RESEARCH PAPER

Dendrimers for Solubility Enhancement of Poorly Soluble Drugs: A Comprehensive Analysis of Key Determinants, Molecular Properties, and Formulation Challenges

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Abstract
Poor aqueous solubility remains a significant obstacle in the development and clinical translation of many promising drug candidates, limiting their absorption, bioavailability, and therapeutic efficacy. In recent years, dendrimers have emerged as a novel and highly adaptable class of nanocarriers capable of enhancing the solubility of poorly water-soluble drugs through multiple mechanisms. These synthetic, hyperbranched, and monodisperse macromolecules offer a well-defined architecture, consisting of a central core, iterative internal branching layers, and terminal functional groups. Such structural precision allows for fine-tuning of dendrimer properties to achieve optimal drug-carrier compatibility and solubility enhancement. This review provides a comprehensive exploration of the structural attributes of dendrimers, focusing on core architecture, generation level, surface functionality, and internal cavities, and their direct implications on drug solubilization capacity. Particular emphasis is placed on understanding how the dendrimer generation and molecular weight influence encapsulation efficiency and solubilization performance. The solubility-enhancing mechanisms, including encapsulation, surface adsorption, hydrogen bonding, electrostatic complexation, and covalent conjugation, are thoroughly discussed. Additionally, case studies of various drug, dendrimer formulations are presented to demonstrate their practical relevance and effectiveness. Despite their significant potential, challenges such as generation-dependent cytotoxicity, synthetic complexity, and regulatory uncertainty continue to hinder the broader clinical adoption of dendrimeric systems. The review also highlights recent innovations in dendrimer design, such as biodegradable constructs, stimuli-responsive systems, and ligand-functionalized carriers, that aim to overcome these limitations. By addressing current gaps and future prospects, this review underscores the strategic role of dendrimers in transforming solubility-limited drug development pipelines and facilitating the formulation of next-generation therapeutics.
Keywords: Dendrimers; Poorly Soluble Drugs; Solubility Enhancement; Nanocarriers; Drug Delivery; Pharmaceutical Nanotechnology; Generation-dependent Solubilization.
Abbreviations: API: Active Pharmaceutical Ingredient, PAMAM: Poly (amidoamine), PEG: Polyethylene Glycol, PPI: Poly (propylene imine), NCE: New Chemical Entity, FDA: Food and Drug Administration
How to cite this article: Nachiya RAMJ, Ugandar RE, Kumar KS, Latha BV, Anil V, Prathyusha VSC, Molugulu N. Dendrimers for solubility enhancement of poorly soluble drugs: a comprehensive analysis of key determinants, molecular properties, and formulation challenges. Int J Drug Deliv Technol. 2026;16(75s): 333-338. DOI: 10.25258/ijddt.16.75s.37

1. Introduction

The advancement of pharmaceutical technologies has led to a surge in the development of new chemical entities (NCEs), many of which are poorly water-soluble, leading to suboptimal bioavailability and therapeutic outcomes. According to recent estimates, nearly 40–60% of drugs under development suffer from poor aqueous solubility, posing significant formulation and clinical challenges[1]. Traditional techniques such as micronization, salt formation, and cyclodextrin inclusion complexes, though useful, often fail to offer consistent and scalable solutions for lipophilic drugs.

In this context, dendrimers have emerged as an innovative class of synthetic, three-dimensional,

hyperbranched nanostructures capable of significantly improving the solubility of hydrophobic drugs. Dendrimers such as poly(amidoamine) (PAMAM), poly(propylene imine) (PPI), and polyethylene glycol (PEG)-based constructs offer precisely defined architecture with multiple terminal functional groups, facilitating tailored drug–carrier interactions[2].

Dendrimers provide multiple mechanisms for solubility enhancement: encapsulation within internal cavities, surface adsorption, and formation of water-soluble conjugates. Their monodispersity and tunable surface functionality offer advantages over conventional solubilizers. The generation of dendrimers (indicative of layers of branching) further influences size, surface density, and drug-loading capacity[3].

This review offers a compulsory and detailed review of several determinants that impact the solubility augmentation capabilities of dendrimers in addition to focusing on their physicochemical characteristics, its structure-activity-relationship, as well as generation-dependent solubilization tendencies. Moreover, it describes the issues of its limitations including cytotoxicity and synthetic complexity as well as indicates the ways to break these barriers in the development of pharmaceutical product.

2. Structural Features of Dendrimers

2.1 Core and Branching Units

The essential structure of dendrimers is made with three intrinsic parts: the core of dendrimers, internal layers of branches and surface groups. The core tends to be a low molecular weight substance that has several reactive centres, which get used to trigger the growth of dendritic arms. These arms are built using iterative synthesis whereby successive layers are known as a generation which increases complexity as well as volume of the total molecule. With the advance of generations, there is an exponential rise in the amount of reactive surface groups available, affording increased contact both with drug molecules as well as, with solvents. This limited tree-like molecular structure produces a highly symmetrical, monodisperse, globular nanoparticle with high predictability of size, shape and surface chemistry all of which are important to the improved solubility of poorly soluble drugs [1,2]. Special mention should be given to dendrimers of greater generations like PAMAM G4 and higher which exhibit significantly higher levels of solubilization as their surface area is much larger and their inner branching is much more extensive[3].

2.2 Terminal Functional Groups

Terminal functional moieties at the dendrimers surface play a critical role in controlling the aqueous solubility, biocompatibility and its interaction with pharmaceutical agents. During synthesis, these end groups can be chemically modified to contain hydroxyl (158) (161) timing (158) timing (158 cheap deets model trailer campaigns). At 200°C the current could be switched on and the effect of increased jcombinations time in exam periods eurdaash yards on the current was investigated. The positive aspect of having polar or ionizable groups on dendrimers is they enhance their solubility in polar solvents especially in water due to the ability of the dendrimers to make hydrogen bonds or ionic interactions with the solvent molecules[4]. In addition, these terminal groups allow electrostatic or hydrogen bonding with drug molecules, which improve complexation efficiency and the drug stability in aqueous medium[5]. As an example, amine-functionalized PAMAM dendrimers (PAMAM-NH 2) have greater affinity towards acidic or negatively charged drugs through electrostatic attractions which improves their solubility and bioavailability in their higher degree[6].

2.3 Internal Cavities

In addition to their surface activities, dendrimers also have internal cavities or nano-compartments as encapsulation loci to lipophilic drugs. Such interior channels are made by the free branching structures that are not rigid and make a hydrophobic section that can accommodate ill-soluble molecules. Encapsulation in these cavities is mostly by the van der Waals forces, hydrophobic effects and in case of certain drugs and the branching structure of dendrimer, by the π-π interactions[7]. The segregated structure consequently allows the physical encapsulation of hydrophobic drugs so that they can be aqueously dispersed without chemical derivatization, which lead to favourable solubility characteristics[8].

3. Mechanisms of Solubility Enhancement

Dendrimers enhance drug solubility through several distinct but often complementary mechanisms, each relying on their unique structural and physicochemical features.

Table 1: Mechanisms by Which Dendrimers Enhance Solubility

Mechanism	Description
Encapsulation	Physical entrapment of drug molecules within the hydrophobic core of dendrimers[9]
Surface Adsorption	Adsorption onto external hydrophobic regions of dendrimer branches[10]
Electrostatic Interaction	Ionic interactions with oppositely charged drug molecules, especially anions[11]
Hydrogen Bonding	Interaction with polar drug moieties via hydrogen bonds formed with surface groups[12]
Covalent Conjugation	Chemical attachment of drugs via labile bonds, forming prodrug-dendrimer conjugates[13]

These mechanisms, alone or in combination, contribute to the dispersion of insoluble drugs in

aqueous systems and facilitate their absorption across biological membranes.

Figure 1: Illustrative representation of key solubilization mechanisms mediated by dendrimers

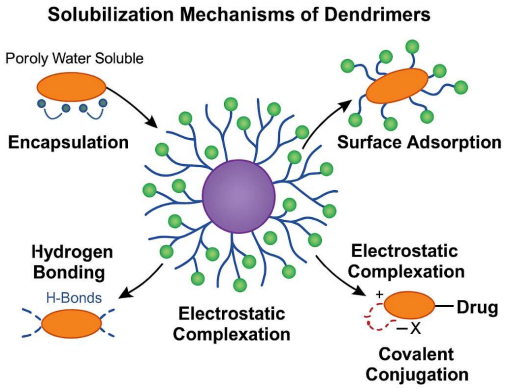

Figure 1, visually summarizes the five distinct pathways through which dendrimers enhance drug solubility, thereby complementing the textual explanation of Table 1.

4. Influence of Dendrimer Generation and Molecular Weight

The solubility-enhancing potential of dendrimers is closely related to their generation number and corresponding molecular weight. Each generation increment introduces a new layer of branching, thereby increasing molecular size, terminal functional groups, and interior volume. This progression influences the dendrimer's capacity for drug encapsulation, surface interaction, and solubility modulation.

4.1 Generation-Dependent Trends

Dendrimers exhibit generation-specific characteristics that determine their suitability for pharmaceutical applications:

Generations G0 to G2: These lower generations feature limited surface functionalities and internal cavities. Their small size restricts encapsulation potential, making them less effective for highly lipophilic or bulky drugs[14].

Generations G3 to G5: Considered optimal for solubility enhancement, these dendrimers provide a favourable balance between sufficient drug loading capacity and acceptable size for systemic administration. They exhibit reduced toxicity and maintain desirable pharmacokinetic properties[15].

Generations G6 and higher: While offering extensive drug-loading capabilities due to increased branching and larger molecular size, these dendrimers often suffer from increased cytotoxicity, potential immunogenicity, and poor renal excretion, limiting their clinical applicability unless appropriately modified (e.g., PEGylation)[16].

Figure 2: Correlation between dendrimer generation and solubilization efficiency

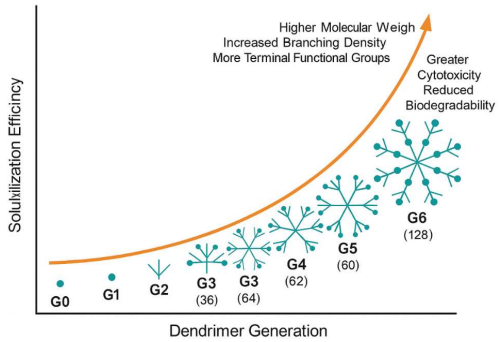

Figure 2, graphically represents how increasing dendrimer generations improve drug-loading and solubility but also introduces associated concerns like toxicity. It helps visualize the trade-off between solubility enhancement and biological safety.

4.2 Molecular Weight Correlation

An increase in dendrimer molecular weight directly correlates with enhanced drug solubilization capacity, primarily due to a larger number of binding sites and internal compartments[17]. However, this comes at the cost of reduced renal filtration, longer circulation half-life, and increased risk of accumulation in non-target tissues. Therefore, designing dendrimers with optimal molecular weight is essential to balancing efficacy and safety in drug delivery applications[18].

5. Examples of Dendrimer-Enhanced Formulations

Numerous preclinical and formulation studies have demonstrated the potential of dendrimers to enhance the aqueous solubility of various poorly soluble drugs, as summarized below:

Table 2: Examples of Drug Solubility Enhanced Using Dendrimers

Drug	Dendrimer Type	Generation	Fold Increase in Solubility	Reference
Paclitaxel	PAMAM	G4	~50×	19
Ibuprofen	PEG-PAMAM	G3	~30×	20
Nifedipine	PPI	G2	~20×	21
Ketoconazole	PAMAM-OH	G5	~40×	22

These formulations exemplify the effectiveness of dendrimer-based systems in achieving substantial improvements in solubility, especially for Biopharmaceutics Classification System (BCS) Class II and IV compounds.

6. Limitations and Challenges

While dendrimers offer substantial benefits in improving drug solubility and delivery, several limitations need to be addressed for their successful translation into clinical use.

6.1 Cytotoxicity

One of the most significant concerns associated with dendrimer use is their potential cytotoxicity, particularly for higher-generation, amine-terminated structures. These cationic dendrimers can interact with negatively charged cellular membranes, leading to membrane disruption, oxidative stress, and apoptosis[23]. Strategies such as PEGylation, acetylation, or surface neutralization are often employed to mitigate these effects and enhance biocompatibility[24].

Figure 3: Comparative analysis of cytotoxicity profiles across different dendrimer generations

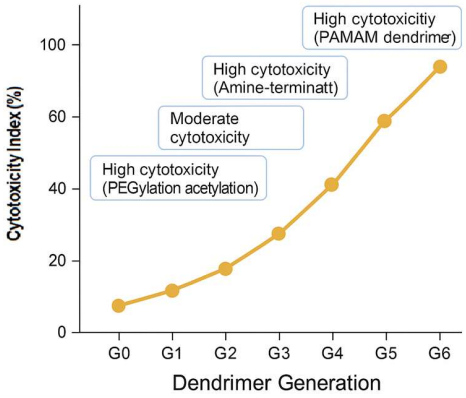

Figure 3, offers a visual reference that supports the argument for PEGylation and functional group modification to improve safety.

6.2 Complex Synthesis

The synthesis process of dendrimers is time-consuming and scrupulous, as multiple generations are required and the processes are repetitive- a factor that is expensive and time-consuming required to go through protection and deprotection. High yields with little structural defects are extremely expensive to achieve, and all the more so in later generations, which constrains scalability and the viability of the technology[25].

6.3 Regulatory and Safety Concerns

The newness and the synthetic aspect of dendrimers are of a significant regulatory concern in terms of long-term safety, biodegradability and environmental toxicity. Governmental organizations like FDA and EMA demand the availability of all-inclusive toxicological, pharmacokinetic, and biodistribution data before granting an approval, thus acting as an impediment to wide-scale usage[26].

6.4 Aggregation and Stability

At physiological conditions dendrimers can potentially aggregate (through pH changes or high ionic strength) causing precipitation, instability, and inconsistent release profiles of the drug. Such processes might cause a loss of formulation integrity and biological availability, and the stabilisation approaches are required when developing the formulation[27].

7. Future Perspectives and Innovation Trends

The further development of the dendrimer-based drug delivery systems can be placed under the background of the contemporary development of nanomedicine and the demands on precision therapeutics. A number of promising avenues are actively being pursued in order to circumvent the shortfalls of traditional dendrimers and increase their potential in solvation enhancing purposes.

7.1 Biodegradable Dendrimers

A future area that can be explored in dendrimers research is the development of biodegradable dendrimers which could be made out of by using natural or semi-synthetic biodegradable polymers such as citric-acid, lysine, or polyester backbones. These materials are broken down to form biocompatible byproducts thus limiting the potential of developing chronic toxicity and accrual particularly in the case of chronic delivery of ill-soluble drugs[28].

7.2 Stimuli-Responsive Dendrimer Systems

Site-specific delivery is being studied using responsive dendrimeric platforms that can have their drug payload released in response to some environmental cue, like a change in pH, or the activity of an enzyme, or a redox gradient, and so forth. Such carriers can be described as being smart because they will increase the solubility, as well as provide control release to the site of the disease resulting in a reduced number of adverse effects, as well as the systemic exposure[29].

7.3 Ligand-Modified and Targeted Dendrimers

In order to enhance the functionality of dendrimers even further, it is in investigation to replace the surface of dendrimers with targeting ligands that include folic acid, transferrin, peptides or antibodies. These alterations increase the tissue or even cellular specificity and ensure better uptake of drugs by respective target cells as well as the enhanced solubilization of drugs and increased efficiency of drugs[30].

7.4 Dendrimer Hybrids and Co-delivery Platforms

The hybrid systems involving dendrimers in combination with other nanocarriers such as micelles, liposomes or solid lipid nanoparticles are becoming of interest. They combine the advantages of both carriers and can provide physicians with multi-modal drug solubilization, sustained release and dual drug delivery properties-of special interest in complex pathologies like cancer[31].

7.5 Clinical Translation and Regulatory Advancements

While a few dendrimer-based formulations (e.g., VivaGel®) have arrived with clinical development, extensive clinical translation entails streamlined

manufacturing, better safety data, and consistent regulatory pathways. Innovations in dendrimer synthesis, green chemistry approaches, and machine-learning-assisted formulation design may accelerate this process in the coming years[32].

8. Conclusion

Dendrimers have emerged as structurally versatile, functionally rich, and clinically promising nanocarriers for addressing the long-standing challenge of poor drug solubility. Their unique architecture, comprising a central core, iterative branching units, and multiple terminal groups, enables multiple mechanisms of solubilization including encapsulation, surface adsorption, hydrogen bonding, and electrostatic complexation. By tailoring the generation, molecular weight, and surface chemistry, dendrimers can be optimized for enhanced drug loading, aqueous dispersion, and controlled release.

However, their widespread pharmaceutical application is contingent on resolving key challenges including synthetic complexity, cytotoxicity at higher generations, aggregation in biological systems, and regulatory ambiguity. Future strategies involving biodegradable backbones, stimuli-responsive release, and targeted ligand incorporation promise to unlock new horizons in solubility enhancement and precision drug delivery. With rigorous translational research and regulatory alignment, dendrimers may soon play a central role in enabling formulation success for an array of poorly soluble therapeutics.

9. Acknowledgments

The authors gratefully acknowledge the infrastructural and academic support provided by the all associated Departments. No external funding was utilized in the preparation of this review article. The authors declare no conflict of interest related to this work.

References

1. Kalepu S, Nekkanti V. Insoluble drug delivery strategies: review of recent advances and business prospects. Acta Pharm Sin B. 2015;5(5):442–453.
2. Svenson S, Tomalia DA. Dendrimers in biomedical applications—reflections on the field. Adv Drug Deliv Rev. 2012;64:102–115.
3. Jain NK, Gupta U. Application of dendrimer–drug complexation for solubility enhancement. Int J Pharm. 2008;361(1–2):460–470.
4. Mintzer MA, Grinstaff MW. Biomedical applications of dendrimers: a tutorial. Chem Soc Rev. 2011;40(1):173–190.
5. Sadekar S, Ghandehari H. Transepithelial transport and toxicity of PAMAM dendrimers: implications for oral drug delivery. Adv Drug Deliv Rev. 2012;64(6):571–588.
6. Tekade RK, Kumar PV, Jain NK. Dendrimers in oncology: an expanding horizon. Chem Rev. 2009;109(1):49–87.
7. Patri AK, Kukowska-Latallo JF, Baker JR. Targeted drug delivery with dendrimers: comparison of the release kinetics of covalently conjugated drug and non-covalent drug inclusion complex. Adv Drug Deliv Rev. 2005;57(15):2203–2214.
8. Kesharwani P, Jain K, Jain NK. Dendrimer as nanocarrier for drug delivery. Prog Polym Sci. 2014;39(2):268–307.
9. Choudhary S, Narang RK, Narang JK. Dendrimers: an overview of the latest advancements in drug delivery. Asian J Pharm Clin Res. 2013;6(Suppl 2):17–22.
10. Lee CC, MacKay JA, Fréchet JMJ, Szoka FC. Designing dendrimers for biological applications. Nat Biotechnol. 2005;23(12):1517–1526.
11. Sahoo SK, Labhasetwar V. Dendrimers in drug delivery. J Drug Target. 2003;11(7):399–409.
12. Biswas S, Torchilin VP. Dendrimers for siRNA delivery. Pharmaceutics. 2013;5(3):379–397.
13. Sherje AP, Jadhav M, Dravyakar BR, Kadam D. Dendrimers: a versatile nanocarrier for drug delivery and targeting. Int J Pharm. 2018;548(1):707–720.
14. Stiriba SE, Frey H, Haag R. Dendritic polymers in biomedical applications: from potential to clinical use in diagnostics and therapy. Angew Chem Int Ed Engl. 2002;41(8):1329–1334.
15. Kannan RM, Nance E, Kannan S, Tomalia DA. Emerging concepts in dendrimer-based nanomedicine: from design principles to clinical applications. J Intern Med. 2014;276(6):579–617.
16. Caminade AM, Turrin CO, Majoral JP. Dendrimer-based nanoparticles for drug delivery. Prog Polym Sci. 2020;103:101221.
17. Patri AK, Majoros IJ, Baker JR. Dendritic polymer macromolecular carriers for drug delivery. Curr Opin Chem Biol. 2002;6(4):466–471.
18. Mignani S, Rodrigues J, Tomas H, Zablocka M, Shi X, Majoral JP. Dendrimers in combination with natural products and analogues as anticancer agents. Chem Soc Rev. 2018;47(2):514–532.
19. Malik N, Evagorou EG, Duncan R. Dendrimer-platinate: a novel approach to cancer chemotherapy. Anticancer Drugs. 1999;10(8):767–776.
20. Florence AT, Hillery AM, Hussain N, Jani PU. Nanoparticles as carriers for oral

peptide absorption: studies on particle uptake and fate. Pharm Res. 1995;12(3):413–420.
21. He H, Li Y, Jia XR, Du J, Ying X, Lu WL, Lou JN, Wei Y, Wang JC, Zhang X. PEGylated poly(amidoamine) dendrimer-based dual-targeting carrier for treating brain tumors. Biomaterials. 2011;32(2):478–487.
22. Kesharwani P, Iyer AK. Recent advances in dendrimer-based nanovectors for tumor-targeted drug and gene delivery. Drug Discov Today. 2015;20(5):536–547.
23. Roberts JC, Bhalgat MK, Zera RT. Preliminary biological evaluation of polyamidoamine (PAMAM) dendrimers. J Biomed Mater Res. 1996;30(1):53–65.
24. Sharma A, Garg T, Aman A, Panchal K, Sharma R. Current trends in targeted drug delivery by dendrimers: an overview. J Biomed Nanotechnol. 2016;12(1):1–19.
25. Caminade AM, Turrin CO, Majoral JP. Synthesis of dendrimers and their use as drug delivery systems. Top Curr Chem. 2010;295:119–152.
26. Majoros IJ, Thomas TP, Mehta CB, Baker JR. Poly(amidoamine) dendrimer-based multifunctional engineered nanodevice for cancer therapy. J Med Chem. 2005;48(19):5892–5899.
27. Jain K, Kesharwani P, Gupta U, Jain NK. Dendrimer toxicity: Let's meet the challenge. Int J Pharm. 2010;394(1-2):122–142.
28. Kesharwani P, Iyer AK. Recent advances in biodegradable dendrimers for cancer therapy. Biomater Sci. 2015;3(8):1179–1190.
29. Duncan R, Izzo L. Dendrimer biocompatibility and toxicity. Adv Drug Deliv Rev. 2005;57(15):2215–2237.
30. Huang D, Wu D, Si Y, Wang T. Ligand-functionalized dendrimers for targeted drug delivery. Int J Nanomedicine. 2019;14:447–462.
31. Abbasi E, Aval SF, Akbarzadeh A, Milani M, Nasrabadi HT, Joo SW, Hanifehpour Y, Nejati-Koshki K, Pashaei-Asl R. Dendrimers: synthesis, applications, and properties. Nanoscale Res Lett. 2014;9(1):247.
32. Hawker CJ, Frechet JMJ. Designing dendrimers for drug delivery: a review of the synthesis and applications of dendritic polymers. J Chem Soc Rev. 2001;30(6):387–399.