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PEGylated Poly(amidoamine) Dendrimer as Drug Loading Vehicles: Bibliometric Analysis Using Google Scholar Indexed VOSviewer

Dendrimer Poli(amidoamine) PEGylated sebagai Kendaraan Pemuatan Obat: Analisis Bibliometrik Menggunakan VOSviewer Terindeks Google Scholar

Jessica Veronica[1], Asep Bayu Dani Nandiyanto[1*]

[1]Departemen Pendidikan Kimia, Universitas Pendidikan Indonesia, Jl. Setiabudi No. 229, Bandung 40154, Indonesia
*email: nandiyanto@upi.edu

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ABSTRAK

Penelitian ini bertujuan untuk menganalisis ruang lingkup penelitian terkait bahan dendrimer PEGylated poly(amidoamine) (PAMAM) sebagai pembawa obat dengan menggunakan evaluasi bibliometrik dan pemetaan data dengan software VOSViewer. Data penelitian bahan dendrimer PAMAM PEGylated dikumpulkan dari database Google Scholar dengan kriteria berupa jurnal dengan kata kunci PEGylated, polyamidoamine, PAMAM, dendrimer, sintesis, dan penghantaran obat pada tahun 2018-2023. Berdasarkan hasil penelusuran, ditemukan 500 artikel jurnal yang relevan. Jumlah artikel pada tahun 2018-2021 terus meningkat namun terjadi penurunan drastis pada tahun 2022-2023. Hal ini disebabkan oleh pandemi COVID-19 yang terjadi secara global. Penelitian ini dapat memberikan informasi mengenai pola sebaran artikel jurnal dan kualitas perkembangan penelitian dendrimer PAMAM PEGylated selama 5 tahun terakhir. Analisis bibliometrik ini diharapkan dapat membantu peneliti untuk mengenali tren penelitian dendrimer PAMAM PEGylated sebagai kendaraan pemuatan obat secara global dan merekomendasikan prospek penelitian di masa depan.

Kata kunci: Dendrimer poli(amidoamine) PEGylated, media pemuatan obat, VOSViewer, bibliometrik.

ABSTRACT

This study aims to analyze the scope of research related to PEGylated poly(amidoamine) dendrimer material (PAMAM) as drug loading vehicles using bibliometric evaluation and data mapping with VOSViewer software. Research data on PEGylated PAMAM dendrimer materials was collected from the Google Scholar database with criteria in the form of journals with the keywords PEGylated, polyamidoamine, PAMAM, dendrimer, synthesis, and drug delivery in 2018-2023. Based on the search results, 500 relevant journal articles were found. The number of articles in 2018-2021 has increased steadily but there has been a drastic decline in 2022-2023. This is due to the COVID-19 pandemic that is happening globally. This study can provide information on the pattern of distribution of journal articles and the quality of research developments on PEGylated PAMAM dendrimer over the last 5 years. This bibliometric analysis is expected to help researchers to recognize research trends in PEGylated PAMAM dendrimer as drug loading vehicles globally and to recommend research prospects for the future.

Keywords: *PEGylated poly(amidoamine) dendrimer, drug loading vehicles, VOSViewer, bibliometrics.*

INTRODUCTION

Recent years, the design and synthesis of new nanomaterials as drug loading vehicles have been extensively researched and resulted in advances in applications. A nanomedical dendrimer polymer is one of the materials that has attracted significant interest due to its monodisperse structure and distinctive hyperbranched (Diaz et al., 2018). According to Rami et al., (2022) and Asghar et al., (2019), dendrimer are globular, three-dimensional, and well-ordered synthetic polymetric nanoparticles (Ahmed et al., 2021; Narmani et al., 2019). The initiator multifunctional core, which serves as a "germination seed" or anchor point for dendrimer growth, the inner layer and branches that will form generations, and the outer layer, which is the terminal branch, are the components of this molecule (de Araújo et al., 2018; Lyu et al., 2019).

One of the first dendrimer families that had been synthesized and characterized was the poly(amidoamine) (PAMAM) dendrimer (Mahmoudi et al., 2019). The PAMAM dendrimer is an advantageous choice for use in drug loading vehicles due to its small dimensions (1-100 nm) and loading characteristics (Narmani et al., 2019). This dendrimer is formed using an ethylenediamine or ammonia core with polyamide repeating units, a tertiary amine, and a rim containing the primary amine (Diaz et al., 2018). PAMAM dendrimer can be synthesized in several ways, namely polymerization of different stepwise growth in layer by layer which is usually expressed in 'generations' (G) (de Araújo et al., 2018). Layers of repeating units radially attach to the core leading to the progressive generation of dendrimer with well-defined molecular structures, branching points, terminal functional chemistry, and very low polydispersity (Kheraldine et al., 2021). Based on previous research, it is known that PAMAM dendrimer with low generation (G0-G3) tend to form open and amorphous structures so that they do not show well-defined internal characteristics, whereas for PAMAM dendrimer with high generation (G4-G10) a spherical dendrimer structure will form and rigidity which allows for the encapsulation of the drug through its branches (Sorroza-Martínez et al., 2020).

PAMAM dendrimer modifications such as PAMAM PEGylation dendrimer (Ho et al., 2019), PAMAM-Pyrrolidine dendrimer (Singhania et al., 2020), PAMAM carboxymethyl chitosan dendrimer (Zhou et al., 2021), PAMAM termination amino dendrimer (Cheng & Kaifer, 2022), and PAMAM acylation dendrimer (Lee et al., 2020) have all been explored in the context of studies. Numerous studies on PAMAM dendrimers have been used considering these findings. However, since there were no studies discussing the bibliometric analysis and mapping procedures using VOSViewer, PEGylated PAMAM dendrimers were selected for analysis. Furthermore, by providing an additional platform for combining drug molecules, the modification of the PAMAM dendrimer using polyethylene glycol (PEG) will increase the solubility of hydrophobic molecules and prolong drug delivery (Ahmed et al., 2021). Therefore, this analysis is important to determine the quantity and novelty of PEGylated PAMAM dendrimer as drug loading vehicles.

The aim of this study is to evaluate the scope of research on PEGylated PAMAM dendrimer materials as drug delivery systems by bibliometric analysis, data visualization, and Google Scholar indexing. Using the keywords PEGylated, polyamidoamine, PAMAM, dendrimer, synthesis, and drug delivery, a total of 500 journal papers from the last five years (2018-2023) have been found. According to

Nandiyanto et al., (2020), bibliometric analysis will be helpful in developing data sets that are used to raise the quality of further research (Nandiyanto et al., 2020). The distribution of publication types and the scope of the topics covered in this study are used in the bibliometric analysis.

METHOD

The bibliometric analysis was carried out in several stages:

(i) Data collection was carried out using Harzing Publish or Perish 8 software. On April 25 2023, data was collected through scanning up journal papers using the keywords dendrimer, synthesis, polyamidoamine, PEGylated, and drug delivery. The Google Scholar database was used to collect research data for the most recent five years (2018–2023). 500 journal papers were the results and these were processed using Microsoft Excel. Since Google Scholar is a free and accessible database of scientific articles, it was selected as the database for bibliometric analysis.

(ii) Data Screening. The data that has been collected is selected based on the relevance of the topic, the title of the article, and the year of publication. The data that has been screened is then processed using Microsoft Excel and VOSViewer software.

(iii) Data analysis and visualization. The data that has been screened and processed is then sorted by year and ranking using Microsoft Excel. VOSViewer is used for analyzing clusters, network visualization, and density mapping. Previous studies have supplied explanations of the analysis and data visualization processes (Al Husaeni & Nandiyanto, 2021).

RESULTS AND DISCUSSION

The results of the bibliometric analysis in relation to the development of study on PEGylated PAMAM dendrimer as drug loading vehicles are divided into the following sections:

3.1. Development of Research on the Topic of PEGylated PAMAM Dendrimer as Drug Loading Vehicles.

The results of research developments on PEGylated poly(amidoamine) dendrimer material as drug loading vehicles over the past 5 years (2018-2023) are processed into the graph shown in **Figure 1**. According to **Figure 1**, the overall number of research publications has been rising continuously through 2021. There were 75 journal publications published in 2018. The number of journal articles that were eventually published increased to 81 in 2019, 103 in 2020, and 118 in 2021. The number of journal papers published decreased to 98 and 25 in 2022 and 2023, respectively. The worldwide COVID-19 epidemic is the reason for this decrease in numbers. The COVID-19 pandemic has impacted access to laboratories, the distribution of synthesis-related raw materials, and the implementation of strict regulations for physical distance (Durant et al., 2020).

The top 20 papers with the highest Google Scholar Rank (GSRank) out of 500 journal articles collected from the Google Scholar database are shown in **Table 1**.

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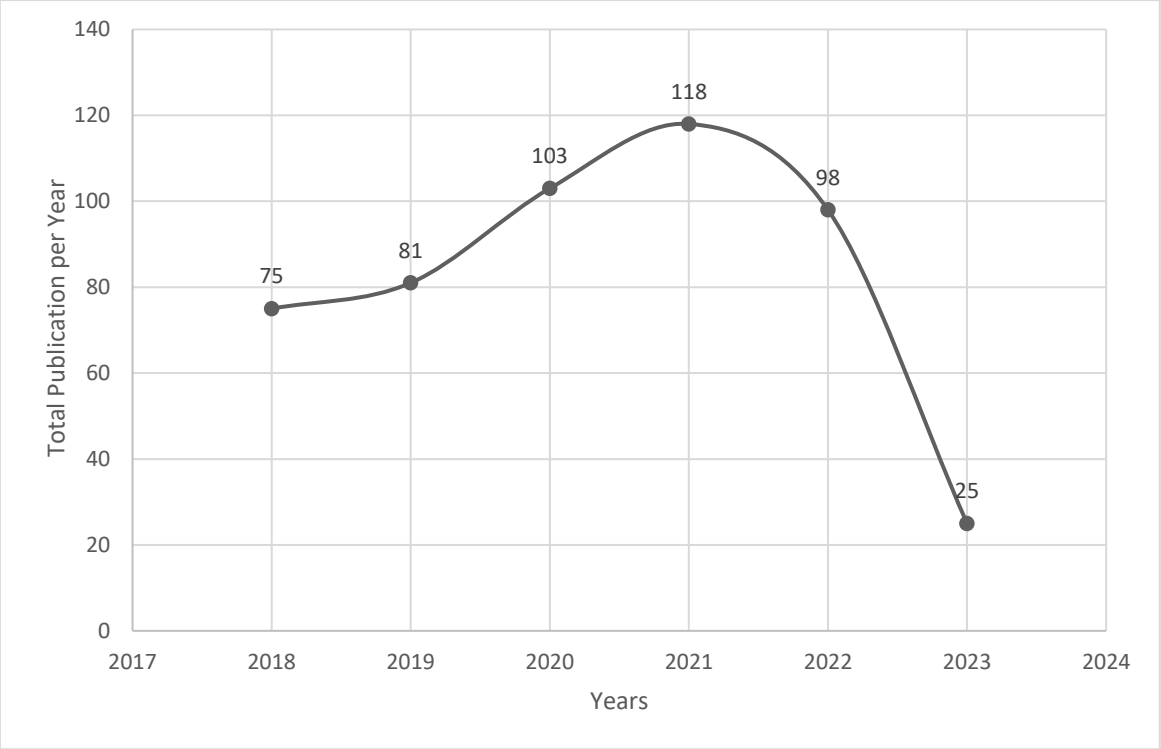

Figure 1. Level of research development related to PEGylated PAMAM dendrimer material as drug loading vehicles.

Table 1. List of articles with GSRank.

Rank	Authors	Year	Title	Source	Cites
1	DTD Nguyen, LG Bach, TH Nguyen, MH Ho, MN Ho, DH Nguyen, CK Nguyen, TTH Thi	2019	Preparation and characterization of oxaliplatin drug delivery vehicle based on PEGylated half-generation PAMAM dendrimer	Journal of Polymer Research	18
2	R Ahmed, M Aucamp, N Ebrahim, H Samsodien	2021	Supramolecular assembly of rifampicin and PEGylated PAMAM dendrimer as a novel conjugate for tuberculosis	Journal of Drug Delivery Science and Technology	10
3	J Li, H Liang, J Liu, Z Wang	2018	Poly (amidoamine)(PAMAM) dendrimer mediated delivery of drug and pDNA/siRNA for cancer therapy	International journal of pharmaceutics	216
4	M Fana, J Gallien, B Srinageshwar, GL Dunbar, J Rossignol	2020	PAMAM dendrimer nanomolecules utilized as drug delivery systems for potential treatment of glioblastoma: a systematic review	International Journal of Nanomedicine	53
5	SVK Rompicharla, P Kumari, H Bhatt, B Ghosh, S Biswas	2019	Biotin functionalized PEGylated poly (amidoamine) dendrimer conjugate for active targeting of paclitaxel in cancer	International Journal of Pharmaceutics	54
6	A Mahmoudi, MR Jaafari, N Ramezanian, L Gholami, B Malaekeh-Nikouei	2019	BR2 and CyLoP1 enhance in-vivo SN38 delivery using pegylated PAMAM dendrimers	International Journal of Pharmaceutics	17

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Rank	Authors	Year	Title	Source	Cites
7	J Wang, B Li, L Qiu, X Qiao, H Yang	2022	Dendrimer-based drug delivery systems: history, challenges, and latest developments	Journal of Biological Engineering	16
8	RS Ambekar, M Choudhary, B Kandasubramanian	2020	Recent advances in dendrimer-based nanoplatform for cancer treatment: A review	European Polymer Journal	72
9	AK Jangid, K Patel, U Joshi, S Patel, A Singh, D Pooja, VA Saharan, H Kulhari	2022	PEGylated G4 dendrimers as a promising nanocarrier for piperlongumine delivery: Synthesis, characterization, and anticancer activity	European Polymer Journal	3
10	Y Lu, S Han, H Zheng, R Ma, Y Ping, J Zou, H Tang, Y Zhang, X Xu, F Li	2018	A novel RGDyC/PEG co-modified PAMAM dendrimer-loaded arsenic trioxide of glioma targeting delivery system	International Journal of Nanomedicine	56
11	RK Sahoo, A Gothwal, S Rani, KT Nakhate, Ajazuddin, U Gupta	2020	PEGylated dendrimer mediated delivery of bortezomib: drug conjugation versus encapsulation	International Journal of Pharmaceutics	16
12	MT Vu, LG Bach, DC Nguyen, MN Ho, NH Nguyen, NQ Tran, DH Nguyen, CK Nguyen, TTH Thi	2019	Modified carboxyl-terminated PAMAM dendrimers as great cytocompatible nano-based drug delivery system	International Journal of Molecular Sciences	35
13	MN Ho, LG Bach, TH Nguyen, MH Ho, DH Nguyen, CK Nguyen, CH Nguyen, NV Nguyen, TTH Thi	2019	PEGylated poly (amidoamine) dendrimers-based drug loading vehicles for delivering carboplatin in treatment of various cancerous cells	Journal of Nanoparticle Research	13
14	SD Santos, M Xavier, DM Leite, DA Moreira, B Custódio, M Torrado, R Castro, V Leiro, J Rodrigues, H Tomás, AP Pêgo	2018	PAMAM dendrimers: blood-brain barrier transport and neuronal uptake after focal brain ischemia	Journal of Controlled Release	51
15	R Kharwade, S More, A Warokar, P Agrawal, N Mahajan	2020	Starburst pamam dendrimers: Synthetic approaches, surface modifications, and biomedical applications	Arabian Journal of Chemistry	37
16	M Alibolandi, F Hoseini, M Mohammadi, P Ramezani, E Einafshar, SM Taghdisi, M Ramezani, K Abnous	2018	Curcumin-entrapped MUC-1 aptamer targeted dendrimer-gold hybrid nanostructure as a theranostic system for colon adenocarcinoma	International Journal of Pharmaceutics	69
17	KS Sadi, A Mahmoudi, MR Jaafari, SA Moosavian, B Malaekeh-Nikouei	2022	The effect of AS1411 aptamer on anti-tumor effects of dendrimers containing SN38	Journal of Drug Delivery Science and Technology	0
18	A Sheikh, P Kesharwani	2021	An insight into aptamer engineered dendrimer for cancer therapy	European Polymer Journal	32
19	D Yadav, BC Semwal, HK Dewangan	2022	Grafting, characterization and enhancement of therapeutic activity of berberine loaded PEGylated PAMAM dendrimer for cancerous cell	Journal of Biomaterials Science, Polymer Edition	1

Rank	Authors	Year	Title	Source	Cites
20	V Saluja, A Mankoo, GK Saraogi, MM Tambuwala, V Mishra	2019	Smart dendrimers: Synergizing the targeting of anticancer bioactives	Journal of Drug Delivery Science and Technology	31

Based on **Table 1**, three journal articles with the highest GSRanks were published in the Journal of Polymer Research, Journal of Drug Delivery Science and Technology, and International Journal of Pharmaceutics.

3.2. Visualization of VOSViewer on the Topic of PEGylated PAMAM Dendrimer as Drug Loading Vehicles

Studies regarding the use of PEGylated PAMAM dendrimer as drug loading vehicles can be categorized into 4 clusters using the mapping analysis, with the following details:

(i) Cluster 1 is marked in red which contains 9 items, namely advance, characterization, drug delivery application, nano, nanomedicine, PEGylated, PEGylated pamam dendrimer, research, and targeted delivery.
(ii) Cluster 2 is marked in green which contains 4 items, namely delivery system, drug carrier, nanotechnology, and tumor.
(iii) Cluster 3 is marked in blue which contains 4 items, namely breast cancer, generation, pamam, and polyamidoamine.
(iv) Cluster 4 is marked in yellow which contains 3 items, namely biomedical application, drug release, and PEGylated dendrimer.

3.3. Network Visualization on the Topic of PEGylated PAMAM Dendrimer as Drug Loading Vehicles

The relationships between items in the four clusters are illustrated through the network visualization shown in **Figure 2**. The relationships in the network visualization are depicted by connected lines between one item and another. Meanwhile, the summary related to total strength and occurrences based on PEGylated poly(amidoamine) dendrimer as drug loading vehicles for each cluster is shown in **Table 2**.

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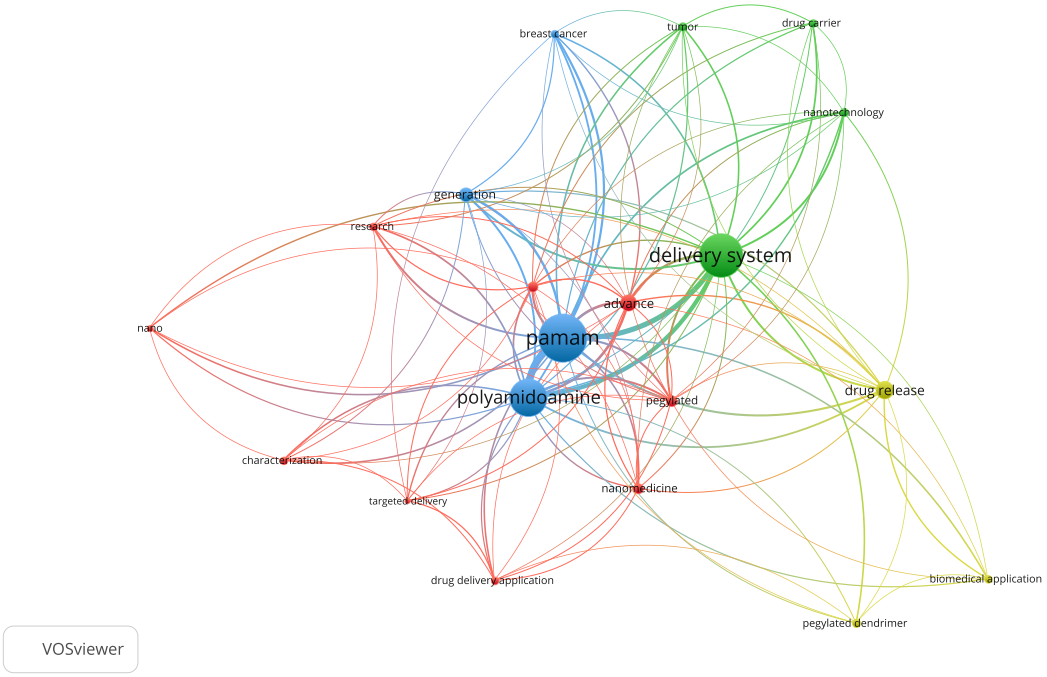

Figure 1. Network visualization on the topic of PEGylated poly(amidoamine) dendrimer as drug loading vehicles.

Table 2. Total strength and occurence based on the topic of PEGylated poly(amidoamine) dendrimer as drug loading vehicles.

Cluster	Total Strength	Total Occurence
1	276	169
2	246	200
3	598	348
4	75	76

3.4. Density Visualization on the Topic of PEGylated PAMAM Dendrimer as Drug Loading Vehicles

Density visualization related to the topic development of PEGylated poly(amidoamine) dendrimer as drug loading vehicles is shown in **Figure 3**. An intense yellow color on an item indicates the closeness between the items in the published article and the green color indicates the distance between the items. Item delivery system, PAMAM, and polyamidoamine in clusters 2 and 3 are the items that have the closest relationship with the topic.

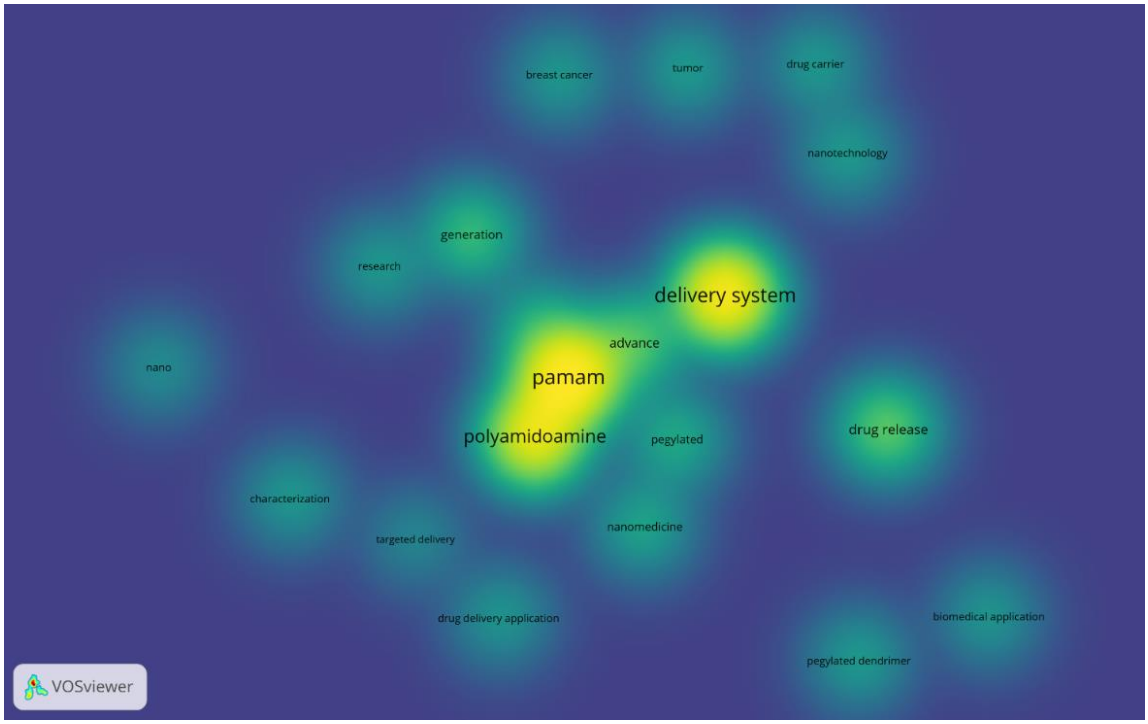

Figure 2. PEGylated poly(amidoamine) dendrimer topic density mapping as drug loading vehicles.

CONCLUSION

Based on the results of bibliometric analysis and mapping using VOSViewer software related to material topics and applications in the last 5 years (2018-2023), 500 relevant journal articles were obtained. The highest number of published articles was 118 in 2021. The decrease in the number of articles in 2022 and 2023 was due to the COVID-19 pandemic. The items that are very closely related to the topic of PEGylated PAMAM dendrimer as drug loading vehicles are delivery systems, pumps, and polyamidoamine which are located in clusters 2 and 3. This bibliometric analysis is expected to be used as material for consideration in research on PEGylation PAMAM dendrimer as drug loading vehicles namely delivery systems in the future.

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