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NANOCARRIERS DENDRIMERS

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Abstract
Targeted drug delivery has showed great promise using nanocarriers made of liposomes, micelles, polymeric nanoparticles, and others. Nanocarriers' biological interaction can be controlled in the desired way by giving them multifunctionality. Dendriners have easily adjustable surfaces and are highly branched polymers. Other moieties that can actively target specific diseases and improve delivery can be added thanks to the functional groups present in the dendrimers' exterior. Since dendrimers have special structural characteristics, they have become viable drug delivery platforms for nanocamers. The well-defined architecture of dendrimers, which are highly branching, monodisperse, nanosized macromolecules, offers a high degree of surface functionality and internal cavities.Applications for dendrimers (PAMAM, PPI, and polyester) in gene delivery, cancer treatment, and antibiotics have been investigated.This study focusses on the design, functionalisation, and biomedical applications of dendrimer-based nanocarriers, highlighting their potential in personalised medicine and next-generation drug delivery systems.
Keywords: Cancer, drugs, dendrimers, nucleic acids, PAMAM [polyamidoamine] Polypropylene [PPI].

Introduction

Nanotechnology is a multidisciplinary field that includes domains such as chemistry, materials science, biology, physics, diagnostics, and engineering, particularly in the synthesis of nanodevices. The pharmaceutical industry integrates nanotechnology across the research and development process. Nanoformulations and nanocarriers have significantly influenced the delivery of therapeutic agents and diagnostics through the development of various nanodevices, including liposomes, nanocrystals, nanoparticles, and dendrimers.Therapeutic agents may be encapsulated within nanoparticles, conjugated to them, or complexed on their surface.Genes and vaccines may also be transmitted.Furthermore, significant efforts have been directed towards the development of targeted nanoparticles for the delivery of therapeutic agents to specific tissues (e.g., brain, kidney, lung), cells (e.g., tumour cells), and intracellular compartments (e.g., nucleus, mitochondria, cytosol) [1].

Dendrimer: Properties

The term "dendrimer" originates from the Greek word "dendron," meaning tree, combined with "meros," which translates to branch.In 1978, Buhle and colleagues synthesised and reported the first "cascade" and "nonskid-chain-like" molecules featuring molecular cavity topologies, which were subsequently acknowledged as early forms of dendritic polymers. Between 1979 and 1985, Donald A. Tomalia and his colleagues at Dow Laboratories achieved a significant advancement in dendrimer development.They synthesised polymers featuring a central hollow core with tendrils that branched outward in an imprecise and unpredictable manner, which Tomaliac termed dendrimers. The early history of dendrimers was shaped by the contributions of these two scientific groups. To date, over 100 dendritic structures have been documented, including polyamidoamine (PAMAM) dendrimers, polypropyleneimine (PPI) dendrimers, and various families based on polyamide, polyether, polyester, and phosphorus. Moreover, the

advancement of various synthetic strategies, such as efficient orthogonal click chemistry and multicomponent reactions (MCR), has led to the emergence of numerous new dendrimers characterised by efficient synthetic processes and structural diversity.The advancements have facilitated the growth of dendrimers and their applications in chemistry, materials science, and biological and medical fields.

Dendrimers differ from traditional linear polymers due to their monodispersity, high symmetry, and surface polyvalency. The iterative growth reactions in dendrimer synthesis result in increased generation levels. Dendrimers are biocompatible nanoparticle macromolecules with unique properties that enhance drug activity and efficiency while minimising toxicity [2].

Choi has proposed a global framework for the modulation of various physicochemical properties, referred to as the 'Choi criteria.' The composition of nanoparticles influences their biodegradation and toxicity effects, while surface properties dictate their targeting and biodistribution. Additionally, size and shape govern their excretion and clearance profiles.Dendrimer and dendron nanostructures, alongside polymeric and metal-based nanoparticles, as well as polymeric micelles and linear polymers, serve as optimal delivery vehicles, presenting significant potential for the advancement of nanomedicine.

Dendrimers, derived from the Greek terms “dendros” and “meros,” represent a class of nanosized macromolecules distinguished by their highly homostructural, branched three-dimensional architecture and compact, spherical geometry in solution.Dendrimers are globular macromolecules characterised by a highly branched three-dimensional architecture, allowing for precise control over their shape and size.They display an exponential number of dendritic branches radiating from a central core.The diameter of the dendrimer increases linearly, whereas the number of surface groups increases exponentially with each generation.Low-generation dendrimers exhibit flexibility, whereas higher generation compounds demonstrate increased density and rigidity.

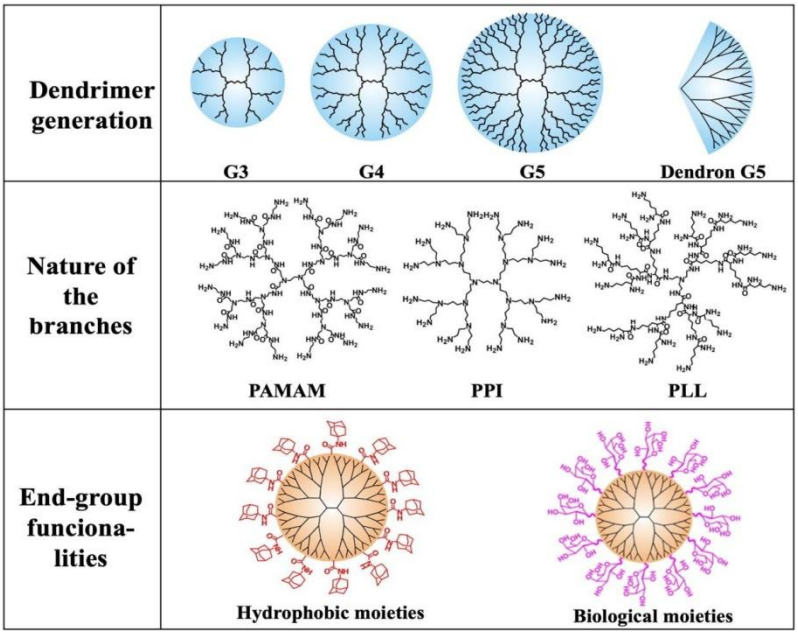
The dendritic macromolecular structure can be categorised into four primary components: (a) a central core moiety; (b) interior layers (generations, Gn, where n is 0, 0.5, 1, 1.5,) composed of regularly arranged units. Repeating branching units are affixed to the core; (c) terminal functionalities are arranged in a three-dimensional space; (d) void spaces serve as compartments for molecular cargo, including anti-cancer agents. [1]The primary types of dendrimers utilised include PAMAM dendrimers, poly-etherhydroxyl-amine (PEHAM) dendrimers, PPI dendrimers, carbosilane dendrimers, and phosphorus-based dendrimers developed by J-P. Majoral and A-M. Caminade.

In 2012, Starpharma initiated two pivotal Phase III trials for the treatment of bacterial vaginosis using VivaGel® (SPL7013 Gel). This active polyanionic G4-poly(L-lysine)-type dendrimer, featuring 32 naphthalene disulphonate groups on its surface, demonstrated significant topical vaginal microbicidal activity.Starpharma has obtained Phase III approval from the Food and Drug Administration. Starpharma/AstraZeneca has recently progressed from Phase I to Phase II with a poly(lysine)-dendrimer-based nanocarrier encapsulating docetaxel (DEP® docetaxel), demonstrating enhanced anticancer activity against various solid tumour types, including breast, prostate, lung, and ovarian cancers [3].

Types: 1. PAMAM (Polyamidoamine): Since the 1980s, various dendrimers have been developed and utilised, with polyamidoamine (PAMAM) derivatives being the most widely employed.They are hydrophilic, biocompatible, and non-immunogenic systems, which favour their use in drug delivery. The core of this is most commonly Ethylenediamine, although more hydrophobic molecules-including diaminododecane, diaminoexane, and diaminobutane-can also are used.Their branching units are derived from methyl acrylate and ethylenediamine, featuring amine groups in full generations and carboxyl groups in half generations.

Poly(propyleneimine) (PPI) dendrimers were first reported by Buhleier et al. in 1978. They described them as a cascade of molecules. In addition to PAMAM, they were also extensively studied. PPIdendrimers can be based on a 1,4-diaminobutane (DAB) core, but they can also be synthesised from an ethylenediamine nucleus and other core molecules through a double Michael addition reaction. Propylene imine monomers serve as branching units. Consequently, their interior comprises various tertiary tris-propylene amines, which generate full layers with primary amines at the surface. The presence of alkyl chains in their branching units imparts a more hydrophobic interior compared to PAMAM dendrimers, which contain amide groups in addition to the alkyl chains, at equivalent generations [4].

Poly-L-lysine (PLL) dendrimers are a class of peptide dendrimers primarily utilised as gene carriers owing to their superior ability to condense with oligonucleotides. Notable characteristics include good biocompatibility, water solubility, biodegradability, and flexibility, akin to other dendrimers. Both the core and branching units of these structures are typically derived from the amino acid lysine, characterised by peptide bonds. PLL dendrimers are distinct from PAMAM and PPI dendrimers due to their predominantly asymmetrical structure. Nonetheless, they remain precise molecules, characterised by a controlled number of lysines extending from the core, along with terminal amine residues. The lysine in the terminal group of PLL contains two primary amines that ar frequently modified [5].



Toxicity of Dendrimers

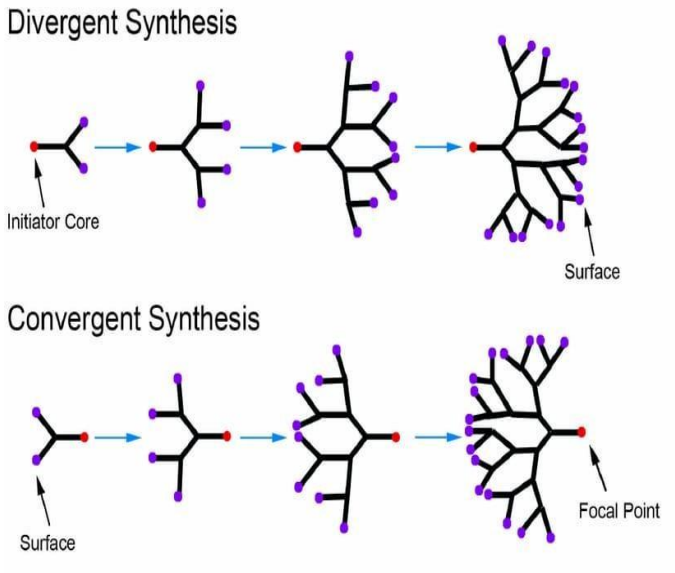
Although dendrimers exhibit significant potential for biological applications, particularly in medication and gene delivery, all classes demonstrate cytotoxic and haemolytic characteristics.Dendrimers are extensively branched polymers featuring readily alterable surfaces. This renders them promising frameworks for functionalisation and conjugation with medicines and DNA/RNA. Their architecture, modifiable through various synthesis techniques, facilitates the regulation of attributes such as form, size, charge, and solubility. Dendrimers enhance the solubility and bioavailability of hydrophobic pharmaceuticals. The medications can be encapsulated within the intramolecular cavity of the dendrimers or coupled to their surface functional groups. Nucleic acids typically form compounds with the positively charged surfaces of most cationic dendrimers, and this methodology has been extensively utilised. The presence of functional groups on the dendrimer's surface facilitates the incorporation of additional moieties that can specifically target certain diseases and enhance delivery, such as folate and antibodies, which are currently commonly employed as tumor-targeting techniques. Dendrimers are highly branching polymeric macromolecules characterised by well-defined and homogeneous sizes and forms.Their basic structure comprises three main components: a central core, Repetitive branching units and terminal groups that offer modifiable surface functionalities. The proliferation of repeated branching units dictates the synthesis of the dendrimer and is accountable for the establishment of a globular structure.The high level of control over their architecture renders them appealing as platforms for medication and gene delivery applications.

Drugs and oligonucleotides may be enclosed within their internal cavities or adhered to their surfaces via hydrophobic or electrostatic interactions. They may also be covalently bonded via processes involving the terminal functional groups [6].

Dendrimer Synthesis

Dendrimers have been synthesized by two major routes: the **divergent method,** introduced by Tomalia and **convergent growth**, developed by Hawker and Freshet There are, however, other less well-explored strategies to synthesize dendrimers, including hyper core and branched monomers growth .exponential growth. lego chemistry , and click chemistry. Dendrimersarejustinbetweenmolecularchemistryandpolymerchemistry.Theyrelatetothe molecular chemistry world by virtue of their step-by-step controlled synthesis, and they relate to the polymer world because of their repetitive structure made of monomers. The three traditional macromolecular architectural classes are broadly recognized to generate rather polydisperse products of different molecular weights. Dendrimers are generally prepared using either a divergent method or a convergent one. In the different methods, dendrimer grows outward from a multifunctional core molecule. The core molecule reacts with monomer molecules containing one reactive and two dormant groups, giving the first-generation dendrimer. Then, the new periphery of the molecule is activated for reactions with more monomers. While chemical reducing agents are usually used to prepare DENs, several alternative routes have been investigated. UV irradiation is effective for the preparation of both Au[23] and Ag DENs. In addition, Ottaviani and co-workers have shown that X-rays can be used to form Ag/dendrimer nanocomposites, but in this case the Ag nanoparticles were not encapsulated within

individual dendrimers. An especially effective means for converting one type of DEN to another involves an intra dendrimer redox displacement reaction. In this approach DENs prepared from a particular metal, such as Cu, can be exchanged with another metal, such as Ag, as long as the latter is nobler than the former [7, 8].

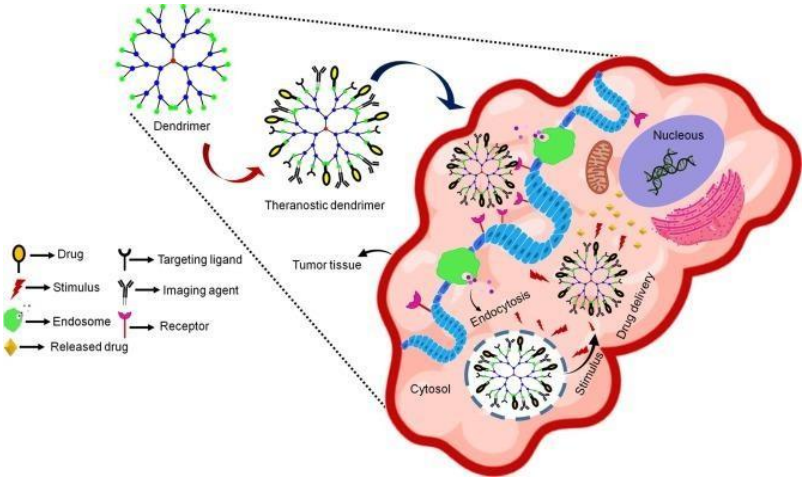


Applications

- Drug Delivery: Dendrimers
- Dendrimers can be utilized for the delivery of medications and genes through various mechanisms, including:
- Solubilizing drugs: Dendrimers with a hydrophobic core and a hydrophilic periphery can encapsulate hydrophobic drugs within their intramolecular cavities.
- Enhancing bioavailability: Dendrimers can improve the oral bioavailability of poorly soluble drugs.
- Targeted drug delivery: Dendrimers can specifically target tumor cells while sparing healthy tissue, minimizing off-target effects.
- Controlled drug release: Dendrimers can regulate the release of anticancer drugs within the tumor microenvironment.
- Gene delivery: Cationic dendrimers can serve as non-viral gene carriers and protect nucleic acid molecules from enzymatic degradation.
- Vaccine development: Dendrimers can be conjugated with antibodies, proteins, and peptides to create vaccines with targeted characteristics.
- Biosensing: Dendrimers can be employed as biosensors.
- Bioimaging: Dendrimers can serve as contrast agents for bioimaging.
- Tissue engineering: Dendrimers can be utilized in tissue engineering applications.
- Dendrimers as Drug Delivery Carriers in Cancer Therapy [9]

Dendrimers play a significant role in cancer therapy by enhancing drug solubility, improving targeting specificity, and enabling controlled drug release, making them a promising tool for advanced treatment strategies. The controllability of dendrimer features, including as structure, size, water solubility, monodispersity, and diverse terminal functional groups, endows them with significant drug delivery capabilities. Drugs can be transported by dendrimers by several techniques, which can be fundamentally categorised into chemical and physical interactions. Physical interactions depend on the trapping of the medication within the dendrimer core via noncovalent associations, such hydrogen bonds, hydrophobic contacts, or electrostatic interactions. The interior holes of dendrimers, a hallmark of their structure, are predominantly hydrophobic and facilitate interaction with poorly soluble medicines. The study demonstrated that the creation of hydrogen bonds between the pharmaceuticals and the -NH groups within PAMAM, along with hydrogen bonding and electrostatic interactions with surface amino groups, accounted for the physical encapsulation of the drugs. This sort of connection, however, is constrained by a quick release that may transpire before the carriers get at their target. Chemical interactions, conversely, entail the covalent conjugation of medicines with the functional terminal groups of dendrimers, which demonstrate greater stability. “Smart” techniques employ labile links that are cleaved upon exposure to a specific environment, thereby releasing the medicine at the target spot. Numerous strong anticancer agents-such as paclitaxel (PTX), camptothecin,

methotrexate, 5-fluorouracil, and DOX freebase—exhibit significant hydrophobicity, resulting in challenges in identifying suitable delivery vehicles for their administration [10].



Dendrimer-drug conjugates

Dendrimer-drug conjugates may reduce systemic effects and enhance efficacy at the targeted site compared to free drugs. Research indicates that the half-life of drugs may be extended through conjugation with dendrimers. The half-life of methotrexate increases from 24 minutes to 24 hours when conjugated with PAMAM dendrimer. The extended circulating half-life can enhance drug efficacy and reduce the frequency of drug administration. Enhancing patient adherence. The solubility of drugs is improved through conjugation with dendrimers.

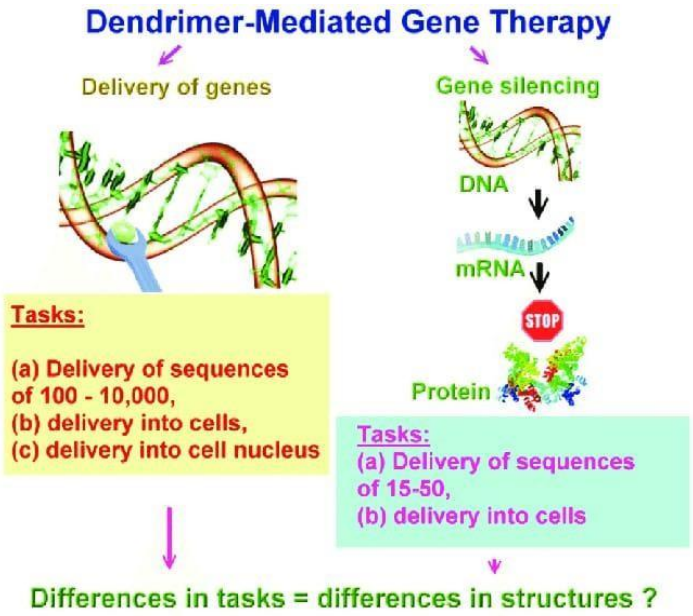
We previously reported a dendrimer-drug conjugate of DenTimol and examined its therapeutic efficacy for glaucoma treatment. A precursor to an antiglaucoma drug, (S)-4-[4-(oxiranylmethoxy)-1,2,5-thiadiazol-3-yl]morpholine (OTM), was conjugated to the surface of a PAMAM dendrimer via a PEG spacer. DenTimol demonstrates effective corneal penetration attributed to the favourable mucoadhesive characteristics of the dendrimer, with approximately 8% of the dendrimer-drug permeating through the cornea within 4 hours. DenTimol exhibited a more significant reduction in intraocular pressure (IOP) compared to timolol maleate in normotensive adult Brown Norway male rats.

According to the United Food and Drug Administration (FDA), dendrimer-drug conjugates may be classified into new drugs or combinational devices. If drugs can be cleaved from dendrimer-drug conjugates while preserving their initial structure, this regulatory issue could be circumvented. It is essential to investigate the release of drugs from dendrimer-drug conjugates. Disulphide and thioketal linkers can be cleaved by glutathione and reactive oxygen species (ROS) in tumour cells, respectively. Consequently, they have been extensively utilised in the design of cleavable dendrimer-drug conjugates [11].

Dendrimer-gene complexation

Amine-terminated PAMAM dendrimers are widely utilised as vectors for gene transfection. PAMAM dendrimers exhibit superior biocompatibility and enhanced nucleic acid loading capacity when compared to branched polyethylenimine (PEI). The proton sponge effect of PAMAM dendrimers facilitates endosomal escape, a crucial step in enhancing transfection efficiency. G4-FA was synthesised and evaluated as a vector for the localised delivery of siRNA targeting vascular endothelial growth factor.

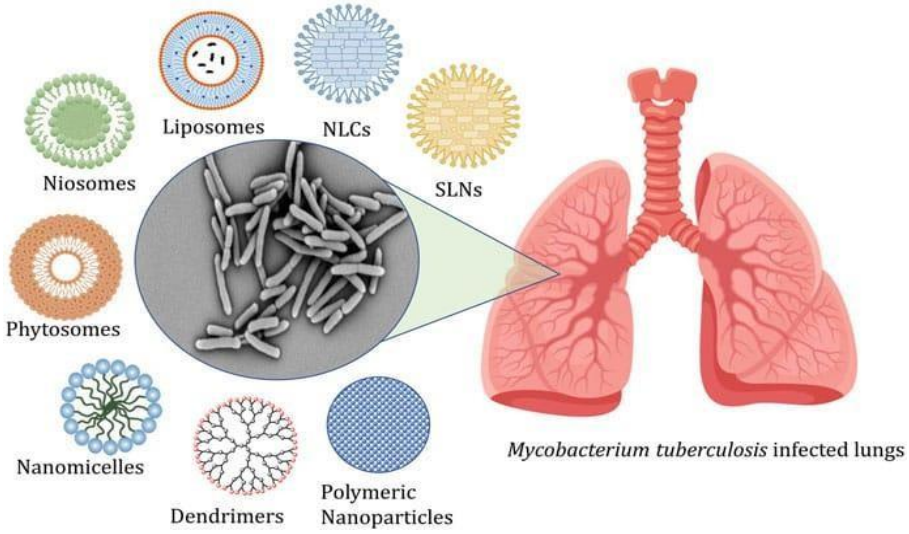
A Dendrimers are frequently modified with supplementary functional moieties, such as peptides, to address intracellular gene delivery challenges. Our group recently reported the use of PAMAM dendrimers complexed with a synthetic diblock nuclear-localization sequence peptide (NLS) for gene delivery. The complexed NLS promoted the nuclear translocation of the entire dendrimer/nucleic acid polyplex, destabilising the association between PAMAM and plasmid in the nucleus, which ultimately enhanced gene transfection. Similar to gene transfection, cationic dendrimers can also bind with other negatively charged molecules, such as heparin or polyanions. For instance, the complex of polylysine dendrimer with heparin has potential applications as a stable agent.



Carcinomas are a type of cancer that originates in epithelial cells. G4-FA enhanced the delivery of siVEGFA, promoted its tumor-specific uptake, and significantly inhibited tumour growth in head and neck cancer.In comparison to the siVEGFA group, two doses of G4-FA/siVEGFA administered intratumorally eight days apart resulted in significant inhibition of tumour growth, along with a marked reduction in angiogenesis. NLSpromotedthe nuclear translocation of the entire dendrimer/nucleic acid polyplex and subsequently destabilised the association between PAMAM and plasmid in the nucleus, ultimately resulting in enhanced gene transfection. The polylysine dendrimer complex with heparin has potential applications as a stable anti-angiogenic therapeutic, as it neutralises the anticoagulant activity of heparin in plasma [12].

Encapsulation of Anti-TBD rugs within Dendrimers

Initial research conducted by Palanirajan Vijayaraj Kumar and colleagues focused on the development of mannosylated dendritic architectures (G5 EDA-PPI dendrimers) for the selective delivery of RIF to alveolar macrophages.The mannosylated G5 EDA-PPIdendrimer is a fifth-generation poly(propyleneimine) (PPI) dendrimer characterised by 64 amino groups on its surface, an ethylenediamine (EDA) core, and approximately 30 D-mannose groups grafted onto its surface. RIF is an essential component of the cocktail of anti-TB combination drugs, as illustrated in Figure 1. The mechanism of action of RIF is associated with the inhibition of the subunit of the bacterial. RNA polymerase inhibits gene transcription. Several side effects of RIF are attributed to its poor pharmacokinetic profile, primarily due to its low solubility in water. Furthermore, under gastric conditions (pH 4–5), RIF undergoes hydrolysis to form the less soluble compound 3-formyl-rifampicin. Mannose was chosen due to its recognition by lectin receptors on the surface of phagocytic cells, which enhances the uptake of nanocarriers that display mannose on their surface and contain drugs in their internal voids by immune system cells [13].



Utilising a widely recognised dissolution technique, approximately 37 RIF have been integrated into PPI dendrimers. SEM studies indicated an irregular shape and agglomeration of mannosylated dendrimers, with a median diameter of less than 5 μm.The solubility of the nanodevice formed by incorporating RIF within the PPI dendrimer is approximately 50 mg/mL. In contrast, a decrease in solubility was noted when RIF was encapsulated in a mannosylated dendrimer, yielding around 5 mg/mL. However, this solubility is still double that of RIF's aqueous solubility alone.

Non-covalent interactions between RIF and the mannosylated dendrimer were observed. Hydrogen bonding and hydrophobic interactions, approximately 37%, were observed with the core. The haemolytic toxicity of the G5 EDA-PPI mannosylated dendrimer was assessed in relation to red blood cells, highlighting a notable reduction in toxicity for mannosylated dendrimers compared to non-mannosylated ones (2.8% versus 15.6%). This decrease is attributed to the inhibition of the interaction between the charged quaternary ammonium ion and the cells. The significant haemolytic toxicity of unmodified PPI dendrimers, characterised by amino group presence on all surfaces, limits their potential for clinical use. Similarly, PAMAM dendrimers must be modified on their surface through the introduction of groups that reduce the cationic surface characteristics and, consequently, toxicity.Mannosylated dendrimers

Demonstrated minimal cytotoxicity towards Vero cells at a concentration of 100 μg/mL, similar to the RIF-loaded mannosylated dendrimer, which maintained approximately 85% viability. In the same assay, the group treated with RIF alone demonstrated a viability of approximately 50% at the identical concentration.

The authors indicated that RIF persisted for an extended period (~120 h) within the interior cavities of mannosylated dendrimers at a physiological pH of 7.4, in contrast to less than 10 hours with the PPI dendrimer. A significant drug release rate was noted at pH 5, which reflects the pH conditions found in phagolysosomes. An observable increase in the intracellular concentration of RIF-loaded mannosylated PPI dendrimers by alveolar macrophages from rat lungs, compared to RIF alone, was noted. The relationship between the aquitelinear curve and the amount of RIF incorporated in AM versus the amount of RIF was analysed. As a result, the mannosylated G5 EDA-PPI dendrimer serves as an effective nanocarrier system for the delivery of hydrophobic drugs like RIF in the tuberculosis domain.

Bellini and colleagues conducted molecular dynamics (MD) simulation studies examining the association of the anti-tuberculosis drug rifampicin (RIF) with the G4-PAMAM dendrimer.Molecular dynamics (MD) simulation is recognised as an effective method for investigating various types of molecular systems, including association systems [14].

The experimental findings indicate that the maximum loading capacity of RIF molecules is 20 RIF molecules per G4-PAMAM dendrimer. This result aligns with the findings of Kumar et al., highlighting the association of approximately 37 RIF molecules per mannosylated G5-PPIdendrimer (as discussed above).Additionally, the authors examined the occupied volumes of RIF and a comparable compound, ibuprofen, both of which fall under the class II biopharmaceutical classification system (BCS) as defined by the FDA, characterised by low solubility and high permeability.

The upper limit of ibuprofen molecules is 78 for each dendrimer, which is roughly four times greater than the quantity of RIF associated with G4 PAMAM dendrimer. It is crucial to recognise that the molecular weight of RIF is roughly four times greater than that of ibuprofen (MW 822 versus 206), and RIF is approximately four times larger than ibuprofen. Based on the docking of RIF molecules within the G4 PAMAM cavities (20 RIF molecules per dendrimer determined experimentally, vide supra), molecular dynamics simulations were generated at neutral and low pH. The complex exhibited reasonable stability at neutral pH; however, at low pH, RIF molecules were rapidly and simultaneously expelled into the solvent bulk. This result highlights the potential function of PAMAM dendrimers as nanocarriers for drug delivery in acidic cellular environments, specifically within alveolar macrophages.

The confirmation of PEGylation in 5G PAMAM dendrimers was achieved through the application of Fourier Transform Infrared Spectrophotometry (FTIR) and 1H-NMR spectra analysis.The efficiency of RIF entrapment in PEGylated dendrimer was determined to be approximately 99%.The drug release rate of RIF is 81% for PEGylated PAMAM dendrimers over 120 hours, while it is 98% for non-PEGylated PAMAM dendrimers over 72 hours. The haemolytic studies indicated that non-PEGylated PAMAM dendrimer exhibited toxicity levels ranging from 11.6% to 25.3%, while the PEGylated PAMAM dendrimer demonstrated significantly lower toxicity effects, recorded at less than 2.5%. This reduction in toxicity is resulting from the suppression of interaction between red blood cells and quaternary structures.

Ammonium groups present on the surface of dendrimers. Early studies indicated comparable effects in dendrimers that had cationic groups on their surface.

In vivo studies conducted on Wistar albino rats revealed notable pharmacokinetic (PK) parameters of PEGylated 5G EDA-PAMAM dendrimers loaded with RIF compared to RIF alone.The pharmacokinetic profile of 5 GEDA-PAMAM dendrimers loaded with RIF over a duration of 0.5 to 120 hours. After 6 hours, RIF was absent in plasma, while in 5G EDA-PAMAM dendrimers, RIF persisted for 120 hours. The low and prolonged release of RIF resulted in increased

values for the area under the plasma drug concentration-time curve (AUC), half-life (t1/2), and mean residence time (MRT) when comparing PEGylated 5G EDA-PAMAM dendrimers loaded with RIF to free RIF. No changes were observed in either appearance or RIF release from 5 GEDA-PAMAM dendrimers loaded with RIF after 3 months of storage at approximately 40 ◦ C [15].

Conclusion

Dendrimer-based nanocarriers have emerged as a promising platform in nanomedicine, owing to their distinctive structural features, including a well-defined, highly branched architecture and customizable surface properties. These attributes enable precise drug loading, controlled release, and targeted delivery, thereby improving therapeutic effectiveness while reducing side effects. Furthermore, their biocompatibility, scalability, and capacity to encapsulate or conjugate a wide variety of drugs make them versatile tools for addressing complex medical challenges. However, significant obstacles such as large-scale production, toxicity concerns, and regulatory issues remain. Future research should focus on optimizing dendrimer design, ensuring safety profiles, and developing cost-effective manufacturing techniques to facilitate the translation of these nanocarriers into clinical practice. With ongoing innovation and collaboration among academia, industry, and regulatory bodies, dendrimer-based nanocarriers are poised to play a pivotal role in advancing drug delivery systems and personalized medicine.

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Not Declared.

Conflict of Interest

No

Informed Consent

Not Applicable.

Ethical Statement

Not Applicable.

Author Contribution

All authors are contributed equally.

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