

MOLECULAR DYNAMICS INVESTIGATION OF THE STABILITY OF NATURAL POLYMER CHITOSAN AND ITS POTENTIAL FOR NANODRUG DELIVERY

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ABSTRACT:

Chitosan, a naturally occurring polysaccharide, has attracted the attention of researchers due to its physical and chemical properties that are useful in drug delivery systems. As its composition is made up of N-acetyl glucosamine units (GlcNAc) and glucosamine (GlcN) units, knowledge on its structure in aqueous solution, is important information required to design drug delivery systems involving this polymer. The aim of this work was, therefore, to investigate chitosan chains in an aqueous environment and obtain information about its stable conformation using Molecular Dynamics (MD) simulations. The results obtained were analyzed by dihedral angle and intramolecular hydrogen bond measurements. The average conformations in the aqueous environment, obtained from 2085 calculated frames were found to be more stable due to changes in the ϕ and ψ dihedral angles which facilitate hydrogen bonding interactions.

Keywords: Molecular dynamics; Chitosan; Dihedral angle; Intramolecular hydrogen bond.

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INTRODUCTION:

Chitosan, a naturally occurring polysaccharide, is found in several sources like plant, animal and fungi [1]. After cellulose, chitosan is the second most abundant biopolymer in nature [2]. Chitosan is the deacetylated form of chitin and obtained usually from Crustaceans [3]. Chemically chitosan is a polymer of randomly distributed N-acetyl glucosamine (GlcNAc) and glucosamine (GlcN) units linked through β -(1, 4) glycosidic bonds. Hydrous and anhydrous crystal forms of chitosan are available with full deacetylation. Recently the crystal structure of chitosan has revealed a fivefold

helical symmetry along the polymer axis [4]. Some of the useful properties of chitosan are its viscous nature, polyelectrolyte behavior, polyoxy salt formation, chelation with metals and easy film formation [5]. Chitosan is widely used today in drug delivery systems as a functional material. It is preferred because of its bio-degradability, compatibility with biological systems and nontoxic nature. It has been used for preparing nanoparticle delivery systems of proteins, insulin, vaccines and drugs. The major problem faced by formulation chemists during the preparation of nanoparticles or

other delivery systems is drug loss during processing of formulations due to degradation of the drug or polymer. The processing temperature at which an aqueous solution of a polymer is used for formulation purposes is usually around 25°C. If one desires to prepare a formulation of nanoparticles using chitosan, it is necessary that the aqueous solution of the polymer is stable at this processing temperature. The stability of the polymer indirectly indicates the structural integrity of the polymer at this temperature. In practice, laboratory studies to investigate the stability of a polymer at different temperatures in aqueous systems require considerable time and is highly expensive. Molecular dynamics (MD) method is one of the best methods for analyzing the chemical properties or behavior of polymers at different temperatures without adopting any experimental procedure [6]. MD simulation helps in the structural study as well as to determine some important properties like dihedral angles, inter and intra molecular hydrogen bonds and interaction with other molecules. Earlier workers have carried out detailed studies on the dynamics of flexibility of chitosan by using Macro model (Version 9.0) and the AMBER force field with the Sanderowitz-Still all atom pyranose parameters [7]. However, the stability of chitosan in aqueous environment at 25°C, the temperature at which drug delivery systems is usually processed has not been studied so far. The authors propose to use chitosan as a carrier for developing drug loaded nanoparticles.

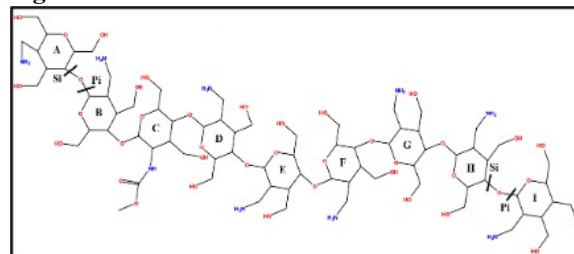
In the present investigation, we report the stability studies on chitosan in aqueous environment at 25°C by molecular dynamics method using the Schrodinger software to confirm its structural integrity and hence its suitability for preparing nanoparticles.

METHODOLOGY:

The calculations were carried out using Macro model (Version 9.2) and the OPLS 2005 force field with the whole atom parameters well parameterized for oligosaccharides. Each oligosaccharide unit was joined together and the energy minimized by using Macro model (version 9.2) method with steepest descent followed by conjugated gradient method using Implicit solvent by Macro model's generalized Born continuum solvent model (GB/SA) for the disaccharides. Conformations were generated by using Monte Carlo Multiple Minimum (MCM) torsional sampling method with a step size of 500. The obtained conformation was clustered and from each cluster one disaccharide was selected and the energy minimized further. The lowest energy conformation amongst these was then selected for building the trimer. A similar procedure was

followed till the octamer units were built. The final octamer was minimized by using steepest decent with 2000 iterations followed by conjugated gradient method with 1000 iterations. It was then subjected to conformational search using MCM with a step size of 2000. The conformers were clustered and from each cluster, cluster centers were selected and further minimized. The lowest of the cluster center with respect to potential energy was selected for explicit molecular dynamics simulations using the Impact module of Schrodinger software. The minimized chitosan structure was then solvated with water molecules. The solvent system was subjected to energy minimization, initially with steepest descent, followed by conjugated gradient method. The minimized solvated chitosan molecule was then simulated by MD simulations performed individually at 100 nanoseconds using OPLS 2005 force field. The Verlet integration method was used for collecting the ensembles (NVT) with a time step of 1 femto seconds. The resultant trajectory file was collected, and the simulation path was analyzed. The dynamics of the solvated chitosan molecule at 25°C were performed using Desmond- Molecular Dynamics with 10 ns of simulation time with the recording interval of 1.2 ps. The total conformations of the chitosan structures were clustered by macro model conformational search. The representative structure of the resultant twenty clusters was then minimized several times to get the lowest potential energies, and the average structure was calculated from the final chitosan conformers. The dihedral angles and intramolecular hydrogen bonding were then measured for the average structure, lowest energy structure and the highest energy structure. The average of all conformations was also taken in order to calculate the dihedral angles of conformers. **Figure 1** shows the chitosan chain denoted by an octamer unit, rings A to I, which were used for calculating the ϕ and ψ angles.

Figure 1: Chitosan Chain

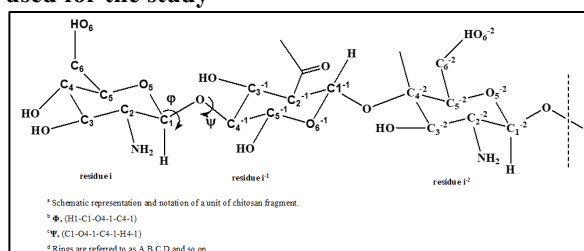


RESULTS AND DISCUSSION:

Temperature is well-known factor to play an important role on the ability of chitosan to aggregate forming insitu gels, and nanoparticles in solution [8]. A structural motif of chitosan in gels has been aggregated with the increase of the temperature in the aqueous media. Nevertheless, and its effect on

the chains of these polysaccharides remains as such. In the present investigation, intramolecular hydrogen bonding interactions of chitosan have been studied in aqueous media maintaining the temperature at 25°C. The glycosidic bond angles, ϕ and ψ , of the low energy conformation (LEC), high energy conformation (HEC) and the average of all the frames from dynamics, were also studied. The values of ϕ and ψ were set initially. The change in dihedral angles from the initial conformation with respect to time leads to a change in intramolecular hydrogen bonds. The influence of the temperature on single chains of chitosan in aqueous solution a time evolution analysis carried out for chitosan and ϕ , ψ at torsional angles shows some influence of the temperature at 25°C on the structural convergence of the chitosan chain, from the low energy, high energy conformation, **Figure 2** shows a schematic representation and the notation used for a unit of chitosan fragment.

Figure 2: Dihedral angles and nomenclatures are used for the study



An analysis of the intra chain hydrogen bond pattern in the high energy and low energy conformations of chitosan reveals that in Ring H, HO3-7---HO6-8 (O---H₂) and in Ring D, HO3-3---HO6-4(O---H) are found in the high energy conformation, low energy conformation as well as the average conformation. The interactions of HO6-5---O5-6(H---O) in Ring F are found to be common in the low energy conformation and the average conformation. Other than these interactions, HO3-2---HO6-3(O---H) and HO3-2---O5-3(H---O) are seen in ring D. Since a change in the number of interactions between high energy, low energy and average conformations was observed, a comparison was conducted on the variation in ϕ and ψ angles of the three conformations. The measured dihedral angles of chitosan clusters shown in **Tables 1 and 2**.

Table 1. Dihedral angles of Chitosan Clusters Rings B to E (in degrees)

Clus	Ring B		Ring C		Ring D		Ring E	
ters	ϕ	ψ	ϕ	ψ	ϕ	ψ	ϕ	ψ
LEC	2	4	-	5	3	4	-	4
	5.	8.	3	1.	0.	5.	9	6.

	1	6	5.	6	0	4	1.	4
			4				6	
HEC	3	5	-	-	-	3	-	4
	1.	1.	1.	5	3	0.	4	3.
	9	9	9	4.	2.	6	8.	3
				8	6		0	
AS	5	-	5	3	5	-	-	-
	1.	1	1.	9.	0.	9.	5	4
	0	4.	7	0	4	3	2.	2.
		6					4	2

LEC: Low Energy Conformations, HEC: High energy Conformations and AS: Average structure

Table 2. Dihedral angles of Chitosan Clusters Rings F to I (in degrees)

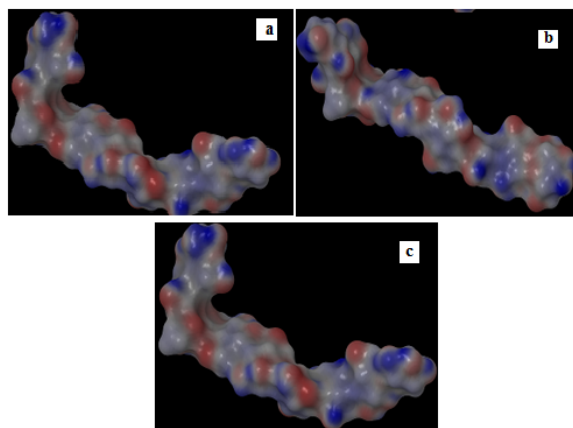
Clus	Ring F		Ring G		Ring H		Ring I	
ters	ϕ	ψ	ϕ	ψ	ϕ	ψ	ϕ	ψ
LEC	-	-	-	5	3	5	-	3
	5	6	1	3.	6.	4.	5	0.
	8.	3.	3.	6	8	1	6.	3
	9	0	8				2	
HEC	-	-	1	5	3	4	-	2
	5	6	2.	1.	5.	8.	9	7.
	9.	4.	6	6	2	8	7.	2
	1	8					7	
AS	4	-	4	-	-	5	5	2
	6.	4	1.	2	3	3.	0.	5.
	2	3.	2	6.	5.	5	3	9
		8		6	9			

LEC: Low Energy Conformations, HEC: High energy Conformations and AS: Average structure

It is observed that the ϕ of the average conformation ranges from about -52.4 to 53.5 and that of the HEC and LEC ranges from -97.7 to 43.3 and -91.6 to 58.9, respectively. It is also observed that hydrogen bonding interactions are affected by a change in the dihedral angle of the chitosan molecule. In order to probe this factor further, the intramolecular hydrogen bonding interactions within the chitosan molecule were studied to maintain the temperature at 25°C. These interactions were studied for all the conformers by forming clusters of the conformers. The process of cluster formation gave a high energy conformation and a low energy conformation. The

intramolecular hydrogen bonding interactions of chitosan shown in **Figure 3**.

Figure 3: Electrostatic potential plotted on to the molecular surface of Chitosan Chain

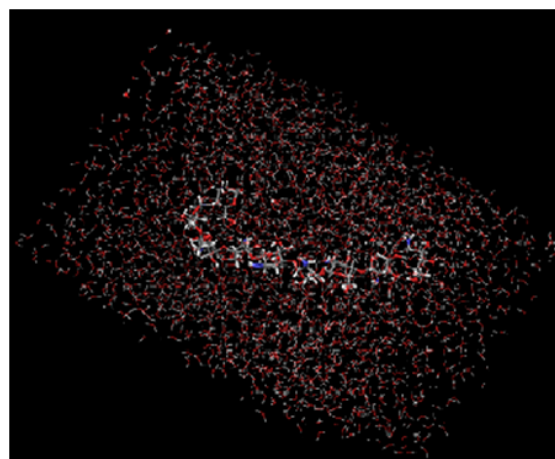


a. Low energy conformation, b. High energy conformation, and c. Average conformation.

Figure 3. reveals that in the high energy conformation there is a smaller number of hydrogen bonding interactions are observed than the low energy conformation. In the average conformation (2085 frames), It is clear from figure that chitosan in aqueous environment at 25°C results in a slower convergence to its equilibrium structure (average conformation). indicates that the measured intrachain hydrogen bonds of chitosan are responsible for the stable crystalline state.

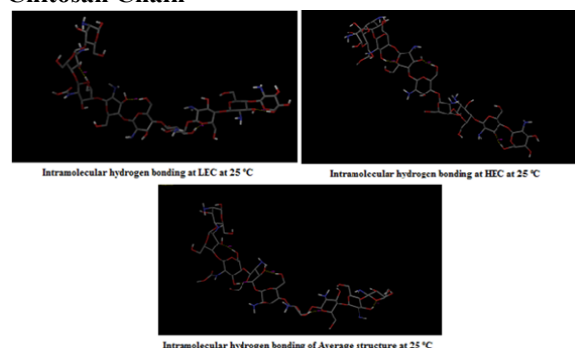
It is also known that chitosan is slightly soluble in water and is highly soluble in acidic media due to less structured in acidic medium due to higher conformational diversity. However, our results show that a chitosan chain in aqueous solution at 25°C shows less conformational change and similar degree of rigidity from low energy and high energy conformations and hence it is confirmed its crystalline nature. It is well known that the crystalline structure of chitosan displays some conformational variability [9]. The solvated chitosan molecule is shown in **Figure 4**.

Figure 4: Solvated Chitosan in Water



During the simulation process, analyses of the intrachain hydrogen bond pattern in chitosan reveal three hydrogen bonding interactions were observed for the high energy conformation and four in the low energy conformation (**Figure 5**).

Figure 5. Intramolecular hydrogen bonding of Chitosan Chain



whereas for the average conformation a total of five interactions were observed and this may be due to the chitosan stability at 25°C possibly because of 2-fold helix motif of chitosan due to changes in the dihedral angle during the simulation process. it is observed that due to a change in the dihedral angle, hydrogen bonding interactions increase and hence chitosan retains its chemical integrity in aqueous solutions.

CONCLUSION:

In the present investigation, the conformational stability of chitosan in an aqueous medium at 25 °C was investigated using molecular dynamics simulations. A correlation between intermolecular hydrogen-bonding interactions and dihedral angles were established. The comparison of low-and high-energy conformations demonstrated that the low-energy conformation was predominantly maintained throughout the simulation, indicating greater conformational stability. The average conformation exhibited a higher number of hydrogen-bonding interactions, which may contribute to the structural integrity and stability of chitosan in aqueous

environments. These findings support the potential of chitosan as a natural polymeric material for the development of nano-based drug delivery systems, particularly for targeted delivery of therapeutic agents to cancer tumors. The observed molecular stability provides a useful computational basis for further investigation of chitosan-based nanoparticles for tumor-targeted drug delivery. Further experimental studies are required to evaluate nanoparticle formulation, drug-loading capacity, cellular uptake, tumor-targeting performance, and therapeutic efficacy.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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