Journal of Particle Science and Technology

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Synthesis and structural properties of polyvinylpyrrolidone based nanocomposite hydrogels for isoniazid drug delivery

Hassan Fathinejadjirandehi[1,*], Maryam Adimi[1], Mokhtar Heydari Naqdali[2]

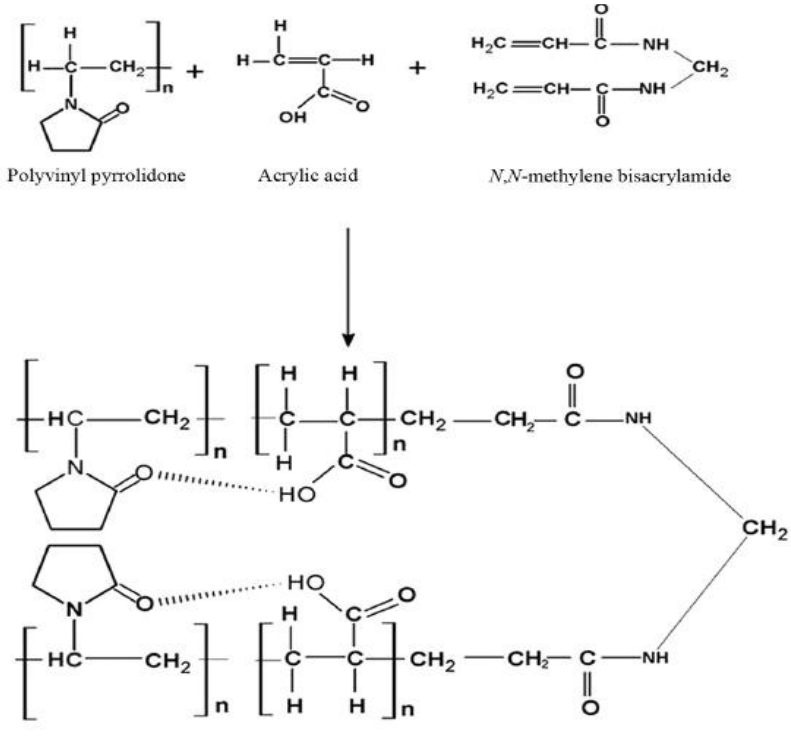
[1] *Young Researchers and Elite Club, Farahan Branch, Islamic Azad University, Farahan, Iran*

[2] *Department of Chemical Engineering, Farahan Branch, Islamic Azad University, Farahan , Iran*

HIGHLIGHTS

- PVP-based nanocomposite hydrogels with different content of nanoclay were prepared.
- The structure of the prepared nanocomposite hydrogels is a sheet structure.
- The addition of hydrophilic layers of nanoclay cloisite 20A reduces swelling.
- The nanocomposite with 4% nanoclay cloisite 20A has the more controlled delivery.
- In both Peppas and Higuchi models, by increasing nanoparticles percent, line slope decreases.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 9 February 2016
Received in revised form
4 March 2016
Accepted 14 March 2016

Keywords:
Hydrogel nanocomposite
Polyvinylpyrrolidone
Swelling
Controlled Release
Isoniazid

ABSTRACT

In this study, several examples of hydrogels and nanocomposite hydrogels based on PVP with different content of montmorillonite nanoclay were prepared. Then, the swelling of hydrogels and kinetics of drug delivery of hydrogel in an environment similar to the body (pH 7.4) were examined. The effect of nanoparticle different percentages on the hydrogel was clearly observed. Then, kinetics of drug (Isoniazid) delivery for various samples of hydrogel with nanoparticles and without nanoparticles were obtained via Peppas and Higuchi models. The comparison of Peppas model results with experimental data showed that nanocomposite with 4 wt.% nanoclay exhibited better compliance. The morphology and microstructure of the prepared nanocomposites were studied by FT-IR, XRD and SEM.

*Corresponding author. Tel.: :+988633723010; fax: :+988633723010
E-mail address:h.fathinejad@gmail.com

1. Introduction

Hydrogel, crosslinked polymers that have the ability to absorb large amounts of water or liquid environments. Recent advances in the use of hydrogels for drug development, delivery and transport of drugs, the use of optical lenses have been achieved, among which a number of biomedical applications hydrogels leads to the potential for controlled drug delivery systems have been designed to deliver the drug at the site of body [1]. The nature, pore size, durability and hydrogels responding to external stimuli are the most important factors that release the behavior of the hydrogels. Hydrogel porosity is due to drug loading and predetermined release in the gel matrix. To improve biocompatibility, increased control over the process of drug delivery and enhance the mechanical properties of nanocomposites, nanoclay has been used in the structure of hydrogels [2, 3]. Figure 1 shows the formation of chemical hydrogels [4].The use of hydrogels for medical applications began in 1960, when Lim and Wichterle synthesized poly-hydroxyethyl methacrylate (PHEMA) [5]. Hydrogels can be in the network physically or chemically, Figure 2 shows the schematic view of the physical formation of hydrogels [6]. Porous hydrogel structure, controlled by the crosslink density. Because of biocompatibility, high water content, low surface tension and mechanical properties of hydrogels similar to the tissue, hydrogels can be used for drug delivery and tissue engineering purposes [7, 8]. Over 40 years, the attention is focused on the development of drug delivery systems [9, 10]. These systems are designed to reduce the frequency of consumption, increase efficacy and reduce side effects of it. The polymer [11] and lipids [12] were identified as the most widely drug delivery used systems. In recent years there are great efforts to reform and increase the mechanical strength of the hydrogel by adding nanoparticles to its structure and nanocomposite hydrogels were prepared which Mechanical properties, chemical and physical characteristics of these hydrogels increased compared to net markedly [13-17].

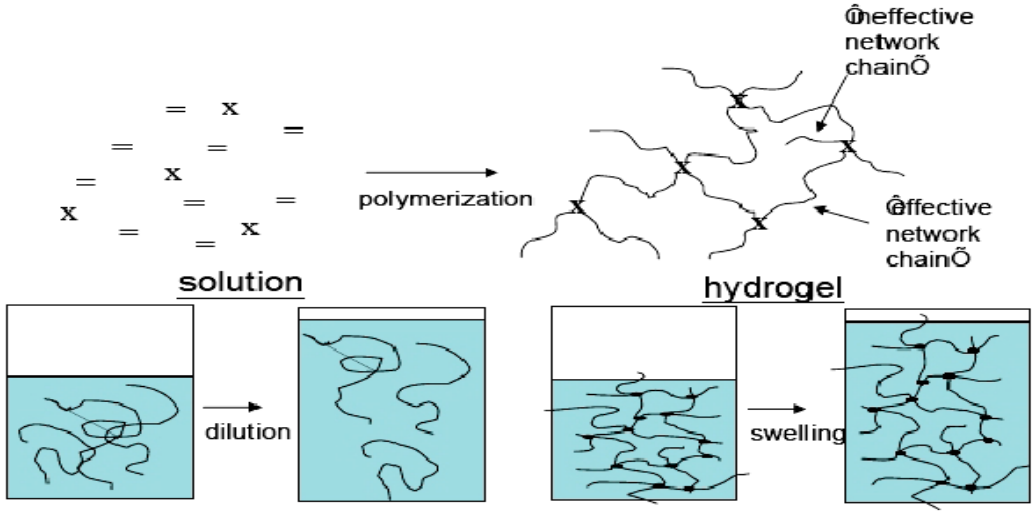


Fig. 1. Schematic feature of chemical hydrogels formation [4].

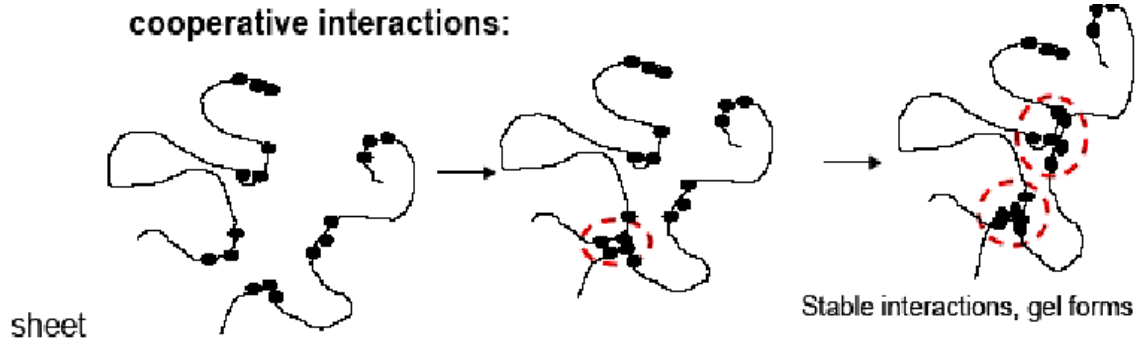


Fig. 2. Shematic view of the physical formation of hydrogels [6].

So if we can get comprehensive information about the kinetics of dehydration of the hydrogel, information can be used in making a controlled drug delivery system [18]. PVP is known a hydrophilic polymer is a biocompatible, non-antigen combination and hence is safe for biological experiments. PVP structure in a manner that can be used as drug carriers in chemotherapy with magnetic conductivity [19].

Isoniazid, Anti-tubercular medication that has a short half-life, the beginning and the peak effect is rapid and can be injected, if you can design a controlled drug delivery system, Isoniazid is taken orally, and this invention can be used for patients with tubercular are very helpful. There are limitations in the preparation Isoniazid orally, including the destruction in the stomach, low permeability across intestinal and high molecular weight due to their lack of lipophilic [20]. There are several ways to overcome the limitations of these methods, pointed to Isoniazid, Polymeric carrier systems can be used to improve absorption. The research was conducted to determine the optimum combination of hydrogels based on PVP by change the amount of main polymer (PVP), the monomer (acrylic acid) and crosslinker (N,N'-Methylenebisacrylamide) and measured release-swelling properties of pure hydrogel, nanoocomposite hydrogels with different percent of Nanoparticle (Cloisite 20A) was constructed by in-situ polymerization [21,22]. By using UV devices, drug (Isoniazid) delivery of the hydrogels at pH 7.4 measured. Well, by using the data obtained from the release the positive impact of Nanocomposite on delivery was determined; two synthetic models were developed to calculate the penetration rate of the hydrogel.

2. Materials and Methods

2.1. Materials

Acrylic Acid 99% (AA, Base Monomer: Merck Chemical Company, $C_3H_4O_2$, M = 72.06 g/mol). Polyvinylpyrrolidone K25 (PVP, Base polymer: Sigma-Aldrich, $[C_6H_9NO]_n$, M = 2.5 g/mol). N,N'-Methylenebisacrylamide 99% (MBA, Crosslinke: Merck Chemical Company, $C_7H_{10}N_2O_2$, M = 154.17 g/mol). Potassium Persulfate 99.99% (KPS, Initiator: Sigma-Aldrich, $K_2O_8S_2$, M = 270.32 g/mol). Isoniazid (INH, Drug: DarouPakhsh Holding Co, $C_6H_7N_3O$, M = 137.139 g/mol). Nanoclay Montmorillonite (Cloisite 20A, Nanoparticle: Penta Chemicals, $Al_2[AlSi_3O_9(OH)](OH)_2$). Deionized water was used in all experiments.

2.2. Method of Nanocomposite hydrogels preparation

Specified amount of monomer acrylic acid (AA) in the beaker was poured in a certain amount of distilled water to obtain a homogeneous solution. Then a certain amount of polyvinylpyrrolidone (PVP) was added to the solution. After complete dissolution, the determined amount of cross linker N,N'-Methylenebisacrylamide (MBA) is added and wait until it completely dissolved, and then initiator Potassium persulfate (KPS) was added and continue to stir until ingredients are well in distilled water. Then put the breaker in a water bath at 70°C for 20 minutes until the hydrogel is produced. Possible structure for a formed hydrogel is presented in Figure 1. To ensure complete polymerization, hydrogel remains in flux containing nitrogen for 4 hours. Then the hydrogel is removed, placed in distilled water for 24 hours to remove the unreacted monomers. Then Hydrogels remain in the oven (temperature 30 to 40°C) for 2 days that are applied to dry completely [23]. For the preparation of nanocomposite hydrogels, after selecting the best combination for the synthesis of the original matrix, dispersed binding material (nanoparticles) of 1, 2, 3 and 4% by weight based on the weight of the base monomer and the base polymer is added to the polymer solution during the polymerization process.Thus, according to the procedure described for the preparation of hydrogels and after thorough mixing the required amounts of acrylic acid, distilled water, PVP and N,N'-Methylenebisacrylamide, adding nanoclay Cloisite 20A and the resulting suspension was mixed for 15 minutes. The amounts of Initiator and all experimental conditions of production Nanocomposite are similar to matrix production procedure; Figure 4 shows the distribution of nanoparticles in the polymer [24].

After the preparation of nanocomposite hydrogels, swelling and delivery tests were taken and the nanocomposites hydrogel containing 4 wt.% nanoclay had the best release rate and delivery. Weight Percent of components of the optimized hydrogel and the nanocomposite hydrogels is given in Table 1.

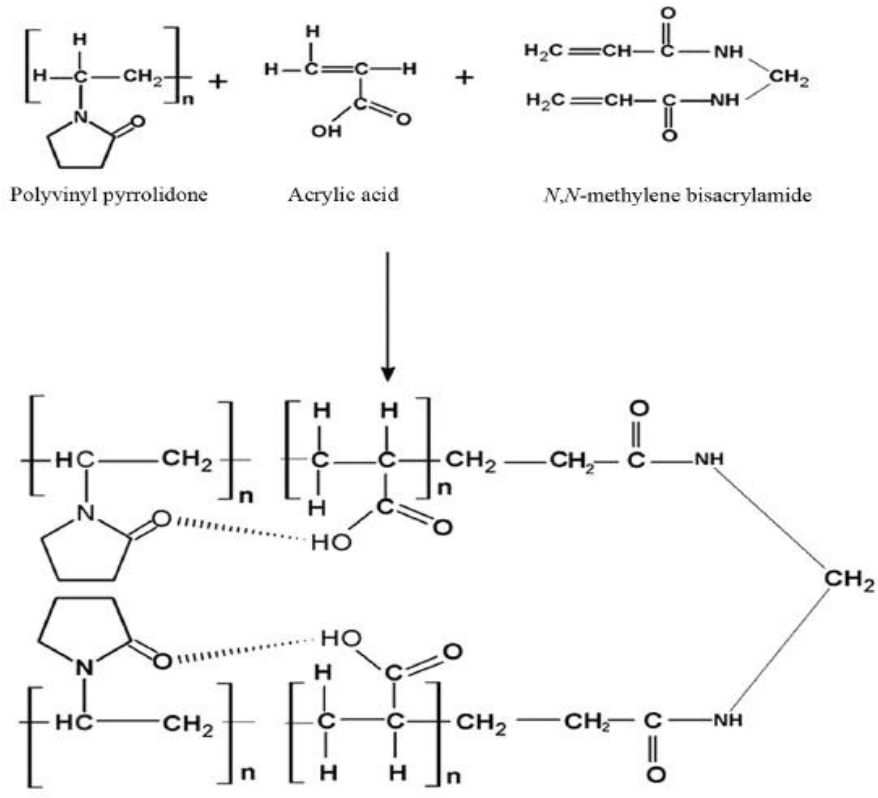


Fig. 3. Possible structure of polyvinylpyrrolidone/acrylic acid hydrogel.

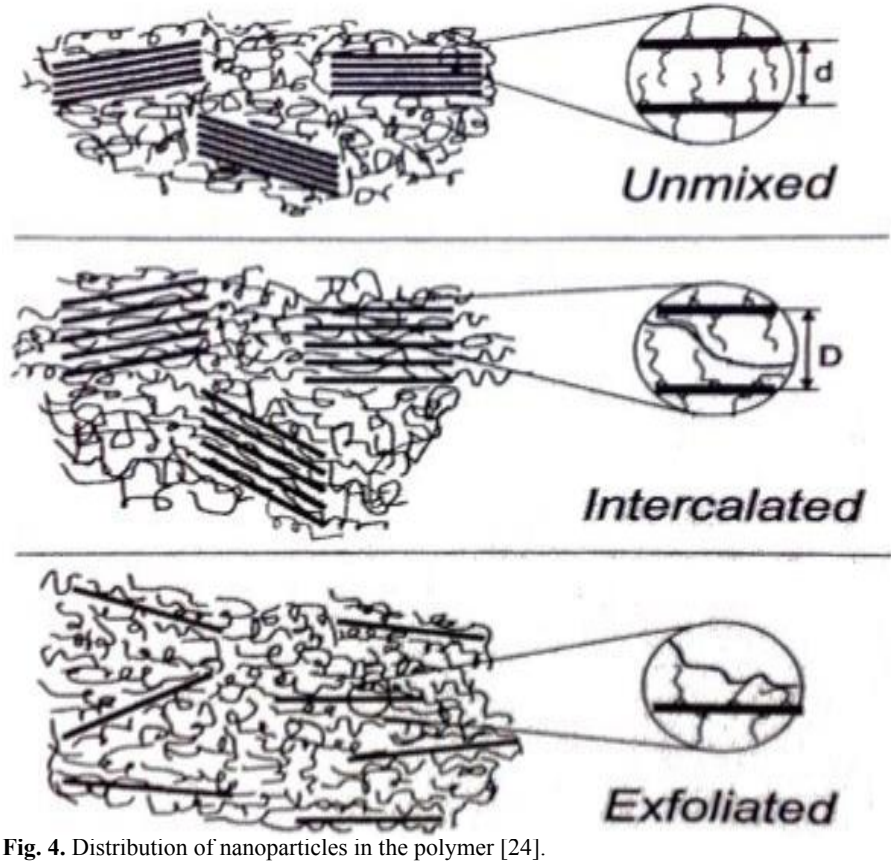


Fig. 4. Distribution of nanoparticles in the polymer [24].

Table 1.
Experimental weight percent of ingredients of the hydrogel.

Sample Designation	Polymer PVP (wt %)	Monomer AA (wt%)	Cross linker MBA (wt%)	Initiator KPS (wt%)	Type and Percentage of Nanoparticle
A (Pure Hydrogel)	0.91	6.398	0.91	0.365	0
B	0.91	6.398	0.91	0.365	1% wt nanoclay
C	0.91	6.398	0.91	0.365	2% wt nanoclay
D	0.91	6.398	0.91	0.365	3% wt nanoclay
E	0.91	6.398	0.91	0.365	4% wt nanoclay

2.3. Uploading drug

Since there is likely to reactions between initiator and drug, the present study used indirect method. For loading drug, the amount of hydrogel (1gr) in 100 mL of solution with a specification concentration of the drug was soaked for 2 hours. To prevent degradation of the drug during this period, the solution was placed in the dark and at room temperature. The drug concentration in the environment was measured by using UV spectrometer Model UVD-3200 made in Labomed companies in America. The amount of drug loaded was determined between initial and final concentrations of the drug in solution.

2.4. Drug delivery

The drug loaded hydrogels were placed in the phosphate buffer solution pH 7.4 for 2 hours and The drug release rate was measured by the UV device at successive time and Delivery rates were fixed for 60-70 minute in duration.

3. Results and discussion

3.1. FT-IR analysis

Of all the tests that are performed on the organic compounds, the infrared spectrum gives the mostinsight into the structure of the composition. Change of vibrations of a molecule, the absorption of infrared light, the light in the visible spectrum from red (lower frequency, longer wavelength, lower energy) is showing the desired configuration [25] In this study, to confirmthe chemical structure of the synthesized hydrogel, we used infrared light FT-IR model Galaxy Series FT-IR 5000 and with assumption of KBr owned by Agilent were made in America. The infrared spectra of Polyvinylpyrrolidone in (Figure 5) In order to confirm the network structure of prepared gels, FT-IR studies were used. It is a sensitive technique to detect the shift in the position of bonds, which confirms the interaction. The main peaks of Acrylic acid are –OH stretch at 3380 cm^{-1}, CH stretch at 2922 cm^{-1} and C=O stretch at 1718.5 cm^{-1}. Polyvinylpyrrolidone shows peaks at 2924 cm^{-1} for CH stretching, a stretching peak between 1650 to 1659 cm^{-1} for carbonyl stretching (C=O) and 1290 cm^{-1} for amide band III (C–N stretch). In the FT-IR spectrum, carbonyl bands in complex were broader than in pure Polyvinylpyrrolidone and Acrylic acid, and are evidence of intermolecular hydrogen bonding N-H stretching between 3330 and 3060 cm^{-1} and C-N stretching at 1650 cm^{-1} indicates the presence of cross-linking agent N,N'-methylenebisacrylamide.

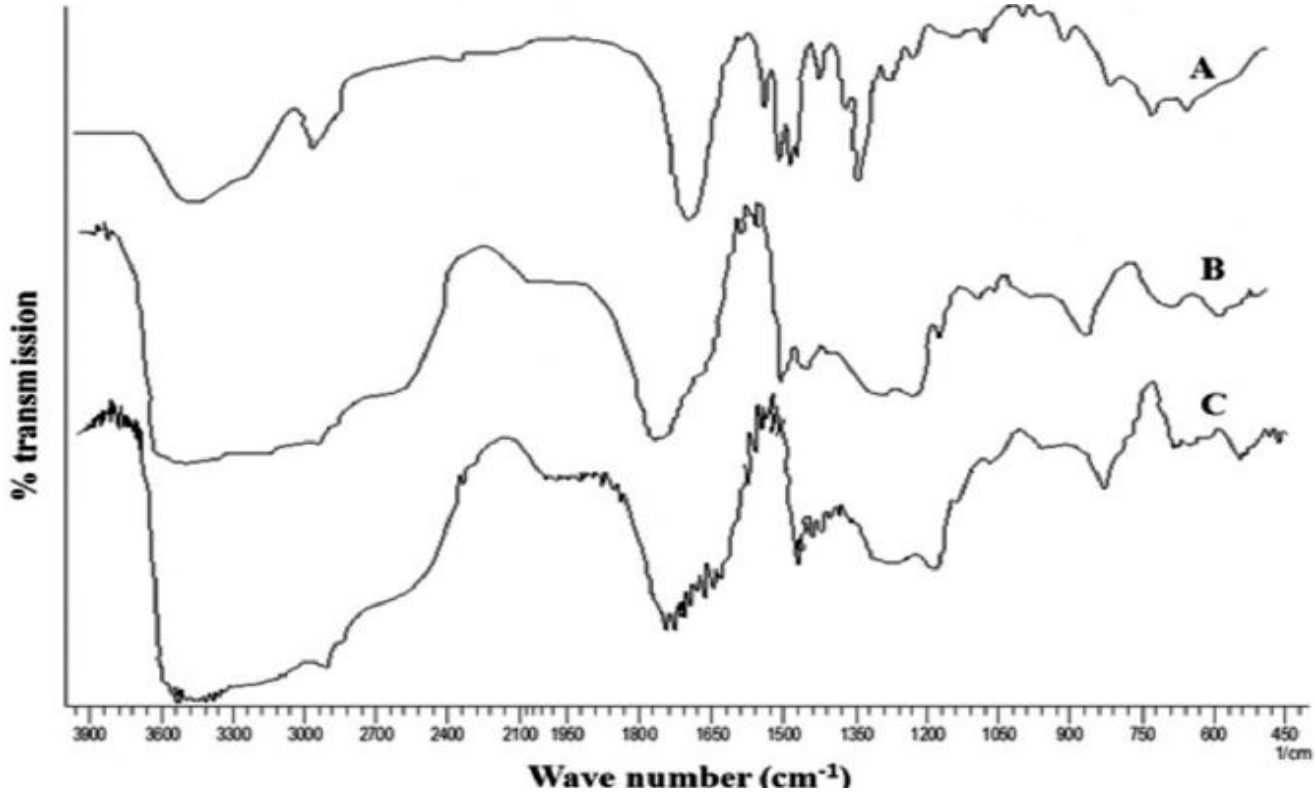


Fig. 5. FT-IR spectra for (A) Polyvinylpyrrolidone, (B) acrylic acid and (C) Polyvinylpyrrolidone/acrylic acid hydrogel.

3.2. X-ray diffraction

Every crystalline drug has a well-defined crystalline pattern that can be observed by XRD analysis and can be used as a tool for their identification. Figure 6 is shown XRD results of the pure montmorillonite nanoclay cloisite 20A and in Figure 7 XRD results of hydrogel with 4% montmorillonite nanoclay Cloisite 20A is shown. It can be seen that for composites prepared, peaks not observed in the graph indicates that the silicate layers dispersed within a polymer matrix is fully. In other words XRD curves indicate the distance between the layer and the preparation of nanocomposites. The result shows that procurement process using nanoclay nanocomposites has been successfully complated and during the intervals between the polymer chains penetrate the layer montmorillonite.

3.3. Morphology of nanocomposite hydrogels

Scanning electron microscopes (SEM) of compounds were taken in Tehran's Amir Kabir University by the model AIS2100 produced Seron companies from South Korea.

SEM tests specifies surface morphology of nanocomposite hydrogels. In Figure 8 is shown SEM results of the pure montmorillonite nanoclay cloisite 20A and SEM results of hydrogel with 4 wt.% montmorillonite nanoclay Cloisite 20A is shown in Figure 9 which shows the hydrogel is well located between the layers of nanoparticles.

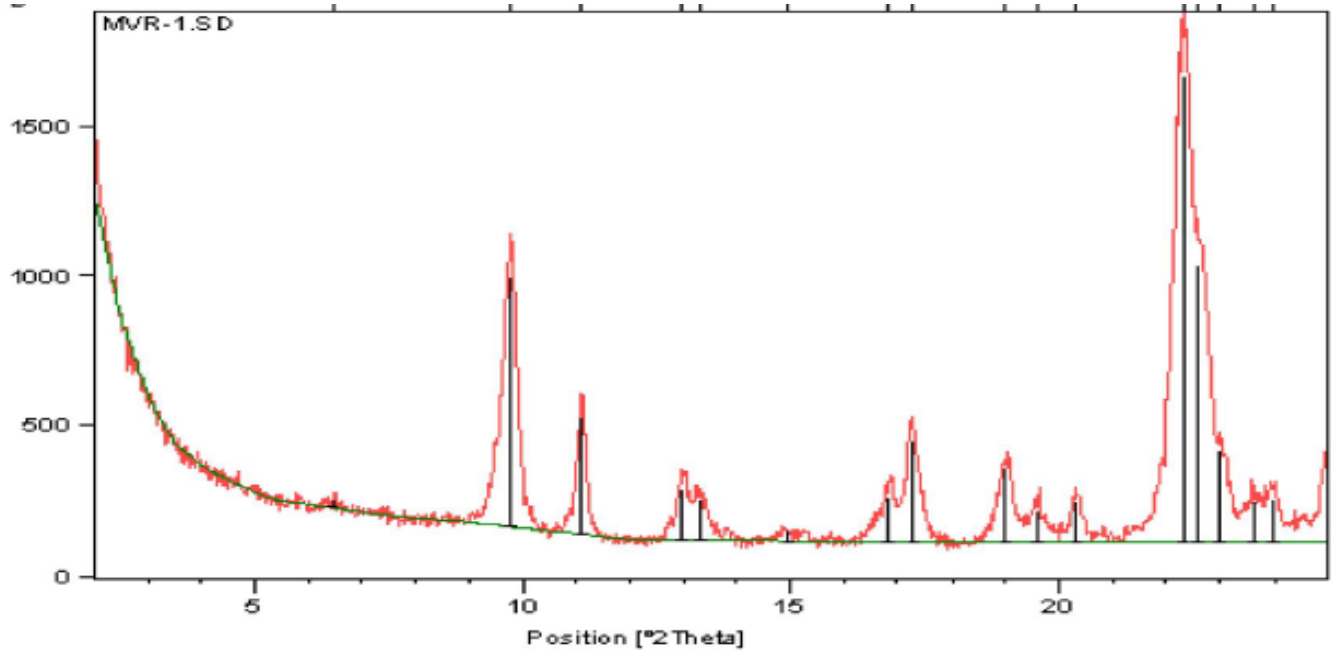


Fig. 6. XRD pattern of pure montmorillonite nanoclay cloisite 20A.

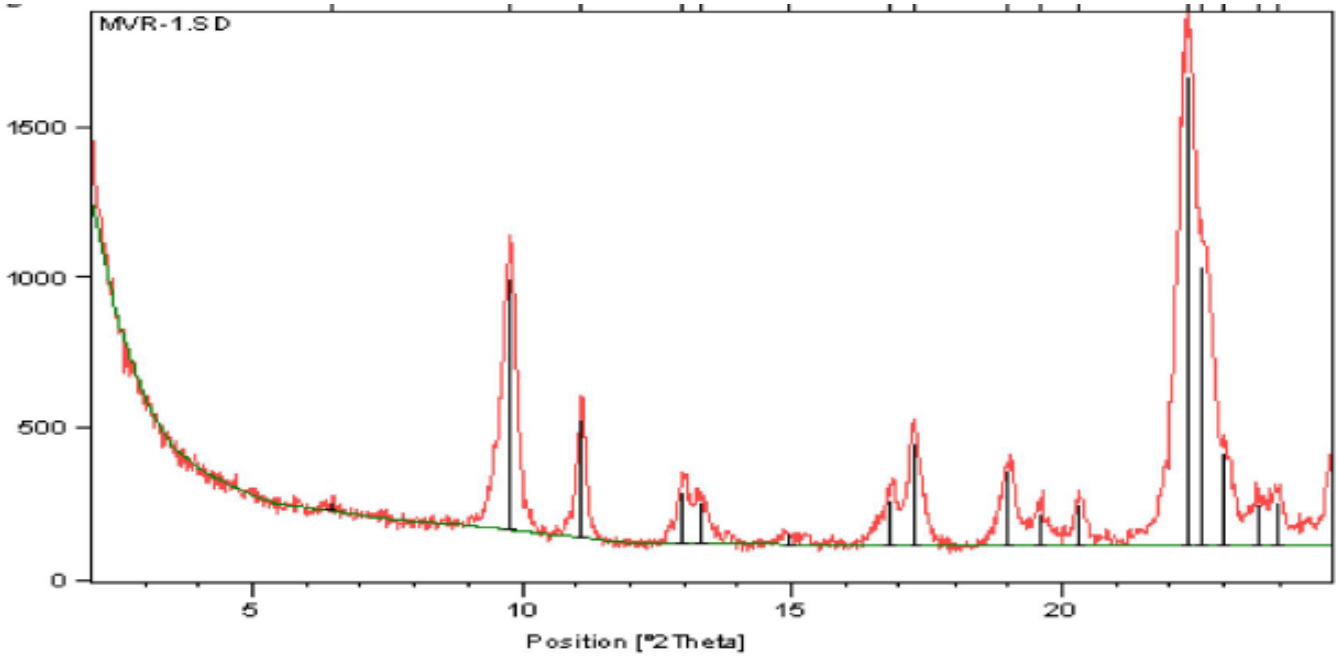


Fig. 7. XRD pattern of nanocomposite hydrogel containing 4 wt.% montmorillonite nanoclay cloisite 20A.

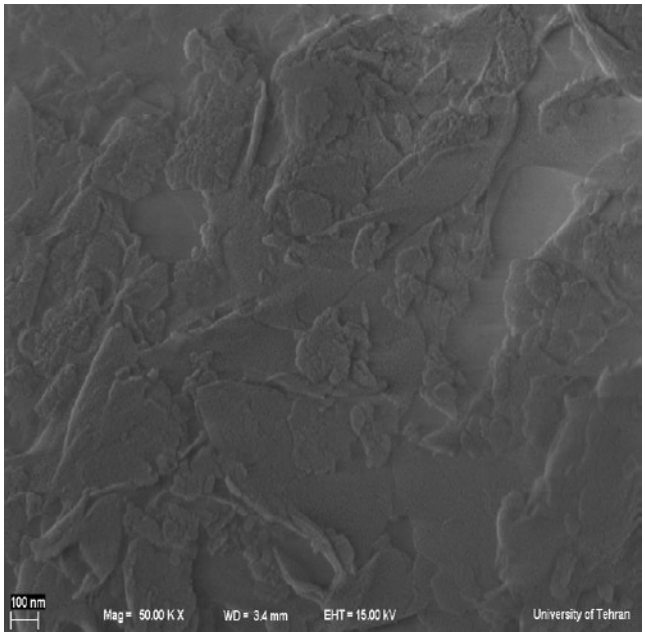


Fig. 8. SEM image for pure montmorillonite nanoclay cloisite 20A.

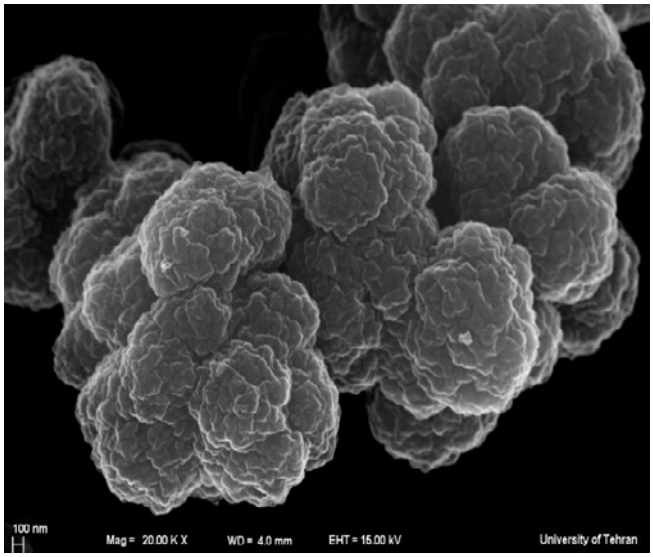


Fig. 9. SEM image for nanocomposite hydrogel containing 4 wt.% montmorillonite nanoclay cloisite 20A.

3.4. Swelling properties of hydrogels

To evaluate the effects of swelling, after the accurate weight measurement of a sample of dried hydrogel, put it in the beaker containing 100 mL of phosphate buffer at 25 °C. At specified intervals, the swells hydrogel get out from the solution, using a towel to gently dry the surface moisture and measure its weight. To check swelling, measured continued to eight hours. The swelling ratio (SM) is used by the following equation.

$$S_M = \frac{M_t - M_o}{M_o} \quad (1)$$

In the above equation, M_t and M_0 are measured weight in each time and the initial weight of dry hydrogel, respectively (Figure 10).

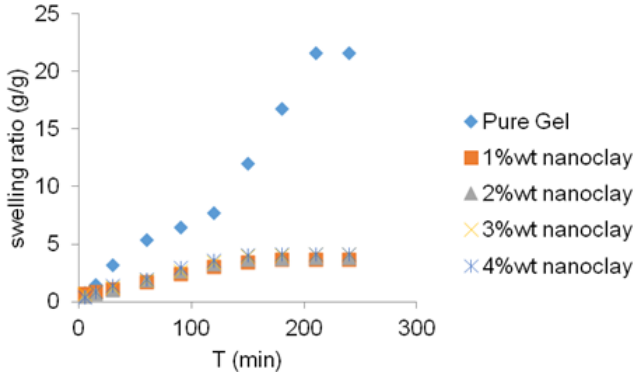


Fig. 10. Swelling ratio of hydrogels vs time.

3.5. Kinetics of drug delivery

Kinetics of drug release from hydrogels based on PVP by plotting values of M_t/M_∞ versus t in Figure 11 indicate that Mt concentrations of the drug delivery solution that hydrogel has been put into it, M_∞ difference between the initial concentration of dissolved before putting hydrogel and secondary levels of concentration of Isoniazid solution after placing the hydrogel for 2 hours.

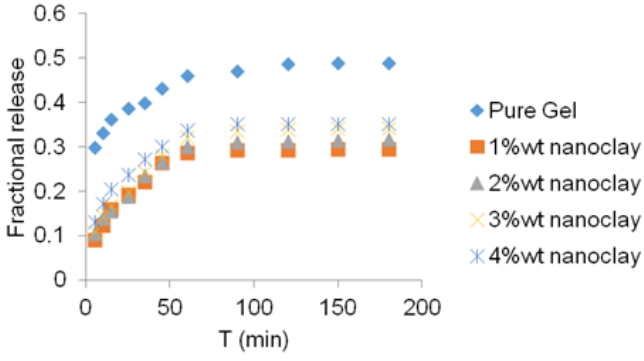


Fig. 11. Fractional release of hydrogels vs time.

3.6. Presentation two kinetic models of Peppas and Higuchi

3.6.1. Peppas Model

$$M_t / M_\infty = k\, t^n \quad (2)$$

In Peppas equation n and k are constants. n, is penetration exponent that depends on the conduction mechanism of the delivery system and the type of transition that can be revealed. (if $0 < n < 0.5$ is the Fick diffusion) [26, 27].

To obtain n and k, we can Ln from both sides of the equation; the following linear equation is obtained:

$$\text{Ln}\,(M_t / M_\infty) = n\,\text{Ln}\,(t) + \text{Ln}\,(k) \quad (3)$$

By Plotting Ln (M_t / M_∞) versus Ln (t), slope (n) is obtained. In Figure 12 hydrogels with different PVP and nare plotted using equation Peppas for hydrogel are obtained. Values were calculated in Table 2.

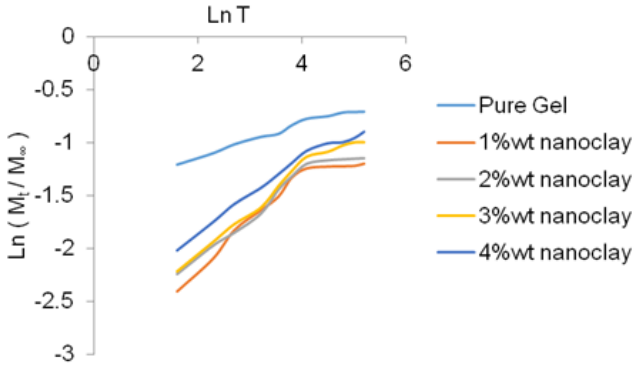


Fig. 12. Peppas Model.

Table 2.
Obtained result based on Peppas model.

Sample	R^2	n	k
Pure Hydrogel	0.987	0.144	0.242
1% wt nanoclay	0.952	0.336	0.061
2% wt nanoclay	0.966	0.325	0.067
3% wt nanoclay	0.968	0.339	0.068
4% wt nanoclay	0.993	0.143	0.093

3.6.2. Higuchi Model

$$M_t / M_\infty = n_1\, t^{1/2} + b \quad (4)$$

Plotting the values of M_t / M_∞ versus $t^{1/2}$, for hydrogels in Figure 13, the slope of the line (n_1) is obtained from the results and is given in Table 3. (If $0 \leq n_1 < 0.5$ is the Fick diffusion) [28, 29].

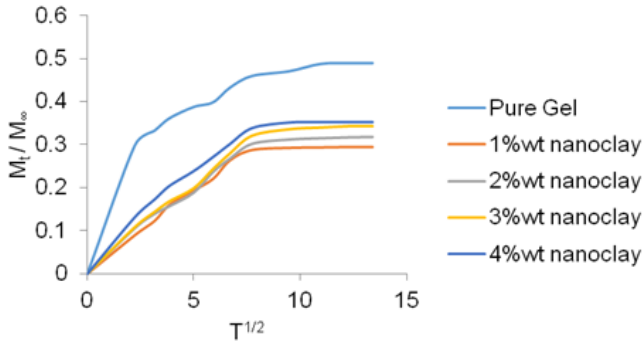


Fig. 13. Higuchi Model.

Table 3.
Obtained results by Higuchi model.

Sample	R^2	n_1
Pure Hydrogel	0.931	0.027
1% wt nanoclay	0.913	0.021
2% wt nanoclay	0.928	0.023
3% wt nanoclay	0.911	0.024
4% wt nanoclay	0.937	0.025

4. Conclusions

1- SEM results of nanocomposite hydrogels indicate the good dispersion of nanoparticles in a hydrogel matrix. Furthermore, the results obtained from SEM analysis specify that the structure of the prepared nanocomposite hydrogels is a sheet structure and the percentage of nanoparticles is an effective factor on the nanocomposite properties.

2- The results of the hydrogel swelling and drug delivery show that the addition of hydrophilic layers of nanoclay cloisite 20A reduces swelling and the release of the drug in an appropriate manner. The reason for this decrease is that the addition of nanoparticles decreased porosity, swelling of the hydrogel and drug delivery.

3- Using two Higuchi and Peppas models it was found that the mass transfer mechanism obeys Fick's diffusion law.

4-Due to the short half-life, rapid onset, peak effect and rapid drug delivery profile, nanocomposite with 4% nanoclay cloisite 20A within tests has the more controlled delivery than the other samples and also two models, Peppas and Higuchi, confirm this result.
5-With comparing linear regression coefficients (R_2), it was observed that Peppas model out performed Higuchi model in optimal hydrogel, nanocomposite with 4% nanoclay and experimental data of Peppas model is better than Higuchi model.
6- In both the Peppas and Higuchi models, by increasing the percentage of nanoparticles in the prepared samples, the slope of the line (n) decreases. For example, in the hydrogel sample with 4% nanoclay cloisite 20A, n is smaller than the other hydrogels and this means that there will have more controlled release when n decreases.

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