Chemical Papers (2021) 75:5759–5772
https://doi.org/10.1007/s11696-021-01760-2

ORIGINAL PAPER

A garlic oil-based organo-hydrogel for use in pH-sensitive drug release

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Received: 18 February 2021 / Accepted: 25 June 2021 / Published online: 2 July 2021

Abstract

In this study, six different organo-hydrogels containing agar-glycerol (AG)-based garlic oil (GO) were synthesized using two different crosslinkers (*N,N*, methylenebisacrylamide (MBA), glutaraldehyde (GA)) to ensure the controlled release of ceftriaxone (Ce) and carboplatin (Cp). Synthesized organo-hydrogels were characterized by FT-IR. Afterward, swelling behaviors were investigated in DI, tap water, ethanol, acetone, ethanol/DI water (1:1), acetone/DI water (1:1) and gasoline environments and different pH. As a result of hemolysis, blood clotting and antioxidant analysis, organo-hydrogels have been shown to have blood compatibility and antioxidant properties. Ce and Cp release properties of the prepared organo-hydrogels were also determined. The highest Ce release rate was obtained to be 37.8% for p (AG-g-GO)^3 at pH 8.0 after 7 days. However, the highest Cp release rate was found to be 95.4% for p (AG-g-GO)^3 at pH 7.4 after 1 day.

Keywords Organo-hydrogel · Agar · Garlic oil · Ceftriaxone · Carboplatin

Introduction

Human beings have used aromatic oils naturally extracted from plants for centuries to support human health. It has also been shown in an academic study that the use of these oils in massages for the treatment of many diseases has an effect on psychological and physiological processes (Ali et al. 2015; Lee et al. 2017; Lizarraga-Valderrama 2021). Garlic is generally consumed in the form of products directly derived from garlic, such as dried garlic, garlic powder, garlic juice, garlic puree, and essential garlic oil. In addition, encapsulated garlic oil or juice, odorless garlic powder tablets, and matured garlic oil are other commercial preparations (Amagase 2006). Garlic and garlic oil contain a very high amount of sulfur compounds (74.9–91.6%) (Satyal et al. 2017). At the same time, it is present in many non-sulfur compounds. These are steroidal glycosides, lectins, essential oils, flavonoids, pectin, anthocyanins, prostaglandins, fructan, adenosine, vitamins B_2, E, B_1, A, B_6, C, biotin, selenium, nicotinic acid,, glycolipids, fatty acids, phospholipids (cysteine, glutamine minerals such as isoleucine and methionine), essential amino acids. These compounds are thought to have synergistic effects with sulfur compounds (27.9%, diallyldisulfide; 17.7%, allylmethyltrisulfide, 16.8% diallyltrisulfide 9.5%, diallylsulfide; 8.3%, allylmethyldisulfide; 3.7% allyl(E)1propenyldisulfide) (Satyal et al. 2017). It also strengthens the immune system, garlic oil in the treatment of cardiovascular diseases, regulates blood pressure, lowers blood sugar and cholesterol and is effective against fungal, bacterial, viral, and antitumor, parasitic infections. There are also drug, capsules and extracts made from garlic oil (Edris 2007; Ernst 2005; Kumar et al. 2016; Sahu et al. 2007).

Various active substance release systems and targeting systems have been developed to minimize the active substance breakdown and loss, prevent harmful side effects, increase bioavailability and affect rates. Some of these systems are liposomes, nano-associates, nanoparticles, active substance-polymer conjugates and polymer. In particular, between the active substance to be released and the support material, embedding, physical absorption, hydrogen bonding and electrostatic interactions play an active role. There has been an increasing interest in polymer (organogel, hydrogel, organo-hydrogel, particle), especially in recent years

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(Pooresmaeil et al. 2018). The polymeric structures that take up large quantities of water and organic liquids, without dissolving the polymer web, are called organo-hydrogels. Chemical polymeric organo-hydrogels are 3-D macromolecular structures that absorb organic solvents. Thanks to technological developments, new organo-hydrogels with the properties sought in controlled release systems have been obtained. The quality of organo-hydrogels synthesized by developing synthesis methods has increased. Recently, organo-hydrogels have been investigated in a wide range of fields comprising chemistry, agriculture, microbiology, biotechnology, drug delivery and pharmaceuticals (Alpaslan et al. 2016; Ersen Dudu et al. 2019; Osada et al. 2004; Pénzes et al. 2004; Vintiloiu et al. 2008; Yang et al. 2008).

Ceftriaxone is a cephalosporin group antibiotic, which is often preferred in the treatment of bacterial infections. Ce is frequently used in children due to its advantages such as long half-life, wide range of activity, high penetration into tissues and high reliability. Currently, although no effective therapy or vaccine has been produced for COVID-19, it has been reported in the literature that ceftriaxone antibiotics are used for treatment in patients with the COVID-19 virus (Arvidsson et al. 1982; Wang et al. 2020).

Carboplatin cis-Diammine (1,1-cyclobutanedicarboxylato) platinum (II) is a second-generation platinum compound. It is designed to stop the growth of cancer cells and kill them. It is effective on carboplatin DNA. The adenine and guanine are linked to the DNA from the N-7 position by a covalent ligament. As a result of the formation of DNA addition products, DNA synthesis and transcription are inhibited and the cell cannot divide. Binding to DNA and cytoplasmic proteins can result in cytotoxic effects. Broad-spectrum carboplatin is a frequently used chemotherapeutic agent for the treatment of childhood cancers. It is used in the treatment of osteosarcoma, hepatoblastoma, neuroblastoma, germ cell tumors, central nervous system tumors, head and neck cancers (Sharma et al. 2019; Wagstaff et al. 1989).

In fact, the main aim of this research was to synthesize organo-hydrogels with the redox polymerization technique in the novel form that had the properties of both organogels and hydrogels. Meanwhile, it was examined and developed the swelling behavior of these organo-hydrogels in different solvent environments, biocompatibility properties, and their effects on the release of the drug active substance. In organo-hydrogels synthesis, it will be synthesized by using two different cross (MBA or GA) ((AG-m-GO), (AG-g-GO)) linkers and 3 different amounts (0.1, 0.2, 0.3 mL) of GO. Thus, 6 different organo-hydrogels will be synthesized. This study presented a synthesis of organo-hydrogels, swelling behaviors in different solvents and in different pH solutions, blood compatibility and antioxidant properties. Characterization of the synthesized organo-hydrogels was made by Fourier transform infrared spectroscopy (FTIR). Another aim of this study is to investigate the drug release behavior of the synthesized organo-hydrogels by installing ceftriaxone, a known antibiotic, and anticancer drug/chemotherapeutic carboplatin.

Materials and methods

Reagents

Glycerol (Gly), agar (99%), *N,N*, methylenebisacrylamide (MBA, 99%), glutaraldehyde (GA, 25% v/v), ethanol, acetone, calcium chloride ($CaCl_2$), sodium hydroxide (NaOH) and hydrochloric acid (HCl) (36.5–38% v/v) were purchased from Sigma; ammonium persulfate (APS) (98%) was purchased from Merck. In terms of analytical grade, all reagents were of the highest cleanliness available, and they were used without additional purification. Garlic oil (GO), gasoline, ceftriaxone and carboplatin were procured from local suppliers. Distilled water (DI, 18.2 MΩ cm; Human I) was also employed from the beginning to the end of this study.

Experimental procedures

Agar-glycerol-based gels, hydrogels and organo-hydrogels synthesis

Agar-glycerol-based gel and hydrogels were synthesized via free radical polymerization in emulsion according to the preparation method given in Table 1 [6]. Gel and hydrogels were synthesized as described by Alpaslan et al. (2021). Gel and hydrogel compositions are given in Table 2. Free radical polymerization in emulsion media method was used to synthesis the Agar-Glycerol-based [6] organo-hydrogels given in Table 1. Briefly, firstly, 2 mL of agar solution and 0.04 mL of glycerol were added to the 20-mL flask and made homogeneous by vigorous mixing (at 2500 rpm). Secondly,

Table 1 Codes of different organo-hydrogels

Gel	Code
Agar-glycerol	AG
Hydrogel	Code
poly (agar-co-glycerol)/MBA	p(AG-m)
poly (agar-co-glycerol)/GA	p(AG-g)
Organo-hydrogel	Code
poly (agar-co-glycerol-co-garlic oil)/MBA-1	$p(AG\text{-}m\text{-}GO)^1$
poly (agar-co-glycerol-co-garlic oil)/MBA-2	$p(AG\text{-}m\text{-}GO)^2$
poly (agar-co-glycerol-co-garlic oil)/MBA-3	$p(AG\text{-}m\text{-}GO)^3$
poly (agar-co-glycerol-co-garlic oil)/GA-1	$p(AG\text{-}g\text{-}GO)^1$
poly (agar-co-glycerol-co-garlic oil)/GA-2	$p(AG\text{-}g\text{-}GO)^2$
poly (agar-co-glycerol-co-garlic oil)/GA-3	$p(AG\text{-}g\text{-}GO)^3$

Table 2 Compositions and codes of different organo-hydrogels

Agar	Glycerol	GO	Crosslinker	Code
2% 2 mL	0.04 mL	–	–	AG
2% 2 mL	0.04 mL	–	MBA	p(AG-m)
2% 2 mL	0.04 mL	–	GA	p(AG-g)
2% 2 mL	0.04 mL	0.1 mL	MBA	p(AG-m-GO)[1]
2% 2 mL	0.04 mL	0.2 mL	MBA	p(AG-m-GO)[2]
2% 2 mL	0.04 mL	0.3 mL	MBA	p(AG-m-GO)[3]
2% 2 mL	0.04 mL	0.1 mL	GA	p(AG-g-GO)[1]
2% 2 mL	0.04 mL	0.2 mL	GA	p(AG-g-GO)[2]
2% 2 mL	0.04 mL	0.3 mL	GA	p(AG-g-GO)[3]

of different amounts (0.1, 0.2 and 0.3 mL) garlic oil was added in the reactions mixture. The organo-hydrogel mixture was stirred at 800 rpm for 15 min until the formation of a clear homogeneous solution emulsion. Thirdly, MBA (0.1%) or glutaraldehyde reagent was added as a crosslinker and further homogenized. Organo-hydrogel compositions are given in Table 2. In the synthesis, strong hydrogen bonds were formed between the -OH groups on garlic oil and glycerol molecules and the -OH groups in the agar structure and at same time crosslinking agent was added to the reaction medium, resulting in crosslinking between garlic oil, agar and glycerol (Kim et al. 2010; Singh et al. 2015; Xia et al. 2011). Finally, the polymerization reaction was initiated by the addition of the initiator solution APS in 100 µL DI water. Reaction temperatures were maintained at 25 °C with a temperature-controlled hot plate. Then, the solution was transferred into a pipet with 6 mm diameter and was allowed to polymerize for 4 h. and cut into 6 mm long cylinders. These preparation steps are schematically given in Fig. 1. The gel, hydrogels and organo-hydrogels were kept in DI water, which was renewed every 2 h for 8 h to eliminate unreactive monomers. Finally, the synthesized gel, hydrogels, p(AG-m-GO) and p(AG-g-GO) organo-hydrogels were dried in the oven at 40 °C until a constant weight was achieved and stored at 4 °C for further uses.

Organo-hydrogel synthesis containing ceftriaxone and carboplatin

With in situ polymerization, paracetamol and carboplatin drugs were added directly to the organo-hydrogels during the synthesis of the organo-hydrogels (Alpaslan et al. 2021; Campbell et al. 2014; Olak et al. 2020). The synthesis of drug-loaded organo-hydrogels was the same as the synthesis procedure of the organo-hydrogels described above. In addition to only the reaction mixture mentioned above, 50 ppm 1 mL ceftriaxone and carboplatin drugs were added. These drugs are physically attached to the structure of organo-hydrogels. Thus, drug-loaded organo-hydrogels were synthesized.

Swelling analysis

Swelling assays were carried out with certain amounts of dried gel, hydrogels, organo-hydrogels placed in water, tap, ethanol, acetone, ethanol/DI water (1:1), acetone/DI water (1:1), gasoline and different pHs (2–12) for 24 h. Swelling tests were performed at room temperature of 25 °C (Alpaslan, 2019; Alpaslan et al. 2020a, b; Ersen Dudu et al. 2019).

Fourier transform infrared spectroscopy (FT-IR) analysis

An Attenuated Total Reflection (ATR) built-in Fourier Transform Infrared Spectroscopy (Thermo, model Nicolet iS10 FT-IR Spectrometer, USA) was used for the FT-IR analysis. The analysis was carried out to investigate the functional groups on the materials and possible interactions between all chemicals utilized to synthesize the gel, hydrogels and organo-hydrogels. The gel, hydrogels and organo-hydrogels were crushed to obtain powder and then placed on the ATR sample plate. The spectral range was investigated from 4000 to 650 cm^{-1} with a resolution of 4 cm^{-1}.

Blood clotting and hemolysis analysis

To evaluate the blood clotting (Alpaslan et al. 2021) and hemolysis analysis (Olak et al. 2020), methods which were explained in the literature were applied.

Antioxidant analysis

To evaluate the antioxidant activity, Folin-Ciocalteu (Alpaslan et al. 2020a, b; Singleton 1965) and ABTS (Alpaslan et al. 2018; Obert and Childs 1975) methods which were explained in the literature were applied.

Drug release studies

Synthesized drug-loaded gel, hydrogels and organo-hydrogels have been used as a controlled release system for Ce and Cp which are frequently used in the medical field. The gel, hydrogels and organo-hydrogels that loaded a certain amount (50 ppm) of Ce were used in 50 mL of 4 different pH (2.0, 5.5 7.4 and 8.0 pH) for Ce release. Cp release (Pasqua et al. 2006) was performed in a 50 mL 7.4 pH solution media (organo-hydrogel amount: 0.05 g, temperature: 37 °C, 750 rpm). Released Ce and Cp quantities were calculated on the calibration curves prepared at 244 nm and 210 nm wavelength in the UV-visible region spectrophotometer, respectively. Each measurement was

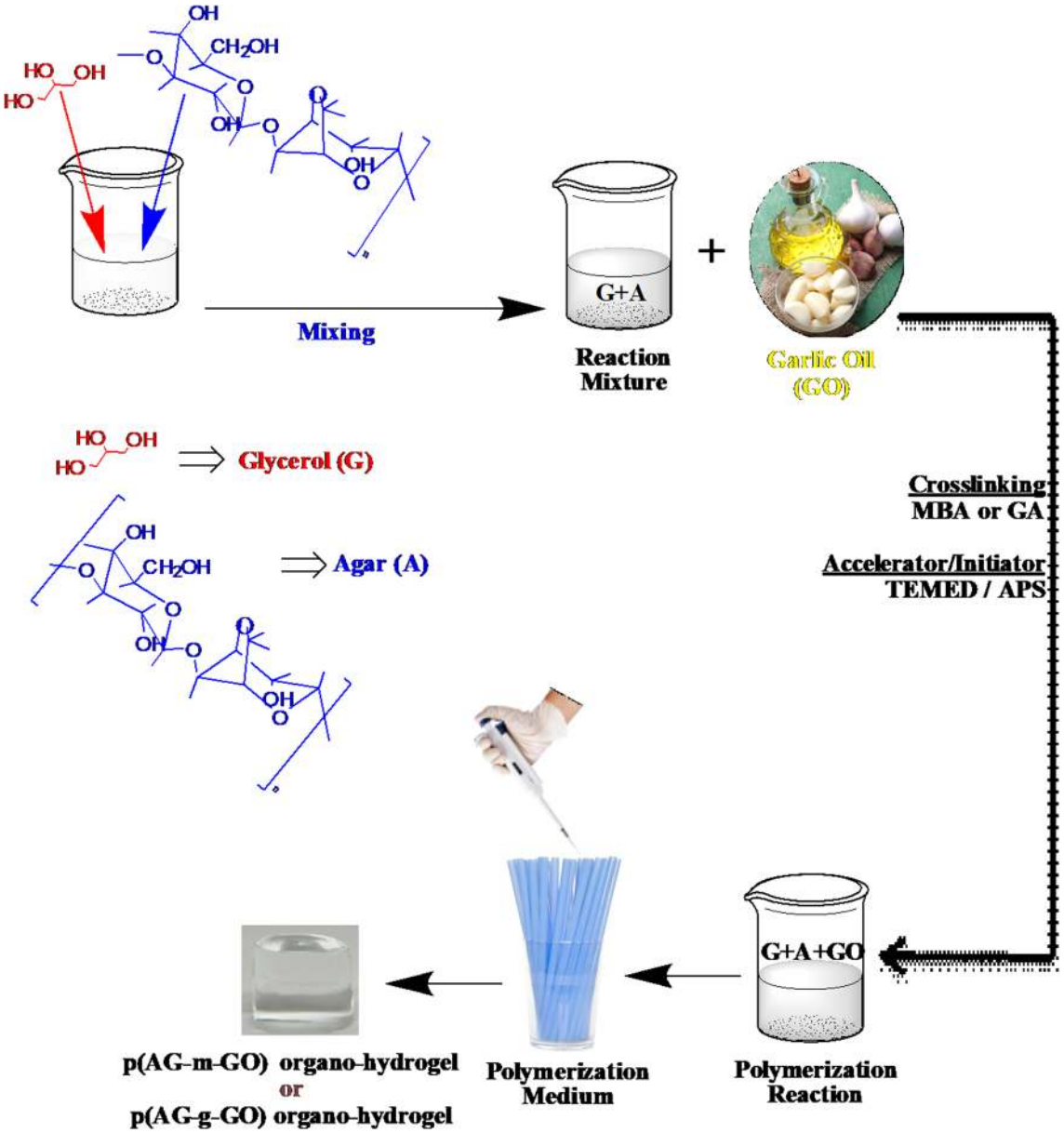

Fig. 1 Synthesis and schematic presentation of organo-hydrogels

performed with 3 replications in itself and averaged with standard deviation values. The most common models, which are Zero order (ZoM) (Eq. (3)) (Korsmeyer and Peppas 1984; Varelas et al. 1995), First order (FoM) (Eq. (4)) (Paulo Costa 2001; Korsmeyer and Peppas 1984; Varelas et al. 1995), Higuci (HM) (Eq. (5)) (Higuchi 1963) and Korsmeyer-Peppas (KPM) (the power law) (Eq. (6)) (Korsmeyer and Peppas 1984), were used to associate the release kinetics. Those equations are given in Table 3.

Results and discussion

FTIR analysis

Organo-hydrogels, AG, p(AG-m) and p(AG-g) were prepared by free radical polymerization in emulsion media and the FTIR spectra are shown in Fig. 2a–c and explain in the literature (Alpaslan et al. 2021; Olak et al. 2020).

Table 3 Mathematical models for drug release

Model	Mathematical equation	Release mechanism	Codes
Zero-order kinetic model	$C_r = C_0 - k_0.t$	Diffusion mechanism	ZoM
First-order kinetic model	$\ln C_r = \ln C_0 - k_1.t$	Fick's first law, diffusion mechanism	FoM
Higuchi model	$\frac{C_r}{C_\infty} = k_H.\sqrt{t}$	Diffusion medium based Mechanism in Fick's first law	HM
Korsmeyer–Peppas model	$\ln\frac{C_r}{C_\infty} = \ln k_{KP} + n.\ln t$	Semi-empirical model, diffusion-based mechanism	KPM

C_r is concentration of urea release in time t (mg/L); C_0 is the initial concentration of urea in the solution (most times, $C_0 = 0$) (mg/L); k_0 is the zero-order release constant expressed in units of concentration/time (mg/(L.min)); t is time (min); k_1 is the first-order release constant (1/min); C_∞ is concentration of fertilizer release in equilibrium (mg/L); k_H is Higuchi release rate constant ($1/\sqrt{\text{min}}$); k_{KP} is Korsmeyer–Peppas release rate constant; n is release exponent which is indicative of the transport mechanism ($M_t/M_\infty < 0.6$ should only be used

Garlic oil contained the band peak at 3600–3000 cm^{-1} belonging to the vibrations of the -OH groups, bands at 1742 cm^{-1} and 1660 cm^{-1} represented to C=O vibrations. The peak in 2922 cm^{-1} and 2853 cm^{-1} belonged to the $–CH_3$ and $–CH_2$ groups, and peak in 1453 cm^{-1} belonged to the C=H bands. The new bonds and structural diversity at organo-hydrogels demonstrated the existence of hydrogen-bond interaction. After the garlic oil got into the structure of the organo-hydrogel, the incoming bands from characteristic aromatic compounds, such as 2922 cm^{-1} (C–H), 1742–1645 cm^{-1}(C=O), 1395 cm^{-1}(O–H) and 1369 cm^{-1}(S=O)(Figueroa López et al. 2014; Visani et al. 2017), exhibited high density, and the peaks appear to be deepened or expanded. The change in these peaks showed that garlic oil joined the structure of the organo-hydrogel. After the addition of ceftriaxone drug to the p(AG-g-GO) structure, it was observed that the peak at approximately 2852 cm^{-1} became more pronounced and the peak at approximately 1637 cm^{-1} disappeared. When carboplatin drug was added to the p(AG-g-GO) structure, it was determined that the intensity of the peak corresponding to approximately 1637 cm^{-1} disappeared and the intensity of the other existing peaks increased. After the addition of ceftriaxone and carboplatin drugs to the p(AG-m-GO) structure, it was determined that a new peak was formed at approximately 1524 cm^{-1}, and the intensity of the existing peaks became deeper, respectively. When the FT-IR spectra of both drug-loaded organo-hydrogels and organo-hydrogels are examined, it can be thought that there is a positive synergistic interaction between the drug and the organo-hydrogel and the interaction contributes positively to the release kinetics.

In the synthesis of AG gel, the agar solution and glycerol were bonded to each other with weak hydrogen bonds without any crosslinker (Akkaya et al. 2016). The structure obtained by hydrogen-strong bridge bonds between the –NH and –OH groups on the agar molecule and the –OH groups on the glycerol was called gel. In the synthesis of p(AG-m) and p(AG-g) hydrogels, the structure obtained by adding crosslinking agent to the agar solution and glycerol medium was called hydrogel (Rossi et al. 2010; Wu et al. 2014). In the synthesis, strong hydrogen bonds were formed between the -OH groups on garlic oil and glycerol molecules and the -OH groups in the agar structure. At the same time, the crosslinking agent was added to the reaction medium and crosslinking was provided between garlic oil, agar and glycerol (Kim et al. 2010; Singh et al. 2015; Xia and Larock 2011). Thus, the structure including both hydrogen bonds and crosslinked was called organo-hydrogel. By increasing the amount of garlic oil added to the structure, both physical and chemical bonding was strengthened. The drug was added to the structure in the synthesis. These drugs were physically attached to the structure of organo-hydrogels. These gel, hydrogels and organo-hydrogels prepared were subjected to the following analyses.

Swelling properties of the organo-hydrogels

The swelling degree of a polymer gel is determined by the interaction between the functional groups in its structure and the solvent. Changes in the ionic intensity and pH of the medium affect the ionic intensity and swelling properties of organo-hydrogels sensitive to pH.

When the swelling values of gel, hydrogel and organo-hydrogels in different swelling environments were compared, it was observed that there was no important difference between water, tap water, acetone/DI water and ethanol/DI water values, as shown in Fig. 3. After the AG gel was crosslinked, the DI water absorption capacity increased (Alpaslan et al. 2021; Olak et al. 2020). After the GO was added with organo-hydrogels, the DI water and tap water absorption capacity decreased according to AG hydrogels in ratio 33–51% and 24–57%, respectively. When organo-hydrogels were compared among themselves, $p(AG\text{-}m\text{-}GO)^2$ and $p(AG\text{-}g\text{-}GO)^1$ organo-hydrogel has higher solution absorption capacity in others and their swelling value in tap water was 60.02% and 49.39%.

It was observed that organo-hydrogels containing garlic oil swell both in DI water environment and in tap water environment that contains different ions. It was concluded that

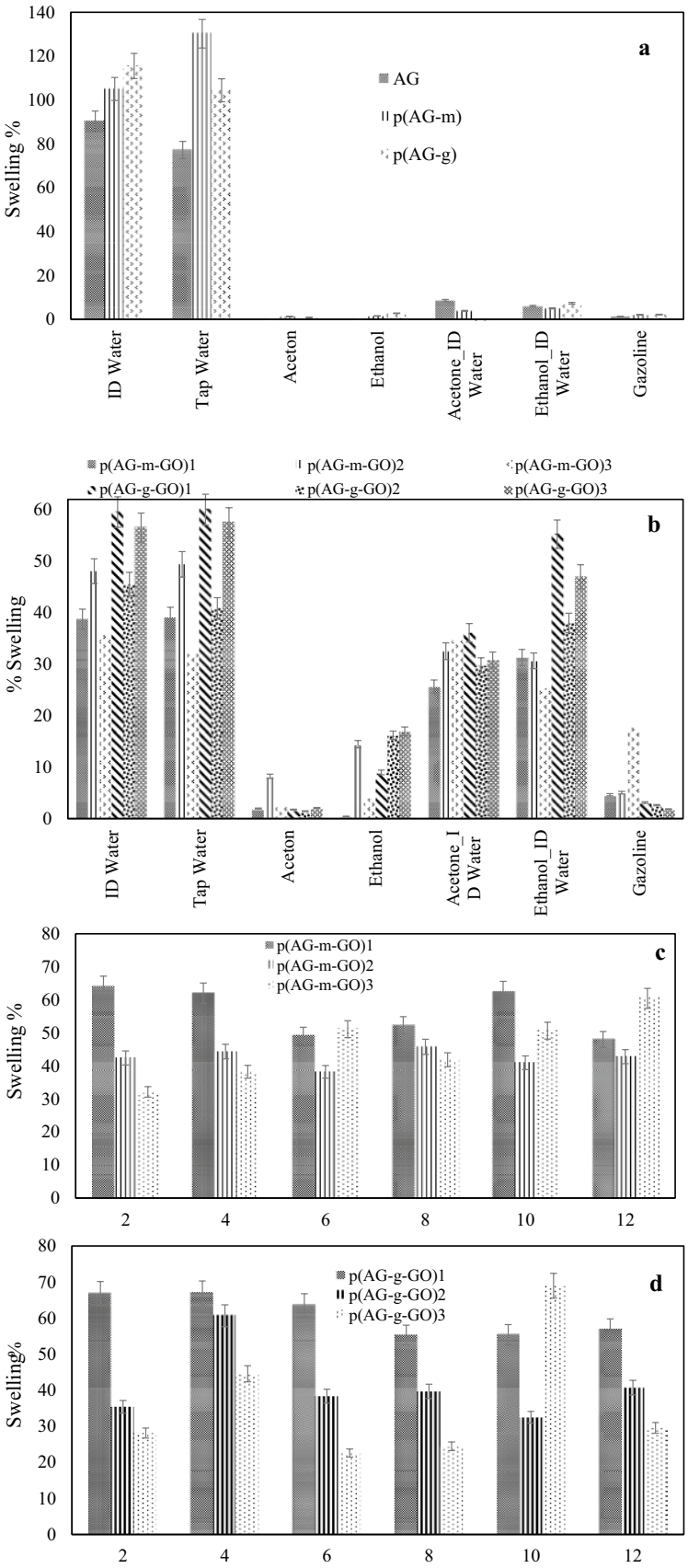

Fig. 2 Percent swelling degree of the **a** AG, p(AG-m), p(AG-g) and **b** organo-hydrogels with time in DI water, tap water, ethanol, acetone, ethanol/ID water (1:1), acetone/DI water (1:1) and gasoline. Swelling % of the **c** AG, p(AG-m), p(AG-g) and **d** organo-hydrogels as a function of 2–12 pH (pH is adjusted by the addition of 0.1 M HCl, 0.1 M NaOH)

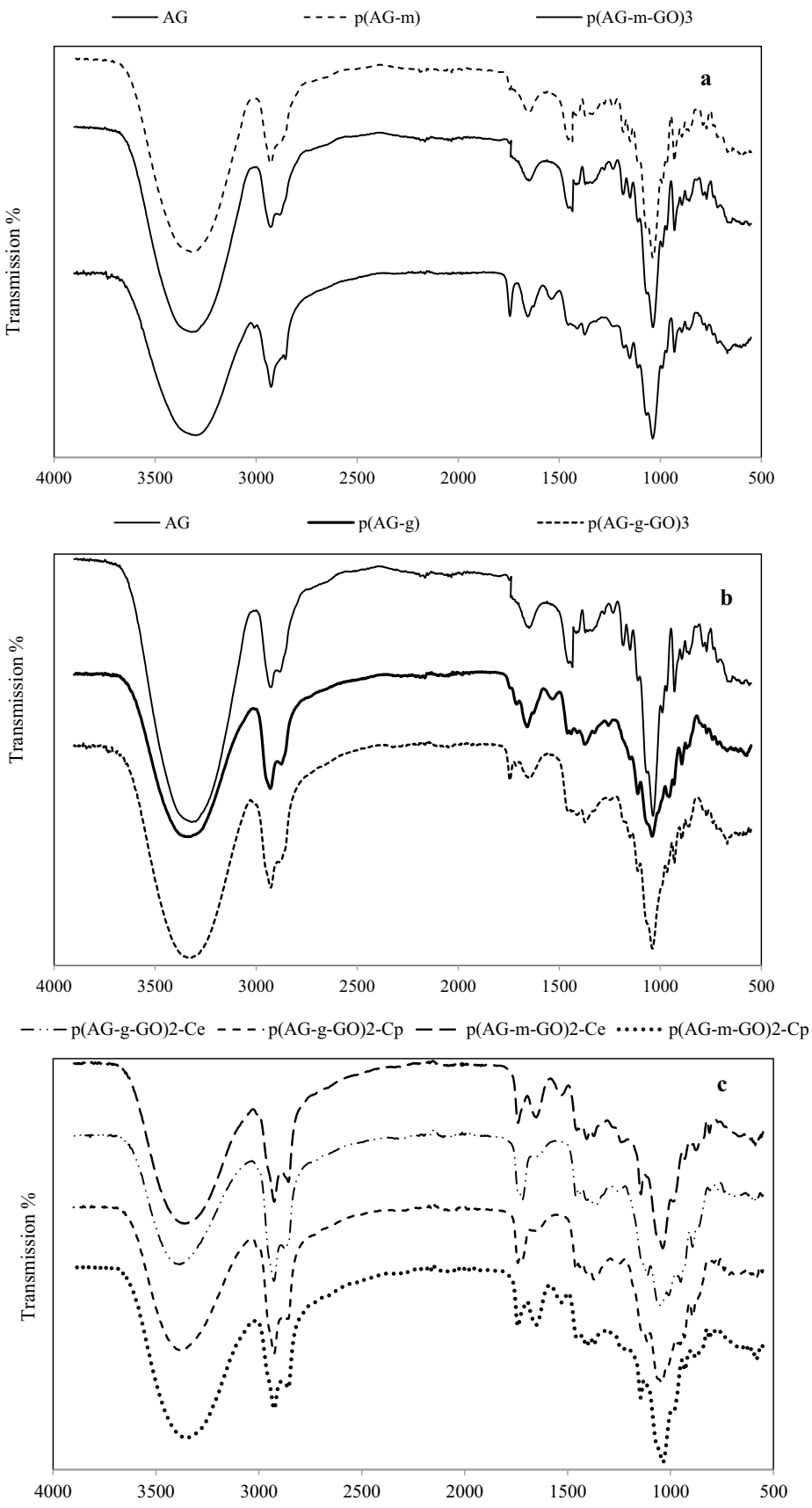

Fig. 3 FT-IR spectra of **a** AG, p(AG-m), and p(AG-m-GO)^3, **b** AG, p(AG-g) and p(AG-g-GO)^3 **c** drugs-loaded organo-hydrogels

the presence of ions did not affect organo-hydrogel swelling behavior. It was generally observed that the organo-hydrogels' S% value decreased with the increase in essential oil in the organo-hydrogel composition.

After the GO was added with organo-hydrogels, the ethanol/DI water and acetone/DI water absorption capacity increased according to AG hydrogels in ratio 19–52% and 19–34%, respectively. A small amount of swelling was observed in acetone and ethanol media compared to acetone/DI water and ethanol/DI water. This was thought to depend upon the hydrophobic character in acetone and ethanol and the number of alkyl groups in molecular structure. The hydrophobic property can be enhanced by increasing the alkyl group of the organic molecule (Üzüm et al. 2010). Therefore, more hydrophobic groups in solvents reduce swelling of organo-hydrogels in water mixtures of ethanol, acetone and gasoline compositions. Therefore, more hydrophobic groups in solvents reduce swelling of organo-hydrogels in water mixtures of gasoline, acetone and ethanol compositions.

If we evaluate organo-hydrogels in terms of crosslinkers, GA crosslinked organo-hydrogels and MBA and crosslinked organo-hydrogels, swelling values in acetone and acetone/DI water environment are close to each other. In contrast, in the ethanol and ethanol/DI water medium, organo-hydrogels that were crosslinked with GA had higher swelling values. When the swelling values in the solvents are evaluated according to the amount of essential oil contained in organo-hydrogels, it was observed that the swelling values changed as the amount of essential oil increased. Swelling of organo-hydrogels in

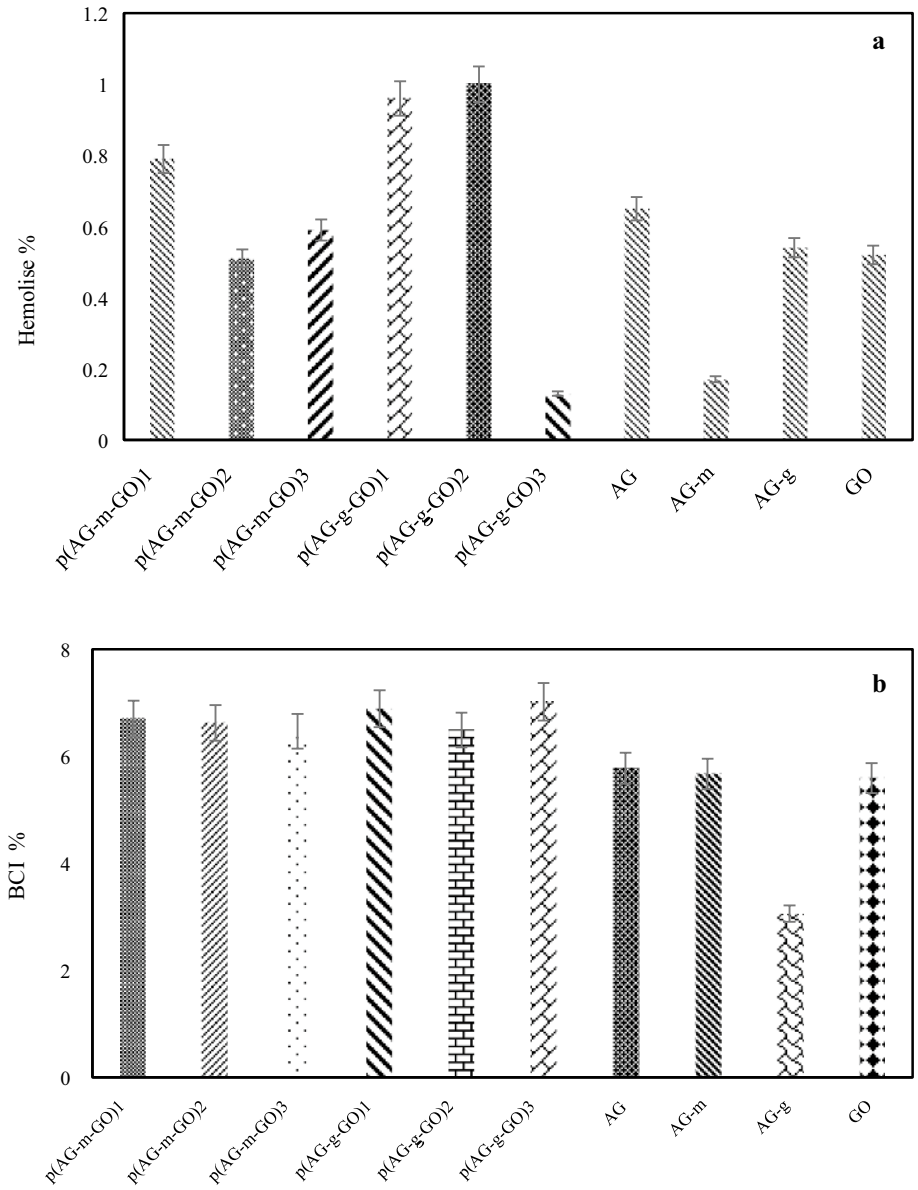

Fig. 4 Blood compatibility of the AG, p(AG-m), p(AG-g) and organo-hydrogels **a** hemolysis **b** blood clotting

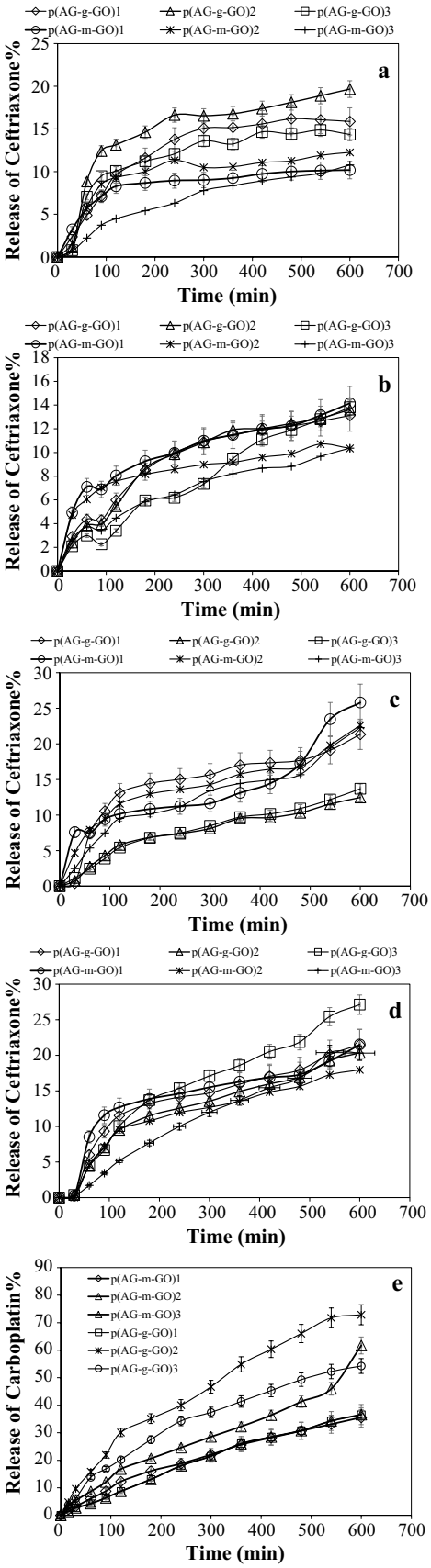

Fig. 5 Release behavior of ceftriaxone **a** 2.0 pHs **b** 5.5 pHs **c** 7.4 pHs ▶ **d** 8.0 pHs from organo-hydrogels and carboplatin **e** 7.4 pHs organo-hydrogels (The first 600 min of ceftriaxone and carboplatin release is given in the graph)

different organic solvent-water mixtures can be controlled by the solvent composition.

The most important factor affecting the swelling of the ionic organo-hydrogels is that the anionic or cationic groups repel each other. But the moving ions that increase concentration in the solvent reduce the electrostatic repulsion by encircling these groups as a cage and affect the swelling of the organo-hydrogel (Orakdogen et al. 2006; Yin et al. 2018). It is not sensitive to pH since it does not contain an ionizable group in AG gel structure. It was observed that AG gel becomes sensitive to changes in different pH values after being synthesized with MBA and GA crosslinkers. When the garlic oil monomer was added to the structure of the organo-hydrogels in different proportions, the anionic and cationic properties of the ionizable groups of organo-hydrogels were increased, and were had different swelling behaviors at different pH values.

Blood clotting and hemolysis tests

One of the main objectives of this analysis is to determine whether hemolysis occurs when blood cells interact with organo-hydrogels. Shanthini et al. Classified the hemolysis rates caused by the materials as highly hemo-compatible if less than 5%, hemorrhagic up to 10%, and non-hemo-compatible if more than 20%. According to the data in Fig. 4, since the hemolysis values of all organo-hydrogels are less than 5%, they can be included in the class of hemo-compatible materials (Shanthini et al. 2015). Organo-hydrogels blood compatibility analysis results were summarized in Fig. 4. Gel, hydrogel, GO and organo-hydrogels were calculated at a concentration of 5 mg/mL gels to be 0.8% (p(AG-m-GO)^{1}), 0.5% (p(AG-m-GO)^{2}), 0.6% (p(AG-m-GO)^{3}), 1% (p(AG-g-GO)^{1}), 1% (p(AG-g-GO)^{2}), 0.1% (p(AG-g-GO)^{3}), respectively.

Since biomaterials are materials that directly or indirectly come into contact with the body, one of the first properties feature it should bear is biocompatibility. Medicinal products that directly contact with blood, drug support materials and properties that will prevent blood clotting should also be found in biomaterials (Wang et al. 2018). Therefore, blood clotting indexes of organo-hydrogels were calculated in blood compatibility studies. In Fig. 4, organo-hydrogel (5 mg/mL) blood clotting indices were founded to be 6.7% (p(AG-m-GO)^{1}), 6.6% (p(AG-m-GO)^{2}), 6.5% (p(AG-m-GO)^{3}), 6.9% (p(AG-m-GO)^{1}), 6.5% (p(AG-m-GO)^{2}), 7.0% (p(AG-m-GO)^{3}) respectively. For these organo-hydrogels blood contact applications, the amount should be less than

Table 4 Total phenol content value

Substance	Total phenol values(mg))
Organo-hydrogel	
p(AG-m-GO)[1]	404
p(AG-m-GO)[2]	473
p(AG-m-GO)[3]	542
p(AG-g-GO)[1]	939
p(AG-g-GO)[2]	996
p(AG-g-GO)[3]	1004
Oil	
Garlic Oil	1107

5 mg/mL. When the blood test results are examined, it is seen that there is no negative effect on organo-hydrogels erythrocyte cells and blood clotting mechanisms.

Antioxidant test

The term antioxidant covers substances such as vitamins C, E and A, beta carotene, bioflavonoids and selenium that help protect our body against oxidizing agents or free radicals that have the potential to damage our body's cells. There is plenty of sulfhydryl's, an excellent antioxidant, in garlic, but raw garlic does not show this effect and even has an undesirable partial oxidant effect. Since garlic and garlic oil also provide protection against radiation, it helps to reduce the damage of free radicals; in this statement, it can significantly reduce the risk of developing degenerative diseases such as cancer and premature aging. Garlic oil also contains amino acids such as cysteine, glutamine, isoleucine and methionine that help protect cells from damage by free radicals. It has been determined that garlic and garlic oil preserve this antioxidant property for after harvest (Durak et al. 2009; Imai et al. 1994). The antioxidant activity of GO, gel, hydrogel and organo-hydrogels is given in Table 4 as the gallic acid equivalent value. The GO, gel, hydrogel and organo-hydrogels reduction capacity can determine it as antioxidant activity. When analyzing Table 4, as the concentration of the substance increases, the reduction power also increases because of the absorbents. When these values are considered, organo-hydrogels show higher antioxidant activity than others.

Ceftriaxone and carboplatin release studies

Gel, hydrogels and organo-hydrogels are widely used in drug release because of their swelling and contraction properties with changes such as pH and temperature. Moreover, the diffusion of the drug from the structure depends on the condition of the hydrogels and organo-hydrogels. Since the chemical structure of the drug may be impaired at high temperatures, drug release experiments were carried out only at constant temperature (37.5 °C) where pH values were changed (Patel et al. 1996).

At the last stage of the study, controlled drug release of Ce and Cp loaded gel, hydrogel and organo-hydrogels in different pH environments was investigated. AG, p(AG-m) and p(AG-g) maximum Ce release was 3.5% at pH 7.4, 12.6% at pH 8.0 and 12.8% at pH 8.0, respectively. Moreover, AG, p(AG-m) and p(AG-g) maximum Cp release was 1.8%, 1.6%, and 2.6% at pH 7.4, respectively. According to the data in Fig. 5 and Table 5, The highest Ce release rate was obtained to be 37.8% for p (AG-g-GO)[3] at pH 8.0 after 7 days. However, the highest Cp release rate was found to be 95.4% for p (AG-g-GO)[3] at pH 7.4 after 1 day. Moreover, some of the other reported material at literature was and p(AG-g-PmO) organo-hydrogels (99.7% at pH 7.4) and p(AG-m-PmO) organo-hydrogels (100% at pH 7.4) (Alpaslan et al. 2021), pure drug (100% Cp), CP-loaded PEG-lated MWCNTs (95% Cp) and enteric-coated PEG-lated MWCNTs (95% Cp) (Sharma et al. 2019), HAP2 (porosity of 2% Hydroxyapatite) (34.78% Ce), HAP4 (49.65% Ce), HAP6 (64.65% Ce), HAP8 (75.01% Ce) and HAP10 (92.61% Ce) (Al-Sokanee et al. 2009), so on. Drug release amounts varied

Table 5 Ceftriaxone and carboplatin % release values

	pH 2.0	pH 5.5	pH 7.4	pH 8.0	pH 7.4	
	Release %				Release %	
p(AG-m-GO)[1]	20.7	22.2	30.3	25.5	p(AG-m-GO)[1]	68.7
p(AG-m-GO)[2]	25.4	27.9	30.2	21.4	p(AG-m-GO)[2]	52.9
p(AG-m-GO)[3]	19.4	23.3	30.0	24.2	p(AG-m-GO)[3]	78.7
p(AG-g-GO)[1]	18.1	16.7	33.3	30.2	p(AG-g-GO)[1]	68.0
p(AG-g-GO)[2]	26.1	18.3	20.6	31.1	p(AG-g-GO)[2]	76.8
p(AG-g-GO)[3]	23.4	17.2	20.2	37.8	p(AG-g-GO)[3]	95.4
AG	2.7	3.0	3.5	2.9	AG	1.8
p(AG-m)	9.5	8.7	8.9	12.6	p(AG-m)	1.6
p(AG-g)	11.0	9.7	13.7	12.8	p(AG-g)	2.5

Table 6 Release kinetic and mechanism of ceftriaxone release

p(AG-m-GO)[1]		2.0	5.5	7.4	8.0	p(AG-g-GO)[1]		2.0	5.5	7.4	8.0
ZoM	C_o	1.746	1.805	1.854	2.107	ZoM	C_o	1.184	0.845	1.540	1.198
	k_o	− 0.003	− 0.004	− 0.007	− 0.007		k_o	− 0.009	− 0.007	− 0.009	− 0.010
	R^2	0.689	0.946	0.854	0.754		R^2	0.826	0.882	0.745	0.834
FoM	C_o	5.208	3.662	1.640	1.571	FoM	C_o	1.985	1.371	7.421	9.056
	k_1	0.009	0.009	0.018	0.002		k_1	0.002	0.002	0.008	0.007
	R^2	1.650	0.868	0.784	0.568		R^2	0.761	0.810	0.718	0.913
HM	k_h	0.033	0.015	0.024	0.024	HM	k_h	0.048	0.945	0.036	0.037
	R^2	0.995	0.956	0.939	0.939		R^2	0.990	0.034	0.991	0.993
KPM	n	0.238	0.261	0.392	0.271	KPM	n	0.106	0.168	0.290	0.254
	k_{kp}	0.211	0.123	0.052	0.134		k_{kp}	2.371	3.104	8.223	6.697
	R^2	0.862	0.935	0.883	0.934		R^2	0.554	0.983	0.987	0.985
p(AG-m-GO)[2]		2.0	5.5	7.4	8.0	p(AG-g-GO)[2]		2.0	5.5	7.4	8.0
ZoM	C_o	1.357	1.340	1.617	0.887	ZoM	C_o	1.935	0.810	0.578	0.914
	k_o	− 0.005	− 0.004	− 0.008	− 0.009		k_o	− 0.008	− 0.006	− 0.006	− 0.009
	R^2	0.619	0.683	0.836	0.863		R^2	0.700	0.888	0.919	1.198
FoM	C_o	5.576	10.318	1.975	2.299	FoM	C_o	3.299	1.474	2.621	6.766
	k_1	0.007	0.007	0.001	0.001		k_1	0.001	0.002	0.005	0.007
	R^2	0.935	0.946	0.885	0.618		R^2	0.761	0.749	0.955	0.975
HM	k_h	0.039	0.012	0.024	0.028	HM	k_h	0.036	0.905	0.038	0.038
	R^2	0.996	0.986	0.952	0.959		R^2	0.997	0.025	0.992	0.992
KPM	n	0.143	0.207	0.378	0.431	KPM	N	0.187	0.350	0.367	0.367
	k_{kp}	0.349	0.139	0.071	0.057		k_{kp}	0.282	0.073	0.064	0.064
	R^2	0.801	0.980	0.929	0.968		R^2	0.963	0.825	0.941	0.941
p(AG-m-GO)[3]		2.0	5.5	7.4	8.0	p(AG-g-GO)[3]		2.0	5.5	7.4	8.0
ZoM	C_o	0.421	0.648	1.004	0.037	ZoM	C_o	1.498	0.291	0.496	0.754
	k_o	− 0.005	− 0.005	− 0.009	− 0.011		k_o	− 0.006	− 0.007	− 0.006	− 0.013
	R^2	0.928	0.913	0.912	0.990		R^2	0.699	0.983	0.953	0.951
FoM	C_o	1.626	1.020	3.453	1.141	FoM	C_o	2.857	1.311	2.596	7.817
	k_1	0.003	0.002	0.009	0.011		k_1	0.001	0.003	0.005	0.010
	R^2	0.676	0.888	0.945	0.984		R^2	0.849	0.882	0.981	0.986
HM	k_h	0.025	0.017	0.025	0.025	HM	k_h	0.022	0.959	0.036	0.036
	R^2	0.944	0.969	0.953	0.953		R^2	0.915	0.040	0.994	0.994
KPM	n	0.514	0.455	0.480	0.480	KPM	n	0.561	0.858	0.594	0.594
	k_{kp}	0.022	1.000	0.031	0.004		k_{kp}	0.031	0.003	0.017	0.017
	R^2	0.939	0.960	0.947	0.893		R^2	0.889	0.972	0.982	0.982

Fickian diffusion mechanism $n \leq 0.45$, non-Fickian (anomalous) diffusion mechanism.$0.45 < n < 0.89$

according to the amount of garlic oil in the organo-hydrogel structure and to the crosslinker type. In addition, experiments showed that by changing the organo-hydrogel structure and the pH of the medium, the release medium where the drugs will be most effective can be manipulated.

Determining the effects of the mechanisms and system parameters underlying the mathematical models of drug release systems plays an important role in the design. Nowadays, both experimental and modeling studies are continuing to fully understand the mechanisms underlying the kinetics of these release systems. At this stage of the study, the drug release capacities of Ce and Cp loaded on the gel, hydrogels and organo-hydrogels; time-dependent drug release fractions; the R^2 values and kinetic parameters of the models were given Tables 6and7. In drug release trials in different pH environments were found that Ce release kinetics conform to HM and KPM and that Cp release kinetics is suitable to ZoM, HM, and KPM. As a result of n values calculated with KPM for p(AG-m-GO)[1], p(AG-m-GO)[2] p(AG-g-GO)[1] and p(AG-g-GO)[2] organo-hydrogels Ce drug, it was seen that the release mechanism complies with the Fick law, whereas p(AG-m-GO)[3] and p(AG-g-GO)[3] organo-hydrogels

Table 7 Release kinetic and mechanism of carboplatin release

p(AG-m-GO)[1]		7.4	p(AG-g-GO)[1]		7.4
ZoM	C_o	1.364	ZoM	C_o	0.713
	k_o	0.024		k_o	0.040
	R^2	0.980		R^2	0.985
FoM	C_o	1.593	FoM	C_o	0.837
	k_1	0.006		k_1	0.005
	R^2	0.816		R^2	0.875
HM	k_h	0.032	HM	k_h	− 0.111
	R^2	0.995		R^2	0.993
KPM	n	0.823	KPM	n	1.200
	k_{kp}	0.003		k_{kp}	0.001
	R^2	0.992		R^2	0.941
p(AG-m-GO)[2]		7.4	p(AG-g-GO)[2]		7.4
ZoM	C_o	0.488	ZoM	C_o	3.304
	k_o	0.380		k_o	0.034
	R^2	0.993		R^2	0.983
FoM	C_o	2.377	FoM	C_o	1.482
	k_1	0.005		k_1	0.003
	R^2	0.875		R^2	0.852
HM	k_h	0.037	HM	k_h	0.076
	R^2	0.992		R^2	0.997
KPM	n	0.940	KPM	N	0.655
	k_{kp}	0.002		k_{kp}	0.015
	R^2	0.994		R^2	0.990
p(AG-m-GO)[3]		7.4	p(AG-g-GO)[3]		7.4
ZoM	C_o	1.291	ZoM	C_o	2.110
	k_o	0.024		k_o	0.032
	R^2	0.648		R^2	0.957
FoM	C_o	1.643	FoM	C_o	1.610
	k_1	0.005		k_1	0.003
	R^2	0.618		R^2	0.908
HM	k_h	0.026	HM	k_h	-0.063
	R^2	0.980		R^2	0.967
KPM	n	1.072	KPM	n	0.629
	k_{kp}	0.001		k_{kp}	0.011
	R^2	0.885		R^2	0.996

Fickian diffusion mechanism $n \leq 0.45$, non-Fickian (anomalous) diffusion mechanism.$0.45 < n < 0.89$

comply with the non-Fick law. *N* values calculated with KPM models of gels, hydrogels and organo-hydrogels were between 0.6 and 1.07 for Cp drug, and this indicated that it complied with the non-Fick law.

Conclusion

In the first stage, the free radicalization polymerization technique was used in the emulsion medium to obtain organo-hydrogels based on agar-glycerol-garlic oil. Swelling, FT-IR, antioxidant and blood compatibility analyses of the synthesized organo-hydrogels were performed. With in situ polymerization, Ce and Cp drugs were loaded on the organo-hydrogels. In the final stage of the study, controlled drug release in organo-hydrogels loaded with Ce and Cp in different pH environments was investigated. The highest drug release for Ce was found to be at pH 8.0 with 37.4% within 7 days in p(AG-g-GO)[3] organo-hydrogel, and the highest drug release within carboplatin was founded at pH 7.4 with 95.4% within 10 h in p(AG-g-GO)[3] organo-hydrogel. In light of the data obtained during our studies, it

can be said that in the selection of drug carrier materials, it was advantageous to use a structure consisting of more than one polymer mixture rather than being attached to a single polymer. In this way, drug loading and drug release rates can be adjusted/changed. It was also possible to ensure that the drug was more effective in the desired release environment. It seen that the methods we developed during the loading and release of vital drug substances such as Ce and Cp can be used appeared to be available. Our study suggests a way that can help achieve active and effective drug systems.

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