Ab Initio DFT Study of Polysaccharides To Predict Their Applicability In Wound Healing

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Research Article

Keywords: Polysaccharides, molecular interaction, DFT, efficient biocomposite, wound healing patch.

Posted Date: January 17th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1233869/v1>

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Abstract

A wound-healing patch is used to help in this repairing process in which the dermal patch has been proven to be the fastest and economical way to help. Nowadays more attention is being paid to the use of biodegradable polymers for making efficient biocomposite films. In this study, we have explored the properties of some polysaccharides that can be used for wound healing. In recent years *ab initio* method for electronic structure study is being used frequently. We have done the density function theory (DFT) calculations of polysaccharides (Alginic acid, Chitosan oligosaccharide, Chitosamine hydrochloride, Ethylcellulose, and Sodium carboxymethyl cellulose) using SIESTA software to know its structure/interaction at the molecular level. This information is helpful to understand the blending possibility of the above-mentioned biopolymers so that their patches can be cast easily for wound healing application. Further MD simulation calculations decipher the virial energy, order parameters, and accumulation time averages of biopolymers that could play useful information in storing biopolymeric blends for long time storage. DFT study has shown that chitosan oligosaccharide is thermally most unstable whereas chitosamine hydrochloride is most stable. Also, chitosan oligosaccharide has the highest density and lowest is of chitosamine hydrochloride at a similar energy level. The range of density at different states and structures of polymer helps in predicting homogenous blends. Overall, this study could help in providing insights for the formulation of effective blends of these polymers to obtain better biocomposite material with desired properties that could be used as efficient biocomposite films/patches in wound healing.

1. Introduction

Revamp of damaged epidermal and dermal tissues in skin is known as wound healing. Repair of internal organs injured tissues is mechanistically similar to the wound healing. Skin wound healing is the most frequently used experimental models to gain insights into the mechanism of repairing process owing to its experimentally convenient location [1]. Drugs assist in wound healing. However, the effect of a drug depends on the route of administration, type of drug, type of wound, and mechanism of action [2]. Most of the polysaccharides contribute to the process of wound healing due to their significant bioactivities such as the ability to absorb enormous quantities of water or physiological solutions, the ability to provide a moist environment at the wound bed, hemostasis, leading to rapid granulation, and re-epithelialization, which make them suitable for wound healing applications most commonly used polysaccharides in wound healing process. Dressings with Alginate can absorb up to 20 times their own weight for finest wound healing. The evidence indicates that chitin, chitosan, and its derivatives would also be beneficial for the wound healing process. More recently, it was also shown that some nano-based materials from chitin and chitosan are beneficial than chitin and chitosan for wound healing [3–5].

In recent years computational analysis of biocomposite for biological application has become quite common. One of such program is SIESTA which stands for Spanish Initiative for Electronic Simulations with Thousands of Atoms. It is a method which is used to perform efficient Electronic simulations and Molecular Dynamics simulations of molecules and solids. The use of basis sets of strictly localized

atomic orbitals makes SIESTA very efficient and produces accurate simulations. Various tuning operations in siesta helps to obtain wide variety of results ranging from quick explanatory calculations to highly accurate simulation matching the quality of other approaches, like plane-wave methods. Siesta is an open source program release under terms of GPL open-source license. Siesta is written in FORTRAN 95 and can be compiled for serial or parallel execution (under MPI). It employs the standard Kohn-Sham self consistent density functional method in the local density (LDA-LSD) and generalized gradient (GGA) approximations, as well as in a non-local functional that includes van der Waals interactions (VDW-DF). It also uses norm-conserving pseudopotentials in their fully nonlocal (Kleinman-Bylander) form. Apart from all these features the siesta package also provides us with many post-processing tools such as EIG2DOS, GNUMBands, etc. SIESTA is currently being used by researchers of many different fields namely geosciences, biology, and engineering, physics and chemistry. It is used for variety of purposes such as Total and partial energies, Atomic forces, Electron density, Band structure, Local, and orbital-projected density of states and many more [6, 7].

The present study was focused on the structural analysis of biodegradable polysaccharides (Alginic acid, Chitosan oligosaccharide, Chitosamine hydrochloride, Ethyl cellulose, and Sodium carboxy methyl cellulose) that also have wound healing and/or antibacterial property. DFT calculation of these polysaccharides was performed using SIESTA. Analysis of electronic structure can help in formulating effective biocomposites by the combination of above mentioned polysaccharide for wound healing and other biomedical application as structural properties affect the mechanical and dynamic property of the biopolymers.

2. Materials And Methods

2.1. Selection of polysaccharides

One needs to have high quality experimental datasets in order to obtain meaningful statistical properties of biopolymer interactions. For wound healing we also need to choose carefully the biopolymer in regards with their physiochemical properties. Set of Five polysaccharides (chitosan oligosaccharide, chitosamine hydrochloride, alginic acid, ethyl cellulose and sodium carboxy methyl cellulose) were taken to understand their structural behaviour at molecular level which can be further used later to form the blends of biocomposite wound healing material.

2.2. DFT calculation of selected polysaccharides

DFT calculation based on first principle of energy conservation of above mentioned polysaccharides were done using SIESTA version 3.0 software (<https://departments.icmab.es/leem/siesta/>). Norm-conserving and GGA-PBE functional pseudo potential files (psf) of each element were used to describe the core nucleus and atoms. Fdf files for each polysaccharide was generated using wxDragon tool. Fdf file consisted of basic structural information such as atomic coordinates and atomic species and split valance with DZP polarization function was employed. Mesh cutoff value of 150 Ry and with energy shift of 0.03eV was taken. For MD simulation CG run type was employed with maximum force tolerance to be

0.04eV/Å and 50 CG steps. Hamilton (H) and overlap (O) matrices compute the atomic coordinates and cells. SIESTA is computer program and implementation to perform *ab initio* MD simulation and electronic structure calculation. It used norm-conserving Kleinman-Bylander form psf files and standard Kohn-Sham self consistent (LDA-LSD) and (GGA) approximations in a non local function including van der Waals interactions.

DFT run using SIESTA provided with density matrix (.DM) file, atomic force (.FA), Atomic coordinates and other details (.ANI and .xyz), Harris enthalpy, molecular dynamic energy (.MDE) etc files. All these output requires many other software to visualize or analyse the results. To plot MDE file, gnuplot was used. Gnuplot is a open source portable command-line graphing utility for windows, LINUX or other platform. To visualize atomic structure and distance and other calculations, a java viewer for chemical 3D structure, Jmol, and VESTA was used. Plotting of density of states (DOS) data obtained from Eigen value (.EIG file) was done using XMGrace [8–10].

3. Results And Discussion

The electronic structure of polysaccharides (Alginic acid, Chitosan oligosaccharide, Chitosamine hydrochloride, Ethyl cellulose, and Sodium carboxy methyl cellulose) have been studied by above mentioned method using SIESTA software and some of results are analyzed (analysis of others are yet in process and some cannot be done because of lack of data). Fdf file provide with all the traditional structure information such as lattice parameters, lattice constants, number of species, number of atoms, lattice vectors, super cells etc. The output of these structural information consisted of <systemlabel>.XV files that gives the coordinates of species. STRUCT_OUT file gives the atomic vectors in Å along with atomic coordinates. All the output related to structure can be further used to calculate the electronic structural variables. The calculation can be done by using either diagonalization which has cubic scaling with size or direct minimization. During last iteration, Eigen value and wave function were obtained associated to appropriate k-point sampling as .EIG file. These <systemlabel>. EIG file were then converted to EIG2DOS file for post processing utility then the dos.dat file obtained from that was used to plot the graph with help of Xmgrace (Figure 1). The graph shows the distribution of density of states from which it is clearly evident that ethyl cellulose has much more higher range of density than others whereas chitosan oligosaccharide have higher density but remains constant with different states. These density distributions can be compared to obtain blend with desired density and homogenous mixture. DOS can be analyzed to study interaction of different blends as DOS strongly affects the electronic structure of polymer. Harris functional logical variables were used to calculate energy and forces (Table 1).

Table 1
Harris enthalpy and free energy of different polysaccharides.

Polysaccharide	Harris Enthalpy (eV)	Free Energy (eV)	Pressure (GPa)	Orbital Volume (Bohr**3)
Chitosan oligosaccharide	-9723.79	-9758.18	0.2	185913.85
Chitosamine hydrochloride	-3548.33	-3560.64	0.2	66588.59
Alginic Acid	-8092.75	-8116.86	0.2	130328.42
Ethyl cellulose	-7847.38	-7882.60	0.2	190411.89
Sodium carboxy methyl cellulose	-3693.18	-3704.89	0.2	63297.09

As we know that molecule with high energy has higher reactivity and less stability and vice versa. Thus free energy and molecular dynamic energy given by DFT calculation shows the stability of polymer. For storing blends for long time and the environment in which this to be stored, this energy analysis plays essential role. Among the analysed five polymers, basis enthalpy of chitosan oligosaccharide is most negative (i.e., -9723.797eV) followed by alginic acid and ethyl cellulose with value of -8092.759eV and -7847.383eV respectively. Whereas, least negative enthalpy is -3548.331eV of chitosamine hydrochloride followed by sodium carboxy methyl cellulose having -3693.184eV enthalpy. Enthalpy gives the idea about energy released while the bond breaks thus highest amount of energy will be released with degradation of chitosan oligosaccharide and least will be released with carboxy methyl cellulose. Also to make stable blend with polysaccharide of higher negative enthalpy, polysaccharide with less negative enthalpy can be mixed (other reactive properties to be considered with this as well).

MDE plotting was done using Gnuplot (Figure 2). MD simulation calculated any variable of interest, such as the virial energy, order parameters, ready for the accumulation time averages. The final plot compares total energy with KS energy (figure 2). The DFT optimized electronic structure was visualized using Jmol (figure 3). Polar groups affect the hydrophilicity of polymer. So with optimized 3D structure we can get the idea about solubilisation of polymer in polar or non-polar solvent, Using Jmol further many calculation such as Gaussian calculation, vector distance, vibration studies etc can also be done. There were many other outputs obtained as well, such as wave function detail, atomic force and conjugant gradient which can also be processed accordingly to get more information.

Conclusions

Ab initio method for determination of structural properties of a few biodegradable polysaccharides (Alginic acid, Chitosan oligosaccharide, Chitosamine hydrochloride, Ethylcellulose, and Sodium carboxymethyl cellulose) is done in this study to get insights into the interaction pattern of these biopolymers to understand their blending capability. The result supports that these biopolymers can have potential in the preparation of wound healing that could be loaded with suitable drugs for future study. Structural analysis has been performed using SIESTA through DFT calculation of these polysaccharides.

The most stable polysaccharide concerning enthalpy is found to chitosamine hydrochloride that has almost similar enthalpy as sodium carboxymethylcellulose. The thermally most unstable polysaccharide is chitosan oligosaccharide followed by alginic acid then ethyl cellulose. These analyses can help in predicting polysaccharide biocomposite material that can be loaded in dermal patches as well as for formulating biocomposite materials for biomedical applications. Further analysis of molecular interactions of these polymers is warranted in the future.

Abbreviation Notation And Nomenclature

DFT: Density function theory; FDF: Flexible data file; GGA: generalized gradient (GGA) approximations; LDA: local density approximation; MD: Molecular dynamics; PSF: Pseudo potential file; SIESTA: Spanish Initiative for Electronic Simulations with Thousands of Atoms.

Declarations

Acknowledgement: We sincerely acknowledge the National Institute of Technology, Raipur (CG), India for providing all kinds of support to this work.

Funding: Nil

Conflicts of interest/Competing interests: None

Availability of data and material: Not applicable

***Code availability:** Not applicable

***Authors' contributions:** SK, BD: Experiment, Writing manuscript; MKT: Analysis and draft writing; AA: Analysis, Draft writing; AK: Design, Analysis, Finalize manuscript.

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Figures

Figure 1

Bulk energy v/s Density of states plot. **A)** Chitosan oligosaccharide, **B)** Chitosamine hydrochloride, **C)** Alginate acid, **D)** Ethyl cellulose, **E)** Sodium carboxy methyl cellulose.

Figure 2

Molecular dynamic energy plot of **A)** Chitosan oligosaccharide, **B)** Chitosamine hydrochloride, **C)** Alginate acid, **D)** Ethyl cellulose, **E)** Sodium carboxy methyl cellulose.

Figure 3

Visualization of optimized 3D structure using Jmol of **A)** Chitosan oligosaccharide, **B)** Chitosamine hydrochloride, **C)** Alginic acid **D)** Ethyl cellulose, **E)** Sodium carboxy methyl cellulose.

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