



## Dendrimers as Drug Delivery Carriers in the Dentistry

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### Abstract

This review gives concise information about the application of dendrimers as drug delivery carrier in the field of drug delivery. Due to their unique architecture these have improved physical and chemical properties. Due to their terminal groups these show high solubility, miscibility and reactivity. Dendrimers have well defined size, shape, molecular weight and monodispersity. These properties make the dendrimers a suitable carrier in drug delivery application. Dendrimers are unimolecular micellar in nature and due to this enhances the solubility of poorly soluble drugs. Their compatibility with DNA, heparin and polyanions make them more versatile. Dendrimers, also referred as modern day polymers, they offer much more good properties than the conventional polymers. Due to their multivalent and mono disperse character dendrimers have stimulated wide interest in the field of chemistry biology, drug delivery, gene therapy and chemotherapy. Self-assembly produces a faster means of generating nanoscopic functional and structural systems. But their actual utility in drug delivery can be assessed only after deep understanding of factors affecting their properties and their behaviour in vivo.

**Keywords:** Dendrimers, Drug targeting, nanoscale carriers.

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## Introduction

Dendrimers are class of well-defined hyper branched synthetic polymer systems, which can be conjugated to various chemical species, such as detection agents, imaging agents, targeting components, biomolecules, pharmaceutical/ therapeutic agents, radio ligands, affinity ligands, for various bioanalytical applications<sup>1</sup>. The term “Dendrimer” arise from two Greek words; “Dendron” meaning tree and “Meros” meaning part. A typical dendrimer structure consists of three basic components: a multi-functional central core moiety where other molecules can be trapped<sup>2, 3</sup>, branched units that emanates from the central core and external capping groups. The highly regular branching units are organized in layers called “generations”, and represent the repeating monomer unit of these synthetic macromolecules<sup>4</sup>. Therefore, dendrimers can be synthesized from simple branched monomer units, in a precise and controlled fashion from trunk to branch and

to leaf “surface groups”. The three-dimensional structure of dendrimers gives them a variety of unique properties, such as nanoscaled globular shape, well-defined functional groups at the periphery, hydrophobic or hydrophilic cavities in the interior and extremely low polydispersity<sup>5</sup>, and thus a wide range of potential applications.

The precise control over the distribution of drugs is highly valuable to abolish the typical drawbacks of traditional medicine. In recent years, improved pharmacokinetics, biodistribution and controlled release of the drug to the specific targeted site has been achieved with polymer based drug delivery<sup>6</sup> Unlike traditional polymers, dendrimers have received considerable attention in biological applications due to their high water solubility,<sup>7</sup> biocompatibility,<sup>8</sup> polyvalency<sup>9</sup> and precise molecular weight.<sup>4</sup> These

features make them an ideal carrier for drug delivery and targeting applications. For investigating dendrimers

as drug delivery vehicles, their biopermeability across the biological membranes should be considered.

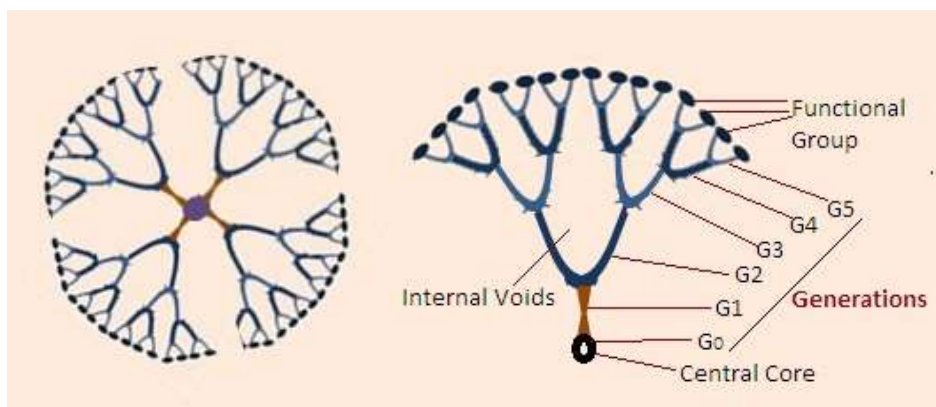


Figure 1: Schematic representation of the Dendrimer Structure<sup>1</sup>

Table 1: Various Dendrimer based marketed products for drug delivery, therapy and diagnosis

Name of Product	Type	Company	Use	Ref
Priostar	PEHAM/PEA	Starpharma	Targeted diagnostic and therapeutic delivery for cancer	10, 11
Starburst	PAMAM	Dow chemical	Targeted diagnostic and therapeutic delivery for cancer	12
Stratus CS	PAMAM	Dade Behring	Cardiac marker	13
Astramol®	PPI	Starpharma	-	14
Taxotere	ND	Sanofi Aventis	Anticancer drug delivery	-
SuperFect	PAMAM	Qiagen	Gene transfection	15,16
Alert ticket	PAMAM	US Army Research Lab.	Anthrax detection	17

ND: not define, PEHAM: Poly (etherhydroxylamine), PEA: Poly (esteramine), PAMAM: Polyamidoamine, PPI: Poly (propylene imine), HIV: Human immunodeficiency virus, STDs: Sexually transmitted diseases

### Application of Dendrimers in Drug delivery for dentistry

The development of dendrimer based efficient drug delivery systems has attracted a great deal of attention over the last few years. Unlike traditional polymers, dendrimers can be obtained in precise molecular weights even at high generations, which as previously highlighted can provide a reproducible pharmacokinetic behavior. This feature makes them ideal candidates for drug delivery applications.<sup>18,19</sup>

PAMAM dendrimers loaded with calcium and phosphate ions and have been used experimentally to prevent tooth decay. The loaded PAMAM dendrimer was effective for prolonged release of calcium and phosphate at low pH, with neutralization of the acidic environment and inhibition of dental caries.<sup>20</sup>

Many potential uses of dendrimer hydrogels (DH) as a drug delivery system in periodontics and implants

dentistry as they allow clinicians to customize drug release kinetics, mechanical properties, and in-situ gelling for specific clinical applications.<sup>21</sup>

Dendrimer-based dental composites have attracted attention because of the higher cross-link density, decreased water sorption and solubility, improved mechanical properties, and higher resin melting temperature.<sup>22,23</sup>

Triclosan, an effective antimicrobial agent encapsulated into the PAMAM dendrimer resulted in the solubilization of TCN, thus slow release of the drug and improved efficacy.<sup>24</sup>

PAMAM dendrimer loaded with different metronidazole concentrations showed prolonged release of the drug, thus proved to be a suitable vehicle for the delivery of antimicrobial drugs at the target site. Hence, it has a relevant application in periodontal therapy.<sup>25</sup>

Table 1: Reported work on dendrimers as drug delivery carrier in dentistry<sup>18</sup>

Source	Type of Dendrimer	Generation	Objective	Methodical approach	Outcome	Ref
(Dodiuk-Kenig et al., 2004)	PAMAM dendrimer	-	To check the adhesive properties of hyper-branched and dendritic polymers in acrylate-based dental composite	Commercial hyper-branched polyesteramide, two dendripolyamides and PAMAM dendrimer	<ul style="list-style-type: none"> <li>Compressive strength of dental composite with 0.3 wt% hyper-branched polyesteramide improved the from <math>253 \pm 20</math>MPa to <math>386 \pm 20</math>MPa</li> <li>The same composite showed reduction in linear shrinkage from <math>2.4 \pm 0.2\%</math> to <math>1.5 \pm 0.2\%</math></li> <li>Improved bond durability and shear bond strength with the above composition</li> </ul>	26
(Paul et al., 2006)	Methyl methacrylate dendrimer	-	To enhance the composite properties in dental additive	Highly branched, globular 2,3-dihydroxybenzyl motif to achieve multi-methacrylate dendritic additive	<ul style="list-style-type: none"> <li>Compared to control, addition of 0.5% multi-methacrylate dendritic additive showed 21–35% increase in flexural strength</li> <li>Flexural strength increased with higher molecular weight dendrimers</li> <li>Increase in additive concentration could not have positive effect on flexural strength</li> </ul>	27
(Gardiner et al., 2008)	PAMAM dendrimer	G3	Incorporation of triclosan in dendrimer to enhance solubility	$\pi$ - $\pi$ stacking between G3 dendrimer and the amino acid, phenylalanine to enhance solubility	<ul style="list-style-type: none"> <li>Solubilization of triclosan increased with increasing concentration of dendrimer due to ionisation effect</li> <li>Solubility of triclosan showed to improve with <math>\pi</math>-<math>\pi</math> stacking between dendrimer and phenylalanine at 1:21 ratio</li> <li>The increase in solubility could to reflected by change in pH</li> </ul>	24
(Kim et al.,	PAMAM dendrimer	G5	Modified G5 dendrimer could	G5 dendrimer with RGD ligand	<ul style="list-style-type: none"> <li>Western blot analysis suggested increase in</li> </ul>	28

<b>2010)</b>			bind to dental pulp cell to increase odontogenic potential		vascular endothelial growth factor, matrix extracellular phosphoglycoprotein, dentin sialoprotein and matrix protein through JNK pathway	
					<ul style="list-style-type: none"> <li>• Application of G5-RGD showed enhanced mineralization as evidenced by Von Kossa assay</li> </ul>	
<b>(Eichler et al., 2011)</b>	PAMAM dendrimer	G5	PAMAM dendrimer could modify adsorption/desorption behaviour of human saliva compared to self-assembled monolayers grafted surface	Surface of the periodontitis model grafted with PAMAM-NH <sub>2</sub>	<ul style="list-style-type: none"> <li>• Covalently bound PAMAM depicted decreased adherence of <i>Streptococcus gordonii</i> in absence of saliva</li> <li>• Same approach of repelling bacteria was observed even after saliva conditioning</li> <li>• Substitution of PAMAM lowers the amount of absorbed protein</li> </ul>	29
<b>(Li et al., 2013)</b>	PAMAM dendrimer	G3 and G4	Restorative substitution with PAMAM in human hard tissues to mimic the functions of noncollagenous proteins to promote mineralization	Carboxyl (-COOH) terminated G3 and G4 PAMAM dendrimers to substitute noncollagenous proteins on dentine surface	<ul style="list-style-type: none"> <li>• Monodispersed characteristics and steric hindrance property were reported advantageous</li> <li>• Bioinspired mineralization process in dentine environment was facilitated by G4 dendrimer</li> <li>• Dendritic structure could be a potential restorative material for biomineralized hard tissue</li> </ul>	30
<b>Dung Th et al. 2013</b>	PAMAM dendrimer	G5	To study the sustained release of metronidazole an antibacterial and antiprotozoal drug	A series of dendrimer G5-pluronic F127 nanofilms (at 1:10, 1:20 and 1:30 mole ratios), loaded with various percent of metronidazole	Dendrimers showed prolonged release of the drug, thus proved to be a suitable vehicle for the delivery of antimicrobial drugs at the target site.	25
<b>(Bengazi et al., 2014)</b>	Methyl methacrylate	-	To investigate the degree of utilization of	The commercial dendrimers of different methyl	<ul style="list-style-type: none"> <li>• Following heat induced polymerization, there</li> </ul>	31

	dendrimer		methyl methacrylate monomers in different dendrimer conjugated resins	methacrylate units (12 in D12 and 24 in D24) were incorporated in dental resin	<p>were 65% and 62% degree of conversion for D12 and D24, respectively</p> <ul style="list-style-type: none"> <li>Residual monomer contents were 1.0% and 1.5%, respectively for D12 and D24</li> <li>Following photo polymerization, degree of conversion decreased with increase in methyl methacrylate proportion and thus increase in residual monomer content</li> <li>Heat induced polymerization method was suggested as best method with degree of conversion and residual monomers</li> </ul>	
<b>(Galli et al., 2014)</b>	Poly(epsilon-n-lysine) dendron	G3	Dendritic approach to titanium surfaces could improve differentiation of osteoblastic cells and the activation of Wnt/b-catenin signalling	Phosphoserine-tethered poly(epsilon-lysine) dendrons in endosseous implants	<ul style="list-style-type: none"> <li>Dendrons showed increased expression of two osteoblastic markers, alkaline phosphatase and osteocalcin in primary bone marrow cells and murine osteoblastic MC3T3 cells</li> <li>Osteoclastogenesis opposing protein osteoprotegerin was found to get expressed significantly higher</li> <li>Wnt target genes, Wisp-2 and b-catenin were also showed increased expression</li> </ul>	32
<b>(Lin et al., 2017)</b>	PAMAM dendrimer	-	Application of dendrimer functionalized with nano-hydroxyapatite in dentin tubule occlusion	Modification of nano-hydroxyapatite with COOH-terminated PAMAM dendrimer	<ul style="list-style-type: none"> <li>Dendrimer functionalized nano-hydroxyapatite found to crosslink with collagen fibres</li> <li>Therefore, effective dental tubule occlusion reported</li> <li>Superior value of microhardness was observed with modified nano-</li> </ul>	33

					hydroxyapatite	
<b>(Tao et al., 2017)</b>	PAMAM dendrimer	G4	Determination of dentin remineralization extent with PAMAM dendrimer	PAMAM-OH, PAMAM-COOH, PAMAM-NH <sub>2</sub> coated dentin	<ul style="list-style-type: none"> <li>• Dentin coated with PAMAM containing different functional groups showed increased hardness of dentin, reduced loss of mineral and lesion depth, with higher remineralization capability</li> <li>• Lower mineral loss and lesion depth with higher dentin tubule blocking effect was shown by PAMAM-COOH, PAMAM-NH<sub>2</sub> than PAMAM-OH</li> <li>• Effects of PAMAM-COOH, PAMAM-NH<sub>2</sub> dentin remineralization were comparable</li> </ul>	34
<b>(Xiao et al., 2017)</b>	PAMAM dendrimer	G3	Development of bioactive multifunctional composite (BMC) <i>via</i> nanoparticles of amorphous calcium phosphate, 2-methacryloyloxyethyl phosphorylcholine, dimethylamino-hexadecyl methacrylate and silver nanoparticles for class V restoration Investigation of BMC with PAMAM dendrimer on remineralization of demineralized root dentin in a cyclic artificial saliva/lactic acid environment for the first time	BMC complex mixture with nanoparticles of amorphous calcium phosphate, 2-methacryloyloxyethyl phosphorylcholine, dimethylamino-hexadecyl methacrylate and silver nanoparticles And BMC with PAMAM dendrimer	<ul style="list-style-type: none"> <li>• PAMAM with BMC showed superior dentin mineralization characteristics</li> <li>• The hardness of the dentin increased enough to match healthy root dentin</li> <li>• PAMAM with BMC induced complete and effective root dentin remineralization in an acid challenge environment</li> </ul>	35
<b>(Ge et al., 2017)</b>	PAMAM dendrimer	G3	The anti-carries effect and mechanical properties of the modified adhesive in biofilm regulation and remineralization	PAMAM and dimethylaminododecyl methacrylate in biofilm adhesive	<ul style="list-style-type: none"> <li>• Addition of PAMAM and dimethylaminododecyl methacrylate in adhesive showed no adverse effect on dentin bond strength</li> </ul>	36

			capabilities		<ul style="list-style-type: none"> <li>The modified adhesive with 1% PAMAM and 5% dimethylaminododecyl methacrylate showed anti-biofilm properties and developed a healthier biofilm to reduce the chances of dental caries</li> <li>Remineralization capabilities of the modified adhesive was found to have similarity with 1% PAMAM modified adhesive</li> </ul>	
<b>El-Aziz Khater et al 2018</b>	PAMAM dendrimer		to evaluate the remineralizing effect of PAMAM dendrimer, Gluteraldehyde and their combination on demineralized dentin	luter aldehyde was applied to the demineralized dentin, Group (III), (n=10): a combination of PAMAM dendrimer and Gluteraldehyde	All treatment materials used were effective in increasing dentin microhardness and produced micromorphological changes of the dentin surface in	37
<b>K. Liang et al 2019</b>	PAMAM dendrimer		Ca Delivery to prevent tooth decay	dendrimers loaded with calcium and phosphate ions	The loaded PAMAM dendrimer was effective for prolonged release of calcium and phosphate at low pH, with neutralization of the acidic environment and inhibition of dental caries	20
<b>Nicholas Yesbeck 2021</b>	PAMAM dendrimer	G5	to prolong the release kinetics of antibiotics	Dendrimer hydrogels were synthesized from PAMAM and PEG diacrylate to contain Cefazolin	Dendrimer hydrogels is a promising platform for long-term release of cefazolin in-vitro	21
<b>Ramyaa Shri K et al 2021</b>	PAMAM dendrimer		To develop PAMAM dendrimer to enhance the antibacterial activity	Entrapping dexamethasone into the dendrimer's cavities was done to ensure a slow release of the drug	PAMAM dendrimer's functionalization to silver nanoparticles to protect the nanoparticles from aggregating and reducing its cytotoxicity without affecting the antibacterial properties	22

## Conclusion

PAMAM dendrimer has shown to have marked prospective to be used as biomimetic biomaterial for remineralisation of enamel.<sup>18</sup> Addition of dendrimers has shown significant enhancement of mechanical properties of adhesive systems and reduction in

polymerization shrinkage of dental composites. It also causes improvement in shear strength and better bonding durability of adhesive systems<sup>26, 27</sup>. Besides drug delivery, dendrimers have been found to have a great emphasis in gene delivery, boron neutron capture therapy, PDT and as magnetic resonance imaging contrast agents. Boosting of commercial applications of

dendrimer technology will provide strength for its usefulness in future.

### Conflict of Interests

The authors declare that there is no conflict of interests

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