Exp Oncol 2018
40, 3, 178–183

REVIEW

Experimental ONCOLOGY

ROLE OF DENDRIMERS IN ADVANCED DRUG DELIVERY AND BIOMEDICAL APPLICATIONS: A REVIEW

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***Aim*: Dendrimers dendritic structural design holds vast promises, predominantly for drug delivery, owing to their unique properties. Dendritic architecture is widespread topology found in nature and offers development of specific properties of chemical substances. Dendrimers are an ideal delivery vehicle candidate for open study of the effects of polymer size, charge, and composition on biologically relevant properties such as lipid bilayer interactions, cytotoxicity, bio-distribution, internalization, blood plasma retention time, and filtration. This article reviews role of dendrimers in advanced drug delivery and biomedical applications.**
***Key Words*: dendrimers, drug delivery vehicle, lipid bilayer interactions, dendritic architecture.**

Dendrimers are exceedingly branched, globular macromolecules with many arms emanating from a central core [1, 2]. The atomistic feature of dendrimer structure has lagged behind this fast progress in synthesis and design [3]. To date, more than fifty families of dendrimers exist, possessing unique properties, since the surface, interior and core can be tailored to diverse types of applications [4].The derivatization of low molecular weight and protein-based therapeutics with polymers has been shown to advance their pharmacokinetic and pharmacodynamic properties [5, 6]. One of the most talented applications of nanotechnology is in the field of medicine. Certainly, a whole novel field of "nanomedicine" is promising [7]. Nanomedicine plays a vital role to advance drug delivery, cancer treatment, and so on. Dendrimers are nano-sized, radially symmetric molecules with fine-defined, homogeneous and monodisperse composition consisting of tree-like arms or embranchment [8, 9]. Dendrimers are identified by unique properties like globular shape, well defined three dimensional structure, cavities, high functionality and small size. These properties make them unique for using in nanotechnology and diverse biomedical applications [10–12]. Dendrimer structures are formed with a fundamental atom or group of atoms tagged as the core. From this central structure, branches of other atoms called "dendrons" raise through diverse chemical reactions [8].

Dendrimers show considerably enhanced physical and chemical properties compared to traditional linear polymers. A number of significant properties of dendrimers are: (1) *monodispersity*; (2) *nano-size and shape*; (3) *biocompatibility*; (4) *periphery charge*; (5) *dendrimer-membrane interaction*; and (6) *pharmacokinetics* [13–17].

Submitted: March 15, 2018
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Abbreviations used: DTPA – diethylenetriamine pentaacetic acid; MRI – magnetic resonance imaging; NSAIDs – nonsteroidal anti-inflammatory drugs; PAMAM – polyamidoamine; PDT – photodynamic therapy; PEG – polyethylene glycol; RNAi – RNA interference; siRNA – small interfering RNAs.

TYPES OF DENDRIMERS

A quick growth of dendritic new carrier has been probable because of recent advances in synthetic chemistry and characterization methods. Also a variety of dendritic scaffolds has become accessible with defined nanoscopic size and plenty numbers of functional end groups [18].

Nowadays there are more than fifty families of dendrimers each with unique properties that are undergoing investigation for use in a diversity of different biomedical applications [19]. Dendritic polymers are similar to proteins, enzymes, and viruses, and are simply functionalized. Dendrimers and other molecules can either be linked to the rim or can be encapsulated in their internal holes. Current medicine uses a diversity of this material as potential blood substitutes, for example polyamidoamine (PAMAM) dendrimers [20]. For instance, phosphorus-containing dendrimers have demonstrated antiprion activity and can potentially be used as inductors for gene therapy Boronated starburst PAMAM dendrimer-monoclonal. Antibody immune compounds as potentially effective anticancer reagent containing boron neutron capture were used [21, 22].

APPLICATIONS

Multifunctional end groups and occurrence of various internal cavities cause to be dendrimers appropriate for possible pharmaceutical uses counting a variety of therapeutic and biomedical applications [23–25].

Dendrimers and various routes of drug delivery. Nano scale materials have unique properties, such as structural uniformity, efficient membrane transport, high purity, high drug pay load, good colloidal, targeting potential, and shelf stability. Because of these unique features, dendrimers are one of the talented technologies of recent times and have served as an exceptional platform to reach the development as new drug delivery scaffolds; for instance, PAMAM dendrimers have carried the antitumor drug methotrexate and fluorescein for tracking [26–28]. The best dendrimer must have a low molecular weight to be effortlessly filtered by the kidneys [29]. Due to the unique characteristics of dendrimers, such as well-defined size, shape, molecular weight and monodispersity, these molecules have wide applications in drug delivery [30, 31]. Drug molecules can be physically trapped inside the dendrimers or be adsorbed on the dendrimer surfaces using electrostatic interaction, hydrogen bonding, or van der Waals force. Drug molecules can also be covalently attached on the dendrimer surfaces to provide dendrimer-drug conjugates [32].

Oral drug delivery. Among the various routes of drug delivery, the oral route is may be the one mostly favored by patients and clinicians. For several available and novel drugs for example peptidomimetics, therapeutic peptides, oligonucleotides and other cases, oral bioavailability is in the most of cases below passable levels. To control this problem and to guaranty an adequate high oral absorption, the use of effective oral drug delivery systems is significant [33]. An effective oral macromolecular drug carrier should have the capability to prevent the drugs from degrading. They might decrease non-specific interactions with food proteins and let increased absorption through the intestinal epithelium. The potential use of PAMAM dendrimers as oral drug delivery carriers have been demonstrated by several studies [34–44]. In a study that was done by Kitchens *et al.* [45] it was demonstrated that transepithelial transport and microvascular extravasation of PAMAM dendrimers are dependent upon their structural properties such as molecular geometry, molecular size, and surface chemistry. These consequences indicate that by optimizing factors such as the size and surface charge of PAMAM dendrimers, it is possible to expand oral drug delivery systems based on these carriers.

Ocular drug delivery. Dendrimers have attracted remarkable attention as ocular drug delivery systems, because of their tailorable structure, well-defined size and potentially favorable ocular biodistribution [46]. Surface-modified PAMAM dendrimers with carboxylic or hydroxyl surface groups, have been reported in increasing residence time and improving bioavailability of pilocarpine in the eye [47]. Conjugating of dendrimers with polyethylene glycol (PEG), create hydrogels that have applications including cartilage tissue production and for sealing ophthalmic injuries [48, 49]. Consequently, the improvement of ocular drug delivery by dendrimers may be a promising method for clinical applications.

Transdermal drug delivery. Drug delivery via the skin to get a systemic effect of drug is generally known as transdermal drug delivery [50]. The permeability of dendrimers via the skin is determined by physicochemical parameters such as surface charge, molecular weight, generation size, composition and concentration [51, 52]. Dendrimers have been demonstrated to be effective as transdermal drug delivery systems for nonsteroidal anti-inflammatory drugs (NSAIDs), antimicrobial, antiviral, anticancer or antihypertensive drugs. Yiyun *et al.* [53] and other researchers have shown that PAMAM dendrimers can considerably increase transdermal delivery of diflunisal and ketoprofen, two model NSAIDs [53, 54]. Encapsulation of cisplatin, a platinum based anticancer drug into PAMAM dendrimers gave conjugates that presented higher accumulation in solid tumors, slower release, and lower toxicity compared to drug [55, 56].

Targeted drug delivery. Targeted drug delivery is a technique of delivering a therapeutic agent to a specific cell type or tissue in a site-specific manner. Dendrimers have been studied as one kind of vehicle for application in targeted drug delivery [1, 2, 57, 58]. Targeted delivery of chemotherapeutics to tumor cells decreased side effects compared to systemic delivery [49]. Patri *et al.* [57] reported the synthesis of generation 5 PAMAM dendrimer conjugated with folic acid for the targeted delivery of methotrexate.

Magnetic resonance imaging (MRI). Recently the use of dendrimers as a new class of macromolecular MRI contrast agents has been explored. The most generally used MRI contrast agents are gadolinium-based contrast agents [59, 60]. The covalent attachment of Gd(III) complexes to PAMAM dendrimers to generate unique macromolecular contrast agents for MRI have been reported by several research groups. Kojima *et al.* [61] have prepared fully PEGylated PAMAM dendrimers loaded with Gd-diethylenetriamine pentaacetic acid (DTPA). For conjugation of Gd-DTPA to the side chain, Lysine (Lys) was attached before the PEG modification [62]. Their results showed that PEGylation of a Gd-labeled PAMAM dendrimer decrease the relaxivity and plasma clearance, and variations susceptibility to temperature. Even though PEGylation decreases relaxivity by reducing access to water, by using a bigger dendrimer (G5 *vs* G4) this effect can be improved with intrinsic higher relaxivities because of slower molecular tumbling rates. The calculation of PEG to a dendrimer increased retention in the vascular pool, a feature that could be useful for vascular imaging in cancer, atherosclerosis, and inflammatory disorders, as well as for improving drug delivery [61].

Photodynamic therapy (PDT). PDT is a talented approach to treat certain kinds of cancer. PDT was planned as a helpful oncology tool more than 30 years ago, but it has restrictions. The success of PDT depends mostly on photosensitizers and improvement of an effective second generation is continuing. PDT is a hopeful treatment methodology whereby diseased cells and tissues are destroyed by reactive oxygen species by using a combination of light and photosensitizers. Dendrimers possess architecture appropriate for incorporating particular functional moieties and are a hopeful venue for further researches [63, 64].

Delivery of bioactive. The core and the interior branches of a dendrimer can be synthetic or based on natural peptide or saccharide structures. When adorned with peptide or carbohydrate ligands throughout surface functional groups, dendrimers are endowed with the bioactivity to mediate the interaction with cell surface receptors. Bioactive dendrimers can attach with particular receptors on cell membrane [65–70]. When linking peptides or carbohydrates, the general ligation strategies can be applied directly to generating bioactive dendrimer conjugates. However, there are at least two factors characteristically related with the ligation of dendrimer scaffolds: one of them is the type and generation of dendrimer trellis that would ascertain the shape and size of final products and another one is the number of peripheral branches and modification level that could affect the multivalent spatial arrangement and receptor binding properties of bioactive ligands [71].

Dendrimers in gene delivery. Dendrimers can be used as a transporter in gene therapy. For instance, PAMAM dendrimers have terminal amino groups which interact with phosphate group of nucleic acid. As a result PAMAM dendrimers have been tested as a genetic material vector [72]. Dendrimers were discovered in 1970 by Tomalia and co-workers [1]. The first article using the term "dendrimer" and describing in detail the preparation of poly(PAMAM) dendrimers was presented in 1984. They are polymeric symmetric monodisperse complexes that comprise of well-defined branches around a small molecule, called core. Dendrimers of lower generations (0, 1, and 2) have highly asymmetric shape and have more open structures as compared to higher generation [73–75]. Dendrimers become densely packed as they extend out to the periphery, which forms a closed membrane-like structure [76]. Dendritic copolymers are a specific group of dendrimers, two different types of copolymers were recognized: Segment-block dendrimers are obtained by attaching different wedges to one polyfunctional core molecule. Layer-block dendrimers consist of concentric spheres of differing chemistry [76].

DNA molecules are well suited for these purposes because of their unique molecular detection features. Linear DNA chains can assemble into a range of non-linear structures: branching of the double helix is induced by breaking the run of the complementarity of the part strands. Dendrimers with arms terminating in oligonucleotides of the same or of different sequences could be used to build cages, cryptands, tubes, nets, scaffolds and other more complex three-dimensional (3-D) structures [76–80]. An important characteristic of nucleic acids is the sharp melting transition of the base-paired double strand. It is important to know how dendrimerisation affects this behavior in order to understand how branched nucleic acids may be used as molecular building blocks [81].

Recognition features ability to deliver pieces of DNA to the required parts of a cell includes many challenges. To maintain the activity of DNA during dehydration, the dendrimer/DNA complexes were encapsulated in a water-soluble polymer, and then deposited on or sandwiched in functional polymer films with a fast degradation rate to mediate gene transfection. Based on this method, PAMAM dendrimer/DNA complexes were used to encapsulate functional biodegradable polymer films for substrate mediated gene delivery. Research has shown that the fast degrading functional polymer has great potential for localized transfection [82, 83]. Apart from small drug particles dendrimers are thoroughly examined for the delivery of DNA. PAMAM dendrimers, and polycationic molecules can form complexes with DNA through sequence-independent electrostatic interaction between anionic phosphate groups of nucleic acid and cationic primary amino surface groups. These opposite charges neutralize; therefore, the net charge modifications result in changes of physicochemical and biological properties. The nature of "dendriplexes" are affected not only by concentration of the DNA phosphate groups and dendrimers surface amino groups, also by the shape of dendritic polymers and

solvent's properties such as pH, salt concentration, buffer strength and the dynamics of mixing [84–87].

Targeted delivery of dicer-substrate siRNAs. Small interfering RNAs (siRNA) are talented as new therapeutic agents, given that convenient delivery systems that are available. Dendrimers, a particular group of synthetic macromolecules, demonstrate an exciting delivery platform by virtue of their well-defined dendritic structure and unique multivalency and cooperativity limited within a nanosized volume. Significant interest has been considered to capitalize on dendrimer nanocarriers for the delivery of the emerging RNA interference (RNAi) based nucleic acid drugs [88, 89]. The delivery of RNAi therapeutics should be not only efficient but also targeted in the right site in order to achieve higher efficacy and less toxicity.

Cancer therapy. During the past few years there has been considerable advancement in the application of biocompatible dendrimers for cancer treatment, including their use as drug delivery systems for chemotherapeutic agents such as cisplatin and doxorubicin [90]. The necessity for using of biodegradable dendrimers appeared as a strategy to generate the desired large molecular weight carriers which lead to high retention and accumulation in tumor tissue, while permitting rapid and safe omission of dendrimer fragments into the urine to prevent nonspecific toxicity [91]. Lee *et al.* [92] synthesized biodegradable cationic G3 dendrons and G2 dendrimers by the convergent synthetic method and introduced them as candidates for biomedical applications. Because of excellent properties of PEGylated dendrimers, such as tunable pharmacokinetics and ability to carry multiple copies of bioactive molecules, these materials are attractive for many biological applications. The fast and efficient synthesis of a robust and biodegradable PEGylated dendrimer based on a polyester-polyamide hybrid core is demonstrate by Frechet, Szoka and coworkers [93].

CONCLUSION

Role of dendrimers in advanced drug delivery and biomedical applications is briefly reviewed. Dendrimers are known as extremely defined artificial macromolecules, which are characterized by a combination of a high number of functional groups and a condensed molecular structure. Pharmacokinetic property is one of the most important aspects in the successful applications of dendrimers, for example, imaging, drug delivery, PDT, etc. The variety of potential applications of dendrimers in medicine results in increasing attention in this area.

ACKNOWLEDGMENTS

The authors thank the Department of Medical Nanotechnology, Faculty of Advanced Medical Science of Tabriz University, for all support provided. This work is funded by a 2017 grant by the Drug Applied Research Center, Tabriz University of Medical Sciences.

CONFLICT OF INTEREST

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES

1. Frechet JMJ, Tomalia DA. Dendrimers and other dendritic polymers. John Wiley & Sons, Ltd, 2002.

2. Newkome GR, CMoorefield CN, Vogtle F. Dendrimers and dendrons: concepts, syntheses, applications. Wiley-VCH: Weinheim, 2001. 623 p.

3. Tomalia DA, Naylor AM, Goddard WA. Starburst dendrimers: molecular-level control of size, shape, surface chemistry, topology, and flexibility from atoms to macroscopic matter. Angew Chem Int Ed 1990; **29**: 138–75.

4. Fischer M, Vogtle F. Dendrimers: from design to application — a progress report. Angew Chem Int Ed 1999; **38**: 884–905.

5. Wang YS, Youngster S, Grace M, ***et al.*** Structural and biological characterization of pegylated recombinant interferon alpha-2b and its therapeutic implications. Adv Drug Deliv Rev 2002; **54**: 547–70.

6. Molineux G. The design and development of pegfilgrastim (PEG-rmetHuG-CSF, Neulasta®). Curr Pharm Des 2004; **10**: 1235–44.

7. Freitas R. Nanomedicine 2. available at http://www.foresight.org/Nanomedicine, 2000.

8. Dufes C, Uchegbu IF, Schatzlein AG. Dendrimers in gene delivery. Adv Drug Delivery Rev 2005; **57**: 2177–202.

9. Sampathkumar SG, Yarema KJ. Dendrimers in cancer treatment and diagnosis. Nanotechnol Life Sci Vol 7. In: Nanomaterials for Cancer Diagnosis. Kumar CSSR, ed. Wiley-VCH: Weinheim, 2007. 43 p.

10. Klajnert B. Dendrimers in biomedical applications. Curr Med Chem 2012; **19**: 4895.

11. Mostafavi E, Babaei A, Ataie A. Synthesis of nanostructured $La_{0.6}Sr_{0.4}Co_{0.2}Fe_{0.8}O_3$ perovskite by co-precipitation method. J Ultrafined Grained Nanostruct Mater 2015; **48**: 45–52.

12. Frechet JM. Functional polymers and dendrimers: reactivity, molecular architecture, and interfacial energy. Science 1994; **263**: 1710–5.

13. Caminade AM, Majoral JP. Engineering CNDP's of dendrimers containing phosphorous interior compositions to produce new emerging properties. J Nanopart Res 2018; **20**: 74.

14. Kumar PMK, Kumar P, Choudhary C, ***et al***. Dendrimer: a novel polymer for drug delivery. J Innovative Trends Pharm Sci 2010; **1**: 252–69.

15. Hawker CJ, Frechet JMJ. Preparation of polymers with controlled molecular architecture. A new convergent approach to dendritic macromolecules. J Am Chem Soc 1990; **112**: 7638–47.

16. Miller TM, Neenan TX. Convergent synthesis of monodisperse dendrimers based upon 1,3,5-trisubstituted benzenes. Chem Mater 1990; **2**: 346–9.

17. Tomalia DA, Baker H, Dewald JR, ***et al***. A new class of polymers: starburst-dendriticmacromolecules. Polym J 1985; **17**: 117–32.

18. Nanjwade BK, Bechra HM, Derkar GK, ***et al***. Dendrimers: emerging polymers for drug-delivery systems. Eur J Pharm Sci 2009; **38**: 185–96.

19. Klajnert B, Bryszewska M. Dendrimers: properties and applications. Acta Biochim Pol 2000; **48**: 199–208.

20. Abbasi E, Aval SF, Akbarzadeh A, ***et al***. Dendrimers: synthesis, applications, and properties. Nanoscale Res Lett 2014; **9**: 247.

21. Solassol J, Crozet C, Perrier V, ***et al***. Cationic phosphorus-containing dendrimers reduce prion replication both in cell culture and in mice infected with scrapie. J Gen Virol 2004; **85**: 1791–9.

22. Barth RF, Adams DM, Soloway AH, ***et al***. Boronated starburst dendrimer-monoclonal antibody immunoconjugates: evaluation as a potential delivery system for neutron capture therapy. Bioconjug Chem 1994; **5**: 58–66.

23. Klajnert B, Bryszewska M. The interaction of tryptophan and ANS with PAMAM dendrimers. Cell Mol Biol Lett 2002; **7**: 1087–94.

24. Menjoge AR, Kannan RM, Tomalia DA. Dendrimer-based drug and imaging conjugates: design considerations for nanomedical applications. Drug Discovery Today 2010; **15**: 171–85.

25. Kesharwani P, Jain K, Jain NK. Dendrimer as nanocarrier for drug delivery. Prog Polym Sci 2014; **39**: 268–307.

26. Mehra NK, Jain K, Jain NK. Pharmaceutical and biomedical potential of surface engineered dendrimers. Drug Discov Today 2015; **20**: 750–9.

27. Jain NK, Asthana A. Dendritic systems in drug delivery applications. Expert Opin Drug Delivery 2007; **4**: 495–512.

28. Kukowska-Latallo JF, Candido KA, Cao Z, ***et al***. Nanoparticle targeting of anticancer drug improves therapeutic response in animal model of human epithelial cancer. Cancer Res 2005; **65**: 5317–24.

29. Lee CC, MacKay JA, Frechet JMJ, ***et al***. Designing dendrimers for biological applications. Nat Biotechnol 2005; **23**: 1517–26.

30. Dwivedi DK, Singh AK. Dendrimers: A novel carrier system for drug delivery. J Drug Delivery Ther 2014; **4**: 1–6.

31. Asadi N, Annabi N, Mostafavi E, ***et al***. Synthesis, characterization and *in vitro* evaluation of magnetic nanoparticles modified with PCL-PEG-PCL for controlled delivery of 5FU. Artif Cells Nanomed Biotechnol 2018; https://doi.org/10.1080/21691401.2018.1439839.

32. Zhu J, Shi X. Dendrimer-based nanodevices for targeted drug delivery applications. J Mater Chem B 2013; **1**: 4199–211.

33. Twibanire JAK, Grindley TB. Polyester dendrimers: smart carriers for drug delivery. Polymers 2014; **6**: 179–213.

34. Cheng Y, Xu Z, Ma M, ***et al***. Dendrimers as drug carriers: applications in different routes of drug administration. J Pharm Sci 2008; **97**: 123–43.

35. Wiwattanapatapee R, Carreno-Gomez B, Malik N, ***et al***. Anionic PAMAM dendrimers rapidly cross adult rat intestine *in vitro*: a potential oral delivery system? Pharm Res 2000; **17**: 991–8.

36. Tajarobi F, El-Sayed M, Rege BD, ***et al***. Transport of poly amidoamine dendrimers across Madin-Darby canine kidney cells. Int J Pharm 2001; **215**: 263–7.

37. El-Sayed M, Ginski M, Rhodes C, ***et al***. Transepithelial transport of poly (amidoamine) dendrimers across Caco-2 cell monolayers. J Controlled Release 2002; **81**: 355–65.

38. El-Sayed M, Ginski M, Rhodes CA, ***et al***. Influence of surface chemistry of poly (amidoamine) dendrimers on Caco-2 cell monolayers. J Bioact Compat Polym 2003; **18**: 7–22.

39. El-Sayed M, Rhodes CA, Ginski M, ***et al***. Transport mechanism(s) of poly (amidoamine) dendrimers across Caco-2 cell monolayers. Int J Pharm 2003; **265**: 151–7.

40. El-Sayed M, Kiani MF, Naimark MD, ***et al***. Extravasation of poly (amidoamine)(PAMAM) dendrimers across microvascular network endothelium. Pharm Res 2001; **18**: 23–8.

41. Jevprasesphant R, Penny J, Jalal R, ***et al***. The influence of surface modification on the cytotoxicity of PAMAM dendrimers. Int J Pharm 2003; **252**: 263–6.

42. Jevprasesphant R, Penny J, Attwood D, ***et al***. Engineering of dendrimer surfaces to enhance transepithelial transport and reduce cytotoxicity. Pharm Res 2003; **20**: 1543–50.

43. Jevprasesphant R, Penny J, Attwood D, ***et al***. Transport of dendrimer nanocarriers through epithelial cells via the transcellular route. J Controlled Release 2004; **97**: 259–67.

44. D'emanuele A, Jevprasesphant R, Penny J, ***et al***. The use of a dendrimer-propranolol prodrug to bypass efflux transporters and enhance oral bioavailability. J Controlled Release 2004; **95**: 447–53.

45. Kitchens KM, El-Sayed MEH, Ghandehari H. Transepithelial and endothelial transport of poly (amidoamine) dendrimers. Adv Drug Delivery Rev 2005; **57**: 2163–76.

46. Kambhampati SP, Kannan RM. Dendrimer nanoparticles for ocular drug delivery. J Ocul Pharmacol Ther 2013; **29**: 151–65.

47. Vandamme TF, Brobeck L. Poly (amidoamine) dendrimers as ophthalmic vehicles for ocular delivery of pilocarpine nitrate and tropicamide. J Controlled Release 2005; **102**: 23–38.

48. Desai PN, Yang H. Synthesis and characterization of photocurable polyionic hydrogels. Mater Res Soc Symp Proc 2008; **1095**: 1095–EE05–05.

49. Kandekar Y, Chaudhari PD, Tambe VS, ***et al***. Dendrimers: Novel Drug Nanocarriers. International Journal of Pharmaceutical Sciences and Research (IJPSR) 2011; **2**: 1086–98.

50. Reddy YK, Reddy DM, Kumar MA. Transdermal drug delivery system: a review. Res J Pharm Dos Forms Technol 2013; **5**: 202–12.

51. Escobar-Chavez JJ, Rodriguez-Cruz IM, Dominguez-Delgado CL. Nanocarriers for transdermal drug delivery. INTECH 2012. http://dx.doi.org/10.5772/50314.

52. Svenson S. Dendrimers as versatile platform in drug delivery applications. Eur J Pharm Biopharm 2009; **71**: 445–62.

53. Yiyun C, Na M, Tongwen X, ***et al***. Transdermal delivery of nonsteroidal anti-inflammatory drugs mediated by polyamidoamine (PAMAM) dendrimers. J Pharm Sci 2007; **96**: 595–602.

54. Tolia GT, Choi HH. The role of dendrimers in topical drug delivery. Pharm Technol 2008; **32**: 88–98.

55. Svenson S, Tomalia DA. Dendrimers in biomedical applications — reflections on the field. Adv Drug Deliv Rev 2012; **64**: 102–15.

56. Malik N, Evagorou EG, Duncan R. Dendrimer-platinate: a novel approach to cancer chemotherapy. Anti-Cancer Drugs 1999; **10**: 767–76.

57. Patri AK, Kukowska-Latallo JF, Baker JR Jr. Targeted drug delivery with dendrimers: comparison of the release kinetics of covalently conjugated drug and non-covalent drug inclusion complex. Adv Drug Delivery Rev 2005; **57**: 2203–14.

58. Madaan K, Kumar S, Poonia N. Dendrimers in drug delivery and targeting: drug-dendrimer interactions and toxicity. J Pharm Bioallied Sci 2014; **6**: 139–50.

59. Langereis S, A Dirksen A, TM Hackeng TM, ***et al***. Dendrimers and magnetic resonance imaging. New J Chem 2007; **31**: 1152–60.

60. Zhou Z, Lu ZR. Gadolinium-based contrast agents for magnetic resonance cancer imaging. Wiley Interdiscip Rev Nanomed Nanobiotechnol 2013; **5**: 1–18.

61. Kojima C, Turkbey B, Ogawa M, ***et al***. Dendrimer-based MRI contrast agents: the effects of PEGylation on relaxivity and pharmacokinetics. Nanomed Nanotechnol Biol Med 2011; **7**: 1001–8.

62. Mostafavi E, Ataie A, Ahmadzadeh M. Characterization of nano-structured multiferroic bismuth ferrite produced via solid state reaction route. Adv Mater Res 2014; **829**: 683–7.

63. Mostafavi E, Ataie A. Destructive interactions between pore forming agents and matrix phase during the fabrication process of porous $BiFeO_3$ ceramics. J Mater Sci Technol 2015; **31**: 798–805.

64. Mostafavi E, Ataie A, Ahmadzadeh M, ***et al***. Synthesis of nano-structured $Bi_{1-x}Ba_xFeO_3$ ceramics with enhanced magnetic and electrical properties. Mater Chem Phys 2015; **162**: 106–12.

65. Lee RT, Lee YC. Affinity enhancement by multivalent lectin — carbohydrate interaction. Glycoconjugate J 2000; **17**: 543–51.

66. Klajnert B, Rozanek M, Bryszewska M. Dendrimers in photodynamic therapy. Curr Med Chem 2012; **19**: 4903–12.

67. Lundquist JJ, Toone EJ. The cluster glycoside effect. Chem Rev 2002; **102**: 555–78.

68. Boas U, Heegaard PMH. Dendrimers in drug research. Chem Soc Rev 2004; **33**: 43–63.

69. Chabre YM, Roy R. Recent trends in glycodendrimer syntheses and applications. Curr Top Med Chem 2008; **8**: 1237–85.

70. Liu J, Gray WD, Davis ME, ***et al***. Peptide-and saccharide-conjugated dendrimers for targeted drug delivery: a concise review. Interface Focus 2012; **2**: 307–24.

71. Mihov G, Grebel-Koehler D, Lubbert A, ***et al***. Polyphenylene dendrimers as scaffolds for shape-persistent multiple peptide conjugates. Bioconjug Chem 2005; **16**: 283–93.

72. Svenson S, Tomalia DA. Dendrimers in biomedical applications — reflections on the field. Adv Drug Deliv Rev 2005; **57**: 2106–29.

73. Koo OM, Rubinstein, Onyuksel H. Role of nanotechnology in targeted drug delivery and imaging: a concise review. Nanomed Nanotechnol Biol Med 2005; **1**: 193–212.

74. Caminade AM, Laurent R, Majoral JP. Characterization of dendrimers. Adv Drug Delivery Rev 2005; **57**: 2130–46.

75. Caminati G, Turro NJ, Tomalia DA. Photophysical investigation of starburst dendrimers and their interactions with anionic and cationic surfactants. J Am Chem Soc 1990; **112**: 8515–22.

76. Hawker CJ, Frechet JMJ. Unusual macromolecular architectures: The convergent growth approach to dendritic polyesters and novel block copolymers. J Am Chem Soc 1992; **114**: 8405–13.

77. Winfree E, Liu F, Wenzler LA, ***et al***. Design and self-assembly of two-dimensional DNA crystals. Nature 1998; **394**: 539–44.

78. Seeman NC. DNA nanotechnology: novel DNA constructions. Annu Rev Biophys Biomol Struct 1998; **27**: 225–48.

79. Newkome GR, Moorefield CN, Vogtle F. Dendritic molecules: concepts, syntheses, perspectives. John Wiley & Sons, 2008.

80. Shchepinov S, Udalova IA, Bridgman AJ, ***et al***. Oligonucleotide dendrimers: synthesis and use as polylabelled DNA probes. Nucleic Acids Res 1997; **25**: 4447–54.

81. Shchepinov MS, Mir KU, Elder JK, ***et al***. Oligonucleotide dendrimers: stable nano-structures. Nucleic Acids Res 1999; **27**: 3035–41.

82. Fu HL, Cheng SX, Zhang XZ, ***et al***. Dendrimer/DNA complexes encapsulated in a water soluble polymer and supported on fast degrading star poly (DL-lactide) for localized gene delivery. J Controlled Release 2007; **124**: 181–8.

83. Dutta T, Garg M, Jain NK. Poly (propyleneimine) dendrimer and dendrosome mediated genetic immunization against hepatitis B. Vaccine 2008; **26**: 3389–94.

84. Dutta T, Jain NK, McMillan NAJ, ***et al***. RETRACTED: Dendrimer nanocarriers as versatile vectors in gene delivery. Nanomed Nanotechnol Biol Med 2010; **6**: 25–34.

85. Sato N, Kobayashi H, Saga T, ***et al***. Tumor targeting and imaging of intraperitoneal tumors by use of antisense oligo-DNA complexed with dendrimers and/or avidin in mice. Clin Cancer Res 2001; **7**: 3606–12.

86. Kukowska-Latallo JF, Bielinska AU, Johnson J, ***et al***. Efficient transfer of genetic material into mammalian cells using Starburst polyamidoamine dendrimers. PNAS 1996; **93**: 4897–902.

87. Szymanski P, Markowicz M, Mikiciuk-Olasik E. Nanotechnology in pharmaceutical and biomedical applications: Dendrimers. NANO 2011; **6**: 509–39.

88. Liu X, Rocchi P, Peng L. Dendrimers as non-viral vectors for siRNA delivery. New J Chem 2012; **36**: 256–63.

89. Sheikhi Mehrabadi F, Fischer W, Haag R. Dendritic and lipid-based carriers for gene/siRNA delivery (a review). Curr Opin Solid State Mater Sci 2012; **16**: 310–22.

90. Doshi M. Dendrimer and its application. Int J Pharm Sci Rev Res 2011; **7**: 104–11.

91. Medina SH, El-Sayed MEH. Dendrimers as carriers for delivery of chemotherapeutic agents. Chem Rev 2009; **109**: 3141–57.