JOTCSA Journal of the Turkish Chemical Society Section: A Chemistry

TURKISH CHEMICAL SOCIETY

# Characterization and Lidocaine Release Behavior of Chitosan/ Sodium Alginate/ Clinoptiolite Nanocomposite Hydrogel

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**Abstract**: In this study, the novel nanocomposites were prepared from the natural biopolymers, chitosan (CS), sodium alginate (SA) and clinoptiolite (CL) particles, and also having glutaraldehyde as a crosslinker by cryogelation technique. CS biopolymer was produced from crayfish *Astacus leptodactylus* Eschscholtz, 1823. Characterization of the prepared CS, CS-co-SA (CS/SA) and drug loaded CS/SA/ CL nanocomposite were performed by Fourier Transform Infrared Spectroscopy (FTIR) and Scanning Electron Microscopy (SEM) analyses. The anesthetic drug release behavior of the prepared nanocomposite was investigated for the model drug lidocaine (LD) using UV-Vis spectrophotometry and High Performance Liquid Chromatography (HPLC) techniques. The effect of different LD and CL content on the drug release behavior of the prepared nanocomposite were studied. LD release data was fitted to various kinetic models to study the drug release behavior. The LD release from all the prepared nanocomposite hydrogels fitted zero-order, first-order, Higuchi, and Korsmeyer-Peppas models. The swelling and drug release properties of the new CS-based nanocomposite hydrogels were improved with the inclusion of SA and CL in the gel structure.

**Keywords:** Chitosan, Clinoptiolite, Drug Release, Lidocaine, Sodium alginate.

**Submitted:** February 20, 2024. **Accepted:** August 28, 2024.

**Cite this:** Sözkes S, Taşdelen B, Erdoğan S, Gülenç NG, Koruyucu A. Characterization and Lidocaine Release Behavior of Chitosan/ Sodium Alginate/ Clinoptiolite Nanocomposite Hydrogel. JOTCSA. 2024;11(4):1483–94.

**DOI:** https://doi.org/10.18596/jotcsa.1440521.

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## 1. INTRODUCTION

In recent years, interest in controlled drug release systems in which polymers are used as a means of controlling drug delivery has increased greatly all over the world (1-5). This technology enables the drug to remove the harmful toxic side effects that will be caused by the systemic route by giving the drug in large doses continuously and in small amounts with controlled drug release systems instead of giving many drugs in the conventional way. Controlled drug release technology, which is developing rapidly day by day, offers many advantages such as transporting the drug to the desired target area only, keeping it in the desired time and therapeutic value, and preventing the breakdown of drugs with a short in vivo half-life. Some limitations on the usage of hydrogels in terms of providing homogeneity and stability have led researchers to search for new materials, namely polymeric nanocomposite hydrogels (6,7). 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 drug release properties, and being economical (8,9). In this study, a natural polysaccharide such as chitosan (CS) was used to synthesize the hydrogel. CS is a bio-polysaccharide of interest in the pharmaceutical industry as a polymeric drugs carrier thanks to its non-toxicity, low allergenicity,

biocompatibility, biodegradability, bioactivity, and mucoadhesiveness (2,4-9). Chitosan exhibits a remarkable water retention ability due to its hydrophilic nature, which renders it a superb choice for drug release applications (4-10). It also forms micelles, forming a hydrophobic center for hydrophobic drugs (2,4). Recent research has brought focus to the CS nanoparticles in the development of a drug delivery system aimed at enhancing the therapeutic effectiveness of anesthetic agents while minimizing the required dosage (9). Sodium alginate (SA) is one of the most promising natural polymers and has also excellent properties like its non-toxicity, biodegradability, good biocompatibility, hydrophilicity properties and low price (3,4).

Since zeolite materials are abundant in nature and are economical, the use of them in gel formulation to improve material properties is increasing today (9-11). The reasons for the interest in zeolite are the swelling capacity of zeolites in water, their effect on stable gel structure, adsorption capacity, and large ion exchange capacity. 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. In the field of dentistry of this material, there are studies in the fields of prosthesis, canal filling material, periodontology and oral surgery (9-12).

The aim of the study is to develop a CA/SA/CL nanocomposite containing lidocaine (LD) as a model drug. Although there are many examples in the literature where SA and CS are used as drug carrier systems, the fact that CL and LD used in this study is not included in the literature and that chitosan was obtained by isolating it from a freshwater crayfish species adds some novelty to the study.

## 2. EXPERIMENTAL SECTION

### 2.1. Materials

Chitosan, derived from the crayfish species *Astacus leptodactylus* Eschscholtz, 1823 was obtained from specimens captured by local fishermen in July 2020 at Kocahıdır Dam Lake located in Edirne, Turkey. Glutaraldehyde (Pcode: 1003100323, Sigma-Aldrich, İstanbul, Turkey), phosphate-buffered saline (Pcode: 1003090549, Sigma-Aldrich, İstanbul, Turkey), alginic acid sodium salt (Pcode:180947, Sigma-Aldrich, İstanbul, Turkey) and lidocaine hydrochloride monohydrate (Pcode: L5647, Sigma-Aldrich Company, İstanbul, Turkey) clinoptiolite (Etibank Company, İstanbul, Turkey) are all chemicals and reagents were of analytical grade and used without further purification. Drug release was calculated using UV-VIS spectrophotometer (Shimadzu UV-VIS 2401, Shimadzu, İstanbul, Turkey) and High Performance Liquid Chromatography (Shimadzu HPLC Prominence Modular LC20A, Shimadzu, İstanbul, Turkey). SEM (FEI-QUANTA FEG 250 SEM, Madrid, Spain) and FTIR (Bruker FTIR VERTEX 70 ATR, Bruker, Switzerland) instruments were used to characterize the prepared hydrogels.

### 2.2. Preparation of chitosan

Crayfish shells, previously washed and dried, were crushed in a mortar. In order to obtain chitin, approximately 40 g of ground crayfish shell, was first demineralized by refluxing with 450 mL of 2.2 M HCl at 80 °C, and 800 rpm for 6.5 hours. After demineralization, it was filtered through a filter paper and washed with distilled water. Then, the filtrate was treated with 450 mL of 2.2 M NaOH for 23 hours at 80 °C for deproteinization. Then it was washed again with distilled water until the pH was neutral and filtered. The resulting chitin was dried in an oven at 45 °C for a few days.In order to produce chitosan, 13.3 g of dry chitin was deacetylated with 199.5 mL of 70% NaOH solution at 150 °C for 4 hours. Then the obtained chitosan was washed with pure water until the pH was neutral, filtered, and dried in the oven at 45 °C.

### 2.3. Preparation of hydrogels

CS, CS/SA, CS/SA/CL, and drug loaded CS/SA/CL composite hydrogels were prepared from chitosan and sodium alginate (SA) using glutaraldehyde as a crosslinker by hydrogelation technique (5). Initially, 0.1 g of crayfish CS was dissolved in a 1% acetic acid solution consisting of 10 mL. This dissolution process took place through stirring on a magnetic stirrer set at 25 °C and 500 rpm for a duration of 10 minutes. Then, a 2% (wt/v) aqueous solution of SA was added to 10 mL of CS solution. Different amounts of CL were added into beakers containing CS/SA solution. Different amounts of a model drug (LD) were added to CS/SA/CL solutions and stirred for one hour. A crosslinker, consisting of a 0.4% glutaraldehyde solution measuring 2.5 mL, was introduced into the resulting solution. The mixture was then agitated for a duration of 10 minutes. Subsequently, the thick gel blend was introduced into compact glass tubes measuring 5 mm in inner diameter and 10 cm in length. These tubes were then placed in a deep freezer set at -20 °C for a duration of 48 hours. Following this, the resultant hydrogels were acquired as cylindrical rods by fracturing the glass tube, and subsequently defrosted in distilled water (5). Since LD was loaded in polymer/CL dispersions, all the amount of drug was entrapped into the hydrogel with maximum drug loading efficiency. The preparation of the hydrogels is shown in Figure 1.

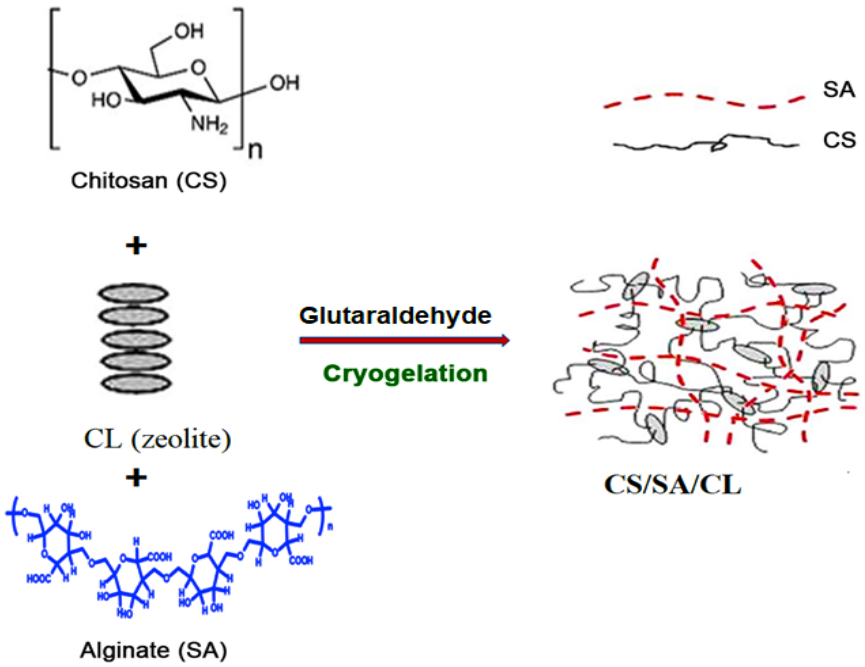


**Figure 1:** The preparation of CS/SA/CL hydrogels.

### 2.4. Drug release

The drug was loaded on the CS/SA/CL gels during gel synthesis. The gel containing the drug was immersed in a phosphate buffer (PBS) solution at a temperature of 37 °C and pH 7.4 to facilitate drug release, and their release behavior was examined using a UV-Vis spectrophotometer at a wavelength of 262 nm depending on time. After selected intervals, 3 mL of the released drug solution was drawn from the solution to conduct spectroscopic measurements at a wavelength of 262 nm using a UV-VIS spectrophotometer and placed again into the same vial so that the liquid volume was kept constant. The amounts of the drug released were calculated using a calibration curve (Figure S1).

How much drug the gels released at equilibrium was calculated using HPLC. HPLC device was worked in the isocratic mobile phase. The mobile phase used 80% ammonium acetate (0.2 mol/L), 20% acetonitrile, and 0.2% (w/v) trifluoroacetic acid. 5 µm C18 (150 × 4.6 mm) column (Kinetex C18 HPLC column, Germany) was used, and the UV-Vis detection wavelength was 262 nm. The injection volume was 20 µL and the flow rate was 1.5 mL/min. In HPLC analysis, as can be seen in Figure S2, the characteristic peak of retention (retention time (RT) LD) appears at 1.819 minutes. Based on the areas in the chromatograms given by standard LD solutions prepared at different concentrations in 1.819 minutes, an HPLC calibration line was created (Figure S2). The amount of time to reach equilibrium was determined as 1 week. The release amount of the synthesized gels at the time of equilibrium was calculated as a result of HPLC analysis.

### 2.5. Theory and calculation for hydrogels

Equations (1) and (2) were used to calculate mass swelling and equilibrium mass swelling (%):

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

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

where $m_0$ is mass of the dry gel, mt and $m_\infty$ are mass of the swollen gel at time t and at equilibrium, respectively (13-15).

Equations 3-5 are applied to analyze the drug release kinetics of the various hydrogels that were assessed using zero-order, first-order, Higuchi, and Korsmeyer-Peppas models.

For zero-order kinetics (16):

$$M_t/M_\infty = K_0\, t \quad (3)$$

where $K_0$ is the zero-order release constant.

For first-order kinetics (17):

$$\ln(1 - M_t/M_\infty) = -K_1 t \quad (4)$$

where $K_1$ is the zero-order release constant.

For Higuchi model (18):

$$F = K_2\, t^{1/2} \quad (5)$$

where $K_2$ is the Higuchi constant.

For Korsmeyer-Peppas model (19)

$$F = \frac{M_t}{M_\infty} = kt^n \quad (6)$$

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

## 3. RESULTS AND DISCUSSION

### 3.1. FTIR and SEM analysis

FT-IR spectra of CS, CS/SA, CL, Lidocaine, and drug loaded CS/SA/CL are shown in Figure 2. The characteristic absorption peaks of CS are 3281 $cm^{-1}$ (–OH stretching band), 2919 $cm^{-1}$ (aliphatic $–CH_2$ groups) and 2897 $cm^{-1}$ (aliphatic $–CH_3$ groups), 1643 $cm^{-1}$ (amide I peak, N–H bending), 1377 $cm^{-1}$ (C-O-C) and 1027 $cm^{-1}$ (C-O stretching) (20,21). The characteristic absorption peaks of SA were shown at 1550 and 1407 $cm^{-1}$ (COO- carboxylic groups) (22). 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) (23). 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) (1,3).

In the FT-IR spectrum of CS/SA/CL hydrogel seen in Figure 2, chitosan's 2821 $cm^{-1}$ (aliphatic $–CH_3$ groups) and 1026 $cm^{-1}$ (C-O stretching) are seen. The characteristic peaks of SA in the FT-IR spectrum of CS/SA/CL are observed at 1550 and 1410 $cm^{-1}$ (COO-carboxyl groups), 2923 $cm^{-1}$ (C-H stretching) and 807 $cm^{-1}$ (Na-O). Characteristic peaks of CL in the FT-IR spectrum of CS/SA/CL are seen at 1627,62 $cm^{-1}$ (the presence of water in the natural zeolite) and 791 $cm^{-1}$ ((T−O−T) symmetrical stretching vibrations, T = Al or Si) The characteristics peaks of LD are illustrated at 1471 $cm^{-1}$ (hydrochloride), 1284 $cm^{-1}$ (tertiary amine), 1152, 714 and 597 $cm^{-1}$ (aromatic ring) in the FT-IR spectrum of CS/SA/CL hydrogel.

Figure 3 shows SEM micrographs of CS, CS/SA, CS/CL, CS/SA/CL and drug loaded CS/CL and CS/SA/CL composite hydrogels. As can be seen in Figure 3, pure CS and CS/SA have a porous structure and a smooth surface morphology. In contrast, it is seen that when zeolite CL particles are added in CS/SA gel formulation, the structure of the hydrogel composites becomes inhomogeneous. This was expected that CS was intercalated in CL because of the strong interaction between the CS/SA matrix and silicate layers (11,20). Finally, when drug LD particles are added to the structure, they filled the porous structure of the hydrogel composites and coated them (Figure 3e and 3f).

### 3.2. Swelling properties of the hydrogels

The swelling properties of the prepared hydrogels in water are shown in Figure 4. As can be seen in Figure 4, the mass of the synthesized gels in distilled water increased with time. The value of Seq% of CS is 1003 but Seq% of CS/SA is 1545 due to the incorporation of SA (ionizable groups) groups into CS chains. SA contains many ionic units (–COOH). The amount of SA included in the CS gel leads to a noticeable increase in swelling since their addition to the reaction medium increases the hydrophilicity of the prepared hydrogel because of their high hydrophilic character (23). So, the CS/SA gel structure has many hydrophilic functional groups including -OH, -COOH, and NH2 groups (4,20,21).

Mass swelling percentages of the synthesized CS/SA/CL and CS/CL hydrogels are less than those without zeolite content (pure CS, CS/SA). This indicates that the CL particles fill the pores and reducing the volume required for swelling in the composite hydrogel (24). When the SEM analyses seen in Figures 5 are examined, it is seen that the CL particles fill the porous structure and empty spaces of the chitosan polymer, and swelling supports the SEM results (9).

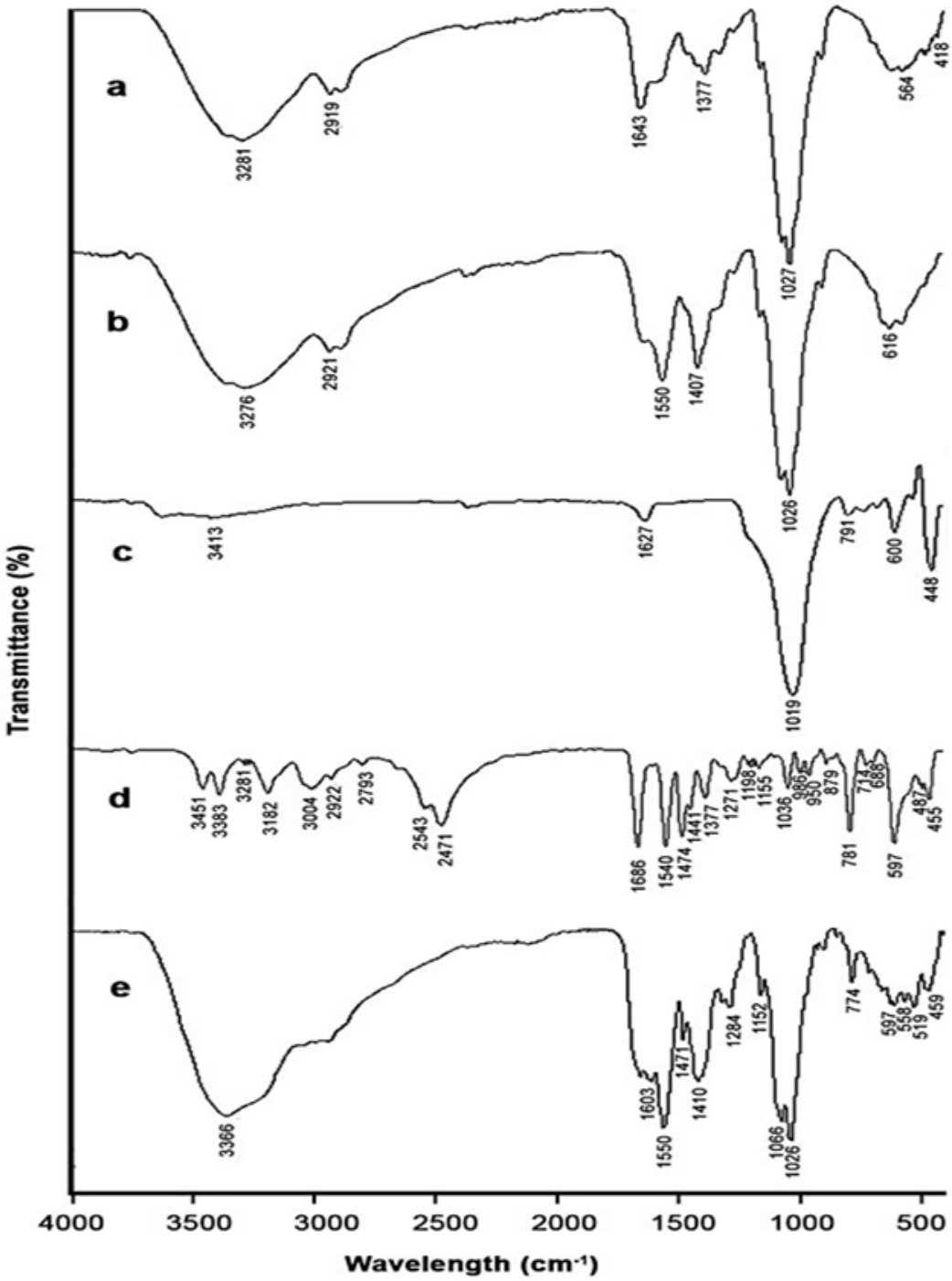


**Figure 2:** Fourier transform infrared spectra of (a) CS, (b) CS/SA, (c)CL, (d) LD drug (e)drug loaded CS/SA/CL.

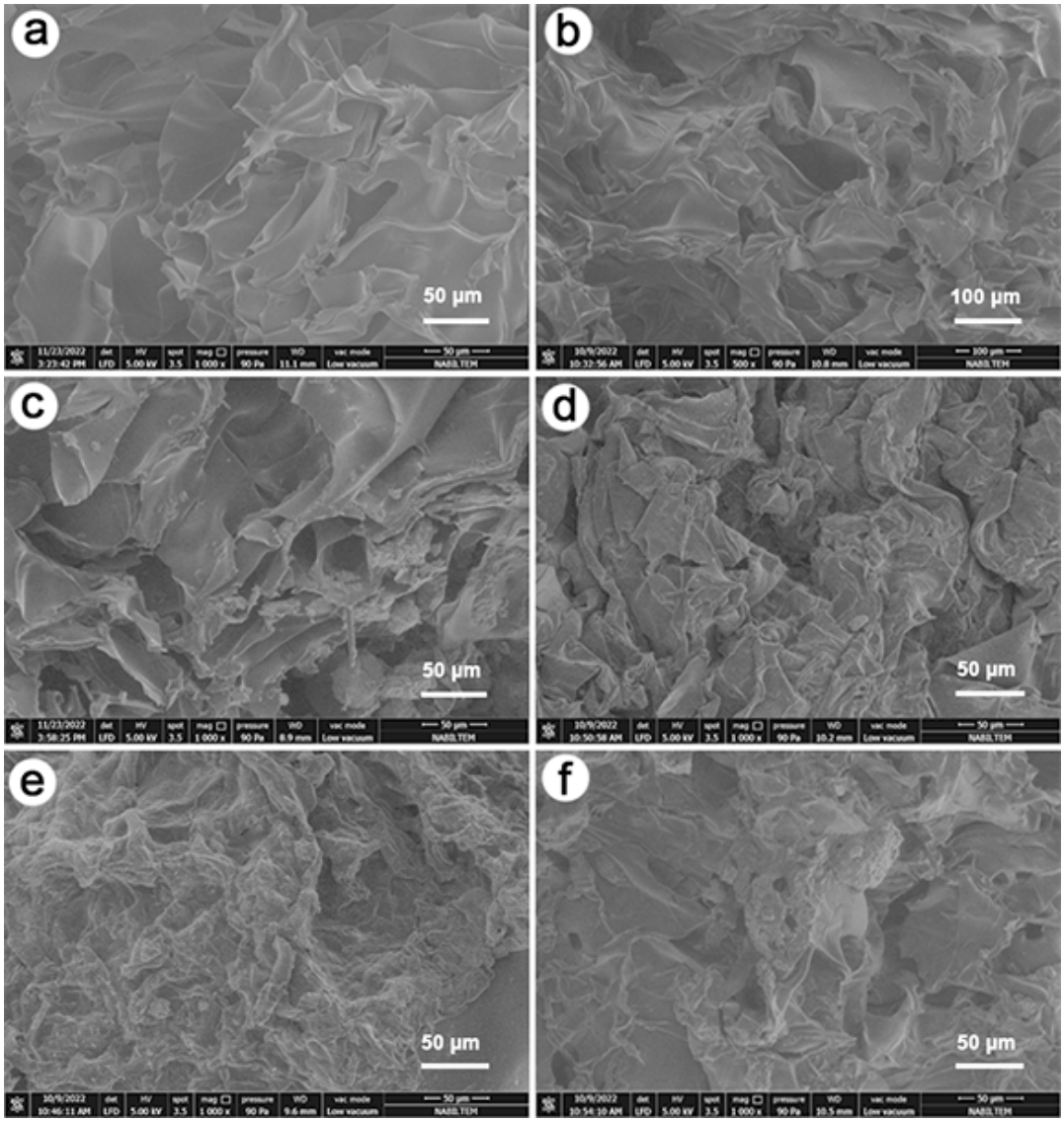


**Figure 3:** The SEM images of the hydrogels: a) CS, b)CS/SA, c) CS/SA/CL, d)CS/CL, e)drug loaded CS/SA/CL, f)drug loaded CS/CL.

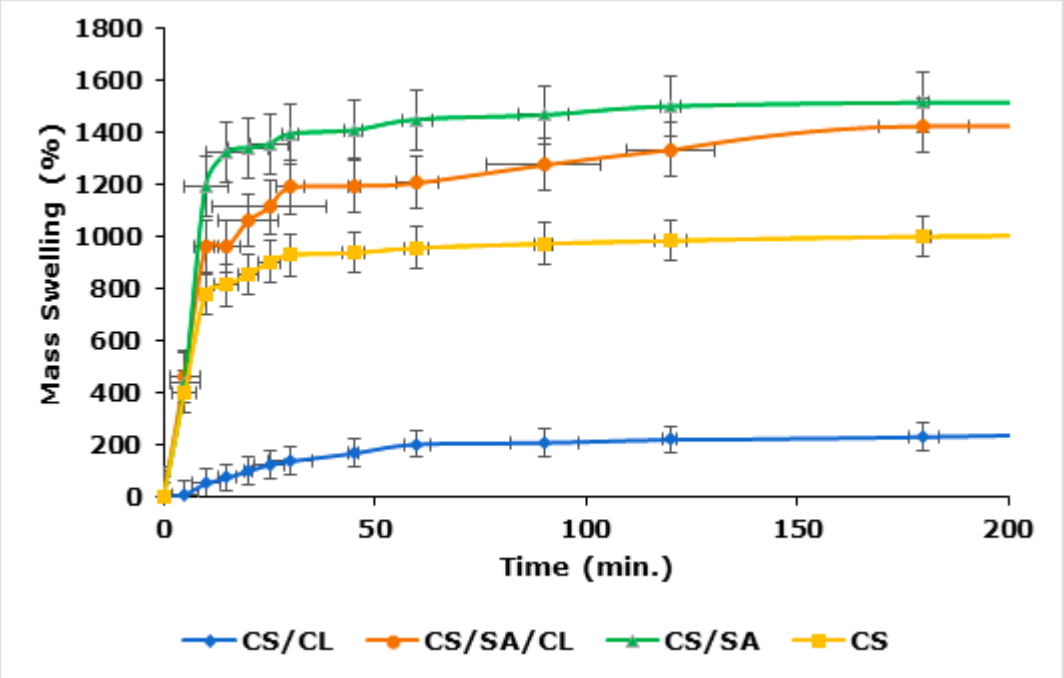


**Figure 4:** The swelling properties of CS, CS/SA, CS/CL, CS/SA/CL.

### 3.3. Effect of CL on drug release amount

As can be seen in Figures 5a and 5b, the time-dependent drug release amounts and release percentages of the CL-free chitosan (CS) hydrogels are higher than that of the CL-containing hydrogels. As seen in the SEM analysis, the structure becomes denser with the increase of the CL content in the structure. Thus, the CL layers act as a barrier and slow the release of drug molecules (9, 22). The absence of burst in drug release from CS/SA/CL samples may be due to surface characteristics of the nanocomposite hydrogels, intrinsic dissolution rate of drug, heterogeneity of matrices (26).

It is seen from Table 1 that an increase in the amount of drug loading leads to an increase in the cationic LD drug adsorption capacity of CS/SA/CL composite hydrogels. At pH 7.4, CL and sodium alginate have negative charge potential on the composite surface and this leads to an increase in the anionic character of CS/SA/CL hydrogel. These gels have many anionic carboxyl groups which can increase the interactions between cationic groups of cationic LD and carboxyl groups of gel (24,25). 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 (25,27).

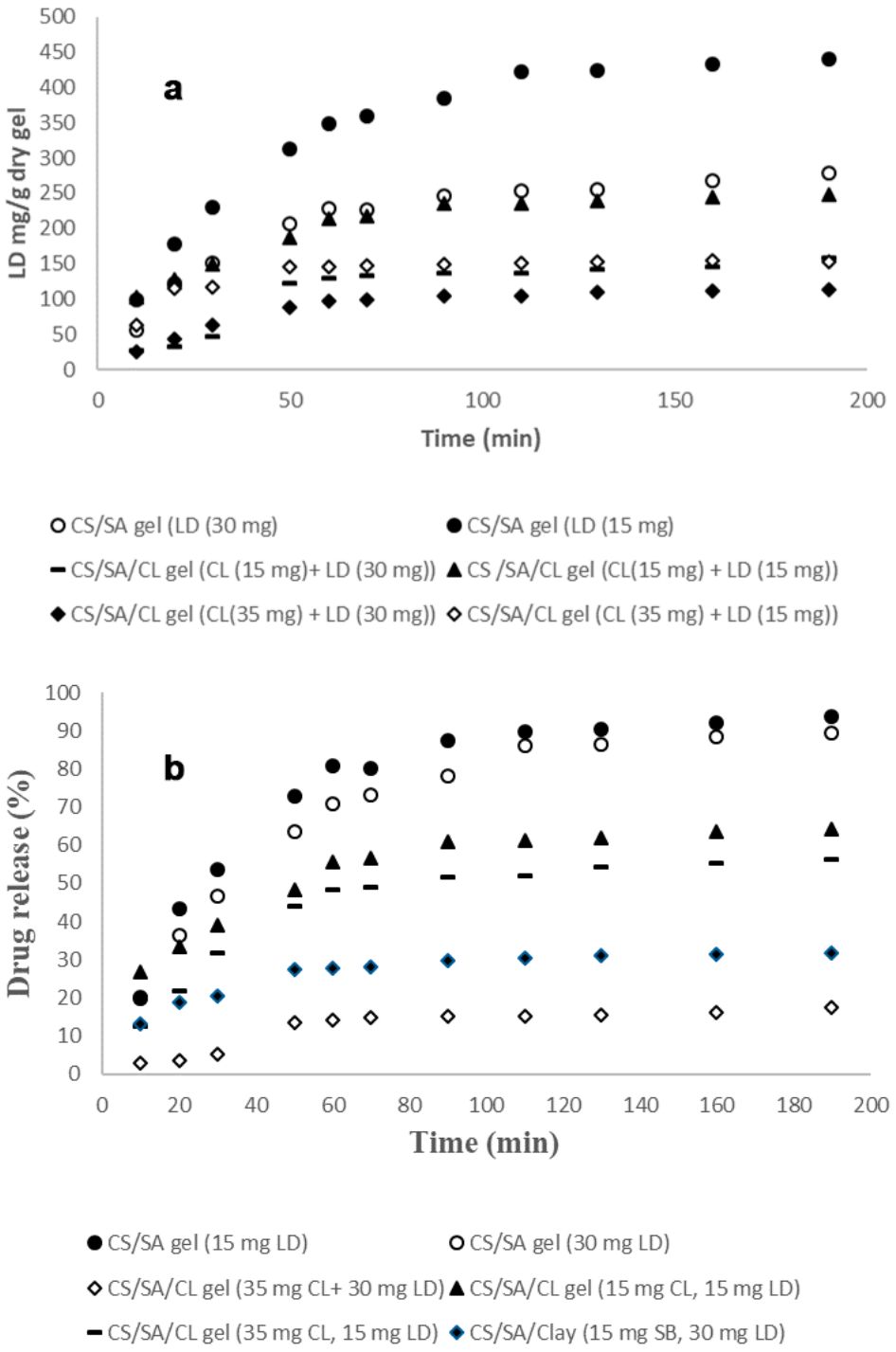


**Figure 5:** Drug release properties of CS, CS/SA, CS/CL, CS/SA/CL hydrogels.

**Table 1:** Equilibrium drug uptake capacity and equilibrium drug release (%).

| LD loaded hydrogels | Equilibrium LD uptake (mg LD/g gel) and eq. LD release | (%) |
|---|---|---|
| CS/SA | 1500291.50 mg/g (LD:15 mg) | 98.97% |
| | 490.30 mg/g (LD:30 mg) | 89.50% |
| CS/SA/CL | 141.25 mg/g (LD:15 mg, CL:15 mg) | 70.30% |
| | 166.63 mg/g (LD:15 mg, CL:35 mg) | 61.70% |
| | 151.22 (LD:30 mg, CL:35 mg) | 44.10% |

### 3.4. Drug release kinetics

In Figure 6, LD release kinetics of all the prepared hydrogels were used by zero-order, first-order, Higuchi, and Korsmeyer-Peppas models. The best-fitted model with the release data was evaluated by the values of the regression coefficient. All the model constants are presented in Table 2 together with the r values. It is evident that all the kinetic models fitted

well to the release data ($r^2$>0.99). The n<0.5 value indicates that the release mechanism is diffusion controlled (27,28). For samples CS/SA and CS/SA/CL, the value of nis between 0.5–1, indicating that the LD released follows a non-Fickian diffusion mechanism, and the LD released by diffusion and relaxation of the polymer chains occurs simultaneously (29).

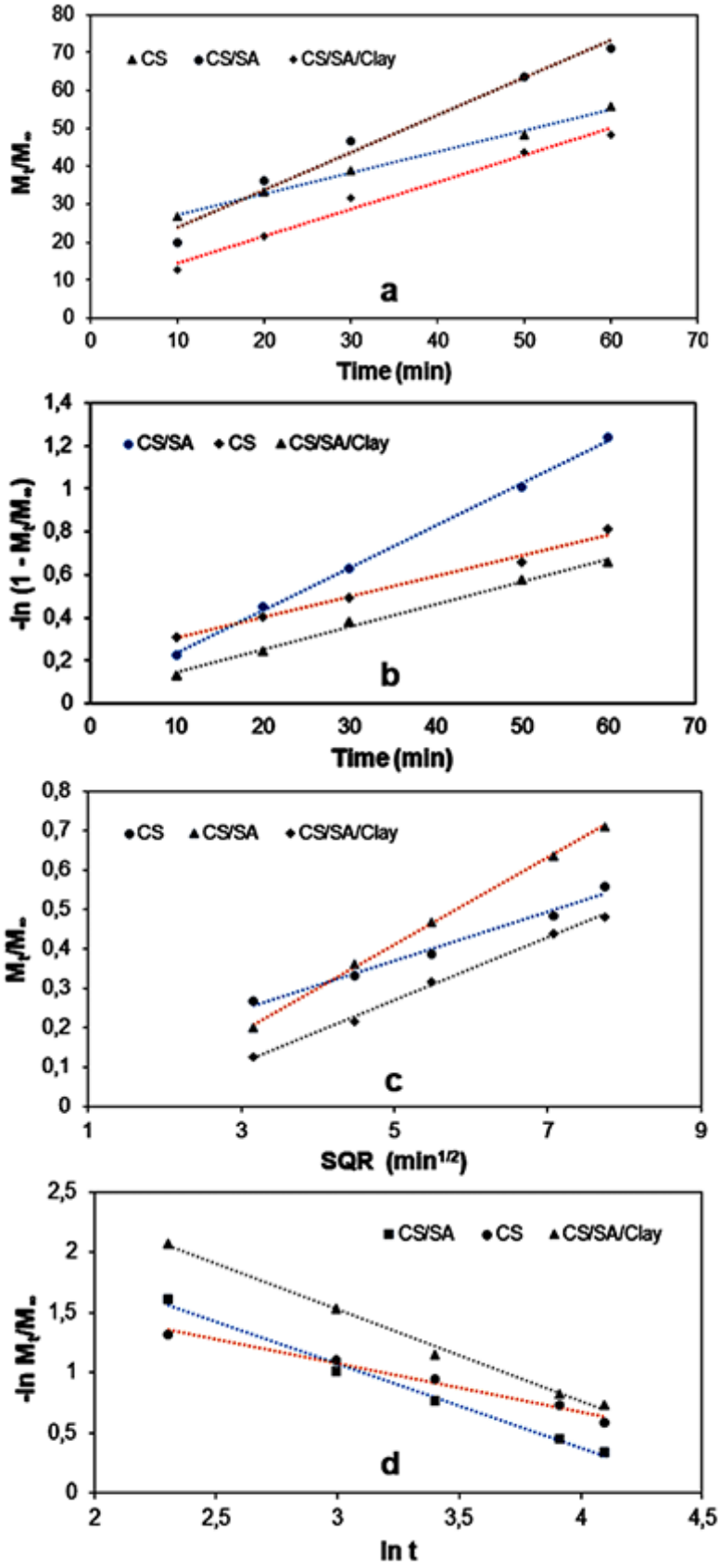


**Figure 6:** LD release kinetics of all the prepared hydrogels were used by (a) zero-order, (b)first-order, (c)Higuchi and (d) Korsmeyer-Peppas models.

**Table 2:** LD release kinetics of all the prepared nanocomposite hydrogels were used by (a) zero-order, (b) first-order, (c) Higuchi and (d) Korsmeyer-Peppas models.

| Kinetic Models | CS | CS/SA | CS/SA/CL |
|---|---|---|---|
| **Zero order Kinetics** | | | |
| $K_o$ ($min^{-1}$) | 0.56 | 0.98 | 0.71 |
| $R^2$ | 0.9983 | 0.9789 | 0.9855 |
| **First-order Kinetics** | | | |
| $K_1$ ($min^{-1}$) | 0.0097 | 0.0199 | 0.0106 |
| $R^2$ | 0.9893 | 0.9988 | 0.9944 |
| **Higuchi Model** | | | |
| $K_2$ ($min^{-1}$) | 0.062 | 0.110 | 0.0795 |
| $R^2$ | 0.9855 | 0.9989 | 0.9970 |
| **Korsmeyer- Peppas model** | | | |
| N | 0.40 | 0.76 | 0.69 |
| K | 0.10 | 0.04 | 0.02 |
| $R^2$ | 0.9833 | 0.9918 | 0.9947 |

## 4. CONCLUSION

In this work, a new type of drug loaded CS/SA/CL nanocomposite hydrogels was prepared by cryogelation technique from the natural biopolymers, chitosan and sodium alginate using glutaraldehyde as a crosslinker. FTIR spectroscopy and SEM analysis confirmed the successful preparation of the nanocomposite hydrogels. The improvements in swelling, diffusion, and drug adsorption and release properties of the new CS composite hydrogels with the addition of sodium alginate and clinoptiolite in the gel structure were achieved. Thus, the experimental results suggest that the prepared nanocomposite hydrogels can be suitable for potential use in biomedical applications.

## 5. CONFLICT OF INTEREST

Authors declare no conflict of interest.

## 6. ACKNOWLEDGMENTS

The authors would thank the Scientific Research Office of Tekirdağ Namık Kemal University (NKUBAP.06.GA.21.330) for funding this work.

## 7. REFERENCES

1. Kevadiya BD, Joshi GV, Mody HM, Bajaj HC. Biopolymer–cl hydrogel composites as drug carrier: host–guest intercalation and in vitro release study of lidocaine hydrochloride. Applied Clay Science, 2011; 52: 364-367. Available from: <DOI>.
2. Fonseca JM, Medeiros SF, Alves GM, Santos DM, Campana-Filho SP, Santos AM. Chitosan microparticles embedded with multi-responsive poly (N-vinylcaprolactam-co-itaconic acid-co-ethylene-glycol dimethacrylate)-based hydrogel nanoparticles as a new carrier for delivery of hydrophobic drugs. Colloids Surfaces B: Biointerfaces, 2019; 175: 73-83. Available from: <DOI>.
3. Wu M, Lin M, Li P, Huang X, Tian K, Li C. Local anesthehtic effects of lidocaine loaded carboxymethyl chitosan cross-linked with sodium alginate hydrogels for drug delivery system, cell adhesion, and pain management. Journal of Drug Delivery and Science, 2023; 79: 104007. Available from: <DOI>.
4. Phan VHG, Mathiyalagan R, Nguyen MT, Tran TT, Murugesan M, Ho TN, Huong H, Li Y, Thambi T. Ionically cross-linked alginate-chitosan core-shell hydrogel beads for oral delivery of insulin. International Journal of Biological Macromolecules, 2022; 222: 262-272. Available from: <DOI>.
5. Kutlusoy T, Oktay B, Apohan NK, Süleymanoğlu M, Kuruca SE. Chitosan-co-hyaluronic acid porous hydrogels and their application in tissue engineering. International Journal of Biological Macromolecules, 2017; 103: 366-378. Available from: <DOI>.
6. Zhao F, Yao D, Guo R, Deng L, Dong A, Zhang J. Composites for polymer hydrogels and nanoparticulate systems for biomedical and pharmaceutical applications. Nanomaterials (Basel), 2015; 5: 2054-2130. Available from: <DOI>.
7. Zhang J, Lin X, Liu J, Zhao J, Dong H, Deng L, Liu J, Dong A. Sequential thermo-induced self-gelation and acid-triggered self-release process of drug-conjugated nanoparticles: A strategy for sustained and controlled drug delivery to tumor. Journal of Materials Chemistry B, 2013; 1: 4667–4677. Available from:<DOI>
8. Serati-Nouri H, Jafari A, Roshangar L, Dadashpour M, Pilehvar-Soltanahmadi Y, Vlierberghe SV, Sarghami N, Biomedical applications of zeolite-based materials: a review, Materials Science and Engineering: C Materials for Biological Applications, 116, 111225, (2020). Available from: <DOI>.
9. Moradi S, Barati A, Tonelli AE, Hamedi H. Effect of clinoptilolite on structure and drug release behavior of chitosan/thyme oil γ-Cyclodextrin inclusion compound hydrogels. Journal of Applied Polymer Science, 2021; 138: e49822. Available from: <DOI>.
10. Dragan ES, Dinu MV. Advances in porous chitosan-based composite hydrogels: Synthesis and applications. Reactive and Functional Monomers, 2020; 146: 104372. Available from: <DOI>.
11. Tondar M, Parsa MJ, Yousefpour Y, Sharifi AM. Shetaboushehri SV. Feasibility of clinoptilolite application as a microporous carrier for pH-controlled

oral delivery of aspirin. Acta Chimica Slovenica, 2014; 61: 688-693. Available from: <DOI>.

12. Barbosa GP, Debone HS, Severino P, Souto EB, Silva CF. Design and characterization of chitosan/zeolite composite films — Effect of zeolite type and zeolite dose on the film properties. Materials Science and Engineering C, 2016; 60: 246-254. Available from: <DOI>.
13. Taşdelen B, Kayaman-Apohan N, Güven O, Baysal BM. Swelling and diffusion studies of poly (N-isopropylacrylamide/itaconic acid) copolymeric hydrogels in water and aqueous solutions of drugs. Journal of Applied Polymer Science, 2004; 91: 911-915. Available from: <DOI>.
14. Lee SB, Seo SM, Lim YM, Cho SK, Lee YM. Preparation of alginate/poly (N-isopropylacrylamide) hydrogels using gamma-ray irradiation grafting. Macromolecular Research, 2004; 12: 269-275. Available from: <DOI>.
15. Taşdelen B, Kayaman-Apohan N, Güven O, Baysal BM. Preparation of poly (N-isopropylacrylamide/itaconic acid) copolymeric hydrogels and their drug release behavior. International Journal of Pharmaceutics, 2004; 278: 343-351. Available from: <DOI>.
16. Akkaya R, Ulusoy U. Preparation and characterization of polyacrylamide/maleic acid - based hydrogels Composites. Hacettepe Journal of Biology and Chemistry, 2011; 39, 359-370. Available from: <DOI>.
17. Francis NL, Hunger PM, Donius AE, Riblett BW, Zavaliangos A, Wegst UG, Wheatley MA. An ice-templated, linearly aligned chitosan-alginate scaffold for neural tissue engineering. Journal of Biomedical Materials Research Part A, 2013; 101: 3493-3503. Available from: <DOI>.
18. Higuchi T. Mechanism of sustained-action medication. theoretical analysis of rate of release of solid drugs dispersed in solid matrices. Journal of Pharmaceutical Sciences, 1963; 52: 1145-1149. Available from: <DOI>.
19. Ullah K, Sohail M, Mannan A, Rashid H, Shah A. Murtaza G, Khan SA. Facile synthesis of chitosan based-(AMPS-co-AA) semi-IPNs as a potential drug carrier: enzymatic degradation, cyto-toxicity, and preliminary safety evaluation. Current Drug Delivery, 2019; 16: 242–253. Available from: <DOI>.
20. Taşdelen B, Çiftçi Dİ, Meriç Pagano S. Preparation and characterization of chitosan/AMPS/kaolinite composite hydrogels for adsorption of methylene blue. Polymer Bulletin, 2022; 79: 9643-9662. Available from: <DOI>.
21. Taşdelen B, Çifçi Dİ, Meriç Pagano S. Preparation and characterization of chitosan/hyaluronic acid/itaconic acid hydrogel composite to remove manganese in aqueous solution. Desalination and Water Treatment, 2021; 209: 204-211. Available from: <DOI>.
22. Taşdelen B. Synthesis, swelling, diffusion and cationic dye adsorption studies of semi-IPN sodium alginate/poly (HEMA-co-MA) hydrogels. ChemistrySelect, 2023; 8, e202300707. Available from: <DOI>.
23. Abukhadra MR, Adlii A, Khim JS, Ajarem JS, Allam AA. Insight into the Technical Qualification of the Sonocogreen CaO/ Clinoptilolite Nanocomposite (CaO(NP)/Clino) as an Advanced Delivery System for 5-Fluorouracil: Equilibrium and Cytotoxicity. ACS Omega, 2021; 6: 31982−31992. Available from: <DOI>.
24. Taşdelen B, Çiftçi Dİ, Meriç Pagano S. Preparation of N-isopropylacrylamide/itaconic acid/pumice highly swollen composite hydrogels to explore their removal capacity of methylene blue. Colloids and Surfaces A: Physicochemical and Engineering Aspects, 2017; 519: 245–253. Available from: <DOI>.
25. Thakur G, Singh A, Singh I. Chitosan-montmorillonite polymer composites: formulation and evaluation of sustained release tablets of aceclofenac. Scientia Pharmaceutica, 2016; 84: 603–618. Available from: <DOI>.
26. Basak SC, Kumar KS, Ramlingam M. Design and release characteristics of sustained release tablet containing metformin HCl. Revista Brasileira de Ciências Farmacêuticas, 2008; 44: 477-483. Available from: <DOI>.
27. Ful Y, Kao WJ. Drug release kinetics and transport mechanisms of nondegradable and degradable polymeric delivery systems. Expert Opinion on Drug Delivery, 2010; 7: 429-444. Available from: <DOI>
28. Ruocco CD, Acocella MR, Guerra G. Release of cationic drugs from charcoal. Materials, 2019; 12: 683-687. Available from: <DOI>.
29. García-Couce J, Vernhes M, Bada N, Agüero L, Valdés O, Alvarez-Barreto J, Fuentes G, Almirall A, Cruz L J. Synthesis and evaluation of AlgNa-g-Poly (QCL-co-HEMA) hydrogels as platform for chondrocyte proliferation and controlled release of betamethasone. International Journal of Molecular Sciences, 2021; 22: 5730. Available from: <DOI>.