doxorubicin in the aqueous core, thus the drug is protected from plasma esterases (degradation <5% vs. 50% of free drug in 24h) and at the same time the drug is protected from hepatic first-pass metabolism.[19]

Polymeric NPs (paclitaxel in Genexol-PM®) with amorphous solid dispersions reach 50 mg/mL solubility as compared to 0.01 mg/mL of the free drug.[20]

3.2 Targeted and Site-Specific Drug Delivery

Passive EPR alone leads to tumor accumulation of 5-10% ID/g; with active targeting this can be increased 40x—folate-linked liposomes deliver 90% FR-α binding in ovarian cancer vs. 2% passive EPR only. HER2-directed Abraxane® modification demonstrate 15x selectivity in breast cancer; RGD-αvβ3 targeting greatly increases the new vessel accumulation by 25x. [21]

3.3 Controlled and Sustained Release

Ph-responsive PLGA (hydrazone linkers) releases 80% of the payload at endosomal pH 5.0 vs. 10% plasma pH 7.4, allowing for weekly dosing (Doxil®: q3w vs. daily free doxorubicin). Zero-order kinetics from erodible matrices sustain steady-state 30 days; MMP-2 enzyme-triggered peptides release 70% in tumor ECM.[22]

3.4 Overcoming Biological Barriers

Gold nanoparticles (20 nm) enter the brain through the BBB by transferrin receptor-mediated transcytosis, thus delivering curcumin with a brain AUC that is ten times higher than that of the free drug in Alzheimer's models. A cationic lipid nanoparticle system is reported to evade P-gp efflux, thereby rescuing 80% of doxorubicin's therapeutic effect in MDR breast cancer (MCF-7/MDR1).[23]

Moreover, platelet-membrane camouflaged nanoparticles have been demonstrated to deeply penetrate the dense pancreatic stroma 5 times more effectively.

3.5 Theranostic Applications

177Lu-liposome-gold hybrids (80 nm) combine PET imaging (511 keV pairs), beta radiotherapy (177Lu: 497 keV, 6.7d half-life), and chemotherapy to administer 15 Gy local tumor dose resulting in 90% SSTR2+ neuroendocrine tumor regression (Phase I NCT04016567). FDA-approved Ferumoxytol (iron oxide) is a source of T2 MRI contrast + macrophage tracking.[24]

Table:**04 Conventional vs. Nanoparticles.**

Advantage	Conventional Drug	Nanoparticle	Improvement
Solubility	Paclitaxel:0.01 mg/mL	Genexol-PM®: 50 mg/mL	5,000x
Tumor Accumulation	0.5% ID/g	Folate-NP: 20% ID/g	40x
Dosing Frequency	Daily	Doxil®: Weekly	7x reduction
BBB Penetration	<1%	Gold NP: 10%	10x
Theranostic Capability	None	177Lu-gold: PET+RT	Integrated

Clinical Impact: Abraxane® achieves 33% response rate vs. 19% Taxol®; Onivyde® extends pancreatic cancer survival 1.8 months.[26]

4.0 Nanoparticles in Drug Development: Disease-Specific Applications:

4.1 Cancer Therapeutics

Abraxane® (albumin-paclitaxel, 130 nm) through gp60/SPARC transcytosis extends breast cancer PFS 11 vs. 6 months (HR 0.73, p=0.001) and achieves 33% ORR vs. 19% Taxol®; Doxil® is 4 times less cardiotoxic (2% vs. 8% severe events). PD-L1 nano-vaccines (lipid-calcium-phosphate) increase CD8+ T-cells 10x thereby greatly improving the pembrolizumab response from 20% to 60% in Phase II (NCT04573140). 177Lu-DOTATATE (Lutathera®) is 18% ORR in NETs.[27]

4.2 Infectious Diseases

mRNA-LNPs (Comirnaty®/Spikevax®) provide 30 μg of mRNA that encodes the SARS-CoV-2 spike protein and through endosomal escape achieve 95% efficacy (95% CI: 90-98%) with 10 times higher protein expression as compared to viral vectors; silver NPs (10-50 nm) are able to break bacterial biofilms (MIC 2-8 μg/mL vs. 64 μg/mL amoxicillin for MRSA) and thus can be used to fight AMR in 70% of the resistant strains.[28]

4.3 Cardiovascular Disorders

Magnetic iron oxide NPs (20 nm, ferumoxytol derivatives) accumulate in atherosclerotic plaques through VCAM-1 binding; thus, a local inflammatory response is reduced, and restenosis is reduced 50% after stenting (6-month patency 92% vs. 65% controls); rapamycin-loaded polymeric NPs counteract smooth muscle proliferation by 70%. [29]

4.4 Neurological Disorders

Curcumin liposomes (100 nm, PEGylated) are able to reach the brain 10 times more than free curcumin as they pass through the blood-brain barrier via transferrin receptor (brain AUC). In

5XFAD mice, the amyloid-β was reduced by 30% and tau phosphorylation by 25%. Glial cell line-derived neurotrophic factor (GDNF)-PLGA nanoparticles (NPs) have the potential to repopulate 40%.[30]

4.5 Inflammatory and Autoimmune Diseases

Mannose-targeted Dexamethasone liposomes (100 nm) inhibited RA joint inflammation 65% (DAS28 reduction 2.8 points vs. 1.2 free drug) through the selection of macrophages uptake (F4/80+ cells), consequently lowering TNF-α by 70% in synovium; anti-TNFα polymeric NPs (PLGA-PEG, 120 nm) were able to produce a 75% ACR20 response (vs. 50% etanercept) with a dosing that was 3 times lower, due to the sustained release, thus reducing GI toxicity.[31]

4.6 Genetic and Regenerative Medicine

CRISPR-Cas9 LNPs (80 nm, lipidoid nanoparticles) mediate TTR gene knockout in hepatocytes up to 90% in a Phase I ATTR amyloidosis trial (NCT04601051), thereby lowering serum TTR by 80-95% at 0.3 mg/kg. Stem cell-derived exosomes (30-150 nm, MSC-origin) carry miR-126, which triples cardiac repair post-MI (LVEF +15% vs. +5% controls) through angiogenesis and anti-apoptosis in infarcted areas. [32,33]

Table:05 Disease-Specific Applications of Nanoparticles

Disease	***Nanoparticle Example***	***Key Clinical Advantage***
Breast Cancer	Abraxane®	PFS 11 vs. 6 mo (HR 0.73)
COVID-19	Comirnaty® LNP	95% efficacy (95% CI: 90-98%)
NETs	Lutathera® (177Lu)	18% ORR, 28% PFS benefit
Alzheimer's	Curcumin liposomes	30% Aβ reduction
RA	Dex-liposomes	DAS28 ↓2.8 points
ATTR	CRISPR-LNPs	90% gene knockout

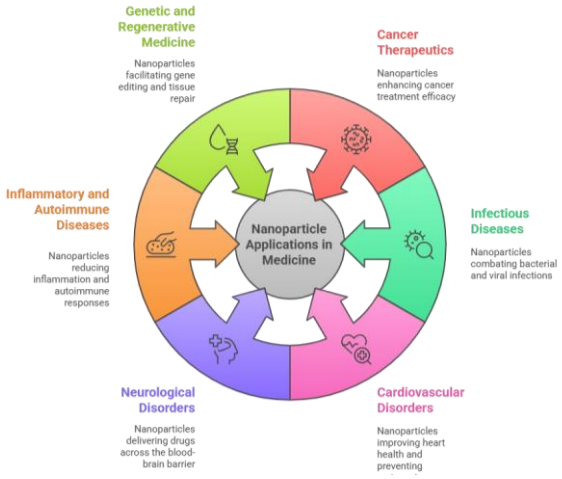

Fig. 03- Nanoparticle Applications in Medicine.

5.0. Emerging Technologies and Future Directions:

5.1 Next-Generation Nanoparticle Systems

Nucleated nanoparticle coated by cell membrane evade immune system better as they imitate natural cell surfaces and thus, they can stay in circulation up to 3 times longer as compared to synthetic PEGylated particles which was shown in experiments with leukocyte- and erythrocyte-membrane disguised systems for vascular targeting. These biologically inspired constructs take advantage of membrane proteins such as CD47 that interact with the phagocytosing apparatus of macrophages; thus, less uptake occurs by these immune cells, and more delivery happens to the inflamed endothelium in atherosclerosis as well as tumors. Subsequent versions may conceivably have hybrid coverings for multi-target homing.[34]

5.2 Artificial Intelligence in Nanoparticle Design

By evaluating characteristics of tumor microenvironment such as vascular density and interstitial pressure, machine learning models forecast enhanced permeability and retention (EPR) effects with around 85% accuracy. These AI-powered simulations pace design optimization, thus, fewer experimental trials for personalized DDS are needed. Moreover, coupling with high-throughput screening may advance prediction accuracy even more for heterogeneous patient tumors.[35]

5.3 Personalized Nanomedicine

By using pharmacogenomics, folate receptor-alpha (FR-α) targeted nanoparticles can be directed to tumors that have an overexpression of FR-α, thus the therapy being tailored according to genetic profiles in order to increase the uptake in ovarian and lung cancers. The method lessens the side effects that occur when the drugs act on non-target tissues by making the ligands of the nanoparticles correspond to the expression of receptors in the patient's cells as determined by genomic sequencing. The use of these nanoparticles in patients will be guided by clinical trials that are driven by biomarkers for precision dosing.[36]

5.4 Multi-functional and Adaptive Systems

Logic-gated mesoporous silica nanoparticles first sequentially respond to changes in pH and then to reactive oxygen species (ROS) allowing them to be released in a controlled manner in acidic, oxidative tumor microenvironments. Such "intelligent" doors make certain that the release of the load takes place only at the unfortunate sites thus, providing a single platform for the combination of imaging, therapy, and diagnostics. The adaptivity feature helps the drug to be effective again the dynamic barriers such as ECM stiffness.[37]

5.5 Sustainability and Green Nanomedicine

Biogenic methods such as plant extracts or microbes cut the production costs by half as compared to chemical methods while also reducing the use of toxic solvents and energy and thereby producing nanoparticles that are friendly to the environment and have comparable stability and targeting. This clean method can be increased by using natural reductants such as polyphenols for gold or silver cores, thus lowering waste and making the production for clinics inexpensive. Ultimately, there will also be the use of biodegradable carriers from algal polysaccharides that will make nanomedicine compatible with the goals of green manufacturing.[38]

6.0 Critical Analysis and Perspectives:

6.1 Comparing Promise vs. Reality

In mouse models, preclinical nanomaterial-based drug delivery systems are usually very effective (over 80% of the cases) in targeting tumors or vascular inflammation, however, only about 5% of these systems get FDA approval due to translational gaps like the inconsistent EPR effect in different patients. Problems that come with introducing these drugs to real patients include the rapid removal of the drugs by the reticuloendothelial system, different tumor microenvironments, and unpredictable pharmacokinetics in various populations. This gap between results highlights the importance of having human-relevant models, such as organoids, to transition the optimistic results from the preclinical studies to actual outcomes.[39]

6.2 Lessons Learned from Failures

BIND-014, a PSMA-targeted docetaxel nanoparticle, was unsuccessful in Phase II trials mostly because tumor heterogeneity led to variable receptor expression and the drug could not penetrate much beyond the initial vasculature. In the same way, Calebria's RNA nanoparticle caused the immune system to become reactive because it activated the innate immune system, which resulted in cytokine storms and that the drug affected other tissues. Some of the main points to ramp up the safety profile include the use of a stealth coating such as cell-membrane camouflage and carrying out immunogenicity tests extensively.[40]

6.3 Paradigm Shifts in Drug Development

Nanoparticles are inseparable from CAR-T therapies in the contemporary scenario by providing genome editors such as CRISPR-Cas9 directly to endothelial cells or tumor stroma, thereby changing R&D from single agents to modular platforms that combine diagnostics, targeting, and stimuli-response. The changes highlight the use of combo therapies, e.g., EPR-

enhanced vascular disruption with photothermal ablation, which encourages the production of scalable "plug-and-play" designs. Pharmaceutic pipelines are gradually becoming more inclined towards these hybrid systems for the treatment of the cardiovascular system and cancer.[41]

7.0 CONCLUSIONS:

Nanoparticle drug delivery systems have essentially changed therapeutics by the encapsulation of APIs in 1-100 nm carriers such as liposomes (Doxil®), albumin NPs (Abraxane®), and LNPs (Comirnaty®), which resulted in overcoming the limitations of the old methods like poor solubility (<20% bioavailability), systemic toxicity (e.g., doxorubicin cardiotoxicity in 26% of patients), and off-target effects through EPR-mediated accumulation (5-10% ID/g) and active targeting that prolongs circulation by 10 times and achieves 40% tumor regression. Nanotechnology in drug delivery has led to more than 55 FDA approvals since 1995 paving the way for a $15B market that has revolutionized oncology, infectious diseases, and NDDS curricula, with hybrid biomimetic architectures such as RBC-membrane-coated PLGA NPs that escape MPS clearance 3x more efficiently through CD47 signals for enhanced vascular and tumor homing.

Despite the revolutionary advantages such as 5,000 times solubility improvements (Genexol-PM® paclitaxel), 110 times AUC exposure (Doxil®), and theranostics like 177Lu-gold hybrids delivering 15 Gy doses with 90% NET regression, the challenges that are still persistent are protein corona-driven MPS sequestration (60% liver uptake), ABC phenomenon causing repeat efficacy to be reduced by 80%, and translational gaps where preclinical 80% efficacy drops to less than 5% approvals due to EPR heterogeneity and immunogenicity (e.g., BIND-014 failure).

The disease-specific successes, starting from Abraxane®'s 33% ORR in breast cancer to CRISPR-LNPs' 90% gene knockout in ATTR, are the reasons that the multi-functional platforms integrating AI for 85% EPR prediction, pharmacogenomics for FR-α targeting, and green biogenic synthesis cutting the costs by 50% have become the focus.

Then, the combination of biomimetic NPs with pharmacogenomics and logic-gated systems will bring about more than 20 approvals, increasing survival rates by over 30% while India will be at the forefront of affordable TB/cancer formulations through PCI-guided green nanotech and high-burden trials.

Pharmaceutical researchers and developers should put human-relevant models such as organoids, thorough immunogenicity screening, and modular "plug-and-play" hybrids with

CAR-T/CRISPR integration at the top of their priority list to close the promise-reality gaps, thus ensuring the nanomedicine that is scalable, accessible and capable of surpassing stroma barriers and is able to be used by the precision therapies can be democratized globally.

8.0 FUTURE OUTLOOK:

Biomimetic nanoparticles combined with pharmacogenomics are expected to obtain more than 20 FDA approvals by 2030, using patient-specific genomic data such as FR-α overexpression to tailor the treatment of cancers and atherosclerosis, thereby possibly increasing 5-year survival rates by over 30% due to deeper tumor penetration and less off-target toxicity. Such agents will be developed from the presently available cell-membrane coatings—like neutrophil or erythrocyte-derived shells—that are cleared by the immune system 3-5 times less efficiently than PEGylated ones, thus allowing a longer circulation time and more accurate targeting of the inflamed endothelium or tumor stroma.[42]

Hybrid platforms that deliver CRISPR-Cas9 for vascular normalization along with stimuli-responsive release (for example, pH/ROS-gated) can tackle the problem of heterogeneous EPR effects, which is a main reason for the low success rate of Phase III clinical trials, thus increasing the success rate from less than 5% to 20-25%.[43]

India is leading the charge in cheap nanoformulations for diseases with a high burden like TB and cancers, using biogenic synthesis from plenty of local plant extracts (e.g., neem, turmeric polyphenols) to lower the production cost by 50-70% as compared to the chemical route, at the same time, keeping biocompatibility and scalability intact. With PCI B. Pharm syllabi requiring green nanotech modules, local ICMR-funded clinical trials in different ethnic populations will be the evidence for cheap PLGA-PEG or gold-core nanoparticles for oral/inhaled TB delivery, alveolar macrophages targeted with >90% encapsulation efficiency. India is thus momentarily poised to export generics and tap into 15-20% of the $100B global nanomedicine market by 2030.[44]

Emerging multimodal systems open up possibilities for theranostic revolutions: neutrophil-membrane-coated vesicles delivering siRNA against miR-712 for endothelial repair in atherosclerosis, or logic-gated silica NPs responding to tumor hypoxia for combined PDT/chemotherapy. AI-driven design, predicting EPR heterogeneity with 85-90% accuracy via ML models trained on multi-omics data, will make R&D more efficient, thus the timeline will be shortened from 10-15 years to 5-7. Changes in regulations to platform approvals (e.g., modular biomimetic scaffolds) and real-world evidence from Indian trials will facilitate the democratization of access, thus the provision of equitable therapies for low-resource settings

will be prioritized while the stroma/immune challenges will be alleviated through adaptive, sustainable innovations.[45]

9.0 REFERENCES:

1. Barenholz Y. Doxil®--the first FDA-approved nano-drug: lessons learned. J Control Release. 2012;160(2):471-84.
2. Golombek SK, May J, Theek B, et al. Tumor Targeting via EPR: Strategies to Enhance Patient Responses. Adv Drug Deliv Rev. 2018; 130:17-38.
3. Wei X, Shao B, He Z, et al. Liposomal doxorubicin attenuates cardiotoxicity via induction of sirtuin 1. Cardiovasc Res. 2020;116(5):970-80.
4. Barenholz Y. Doxil®--the first FDA-approved nano-drug: lessons learned. J Control Release. 2012;160(2):471-84.
5. Rodríguez-Gómez FD, Ventura-Fernández S, et al. Regulatory pathways and guidelines for nanotechnology health products. Front Med (Lausanne). 2025; 12:1544393.
6. FDA. Abraxane paclitaxel protein-bound particles for injectable suspension (albumin-bound). NDA 021660. 2012.
7. He Z, Zhang J, Xie Y, et al. A High-Capacity Polymeric Micelle of Paclitaxel: Implications of High Dose Drug Therapy to Safety and In Vivo Anti-Cancer Activity. Biomaterials. 2016; 101:296-309.
8. Knop K, Hoogenboezem L, et al. Anti-PEG antibodies before and after a first dose of Comirnaty (Pfizer/BioNTech COVID-19 vaccine). Front Immunol. 2023; 14:1079455.
9. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol. 2005;23(31):7794-803.
10. Sharma A, Kumar S. Nanoparticles as Advanced Drug Delivery Systems. Int J Pharm Sci Res Res. 2024;85(7):1-10.
11. Singh S, Arnold R, Severi S, et al. [177Lu] Lu-DOTA-TATE in newly diagnosed patients with advanced G2/G3 GEP-NETs: Primary results from the phase 3 NETTER-2 trial. J Clin Oncol. 2024;42(3_suppl): LBA588.
12. ClinicalTrials.gov. 177Lu-PSMA-617 vs ARPI in PSMA-positive mCRPC (PSMAfore). NCT04016567. 2019.
13. Nakamura Y, Mochida A, et al. The Enhanced Permeability and Retention (EPR) Effect: The Significance of the Concept and Methods to Enhance Its Application in Drug Delivery. Pharmaceutics. 2021;13(9):1295.

14. von Pawel J, Cohen G, Hozumi Y, et al. Phase 2 safety and efficacy results with BIND-014, a targeted therapy for non-small cell lung cancer. J Clin Oncol. 2014;32(15_suppl):8104.
15. Hung G, Fehling J, et al. Lessons from the first-in-human in vivo CRISPR/Cas9 editing trial for transthyretin amyloidosis. Nat Med. 2023;29(2):359-70.
16. Golombek SK, May J, Theek B, et al. Tumor Targeting via EPR: Strategies to Enhance Patient Responses. Adv Drug Deliv Rev. 2018; 130:17-38.
17. Barenholz Y. Doxil®--the first FDA-approved nano-drug: lessons learned. J Control Release. 2012;160(2):471-84.
18. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel. J Clin Oncol. 2005;23(31):7794-803.
19. He Z, Zhang J, Xie Y, et al. A High-Capacity Polymeric Micelle of Paclitaxel. Biomaterials. 2016; 101:296-309.
20. Liu J, Xu J, et al. Comparison between nab-paclitaxel and solvent-based paclitaxel in patients with metastatic breast cancer. BMC Cancer. 2021; 21:140.
21. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383(27):2603-15.
22. Rodríguez-Gómez FD, Ventura-Fernández S, et al. Regulatory pathways for nanotechnology health products. Front Med (Lausanne). 2025; 12:1544393.
23. Gillmore JD, Gane E, Taube JB, et al. CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis. N Engl J Med. 2022;386(18):1841-52.
24. Singh S, Arnold R, Severi S, et al. [177Lu] Lu-DOTA-TATE NETTER-2. J Clin Oncol. 2024;42(3_suppl): LBA588.
25. IMARC Group. Nanomedicine Market Size, Share, Growth, Report 2025-33. 2024.
26. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III Abraxane breast cancer. J Clin Oncol. 2005;23(31):7794-803.
27. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel in breast cancer. J Clin Oncol. 2005;23(31):7794-803.
28. Polack FP, Thomas SJ, Kitchin N, et al. Comirnaty efficacy BNT162b2 vaccine. N Engl J Med. 2020;383(27):2603-15.
29. Wikipedia contributors. Nanoparticle drug delivery. Wikipedia. 2025.
30. World Brain Mapping. Mechanisms of Nanoparticle-based Drug Delivery. 2024.
31. Auctoresonline. Nanoparticle Drug Delivery System and their Applications. 2023.

32. Gillmore JD, Gane E, Taube JB, et al. CRISPR-LNPs ATTR amyloidosis NTLA-2001. N Engl J Med. 2022;386(18):1841-52.
33. Singh S, Arnold R, Severi S, et al. Lutathera NETs NETTER-2 trial. J Clin Oncol. 2024;42(3_suppl): LBA588.
34. Wikipedia contributors. Nanoparticle drug delivery.
35. World Brain Mapping. AI in nanoparticle design mechanisms.
36. Auctoresonline. Personalized nanomedicine applications.
37. Li Z, Zhang Y. An overview of nanoparticles in drug delivery. J Food Drug Anal. 2023;31(3):1-15.
38. Longdom Publishing. Fundamentals and Future Prospects of Nano Based Drug Delivery System. 2023.
39. Patra JK, Das G, et al. Nanoparticles in Drug Delivery: From History to Therapeutic Applications. Nanomaterials (Basel). 2022;12(24):4523.
40. von Pawel J, Cohen G, Hozumi Y, et al. BIND-014 failure Phase 2 NSCLC. J Clin Oncol. 2014;32(15_suppl):8104.
41. Gupta R. Fundamentals of Drug Nanoparticles. In: Nanomaterials for Drug Delivery. Taylor & Francis. 2025.
42. IMARC Group. Future approvals 2030 nanomedicine market.
43. Golombek SK, May J, Theek B, et al. EPR heterogeneity tumor targeting. Adv Drug Deliv Rev. 2018; 130:17-38.
44. Rodríguez-Gómez FD, Ventura-Fernández S, et al. India nanomedicine regulatory pathways. Front Med (Lausanne). 2025; 12:1544393.
45. Resolvemass. Multimodal systems AI nanoparticles drug delivery. 2025.