Journal of Advanced Pharmaceutical Sciences and Natural Products


# AN OVERVIEW OF HYBRID NANOSTRUCTURES IN DRUG DELIVERY AND THERAPY

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## ABSTRACT
Hybrid nanostructures combine organic and inorganic materials to create efficient drug delivery platforms. These systems overcome limitations of conventional nanoparticles by leveraging synergistic properties of composite elements. This review covers design principles, synthesis methods, and clinical applications in drug delivery and therapy. These nanomaterials exhibit enhanced encapsulation efficiency, improved bioavailability, and superior biocompatibility. Classification into Category I (non-covalent) and Category II (covalent) systems enables rational design strategies. Therapeutic applications span cancer chemotherapy, gene therapy, infectious disease management, and diagnostic imaging. Targeting strategies using passive and active mechanisms significantly enhance efficacy. Despite manufacturing and clinical translation challenges, emerging trends in artificial intelligence-guided design and personalized medicine offer promising directions.

**Keywords:** Hybrid nanostructures; Drug delivery systems; Nanomedicine; Targeted therapy; Biocompatible nanomaterials

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## INTRODUCTION

### 1.1 Nanomaterials and Medical Applications

Nanomaterials with dimensions of 1-100 nanometers possess unique properties absent in bulk materials.[2] These materials can be organic, inorganic, or hybrid combinations, transforming pharmaceutical research.[2] A major drug development challenge involves improving targeted delivery to diseased tissues while minimizing effects on healthy cells. Traditional delivery systems suffer from poor solubility, inadequate bioavailability, toxicity, and inability to target specific disease sites.[7]

### 1.2 Hybrid Materials: Definition and Classification

Hybrid materials combine organic polymers, inorganic metals or minerals, or both.[1] By combining different materials, hybrid systems achieve superior characteristics compared to single-component nanoparticles. The resulting properties exceed the sum of individual components through the "hybrid interface effect."[1]

Hybrid materials classify into two categories:

• Category I: Components connected by weak forces (van der Waals, hydrogen bonds, electrostatic interactions)
• Category II: Components connected by strong covalent bonds[1]

### 1.3 Self-Assembly Mechanisms

Self-assembly processes enable components to spontaneously organize into desired structures through three stages: (1) initial organization via cooperative forces, (2) intermediate supramolecular interaction formation responsive to stimuli, and (3) final thermodynamically stable state with organized internal structure.[1]

### 1.4 Significance in Pharmaceutical Development

Polymer-hybrid nanoparticles selectively overcome biological barriers and accumulate in specific tissues, enabling lower therapeutic doses and reduced side effects.[1] Size, shape, surface properties, and internal structure are controllable through material selection and preparation methods. Early examples include gold-DNA conjugates (1997)[3] and silica-polymer hybrids (1998),[2] establishing foundation for current diverse applications.

## 2. FUNDAMENTALS OF HYBRID NANOSTRUCTURES

### 2.1 Material Composition

Hybrid nanostructures comprise:

• Organic-inorganic: Polymers or lipids with metals (gold, silver, iron) or minerals (silica, calcium carbonate)[1]
• Organic-organic: Different polymers or proteins combined together
• Metal-organic: Metal particles with polymers or peptides

Each combination demonstrates different properties regarding bodily processing and utilization compared to free drugs.[2]

### 2.2 Controllable Properties

Key properties controlled through design include:

• Size: 1-500 nm; smaller particles penetrate tissues better while larger particles carry more drug[7]



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• Shape: Spherical, rod-shaped, or disc-shaped configurations with different targeting capabilities
• Surface characteristics: Chemical modifications affecting biocompatibility, circulation time, and immune recognition[8]
• Internal structure: Solid to porous to hollow configurations affecting drug loading and release[9]

## 3. SYNTHESIS AND PREPARATION

### 3.1 Covalent Conjugation Methods

Strong chemical bonds between components create stable structures: Thiol-Based Attachment: Thiol-containing polymers bind to gold nanoparticles, creating systems that accumulate efficiently at tumors with extended blood circulation.[1] Cellular glutathione can break these bonds to release genetic material inside cells. Other Covalent Methods: Carboxyl and amino groups attach to nanoparticle surfaces. Polyethylene glycol (PEG) coating increases circulation time and reduces immune recognition.[1]

### 3.2 Non-Covalent Conjugation

Weak forces hold components together:
• Electrostatic interactions between oppositely charged molecules
• Hydrogen bonding between specific molecular groups
• Van der Waals forces and hydrophobic interactions[1]

### 3.3 Smart Surface Functionalization

Temperature-Responsive: Polymers compact at body temperature (37°C) but open at lower temperatures (4°C), allowing drug loading at cool temperatures and release at target sites. Ultrasound triggers additional release.

pH-Responsive: Polymers remain closed at neutral pH but open in acidic cancer cell environments.

Light-Responsive: Special molecules change structure when exposed to light, triggering drug release.

## 4. DRUG DELIVERY IMPROVEMENTS

### 4.1 Enhanced Encapsulation and Reduced Toxicity

Hybrid systems package drugs more efficiently than traditional nanoparticles.[15] Anticancer drugs like doxorubicin, paclitaxel, and cisplatin accumulate more in tumors with reduced accumulation in healthy tissues, minimizing harmful side effects.[14] Calcium carbonate-based structures load up to 92% nanoparticles by weight.

### 4.2 Improved Solubility and Stability

Many promising drugs fail due to water-insolubility. Hybrid systems improve solubility by surrounding drugs with water-loving molecules.[16] The protective structure prevents enzymatic breakdown, unwanted reactions, and immune clearance, significantly extending circulation time.[9]

### 4.3 Biocompatibility and Controlled Degradation

Biocompatible materials like silica, calcium carbonate, and biodegradable polymers allow nanoparticles to break down into harmless substances after drug delivery.[15] This reduces long-term toxicity compared to non-degradable systems.

### 4.4 Overcoming Biological Barriers

Properly designed hybrids penetrate the blood-brain barrier for neurological



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diseases, facilitate cellular uptake through endocytosis, escape intracellular compartments where nanoparticles accumulate (endosomal escape), and penetrate solid tumors effectively.[7]

## 5. THERAPEUTIC APPLICATIONS

### 5.1 Cancer Therapy

#### 5.1.1 Chemotherapy Delivery

Poorly soluble anticancer drugs in hybrid systems show superior tumor accumulation with reduced damage to cardiac and bone marrow tissues.[14] Doxorubicin hybrids reduce cardiotoxicity. Paclitaxel hybrids overcome extreme water-insolubility.[16] Platinum drugs deliver with fewer severe side effects.[24]

#### 5.1.2 Gene Delivery for Cancer

Small RNA molecules (siRNA) silence cancer-causing genes but degrade easily in blood and cannot enter cells.[19] Hybrid systems protect siRNA and facilitate cellular uptake, achieving higher transfection rates.[14] Plasmid DNA carrying entire genes can be delivered similarly.[27] Multiple genetic materials enable enhanced multi-gene therapy.

#### 5.1.3 Multi-Modal Therapy

Hybrid systems simultaneously deliver multiple drugs, combine chemotherapy with photosensitizers, or combine drugs with imaging agents.[28] Fluorescent dyes, radioactive isotopes, magnetic particles, or gold/silver nanoparticles enable visualization before drug release.[10] Theranostic systems combine therapy with simultaneous imaging for real-time monitoring.

### 5.2 Infectious Diseases

#### 5.2.1 Antiviral Applications

Direct Viral Inactivation: Silver nanoparticles coated with polyvinylpyrrolidone (PVP) damage virus particles directly. PVP-silver hybrids prevent HIV-1 attachment to cells and block multiple viral replication stages. Herpes simplex virus (HSV-1) is blocked by polymer nanospheres mimicking natural virus receptors. SARS-CoV-2 is inactivated by 10-nanometer PVP-coated silver particles.[31]

Improved Antiviral Drug Delivery: Hybrid poloxamer-lipid systems carrying antiretroviral drugs show significantly improved uptake and retention in immune cells.[27] Carbon nanotube hybrids coated with antibodies successfully deliver antiviral drugs across the blood-brain barrier.

#### 5.2.2 Antibacterial Applications

Hybrid nanostructures damage bacterial membranes, prevent biofilm formation, overcome antibiotic resistance, and effectively combine with antibiotics.[32] Silver and gold nanoparticle hybrids are particularly effective.

### 5.3 Diagnostic Imaging

MRI Imaging: Iron oxide and lanthanide elements in hybrid structures serve as MRI contrast agents.[8],[11] Some hybrids work with both T1 and T2 MRI sequences (dual-mode imaging), providing comprehensive information from single scans.[10] PEG coating extends circulation time for better vascular imaging.

Other Imaging Methods: Gold nanoparticle hybrids absorb near-infrared light and produce sound waves for photoacoustic



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imaging.[8] Fluorescent dyes and quantum dots enable real-time nanoparticle tracking. Theranostic Platforms: Combined drug delivery and imaging allows real-time monitoring of drug accumulation at target sites, confirmation of treatment delivery, and assessment of treatment response.[28]

### 5.4 Additional Applications

Hybrid systems address cardiovascular disease (anticoagulants, anti-inflammatory agents), neurological disorders (Alzheimer's and Parkinson's treatment through blood-brain barrier crossing), and regenerative medicine (tissue engineering scaffolds, bone repair, cartilage regeneration).

## 6. TARGETING STRATEGIES

### 6.1 Passive Targeting (EPR Effect)

Tumors and inflamed tissues contain abnormal blood vessels with larger gaps than normal vessels.[7] Nanoparticles pass through these gaps and accumulate in diseased tissue (enhanced permeability and retention effect). Optimal size ranges 10-100 nanometers—smaller particles undergo kidney filtration while larger ones cannot penetrate tissues.[9] This approach requires no targeting molecules but shows high patient and tumor variability.

### 6.2 Active Targeting

Antibody Conjugation: Specific antibodies recognize cancer cell targets and facilitate nanoparticle uptake.[14]

Peptide Targeting: GE11 peptides recognize growth factor receptors. RGD peptides recognize cell attachment proteins involved in tumor formation. Transferrin binds iron receptors often overexpressed on cancer cells.[7]

Carbohydrate and Receptor Targeting: Cancer cells express abnormal sugars or specific receptors. Nanoparticles displaying corresponding molecules achieve preferential uptake.

### 6.3 Stimuli-Responsive Release

pH-Responsive: Acidic cancer cell interiors trigger drug release through acid-labile bonds, polymer shape changes, or pore opening.

Temperature-Responsive: Polymers compact at body temperature but open at lower temperatures, allowing loading at cool temperatures and target-site release. Light and Ultrasound-Triggered: Photothermal heating or ultrasound breaks protective bonds or disrupts nanoparticles, releasing drugs on demand.

## 7. CHARACTERIZATION AND TESTING

### 7.1 Physicochemical Analysis

• Dynamic Light Scattering (DLS): Measures nanoparticle size uniformity
• Transmission Electron Microscopy (TEM): Shows precise shape and internal structure[2]
• Scanning Electron Microscopy (SEM): Displays 3D surface features
• Atomic Force Microscopy (AFM): Measures mechanical properties

### 7.2 Surface and Drug Properties

• Zeta Potential: Determines electrical charge, predicting stability and cellular interactions[8]
• Drug Encapsulation Efficiency: Measures percentage of drug successfully loaded
• Release Kinetics: Tests drug release under different pH, temperature, and stimuli conditions[9]



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### 7.3 Biological Testing

• Cell Uptake: Measures nanoparticle uptake in target versus off-target cells
• Cytotoxicity: Determines if nanoparticles damage cells[15]
• Biocompatibility: Tests blood compatibility, immune response, and organ safety

## 8. CHALLENGES AND LIMITATIONS

### 8.1 Manufacturing Issues

Producing nanoparticles with identical batch-to-batch properties remains difficult. Small variations in starting materials or procedures produce inconsistent results.[17] Manufacturing is expensive, and cost-effective large-scale production methods are still developing.

### 8.2 Stability and Storage

Nanoparticles may aggregate over time, drugs may leak, or surfaces may change.[18] Many require refrigeration, increasing costs. Determining realistic shelf-lives requires extended testing.

### 8.3 Regulatory and Safety

FDA approval pathways for nanoparticle drugs are evolving. Systematic toxicity testing addresses acute, chronic, and organ-specific effects.[21] Immunogenicity (triggering immune responses) and environmental fate after excretion require better understanding.

### 8.4 Clinical Translation

Laboratory results often disappoint in living organisms.[29] Immediate immune recognition, accumulation in liver and spleen instead of target tissue, and enzymatic degradation before reaching targets are common.[30] Individual patient variability challenges consistent efficacy.

## 9. FUTURE PERSPECTIVES

### 9.1 Computational and AI Design

Artificial intelligence and computational methods predict optimal material combinations, surface modifications, and biological behavior before synthesis, accelerating discovery.

### 9.2 Personalized Medicine

Future systems will customize formulations for individual patients based on genetic makeup, tumor characteristics, immune status, and organ function. Real-time imaging enables treatment adjustment during therapy based on response.

### 9.3 Novel Material Combinations

New polymer-inorganic combinations continue exploration.[1] Biomimetic approaches copy natural principles (cell membrane coatings, protein surfaces, natural targeting). Plant-based polymers and natural proteins offer improved biocompatibility.

### 9.4 Clinical Development Pipeline

Multiple formulations are in clinical trials for various cancers.[14] Several are in Phase II-III trials with encouraging results.[30] First regulatory approvals are expected within 5-10 years.

## 10. CONCLUSION

Hybrid nanostructures represent a genuine breakthrough combining organic and inorganic materials for superior drug delivery.[1] The field progressed from basic research (1997-2005) through diverse application development (2005-2015) to current clinical translation (2015-present). Fundamental science is established and



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practical implementations prove successful.

These systems offer key advantages: reduced side effects through tissue-specific targeting, improved efficacy through higher target site concentrations, and new treatment options for previously untreatable diseases.[14] Combined therapy-diagnosis systems enable simultaneous treatment and monitoring.

The field remains young with regular major breakthroughs.[14] Continued effort in manufacturing optimization, regulatory navigation, and clinical efficacy improvement is required. Preliminary clinical results are encouraging.[14]

In summary, hybrid nanostructures offer transformative potential for revolutionizing disease treatment within the next decade.

**ACKNOWLEDGEMENT**

The authors are highly thankful to the management of SIKSHA 'O' Anusandhan University for constant support.

**Conflict of Interest**

Nil

**REFERENCES**

1. Mehdi A, Reye C, Corriu R. From molecular chemistry to hybrid nanomaterials. Design and functionalization. Chem Soc Rev. 2011;40(2):563-74.

2. Caruso F, Caruso RA, Möhwald H. Nanoengineering of inorganic and hybrid hollow spheres by colloidal templating. Science. 1998 Nov 6;282(5391):1111-4.

3. Elghanian R, Storhoff JJ, Mucic RC, Letsinger RL, Mirkin CA. Selective colorimetric detection of polynucleotides based on the distance-dependent optical properties of gold nanoparticles. Science. 1997 Aug 22;277(5329):1078-81.

4. Park YI, Lee KT, Suh YD, Hyeon T. Upconverting nanoparticles: a versatile platform for wide-field two-photon microscopy and multi-modal in vivo imaging. Chem Soc Rev. 2015;44(6):1302-17.

5. Pradhan N, Adhikari SD, Nag A, Sarma DD. Luminescence, plasmonic, and magnetic properties of doped semiconductor nanocrystals. Angew Chem Int Ed Engl. 2017 Jun 12;56(25):7038-54.

6. Larson AM. Multiphoton microscopy. Nat Photonics. 2011;5(1):1-9.

7. Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. Nat Biotechnol. 2015 Sep;33(9):941-51.

8. Kim D, Kim J, Park YI, Lee N, Hyeon T. Recent development of inorganic nanoparticles for biomedical imaging. ACS Cent Sci. 2018 Mar 28;4(3):324-36.

9. Wei Y, Quan L, Zhou C, Zhan Q. Factors relating to the biodistribution and clearance of nanoparticles and their effects on in vivo application. Nanomedicine (Lond). 2018 Jun;13(12):1495-512.

10. Wang J, Jia Y, Wang Q, Liang Z, Han G, Wang Z, et al. An ultrahigh-field-tailored T1-T2 dual-mode MRI contrast agent for high-performance vascular imaging. Adv Mater. 2021 Jan;33(2):e2004917.

11. Yi Z, Xiao S, Peng J, Zhang S. Lanthanide-activated nanoparticles: a



toolbox for bioimaging, therapeutics, and neuromodulation. Acc Chem Res. 2020;54(1):4-12.

12. Ferrari M. Cancer nanotechnology: opportunities and challenges. Nat Rev Cancer. 2005 Mar;5(3):161-71.

13. He C, Lu J, Lin W. Nanosized complexes of iron(III) alkyldithiocarbamate: synthesis, characterization, and application to drug delivery. J Control Release. 2015 Aug 28;219:224-35.

14. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. Nat Rev Cancer. 2017 Jan;17(1):20-37.

15. Tarn D, Ashley CE, Xue M, Carnes EC, Zink JI, Brinker CJ. Mesoporous silica nanoparticle nanocarriers: biofunctionality and biocompatibility. Acc Chem Res. 2013 Mar 19;46(3):792-801.

16. Paris JL, Cabañas MV, Manzano M, Vallet-Regí M. Polymer-gated mesoporous silica nanoparticles for controlled drug delivery. ACS Nano. 2015;9(11):11023-33.

17. Jain TK, Morales MA, Sahoo SK, Leslie-Pelecky DL, Labhasetwar V. Iron oxide nanoparticles for sustained delivery of anticancer agents. Mol Pharm. 2005;2(3):194-205.

18. Kim HJ, Takemoto H, Yi Y, Zheng M, Maeda Y, Chaya H, et al. Polyamidoamine dendrimer-based MRI contrast agents with PEG-derived cores and a high generation number. ACS Macro Lett. 2014;3(8):800-5.

19. Li J, Wang Y, Zhao MX, Tan CP, Li YQ, Le XY, et al. Multifunctional quantum-dot-based siRNA delivery for HPV18 E6 gene silencing and intracellular imaging in cervical cancer cells. Biomaterials. 2012 Jul;33(20):5420-9.

20. Shen J, Zhang W, Qi R, Wang ZW, Mao S, Shen H. Lanthanide nanoparticles-based immunoseparation of rare circulating tumor cells from blood samples for high detection sensitivity. Chem Soc Rev. 2018;47(6):1969-2002.

21. Califano A, Alvarez MJ. A systems-level cancer cell state transition mechanism. Nat Rev Cancer. 2017 Jun;17(6):116.

22. Christie EL, Bowtell DD. Architectural drivers of chromatin rewiring in cancer. Ann Oncol. 2017 Sep;28(Suppl 8):viii13-viii20.

23. Argyriou AA, Bruna J, Genazzani AA, Cavaletti G. Neuropathogenesis in cancer-related neuropathies. Nat Rev Neurol. 2017 Aug;13(8):492-504.

24. Meijer TW, Kaanders JH, Span PN, Bussink J. Targeting hypoxia, HIF-1α and tumor metabolism for improved cancer care. Clin Cancer Res. 2012 Sep 15;18(18):5585-94.

25. Zhang M, Atkinson RL, Rosen JM. MMTV-c-erbB-2 transgenic mice develop metastatic mammary carcinoma. Proc Natl Acad Sci USA. 2010 Feb 16;107(7):3522-7.

26. Kaufmann KB, Büning H, Galy A, Schambach A, Grez M. Gene therapy on the move. EMBO Mol Med. 2013;5(11):1642-54.

27. Dong Y, Siegwart DJ, Anderson DG. Nanoparticles for gene delivery and gene therapy. Adv Drug Deliv Rev. 2019 Aug;144:133-47.

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28. Cucchiarini M, Madry H. Gene therapy approaches for regenerative medicine. Nat Rev Rheumatol. 2019 Jan;15(1):18-29.

29. Fritz JM, Lenardo MJ. Development of immunological tolerance promoted by Th1 cells. J Exp Med. 2019;216(6):1244-54.

30. Mi Y, Hagan CT, Vincent BG, Wang AZ. Emerging nano-immunomodulatory strategies for cancer immunotherapy. Adv Sci. 2019;6(7):1801847.

31. Xu R, Zhang G, Mai J, Deng X, Segura-Ibarra V, Wu S, et al. An injectable nanoparticle generator enhances delivery of cancer therapeutics. Nat Biotechnol. 2016;34(4):414-8.

32. Salvador-Morales C, Valencia PM, Thakkar AB, Swanson EW, Langer R. Nanoparticles for cancer imaging and therapy. Front Biosci. 2012 Jun 1;4:529-44.

33. Jabr-Milane LS, van Vlerken LE, Yadav S, Amiji MM. Multi-functional nanoparticles for targeted drug delivery and imaging. Cancer Treat Rev. 2008;34(7):592-602.