Comprehensive Review on Dendrimers and Approach to Multiples

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Abstract—Dendrimers are structurally sophisticated, highly branched polymeric nanoparticles distinguished by their uniform size, precise molecular architecture, and three-dimensional tree-like configuration. Their structure is composed of a central core from which successive layers of repeating branching units, known as generations, extend outward, culminating in numerous reactive terminal functional groups. Due to their nanoscale dimensions (generally ranging from 1–10 nm), controlled molecular weight, and high density of surface functionalities, dendrimers have gained considerable attention as advanced nanocarriers in pharmaceutical and biomedical research. The presence of internal cavities allows the encapsulation of therapeutic molecules, while the abundant surface groups enable covalent attachment of drugs, targeting ligands, and diagnostic agents, thereby facilitating multifunctional delivery within a single nanosystem.

Several classes of dendrimers, including poly(amidoamine) (PAMAM), poly(propylene imine) (PPI), and polyester-based dendrimers, have been extensively explored for drug delivery applications. These nanosystems significantly improve the solubility, physicochemical stability, bioavailability, and controlled release behavior of poorly water-soluble drugs. In the field of gene therapy, positively charged (cationic) dendrimers readily interact with negatively charged nucleic acids, forming stable complexes that protect genetic material from enzymatic degradation and enhance intracellular transport. Moreover, advanced surface modification techniques have enabled the design of targeted, stimuli-responsive, and biocompatible dendrimer formulations tailored to specific therapeutic requirements.

Although dendrimers offer notable advantages such as structural uniformity, high loading capacity, and multifunctionality, certain limitations remain. Challenges including complex multi-step synthesis, difficulties in large-scale production, potential cytotoxicity—particularly with highly cationic surfaces—and limited biodegradability must be carefully considered. Current research efforts are therefore directed toward the development of safer, biodegradable, and clinically translatable dendrimer systems with improved therapeutic performance and reduced toxicity.

In summary, dendrimers constitute a highly promising category of polymeric nanoparticles with wide-ranging applications in drug delivery, gene therapy, diagnostic imaging, and nanomedicine, holding substantial potential for future clinical advancements.

Index Terms—Dendrimers, Polymeric nanoparticles, Nanocarrier systems, Drug delivery, Gene therapy, Surface modification, Targeted therapy, Nanomedicine.

I. INTRODUCTION

Nanotechnology has profoundly influenced modern pharmaceutical research by enabling the development of nanoscale delivery systems that improve drug solubility, enhance therapeutic efficiency, minimize systemic toxicity, and enable site-specific targeting (1,2). Conventional drug delivery systems frequently encounter challenges such as poor aqueous solubility, rapid metabolic degradation, limited bioavailability, and nonspecific biodistribution. Polymeric nanoparticles have therefore emerged as promising carriers due to their controlled release properties, structural versatility, and improved pharmacokinetic profiles (3). Among these systems, dendrimers represent a uniquely engineered and highly sophisticated class of polymeric nanoparticles characterized by precise molecular architecture, monodispersity, and multifunctional surface characteristics (4).

Dendrimers are synthetic, highly branched macromolecules constructed in a stepwise manner around a multifunctional core. Their architecture consists of three principal components: a central core, repeated branching layers known as generations, and numerous terminal functional groups distributed uniformly on the surface (5). With each successive generation, the dendrimer increases in molecular weight, size, and surface group density, ultimately forming a compact and nearly spherical nanostructure (6). Unlike conventional linear polymers that exhibit broad molecular weight distribution, dendrimers are monodisperse systems with precisely controlled size and shape, typically ranging between 1–10 nm depending on the generation (7). This nanoscale dimension allows dendrimers to interact efficiently with biological membranes and cellular components, enhancing their biomedical applicability.

One of the most distinctive features of dendrimers is the presence of internal nanocavities created by their branched architecture. These cavities serve as reservoirs for therapeutic agents and allow drug encapsulation through hydrophobic interactions, hydrogen bonding, or electrostatic forces (8). In addition to internal entrapment, the large number of terminal functional groups on the dendrimer surface enables covalent conjugation of drugs, targeting ligands, imaging probes, and solubility-enhancing polymers (9). This dual mechanism of drug incorporation—encapsulation within the core and conjugation to the surface—provides exceptional multifunctionality and controlled drug delivery potential.

Mechanism of Drug Delivery by Dendrimers

Dendrimers exhibit multiple mechanisms through which they enhance therapeutic delivery and efficacy:

1. Drug Encapsulation Mechanism

Hydrophobic or hydrophilic drug molecules can be physically entrapped within the internal cavities of dendrimers. The mechanism involves:

- Hydrophobic interactions between nonpolar drug molecules and the dendrimer interior.
- Hydrogen bonding between drug molecules and internal amide or ether linkages.
- Electrostatic interactions in the case of charged drugs.

This encapsulation improves aqueous solubility of poorly soluble drugs and protects them from premature degradation (10).

2. Surface Conjugation Mechanism

Drugs may be covalently attached to terminal functional groups of dendrimers via cleavable linkers. Drug release occurs through:

- Hydrolysis of ester or amide bonds,
- Enzymatic cleavage,
- pH-sensitive bond disruption in acidic tumor microenvironments.

This mechanism allows controlled and stimuli-responsive drug release, enhancing therapeutic specificity (11).

3. Gene Delivery Mechanism

Cationic dendrimers such as PAMAM and PPI contain positively charged amine groups that electrostatically bind negatively charged DNA or RNA molecules, forming compact complexes known as dendriplexes (12). These dendriplexes:

- Protect nucleic acids from enzymatic degradation,
- Facilitate cellular uptake via endocytosis,
- Promote endosomal escape through the "proton sponge effect," where buffering capacity of amine groups leads to osmotic swelling and rupture of endosomes, releasing genetic material into the cytoplasm (13).

4. Targeted Delivery Mechanism

Surface modification with targeting ligands such as folic acid, antibodies, or peptides enables receptor-mediated endocytosis. Upon binding to overexpressed receptors on cancer cells, dendrimer-drug conjugates are internalized selectively, reducing off-target toxicity (14).

5. Enhanced Permeation and Retention (EPR) Effect

Due to their nanoscale size, dendrimers can passively accumulate in tumor tissues through the enhanced permeation and retention effect, where leaky tumor vasculature allows nanoparticle penetration and retention (15).

Types of Dendrimers in Biomedical Applications

Several dendrimer families have been extensively studied:

- Poly(amidoamine) (PAMAM) dendrimers, widely used in drug and gene delivery due to their well-defined structure and high amine density (16).
- Poly(propylene imine) (PPI) dendrimers, known for strong DNA binding capacity (17).
- Polyester dendrimers, valued for improved biodegradability (18).
- Carbosilane and peptide-based dendrimers, investigated for antimicrobial and anticancer applications (19).

Advantages and Challenges

Dendrimers offer several advantages including high drug loading capacity, controlled release behavior, precise structural control, and multifunctional surface modification capability (20). However, certain challenges remain, such as complex multistep synthesis, high production cost, scalability issues, and potential cytotoxicity—particularly with highly cationic surfaces that may disrupt cellular membranes (21). Surface modification strategies such as PEGylation, acetylation, and incorporation of biodegradable linkages are being developed to mitigate toxicity and improve clinical translation (22).

Dendrimers represent an advanced class of polymeric nanoparticles distinguished by their well-defined architecture, nanoscale dimensions, and adaptable surface chemistry. Through mechanisms including drug encapsulation, surface conjugation, gene complexation, receptor-mediated targeting, and the proton sponge effect, dendrimers enhance therapeutic efficacy and specificity. Ongoing research is focused on designing biodegradable, biocompatible, and stimuli-responsive dendrimer systems to expand their clinical applications in nanomedicine (23,24).

The continuous advancement of nanotechnology has significantly reshaped contemporary drug delivery strategies by enabling the development of nanoscale carrier systems that enhance therapeutic efficiency, minimize systemic toxicity, and improve site-specific targeting accuracy (30,31). Numerous nanocarriers—including liposomes, polymeric nanoparticles, micelles, hydrogels, and lipid-based nanoparticles—have been extensively explored for optimizing drug pharmacokinetics and biodistribution. Despite their advantages, conventional nanocarrier systems often encounter challenges such as premature drug leakage, insufficient structural stability, rapid clearance by the reticuloendothelial system (RES), and limited targeting capability (32). These shortcomings have driven the emergence of hybrid nanosystems designed to integrate the strengths of multiple delivery platforms.

Dendrimers have emerged as highly promising components within such hybrid systems due to their precisely engineered molecular architecture, nanoscale uniformity, high density of surface functional groups, and well-defined internal cavities (33). Their structural features enable multiple drug delivery mechanisms, including internal drug encapsulation, covalent surface conjugation, electrostatic complexation with charged biomolecules, and stimuli-responsive release triggered by environmental factors such as pH or enzymatic activity (34). When incorporated into liposomes and other nanocarrier systems, dendrimers substantially enhance

drug loading capacity, improve stability, facilitate active targeting, and provide controlled and sustained drug release (35).

II. ROLE OF DENDRIMERS IN LIPOSOMAL DRUG DELIVERY

2.1 Overview of Liposomes

Liposomes are spherical vesicular systems composed of one or more phospholipid bilayers enclosing an aqueous core (36). Due to their structural resemblance to biological membranes, they demonstrate excellent biocompatibility and biodegradability. Liposomes are capable of encapsulating hydrophilic drugs within their aqueous core and lipophilic drugs within the lipid bilayer region. However, despite their clinical relevance, liposomes present limitations such as drug leakage during storage or circulation, limited encapsulation efficiency, rapid uptake by the RES, and in some cases, inadequate intracellular delivery (37). The incorporation of dendrimers into liposomal formulations has been proposed as a strategy to overcome these limitations.

2.2 Dendrimer–Liposome Hybrid Systems (Dendrosomes)

Hybrid nanocarriers formed by combining dendrimers and liposomes are commonly referred to as dendrosomes (38). These systems synergistically integrate the structural precision and multifunctionality of dendrimers with the membrane compatibility and biocompatibility of liposomes.

Mechanisms of Action

1. Dual Drug Loading Mechanism

In dendrosomal systems:

- Drug molecules are initially encapsulated within dendrimer internal cavities through hydrophobic or electrostatic interactions.
- These drug-loaded dendrimers are subsequently entrapped inside liposomes.

This “carrier-within-carrier” strategy significantly increases overall drug entrapment efficiency and reduces premature drug leakage (39).

2. Stabilization of the Liposomal Bilayer

Electrostatic interactions between dendrimer surface functional groups and phospholipid head groups strengthen the integrity of the lipid bilayer. This interaction enhances membrane stability and minimizes drug diffusion during systemic circulation (40).

3. Controlled and Stimuli-Responsive Release

Drug release from dendrimer-liposome hybrids may occur through multiple coordinated pathways:

- Diffusion of drug from dendrimer cavities
- Liposomal membrane destabilization

- pH-sensitive bond cleavage in acidic tumor environments
- Enzymatic degradation within target tissues

These mechanisms promote sustained and site-specific therapeutic delivery (41).

4. Enhanced Cellular Uptake

Surface-functionalized dendrimers can be conjugated with targeting ligands such as folate or peptides, facilitating receptor-mediated endocytosis and improving intracellular drug accumulation (42).

2.3 Applications in Cancer Therapy

Dendrimer-liposome hybrid systems demonstrate significant potential in cancer treatment due to:

- Passive targeting through the Enhanced Permeation and Retention (EPR) effect (43)
- Active targeting via ligand-functionalized dendrimer surfaces
- Simultaneous co-delivery of chemotherapeutic agents and genetic materials such as siRNA
- Reduced systemic toxicity compared to conventional chemotherapy

Examples include dendrimer-enhanced liposomal doxorubicin formulations and gene-loaded dendrosomal delivery systems designed for improved anticancer efficacy (44).

III. ROLE OF DENDRIMERS IN OTHER DRUG DELIVERY SYSTEMS

Delivery System	Mechanism	Major Advantage	Application
Direct Dendrimer	Encapsulation/Conjugation	High drug loading	Cancer therapy
Liposomal Hybrid	Dual loading	Enhanced stability	Oncology
Polymeric NP	Matrix embedding	Sustained release	Long-term therapy
Micelles	Core loading	Solubility enhancement	Hydrophobic drugs
Hydrogel	Diffusion control	Localized therapy	Wound healing
Gene Delivery	Dendriplex formation	Efficient transfection	Gene therapy

3.1 Dendrimers in Polymeric Nanoparticles

Biodegradable polymers such as PLGA are widely utilized for sustained drug delivery applications (45). The incorporation of dendrimers into polymeric nanoparticles enhances therapeutic performance and drug stability.

Mechanism

- Drug-dendrimer complexes are embedded within the biodegradable polymer matrix.
- Controlled polymer degradation governs sustained drug release.
- Dendrimers enhance solubility and increase drug loading capacity (46).

Advantages

- Reduction of initial burst release
- Prolonged therapeutic effect
- Improved pharmacokinetic profile

- Enhanced tissue penetration

3.2 Dendrimers in Micellar Systems

Polymeric micelles are amphiphilic self-assembled nanostructures designed for solubilizing hydrophobic drugs (47).

Mechanism

- Hydrophobic drugs are encapsulated within dendrimer interiors.
- The micellar shell provides steric stabilization and protects the complex during systemic circulation.

This synergistic system improves solubility and extends circulation time (48).

Therapeutic Benefits

- Enhanced oral bioavailability
- Increased tumor accumulation
- Reduced off-target toxicity

3.3 Dendrimers in Hydrogel-Based Systems

Dendrimers are incorporated into hydrogel matrices to enable localized and controlled drug delivery (49).

Mechanism

- Drug-loaded dendrimers are dispersed within the hydrogel network.
- Drug release is governed by diffusion, hydrogel swelling behavior, and matrix degradation kinetics.

Applications

- Wound healing
- Transdermal drug delivery
- Ocular therapy
- Anti-inflammatory treatment

3.4 Dendrimers in Gene Delivery Systems

Cationic dendrimers serve as efficient non-viral vectors for gene delivery (50).

Mechanism of Gene Delivery

1. Electrostatic interaction between positively charged dendrimer amine groups and negatively charged DNA/RNA
2. Formation of compact dendrimer–nucleic acid complexes (dendriplexes)
3. Cellular internalization via endocytosis
4. Proton sponge effect:
   - Amine groups buffer endosomal pH
   - Osmotic swelling leads to endosomal rupture
   - Release of genetic material into the cytoplasm (51)

Combining dendrimers with liposomes improves transfection efficiency while reducing cytotoxicity (52).

Comparative Overview

Hybrid dendrimer-based systems exhibit superior performance compared to individual carriers (53).

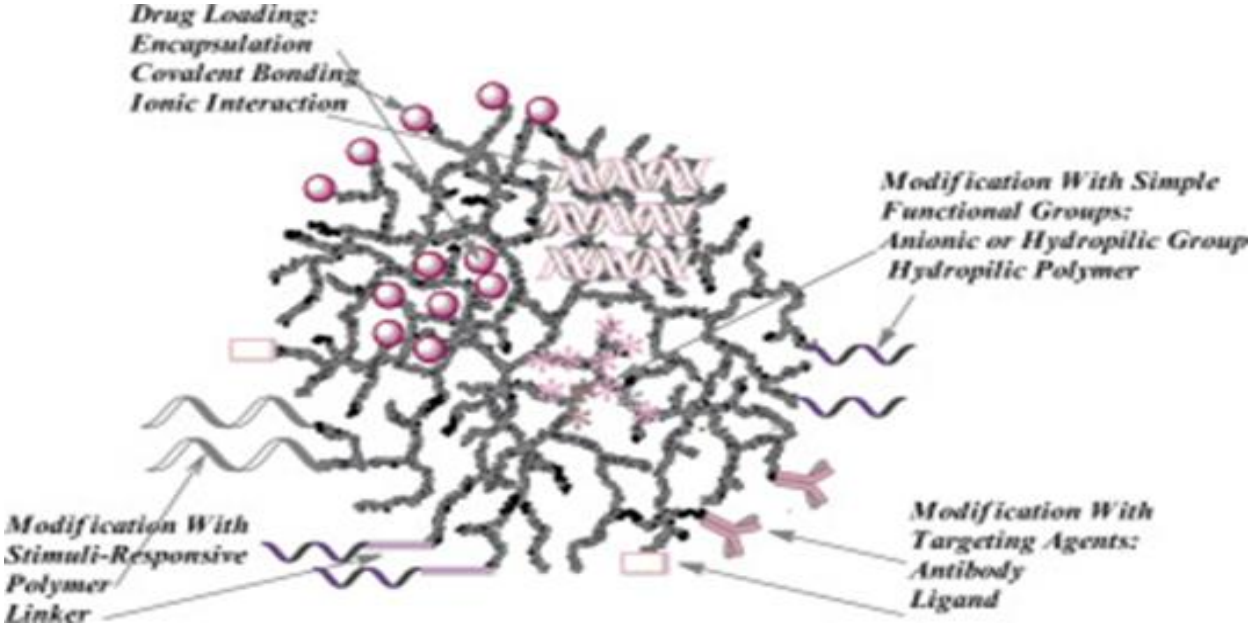
Parameter	Liposomes	Dendrimers	Hybrid Systems
Drug Loading	Moderate	High	Very High
Stability	Moderate	High	Significantly Enhanced
Targeting Efficiency	Limited	Tunable	Superior
Gene Delivery	Limited	Efficient	Optimized
Controlled Release	Moderate	Adjustable	Highly Controlled

Formulation Strategies of Dendrimers with Mechanisms and Therapeutic Applications

Dendrimers are nanosized, highly branched polymeric systems that can be engineered either as standalone nanocarriers or as integral components of hybrid drug delivery platforms. The formulation design is influenced by several factors, including the dendrimer type (such as PAMAM, PPI, polyester, or peptide-based dendrimers), the physicochemical characteristics of the drug (hydrophilic or hydrophobic), and the intended route of administration (oral, parenteral, topical, nasal, or ocular). Their adaptable surface chemistry and internal nanocavities allow customization according to therapeutic requirements.

1. Formulation Approaches of Dendrimers

1.1 Drug Encapsulation (Physical Entrapment Method)



Formulation Process

1. Selection of an appropriate dendrimer generation (commonly G2–G5 for optimal balance of size and functionality).
2. Dissolution of dendrimer in a suitable solvent, usually aqueous medium.
3. Gradual addition of the therapeutic agent under continuous stirring.
4. Formation of a host–guest complex through intermolecular interactions such as:
   - Hydrophobic forces
   - Hydrogen bonding
   - Electrostatic interactions

Removal Of Unbound Drug Via Dialysis Or Filtration

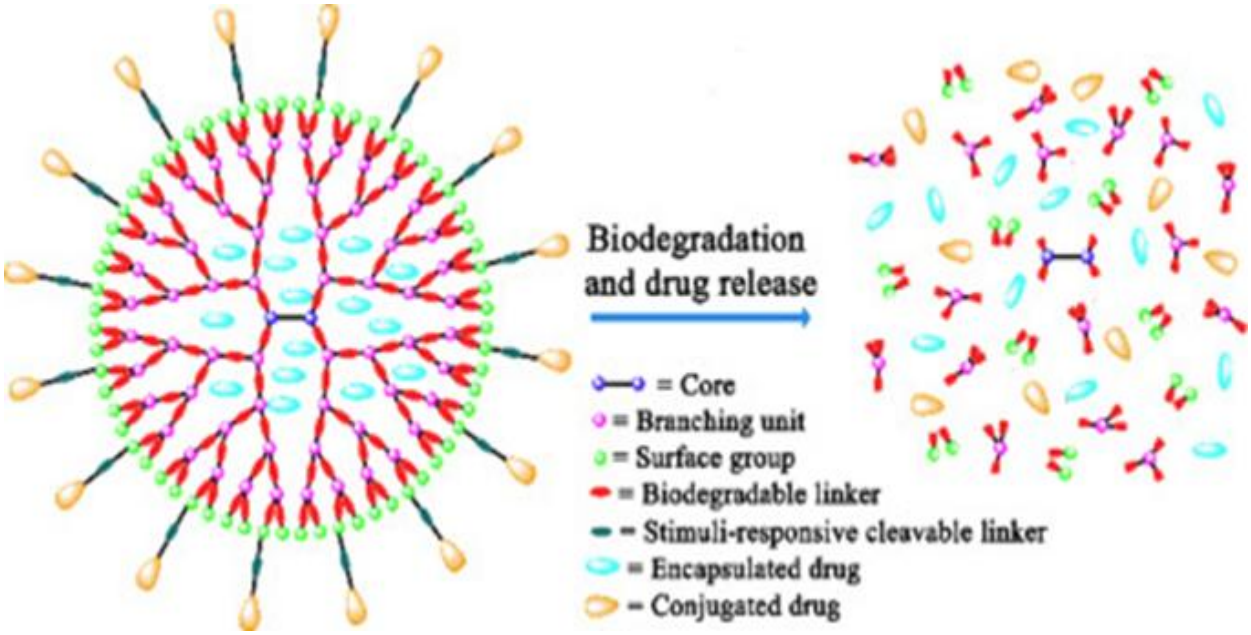
Mode of Action

In this system, drug molecules are physically entrapped within the internal cavities of the dendrimer. This entrapment improves aqueous solubility of poorly soluble drugs and protects them from premature degradation. Drug release typically occurs through diffusion-controlled mechanisms. In cancer therapy, the nanoscale size enables passive targeting through the Enhanced Permeation and Retention (EPR) effect.

Therapeutic Applications

- Anticancer agents (e.g., doxorubicin, methotrexate)
- Anti-inflammatory medications
- Antifungal and antimicrobial drugs

1.2 Surface Conjugation (Covalent Attachment Method)



Formulation Process

1. Activation of terminal functional groups on dendrimer surface (–NH_2, –COOH, –OH).

2. Covalent coupling of drug molecules via cleavable linkers such as ester or amide bonds.
3. Optional conjugation of targeting ligands (e.g., folic acid, antibodies).
4. Purification and physicochemical characterization.

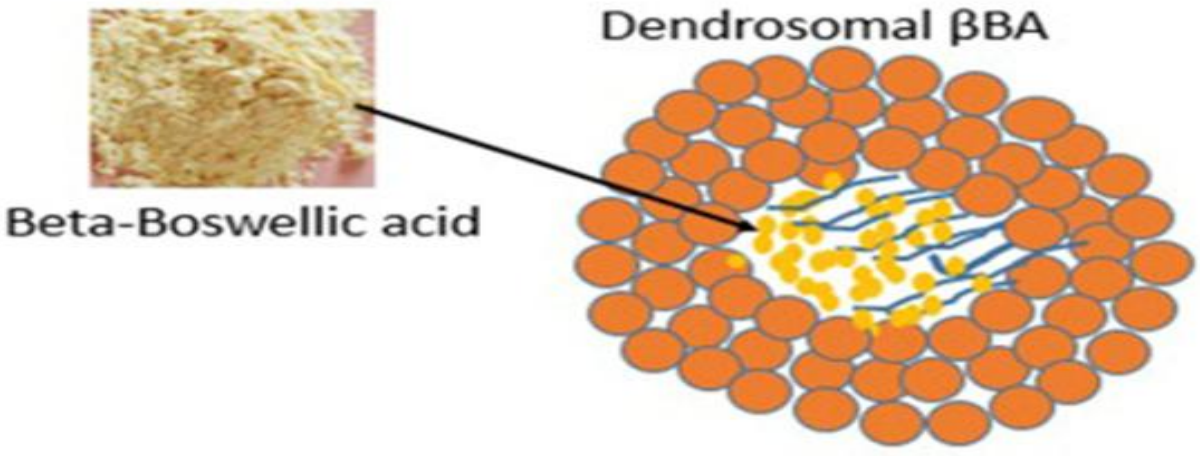
Mode of Action

Drugs are chemically bonded to the dendrimer surface, enabling controlled and stimuli-responsive release. Drug liberation occurs through mechanisms such as hydrolysis, enzymatic degradation, or pH-sensitive cleavage within the tumor microenvironment. When targeting ligands are attached, receptor-mediated endocytosis enhances selective cellular uptake.

Therapeutic Applications

- Targeted cancer therapy
- Brain-targeted drug delivery
- Treatment of rheumatoid arthritis and chronic inflammatory disorders

1.3 Dendrimer–Liposome Hybrid Systems (Dendrosomes)



Formulation Process

1. Initial loading of drug into dendrimer (via encapsulation or conjugation).
2. Preparation of liposomes using thin-film hydration technique.
3. Encapsulation of drug-loaded dendrimer into liposomal vesicles.
4. Size optimization through sonication or extrusion.

Mode of Action

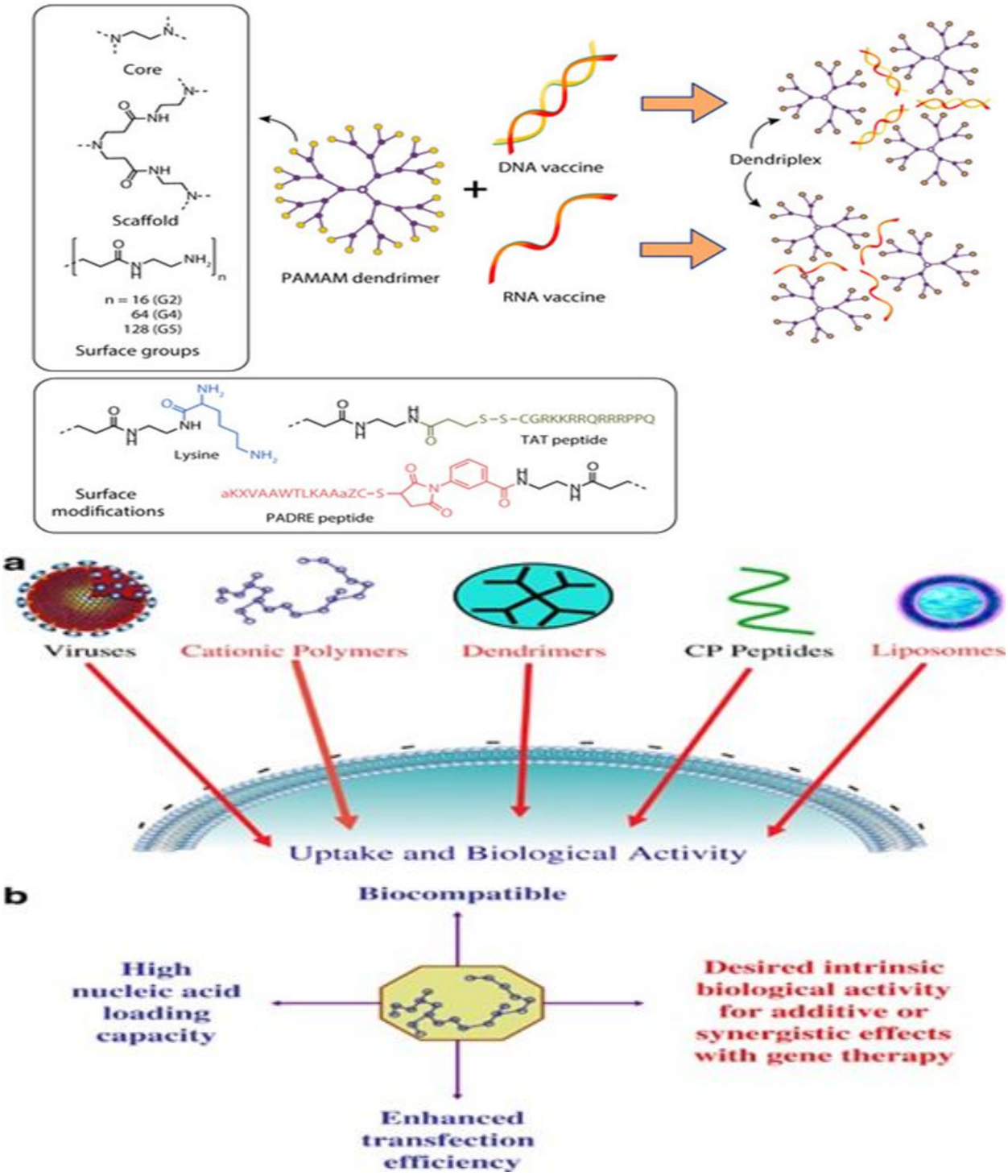
This hybrid system allows dual drug loading. The liposomal bilayer protects the dendrimer complex, enhancing stability and circulation time. Drug release occurs in a controlled manner, while targeting efficiency is improved through both passive and active mechanisms.

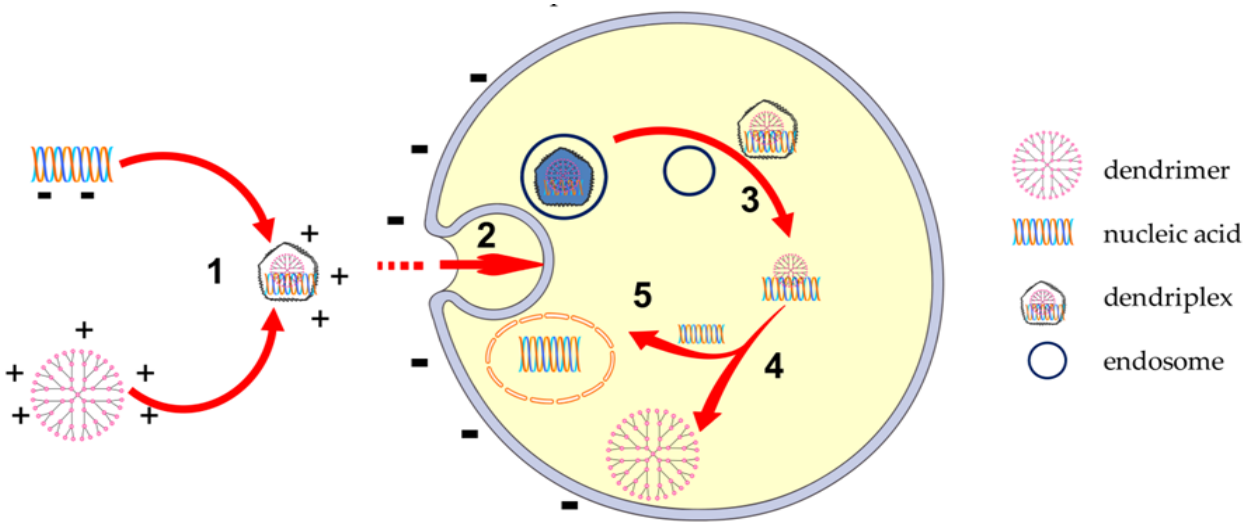
Therapeutic Applications

- Combination chemotherapy
- Co-delivery of drug and gene

- Antiviral therapy

1.4 Gene Delivery Systems (Dendriplex Formation)





Formulation Process

1. Mixing of cationic dendrimer with negatively charged DNA or siRNA.
2. Formation of electrostatic complexes (dendriplexes).
3. Optimization of nitrogen-to-phosphate (N/P) ratio.
4. Characterization of particle size and zeta potential.

Mode of Action

The positively charged dendrimer binds nucleic acids, forming stable nanoscale complexes. These are internalized into cells via endocytosis. The proton sponge effect—caused by buffering of endosomal pH—induces osmotic swelling and endosomal rupture, releasing genetic material into the cytoplasm for therapeutic action.

Therapeutic Applications

- Gene therapy
- siRNA-mediated silencing
- CRISPR-based genome editing

2. Comparative Overview of Dendrimer Formulation Strategies

Formulation Strategy	Preparation Technique	Mechanism of Action	Key Advantage	Major Therapeutic Use
Drug Encapsulation	Physical entrapment	Diffusion-controlled release	Solubility enhancement	Cancer, Anti-inflammatory
Surface Conjugation	Covalent linking	Stimuli-responsive cleavage	Target specificity	Oncology, Arthritis
Dendrimer–Liposome Hybrid	Liposomal encapsulation	Dual protection and controlled release	Improved stability	Cancer, Antiviral
Gene Delivery	Electrostatic	Proton sponge-	Efficient	Gene therapy

(Dendriplex)	complexation	mediated escape	transfection	
Hydrogel Integration	Polymer matrix embedding	Diffusion and matrix degradation	Localized therapy	Wound healing
Micellar Hybrid	Core–shell self-assembly	Solubilization and prolonged circulation	Increased bioavailability	Hydrophobic drugs

IV. ADVANTAGES OF DENDRIMER-BASED FORMULATIONS

- High drug loading efficiency due to multivalent structure.
- Controlled and sustained drug release.
- Improved pharmacokinetic profile.
- Targeted delivery through surface modification.
- Enhanced solubility of hydrophobic drugs.

V. LIMITATIONS

- Potential cytotoxicity, especially with highly cationic dendrimers.
- Multistep and complex synthesis procedures.
- High production costs.
- Regulatory and clinical translation challenges.

Pharmacological Profile of Dendrimers

Dendrimers are nanosized, three-dimensional, highly branched polymeric macromolecules characterized by a precisely controlled architecture and a high density of functional groups on their surface. Their structural uniformity (monodispersity), internal nanocavities, and modifiable surface chemistry provide exceptional flexibility in pharmaceutical applications. Because of these attributes, dendrimers serve not only as advanced nanocarriers for drug delivery but, in certain cases, also act as pharmacologically active agents. Their ability to modulate drug solubility, stability, biodistribution, and release kinetics distinguishes them from conventional small-molecule therapeutics.

1. Pharmacokinetics of Dendrimers (ADME Profile)

The pharmacokinetic behavior of dendrimers depends largely on their generation, size, surface charge, chemical composition, and route of administration. These parameters collectively influence absorption, distribution, metabolism, and excretion.

1.1 Absorption

Absorption characteristics vary according to molecular size and surface properties. Lower-generation dendrimers (G0–G3) possess smaller hydrodynamic diameters and may cross epithelial barriers more readily than higher-generation analogues. Surface charge plays a critical

role; cationic dendrimers interact strongly with negatively charged biological membranes, thereby enhancing mucosal penetration. Surface engineering strategies such as PEGylation improve permeability and systemic bioavailability by reducing aggregation and increasing stability. In transdermal and intranasal delivery, dendrimers can temporarily loosen tight junctions and enhance epithelial transport, promoting improved drug absorption.

1.2 Distribution

Following systemic administration, dendrimer distribution is governed by molecular size and surface chemistry. Smaller dendrimers may traverse certain biological barriers more efficiently, while larger generations tend to remain within the vascular compartment. In oncology, dendrimers accumulate in tumor tissue through the Enhanced Permeation and Retention (EPR) effect, a phenomenon resulting from leaky tumor vasculature and impaired lymphatic drainage. Additionally, conjugation of targeting ligands enables active targeting of specific tissues such as cancer cells or inflamed tissues. Typically, nanoparticles—including dendrimers—show distribution to the liver and spleen due to uptake by the mononuclear phagocyte system, whereas smaller dendrimers may undergo renal filtration. Tumor tissues often demonstrate enhanced passive accumulation.

1.3 Metabolism

Metabolic stability depends on dendrimer composition. Biodegradable dendrimers, such as polyester- and peptide-based systems, undergo enzymatic or hydrolytic degradation into smaller, biocompatible fragments. In contrast, non-biodegradable dendrimers like PAMAM and PPI exhibit greater metabolic resistance, potentially prolonging systemic circulation. Surface modifications significantly influence metabolic pathways, as neutral or PEGylated surfaces may reduce recognition by metabolic enzymes.

1.4 Excretion

Excretion mechanisms are primarily size-dependent. Lower-generation dendrimers with diameters below approximately 5–6 nm may be eliminated through renal filtration. Larger dendrimers are generally cleared via hepatobiliary pathways. Surface PEGylation increases plasma half-life by reducing renal clearance and reticuloendothelial uptake.

2. Pharmacodynamics of Dendrimers

Pharmacodynamically, dendrimers exert therapeutic effects through two principal roles:

A. As Drug Delivery Carriers

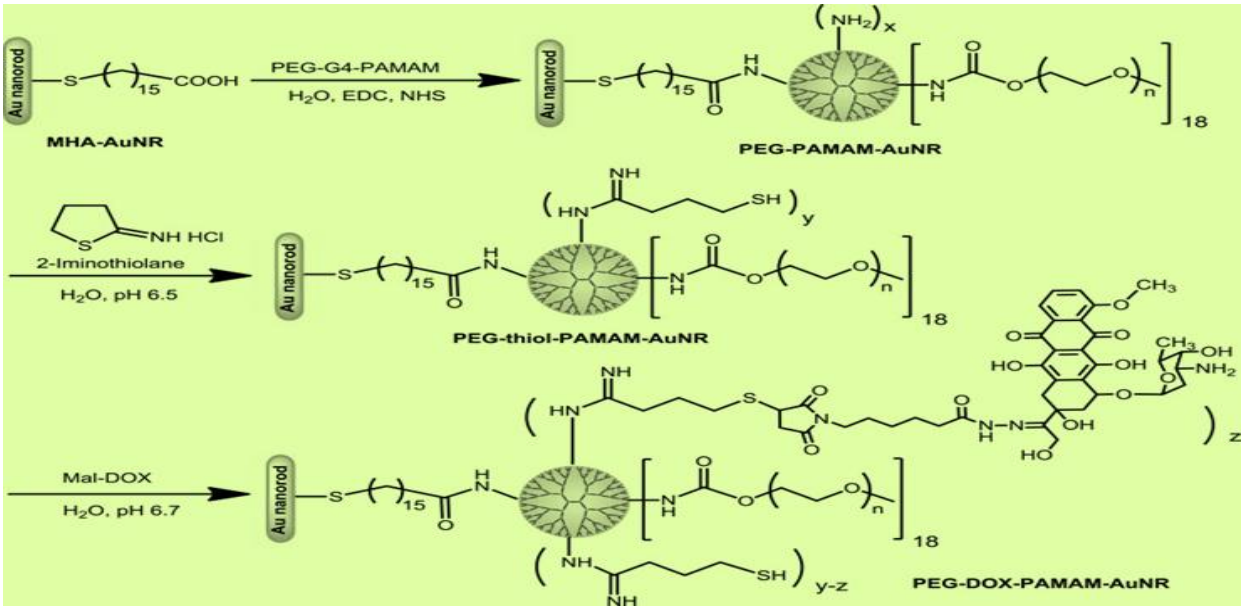
They enhance drug solubility, protect active molecules from degradation, facilitate targeted delivery, and enable controlled or stimuli-responsive release.

B. As Active Therapeutic Agents

Certain dendrimers possess intrinsic biological activity, including antimicrobial, antiviral, anti-inflammatory, and anticancer properties.

3. Pharmacological Activities of Dendrimers

3.1 Anticancer Activity



Dendrimers play a significant role in cancer therapy through both passive and active targeting mechanisms.

Mechanisms:

- Passive tumor targeting via the EPR effect.
- Active targeting through ligand-receptor interactions.
- pH-sensitive drug release in acidic tumor microenvironments.
- Enhanced intracellular uptake via endocytosis.

Therapeutic Benefits:

- Increased tumor drug concentration.
- Reduced systemic toxicity.
- Improved therapeutic index and treatment efficacy.

3.2 Antimicrobial Activity

Certain cationic dendrimers exhibit direct antimicrobial properties due to their interaction with microbial membranes.

Mechanism:

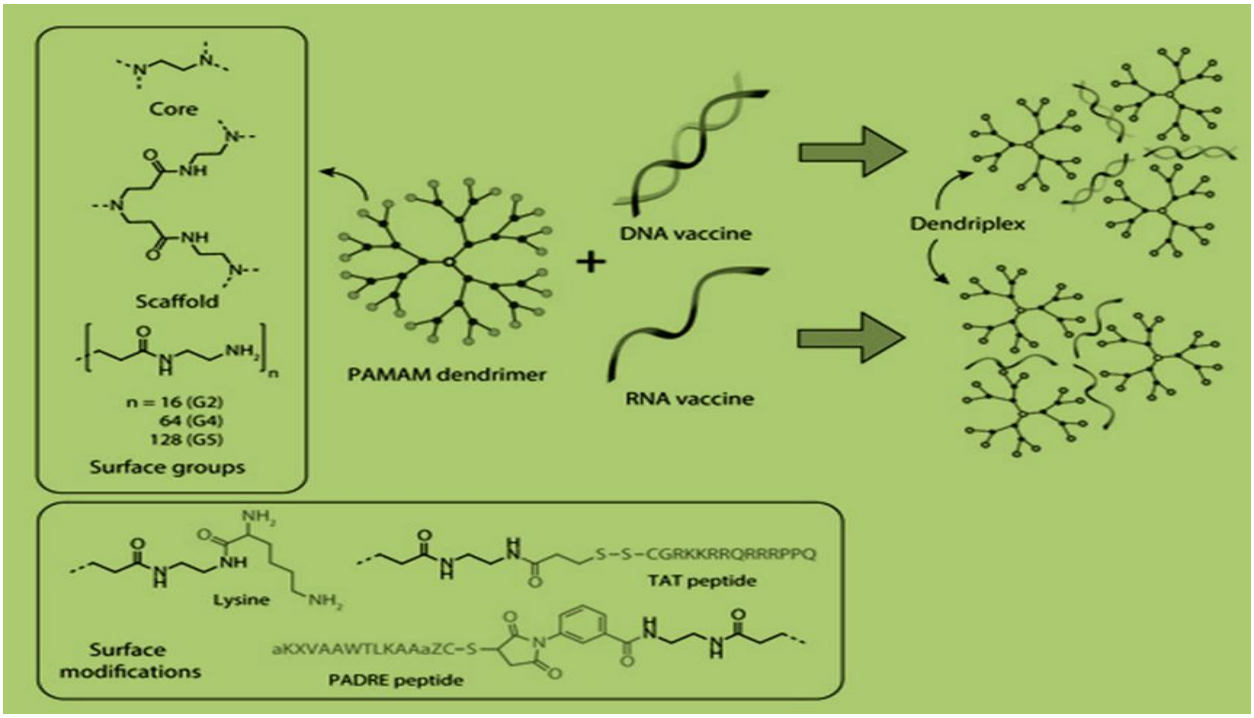
- Electrostatic attraction to negatively charged bacterial cell membranes.
- Membrane destabilization and disruption.
- Leakage of intracellular components.
- Bacterial cell death.

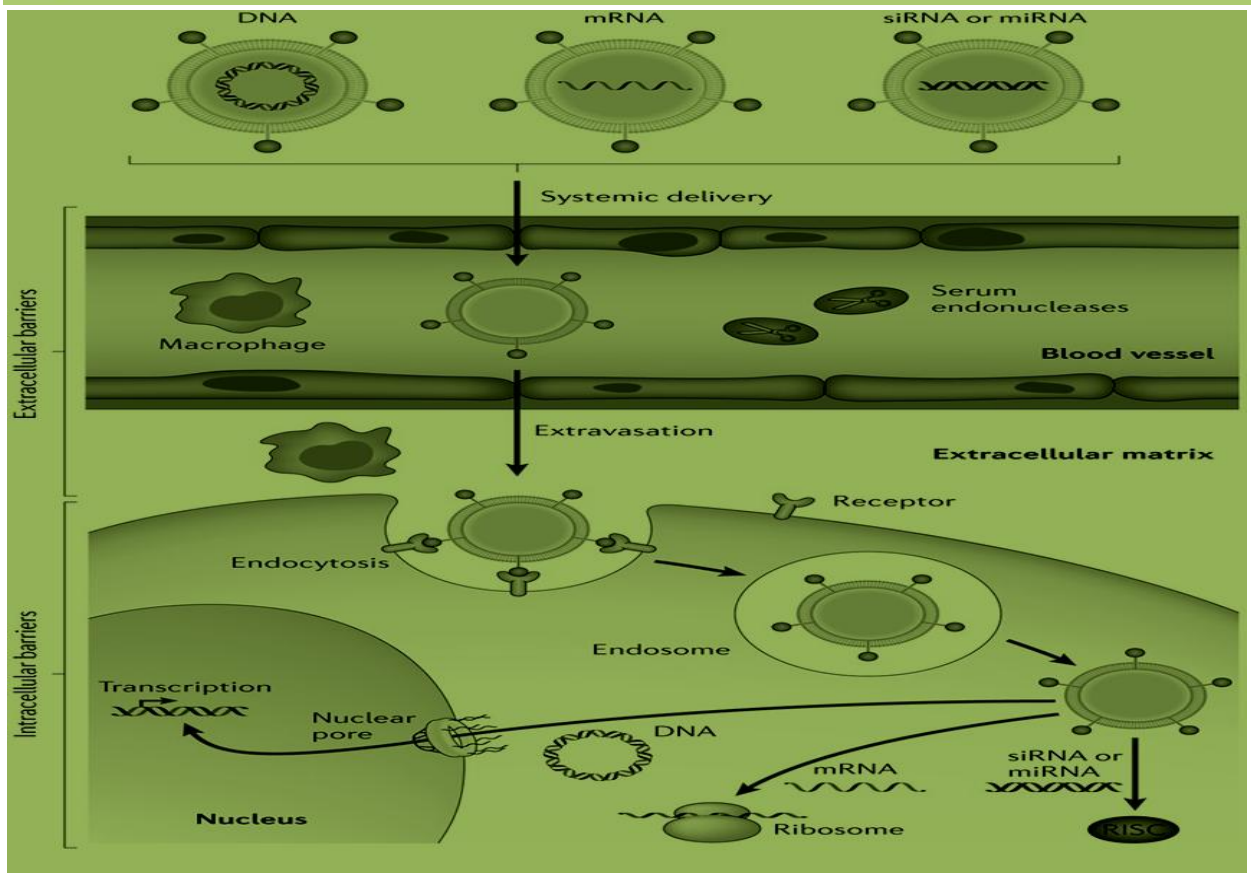
Applications:

- Topical antimicrobial formulations.
- Antibacterial surface coatings.

- Antiviral applications, including HIV inhibition.

3.3 Gene Delivery (Non-Viral Vectors)





Cationic dendrimers serve as efficient non-viral gene carriers.
Mechanism:
2. Electrostatic complexation with negatively charged DNA or RNA.
3. Formation of compact dendriplexes.
4. Cellular uptake via endocytosis.
5. Proton sponge effect:
   - Buffering of endosomal pH.
   - Osmotic swelling of endosome.
   - Endosomal rupture.
   - Release of genetic material into cytoplasm.

Applications:
- Gene therapy.
- siRNA delivery.
- CRISPR-based genome editing.

3.4 Anti-Inflammatory Activity
Some dendrimers possess intrinsic anti-inflammatory properties.
Mechanism:
- Suppression of pro-inflammatory cytokine production.
- Reduction of oxidative stress.
- Modulation of immune cell activation.

Applications:
- Rheumatoid arthritis.
- Neuroinflammatory disorders.
- Ocular inflammation.

3.5 Antiviral Activity
Carbosilane and peptide dendrimers demonstrate antiviral efficacy.
Mechanism:
- Prevention of viral entry into host cells.
- Binding to viral surface proteins.
- Inhibition of viral replication.

Applications:
- HIV prevention.
- Herpes virus treatment.
- Emerging viral infections.

3.6 Vaccine Adjuvant Activity
Dendrimers enhance immune responses by acting as multivalent antigen carriers.

Mechanism:
- Presentation of multiple antigen copies on surface.
- Enhanced dendritic cell activation.
- Increased antibody and cellular immune response.

Applications:
- Cancer immunotherapy.
- Viral vaccines.
- mRNA-based vaccine platforms.

4. Toxicological Considerations

Toxicity is influenced by:
- Surface charge (cationic dendrimers generally exhibit higher toxicity).
- Generation size.
- Dosage and route of administration.

Potential Toxic Effects:
- Hemolysis.
- Membrane disruption.
- Inflammatory responses.

Toxicity Mitigation Strategies:
- PEGylation.
- Surface acetylation.
- Use of biodegradable dendrimers.
- Neutral or anionic surface modification.

5. Clinical Relevance

A notable clinical example is VivaGel, a dendrimer-based antiviral microbicide developed for prevention of sexually transmitted infections. It demonstrates targeted local action with minimal systemic absorption and reduced potential for resistance development.

6. Pharmacological Advantages
- High drug loading efficiency.
- Controlled and sustained drug release.
- Targeted tissue delivery.
- Enhanced solubility of poorly soluble drugs.
- Reduced systemic adverse effects.

VI. LIMITATIONS

- Possible cytotoxicity, particularly with highly cationic dendrimers.
- Complex and multistep synthesis.

- Manufacturing cost considerations.
- Regulatory challenges for clinical translation.

VII. CHALLENGES AND LIMITATIONS

Despite their potential, dendrimer-based hybrid systems face several challenges:

- Complex multistep formulation procedures (54)
- Scale-up and manufacturing difficulties
- Stability concerns during long-term storage
- Cytotoxicity associated with highly cationic dendrimers
- Regulatory and translational barriers

Surface neutralization, PEGylation, and development of biodegradable dendrimers are being explored to address these issues (55).

VIII. FUTURE PERSPECTIVES

Ongoing research emphasizes:

- Stimuli-responsive dendrimer hybrids
- Theranostic nanocarriers integrating therapy and imaging
- Co-delivery platforms for drugs and genes
- Advanced vaccine delivery systems
- Targeted therapy for neurological and inflammatory disorders

Integration with lipid nanoparticles and biomimetic exosome-like carriers represents a promising next-generation strategy (56).

IX. CONCLUSION

Dendrimers significantly enhance the functionality of liposomal and other nanocarrier systems by improving drug loading efficiency, structural stability, targeting specificity, and controlled release characteristics. Through mechanisms such as dual encapsulation, membrane stabilization, electrostatic complexation, and proton sponge-mediated endosomal escape, dendrimer-based hybrid systems represent a substantial advancement in nanomedicine. Continued efforts to improve biocompatibility, biodegradability, scalability, and regulatory compliance will accelerate their clinical translation (57).

Dendrimers represent a highly versatile and promising class of nanopharmaceutical systems with significant pharmacological potential. Their controlled architecture, tunable surface chemistry, and multifunctional capabilities allow them to improve pharmacokinetic behavior, enhance targeted delivery, and in certain cases exert intrinsic biological activity. Continued research into biodegradable and biocompatible dendrimer systems is expected to broaden their clinical applications in oncology, gene therapy, infectious diseases, and immunotherapy

Dendrimer-based formulations represent sophisticated nanopharmaceutical systems designed to optimize drug solubility, stability, targeting precision, and controlled release. Through strategies such as physical encapsulation, covalent conjugation, hybridization with liposomes, and nucleic acid complexation, dendrimers can be tailored to meet specific therapeutic demands including oncology, gene therapy, inflammatory disorders, and antiviral treatment. The development of biodegradable and biocompatible dendrimers is expected to further enhance their clinical applicability in next-generation drug delivery systems.

REFERENCES

[1] Tomalia DA, Baker H, Dewald J, Hall M, Kallos G, Martin S, et al. A new class of polymers: starburst-dendritic macromolecules. Polym J. 1985;17(1):117–32.
[2] Newkome GR, Yao Z, Baker GR, Gupta VK. Cascade molecules: a new approach to micelles. J Org Chem. 1985;50(11):2003–6.
[3] Frechet JMJ. Dendrimers and supramolecular chemistry. Proc Natl Acad Sci USA. 1994;91(12):4807–14.
[4] Tomalia DA, Naylor AM, Goddard WA. Starburst dendrimers. Angew Chem Int Ed Engl. 1990;29(2):138–75.
[5] Svenson S, Tomalia DA. Dendrimers in biomedical applications. Adv Drug Deliv Rev. 2005;57(15):2106–29.
[6] Duncan R, Izzo L. Dendrimer biocompatibility and toxicity. Adv Drug Deliv Rev. 2005;57(15):2215–37.
[7] Lee CC, MacKay JA, Frechet JMJ, Szoka FC. Designing dendrimers for biological applications. Nat Biotechnol. 2005;23(12):1517–26.
[8] Chauhan AS. Dendrimers for drug delivery. Mol Pharm. 2018;15(6):2301–23.
[9] Kesharwani P, Jain NK. Dendrimer as nanocarrier. Drug Discov Today. 2014;19(10):1570–83.
[10] Malik N, Evagorou EG, Duncan R. Dendrimer–drug conjugates. J Drug Target. 1999;7(6):543–54.
[11] Mintzer MA, Grinstaff MW. Biomedical applications of dendrimers. Chem Soc Rev. 2011;40(1):173–90.
[12] Jain K, Gupta U, Jain NK. Dendrimer toxicity. Int J Pharm. 2010;394(1–2):122–42.
[13] Maeda H. The EPR effect in tumor targeting. Adv Enzyme Regul. 2001;41:189–207.
[14] Allen TM, Cullis PR. Liposomal drug delivery systems. Adv Drug Deliv Rev. 2013;65(1):36–48.
[15] Immordino ML, Dosio F, Cattel L. Stealth liposomes. Int J Nanomedicine. 2006;1(3):297–315.
[16] Danhier F, Ansorena E, Silva JM, Coco R, Le Breton A, Préat V. PLGA nanoparticles overview. J Control Release. 2012;161(2):505–22.
[17] Torchilin VP. Multifunctional nanocarriers. Eur J Pharm Biopharm. 2014;71(3):431–44.

[18] Caló E, Khutoryanskiy VV. Biomedical hydrogels. Eur Polym J. 2015;65:252–67.
[19] Kesharwani P, Iyer AK. Proton sponge effect. J Control Release. 2015;220:651–64.
[20] Mintzer MA, Simanek EE. Nonviral gene delivery vectors. Chem Rev. 2009;109(2):259–302.
[21] Pathak R, Chawla M, Shukla P. PAMAM dendrimers: biomedical applications. J Drug Target. 2017;25(5–6):505–31.
[22] Gupta U, Kesharwani P, Jain NK. Targeted dendritic nanotherapeutics. Drug Discov Today. 2011;16(21–22):944–52.
[23] Mignani S, Majoral JP. Dendrimers in nanomedicine. Curr Pharm Des. 2017;23(9):1257–67.
[24] Cheng Y, Zhao L, Li Y. Dendrimer-based drug delivery. J Mater Chem B. 2019;7(47):7279–302.
[25] Svenson S. Dendrimers in drug research. Drug Discov Today. 2005;10(1):35–43.
[26] Malik N, Wiwattanapatapee R. Dendrimers and biodistribution. J Control Release. 2000;65(1–2):133–48.
[27] Burnett JC, Rossi JJ. RNA-based therapeutics. Chem Biol Drug Des. 2012;79(4):547–59.
[28] De Jong WH, Borm PJ. Nanoparticles hazards. Int J Nanomedicine. 2008;3(2):133–49.
[29] Chishti R, Farooqi H. Surface-engineered dendrimers. Int J Pharm. 2018;552(1–2):214–28.
[30] Tomalia DA, Reyna LA, Svenson S. Dendrimers as multi-purpose nanodevices. Biochem Soc Trans. 2007;35:61–7.
[31] Tekade RK, Kumar PV, Jain NK. Dendrimer-stabilized drug delivery. Chem Rev. 2009;109(1):49–87.
[32] Chauhan AS, Jain NK. Dendrimers as carriers for lipophilic drugs. J Control Release. 2014;192:127–43.
[33] Kannan RM, Nance E. Emerging dendrimer nanomedicine. J Intern Med. 2014;276(6):579–617.
[34] Singh P, Pandey MK. Nonviral gene delivery strategies. Pharmaceutics. 2016;8(2):11.
[35] Yang Z, Zhang G. Polymeric micelles. Nano Res. 2019;12:845–55.
[36] Luo Z, Zhang X. Polymeric nanoparticles review. Polymers. 2020;12(6):1344.
[37] Parihar HS, Singh S. Pharmaceutical dendrimers review. J Drug Deliv Sci Technol. 2021;61:102291.
[38] Mignani S, Rodrigues J. Dendrimers and anticancer agents. Chem Soc Rev. 2018;47(9):3391–418.
[39] Klajnert B, Bryszewska M. Dendrimers: properties and applications. Acta Biochim Pol. 2001;48(1):199–208.
[40] Duncan R. Polymer therapeutics as nanomedicines. Curr Opin Biotechnol. 2011;22(4):492–501.
[41] Tajarobi F, Akhter S. Dendrimers in chemotherapy. Biomed Pharmacother. 2018;102:208–20.

[42] Gupta U, Jain NK. Dendrimers in drug targeting. J Pharm Pharmacol. 2010;62:153–69.
[43] Cheng Y, Xu Z. Functional dendrimers in drug delivery. Prog Polym Sci. 2008;33(11):1088–111.
[44] Jain S, Jain NK. Dendrimer toxicity and safety. Int J Pharm Sci Rev Res. 2008;1(1):10–21.
[45] Sharma AK, Garg T. Dendrimer-mediated transdermal delivery. Artif Cells Nanomed Biotechnol. 2016;44(2):560–6.
[46] Caminade AM, Majoral JP. Dendrimers and nanomedicine. Acc Chem Res. 2010;43(1):24–36.
[47] Astruc D, Boisselier E. Dendrimers in nanoscience. Chem Rev. 2010;110(4):1857–959.
[48] Heegaard PMH, Boas U, Sorensen NS. Dendrimers for vaccine delivery. J Control Release. 2010;141(2):131–43.
[49] Khandare J, Calderon M. Multifunctional dendrimers. Chem Soc Rev. 2012;41(7):2824–48.
[50] Rolland O, Turrin CO. Dendrimers in antiviral therapy. Antiviral Res. 2009;83(3):207–19.
[51] Caminade AM, Turrin CO. Peptide dendrimers. New J Chem. 2014;38:543–51.
[52] Grayson SM, Frechet JMJ. Convergent dendrimer synthesis. Chem Rev. 2001;101(12):3819–67.
[53] Majoros IJ, Myc A. PAMAM dendrimers in cancer therapy. J Med Chem. 2006;49(2):612–21.
[54] Patri AK, Majoros IJ, Baker JR. Dendritic polymer macromolecular carriers. Curr Opin Chem Biol. 2002;6(4):466–71.
[55] Kukowska-Latallo JF, Candido KA. Nanoparticle targeting of anticancer drug. Cancer Res. 2005;65(12):5317–24.
[56] Boas U, Heegaard PMH. Dendrimers in vaccine design. Chem Soc Rev. 2004;33(1):43–63.
[57] Mignani S, Shi X. Dendrimers in precision medicine. Nanoscale. 2016;8:11990–205.
[58] Tiwari SB, Amiji MM. Dendrimers in oral drug delivery. J Nanosci Nanotechnol. 2006;6(9–10):3215–21.
[59] Esfand R, Tomalia DA. Poly(amidoamine) dendrimers. Drug Discov Today. 2001;6(8):427–36.
[60] Gillies ER, Frechet JMJ. pH-responsive dendrimers. Bioconjug Chem. 2005;16(2):361–8.
[61] Caminade AM, Laurent R. Dendrimers in therapy and imaging. Chem Soc Rev. 2010;39(6):2034–47.
[62] Tekade RK, Dutta T. Dendrimers in oncology. J Pharm Pharmacol. 2009;61(3):279–92.
[63] Cheng Y, Zhao L. Functional dendrimers in nanomedicine. Biomaterials. 2008;29(32):4176–84.
[64] Shcharbin D, Klajnert B. Dendrimer interactions with cells. Chem Rev. 2011;111(9):5296–321.

[65] Svenson S, Chauhan AS. Dendrimers in drug delivery: clinical translation. Ther Deliv. 2012;3(10):1131–49.

[66] Mignani S, Majoral JP. Dendrimers in nanotherapeutics. Expert Opin Drug Deliv. 2013;10(3):409–21.