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Spectroscopy analysis of chitosan-glibenclamide hydrogels

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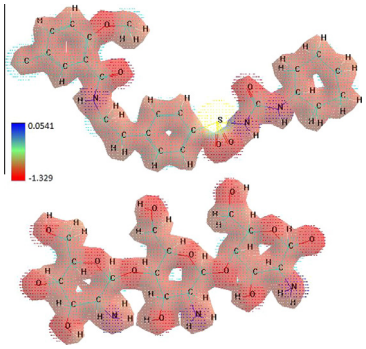
HIGHLIGHTS

- The Gibbs free energy was obtained.
- FTIR studies were an option to apply theoretical calculations.
- Using QSAR properties to estimate of the activity of a structure chemical.
- The MESP gives information about the proper region.

GRAPHICAL ABSTRACT



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ABSTRACT

The structure of glibenclamide, 5-chloro-N-(2-{4-[(cyclohexylamino)carbonyl] aminosulfonyl}phenyl) ethyl)-2-methoxybenzamide, an important antidiabetic drug, has been studied both chitosan using theoretical calculations like Gibbs free energy, electrostatic potential, FTIR and NMR spectroscopy. Fourier transform infrared (FT-IR) spectroscopy reveals information about the molecular interactions of chemical components and is useful to characterization of hydrogel. Nucleophilic and electrophilic regions were calculated using the electrostatic potential.

Introduction

Environmentally friendly bio-based polymeric materials are becoming increasingly popular due to their biocompatibility, biodegradability, non-toxicity, antimicrobial activityand other properties. These materials are usually made from biopolymers such aspolysaccharides, proteins, lipids and resins. Chitosan is obtained by partial N-deacetylation of chitin which is the second most abundant natural polysaccharide after cellulose, and is a high molecular weight polymer formed by β-(1-4)-2-amino-2-deoxy-D-glucopyranose units [1]. Chitosan is a biopolymer composed of glucosamine (70–100%) and acetylglucosamine (0–30%) units with molecular weight ranging from 50–1000 kDa [2]. Due its hydrophilic, cationic, and biodegradable nature, chitosan has been evaluated for wide variety of applications in the agricultural and pharmaceutical industries [1,2].

Chitosan (Fig. 1) is soluble in acid aqueous solutions with pH values between 4.5 and 6.5 which constitute a limitation on certain applications in food industry. In an attempt to improve the water solubility of chitosan, different strategies have been described. The introduction of hydrophilic groups by removing hydrogen atoms of free amino groups through different reactions provides chitosan modifications expanding its rate of solubilization. Thus acylation, alkylation and carboxymethylation, among other

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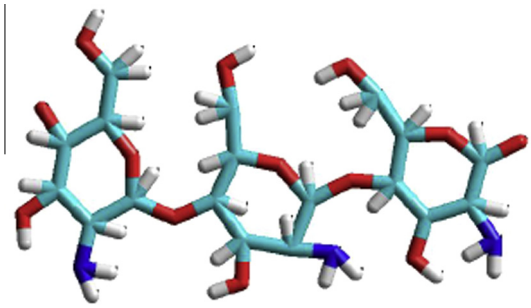

Fig. 1. General structure of chitosan.

reactions, give derivatives with modified properties respect to those of native chitosan. Because of their high hydrophilicity and specificity, carbohydrates and derivatives have been used for chitosan modifications [3]. Besides well-documented metal binding, protein binding, antimicrobial, and film-forming properties, its antioxidant activity has been often claimed. However, the mechanism of antioxidant activity of chitosan is still disputable. While some studies indicate considerable *in vitro* antioxidant properties of chitosan, many have clearly shown low or no antioxidant activity of native chitosan, although the activity significantly increased with appropriate chemical modifications of the biopolymer [2].

Hydrogels are a unique class of macromolecular networks that can hold a large fraction of an aqueous solvent within their structures. They are particularly suitable for biomedical applications, including controlled drug delivery, because of their ability to simulate biological tissues. Many hydrogel-based networks have been designed and fabricated to meet the needs of pharmaceutical and medical fields [4,5]. Hydrogels have been successfully used in biomedical fields due to their high water content and the consequent biocompatibility. Potential applications of hydrogels in tissue engineering, synthetic extracellular matrix (ECM) and three dimensional scaffolds are well highlighted in a recent work [6].

Glibenclamide, 1-[4-[2-(chloro-2-methoxybenzamido)ethyl]-benzenesulphonyl]-3-cyclohexyl-urea, 5-chloro-N-[2-[4[[[(cyclohexyl(amino) carbonyl]-amino] sulfonyl]-phenyl]ethyl]-2-methoxy benzamide, a sulphonyl urea derivative (Fig. 2) having melting point 169–174 °C is a white or almost white crystalline odorless powder, practically without taste, insoluble in water, sparingly soluble in methylene chloride, slightly soluble in ethanol, methanol and insoluble in diethyl ether. It dissolves in dilute solutions of alkali hydroxides. Glibenclamide is a second-generation oral hypoglycemic agent which is more potent than those of first group and is used to assist in the control of mild to moderately severe type II diabetes mellitus (adult, maturity-onset) that does not require insulin, but that can be adequately controlled by diet alone. It is a drug of choice for initiating treatment in noninsulindependent diabetes when diet and weight control fails. It stimulates the secretion and enhances the utilization of insulin by appropriate tissues [7,8].

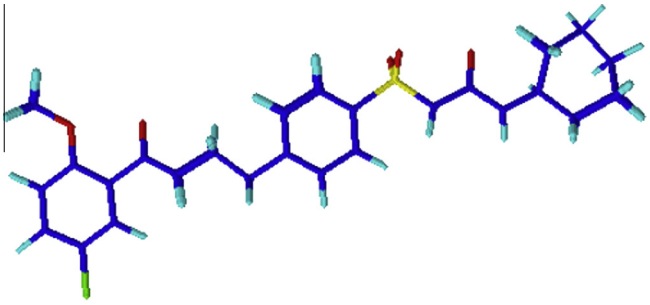

Fig. 2. Glibenclamide structure.

The analysis techniques applied in this study were, FTIR to study this effect and an option to justify the obtained results is using theoretical calculations by means of the computational chemistry tools [9]. Using QSAR properties, we can obtain an estimate of the activity of a chemical from its molecular structure only. Sorption of organic chemicals in soils or sediments is usually described by sorption coefficients [10]. The molecular electrostatic potential (MEP) was investigated using AM1 method. This method gives information about the proper region by which compounds have intermolecular interactions between their units [11]. The electrostatic potential is the energy of interaction of a point positive charge (an electrophilic) with the nuclei and electrons of a molecule. Negative electrostatic potentials indicate areas that are prone to electrophilic attack. The electrostatic potential can be mapped onto the electron density by using color to represent the value of the potential [12].

Experimental procedure

Method

The method for performing quantum mechanical calculations includes the following steps: (1) draw the molecular structure. The initial geometry can generally be designed by applying chemically reasonable atomic distances, angles, and dihedral angles. With a molecular editor the molecule can be built interactively including the chemically reasonable bonds and angles; (2) set up the molecular mechanic and optimize the structure parameters.

Once the molecular geometry has been defined, considerations involved in selecting the quantum mechanical method, checking numbers of unpaired electrons present in the molecule, and understanding the effect of the environment, are required; (3) select a calculation model. The semi-empirical method, AM1, is selected (the HyperChem software, release 7.0, being used). This method can automatically optimize the bond length, angle, and twist angle, and yield a lot of information on the structure; (4) define and select the output parameter.

Quantum chemical calculations produce a large amount of output data. Therefore it is important to decide which output is relevant for the chemical, biochemical, or biological mechanism underlying the phenomenon under investigation, (5) run the calculation job. After the method and all generated output have been defined, the calculation can begin. The geometry optimization is the most time-consuming part of many quantum mechanical calculations. The extent to which the geometry is converging to an energy minimum is listed in the output file and indicates when the calculation is about to be completed [13]. The molecular structures were optimized using the conjugate gradient algorithm (Polak-Ribiere) with the termination condition being RMS gradient less than 0.1 kcal/(Å × mol) (in vacuo) and 0.5 kcal/(Å × mol) (in explicit solvent (H_2O)) [7].

Electrostatic potential

HyperChem software displays the electrostatic potential as a contour plot when you select the appropriate option in the Contour Plot dialog box. Choose the values for the starting contour and the contour increment so that you can observe the minimum (typically about −0.5 for polar organic molecules) and so that the zero potential line appears. A menu plot molecular graph, the electrostatic potential property is selected and then the 3D representation mapped isosurface for both methods of analysis. Atomic charges indicate where large negative values (sites for electrophilic attack) are likely to occur. However, the largest negative value of the electrostatic potential is not necessarily adjacent to the atom with the largest negative charge (HyperChem® [14]).