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Synthesis and properties of a novel pH sensitive poly(N-vinyl-pyrrolidone-co-sulfadiazine) hydrogel

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Abstract. Sulfadiazine monomer (SDM) was synthesized by the reaction of sulfadiazine with acryloyl chloride. The SDM was characterized by ^{1}H-NMR and IR spectra. A novel hydrogel with –SO_2NH– group was obtained by the radical copolymerization of SDM with N-vinyl-pyrrolidone (NVP). Effects of the reaction temperature, reaction time, the monomer ratio, and the amount of the cross-linker on the pH sensitivity of the hydrogel were investigated. Results indicate that the hydrogel shows strong pH sensitivity in the pH range of 6.5 to 7.2. It also exhibits a good swelling reversibility at buffer solutions of pH 6.5 and 7.2. At last, drugs tests demonstrated the release effect of the hydrogel in pH range of 6.5 to 7.2.

Keywords: *polymer gels, pH-sensitive, sulfadiazine, N-vinyl-2-pyrrolidone, drug release*

1. Introduction

Hydrogels are three-dimensional polymeric networks in which there are a lot of hydrophilic groups, those swell quickly by imbibing a large amount of water or de-swell in response to changes in their external environment. Some hydrogels can swell or shrink when changing the pH of the environment, because of the existence of the acid/basic groups in the molecular network of the pH-sensitive hydrogel. They have therefore found wide application in the bio-medical materials field, including drug control and release [1], artificial organs [2], and bio-sensor [3], etc. In particular, much attention has been paid in the last twenty years to pH-responsive polymers for drug delivery application. However, pH sensitive range of most hydrogels that contain weak acid group, is between 4 and 6. On the other hand, hydrogels that contains basic group show the sensitivity only above pH 8 [4], which leads to the limitation of the hydrogel application in the body fluid where pH is around 7.4 and changes are within 0.2~0.4 [5]. So copolymerization of monomers that contains weak acidic/basic group with the hydrophobic monomer was attempted in order to adjust the pH sensitive range to the neutral range [6]. Nevertheless, these copolymers can hardly find application in the bio-medical materials field because of the toxicity or the biocompatibility limitation of the monomer. N-vinyl-pyrrolidone (NVP) is a hydrophobic compound with excellent bio-compatibility, and high polymer surface activity, etc. It is widely used as the blood extender and drug control/release material.

Sulfonamide compounds are the derivatives of p-aminobenzene sulfonamide. The p-aminobenzene sulfonamide was first synthesized in 1908 and then widely applied in the dye industry. It was later used as antimicrobial [7], anticancer reagent [8], and chelating ligand [9], etc. Up to now, more than 5400 sulfonamide compounds have been synthesized and investigated. The sulfonamide group (structure showed in Figure 1) is a weak acid group. Due to the high electronegative attraction of oxygen atoms in –SO_2NH–, electrons of the sulfur

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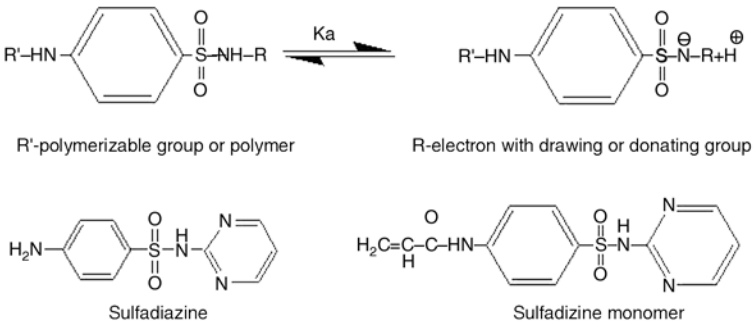

Figure 1. Chemical structures of sulfonamide, sulfadiazine, and sulfadiazine monomer

are attracted, which leads to the movement of the N–H electronic cloud toward the nitrogen atom and results in the ionization. The pK_a value of sulfonamide compounds depends on their substituents and varies in the range of 3~11 [10].

By introducing sulfonamide groups into the hydrogel, it is expected that its swelling property will have severe changes corresponding to the in vivo environment. Herein, we introduced the sulfadiazine with pK_a of 6.8, prepared a novel pH sensitive hydrogel, and investigated its pH sensitivity.

2. Experimental

2.1. Materials

Acryloyl chloride was supplied by Hengyuan Zhongye Limited Company (Beijing,China) and sulfadiazine was supplied by Southwest medicine Co. Ltd, which were used directly. N-vinyl-pyrrolidone (NVP) was supplied by Nankai University Fine Chemicals Factory (Tianjin, China). N,N-methylene-bis-acrylamide (MBA) was supplied by Zhejiang Huangyan Renmin Chemical Engineering Factory, and acrylic acid (AA) was purchased from Tianjin 5th Chemicals Factory. N-vinyl-pyrrolidone, N,N- methylene-bis-acrylamide, and acrylic acid monomers were used after vacuum distilling. 2-2'-azobis-(isobutyronitrile) (AIBN) was purchased from Tianjin 1st Chemicals Factory, which was recrystallized from methanol. Other chemicals were of analytical grade and used without any pretreatment.

2.2. Instruments

Following instruments were used for characterizations: FTIR (FTS3000, BIO-RAD, USA), pellets were made with KBr by pressing; NMR (AV400, Bruker) with DMSO-d6 as solvent; constant temperature water bath vibration machine (SHZ-88); SEM (Panasonic X-650).

2.3. Synthesis of the monomer

The preparation method of the SDM was the same as described in the literature [11]. In brief, sulfadiazine (5.3 g) was dissolved in 40 ml water/acetone (1:1 v/v) solvent, which contains 0.8 g sodium hydroxide, and poured into a four-neck flask with stirring device, condensing tube, and thermometer. The flask was placed in an ice-water bath and the reaction temperature was kept under 5°C. When the temperature became stable, the acryloyl chloride (2.5 ml) was added to the mixture with constant stirring and the temperature was kept under 10°C for 3 hrs. The precipitated product was washed with distilled water for three times. Fine yellow powder was obtained after drying in vacuum at room temperature for 24 hrs. The synthetic route is shown in Figure 2.

2.4. Preparation of the hydrogel

Poly(SDM-co-NVP) hydrogel was synthesized by free radical copolymerization of SDM(1.82 g), NVP(1.56 g), MBA(0.03 g), and AIBN(0.018 g) in DMSO. The synthetic route is shown in Figure 3. The polymerization proceeded for 10 hrs at 55°C

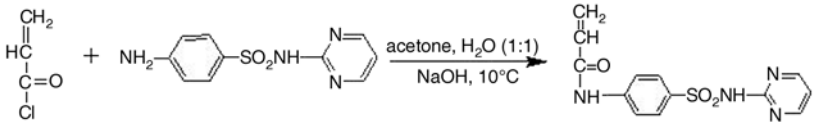

Figure 2. The synthetic route of SDM

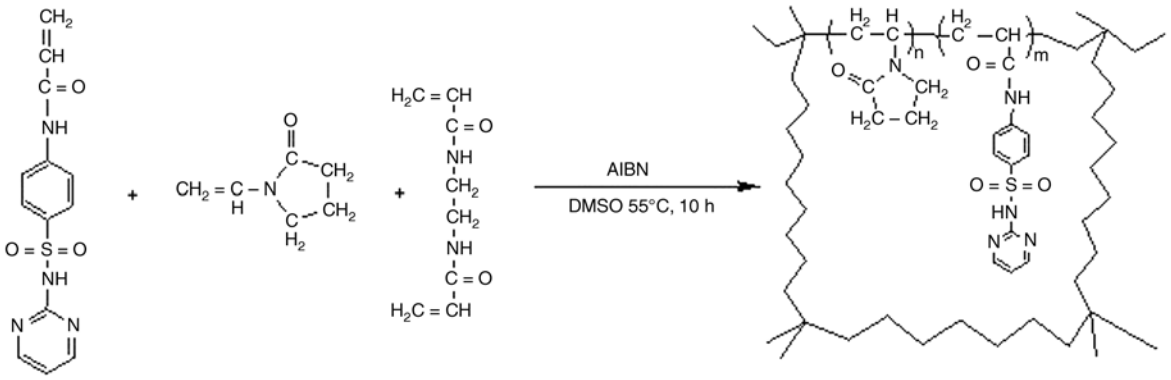

Figure 3. Chemical structures of gel components and the synthetic route of the hydrogel

under a nitrogen atmosphere. The synthesized hydrogel was separated from the tube and soaked in ethanol for 30 min. It was then immersed in an aqueous sodium hydroxide solution (pH 8) for 2 days and followed by soaking in aqueous hydrogen chloride solution (pH 3) for 1 day. Finally, the hydrogel was washed using deionized water for several times and dried in vacuum at 40°C for 2 days.

2.5. Swelling measurement

The swelling ratio (SR) of hydrogels was measured at 37°C in buffer solutions and pH varying from 4.0 to 9.0. 0.2 M $KHC_8H_4O_4$/0.1 M NaOH was used as pH 4.0–5.5 buffer, 0.2 M KH_2PO_4/0.1 M NaOH for pH 5.8–8.0 buffer, and 0.025 M $Na_2B_4O_7$/0.1 M HCl for the rest of pH value buffers. The total ionic strength of each buffer was adjusted to 0.2 M with calculated amount of 0.1 M NaCl. The incubation time was approximately 2 days. Periodically, gels were withdrawn from the buffer solution and weighed after removal of excessive surface water by lightly blotting with a filter paper. The weight-swelling ratio (SR) was calculated by Equation (1):

$$\mathrm{SR} = \frac{W_{swollen} - W_{dry}}{W_{dry}} \quad (1)$$

where $W_{swollen}$ and W_{dry} are weights of the fully swollen gel and dried gel, respectively.

2.6. In vitro release studies

The chloramphenicol was used as the standard drug in the drug release experiment. 50 mg chloramphenicol was dissolved in 20 wt% ethanol and adjusted to 50 ml. 0.1~0.8 ml (with 0.1 ml interval) solution were taken from above solution and diluted to 25 ml. The light absorption degree was measured by WFZ-26A UV spectrophotometer and the standard calibration curve of the chloramphenicol was obtained. Its linear regression equation is $C = 0.05396A + 4.81022e - 4$ ($R = 0.9994$, $p < 0.0001$).

Dry hydrogels were immersed in a concentrated ethanol solution of chloramphenicol and left soaking for 2 days at room temperature. After this period, the hydrogels were rapidly washed with ethanol and dried to a constant weight. The loaded amount of drug in hydrogel disk is defined as Equation (2):

$$\text{Loaded amount of drug} = W_{p+d} - W_p \quad (2)$$

where W_{p+d} is the weight of a dried disk after the drug is loaded, and W_p is the weight of the dried disk before the drug is loaded.

Drug-loaded hydrogels (25 mg) were placed in dialysis bags and those bags were placed in flasks containing 50 ml buffer solutions (pH 6.5). The drug-release experiment was carried on in a SHZ-88 water bath shaker incubator with reciprocating motion (100 rpm). Equal portions were withdrawn and assayed with UV spectrophotometer every other hour. After each sampling, an equal volume of fresh buffer solution was added as release medium. The sample was quickly moved to another buffer solution (pH 7.2) after 4 hrs to continue the release experiment. All the release determinations were carried out in triplicate.

3. Results and discussion

3.1. Structure characterization of SDM

To investigate the structure of sulfadiazine monomer, IR spectra of sulfadiazine and sulfadi-

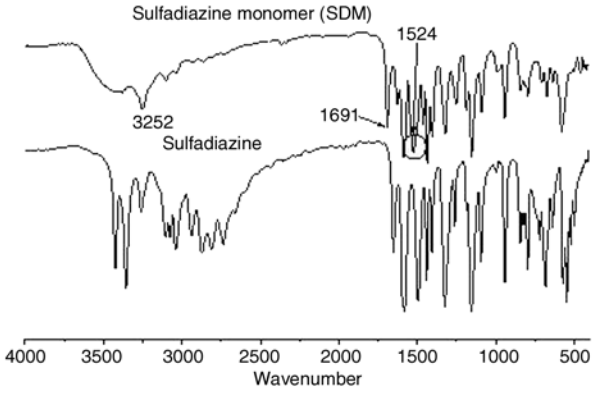

Figure 4. IR spectra of sulfadiazine and sulfadiazine monomer

azine monomer were recorded as shown in Figure 4. The IR spectrum of sulfadiazine reflects that the $–NH_2$ vibration absorption peaks are at 3424 cm^{-1}, 3356 cm^{-1}, and 3259 cm^{-1}. However, the IR spectrum of the sulfadiazine monomer shows only one strong absorption peak at 3252 cm^{-1}, which indicates that the $–NH_2$ is not existent. Peaks at 1691 cm^{-1} and 1524 cm^{-1} are the characteristic absorption peaks of the –CONH– group. The symmetric and asymmetric vibration absorption peaks of $–SO_2–$ can be observed in both IR spectra of sulfadiazine and sulfadiazine monomer at 1322 cm^{-1} and 1154 cm^{-1}. Figure 5 shows the ^1H NMR (400 MHz, DMSO-d6) spectrum of sulfadiazine monomer with δ = 5.8, 6.3 (s, 2H, CH_2–C), 6.55 (s, 1H, CH_2–CH), 7.0, 8.55 (s, 3H, pyridine-H), 7.82, 7.94 (d, 4H, benzene-H), 10.4 (s, 1H, –CONH–), 11.7 (s, 1H, $–SO_2NH–$). When combining both the NMR and the IR spectra of SDM, it is indicated that the SDM is generated from the reaction of sulfadiazine with acryloyl chloride. The results of the NMR and the IR spectra coincide with the previous results [11, 12].

3.2. SEM studies

The dry blank hydrogel was placed on the glass substrate and coated with gold. Its surface morphology and cross-sectional view were observed under SEM. Figure 6a shows that the surface of the blank hydrogel is smooth. Figure 6b shows that the hydrogel has big hollow canal-like structure, which indicates its suitable application in drug loading.

3.3. pH sensitivity of the hydrogel

3.3.1. Effect of temperature on pH sensitivity

Temperature is a crucial factor when the hydrogel is synthesized by free radical copolymerization. It can be observed from Figure 7 that the higher the copolymerization temperature, the lower the

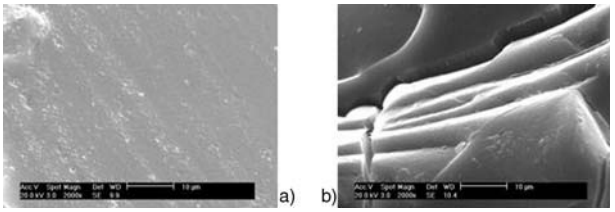

Figure 6. SEM images of blank hydrogels: a) the surface morphology; b) the cross-sectional view

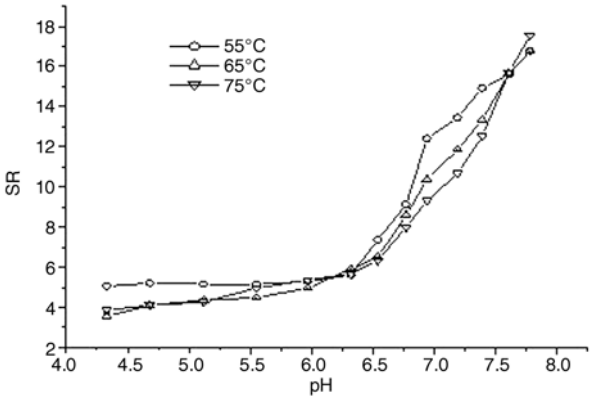

Figure 7. Effect of temperature on pH-sensitivity of hydrogel

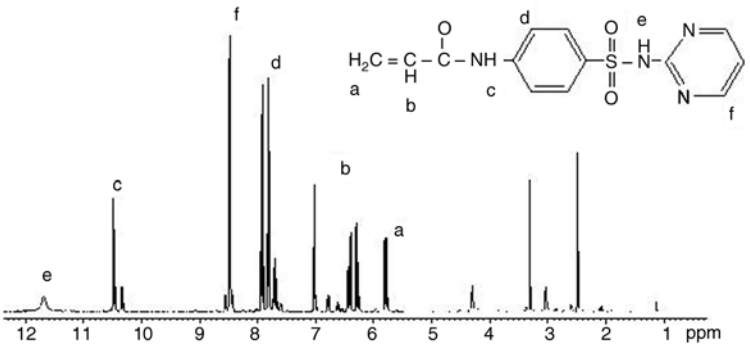

Figure 5. ^1H NMR spectrum of sulfadiazine monomer in DMSO-d6

swelling degree of the hydrogel under the acidic condition. Due to the increasing of the temperature, the decomposition rate of the AIBN increased, which increases the copolymerization rate. The network formation under these conditions is relatively complete. Therefore, the crossing degree of the polymer is higher but the swelling degree is lower. Within the pH range of 6.5 and 7.2, poly(NVP-co-SDM) hydrogel has excellent pH sensitivity, when the copolymerization temperature increases, the pH sensitivity of the hydrogel decreases. This is possibly due to the suitable decomposition rate of AIBN at 55°C, which results in the formation of a homogeneous hydrogel structure. When the temperature rose to 65°C or 75°C, the AIBN rapidly decomposes which affects the structure of the hydrogel and decreases its mechanical property due to the existing bubbles (N_2 from the decomposition) in the hydrogel.

3.3.2. Effect of reaction time on pH-sensitivity

The reaction time directly affects the copolymerization reaction. In order to assure the lowest residual monomer amount in the final hydrogel product, enough reaction time must be provided to complete the reaction. Figure 8 shows that effect of the reaction time on pH-sensitivity of the hydrogel. The reaction time of the hydrogels is 6 h, 8 h and 10 h in Figure 8. From the trends of the swelling curves, it is revealed the swelling ratio of the hydrogels increase slowly under lower pH 4.0~6.3, whereas it increases rapidly and reaches the highest under higher pH ,which reveals high pH sensitivity of the hydrogel. The hydrogel whose reaction time is 10 h shows the highest PH sensitivity, and its swelling degree changes the most distinctly due to its complete and homogeneous structure, that is, it is more pH sensitive.

3.3.3. Effect of different amount of monomers

Poly(NVP) hydrogel and samples with the molar ratio of SDM to NVP 1/8, 2/8, 3/8 were synthesized at the same condition in order to compare the effect of the monomers ratio to pH sensitivity of the hydrogel. The pH sensitivity measurement results are shown in Figure 9. It is indicated that the swelling property and pH sensitivity have been greatly improved after introducing the SDM, especially between pH 7.0~7.5. When the molar ratio of SDM to NVP is 1/8, 2/8, as the amount of the SDM increases, pH sensitivity of the hydrogel increases as well. On the other hand, pH sensitivity becomes obvious only at higher pH values when only a small amount of the SDM is introduced. For the hydrogel contains 3/8 SDM, it shows similar pH sensitivity and the swelling degree as the 2/8 SDM hydrogel.

3.3.4. Effect of different amount of the cross-linker

The amount of the cross-linker also affects the swelling property of the hydrogel. Here, we investigated the effect of different amount of cross-linker on pH sensitivity of the hydrogel, as shown in Figure 10. It is shown that polymer with complete network structure can be formed when a significant amount of the cross-linker was added. Such formulated polymer has high cross-linking degree and low swelling degree. However, when excess amount of cross-linker is applied, the yielded

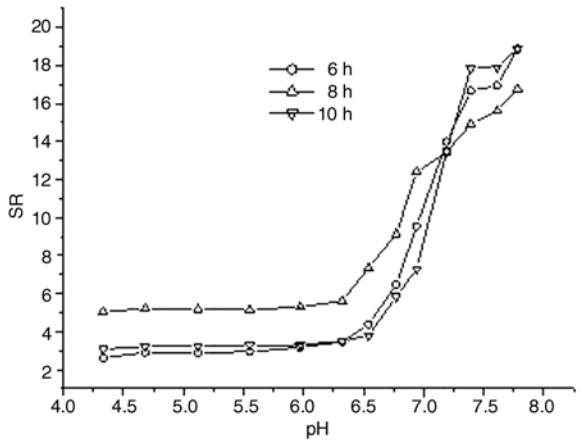

Figure 8. Effect of reaction time on pH-sensitivity of hydrogel

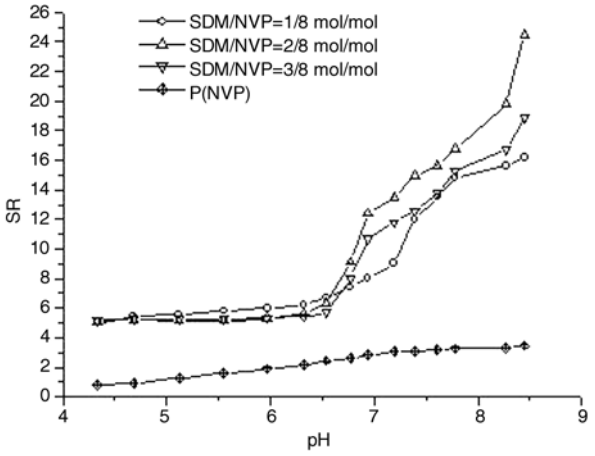

Figure 9. Effect of different amount of monomers on pH-sensitivity of hydrogel

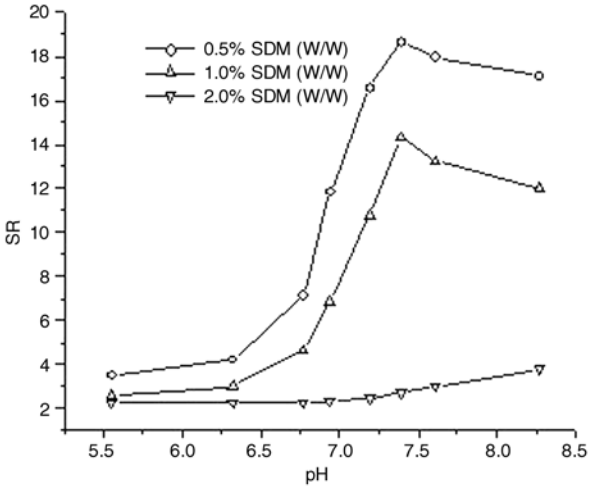

Figure 10. Effect of amount of cross-linker on pH-sensitivity of hydrogel

hydrogel is brittle and rigid. Even if it is immersed in the solvent for a long time, the cross-link network cannot be expanded completely. After the ionization of $–SO_2NH–$, the network cannot be further expanded due to the electrostatic repulsion. Hence, it shows low pH sensitivity. When lower amount of the cross-linker is used, the hydrogel formed has better swelling property and pH sensitivity, but with lower strength and poor mechanical property. Hence, proper amount of cross-linker should be applied.

Here we chose 1wt% cross-linker to SDM. Both the swelling property and pH sensitivity of the obtained hydrogel are ideal.

3.4. Swelling-deswelling-reswelling kinetics

The reversibility in swelling and swelling/deswelling kinetics of hydrogels is demonstrated as shown in Figure 11 in two different pH buffer solutions at 37°C. The cycle started from a dry polymer, followed by repeated cycles between two fixed pH values.

It shows that the hydrogel was swelling when the pH was equal to 7.2. On the contrary, the deswelling process was exhibited when the hydrogel was transferred to the buffer solution of pH 6.5. Therefore, the hydrogel synthesized from SDM and

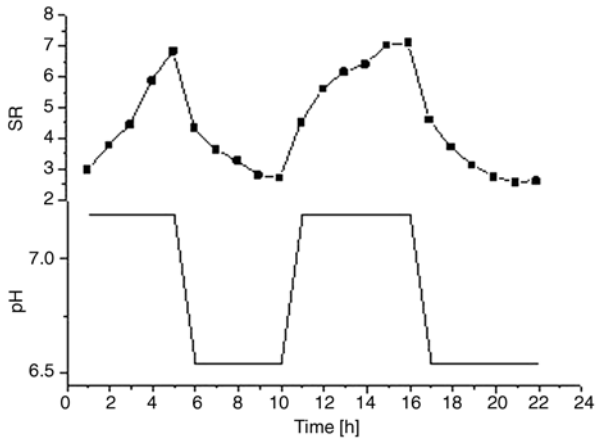

Figure 11. Swelling reversibility test of hydrogels as a function of time at 37°C under repeated changes in pH between 7.2 and 6.5

NVP has excellent response to small pH changes and its swelling process is reversible.

The pH sensitivity measurements of the hydrogel show that the ionization of $–SO_2NH–$ in the weak base environment can be shown as Figure 12.

There are considerable amounts of $–SO_2NH–$ groups in the network of this polymer. Due to the electrostatic repulsion, the cross-link network expands and swelling degree increases rapidly. Hence, it shows great pH sensitivity. Foregoing researches also revealed its excellent pH sensitivity in between the pH range of 6.5 to 7.2.

3.5. Release behavior of the hydrogel

A more reliable and informative analysis can be obtained considering that in swellable polymers two phenomena affect the solute release: the swelling property of the hydrogel and the rate of drug-dissolution from the polymer. For the investigation of drug-release behavior of P(SDM/NVP) hydrogels, drug loading experiments were firstly conducted in 1 mg/ml of chloramphenicol ethanol solution. Loading amount of the drug is 1.6 mg in 0.1 g hydrogels.

Figure 13 shows that the drug is released slowly as the hydrogel gradually swells. The drug release shows an increasing trend in the releasing curve. Once the sample was moved to the pH 7.2 buffer solution, there is a sudden release which can be

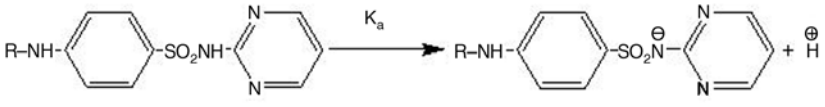

Figure12. The ionization of $–SO_2NH–$ in the weak base environment

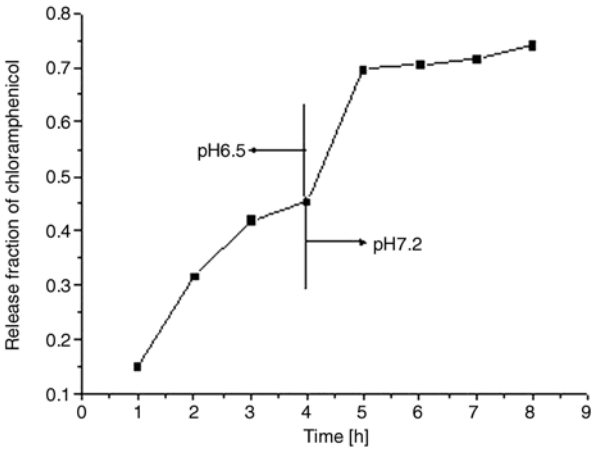

Figure 13. Release of chloramphenicol from hydrogels (37°C)

observed from the curve as a rapid increase of the slope. In Figure 13, the drug release ratio in pH 6.5 buffer solution is 41%; when the hydrogel is transferred to pH 7.2 buffer solution, the release ratio increases to 70%. The drug release experiment demonstrates the excellent pH sensitivity of the synthesized hydrogel.

4. Conclusions

By introducing SDM in P(NVP) hydrogel, a novel pH sensitive hydrogel, poly(NVP/SDM), was synthesized. SEM images show that this hydrogel has canal-like structure, which is favorable in application of drug release. pH sensitivity measurements reveal that the hydrogel shows strong sensitivity in between pH 6.5 and 7.2. It exhibits excellent swelling reversibility in the above pH range at 37°C. Drug release investigation also demonstrates that the hydrogel has strong sensitivity to pH changes.

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