World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 5.088

MOLECULE DYNAMICS STUDIES OF G3 PAMAM DENDRIMER CONJUGATED HO (III) DTPA-FOLIC ACID IN VACUUM AND AQUEOUS CONDITIONS AT 25 °C AND 37°C AS COMPOUND CONTRAST AGENT MAGNETIC RESONANCE IMAGING (MRI)

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Article Received on 19/06/2018 **Article Revised on 09/07/2018** **Article Accepted on 30/07/2018**

ABSTRACT

Objective: Molecular modeling has been carried out G3 PAMAM dendrimer conjugated Holmium (III)-penta acetic acid diethylene triamin (DTPA) and folic acid in vacuum and aqueous conditions at 25 ° C and 37 ° C by using the program ChemBio 3D 12.0. This study aims to model the G3 PAMAM dendrimer molecules are conjugated with Holmium (III) CHX-A "-DTPA and folic acid, and study the stability of the model. These compound was expected to be used as MRI contrast compounds that specific for diagnostic cancer cells and also serve as a cancer therapy. **Methods:** Prior to molecular modeling and molecular dynamics studies, first performed Holmium parameterization for compounds that have not been found on the Chem 3D program. Parameterization, including bond lengths, bond angles, angles and force constants respectively. Further molecular modeling performed with the program chem draw and molecular dynamics calculations to see the value of the stability of the total energy and potential energy. **Results:** The results showed that molecular dynamics simulation obtained value of the potential energy and total energy of the compound conjugated PAMAM G3 Ho (III) DTPA and folic acid is more stable at 25 ° C in aqueous conditions.

KEYWORDS: Molecular Dynamics PAMAM G3, DTPA, Holmium, folic acid, total energy, potential energy.

INTRODUCTION

The ideal molecular imaging contrast agent would contain a targeting moiety and deliver an imaging payload, while allowing the *in vivo* imaging properties to be manipulated to improve bio-distribution and excretion of the agent, thus customizing the agent for the desired imaging application (Steven C, 2001). Conventional imaging agents for magnetic resonance (MR) and computer tomography (CT) are low in molecular weight (LMW) and thus, their *in vivo* behavior is difficult to control. LMW agents exhibit rapid clearance from vascular circulation and rapid renal excretion, thus limiting their availability for time-dependent imaging studies stretching over hours. Unlike LMW agents however, dendrimer-based contrast agents offer much greater flexibility for *in vivo* applications. Dendrimer based contrast agents offer a sufficient number of binding sites to which numerous imaging and targeting moieties can be conjugated (Srinivasa-Gopalan, 2007).

Dendrimers are composed of combinations of core types,including ethylenediamine (EDA), diaminobutyl (DAB), polyamidoamine (PAMAM) and polypropylimine (PPI). In addition, surface residues such as amine, carboxyl, and alcohol groups contribute to the chemical signature of the specific agent. Those that have been used as platforms for imaging agents, such as PAMAM or PPI dendrimers, are highly soluble in aqueous solution and possess a primary amine rich surface that is uncharged at pH greater than 9.0 (Carolyn, 2011).

Targeting by Folate, a Small Molecule Ligand. Folate is an attractive small molecule for use as a tumor targeting ligand because the membrane-bound folate receptor (FR) is breast, endometrium, kidney and brain. Recently, folate has been enlisted in an innovative dendrimer-based targeting schemes (Longmire, 2006).

The folate receptor gene family includes four members (FRá or FOLR1, FRâ or FOLR2, FRã or FOLR3, and FRä or FOLR4, whose encoded products bind folic acid with high affinity.The high affinity of FRá and FRâ for folate binding, their endocytic capacity, and their restricted expression have prompted the evaluation of the

potential therapeutic value of folate-drug conjugates in cancer and inflammatory pathologies (Kim Y, 2004).

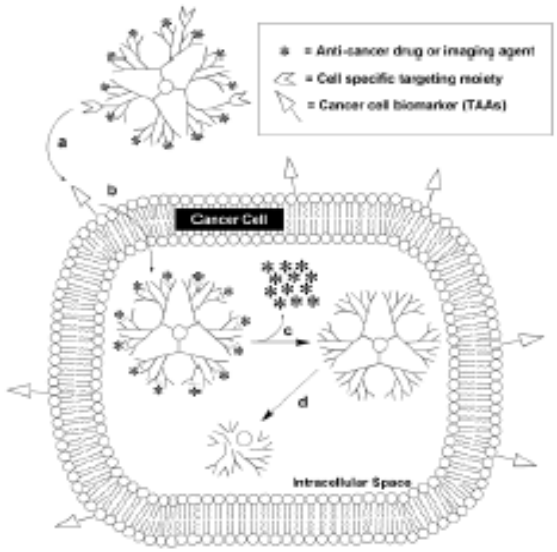

Fig. 1 Requirements for dendrimer-based cancer-targeted drug delivery. (a) Dendrimers with multiple surface functional groups can be directed to cancer cells by tumor-targeting entities that include folate or antibodies specific for tumor-associated antigens (TAAs). (b) The next step is intake into the cell, which in the case of folate targeting occurs by membrane receptor-mediated endocytosis. (c) Once inside the cell, the drug generally must be released from the dendrimer, which, for the self-immolative method, results in the simultaneous disintegration of dendritic scaffol

MRI

Contrast agents based on the lanthanide elements gadolinium and holmium have recently been developed for magnetic resonance imaging (MRI) (Botrill, 2006).

Since the observation that paramagnetic chelates such as Gd(III)-diethylenetriaminepentaacetic acid Gd(III)-DTPA] (Magnevist) and Gd(III)-N,N',N'',N'''-tetracarboxymethyl-1,4,7,10-tetraazacyclododecane-[Gd(III)-DOTA] increase relaxation rates of surrounding protons, these agents have been widely used in MR contrast media (Hari Krishna, 2009). However, the rapid clearance of these LMW contrast agents from the vascular space limits their application in time-dependent imaging studies (Aime, 2002).

This study aims to model the G3 PAMAM dendrimer molecules are conjugated with Holmium (III) CHX-A "-DTPA and folic acid, and study the stability of the model. These compounds are expected to be used as MRI contrast compounds that specific for diagnostic cancer cells and also serve as a cancer therapy (Da Costa, 2005).

MATERIALS AND METHODS

Materials

The materials for this study, PAMAM Dendrimer G3 (5) and data Ho-CHX-A "-DTPA (6).

Software and Hardware

a. CambridgeSoft Chem3D Ultra 12.0
b. Hyperchem 8.07 (freeware)
c. Processor Intel Core i7 2.6 GHz
d. DDRIII RAM 4 GB Memory
e. Hard drive 320 GB SATA II Seagate
f. VGA Nvidia Quadro FX-3700-Cuda Enabled.

Methods

Parameterization Holmium Compounds

Ho complex parameterization, including bond lengths, bond angles, angles and force constants respectively (Cundari, 1995).

Molecular Modeling

Modeling complex molecules Ho (III)-CHX-"A-DTPA done with the program ChemDraw Ultra 12.0 then moved to Chem 3D12.0. Then conjugated to the dendrimer PAMAM G3 and folic acid.

Analysis of Molecular Dynamics

Analysis of the dynamics of molecular compound conjugated PAMAM G3 Ho-CHX-A "-DTPA and folic acid through the following provisions:

1. Analysis of the steric energy of G3 PAMAM Conjugated compounds Ho (III)-CHX-A "-DTPA and folic acid in a vacuum and watery with a temperature variation 25 ° C and 37 ° C, the strain energy includes energy, bend, stretch-bend energy, torsional energy, the energy of non-1, 4 van der Walls, 1.4 van der Walls energy and energy dipole.
2. Analysis of the average distance, done by looking at the value of the average distance between the C atom farthest.
3. Trajectory analysis of the value of the potential energy and total energy of the compound conjugated PAMAM G3 Ho (III)-CHX-A "-DTPA and folic acid with a variety of vacuum and watery and variations in temperature of 25°C and 37°C (Ryszard, 2010).

RESULTS AND DISCUSSION

Compounds Ho(III)-CHX-A"-DTPA

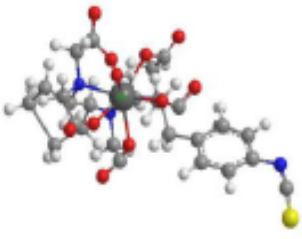

Fig. 2. Compounds Ho(III)-CHX-"A-DTPA

G3 PAMAM dendrimer conjugated

compounds with Ho (III) DTPA and folic acid. The structure of G3 PAMAM dendrimer conjugated with Ho (III) DTPA can not be conjugated directly for Ho (III)

DTPA is a chelate (ring) so that groups are used to conjugate Ho (III) DTPA with PAMAM dendrimer. Force used is [(R)- 2- Amino – 3 - (4 - isothiocyanatophenyl) propyl] – trans - (S,S) - cyclohexane-1 ,2-diamine-pentaacetic acid or CHX-A"-DTPA, and this structure thus becomes tied with Holmium Ho-CHX-a "-DTPA, as shown in Figure 3.

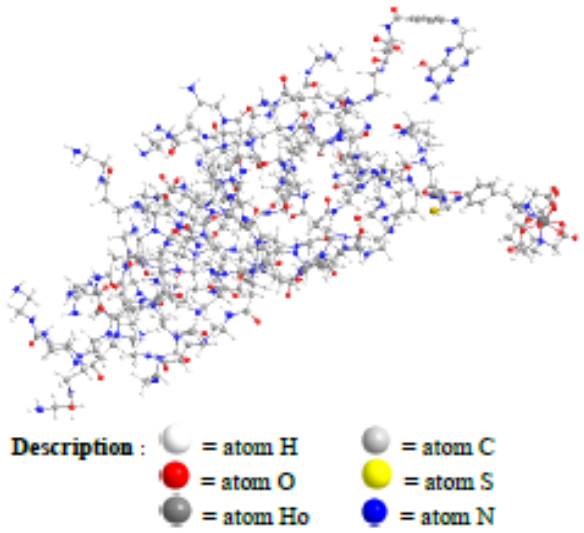

Fig 3. G3 PAMAM dendrimer conjugated compounds with Ho (III) DTPA and folic acid.

G3 PAMAM dendrimer conjugates with folic acid is based on the binding of folic acid and amine groups on the surface of PAMAM G3 dendrimer that the amidation reaction with the amide bond carbonyl group in folic acid (especially on the part glutamate) with terminal amine groups in the dendrimer (Gunsteren,W.F, 1990).

Analysis of Steric Energy PAMAM Compounds.

G3 conjugated with Ho(III)-CHX-A'-DTPA and folic acid. Steric energy can be used to analyze the stability of a compound. Steric energy value of G3 PAMAM dendrimer conjugated compounds Ho (III) DTPA and folic acid can be found in Table 1.

Table 1: Steric Energy of PAMAM Compounds.

Energy	Vaccum Conditions		Watery Conditions	
(k.kal/mol)	25 °C	37 °C	25 °C	37 °C
Stretch	66,2404	66,2348	67,4373	67,4340
Bend	387,9679	387,9765	380,7530	380,7504
Stretch-Bend	11,8768	11,8795	11,7070	11,7103
Tortion	1320,6437	1320,6447	1338,1087	1338,1147
Non-1,4 VDW	-394,2267	-394,2291	-394,3469	-394,3473
1,4 VDW	381,6163	381,6171	383,7113	383,7101
Dipole	38,5627	38,5627	39,2637	39,2643
Total energy	1812,6812	1812,6862	1826,6343	1826,6365

Total energy value can be seen that the compound conjugated PAMAM G3 Ho (III)-CHX-A'-DTPA and folic acid are relatively stable both at 25 ° C and 37°C in vacuum and water. This is evident from the increase in the total energy that is not too significant.

Analysis of Average Distance

Spacing of the atoms furthest done to see structural changes that occur, whether the structure of the compound having development (expansion) or shrinkage (contraction). The average distance value sought by the same conditions, to 25° C under vacuum average distance (Δd) is 31.1386 A; 37°C under vacuum (Δd) = 41.518 A; aqueous conditions 25°C (Δd) = 35.505 A; aqueous conditions 37°C (Δd) = 37.0698 A. Under vacuum and the aqueous at 25°C looks shorter distances between atoms or shrinkage occurs, whereas at 37°C are relatively longer or be development. This is caused by the higher temperatures will make the distance between the atoms become more tense (Haile, J. M. 1992).

Trajectory Compounds

G3 PAMAM dendrimer conjugated compounds Ho (III) DTPA and folic acid in a vacuum at a temperature of 25° C and 37°C

Data obtained from the molecular dynamics G3 PAMAM dendrimer conjugated compounds Ho (III) DTPA and folic acid under vacuum at a temperature of 25°C and 37°C was made into a trajectory as follows:

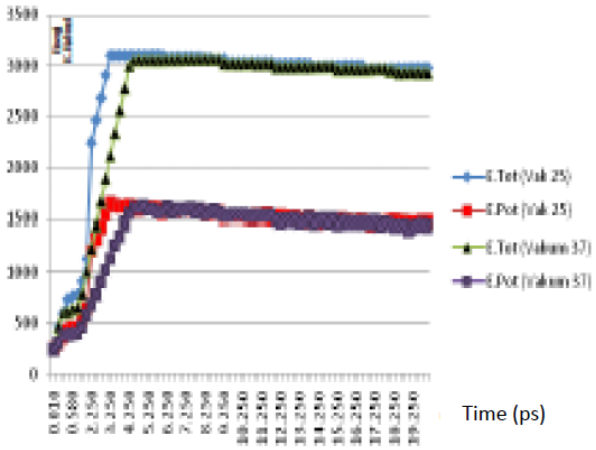

Fig 4: Total energy, potential energy of G3 PAMAM dendrimer conjugated compounds Ho(III) DTPA and folic acid in a vacuum at a temperature of 25 ° C and 37 ° C.

The length of the simulation time used is 20 ps. Temperature under vacuum at 25°C span of time from 0 to 3.090 ps energy increased significantly both total energy and potential energy. The energy generated increased accompanied by heating (increase in temperature). This is because the structure of moves to reach equilibrium. To obtain the energy equilibrium molecular cooling will occur (in molecules with high energy) or heating (in molecules with low energy), in order to obtain molecules with energy equilibrium.

Meanwhile, at 3.220 ps both potential energy and total energy begins significant energy stability. This is indicated by the value of the total energy and the potential energy tends to a constant.

G3 PAMAM dendrimer conjugated compounds Ho (III) DTPA and folic acid in aqueous conditions at 25 ° C and 37 ° C.

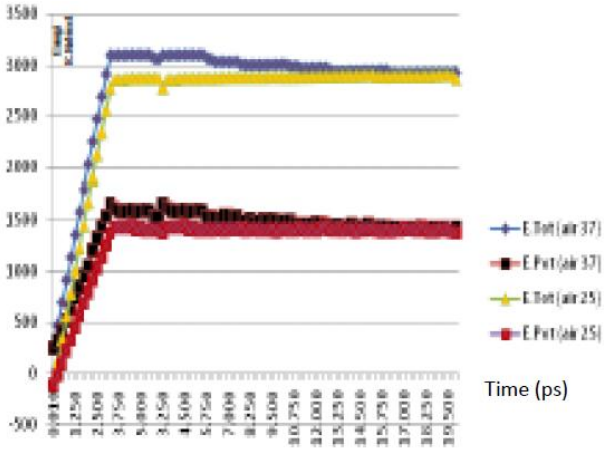

Fig 5: Total energy, potential energy of G3 PAMAM dendrimer conjugated compounds Ho (III) DTPA and folic acid in aqueous conditions at 25°C and 37°C.

In aqueous conditions 25°C span of time from 0 to 2.600 ps energy increased significantly both total energy and potential energy. This is because the system is a process of heating (heating), so that the structure moves to reach a stable state. Meanwhile, at 3.210 ps begins stability total energy and the potential energy is significant. This may be due to the compound has begun to find the ideal geometry conformation, which is characterized by the stability of the potential energy and total energy. In aqueous conditions at 37°C span of time from 0 to 2.820 ps there was an increase in total energy and potential energy, which is quite significant. Meanwhile, at 3.340 ps begins stability total energy and the potential energy is significant.

CONCLUSIONS

The experimental results obtained the following conclusions:

1. The model has been obtained from G3 PAMAM dendrimer molecule compounds are conjugated with Ho (III) DTPA and folic acid.
2. The study of molecular dynamics in vacuum and aqueous at 25°C C and 37°C obtained structure G3 PAMAM dendrimer conjugated compounds Ho (III) DTPA and folic acid is more stable at a temperature of 25°C in aqueous conditions.

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