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Effect of increasing alkyl chain of 1st tier dendrimers on binding and release activities of methotrexate drug: An in vitro study

Reena Tondwal, Man Singh *

School of Chemical Sciences, Central University of Gujarat, Gandhinagar 382030, India

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ABSTRACT

Methotrexate (MTX)–dendrimer complexes have been an effective model for easy administration through enhanced permeability with the controlled MTX release. MTX binding and corresponding release out of trimesoyl 1,3,5-tridimethyl malonate (TTDMM), trimesoyl 1,3,5-tridiethyl malonate (TTDEM) and trimesoyl 1,3,5-tridipropyl malonate (TTDPM) were investigated. FTIR, DLS and SEM inferred their binding abilities as TTDMM < TTDEM < TTDPM with an increase in the alkyl chain. UV–vis spectroscopy has depicted 0.12, 0.10 and 0.06 mg/h MTX in vitro release rates out of MTX–TTDMM, MTX–TTDEM and MTX–TTDPM complexes respectively in phosphate buffer saline (PBS) + 10% dimethyl sulfoxide (DMSO) medium at 310.15 K. The medium (PBS + 10% DMSO) is abbreviated as PD. The TTDPM complex released 51.47% drug in PD after 10 h. The MTX release in 2:1.67:1 ratio out of TTDMM, TTDEM and TTDPM complexes is a function of $–CH_3$, $–CH_2CH_3$ and $–CH_2CH_2CH_3$ with their increasing hydrophobicity respectively. The factors like length of the alkyl chain with their simulation, inductive effect (IE) and additional electron cloud affect the MTX release. Thus, the dendrimer with higher alkyl chain or TTDPM may be useful in controlling the drug release rate over an extended period.

1. Introduction

For the last few decades, dendrimers are the promising architectural molecules with varieties of applications in medical diagnostics and therapeutics. Monodispersity, globular shape with embedded interstices, well-defined size, multifunctional peripheral groups, and nonpolar cavities with an extraordinary drug's binding capacity make them potent materials in miscellaneous areas of research and industries especially as an effective drug carrier [1–5]. Also, starch and polyethylene glycol (PEG) have been used for effective and safe drug delivery agents for many years. But these molecules have poor solubility, poor bioavailability, less drug loading capacity, poor control of drug release and transdermal permeation through the skin [6,7]. Also the chitosan with higher swelling degree or nature in an aqueous environment causes fast drug release and many other problems make it functionally inoperative [8–10], similar to starch [6,7,10] and PEG [10]. There are many other challenges in the areas of efficient drug designing like the discovery of new classes of chemical compounds with anticancer activity, specific for cancerous cells, steric, electrostatic and hydrophobic/hydrophilic complementary to active sites. In the context above, scientists have been evolving new methods and models showing the higher impact for medical sciences. The above mentioned obstacles could be minimized by modifying the structure of the drug, as well as a binder and carrier to desired level. Therefore, the study of structure and property relationship is one of the most thrust areas of science where the dendrimers are found suitable in this regard, due to their symmetric structure with adequate void spaces. Synthesis and characterization of dendrimers were initiated by Vogtle [11], followed by Denkewalter et al. to describe a pathway of polypeptide dendrimers via divergent synthesis [12]. Maciejewski reported a densest packing concept for a cascade likes structure [13,14] and Tomalia [15] developed a 1st family of hyperbranched, poly(amidoamines) (PAMAM), designated as starburst dendrimers [16].

Due to the unequaled properties, dendrimers have been widely used in drug delivery system and developed as a new drug carrier in biomedical and biochemical sciences with fewer side effects and safer drug binding and release without any structural deformities [4]. Drugs are introduced into the interior or attach to the periphery of dendrimer coercing a clear picture of the well-defined core structure and functionalized periphery optimized by controlled intramolecular thermodynamics i.e. both entropy and tentropy. Such efficient and safer drug carrier with unique networking are compatible for drug structure, binding, transporting and sustainable release [17]. For example, a biocompatible drug carrier, fully acetylated PAMAM using dexamethasone 21-phosphate (Dp21) as a model drug was proposed with a pH-dependent release of Dp21 from the acetylated and nonacetylated dendritic matrix [18]. The competitive binding of multiple drugs by a single dendrimer in aqueous solutions was investigated by ^{1}H NMR and 2D-NOESY [19,20]. The host–guest chemistry of guanosine monophosphate (GMP) with dendrimer was studied via elaborating significant

* Corresponding author.
E-mail addresses: reenatondwal@gmail.com (R. Tondwal), mansingh50@hotmail.com (M. Singh).

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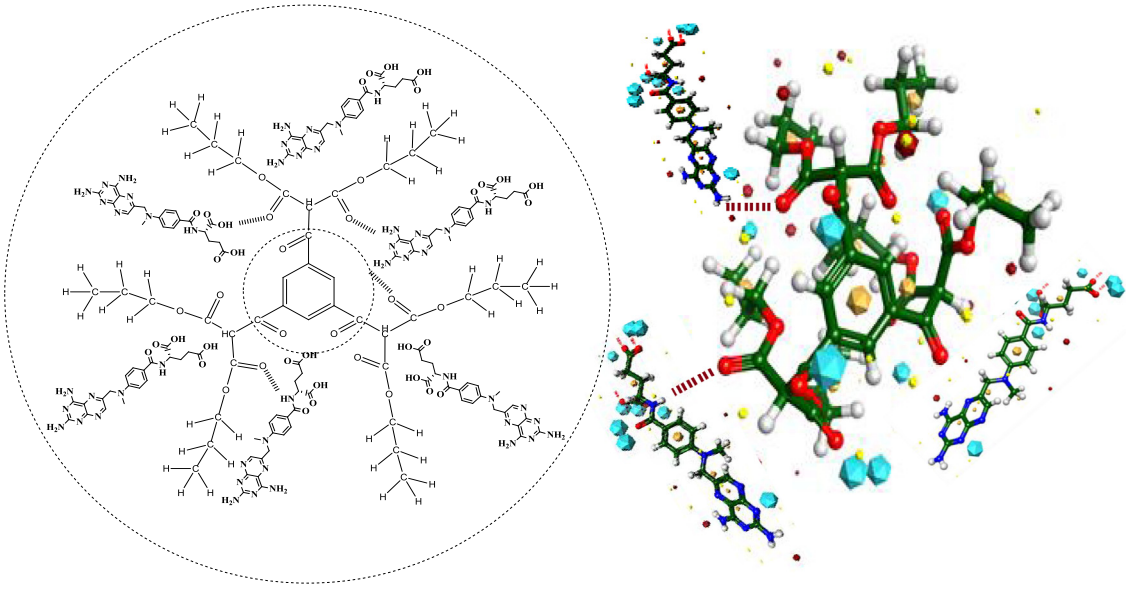
downfield shift of methylene protons in the outermost layer of the G5 dendrimer [21]. However to our best understanding, the dendrimers of higher tiers with more entropic stabilization could optimize the drug in void spaces and lead to have a considerable prolonged release, but may not be suitable for those cases where instant drug release is required. In this respect, we synthesized extended carbon chain length of 1st tier dendrimer rather than increasing their branching or tiers. Our approach of increasing the size of branching material seems to be most appropriate in terms of offering larger void spaces along with required entropic stabilization. In light of the above, the exceptional structural features of dendrimer play an immensely critical role for entering the drug facilitated by their tentacles enabling modifications in their structural activities suited for better transportation. Despite such extraordinary structural capabilities for MTX binding, no specific and systematic research work with TTDMM, TTDEM and TTDPM has ever been reported so far; hence our study on developing models of dendrimer–drug designing is aimed to provide an advance understanding of complexities of drug–carrier interfaces.



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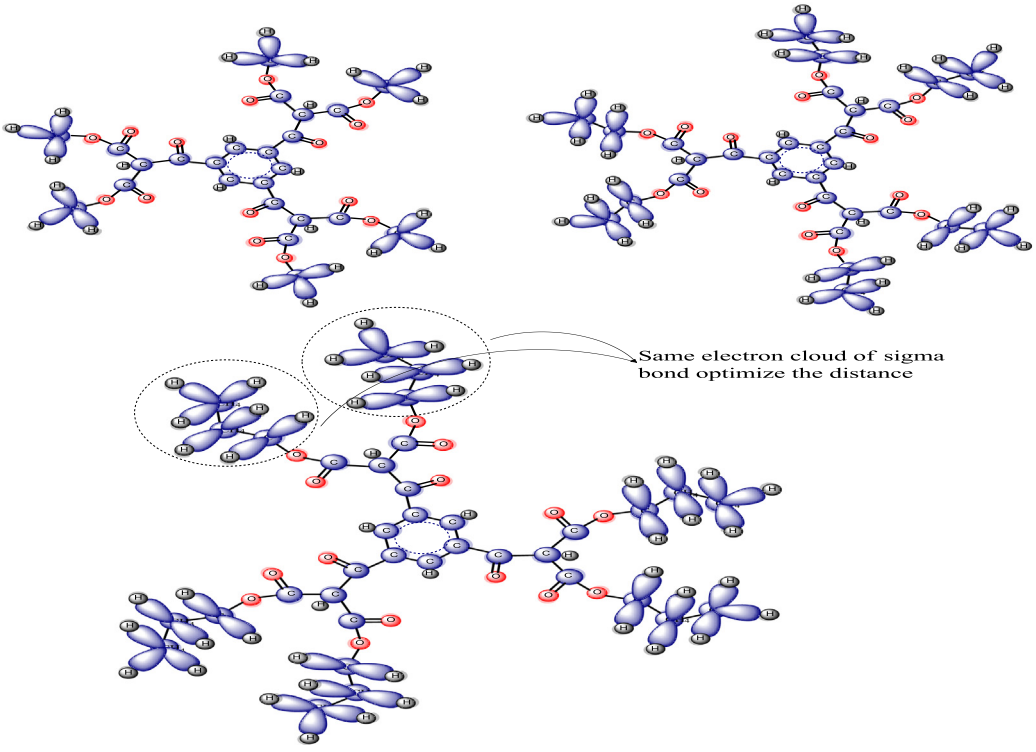

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Fig. 1. (a) Proposed model for MTX encapsulation in void spaces of TTDPM facilitated by hydrogen-bonding (HB) and London dispersive forces (LDF). (b) Steric stabilization.