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Research

Diclofenac on Chitosan Hydrogels: Adsorption Process Using Quantum Mechanics

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Abstract

Nanotechnology allows the design and development of new release systems controlled at nanometer scale by computational chemistry studies in which hydrogels based on chitosan are studied for the adsorption of drugs in order to provide a better quality of life for patients in various medical treatments. The computational models generate a punctual analysis of the affinity of a drug for its receptor in addition to the study of pharmacokinetic and physicochemical properties using various external factors such as pH, temperature, ionic properties, etc. In this research, the adsorption of diclofenac on chitosan hydrogels was studied using Quantum mechanics with the objective of using it in patients with skin cancer, caused by the increase of cases to worldwide. The calculated properties were Gibbs free energy, QSAR properties such as partition coefficient, surface area, volume, mass as well as molecular vibrations before and after adsorption using the FTIR technique and finally the MESP corroborated the process of adsorption.

Keywords: Quantum Mechanics; FTIR; MESP; Gibbs; Skin Cancer

Introduction

During the 1980s, controlled release technology emerged as an alternative to traditional release mechanisms, with the main objective being optimal transport of the active ingredient, i.e. adequate doses released at specific sites, reducing side effects in other areas of the organism and maintaining a prolonged effectiveness [1]. A successful methodology for controlled release systems has been the use of polymer systems based in hydrogels consisting of a three–dimensional network of flexible polymer chains that absorb considerable amounts of water [2,3]. These materials aroused great scientific interest because of their biocompatibility characteristics attributed to the physical properties of the organism making them like living tissues. They are also characterized by their soft and elastic consistency and their low surface tension [2]. Also, they are used in adsorption process of different molecules, representing one of the main forms where the high energy interfaces are modified to decrease the total energy of the system. In the adsorption process it is important to consider two relevant aspects, a) the thermodynamics present in the energy of the system in equilibrium and b) the kinetics of the system, that is, the speed of the adsorption process [4]. Hydrogels are used in the pharmaceutical industry for the treatment of various diseases, for example cancer because is one of the most important health problems in the world [5]. Cancer is the uncontrolled growth of cells in the body [6]. Skin cancer is one of the most common neoplastic diseases in humans [7]. The most common types of skin cancer are basal cell carcinomas, squamous cell carcinomas, melanomas, and actinic keratoses.

In 2016 the American Cancer Society detected approximately 5.4 million basal cell and squamous cell cancers [8]. 95,360 new cases were estimated in the United States in 2017 [5]. One of the major factors causing this type of cancer is prolonged exposure to ultraviolet (UV) radiation particularly in people with white skin [9]. Therefore, it is more frequent to appear in areas of the skin more exposed to the sun such as the head, face, neck, hands and arms, although it may appear in any area of the body [10]. The treatment for skin cancer depends essentially on the type and degree of progress in which it is detected, among the main treatments are surgery, radiotherapy, chemotherapy and topical chemotherapy, among others [6].

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Diclofenac ($C_{14}H_{11}C_{l2}NO_2$) is one of the non–steroidal anti–inflammatory drugs with antipyretic and analgesic actions [11-12]. According to recent studies diclofenac is used for the prevention and treatment of some types of skin cancer since it can prevent the formation of new blood vessels needed by the development cancer cells, as well as block substances that produce inflammation and pain [13]. In previous studies, its efficacy has been demonstrated in the treatment of actinic keratosis, where it was applied as a gel containing 3% diclofenac and 2.5% hyaluronic acid [14]. The use of this drug in some cases has some adverse effects such as dry skin and eruptions where it is applied, among others, these effects are usually less than those caused by 5–Fluororacil (a drug used to treat some types of cancer skin) [15].

New systems of controlled release using computational chemistry allow for the design, transformation and calculate properties of the molecules at nano scale due to the study of atoms, molecules and macromolecules to simulate the interactions between the atoms [16,17]. Molecular modeling has become an important tool to complement scientific research, and is a fundamental way to understand complex systems or phenomena. In addition, it provides accessibility to regions of the parameter space that are inaccessible experimentally. It is also possible to determine properties of materials that have not yet been synthesized. For this reason, computational chemistry is complementary to experimental techniques and vice versa [18].

The computational methods are based on the calculation of the surfaces of potential energies, which are described as the interaction of forces between their atoms, which is why they differ in the way of calculating [19]. This includes mathematical methods and computational algorithms combined with the fundamental laws of physics [16]. Computational methods are divided in molecular mechanics and quantum mechanics. The first is based on simple models of molecular structure applying the laws of classical physics [20]. On the other hand quantum mechanics is based on the Schrödinger equation to describe a molecule as a direct treatment of the electronic structure which is subdivided into two classes: semi–empirical methods and AB initio methods (from the beginning) [21].

AMBER (Assisted Model Building with Energy Refinement) is a model based on molecular mechanics and is parameterized for macromolecules such as nucleic acids and proteins [22]. Moreover, semi–empirical methods are derived from the AB initio methods, relating certain elements of the Fock matrix with empirical or semi–empirical parameters [23]. Some semi–empirical methods are based on the Dewar approximation, among which are MINDO, AM1 and PM3. These only treat the valence electrons and use a minimal base set Slater type for atomic orbital's to expand molecular orbital's [24]. Parameterization method 3 (PM3) is a semi–empirical model that works similarly to the AM1 method since it uses the same equations with an improved set of parameters, but unlike this, PM3 slightly improves the results in both normal and in hydrogen bonds treatments [19].

This method takes the monocentric electronic repulsion integrals as parameters to be optimized (rather than obtained by means of atomic spectral data) [25]. The objective of this research was to determine the molecular analysis using the AMBER/PM3 hybrid model in the adsorption of diclofenac on chitosan hydrogels.

Methodology

Geometry Optimization

The calculation of the optimization geometry was carried out on a DELL I5 computer. Using the Hyperchem software, the AMBER model of molecular mechanics was firstly selected using the gradient conjugated method with a Polak–Ribiere algorithm and an RMS of 0.001 Kcal/Å–mol, respectively. Later, the calculation was performed using the PM3 model of quantum mechanics under the same conditions.

QSAR Properties

Hyperchem has the QSAR properties module in the Compute menu, where properties related to biological activity can be obtained. In drug delivery systems, the partition coefficient parameter (Log P) shows the octanol/water ratio to determine whether the molecule is hydrophilic or hydrophobic, evaluating the similarity of the drug with a pharmacological or biological activity that could make it a possible active drug in the human body.

FTIR Spectrum

From the Compute menu, the Vibration and rotation analysis option was selected and once the calculation is completed through the Compute–Vibration spectrum option, the FTIR spectrum was selected and the vibration mode is chosen by observing the different vibration modes at different wavelengths.

MESP

Once the FTIR spectrum has been obtained, the three–dimensional contour diagram, where the electronic distribution of the molecule, was obtained from the Compute menu and the plot molecular graphs option, with the objective of observing the nucleophilic zones and electrophiles, in addition to the distribution of the electron density of the HOMO and LUMO molecular orbital's.

Results and Discussions

Structural and Energy Parameters

Figure 1 shows the optimization geometry of the molecules of diclofenac, chitosan and the interaction between both, obtained by the application of the AMBER/PM3 hybrid model, from which the

corresponding thermodynamic data set are shown in Table 1. The negative value of the Gibbs free energy in the molecules individually shows a high stability in them, whereas in the interaction between the drug and the hydrogel it reflects a highly negative value showing an energetically favorable union between the OH groups of the chitosan with the diclofenac causing spontaneity in the reaction and indicating favorable direction to the products at a temperature of 298.15 K with slightly less stable and strong bonds than the molecules per individual [3,26,27]. According to the dipole moment of 11.91 debyes, diclofenac/chitosan hydrogel is characterized by being a highly polar molecule. The QSAR methodology is an important tool used to describe the biological activity relationships and the physicochemical characteristics of the molecules, mainly the logarithm of the partition coefficient (Log P).

Figure 1. Geometry molecular: a) Diclofenac, b) Hydrogel and c) Adsorption diclofenac/hidrogel.

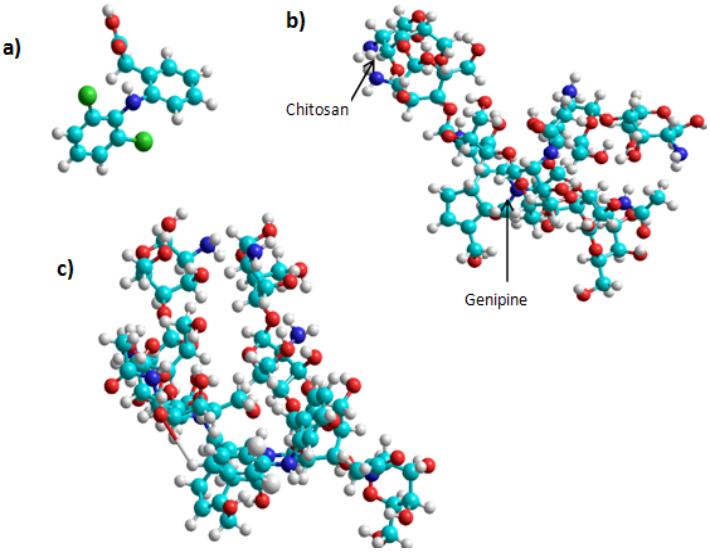

Table 1. Thermodynamic properties obtained by AMBER/PM3 hybrid model.

Properties	Units	Diclofenac	Chitosan	Diclofenac/ chitosan
Bond energy	Kcal/mol	– 3,308.10	– 20,815.47	– 24,130
Formation heat	Kcal/mol	– 52.420	– 1,574.88	– 1,633
Gibbs free energy	Kcal/mol	– 74,052.6	– 500,510	– 574,569
Dipolar moment	Debyes	2.15	6.95	11.91

Diclofenac/chitosan hydrogel with a Log P value of –15.11indicate a hydrophilic character molecule with a considerable capacity of adsorption of the drug. It was also possible to determine the physicochemical characteristics of the molecules as the volume, mass and surface area according to these it is verified the capacity of adsorption and swelling of the hydrogel (Table 2) [28].

Table 2. QSAR properties.

Properties	Units	Diclofenac	Chitosan	Diclofenac/chitosan
Surface area	Å^2	455.64	1,517.77	1,698.5
Volumen	Å^3	758.8	3,341.68	3,903.58
Mass	Amu	296.15	1,585.54	1,881.69
Log P	———	– 0.21	– 14.1	– 15.11

FTIR

Tables 3–5 show the main theoretical assignments of the diclofenac, chitosan and the diclofenac/chitosan respectively, determined by the AMBER/PM3 hybrid model.

Table 3 shows the vibrations of diclofenac molecule where of the OH stretching was localized at 3851 cm^{-1}. Stretching of the methyl aliphatic groups was observed in the range of 3076–3046, 629–555 cm^{-1} respectively. NH stretching of the secondary amine was observed 3574–3418 cm^{-1}, at 1975 cm^{-1} was attributed at carbonyl group stretching and at 715–698 cm^{-1} because of C–Cl stretching [29].

Table 3. FTIR vibrations for the diclofenac molecule.

Bond	Frequencies (cm^{-1})	Vibration type
O–H	3851	Stretching
N–H	3574-3418	Stretching
C–H	3076–3046, 629–555	Stretching
C=O	1975	Stretching
C=C	1789–1347	Stretching
C–O	1447	Stretching
O–H	1241, 555–514	Wagging
C–H	1049–781	Torsion
C–Cl	715-698	Stretching

In the case of the chitosan molecule the table 4 shows that, the OH stretching was appreciated at 3485–3442 cm^{-1}, at 1554–1507 cm^{-1} as a flexion [27]. The stretching of the carbonyl bond of the acetyl group and of the genipine was localized between 2001 and 1950 cm^{-1} while the symmetric and asymmetric stretching vibration of the primary amine bonds were appreciated at 2458 cm^{-1} and 3408–3994 cm^{-1}, respectively.

Table 5 shows the diclofenac/chitosan cross–linking, the vibrational stretching modes present in the OH, C=O and CN groups at 3893–3753, 2001 and 1476–1456 cm^{-1} respectively, as well as the adsorption signals corresponding to the CH groups showing a vibration mode of torsion at 2001 cm^{-1} while the adsorption of diclofenac was observed like a torsion of the OH at 819 cm^{-1}, from these signals it was possible to determine the adsorption of the diclofenac in the hydrogel since these signals ensure the existence of the cross–linking [27, 30,31].

Table 4. FTIR vibrations of hydrogel.

Bond	Frequencies (cm^{-1})	Vibration
O–H	3485–3442	Stretching
H–N–H	3458	Symmetric stretching
H–N–H	3993–3408	Asymmetric stretching
C–H	3235–3111	Stretching
H–C–H	3095–3093	Symmetric stretching
C=O	2001–1950	Stretching
C=C	1850	Stretching
C–N	1643–1603	Stretching
O–H	1554–1507	Flexion
C–C	1457	Flexion
C–O	1435–945	Stretching

Table 5. Diclofenac/hydrogel vibrations.

Bond	Frequencies (cm^{-1})	Vibration
O–H	3893–3753	Stretching (Hydrogel)
N–H	3515–3359	Stretching (Hydrogel)
C–H	3064–3052	Stretching (Diclofenac/hydrogel)
C=O	1970–1822	Stretching
C–N	1476–1456, 1279–1270, 988	Stretching (Hydrogel)
C–C–O	1450	Asymetric stretching (Diclofenac)
O–H	1437–1378, 1237	Torsion (Hydrogel)
C–H	1222–1180, 1028–1002, 999–997	Torsion (Hydrogel)
C–H	1001	Torsion (Diclofenac/hydrogel)
C–H	959, 925–924, 780	Torsion (Diclofenac)
O–H	823–822, 809–808, 727–663, 592–215	Torsion (Hydrogel)
O–H	819	Torsion (Diclofenac/hydrogel)
C–OH	32	Torsion (Diclofenac/hydrogel)
C–Cl	207–206	Torsion (Diclofenac)

Electrostatic Potential Map

Electrostatic potential map (MEPS) is related to electron density as a descriptor to determine the sites of electrophilic attacks and nucleophilic reactions and hydrogen bonding interactions [26]. The importance of MEP lies in the fact that it simultaneously presents molecular size, shape and regions of positive, negative and neutral electrostatic potential in terms of color classification and is very useful in the investigation of the molecular structure with its relation of physicochemical property [30,32]. Figure 2a shows the MEPS of the molecule of diclofenac in which a homogeneous distribution is observed in its charges, the neutral region is represented in green color observed in the carbon chains characteristic of them, on the other hand the negative regions identified with the red color are located mainly in the oxygen atoms and in blue color the positive zones present in the hydrogen atoms with average values of –0.094 eV and 0.28 eV respectively [26-28,32]. Figure 2b shows the result of the MEPS obtained from the hydrogel crosslinked with genipine itself showing a homogeneous electron distribution with negative density at the oxygen atoms, this region being prone to an electrophilic attack due to the absence of electrons with an average value of –0.151eV. Finally, Figure 3 shows the distribution of electrostatic adsorption of diclofenac in chitosan, also showing a neutral trend with a slight modification in the intensity of the zones compared to the molecules per individual.

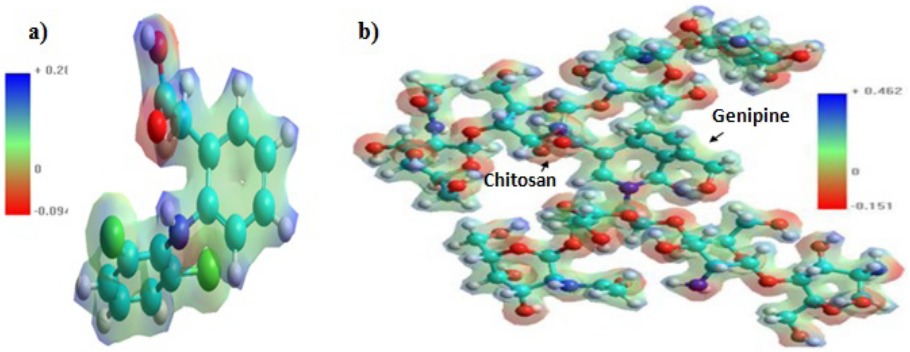

Figure 2. MESP about a) diclofenac and b) hydrogel.

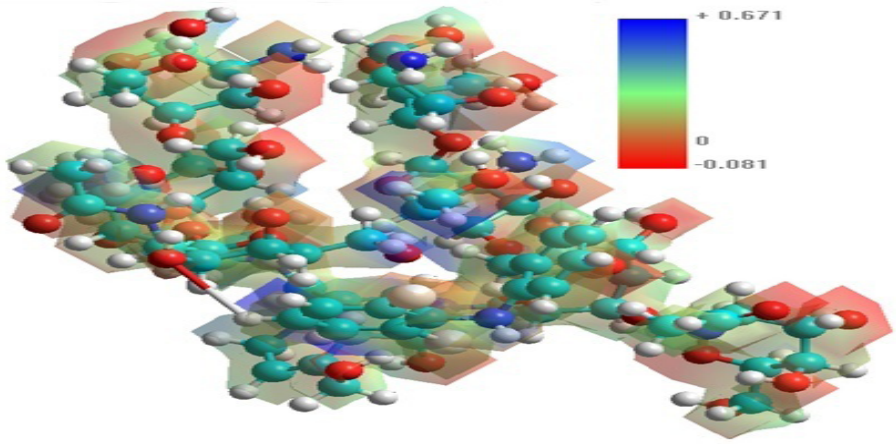

Figure 3. Diclofenac/hydrogel mesp.

Conclusions

The adsorption process of diclofenac in hydrogels (chitosan/genipin) was first verified by the Gibbs free energy which indicated spontaneity in the process and was verified by the value of the coefficient of partition that indicated an affinity to the water contained in the hydrogel. In addition, the optimization geometry was determined with the most stable conformation in which the formation of hydrogen bonds for the adsorption of diclofenac was appreciated. By means of the QSAR properties it is verified that the surface area and volume of the hydrogel presents the space required for the diclofenac molecule to be adsorbed.

The MESPs showed the electronic distribution before and after the adsorption. FTIR vibrations also indicated a displacement that was attributed to the energy released during the adsorption of diclofenac.

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