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Preparation, Characterization and Drug Release Behavior of a Clinoptiolite Incorporated Polyacrylamide Grafted Gelatin Nanocomposite in Situ Hydrogel

Klinoptiolit İçerikli Poliakrilamid ile Graftlanmiş Jelatin Nanokompozit Hidrojelinin Sentezi, Karakterizasyonu ve İlaç Salim Davranışı

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ABSTRACT

In this study, the novel gelatin based in situ hydrogel nanocomposites were prepared from incorporating clinoptiolite (CL) and Lidocaine (LD) as a model local anesthetic drug within polyacrylamide-g-gelatin (PA-g-GA) hydrogel during the synthesis by free radical polymerization. The prepared PA-g-GA, PA-g-GA/CL and drug loaded PA-g-GA/CL in situ hydrogel nanocomposites were analyzed by FTIR and SEM. The drug release behavior of the synthesized composite hydrogel was investigated with UV-Vis spectrophotometry. Swelling and drug release behavior of the new prepared hydrogel nanocomposites were investigated with different CL and drug content in the gel structure. FTIR and SEM analysis revealed that the LD loaded PA-g-GA/CL nanocomposite was successfully prepared. Drug release (%) decreased when the drug loading and CL amount in the composite increased. Various kinetic models for all drug release data were applied in order to study drug release behavior. Korsmeyer-Peppas model fitted for the drug release data of all samples. Swelling, drug release properties of the new nanocomposites were improved with the incorporation of clinoptiolite in the gel structure.

Key Words

Gelatin, acrylamide, clinoptiolite, nanocomposite.

ÖZ

Bu çalışmada, jelatin (GA), akrilamid (AAm), klinoptiolit (CL) ve model anestetik ilaç Lidokain (LD)'den oluşan yeni tip jelatin bazlı kompozit hidrojeli serbest radikal polimerizasyon ile hazırlandı. Sentezlenen poliakrilamid ile graftlanmış jelatin (PA-g-GA), CL içerikli PA-g-GA ve ilaç yüklü PA-g-GA/CL kompozit hidrojellerinin karakterizasyonu FTIR ve SEM kullanılarak yapıldı. Sentezlenen yenkompozit hidrojelin ilaç salım davranışı, UV-Vis spektrofotometri ile incelendi. Farklı CL miktarı ve farklı ilaç konsantrasyon içeriklerinde sentezlenen yeni tip nanokompozit hidrojellerin, şişme ve ilaç salım davranışları incelendi. FTIR ve SEM analizleri, PA-g-GA/CL kompozit hidrojelinin başarıyla sentezlendiğini ve LD ilacıyla yüklendiğini ortaya koydu. Kompozitteki ilaç yükleme ve CL miktarı arttıkça LD salınımı (%) azalmıştır. İlaç salınım davranışını incelemek için LD salınım verilerine çeşitli kinetik modellere uyarlandı. Hazırlanan tüm hidrojellerin ilaç salımı Korsmeyer-Peppas modeline uymaktadır. Yeni nanokompozitlerin şişme ve ilaç salım özellikleri, jel yapısına klinoptiolitin eklenmesiyle geliştirildi.

Anahtar Kelimeler

Jelatin, akrilamid, klinoptiolit, nanokompozit.

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INTRODUCTION

In recent years, interest in controlled drug release systems in which polymers are used as a means of controlling drug delivery has been increased greatly all over the world [1]. Drug delivery systems DDS offer many advantages compared to traditional methods, such as reduced toxicity, patient compliance and comfort [2-4]. Gelatin (GA)-based hydrogels are excellent features such as cell adhesion, hydrophilic, noncarcinogenic, low cost, and biodegradability [5-8].

In addition, many studies have carried out using two-component polymer systems based on modified gelatin and polyacrylamide (PA) were synthesized, characterized and used in drug delivery applications [9-12]. In numerous studies conducted today, zeolite minerals in polymeric composite nanohydrogels are used in the formulations of polymer composites and drugs for many reasons such as increasing the stability of the drug, extraordinary swelling, improving mechanical and rheological properties, and being economical [13]. Moreover, zeolite minerals are used in the field of health due to their anti-inflammatory, antibacterial and wound healing properties. In addition, since zeolite materials are abundant in nature, large ion exchange capacity, the swelling capacity of zeolites in water, their effect on stable gel structure, and adsorption capacity, the use of them in gel formulation to improve material properties is increasing today [14]. Clinoptiolite (CL), one of the most common zeolite minerals in nature, is used in many fields such as dentistry, medicine, treatment of burn wounds and cancer treatment [13, 15-17] for the preparation of polymeric nanocomposites and superabsorbent nanocomposite hydrogels [16, 17]. Hydrogel nanocomposite containing clinoptilolite has been reported to exhibit water retention and slow-release properties [18]. In this work, clinoptilolite was used to improve controlled release behavior of the synthesized nanocomposite.

Lidocaine (LD) is a local anesthetic drug that is frequently used in the treatment of chronic and acute pain [19, 20]. In particular, lidocaine hydrochloride (LDC) is the most frequently used drug for local administration due to its rapid onset, and its effectiveness [21]. A large number of anesthetic-based controlled drug systems have been developed in the last decade. In these systems, drugs loaded into polymeric materials make a controlled release in a physiological environment [22-24]. In treatments requiring local anesthesia, anesthetics are normally administered to the oral area by injection. Anesthetics are administered to the patient in several doses throughout the treatment. Apart from the pain caused by these applications and the discomfort they cause to the patient, there are also other problems. However, it seems that there are relatively few studies on general and anesthetic drug-releasing systems used as dental patches in the field of dentistry.

The aim of the study is to develop CL incorporated PA-g-GA nanocomposites containing LD as a model local anesthetic drug for developing anesthetic-based controlled drug systems in dental applications. Although there are many examples in the literature where GA and PA are used as drug carrier systems, the fact that developing a new gelatin based in situ hydrogel nanocomposite by incorporating clinoptiolite and LD drug within polyacrylamide-g-gelatin hydrogel during the synthesis brings some novelty to the study.

MATERIALS AND METHODS

Materials

Gelatin (300 Bloom, type A), acrylamide, N,N methylene bisacrylamide (MBA), potassium persulfate (KPS), N,N,N‴″′,N′ tetramethyl ethylenediamine (TEMED) and phosphate-buffered saline (PBS) were purchased from Sigma Aldrich. Clinoptiolite (CL) was supplied from commercial company (Etibank Company, Turkey). Lidocaine hydrochloride monohydrate (LD, $C_{14}H_{22}N_2O$, Merck, Germany) was used as a model drug.

Hydrogel Synthesis

PA-g-GA, PA-g-GA/CL, and drug loaded PA-g-GA/CL composite hydrogels were prepared from gelatin and acrylamide (AAm) using methylene bis acrylamide (MBA) as a crosslinker and potassium persulphate (KPS) as an initiator by solution polymerization. First, 0.063 g of gelatin was dissolved in 10 mL of pure distilled water at 45°C for 3 hours and waited for it to reach room temperature. Then, a 10% (wt/v) aqueous solution of AAm was put into 10 ml of GA solution [9,25]. Different amounts of CL were added into beakers containing AAm/GA solution. Different amounts of a model drug (LD) were added to AAm/GA/CL solutions and stirred at room temperature for one hour. Then, 0.01 gram of MBA as a crosslinker and 0.014 gram of KPS as an initiator and 10-20 µL TEMED accelerator were put into the solution and the solution was mixed. Finally, the solution was

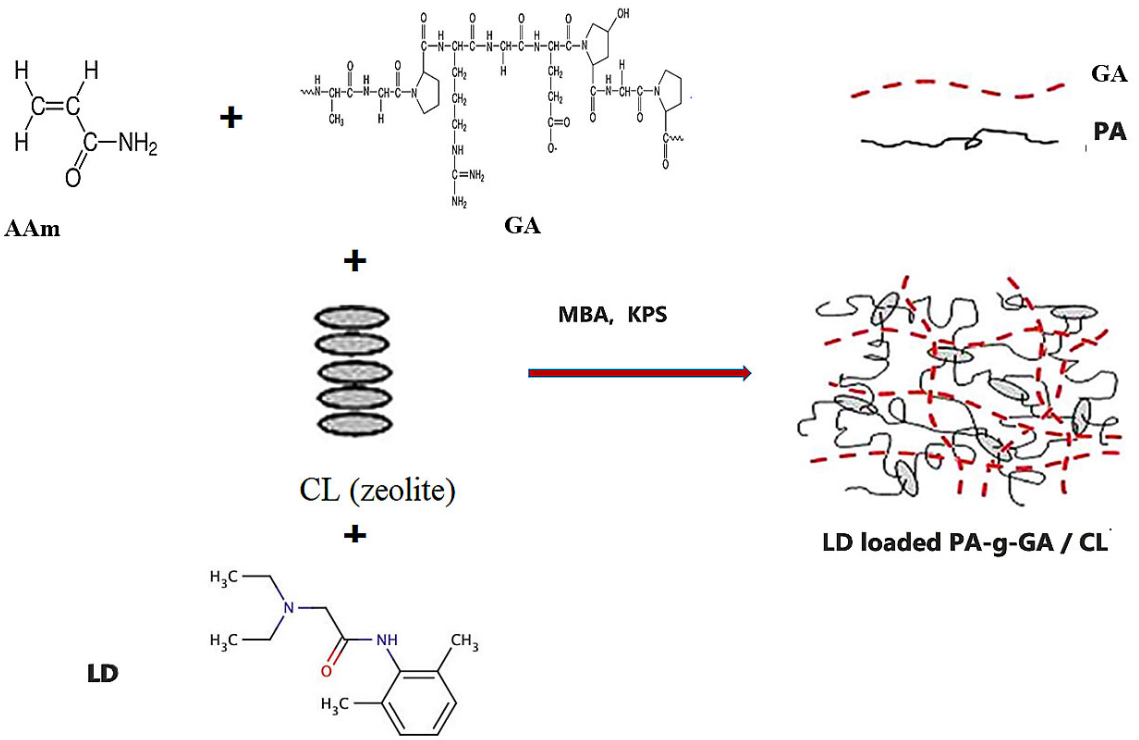

Figure 1. Preparation of PA-g-GA/CL nanocomposite in situ hydrogel.

transferred into a glass tube and the mouth of the tube was covered with parafilm and kept in the glass tube for 24 hours at room temperature. The preparation of the hydrogels is shown in Figure 1.

Characterization

Drug release was calculated using UV-VIS spectrophotometer (Shimadzu 2401 Model, Holland). In order to characterize the samples, SEM (FEI-QUANTA FEG 250, Spain) and FTIR (Bruker VERTEX 70 ATR, Belgium) instruments were used.

Drug Release and Encapsulation Efficiency

The drug was loaded on the composite gels during the synthesis. Encapsulation efficiency of the prepared LD loaded PA-g-GA/CL was found by using indirect method as explained previously [26]. Drug release behavior was examined using a UV-VIS spectrophotometer at a wavelength of 262 nm depending on time.

Theory and Calculation for Hydrogels

Equations 1-4 were used to calculate mass swelling, equilibrium mass swelling (%), encapsulation efficiency and cumulative release (%), respectively:

$$\text{Mass Swelling}\,(\%) = \frac{(m_t - m_0)}{m_0} * 100 \quad (1)$$

$$\text{Equilibrium Mass Swelling}\,(S_{eq}\%) = \frac{(m_\infty - m_0)}{m_0} * 100 \quad (2)$$

where m_0 is mass of the dry gel, m_t and m_∞ are mass of the swollen gel at time t and at equilibrium, respectively [26,27]. (3)

$$\text{Cumulative Release}\,(\%) = \frac{W_t}{W_{total}} * 100 \quad (4)$$

where W_t is the weight of LD released in water at any time and W_{total} is the initial total weight of LD loaded in the gel system during the synthesis [26, 27].

Equations 5-8 are used for the drug release kinetics of all synthesized gels [28,29]:

Zero-order kinetics:

$$M_t / M_\infty = K_0\, t \quad (5)$$

where K_0 is the zero-order release constant.

First-order kinetics:

$$\ln(1 - M_t / M_\infty) = -K_1 t \quad (6)$$

where K_1 is the zero-order release constant.

Higuchi model:

$$F = K_2 t^{1/2} \quad (7)$$

where K_2 is the Higuchi constant.

Korsmeyer-Peppas model:

$$F = \frac{M_t}{M_\infty} = kt^n \quad (8)$$

where M_t/M_∞, where M_t is the amount of absorbed at time t, M_∞ is the maximum amount absorbed, k is a constant, n is the diffusional exponent.

RESULTS and DISCUSSION

FTIR and SEM Analysis

FT-IR spectra of PA, PA-g-GA, CL, LD and LD loaded PA-g-GA/CL are shown in Figure 2. In Figure 2a, the characteristic absorption peaks of PA hydrogel seen in are seen at 3331 cm^{-1} (N-H stretching), 3186 cm^{-1} (N-H bending), 2926 cm^{-1} (CH_2 stretching), 1648 (C=O group) [25]. In Figure 2b, the peaks at 1221 cm^{-1} (the amide-III) and 1354 cm^{-1} (the symmetric and asymmetric bending vibrations of methyl group) come from gelatin and the peaks at 3190 cm^{-1} (N-H bending), 2926 cm^{-1} (CH_2 stretching), 1650 cm^{-1} (C=O group) come from PA [30,31]. In Figure 2c, characteristic peaks of CL are seen at 1627,62 cm^{-1} (the presence of water in the natural zeolite) and 1019,72 cm^{-1} (Al-O or Si-O bonds), and 791 cm^{-1} ((T–O–T) symmetrical stretching vibrations, T = Al or Si) and 448,77 cm^{-1} (O-Al-O or Al-O group ; O-Si-O or Si-O group) [15]. In Figure 2d, characteristic peaks of LD, as seen in the FT-IR spectrum of the model drug Lidocaine: 3451 cm^{-1} (N-H stretch), 3383 cm^{-1} (N-H stretch), 1686 cm^{-1} (carbonyl group of amide group), 1474 cm^{-1} (hydrochloride), 1271 cm^{-1} (tertiary amine), 1152, 714 and 597 cm^{-1} (aromatic ring) [21]. In the drug loaded PA-g-GA/CL hydrogel shown in Figure 2e, the characteristic peaks of PA are 3340 cm^{-1} (N-H stretching), 3191 cm^{-1} (N-H bending), 2932 cm^{-1} (CH_2 stretching),1650 (C=O group) and that of GA are at 1354 cm^{-1} was the symmetric and asymmetric bending vibrations of the methyl group of gelatin. Characteristic peaks of CL and LD in the FT-IR spectrum of drug loaded PA-g-GA/CL are seen at 1032 cm^{-1} (Al-O or Si-O bonds of CL) and 597 cm^{-1} (aromatic ring of LD), respectively.

Figure 3 shows SEM micrographs of PA-g-GA, PA-g-GA/CL and drug loaded PA-g-GA/CL composite hydrogels. As can be seen in Figure 3, PA-g-GA has a smooth surface morphology. In contrast, it is seen that when zeolite CL particles were added in PA-g-GA gel formulation, the structure of the hydrogel composites became inhomogeneous. This was expected the strong electrostatic interactions occur between the PA-g-GA matrix and silicate layers [32]. Finally, when drug LD particles were added to the structure, they filled the porous structure of the hydrogel composites and coated them. Thanks to the amide group in the structure of lidocaine, it interacts with the polymer by forming hydrogen bonds, and lidocaine drug molecules fill the network area [20]. Therefore, adding Lidocaine to the porous hydrogel reduces the pore size.

Swelling Behavior

The swelling behavior of the synthesized samples in water are illustrated in Figure 4. The mass of the synthesized gels in distilled water increased with time. Swelling experiments were performed with the average of three measurements for the standard deviation of the measurements. The equilibrium mass swelling % of PA is 1184±0.9 but that of PA-g-GA is 962±1.2 since physical entanglement between GA and PA reduces the volume required for swelling in the PA-g-GA hydrogel [10]. The equilibrium mass swelling percentage of the synthesized PA-g-GA/CL composite hydrogel (%711±1.1) is less than those without zeolite content (pure PA, PA-g-GA). This indicates that the CL particles fill the pores and reduce the volume required for swelling in the composite hydrogel. From the SEM analyses seen in Figure 3, it is clear that the CL particles fill the porous structure and empty spaces of the PA-g-GA polymer, and swelling supports the SEM results.

Effect of Zeolite on Drug Release and Entrapment Efficiency

For in-situ synthesis of drug loaded PA-g-GA and PA-g-GA/CL samples, entrapment efficiency (%) was studied in triplicates and presented in Table 1.

Figure 5 shows that the time-dependent drug release percentages of the zeolite-free PA-g-GA hydrogels are higher than that of the zeolite-containing hydrogels (PA-g-GA/CL). As seen in the SEM analysis, the structure

of the prepared hydrogels becomes denser with the increase of the zeolite (CL) content in the structure. Thus, the CL layers act as a barrier and slow the release of drug molecules [32]. The absence of burst in drug release from PA-g-GA/CL hydrogels indicates that the drug molecules loaded on the samples are not only on the surface of the composite hydrogels but that the drug is distributed homogeneously.

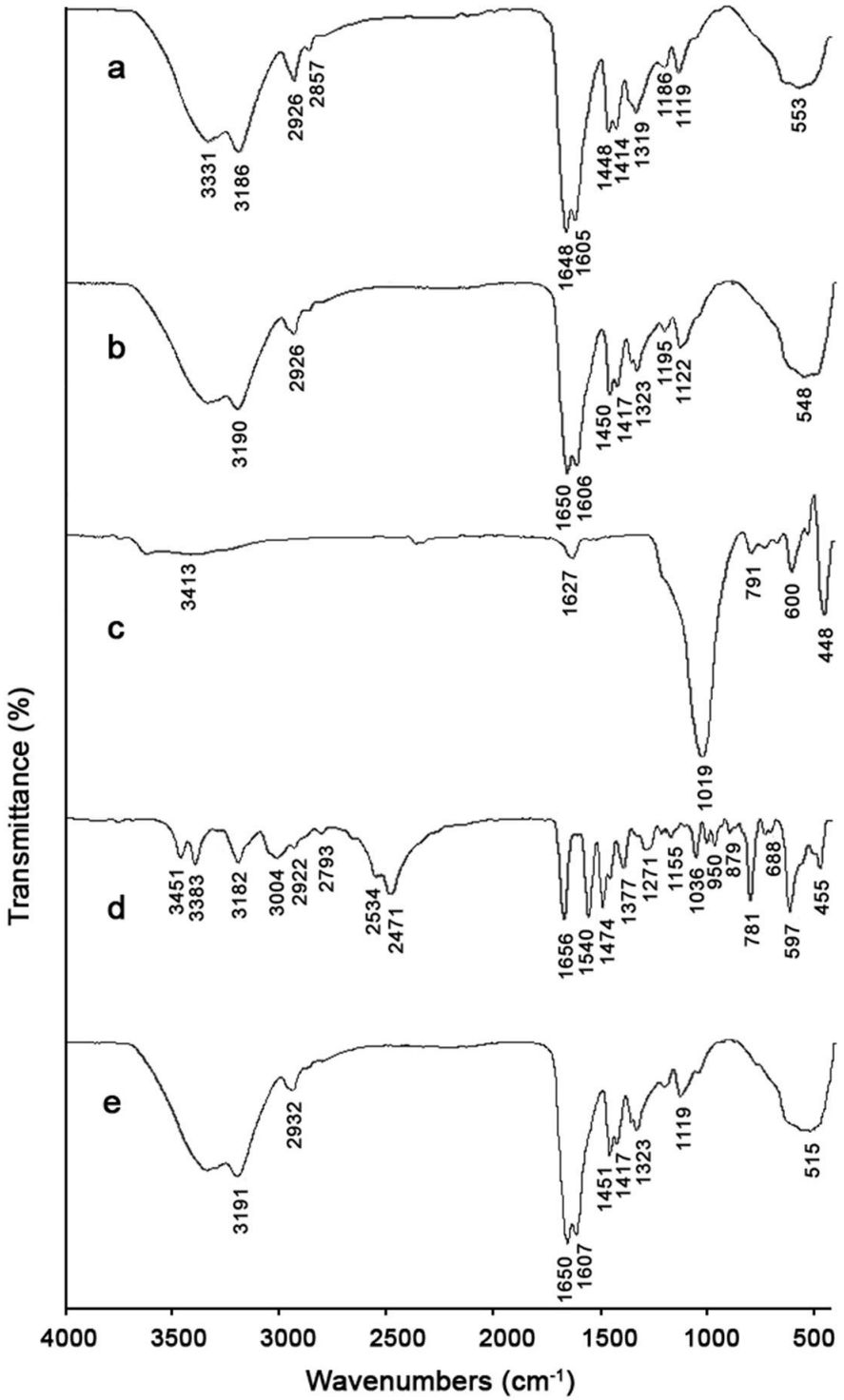

Figure 2. Fourier transform infrared spectrums of (a) PA, (b) PA-g-GA, (c) CL, (d) LD (drug), (e) drug loaded PA-g-GA/CL.

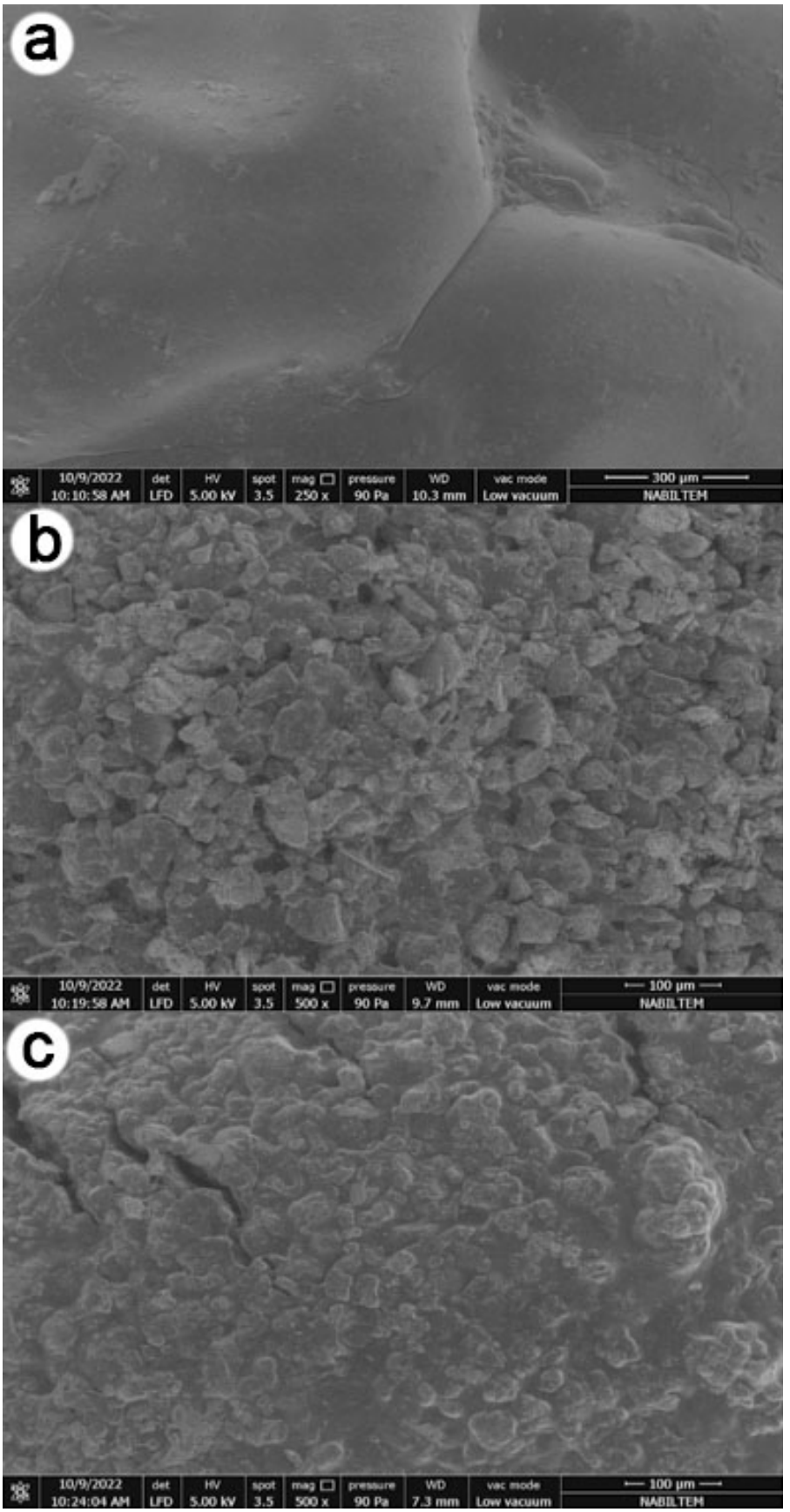

Figure 3. The SEM images of the hydrogels: a) PA-g-GA, b) PA-g-GA/CL, c) drug loaded PA-g-GA/CL.

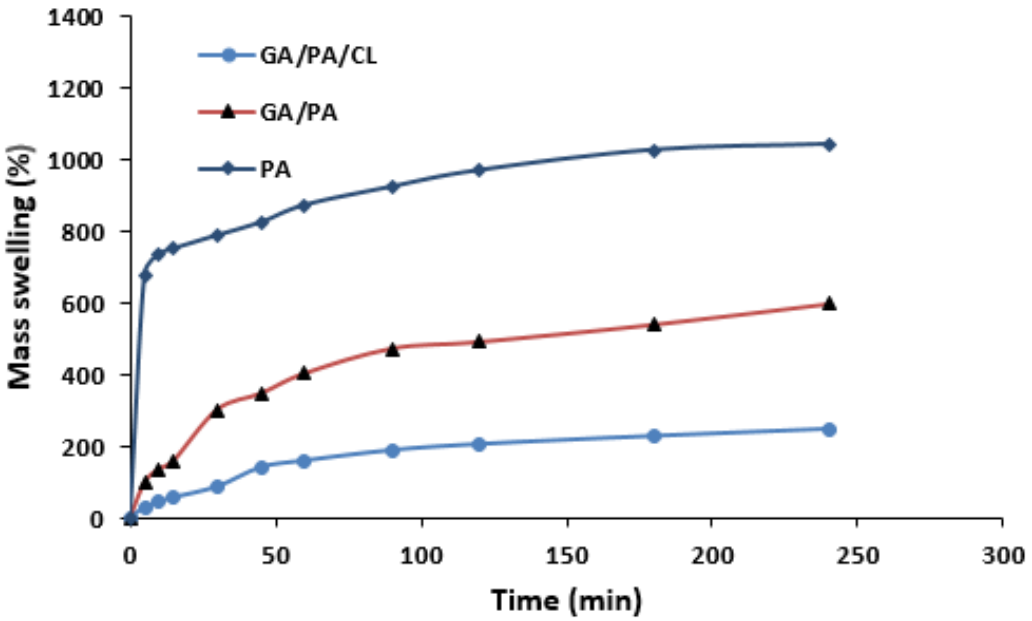

Figure 4. The swelling properties of PA, PA-g-GA, PA-g-GA/CL in distilled water.

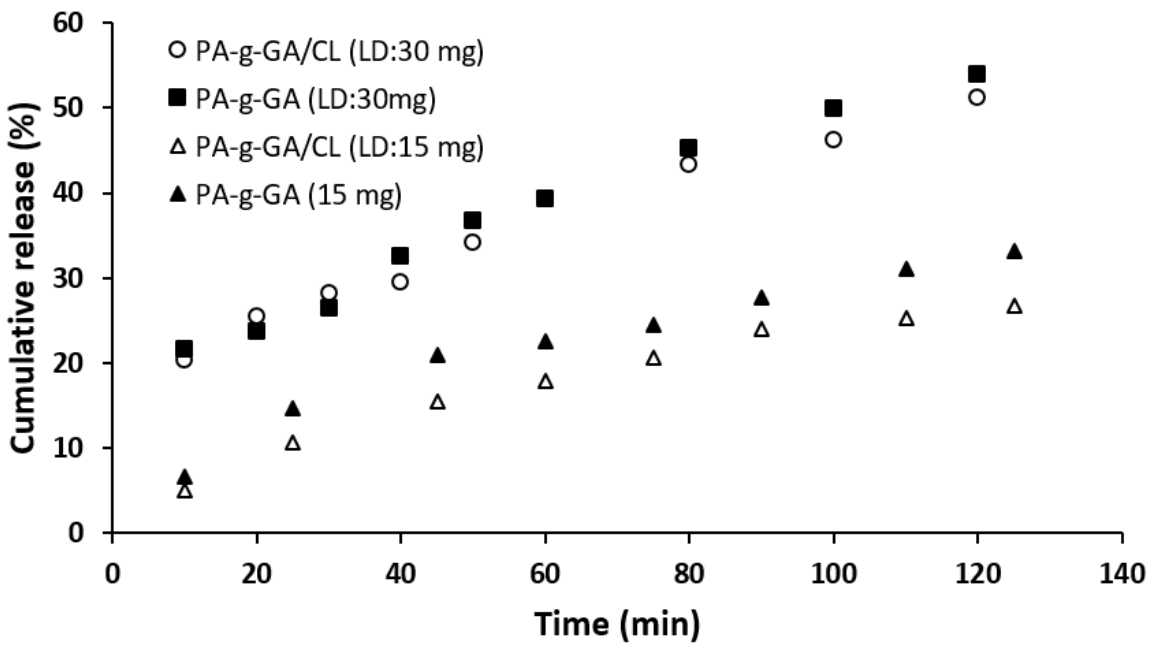

Figure 5. Cumulative LD release (%) from PA-g-GA and PA-g-GA/CL hydrogels at 37 ºC and pH 7.4.

Effect of Drug Loading Amount on Drug Release

It was found that an increase in drug encapsulation into the gel structure during the synthesis from 15 mg to 30 mg caused an increase in the cationic LD drug adsorption capacity of PA-g-GA/CL composite hydrogels from 20.2 mg to 67.5 mg per 1 gram of dry gel. These gels have zeolite particles which are negatively charged framework silicates prepared from ash and have cation exchange properties [14]. As shown in Figure 5, these interactions cause the release of the drug to be delayed from the composite having higher drug content, and LD release (%) decreases when the drug loading amount in the composite increases.

Release Kinetics

LD release kinetics of all the prepared hydrogels were used by zero-order, first-order, Higuchi and Korsmeyer-Peppas models by using equations 5-8. The best-fitted model with the release data was evaluated by the values of regression coefficient. Korsmeyer-Peppas kinetic models better fitted the release of LD (r^2>0.99) than the other models for all type of synthesized hydrogels. All the model constants are presented in Table 2 together with the r values. For all samples, the value of n is between 0.5–1, indicating that the LD released follows a non-Fickian diffusion mechanism [27, 33].

CONCLUSION

In this work, a new type of drug loaded PA-g-GA/CL nanocomposite hydrogels was prepared by free radical polymerization from gelatin, acrylamide and clinoptiolite using MBA as a crosslinker. FTIR spectroscopy and SEM analysis confirmed the successful preparation of the nanocomposite hydrogels. The improvements in drug adsorption and release properties of the new PA-g-GA/CL composite hydrogels with the addition of clinoptiolite in the gel structure were achieved. For all samples, the LD released follows a non-Fickian diffusion mechanism and Korsmeyer-Peppas kinetic models better fitted the release of LD (r^2>0.99) than the other models for all type of synthesized hydrogels. Thus, the

Table 1. Drug entrapment efficiencies of all samples.

Sample	Encapsulation Efficiency (%)
PA-GA (LD:15 mg)	1.333
PA-GA (LD:30 mg)	1.334
PA-g-GA/CL (LD:15 mg)	1.336
PA-g-GA/CL (LD:30 mg)	98.2 ±0.9
98.7±1.1	1.345
99.1±0.8	1.358
99.4±1.2	1.371

Table 2. LD release kinetics of all samples.

	PA	PA-g-GA	PA-g-GA/CL
Zero order	Kinetics		
K_o (min^{-1})	0.0026	0.0059	0.0069
R^2	0.9503	0.9789	0.9518
First-order	Kinetics		
K_1 (min^{-1})	0.0097	0.0199	0.0106
R^2	0.9771	0.9705	0.9671
Higuchi	Model		
K_2 (min^{-1})	0.0252	0.0625	0.0835
R^2	0.9596	0.9723	0.9531
Korsmeyer-	Peppas model		
N	0.5876	0.6163	0.6158
K	0.0267	0.0370	0.0354
R^2	0.9873	0.9918	0.9947

experimental results suggest that the prepared nanocomposite hydrogels can be suitable for potential use in biomedical applications.

According to our experimental results, the synthesized polyacrylamide grafted gelatin /clinoptiolite nanocomposite in situ hydrogel suggests the potential use of a future local anesthetics drug-releasing systems used as dental patches in the field of dental treatment.

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