Materials Science and Engineering C 75 (2017) 425–432

Contents lists available at ScienceDirect

Materials Science and Engineering C

journal homepage: www.elsevier.com/locate/msec

Modeling of drug release behavior of pH and temperature sensitive poly(NIPAAm-*co*-AAc) IPN hydrogels using response surface methodology and artificial neural networks

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ARTICLE INFO

Article history:
Received 14 November 2016
Received in revised form 21 December 2016
Accepted 15 February 2017
Available online 20 February 2017

Keywords:
Smart hydrogel
IPN
Drug release
RSM
ANN

ABSTRACT

An interpenetrated polymer network (IPN) poly(NIPAAm-*co*-AAc) hydrogel was synthesized by two polymerization method: emulsion and solution polymerization. The pH- and temperature-sensitive hydrogel was loaded by swelling with riboflavin drug, a B2 vitamin. The release of riboflavin as a function of time has been achieved under different pH and temperature environments. The determination of experimental conditions and the analysis of drug delivery results were achieved using response surface methodology (RSM). In this work, artificial neural networks (ANNs) in MATLAB were also used to model the release data. The predictions from the ANN model, which associated input variables, produced results showing good agreement with experimental data compared to the RSM results.

1. Introduction

The study of hydrogels has gained great potential in recent years because of their properties and high capacity to absorb large quantities of water. Hydrogels play an important role in many fields, such as tissue engineering scaffolds, biosensors, BioMEMS devices, and drug carriers [1,2]. Among these applications, hydrogel-based drug delivery systems have become a major area of research interest and many products have been developed [3,4]. Their unique properties make them useful for delivering biomolecules. One of the important characteristics of hydrogels is their responsiveness to stimuli, which can be easily tailored into hydrogel networks during fabrication [5,6]. The mechanical properties of hydrogels and their swelling and shrinking behaviors change in response to physical or chemical stimuli, such as temperature, pH, ionic strength, solvent composition and electric fields. These characteristics make hydrogels intelligent materials and thus potential devices for drug delivery [7,8]. Hydrogels that are sensitive to temperature and pH are the most frequently used because they exploit changes in temperature and pH as triggering agents for controlled release of drugs [9,10]. One of the most popular thermosensitive polymers is poly(*N*-isopropylacrylamide) because it possesses a phase transition temperature (lower critical solution temperature, LCST) in water close to human body temperature (32 °C), making it very attractive for biomedical applications [11–13]. The cross-linked hydrogel swells below the LCST and collapses above the LCST, which is a desirable behavior used for pulsed release of drugs [14,15]. According to the targeted applications, to obtain a much more favorable system that is sensitive to several stimuli simultaneously, *N*-isopropylacrylamide (NIPAAm) is copolymerized with ionic monomers [16]. To prepare pH and temperature responsive hydrogels, the combination of acrylic acid (AAc), an anionic monomer, and NIPAAm is mainly used because AAc is hydrophilic and can increase the volume phase transition temperature (VPTT) [17,18].

The loading of hydrophilic drug molecules such as riboflavin to hydrogel matrix from aqueous solution by hydrogel swelling is relatively simple method. The loading of drug molecules into stimuli-responsive hydrogel matrix is depended on hydrogel swelling behavior. On the other hand, release of drug from the hydrogels is depended on deswelling behavior [19]. The hydrogel swelling capacity increases with increasing AAc content because of electrostatic repulsion between the polymer chains. Poly(NIPAAm-*co*-AAc) hydrogels with 10% AAc (molar ratio) contents have a broad phase transition at near the human body temperature [20,21].

The synthesis of hydrogels is accomplished through different types of methods, one of which is an interpenetrated polymer network (IPN). This type of hydrogel consists of two or more interpenetrating polymer networks made in one or two steps [22]. In the two step IPN type, the hydrogel synthesized in the first step is dried and then re-swelled in a solution containing the monomers and a suitable cross-linking agent that will react to give the IPN

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http://dx.doi.org/10.1016/j.msec.2017.02.081
0928-4931/

Table 1
Independent variables in central composite design and their levels for drug release investigations.

Independent variables	Symbol	Lower limit	Upper limit
pH (X_1)	A	2.00	12.00
Temperature (°C) (X_2)	B	22.00	52.00
Time (min) (X_3)	C	3.00	420.00

structure hydrogel [23,24]. The synthesis of hydrogels through the IPN method allows the improvement of the elastic and mechanical properties of the resulting gel compared to those synthesized by other methods [25,26].

The accuracy of mathematical modeling can also play an important role in the success of drug delivery devices, such as in the design of intelligent networks. Moreover, mathematical modeling presents some advantages, such as limiting the number of experiments and contributing to enhanced performance [27].

Response surface methodology (RSM), which is a combination of mathematical and statistical methods, is useful for data analysis and modeling in different fields of engineering. Additionally, RSM allows the determination of optimum operating conditions of the system, as shown by the response surfaces influenced by several process variables, and computation of the relationship between input parameters and developed response surfaces [28,29].

Artificial neural networks are powerful tools that are built under the basis of the functioning of the human neuron system, which computes the relationship between input and output data [30,31]. They can be successfully used to model difficult and complex problems [32,33]. Boztepe et al. found good results by using ANNs to model the swelling behaviors of acrylamide-based hydrogels [34].

In this study, using the thermosensitive NIPA monomer and pH sensitive AAc as a comonomer, poly(NIPA-*co*-AAc) microgels were synthesized by free radical emulsion polymerization. Then, poly(NIPAAm-*co*-AAc) interpenetrated network (IPN) hydrogels were prepared by free radical solution polymerization in the presence of pre-synthesized poly(NIPAAm-*co*-AAc) microgels. The synthesized IPN poly(NIPAAm-*co*-AAc) hydrogel was loaded with riboflavin (B2 vitamin) and the drug releases were performed in different mediums under various pH and temperature conditions. Drug release modeling was performed using response surface methodology (RSM)-central composite design of Design Expert-10 software (trial-version) and artificial neural networks (ANNs) in MATLAB.

Table 2
The proposed experimental design.

Experience no	pH	Temperature (°C)	Time (min)	% release
1	7.00	52.00	3.00	6.28
2	7.00	37.00	211.50	59.3
3	7.00	37.00	211.50	59.3
4	12.00	37.00	420.00	42.1
5	12.00	22.00	211.50	37.5
6	2.00	37.00	420.00	62.4
7	2.00	37.00	3.00	11.1
8	7.00	37.00	211.50	59.2
9	7.00	22.00	420.00	43.6
10	2.00	22.00	211.50	49.6
11	7.00	37.00	211.50	59.26
12	2.00	52.00	211.50	75
13	12.00	52.00	211.50	45.1
14	7.00	22.00	3.00	3.3
15	7.00	37.00	211.50	59.3
16	7.00	52.00	420.00	91.5
17	12.00	37.00	3.00	4.2

Table 3
Percentage of drug released amount.

Temperature(°C)	pH 2	pH 3	pH 4	pH 5	pH 7	pH 11	pH 12
22	50.54	48.43	48.05	40.04	43.6	37.22	37.46
30	57.38	53.54	51.10	42.52	44.07	38.35	40.37
37	62.45	54.66	53.87	50.60	69.57	39.72	42.05
40	62.77	61.20	58.79	54.71	70.89	41.94	42.94
45	77.97	77.02	71.92	54.43	76.52	49.70	52.98
52	76	61.56	60.48	56.31	91.47	44.07	45.10

2. Materials and methods

2.1. Materials

N-isopropylacrylamide as a monomer (NIPAAm, from Merck, Germany) was crystallized from ethanol solution under reduced pressure at 30 °C. Acrylic acid (AAc, from Sigma-Aldrich, Germany) was used as a monomer, *N*,*N*′-methylenebisacrylamide (MBAAm, from Merck, Germany) was used as the crosslinker, and sodium dodecyl sulfate was used as the surfactant (SDS, from Sigma-Aldrich, Germany). Ammonium persulfate (APS, from Merck, Germany) and tetraethylenemethylenediamine (TEMED, from Merck, Germany) were used as an initiator and an accelerator, respectively. Because the chemicals were of high purity, they were used without further purification.

2.2. Synthesis of poly(NIPAAm-co-AAc) microgels by emulsion polymerization

The synthesis of poly(NIPAAm-*co*-AAc) microgels was performed in a three-necked flask. The microgels were prepared by free radical polymerization. In 150 ml of distilled water heated at 80 °C under stirring at 750 rpm, 0.15 g (0.52 mmol) of sodium dodecyl sulfate dissolved in 30 ml of water was added. Then, 2.8 g (24.74 mmol) of *N*-isopropylacrylamide (NIPAAm) monomer, 2.5 ml (2.47 mmol) of acrylic acid (AAc) as a comonomer and 0.08 g (0.519 mmol) of *N*,*N*-methylene-bis-acrylamide (MBA) as a crosslinker dissolved in 10 ml of water was added. A small amount of EDTA was added to the flask as a stabilizer. The reaction mixture was purged with pure nitrogen gas for 20 min to remove excess oxygen. After 30 min, 0.15 g of initiator APS dissolved in 10 ml of water was added drop wise to the mixture to begin the polymerization reaction. After 3 h, the temperature and stirring speed were adjusted to 52 °C and 750 rpm, respectively, and the emulsion polymerization continued for 24 h. To remove the unreacted monomers, surfactant and initiator, the obtained microgels were dialyzed in a membrane for one week while periodically changing the water.

2.3. Synthesis of IPN poly(NIPAAm-co-AAc) hydrogel by solution polymerization

To synthesize an interpenetrated polymer network (IPN) hydrogel, the poly(NIPAAm-*co*-AAc) microgels formed by emulsion polymerization were used in the solution polymerization. First, 0.1 g of poly(NIPAAm-*co*-AAc) microgels, 0.25 g (2.209 mmol) of NIPAAm

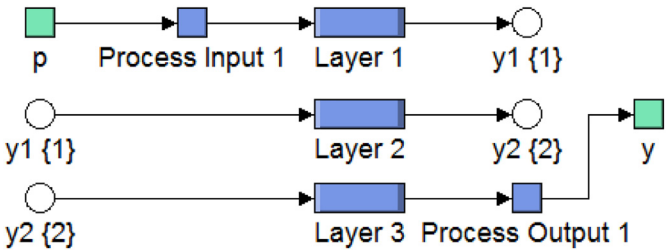

Fig. 1. Three layers of neural network block diagram.