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Preparation and Characterization of Hydrogels with Potential for Use as Biomaterials

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Hydrogels have been extensively explored for biomedical applications due to their ability to absorb high water content in its structure, which gives excellent biocompatibility. This work aims at obtaining biocompatible hydrogels with potential for use in increasing the mechanical strength of bone substitutes, or controlled drug release. Poly (N-vinyl-2-pyrrolidone) hydrogels were prepared by free radical polymerization with and without the addition of acrylic acid. *A*zobisisobutyronitrile and ammonium persulfate were used as initiator and N,N-methylenebisacrylamide was used as the crosslinking agent. The characterization of the hydrogels was performed by thermogravimetric analysis, differential scanning calorimetry, infrared spectroscopy and swelling properties. The results obtained demonstrate different degrees of crosslinking and swelling of up to 490 ± 30%. The different properties of the hydrogels suggest different applications.

Keywords: *biocompatible, hydrogel, PVP, PAA, polymerization*

1. Introduction

Polymers are today the largest group of materials used for biomedical purposes. They are used separately and/or in combination with other materials. The main areas of today's applications of hydrogels materials include wound dressing, drug delivery systems, transdermal systems, dental applications, injectable polymers, implants and ophthalmic applications[1]. Hydrogels are polymer-based three dimension network systems that are formed by chemical or physical crosslinking of individual polymer chains, which can absorb large amounts of water and biological fluids in their structure[2,3]. Limited water-absorption capabilities (ca. 5-10 wt%) of certain polymeric networks, exhibit the ability to retain the drugs for longer periods[4,5].

The hydrogels have been extensively exploited for biomedical applications due to their high water content which imparts excellent biocompatibility[6,7]. Drug delivery systems developed for many different purposes have been based on hydrogels, mostly the neutral hydrogels. In addition, hydrogels have been applied in gel casting approach to reinforce α-tricalcium phosphate-based calcium phosphate cement during the first stage of setting, for use as biomaterial[8,9].

N-vinyl-2-pyrrolidone (VP) is a water-soluble, non-ionic monomer that can be used to prepare hydrogels[10]. VP-based materials have been of interest in, for example, biomedical applications[11,12]. In recent years, polyacrylic acid (PAA) and its copolymers have often been used as carriers in drug release systems, because of their multifunctional nature, unique properties and good biocompatibility[13,14].

Several studies of the water swelling and drug release behaviours of poly(AA-co-VP) hydrogels have been reported[15-17]. In these hydrogels strong hydrogen bonds can be formed between the AA and VP constituents[16]. These copolymer hydrogels have been shown to display properties ranging between those of the two homopolymers and reported that the extent of swelling depends on the copolymer composition and crosslink density.

In the current investigation, we have attempted to develop a biodegradable and biocompatible hydrogel with potential for use in increased resistance of calcium phosphate cement implants or as controlled drug delivery. New formulations of hydrogels have been developed using N-Vinyl-2-pyrrolidone with and without acrylic acid, employing azobisisobutyronitrile or ammonium persulfate as initiator, by the free radical polymerization method. N,N-methylenebisacrylamide was used as crosslinking agent. The aim was to compare the properties obtained by the different formulations prepared. This comparison is not reported in the literature and can be used for the development of future work. The two monomers used have very fair reputation as non-toxic and biocompatible materials[18]. Hydrogels based on poly (vinylpyrrolidone) have been applied successfully as local dressings on wound treatments, such as burns, skin's ulceration and postoperative dressings[19] or controls release system for drug delivery[20,21] because of their biocompatibility with the human body. Moreover, polyacrylic acid is known to be a good mucoadhesive and may increase the transit time of formulation, in drug delivery systems[22]. These hydrogels were characterized by TGA, DSC, FTIR and equilibrium swelling studies.

2. Experiment

2.1. *Material*

The hydrogels polymerization occurred by free radical polymerization using N-vinyl-2-pyrrolidone (NVP) (Merck, Germany) and acrylic acid anhydrous (AA) (Aldrich,

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Germany). As initiator was used azobisisobutyronitrile (AIBN) (Aldrich, Germany) or ammonium persulfate (AP) (Merck, Brazil). The bifunctional compound N,N'-methylenebisacrylamide (MBAM) (Aldrich, Germany) were used as crosslinking agent and N,N,N',N'-tetramethylethylenediamine (TEMED) was used as catalyst.

2.2. *Preparation of hydrogels*

The composition of the hydrogels is shown in Table 1. The solutions were warm to 80 °C washed and lyophilized for subsequent characterization.

2.3. *Hydrogels characterization*

2.3.1. Thermogravimetric Analysis (TGA)

Thermal stability was evaluated in a thermogravimetric analyzer TGA 2050 (TA Instruments). The samples were heated to 970 °C at the rate of 10 °C.min^{-1}, under flowing nitrogen of 20 ml.min^{-1}.

2.3.2. Differential Scanning Calorimetry (DSC)

DSC measurements were performed using a DSC Q20 (TA Instruments) at 10 °C.min^{-1}. Nitrogen was the carrier gas, and its flow rate was 50 mL.min^{-1}. The second heating cycles of these runs were used to determine the Tg.

2.3.3. Infrared spectroscopic analysis (FTIR)

Infrared spectra of hydrogels were obtained using Spectrum 1000 (PerkinElmer) spectrometer in the range of 400-4000 cm^{-1} using KBr discs.

2.3.4. Swelling behavior studies of hydrogels

The equilibrium swelling of the hydrogels was determined by swelling the hydrogels samples (lyophilized previously) in water distilled at room temperature until equilibrium was attained. Three samples were used for each swelling determination. The swollen weight of the pellet was determined by blotting of the pellet every hour until equilibrium was attained. The percent swelling was calculated by the Equation 1.

$$\%Swelling = \frac{W_t - W_o}{W_o} x100 \quad (1)$$

where W_o is the initial weight and the W_t is the final weight of the sample.

3. Results and Discussion

The hydrogel system consists of Poly (N-vinyl-2-pyrrolidone) which is slowly degradable and has a high glass transition temperature. Polyacrylic acid was also included in the system which imparts pH sensitivity. This pendent acidic moiety changes ionization in response to the changes in pH. The hydrogels also displays pH sensitive nature which can be exploited for site specific controlled drug delivery.

The composition used in the M3 formulation sample didn't result in polymerization, therefore was not possible to characterize this sample.

3.1. *Thermogravimetric Analysis (TGA)*

The thermal analysis of hydrogels by TGA (Figure 1) demonstrates the stability of the polymeric matrix to 200 °C. For the M1 sample there was initial weight loss

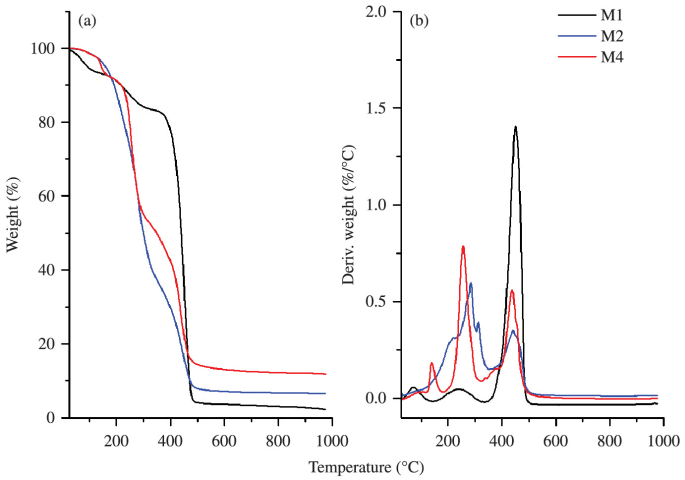

Figure 1. Thermo-gravimetric curve (a) and derivative thermo-gravimetric curve (b) scan of hydrogels in nitrogen.

Table 1. Composition of the hydrogels.

Sample	NVP	AA	MBAM	TEMED	AIBN	AP
	(mol.L^{-1})	(mol.L^{-1})	(%)	(%)	(%)	(%)
M1	2.6	-	2.0	0.2	3.0	-
M2	2.6	1.0	2.0	0.2	3.0	-
M3	2.6	-	2.0	0.2	-	6.0
M4	2.6	1.0	2.0	0.2	-	6.0

due to loss of moisture in the gel from 60-120 °C. The discontinuous TGA curve also indicates the not formation of interpolymeric matrix.

Since the proposed hydrogel system is intended to be used for the release of drug from the varying medium or as a booster for use as a biomaterial, and the release process is normally carried out at physiological temperature 37 °C, the polymer is totally stable in the vicinity of room temperature which normally varies between 27 and 38 °C.

3.2. *Differential Scanning Calorimetry (DSC)*

Figure 2 shows the thermograms of the samples prepared, obtained by differential scanning calorimetric and the Table 2 presents the thermal characteristics of hydrogels. The glass transition temperature of each sample was calculated as the midpoint of the transition. Three DSC runs of each sample were taken to determine the average Tg value and the standard derivation. From the literature, the Tg of PVP having an *Mw* value of 1.2×10^6 is 178 °C[23] and the experimental value of M1 sample (without AA) is 173.51 °C, which agrees well with the literature value. Wu and Freeman[24] found that, in the temperature range of 0-350 °C, was not observed Tg in a polymerized MBAM sample, probably due to its very high crosslink density. Generally, in highly crosslinked polymers, Tg may be difficult or impossible to observe due to restriction on main-chain motion by the crosslinks.

Based upon these results and the large difference in reactivity ratio between NVP and MBAA, two regions (NVP-rich and MBAA-rich) form during polymerization. Due to the dense crosslinking of MBAA-rich regions, there was no Tg related to crosslinked MBAA observed in the polymer network, and only one Tg, corresponding to that of the NVP-rich regions, was observed.

Analyzing the thermal characteristics of hydrogels, we can verify that the samples showed a single Tg and this is affected by the presence of the AA and also by the initiator used. The presence of AA resulted in the decrease of Tg in both cases. The reduction was more significant when used Ammonium Persulfate as initiator.

3.3. *Infrared spectroscopic analysis (FTIR)*

The hydrogels were characterized by FT-IR spectroscopy as showed in Figure 3. Száraz and Forsling[25] reported two very strong bands in the IR spectrum of pure liquid NVP that are sensitive to extent of reaction. The first, at 1629cm^{-1}, is ascribed to C=C bond stretching vibrations. The second, attributed to carbonyl stretching (C=O), is located at 1706cm^{-1}. Greever et al.[26] also identified characteristic IR absorptions for NVP at 1623 cm^{-1} (C=C) and 1700 cm^{-1} (C=O). The non-appearance of these bands indicates polymerization of the NVP monomer, and a broad C=O bond appears at 1650cm^{-1} in polyvinylpyrrolidone (PVP). The characteristic IR absorption at ~1630 cm^{-1} is assigned to the C=C bond stretching vibration of MBAM[27]. The infrared region of 3800-3000 cm^{-1} is attributed to OH stretch mode of water.

Consistent with the literature discussed above, the disappearance of the characteristic NVP and MBAA absorptions in the FTIR spectra of the crosslinked NVP films and the appearance of a broad C=O absorption, characteristic of PVP, at 1650 cm^{-1} both suggest that the polymerization conditions were sufficient to essentially completely react the double bonds in the NVP and MBAA. The appearance of an absorption in the region of 1550cm^{-1} (amide II band) suggests that the MBAM was successfully crosslinked with NVP during polymerization.

According to Devine and Higginbotham[28], the carbonyl group of PVP exhibits a stretching vibration peak between 1650 and 1680 cm^{-1} and the carbonyl group of carboxylic acid group on the PAA chain exhibits a peak at approximate 1750 cm^{-1}. When the carbonyl group forms intermolecular bond (such as hydrogen bond), there is a negative shift exhibited in the FTIR Spectrum, that can be observed in M4 sample. It is also evidence that a small shoulder

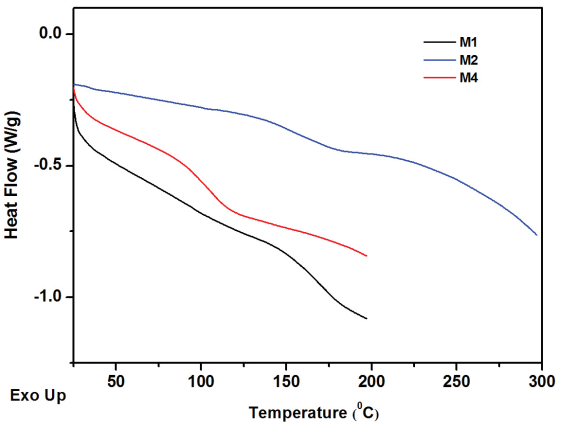

Figure 2. Differential scanning calorimetric thermogram of hydrogels.

Table 2. Thermal characteristics of hydrogels.

Sample	T_{dmax} (°C)	Tg (°C)	Residue at 976 °C (%)
M1	450.41	173.51	2.24
M2	441.33	151.67	6.56
M4	437.49	106.21	11.82

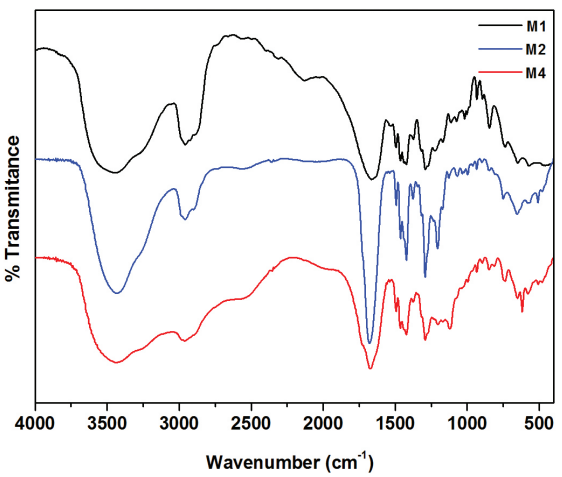

Figure 3. Fourier transform infrared spectrum of hydrogels.

appeared in this sample at about 1730 cm^{-1} corresponding to stretching vibration of carbonyl group of carboxylic acid group on the PAA chain, which further illustrated that some intermolecular hydrogen bond did occur and the complexation formed between PVP bead and PAA. Therefore, this suggests that, for the M4 sample, may have been the formation of a semi-interpenetrating network. However this did not occur in this sample, because there was a decreased in the Tg and was totally dissolved in water shortly after immersion, as shown below.

3.4. *Swelling behavior studies of hydrogels*

In the equilibrium swelling studies was possible to observe different swelling capacities. The M1 sample presented swelling capacities very high, around 490 ± 30%, however the hydrogel integrity was lost with the time and the M2 sample presented around 90 ± 2% swelling at equilibrium indicating a high degree of crosslinking. We know that the increase in the crosslinked density result in a lower equilibrium swelling degree[29]. The M4 sample showed a low degree of crosslinking, and dissolved in contact with water. This may be associated with the formation of oligomeric products due to low initiation efficiency compared to the AIBN.

Literature reports suggest that hydrogels containing NVP require high concentrations (5-20 wt%) of crosslinker to produce a material with useful mechanical properties[12]. Ordinarily, higher crosslinker concentrations would lead to higher crosslink density and, thus, better mechanical properties.

4. Conclusion

The new formulations of hydrogels allowed to obtain different properties which leads to different applications. The product of polymerization of N-vinyl-2-pyrrolidone initiated only with ammonium persulfate, was totally soluble in water, this may be associated with the formation of oligomeric products due to low initiation efficiency compared to the AIBN. The hydrogels showed good thermal stability around 200 °C and a single Tg, indicating possibly the formation of random copolymers. The M1 sample showed a low degree of crosslinking may lead to use as absorbable material or controlled delivery of drugs. The M2 sample had a higher degree of crosslinking may potentially strengthen structure of bone cement. The M4 sample can also be used in controlled delivery of drugs, but for short periods of time, since it dissolves easily. The hydrogels studied are known for their biocompatibility, but no more specific tests were carried out to confirm such biocompatibility, which will be performed posteriorly.

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