

# Analysis about the Behavior and Modeling of pH-Sensitive Hydrogels with Different Ratios of Chitosan and Polyvinylpyrrolidone

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## Abstract

Smart material can be defined as a material that can dock or convert energy between physical domains or as a material that can generate a response, in their characteristics, properties or geometries, when submitted to an external stimulus, for example, to heat, water presence, light, etc. In this paper, the second definition will be approached. Hydrogels are crosslinked materials that can absorb a big amount of water. They generally can be considered as smart materials once they exhibit sensibility to external stimuli like to pH variation, as will be approached in this paper. Thus, chitosan/polyvinylpyrrolidone hydrogels of three different ratios between these two polymers (1:1, 7:3 and 3:7) were synthesized and putted in aqueous solution with different pHs. The pH was adjusted adding drops of NaOH and HCl, slowly. After the collection of results and in order to understand the phenomena in a visual way, models of the molecules were also elaborated using the Avogadro software. Therefore, it was possible to realize that the greater the ratio of chitosan in the hydrogel, the greater its sensitivity to pH. Such characteristic is associated with the amino ( $-NH_2$ ) groups in its structure, which are capable of protonating and deprotonating (depending of the pH), generating charges under the chemical structure of the material, which will expand its volume in order to minimize the repulsion between charges. In addition, it was also noted that the hydrogel expansion is inversely proportional to the pH increase. By practical tests, it was possible to conclude that chitosan/PVP hydrogel with ratio 7:3 is the most interesting once it presented a greater quantity of chitosan in its composition, what implied in more rigidity than the others and greater ease of handling, resulting in more reliable results. This hydrogel also showed higher sensitivity to pH.

## Keywords

Chitosan, Hydrogel, Smart Material, pH Sensitivity, Polyvinylpyrrolidone,

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## Modeling

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### 1. Introduction

Hydrogels are three dimensional crosslinked polymeric networks that are able to absorb a big amount of water and/or biological fluids [1]. They usually are transparent, biocompatible and inexpensive materials that can be utilized for create materials such as actuators, ionic skins, drug delivery devices, etc. [2] [3]. For these and others applications, the hydrogel applied needs to be sensible to an environmental condition. For the drug delivery device, the hydrogel will only release drug to the body if it detects some change and be sensible to it. For example, if it is sensible to pH variation, it can break and release some component that was inserted on it.

Chitosan is a copolymer of N-acetyl-glucosamine and glucosamine that can be used to produce sensible hydrogels [4]. It is derived from the deacetylation of chitin and its properties depend on the degree of deacetylation. For example, if the degree of deacetylation is high, chitosan is quite soluble and if the degree of deacetylation is low, the material is quite biocompatible [5]. In general, chitosan is non-toxic, biodegradable and has high capacity to absorb water [4] [6] [7].

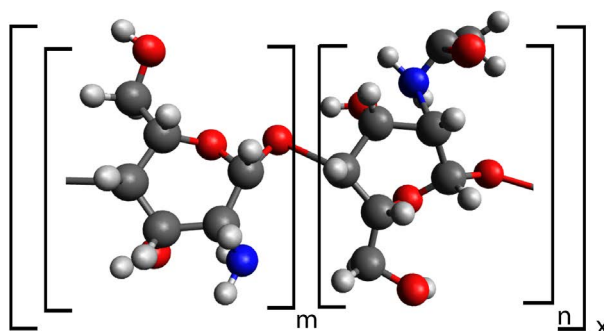
This linear polysaccharide has amino groups that are capable of ionizing, depending on the pH of the material [8], and on connecting with species like ions, phosphates, etc. [9].

In this way, the material is called smart, since it presents a response to external stimuli [10]. Such behavior will be explored and demonstrated experimentally in this paper.

However, it is important to mention that there is a discussion about the definition of “smart material”. Some researchers define it as materials that can dock or convert energy between physical domains, but others define it as materials that can generate a response, in their properties or geometries, when submitted to an external stimulus, such as temperature, pH variation, etc. [11]. In this research, the second definition will be approached.

The chitosan (molecular structured approached in **Figure 1**) hydrogel has been receiving attention of researchers due to its ability in reaching the complexity of living tissues [12]. For this reason, this material is studied for its application in the biomedical area, as well as its use in devices capable of releasing drugs into the human body [13].

This ability is mainly due to the high capacity of water absorption and the fact that its characteristics can be easily molded. Thus, the chitosan hydrogel is commonly applied in tissue engineering and in controlled drug delivery systems [14]. However, some properties, such as mechanical strength, do not favor certain applications [15]. Thereby, composite hydrogels are often used to obtain more interesting characteristics, for example, hydrogels formed by chitosan and polyvinylpyrrolidone.



**Figure 1.** Molecular structure of chitosan (Blue—Nitrogen, Grey—Carbon, Red—Oxygen, White—Hydrogen).

Polyvinylpyrrolidone (PVP) is a synthetic polymer formed from the vinylpyrrolidone monomer. Such material is bulky, non-ionic and it is in the form of white powder at room temperature [16]. Part of its molecule is hydrophilic due to pyrrolidone, and part is hydrophobic due to alkyl groups [17]. The molecular structure is approached in **Figure 2**.

This polymer is soluble in water and has a humidifying property, which implies in its use in the adhesives formulation, envelopes, seals, etc. In addition, the material is biocompatible and composes various medicaments as an excipient and it is used as a blood plasma expander [16].

There are several hydrogels containing PVP in their structure, such as PVP, hydroxyapatite and polyvinyl alcohol hydrogels, which have applications in biology [18] and PVP and polyacrylic acrylic hydrogels, which are used in the production of nanofibers [19].

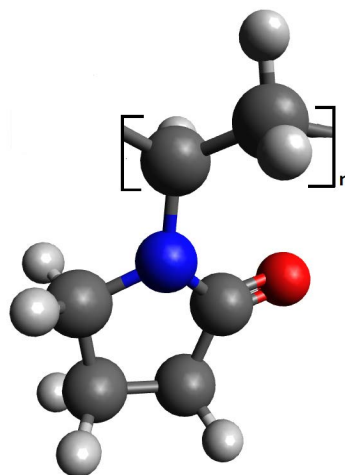
Hydrogels composed of PVP and chitosan are called responsive pH, because its volume changes due to this factor [20]. For this reason, this type of hydrogel has been studied for application in 4D printing [21].

4D Printing is a new type of additive manufacturing that has one extra dimension, which is described as the ability of transformation. This technique is able to print materials capable of changing over time and a material system that can transform its shape directly after being printed (change color, shape, properties, etc). Therefore, 4D printing doesn't produce static materials, but dynamic objects that are programmably active and that transform independently [22].

In order to collaborate with the studies of smart materials that can be applied in 4D printing, this paper approach the synthesis of sensible hydrogels of chitosan/PVP, its behavior in relation to pH and the explanation of the phenomena observed through computational modeling.

## 2. Materials

To synthesize the chitosan/PVP hydrogel, chitosan (molecular weight = 200) and polyvinylpyrrolidone K30 (molecular weight = 40,000) of the Synth brand, and 25% glutaraldehyde (molecular weight = 100.12) of Sigma-Aldrich were used.



**Figure 2.** Molecular structure of polyvinylpyrrolidone (Blue—Nitrogen, Grey—Carbon, Red—Oxygen, White—Hydrogen).

### 3. Methods

#### 3.1. Synthesis of Chitosan/PVP Hydrogel

For the synthesis of the hydrogel of chitosan and polyvinylpyrrolidone, the paper of Risbud, Hardikar and Bhonde (2000) was used as base [23] once it describes a simple method to produce hydrogels with interesting areas of application, like in growth modulation of fibroblasts and membranes [23] [24].

Thus, an aqueous solution of 196 ml of 0.1 M acetic acid was prepared in a beaker. Such beaker was placed on a magnetic stirrer (360 rpm) and 4 g of chitosan were slowly added to the system. Then, it was covered with film plastic and the stirring continued for 24 hours. After such period, the solution was name solution 1.

In another beaker, 192 ml of distilled water were added and placed on a magnetic stirrer.

Thus, 8 g of PVP were also slowly added. The system was covered with film plastic and allowed to stir for 3 hours. Such solution was named solution 2.

Then, solutions 1 and 2 were mixed in different ratios (1: 1, 7:3 and 3:7 (volume/volume)). These solutions were named as 3A, 3B and 3C, respectively.

An aqueous solution of 3 ml of 25% glutaraldehyde was added to solutions 3 (1 ml each). Such solutions were placed on a magnetic stirrer for 10 minutes at room temperature. After that, the solutions were placed in Petri dishes which were dried at 32°C for 72 h in a sterile atmosphere. These hydrogels were named Hydrogel 1, Hydrogel 2 and Hydrogel 3, as shown in **Table 1**.

#### 3.2. pH Sensitivity Tests of Chitosan/PVP Hydrogels

In order to analyze the behavior of the hydrogels at different pHs, six samples of each hydrogel were collected, their masses were measured and, in pairs, they were immersed in solutions of pH 3, 3; 7.3 and 9.6, as shown in **Table 2**. These

**Table 1.** Compositions of the hydrogels synthesized.

	Chitosan (ml)	PVP (ml)	Glutaraldehyde (ml)
Hydrogel 1	50	50	1
Hydrogel 2	70	30	1
Hydrogel 3	30	70	1

**Table 2.** Relation of Masses of Samples Collected.

	Sample Name	Hydrogel Dry Mass (g)	pH of Test
Hydrogel 1	H1AX	1.5030	3.3
Hydrogel 1	H1AY	3.0440	3.3
Hydrogel 1	H1BX	2.2565	7.3
Hydrogel 1	H1BY	3.0588	7.3
Hydrogel 1	H1CX	2.7306	9.6
Hydrogel 1	H1CY	3.1892	9.6
Hydrogel 2	H2AX	4.1736	3.3
Hydrogel 2	H2AY	1.8570	3.3
Hydrogel 2	H2BX	2.5134	7.3
Hydrogel 2	H2BY	3.4033	7.3
Hydrogel 2	H2CX	1.8634	9.6
Hydrogel 2	H2CY	3.2295	9.6
Hydrogel 3	H3AX	1.7269	3.3
Hydrogel 3	H3AY	3.3036	3.3
Hydrogel 3	H3BX	2.0389	7.3
Hydrogel 3	H3BY	2.5683	7.3
Hydrogel 3	H3CX	2.6103	9.6
Hydrogel 3	H3CY	2.7704	9.6

solutions were prepared with distilled water and the pHs were handled with the aid of NaOH and HCl.

### 3.3. Swelling Results Analysis

The bodies were removed from the solution after 36 h, the surface of the material was dried with paper and the mass was measured again to determine the percentage of water absorbed. Thus, the following formula was used to determine the water absorbed in the hydrogels:

$$\% \text{ of water absorbed} = \left( \frac{\text{Hydrogel swollen mass}}{\text{Hydrogel dry mass}} \right) \times 100\% \quad (1)$$

### 3.4. Modeling Step

There is currently little research related to the molecular simulation of hydrogels

at the nanoscale [25]. So, in order to contribute to the studies related to the computational chemistry of hydrogels and obtain a better visual comprehension of the phenomenon observed in the experiment, the modeling of Polyvinylpyrrolidone (PVP), chitosan and hydrogel chitosan/PVP was carried out by using the Avogadro software (2018 version).

It is a free license software that allows to edit, visualize and simulate three-dimensional molecules, in order to reveal and study details at microscopic levels and to provide information about chemical properties, reactions and laws [26]. In addition, it has simpler manipulation tools for software such as VMD, NAMD and LAMMPS, allowing modeling and simulation of chemical structures in a simple way. In addition, as a way of visualizing the reaction of the hydrogel to different pH values, the same software was used to represent the chitosan/ PVP molecule in situations of protonation and deprotonation, as well as its interaction with water molecules.

## 4. Results and Discussion

### 4.1. Rigidity and Deacetylation Approach

After prepare solution 1, it was possible to see some areas with chitosan accumulation, what indicates that the polymer wasn't totally dissolved, as shown in **Figure 3**.

Consequently, after the synthesis of hydrogels 1, 2 and 3, it was possible to perceive that the higher the amount of chitosan in the hydrogel, more rigid was hydrogel.

The rigidity due high values of chitosan is related to the degree of deacetylation, which consists in the transformation of an acetamino group ( $-NCOCH_3$ ) into an amine group ( $-NH_2$ ), as shown in **Figure 4** [27].

Thereby, it is possible to conclude that the chitosan used in the experiment hasn't got a high degree of deacetylation since the higher the degree of chitosan deacetylation, the greater its flexibility is [28]. This happens because, when such a value is low, there is difficulty in the spatial rotation of the glycosidic bond due to the presence of several- $NCOCH_3$  units, which causes a high steric hindrance and consequently stiffening of the material. However, when the number of amine units is high, the rotation of the glycosidic bond is favored since the steric hindrance is smaller, allowing for greater flexibility [29].

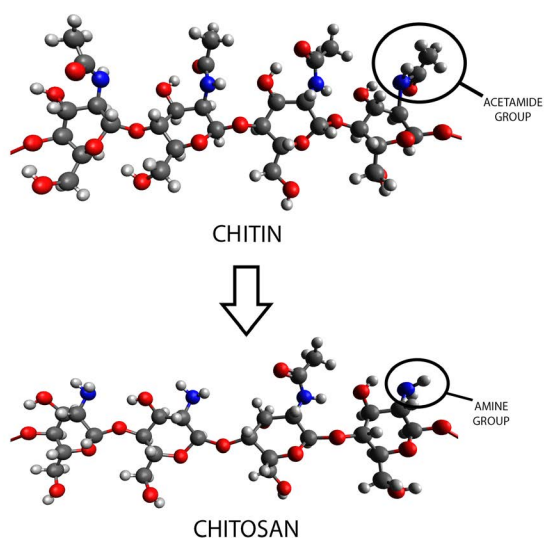
It is important to mention that not all acetamine groups turn into amine group, that is why chitosan is a copolymer (*N*-acetyl-glucosamine + glucosamine).

After the experiment had been carried out, it was also detected that the higher the proportion of chitosan in the hydrogel (in relation to the proportion of PVP), the greater the stiffness and the gelatinous characteristic of it. So, the hydrogel 2 presented the highest stiffness, hydrogel 3 was quite liquid and hydrogel 1 had intermediate characteristics between those previously mentioned.

Such phenomenon is associated with the fact that amine groups are capable of



**Figure 3.** Solution 1 with chitosan accumulation.



**Figure 4.** Deacetylation process for the production of chitosan from chitin (Blue—Nitrogen, Grey—Carbon, Red—Oxygen, White—Hydrogen).

forming crosslinks. Thus, the more units of such a group are present, the greater the gelation rate and the lower the gelation temperature [30].

Thereby, it was difficult to handle hydrogel 3 samples because they were quite brittle and sensitive, as it is possible to see in **Figure 5** and **Figure 6**. Moreover, when inserted in the solutions of different pHs, these were broken to numerous pieces, which made the measurement of absorbed water difficult. Hence, it became essential to disregard hydrogel 3 for the analyses, since its results were not reliable and conclusive.

#### 4.2. Analysis of Swelling in Relation to pH

After the experiment presented, the Average Mass of the samples of the same hydrogel that were immersed in the same pH was calculated. Thus, it was possible to determine the percentage of water absorbed, presented in **Table 3**.



**Figure 5.** Hydrogel 3AY before (a) and after (b) contact with pH 3, 3 solution.

**Table 3.** Relation between mass of dry and swollen hydrogels.

Sample Name	Average Mass of the Dry Hydrogel (g)	Average Mass of the Swollen Hydrogel (g)	pH	% water absorbed
H1A	2.2735	8.2776	3.3	364%
H1B	2.6577	10.1585	7.3	382%
H1C	2.9599	11.1860	9.6	378%
H2A	3.0253	12.8863	3.3	427%
H2B	2.9584	12.0519	7.3	407%
H2C	2.5465	9.8933	9.6	388%
H3A	2.5153	15.2238	3.3	605%
H3B	2.3036	23.7500	7.3	1031%
H3C	2.904	27.8738	9.6	1036%

By analyzing **Table 3**, it is possible to notice that all samples expanded when in contact with solutions of different pHs. To understand such phenomenon, it is necessary to analyze the structure of PVP and chitosan in order to conclude if only one or both of them are responsible for the hydrogel sensibility to pH.

The glucosamine part of the structure of chitosan, approach in **Figure 1**, shows that it has amino groups capable of protonating and deprotonating. Such aspect is responsible for the material sensitivity to pH variation [31]. In chitosan, at low pHs (usually below 6), its amine groups are protonated as a quaternary ammonium salt with positive charges. And at high pH values (usually above 6), they are deprotonated [6].

The pka is the magnitude associated with this phenomenon so that this value determines at what pH this transition occurs and depends directly on the degree of deacetylation during chitosan production [6]. In general, the pka of the amino groups of chitosan is between 6.2 and 6.3 [32].

In addition, the variation in the volume of the material occurs in the sense of minimizing the repulsion of the charges present in the chemical structure [33].

However, PVP structure approach in **Figure 2**, shows that it is a non-ionic polymer [34], what means that it can't pronotate/deprotonate, and consequently, it is not responsible for the sensibility to pH presented by the hydrogel.

As a way of visualizing the phenomenon, the reaction below was developed using the Avogadro software, based on the hydrogel formation proposed by



Zhang, Jin, Li, Zhang & Wu (2018), so that the geometry of the structure was constructed and adjusted according to the optimization tool geometry provided by the software itself, minimizing the total energy of the molecule. Such modeling can be observed in **Figure 7** and the red, blue, gray and white spheres represent, respectively, the oxygen, nitrogen, carbon and hydrogen atoms.

The modeling of the chitosan/PVP complex was also developed under pH values of 3.3; 7.3 and 9.6, as approached in **Figure 8**, where the prominent figures represent the amino groups in situations of protonation and deprotonation.

Analyzing the hydrogels 1 and 2, it is also noted that the volumetric expansion varied according to the different ranges of pHs and there was no pattern in relation to these samples. In this way, bibliographical references were consulted to understand what behavior was appropriate.

Firstly, it was raised the hypothesis that the hydrogel 2 presented the most coherent behavior since, because it possessed more chitosan in its composition, it was more rigid and easier to handle, besides demonstrating a better consistency of gel.

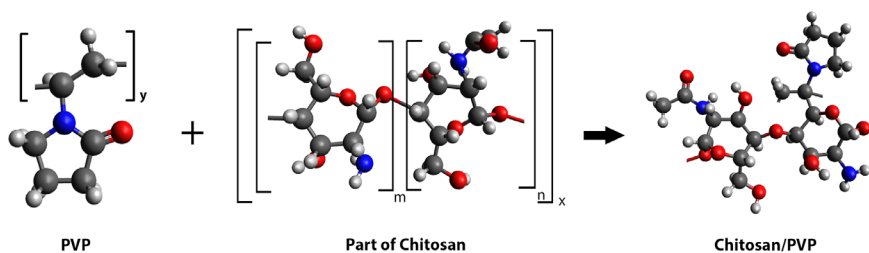
After the search, the hypothesis was confirmed. That is, as in Risbud, HdardikarBhat and Bhonde (2000), it was expected that the volumetric variation of the materials studied would respond negatively as the pH increased.

In addition, it was expected that the higher the proportion of chitosan in the hydrogel, the greater its sensitivity to pH, ie, the greater its swelling mechanism, which could also be confirmed when comparing hydrogels 1 and 2.

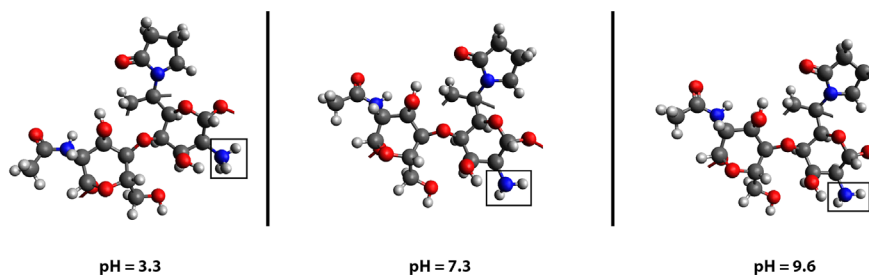
## 5. Conclusions

Hydrogels that have chitosan in their composition always showed sensitivity to the pH since this material has groups capable of protonating and deprotonating. This effect implies an increase in volume due to some factors, such as the occurrence of electrostatic repulsion among ionized groups.

As PVP does not present groups with this characteristics, its application does not attribute sensitivity to the hydrogel. Thus, the tests carried out in the laboratory of the Federal University of ABC showed that the higher the proportion of chitosan in the hydrogel, in relation to the PVP, the greater its swelling as well as confirming that the swelling mechanism of the hydrogel is unfavorable to increasing the pH of the medium.



**Figure 6.** Demonstration of the formation of Chitosan/PVP Structure.



**Figure 7.** Demonstration of Hydrogel under different pH values.



**Figure 8.** Hydrogel H3AX before being submitted to aqueous solution.

When synthesizing three different types of hydrogels of chitosan:PVP with ratios equal to 1: 1, 7:3 and 3:7 (volume/volume), it was possible to conclude that the hydrogel of easier handling and execution of the experiment was that of 7:3 due to its stiffness. As it was also shown to be the most interesting hydrogel for paper article proposal due to its greater sensitivity to external pH.

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### Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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