Research Article
AMERICAN JOURNAL OF PHARMACY AND HEALTH RESEARCH
www.ajphr.com
2015, Volume 3, Issue 2
ISSN: 2321–3647(online)

Molecular Modeling Tool for Dendrimer Based Drug Delivery

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ABSTRACT

Recent approaches in molecular modeling simulation techniques and interaction studies have allowed accurate predictions of dendrimer dimensions, contour, and relations with drugs, biosensors, and conformational behavior of peptides, vectors as well as many others. This paper shows docking and dynamics of pharmacological screening of dendrimers in different therapeutic studies from various peer reviewed published data. Anti-inflammatory studies enable the computational learn of connections of the unchanged dendrimer, glucosamine, and of the partially glycosylated dendrimer with Toll-like receptor and Myeloid differentiation factor. Anti-tumor studies including biogenic polyamines, show stronger similarity toward dendrimers than those of artificial polyamines suggesting that dendrimers can act as transporter vehicle for deliver antitumor polyamine analogues to goal tissues. Ployamidoamine modified Gallium nitride nanowires provide great density of docking location to immobilize crucial number of probe Deoxyribonucleic acid covalently. Molecular docking studies exposed that the β-sitosterol can bind in the great hydrophobic hollow of Human Serum Albumin. Simulation have manifested that the hydrophobic interactions, hydrogen-bond interactions, and electrostatic appeal play critical roles in the pattern of dendrimer–drug complexes. In case of Small interfering Ribonucleic acid simulations reveal that the time taken for the dendrimer-gene complex (dendriplex) to reach equilibrium is appreciably longer at low pH and this is accompanied by more compact packaging of the dendriplex, as compared to simulations performed at neutral pH. Due to their possible use in various disease studies, molecular modeling with dendrimer complex configuration are chief choice in manipulating better drug carriers and tackle issues that are difficult in laboratory experiment.

Keywords: Dendrimer, Molecular Dynamics, polyamidoamine Dendrimer, Simulation

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Received 14 January 20154, Accepted 21 January 2015

Please cite this article as: Baig T *et al*., Molecular Modeling Tool for Dendrimer Based Drug Delivery . American Journal of Pharmacy & Health Research 2015.

INTRODUCTION

Molecular modeling:

Molecular modeling encompass all hypothetical method and computational technique used to model or impersonate the behavior of molecules.[1] The techniques are used in the field of computational chemistry, drug design, computational biology and materials science for study molecular system range beginning miniature chemical system to large biological molecules and substance assembly.[2] The simplest calculation can be perform by hand over, but unavoidably computers are required to perform molecular modeling of any logically sized arrangement. The general feature of molecular modeling techniques is the atomistic level narrative of the molecular systems.[3,4] This may comprise treat atom as the minimum personality unit (the Molecular mechanics approach), or explicitly modeling electrons of both atom (the quantum chemistry approach).[5] The techniques describe incorporate-Molecular visualization, Methods for Equilibrium and transition state geometry location, Introduction to Molecular mechanics methods, Applications of Semi-empirical, initio and density functional molecular orbital methods, Methods for topological analysis of wave functions.

Molecular modeling methods are now habitually used to examine the structure, dynamics, surface property and thermodynamics of inorganic, [6] biological and polymeric systems. The types of biological commotion that have been investigated using molecular modeling contain folding, enzyme catalysis, protein stability, [7] conformational changes connected with bimolecular, and molecular gratitude of proteins, DNA, and covering complex. [8, 9]

Dendrimers are frequently pronged molecules, [10] which translate to "tree". One and the same terms for dendrimer consist of arborols and tumble molecules. However, dendrimer is presently the worldwide conventional term. A dendrimer is typically symmetric about the core, and often adopts a sphere-shaped three-dimensional morphology.[11] The word Dendron is also encounter frequently. A dendron typically contains a solitary chemically addressable collection called the focal point [12] Dendritic molecules are considered by structural aptness. Dendrimers and dendrons are monodisperse and frequently enormously symmetric, spherical compounds. The properties of dendrimers are subjected by the useful groups on the molecular surface; however, there are examples of dendrimers with internal functionality. Dendritic encapsulation of efficient molecules permits for the segregation of the active site, and also, it is possible to make dendrimers water soluble, disparate most polymers, by functionalizing their outer shell with exciting species or other hydrophilic groups.[13] Other suitable properties of dendrimers comprise

toxicity, crystallinity, tecto-dendrimer formation, and chirality.

The primary dendrimers were made by diverse synthesis by Fritz Vögtle in 1978,[14] R. G. Denkewalter at Allied Corporation in 1981, [15, 16] Donald Tomalia at Dow Chemical in 1983 [17-19] and by George Newkome in 1985.[20] In 1990 a convergent imitative draw was introduced by Jean Fréchet.[21] Dendrimer attractiveness then deeply amplified, ensuing in more than 15,000 scientific papers and patents by the year 2014. (shown in figure. 1)

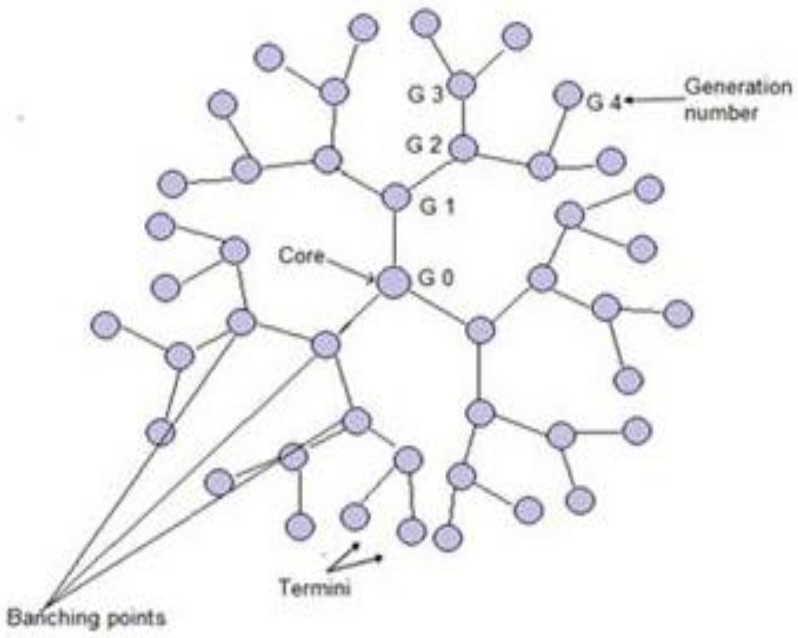

Figure. 1: Represent different generation of dendrimer

MOLECULAR DYNAMICS AND DOCKING OF DENDRIMER:

Molecular dynamics provide model equal to the examination by diffusion- Nuclear Magnetic Resonance (NMR) arrangement that the dendrimers subsist as conformational elastic molten globules in aqueous explanation.[22] Packing is confirmation of close associates between topologically remote amino acids in the dendrimer model. Dock of the substrate to weak conformations of the dendrimers expects the configuration of dendrimer substrate complex with one or two salt bridge between the sulfonate and protonated arginine or histidine residue. Substrate requisite in the docked form also involves 4−6 van der Waals associates. The docking associates are determined at the dendritic core.[23]

PHARMACOLOGICAL SCREENING OF DENDRIMER BY MOLECULAR MODELING

Anti-inflammatory studies

These studies investigate the correlation between the inhibitory events of low generation

dendrimers in motivated microglia and dendrimer-enzyme connections using in silico molecular modeling. First and second generation dendrimers with acetylene and hydroxyl terminal groups were hardened for their anti-inflammatory action in microglia stimulated by lipopolysaccharides (LPS), and the outcome were compared with those from the recognized anti-inflammatory agents, ibuprofen and celecoxib. The enzymatic action was resolute in the existence of low generation dendrimers using biochemical assays and their standards associated to dendrimer docking confirmations from in silico molecular modeling.[24]

The crystal structure of the toll like receptors- myeloid differentiation factor 2-lipopolysaccharide (TLR4-MD-2-LPS) complex dependable for trigger controlling pro-inflammatory cytokine response has newly become accessible. Central to cell exterior compound development is binding of LPS to soluble MD-2. Generation 3.5 Polyamidoamine (PAMAM) dendrimer with 64 carboxylic acid group acts as an opponent of pro-inflammatory cytokine production after exterior alteration with 8 glucosamine molecules. Furthermore study also discover the molecular modeling approach that this incompletely glycosylated dendrimer has the litheness, cluster density, surface electrostatic charge, and hydrophilicity to create it a therapeutically helpful challenger of multifaceted arrangement. These studies enable the computational learn of the connections of the unchanged dendrimer, glucosamine, and of the partially glycosylated dendrimer with TLR4 and MD-2 with molecular docking and molecular dynamics technique.[25]

Anticancer Studies:

The complexation of a possible anticancer agent 2-methoxyestradiol (2-ME) with fifth generation (G5) PAMAM dendrimers have different surface purposeful groups for therapeutic application. The complexation trial shows that approximately 6-8 drug molecules can be complexes with one dendrimer molecule nevertheless the type of the dendrimer terminal groups. The bioactivity of 2-ME complexed with dendrimers was originated to be considerably reliant on the surface charge of G5 dendrimers. The surface alteration of dendrimers with unlike charges is critical for the expansion of formulations of different anticancer drugs for therapeutic applications.[26]

Dendrimer-based nanotechnology considerably advances the area of under fire cancer imaging and therapy. The difference of outside acetylated fluoresce in isocyanate (FI) and folic acid (FA) modified G5 PAMAM dendrimers, and dendrimer-entrapped gold nanoparticles through parallel modifications in terms of their precise internalization to FA receptor which express cancer cells.

Molecular dynamics imitation of the two dissimilar nanostructures reveals that the exterior area and the FA moiety allocation from the center of the geometry are somewhat dissimilar.[27]

Biogenic polyamines are important for cell growth and discrimination, while polyamine analogues exert antitumor activity in numerous experimental model systems, counting breast and lung cancer. Dendrimers are extensively used for drug delivery in vitro and in vivo. the bindings of biogenic polyamines, spermine (spm), and spermidine (spmd), and their artificial analogues, 3,7,11,15-tetrazaheptadecane.4HCl (BE-333) and 3,7,11,15,19-pentazahenicosane.5HCl (BE-3333) to dendrimers of dissimilar composition, PEGylated poly(amidoamine) dendrimer (mPEG-PAMAM) G3, mPEG-PAMAM G4 and PAMAM G4. Biogenic polyamines show stronger similarity toward dendrimers than those of artificial polyamines, while weaker interface was experiential as polyamine cationic charges improved and suggested that dendrimers can act as transporter vehicle for deliver antitumor polyamine analogues to goal tissues.[28]

DNA biosensor studies

This study reveals a very straightforward and general procedure for ultrasensitive in-situ label-free finding of Deoxyribonuclic acid (DNA) hybridization using third generation poly (amidoamine) dendrimer (G3-PAMAM) functionalized Gallium nitride (GaN) nanowires (NWs). PAMAM modified GaN NWs provide great density of docking location to immobilize crucial number of probe (p-) DNA covalently. These p-DNA/PAMAM/GaN NWs sensor probes are employed to carry out an ultra-high finding limit down to attomolar level attention of balancing target (t-) DNA. This narrative methodology for specific DNA succession discovery, as compare with the accessible methods, is originated to be very vigorous, highly receptive, and reproducible.[29]

For Human serum albumin studies

β-Sitosterol is a physically happening phytosterol that is generally used to cure atherosclerosis, diabetes, cancer, and inflammation and is also an antioxidant. Here, we studied the communication of β-sitosterol, inaccessible from the aerial roots of Ficus bengalensis, with human serum albumin (HSA) at physiological pH 7.2 by using fluorescence, circular dichroism (CD), molecular docking, and molecular dynamics facsimile methods. The molecular dynamics revise make an important involvement to considerate the result of the binding of β-sitosterol on conformational change of HSA and the steadiness of a protein−drug complex scheme in aqueous solution. Molecular docking studies exposed that the β-sitosterol can bind in the great hydrophobic hollow of subdomain IIA.[30]

Alteration of pH on the Binding and Release Pattern of drug

The dendrimer–drug interface is of great significance to propose and optimize the dendrimer-based drug delivery system. Using atomistic molecular dynamics (MD) simulations, the free model of four ligand (two soluble drugs, namely, salicylic acid (Sal), l-alanine (Ala), and two insoluble drugs, namely, phenylbutazone (Pbz) and primidone (Prim)), which were originally encapsulated within the ethylenediamine (EDA) cored polyamidoamine (PAMAM) dendrimer using the docking method. The potential mean force (PMF) variation by generation 5 (G5)-PAMAM dendrimer complex with drug molecules with umbrella sample. Soluble drugs like Sal and Ala have lower energy barrier than insoluble drugs like Pbz and Prim. The position of ease of liberate model for these drugs from G5 protonated PAMAM dendrimer was establish to be Ala > Sal > Prim >Pbz. Insoluble drugs (Prim and Pbz),with larger size, nonpolar part, and their better energy barriers can be rational to van der Waals involvement. Encapsulation of the drug molecule into the host PAMAM dendrimer must be accepted out at higher pH values (near pH 10). When such composite enter the human body, the pH is around 7.4 and at that physiological pH, the dendrimer hold the drug firmly. Hence the release of drug can take place at a forbidden rate into the bloodstream.[31]

Conformational Behavior of Peptide

This was first common structural explanation of peptide dendrimers through molecular simulation methods. Several long molecular dynamics simulations are used to expansively sample the conformational preference of third-generation peptide dendrimers, counting some known to bind aquacobalamine. A more complete analysis is then performing using difference actions, principal organize examination, and free energy landscape, with the plan of identify groups of comparable conformations. Thus study bring new imminent into the conformational activities of peptide dendrimers and may provide improved routes for their purposeful design.[32]

Vectors studies

It is a great confront for nanomedicine to expand novel dendrimers with utmost therapeutic potential and minimum side-effects for drug and gene delivery. As delivery vectors, dendrimers must conquer lots of barriers previous to deliver the bio-agents to the intention in the cell. Widespread experimental investigation have been carried out to explain the physical and chemical property of dendrimers and investigate their behaviors when interact with biomolecules, such as gene materials, proteins, and lipid membranes. The structure of dendrimers in adulterate solutions has been intensively investigated by monomer-resolved simulation, coarse-grained simulations, and atom-resolved simulations. Atomistic simulation

have manifest that the hydrophobic interactions, hydrogen-bond interactions, and electrostatic appeal play critical roles in the pattern of dendrimer–drug complexes. They focus on the present status and standpoint of theoretical and computational assistance in this field in recent years.[33]

An effortless novel assay for heparin requisite in serum functional to multivalent PAMAM dendrimers:

Heparin is the mainly charge-dense unsurprisingly occurring polyanion in biological systems, [34] and is used as an anti-coagulant drug, for example during surgical treatment. There has been a surge of curiosity in developing heparin sensors, [35] and newly reported an easy new sensor, Mallard Blue (MalB) accomplished of ultra-high-annuity intelligence of clinically-relevant heparin level in serum.[36] In this paper, we express the use of MalB in a novel spectroscopic examine to explore the heparin binding ability of synthetic systems with potential application for post-surgical heparin removal. Currently, the only standard heparin reverse mediator is protamine sulfate: a cationic arginine-rich protein of ill- defined arrangement.[37] Protamine cause adverse reaction in up to 10% of patients and 2.6% of cardiac surgeries familiarity severe impediment.[38] They intended a simple dye- dislodgment competition assay to probe imitation heparin binder. Heparin was mixed with MalB and then the possible heparin binder was supplementary. In the occurrence of escalating amount of the heparin binder, MalB should be displacing from heparin and the absorbance effectiveness should increase. This assay can be used to estimate binding parameters. The EC50 (elective concentration) is the concentration of binder requisite to displace 50% of MalB from heparin. The CE50 (charge excess) is the number of positive charges essential per heparin negative charge to achieve 50% disarticulation of MalB. To test the assay, studied PAMAM dendrimers with different generations of branch. PAMAMs was primary reported by Tomalia and co-workers, [39] which endure as monodisperse entity nanoscale units in water, are known heparin binders.[40] Dendrimers can mimic lots of aspect of protein behaviour, and hope that by assay PAMAMs and bench marking the data to protamine, They could conclude which PAMAM is the most effective practical mimetic of protamine, and whether it can operate in human serum.

The information can also be reported in requisites of the mass of binder essential to bind 100 international units of heparin – the clinical standard. They examine binding in buffered water (pH 7.4) with 150 mM sodium chloride (NaCl) as aggressive electrolyte. In this pH command only the peripheral principal amines on PAMAMs are protonated.[41] G0-PAMAM was ineffective at binding heparin and was incapable to displace MalB, evidently signifying that MalB is structurally optimized to bind heparin, i.e., charge is not the only feature that calculating heparin

binding.[42] Higher generation dendrimers were able to use their superior surface charge to bind heparin and hence relocate MalB. As the dendrimer become larger, the effective absorption required to displace 50% of MalB (EC50 value) from 10.10 mM for G1-PAMAM to 0.22 mM for G6-PAMAM. This paper reports the use of MalB in an antagonism assay to test synthetic heparin binders. The assay identified G2-PAMAM as the ideal dendrimer in terms of maximize its use of charge and working at low effective dose. In silico experiments support the data and unveil a molecular justification. The new assay also work using heparin delivers in 100% human serum – G2-PAMAM remains an effective heparin binder beneath these circumstances. Amusingly, G2-PAMAM, as a low-generation dendrimer is often overlooked, yet is one of the less toxic PAMAMs.[43] Nonetheless, for clinical use it would be attractive to use a more degradable system and are presently using this assay to screen new potential therapeutic candidates.

Tumor Targeting and Imaging of Intraperitoneal Tumors by Use of Antisense Oligo-DNA Complexed with Dendrimers and/or Avidin in Mice:

Non viral gene transfection systems, which can carry both oligonucleotides and plasmid DNA (44), have an advantage of lower immunogenicity. A number of nonviral carriers for gene transfer have been synthesized, including polylysines, [46] cationic liposomes, [47] polypeptides (48, 49), recombinant histones,[50] and other reagents.[51–53] Recently, starburst polyamidoamine dendrimers have emerged as a novel synthetic gene carrier.[54, 55] Dendrimers form stable electrostatic complexes with negatively charged nucleic acids in buffer at physiological pH. Dendrimers facilitate gene transfer to various cell lines with a higher efficiency than polylysines and are also less cytotoxic.[56, 57] Moreover; dendrimers are efficient in delivering oligonucleotides even in the presence of high concentrations of serum proteins by protecting the oligonucleotides from the degradation by exonuclease.[58] Dendrimers buffer the endosome and inhibit pH-dependent lysosomal nucleases; at the same time, the electrostatic bonding between oligo-nucleotide and dendrimer is weakened by the low pH environment in the lysosome, which allows migration of intact DNA to the nucleus.[45]

Biomedical Applications

The design and expansion of dendrimers for biomedical applications is accelerating while there isaperceptive of a number of their properties in a physiological environment. Molecular modeling techniques can offers the resources to gain an amplified consideration of imperative molecular structural features and dynamic behaviors that are fundamental to a biomedical application. Many methods have been developed and validate to model these molecules with

excellent correlation with experimental results. It will focus on the use of molecular modeling paraphernalia for the study and design of dendrimers, with particular prominence on the efforts that have been finished to progress the effectiveness of this class of molecules inbiomedical applications.[59]

Several biomedical applications are-

- Impact of Solvent and Dendrimer Topology.
- Impact and Versatility of the End Groups.
- Dendrimers Interaction with Lipid Membranes.
- Modeling Dendrimers for Drug Delivery Applications.
- Modeling Dendrimers as Therapeutic Agents

Several other modes of drug delivery with the help of dendrimer can be listed in table no., which are given below-

Table 1.Simulation of self-assembling macromolecules

S.No	Dendrimer + drug	Aim of research
1.	Coarse-grained (CG) mlecules	The application of CG models to investigate surfactant and lipid self-assembly counting liposome and dendrimer some configuration as well as the interface of biomembranes with nanoparticles. [60]
2.	PAMAM dendrimers (G0 and G1) + primary, secondary and tertiary amines	These works of fiction simulation offer a more comprehensive consideration of low molecular-weight polymer-siRNA actions, and offer input of straight consequence to the "proton sponge theory". [61]
3.	Dendrons pack + C(12) alkane	The relations between the soft dendrimer balls are establish to be lattice needy when describe by a two-body potential because the soft ball self-adjusts its shape and interaction in different lattices. [62]
4.	Statics and dynamics of model dendrimers as studied by molecular dynamics simulations.	The methodical and proportional nature of this study affords thorough approaching into the origin and the comparative involvement of different relaxation mechanisms in the experimental dynamic spectra. [63]
5.	G5 PPI^{EDA} (G5 ethylenediamine cored poly(propylene imine)) dendrimer + Famotidine and Indomethacin	The pH-induced conformational change in dendrimer, ionization state, dendrimer type and pK_a of the visitor molecules influence the free energy blockade and steadiness of complexation, and thus control drug loading, solubility and release. [64]
6.	PAMAM dendrimer (G2) + Effects of pH	Evolution to high-density stuffing occurs between generations 4 and 5. Volume difference between neutral and low pH calculated from R_G show a theatrical enhance commencement at generation 5. [65]
7.	Poly(propyleneimine) dendrimers (G1-G5)	Dendrimer can be consider as elastic molecules with a comparatively uniform radial density allocation. This view obviously deviates from both the opaque shell and dense interior models. [66]

8.	Bifurcation in its stress-strain relation	Bifurcation provides a link in arrangement space between cubic and hexagonal close stuffing. It is optional that such an alteration could possibly be observed experimentally under extreme situation of shock. [67]
9.	Acetylated G5 PAMAM dendrimers	Hydrogen bonds that quickly split and re-form as solvent molecules struggle for hydrogen-bonding sites on the monomers. The water and methanol solvents seem to create comparable numbers of hydrogen bond interactions between monomers. [68]
10.	PAMAM dendrimers (G2,G5)	The radius of gyration scales roughly with the cubic source of the number of monomers. Interpenetration of character dendrimer molecules decrease with creation. [69]
11.	Molecular dynamics (MD) simulations	The method is effortlessly extendable to other variables and to gradient, and can be practical also to polyatomic molecules connecting interior constraint. [70]
12.	Computational method	Computational simulations are predominantly expensive in conniving improved drug carrier and address issues that are not easy to be explore by laboratory experiment, such as diffusion, dynamics, etc. [71]

CONCLUSION:

The extensive series of examples illustrated and discussed above - taken from peer review of published data emphasize the role and potentiality of molecular modeling in the pre and post development of its dendrimer complex. Accurate and reliable molecular modeling can be performed more easily than experiments. In silico evaluation can take into account the molecular specificity of the problem and dramatically reduce the time and cost required to formulate a new device and therapeutic intervention, and eventually translate it into the clinical setting. Much functional information regarding the construction and dynamics of dendrimers has been gain. The successful simulation of the dendrimer arrangement has provide a foundation for extend the simulation to the connections of dendrimers with additional molecules. Because of their possible use in various disease studies as mentioned above, Molecular Modeling with Dendrimer complex configuration are chiefly expensive in conniving better drug carrier and address issues that are tricky to be explore by laboratory experiment.

ACKNOWLEDGEMENT

The authors wish to thank Dr. Pushpendra K. Tripathi (Director), Department of Pharmacy, Rameshwaram Institute of Technology & Management, Lucknow, for their kind support and encouragement during the tenure of this work.

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