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ORIGINAL PAPER

Application of Poly (Agar-Co-Glycerol-Co-Sweet Almond Oil) Based Organo-Hydrogels as a Drug Delivery Material

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Abstract

In this study, it was aimed to investigate the synthesis, characterization and drug release behaviors of organo-hydrogels containing pH-sensitive Agar (A), Glycerol (G), Sweet Almond oil (Wu et al. in J Mol Struct 882:107–115, 2008). Organo-hydrogels, which contained Agar, Glycerol and different amounts of Sweet Almond oil, were synthesized via the free-radical polymerization reaction with emulsion technique using glutaraldehyde or methylene bis acrylamide crosslinkers. Then, the degree of swelling, bond structures, blood compatibility and antioxidant properties of the synthesized organo-hydrogels were examined. In addition, Organo-hydrogels which loaded with Ceftriaxone and Oxaliplatin were synthesized with the same polymerization reaction and release kinetics were investigated. In vitro release studies were performed at media similar pH to gastric fluid (pH 2.0), skin surface (pH 5.5), blood fluid (pH 7.4) and intestinal fluid (pH 8.0), at 37 °C. The effects on release of crosslinker type and sweet almond oil amount were investigated. Kinetic parameters were determined using release results and these results were applied to zero and first-order equations and Korsmeyer-Peppas and Higuchi equations. Diffusion exponential was calculated for drug diffusion of organo-hydrogels and values consistent with release results were found.

Keywords Organo-hydrogel · Agar · Swelling · Sweet Almond Oil · Ceftriaxone · Oxaliplatin

Introduction

Recently, it has been hypothesized that fatty acid-based hydrophobic organogels will form a matrix suitable for long-term release of hydrophilic molecules. Organogels have advantages as a drug delivery system. Since drug carrier organo-hydrogels are not affected by moisture; Since they provide the drug to pass easily through the skin; as they are resistant to microbial contamination; they have many advantages. As a drug carrier of organo-hydrogels, the gelling and trapping procedures were quite simple and useful. Biocompatibility, biodegradability and non-immunogenic properties of the organogel show that it is non-hazardous in their long-term use. However, the use of organogels as drug carriers is becoming widespread [1–6].

In sweet almond oil, the main components are contained 5.26–7% palmitic acid, 0.33–0.6% palmitoleic acid, 1.61–4.40% stearic acid, 65.33- 76.73% oleic acid, 17.36–25.17% linoleic acid, 0.44–0.64% myristic acid, 21.25–17.89% linoleic acid, 90.50- 92.1% unsaturated fatty acids, 7.61–11.48% saturated fatty acids ratio. There is a great deal of scientific research that sweet almond oil has anti-inflammatory, immune-enhancing and anti-hepatotoxicity effects and prevents the growth of primary and metastatic colon cancer cells [7–10].

Ceftriaxone is a cephalosporin group antibiotic, which is often preferred in the treatment of bacterial infections. Ceftriaxone 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 [11, 12].

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Oxaliplatin is a third-generation platinum analog used in the treatment of colorectal cancer (CRC). The platinum compound used in colorectal cancer treatment causes oxaliplatin, acute motor and sensory symptoms, and chronic neuropathy with cumulative dose. The anti-tumor effect of oxaliplatin is thought to be due to the formation of linkages that disrupt DNA synthesis [13–15].

Within the scope of the study presented, preparation of organo-hydrogels based on different cross-linker type [glutaraldehyde (G)] and Agar Glycerol and Sweet almond oil loaded with different types of ceftriaxone and carboplatin [p(AG-co-SAO)], swelling and FT-IR analysis and its characterization, antioxidant and blood compatibility properties, and these organo-hydrogels drug-release studies have been investigated in vitro conditions Organo-hydrogels systems have been prepared using the free radical polymerization technique in the emulsion media method. The drug-loaded organo-hydrogels release kinetics at different pH were interpreted to investigate the release behaviors. Organo-hydrogels release behaviors were compared to investigate the effect of ceftriaxone and carboplatin drugs on release kinetics.

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%) were purchased from Merck. In terms of analytical grade, all reagents were of the highest cleanliness available, and they were used without additional purification. Sweet Almond Oil [16], gasoline, Ceftriaxone and Oxaliplatin 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. Gel and hydrogels were synthesized as described by Alpaslan et al.[17]. Gel and hydrogel compositions were given in Table 2. For the preparation of organo-hydrogels above given method was used (Table 1). Briefly, firstly, 2 mL of agar solution and 0.04 mL of glycerol were added to the 20 mL flask and vigorous mixed (at 2500 rpm) to obtain homogeneous solution. Secondly, different amounts of sweet almond oil (0.1, 0.2 and 0.3 mL) were added in the reactions mixture, and stirred at 800 rpm for 15 min until a homogeneous mixture was formed. Thirdly, MBA (0.1%) or glutaraldehyde reagent was added as a crosslinker and further homogenized. Organo-hydrogel compositions were given in Table 2. 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, hydrogels and organo-hydrogels were removed from plastic petri dish, cut into 6 mm thick cylindrical form and were stored at 25 °C for further uses. These preparation steps are schematically given in Fig. 1. The gel, hydrogels and organo-hydrogels were kept in DI water and washing water was renewed every 2 h for 8 h to eliminate unreactive monomers. The synthesized gel, hydrogels, p(AG-m-SAO) and p(AG-g-SAO) organo-hydrogels

Table 1 Codes of different organo-hydrogel

Gel	Code
Agar-Glycerol	AG
Hydrogel	
poly (Agar-co-Glycerol)/MBA	p(AG-m)
poly (Agar-co-Glycerol)/GA	p(AG-g)
Organo-ydrogel	
poly (Agar-co-Glycerol-co-Sweet Almond Oil)/MBA-1	$p(AG\text{-}m\text{-}SAO)^1$
poly (Agar-co-Glycerol-co-Sweet Almond Oil)/MBA-2	$p(AG\text{-}m\text{-}SAO)^2$
poly (Agar-co-Glycerol-co-Sweet Almond Oil)/MBA-3	$p(AG\text{-}m\text{-}SAO)^3$
poly (Agar-co-Glycerol-co-Sweet Almond Oil)/GA-1	$p(AG\text{-}g\text{-}SAO)^1$
poly (Agar-co-Glycerol-co-Sweet Almond Oil/GA-2	$p(AG\text{-}g\text{-}SAO)^2$
poly (Agar-co-Glycerol-co-Sweet Almond Oil)/GA-3	$p(AG\text{-}g\text{-}SAO)^3$

Table 2 Compositions and codes of different organo-hydrogel

Agar	Glycerol	SAO	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	$p(AG\text{-}m\text{-}SAO)^1$
2%–2 mL	0.04 mL	0.2 mL	MBA	$p(AG\text{-}m\text{-}SAO)^2$
2%–2 mL	0.04 mL	0.3 mL	MBA	$p(AG\text{-}m\text{-}SAO)^3$
2%–2 mL	0.04 mL	0.1 mL	GA	$p(AG\text{-}g\text{-}SAO)^1$
2%–2 mL	0.04 mL	0.2 mL	GA	$p(AG\text{-}g\text{-}SAO)^2$
2%–2 mL	0.04 mL	0.3 mL	GA	$p(AG\text{-}g\text{-}SAO)^3$

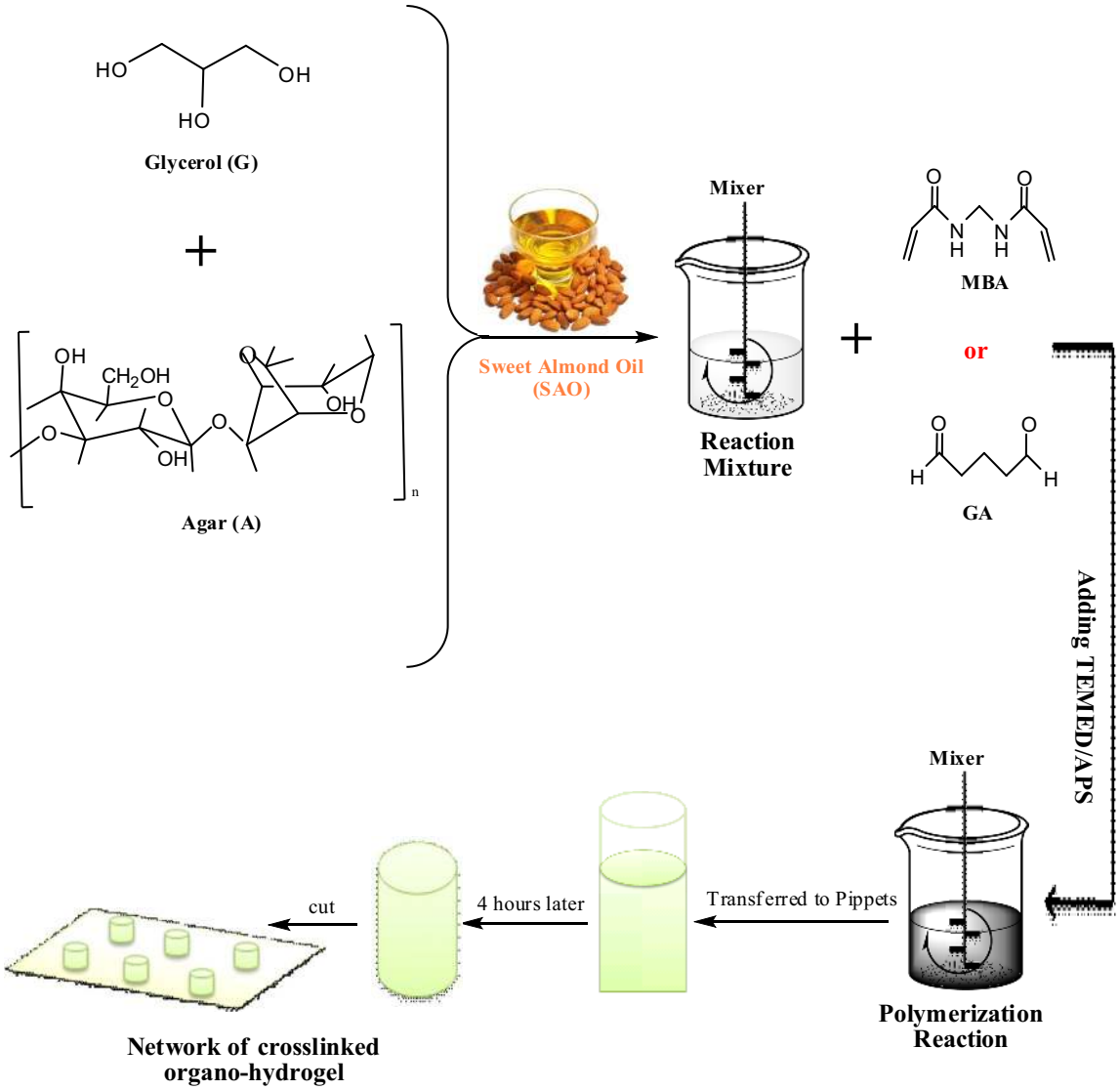

Fig. 1 Synthesis and schematic presentation of organo-hydrogels

were dried in the oven at 40ºC until a constant weight was achieved and stored at 4 °C for further uses.

Organo-Hydrogel Synthesis Containing Ceftriaxone and Oxaliplatin

Ceftriaxone or Oxaliplatin drugs were directly synthesized with organo-hydrogel [18]. 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 or Oxaliplatin 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, and organo-hydrogels placed in water, ethanol, acetone, ethanol/ID water (1:1), acetone/ID water (1:1) and gasoline and at different pHs (2.0–12.0) for 24 h. Swelling tests were performed at room temperature of 25 °C [19, 20].

Fourier Transform Infrared Spectroscopy (FT-IR) Analysis

Fourier Transform Infrared Spectroscopy (FTIR) (Thermo, model Nicolet iS10 Spectrometer, USA) was used for FTIR analysis. The analysis was performed to investigate the functional groups 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 a powder 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 and hemolysis analysis [17, 21] methods which were explained in the literature were applied.

Antioxidant Analysis

To evaluate the antioxidant activity, Folin-Ciocalteu [22–24] and ABTS [23, 25] methods which were explained in the literature were applied.

Ceftriaxone and Oxaliplatin Release Studies

Synthesized drug-loaded gel, hydrogels and organo-hydrogels were used as controlled release systems for Ceftriaxone and Oxaliplatin which are frequently used in the medical field. The gel, hydrogels and organo-hydrogels loaded with a certain amount (50 ppm) of Ceftriaxone, were used in 50 mL at four different pH values (2.0, 5.5, 7.4 and 8.0 pH) for Ceftriaxone release. Oxaliplatin release was performed in a 50 mL 7.4 pH solution media. Released Ceftriaxone and Oxaliplatin 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 performed with 3 replications in itself and averaged with standard deviation values. The most common models, which are Zero order [26, Eq. (3); 27, 28], First order (FoM) (Eq. (4)) [27–29], Higuci (HM) [Eq. 5, 30] and Korsmeyer-Peppas (KPM) (the power law) [Eq. 6, 27] were used to associate the release kinetics. Those equations were given in Table 3.

Results and Discussion

Swelling Properties of the Organo-Hydrogels

Swelling work carried out in polar and apolar environments is a widely used technique for characterizing gel, hydrogel and organo-hydrogels. Both kinetic and dynamic swelling studies; based on determining the increase in mass or volume of a crosslinked gel soaked in solvent. It is important to know the swelling behavior of gel, hydrogel and organo-hydrogels to be used in controlled release studies in physiological environments. Since the pH of the human body is not constant, at 2–12 pH balance range swelling analyzes were performed.

The change in percent swelling of gel, hydrogel and organogels as a function of solvent concentration in water-organic solvent mixtures was shown in Fig. 2. After the AG gel was crosslinked, the ID water absorption capacity increased in ratio [17, 21]. On the contrary, after the hydrogel added SAO, the ID water absorption capacity approximately decreased in 40–52% for p(AG-m) and 27–60% for p(AG-g) the tap water absorption capacity decreased in 37–57% for p(AG-g) and 47–73% for p(AG-m). p(AG-g-SAO)[1] organo-hydrogel in DI water and ethanol/DI water medium swollen at a rate of about 83% and 77% of its dry mass, respectively. % S values of p (AG-g-SAO)[1] organo-hydrogel in acetone and gasoline media were approximately 7.6% and 2.4%. In this situation; organo-hydrogels are associated with functional groups in their structure and these groups are; very prone to hydrogen bonding with water molecules. As a result of the said groups forming hydrogen bonds with water molecules, more water molecules enter the organo-hydrogel structure and as a result, the organo-hydrogel swells more. On the other hand, swelling behavior in the polar environment; relates to protonation of functional groups. Functional groups formed in organo-hydrogel repel each other and cause organo-hydrogel pores to grow. Hereat;

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	$\frac{C_r}{C_\infty} = k_H \cdot \sqrt{t}$	Diffusion medium based Mechanism in Fick's first law	HM
Korsemeyer-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

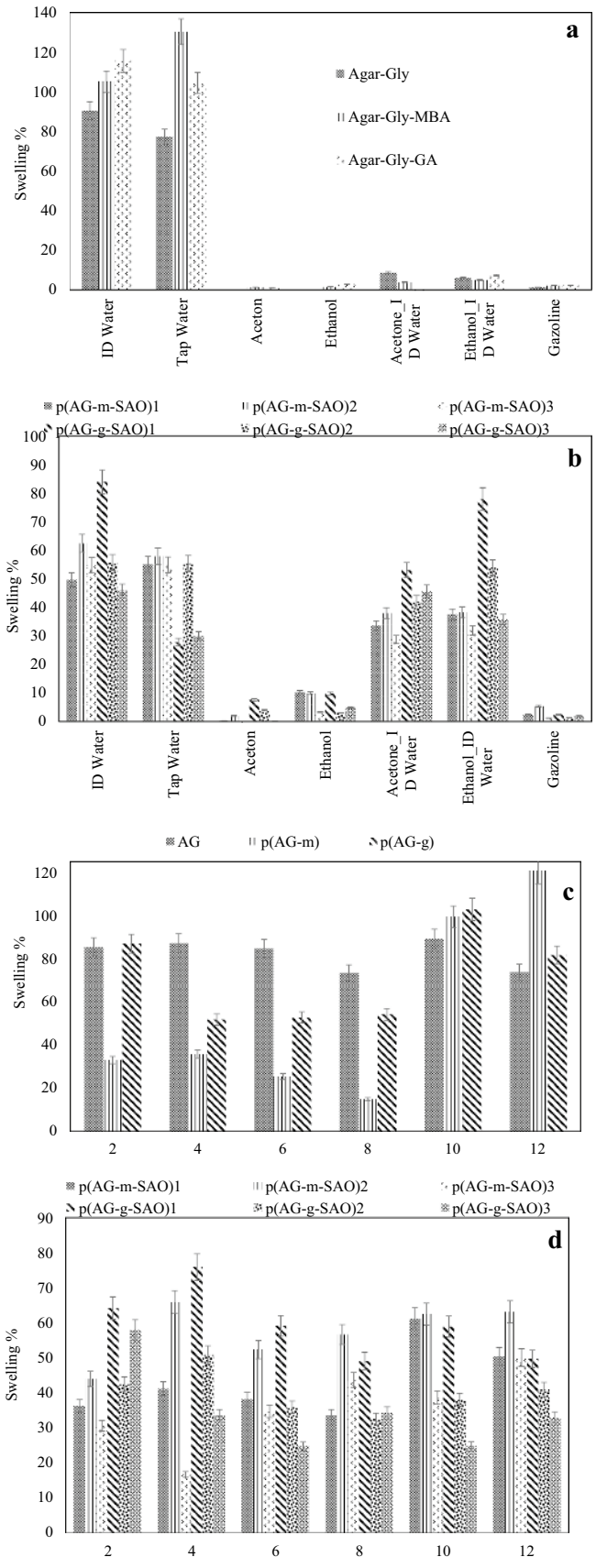

Fig. 2 Percent swelling degree of the **a** AG, p(AG-m), p(AG-g) and **b** organo-hydrogels with time in DI water, tap water, ethanol, acetone, ethanol/DI water (1:1), acetone/DI water (1:1) and gasoline. Swelling % of the **c** AG, p(AG-m), p(AG-g) and **d** organo-hydrogel as a function of 2–12 pH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

more solvent molecules enter the growing pores of organo-hydrogels, causing it to swell [31].

If we evaluate organo-hydrogels in terms of cross-linkers; GA cross-linked organo-hydrogels were found to have higher swelling values in different the solvent medium than MBA cross-linked organogels. When the swelling values in solvents are evaluated according to the amount of essential oil in organo-hydrogels; It was observed that the swelling values changed as the amount of essential oil increased. Swelling of organogels in different organic solvent–water mixtures can be controlled by the solvent composition. It is understood from the balance swelling graphs that the swelling behavior of organo-hydrogels is pH-sensitive. This behavior; was an important feature of organo-hydrogels that release controlled drugs to be used especially in the stomach, intestine, skin and blood systems.

Fourier Transform Infrared Spectroscopy (FT-IR) Analysis

Organo-hydrogels, AG, p(AG-m), p(AG-g) were prepared by free radical polymerization in emulsion media and the FTIR spectra were shown in Fig. 3 and explain in the literature[17, 21]. Sweet almond oil contained the band peak at 3600–3000 cm^{-1} belonging to the vibrations of the –OH groups, peak in 3007 cm^{-1} belonged –CH, bands at 1742 cm^{-1} and 1650 cm^{-1} represented to C=O and –NH vibrations. The peak in 2923 cm^{-1} belonged to the –C–H, peak in 1460 cm^{-1} belonged to the CH_2 bands and 1375 cm^{-1} belonged to the carboxylates acid [32, 33]. The new bonds and structural diversity at organo-hydrogels were demonstrated the existence of hydrogen-bond interaction. After the SAO got into the structure of the organo-hydrogel, the incoming bands from characteristic aromatic compounds (such as 2922 cm^{-1}, – 2853, cm^{-1}, 1640 cm^{-1}

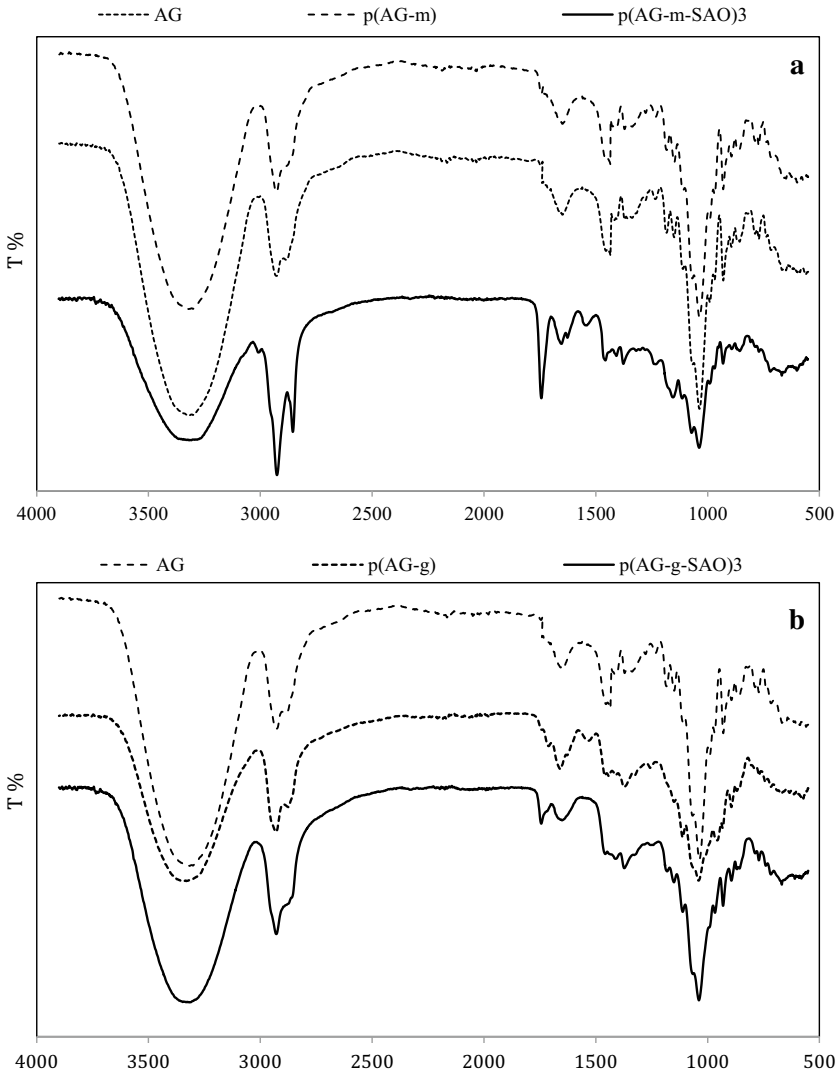

Fig. 3 FT-IR Spectra of **a** AG, p(AG-m), and p(AG-m-SAO)[2], **b** AG, p(AG-g) and p(AG-g-SAO)[3] organo-hydrogels

and 1532 cm^{-1}) exhibited high density, and the peaks appear to be deepened or expanded. Considering the peaks in the organo-hydrogel, the peak at 1742 cm^{-1}, 1375 cm^{-1} and 1650 cm^{-1} expanded and deepened, and the peak depth in the 1037 cm^{-1} increased. The change in these peaks indicated that SAO entered the structure of the organo-hydrogel.

Antioxidant Test

Almond oil contains high amounts of phenolic compounds, an important class of antioxidants in the diet. Tocopherols are natural monophenols with antioxidant properties and are particularly rich sources of α-tocopherol. The antioxidant activity of SAO, AG, p (AG-m), p (AG-g) and organo-hydrogels was given in Table 4 as the gallic acid equivalent value. The SAO, AG, p (AG-m), p (AG-g) and organo-hydrogels reduction capacity can determine it was antioxidant activity. When Table 4 was analyzed, reduction capacities of the SAO, AG, p (AG-m), p (AG-g) and organo-hydrogels could determine their antioxidant activity. When Table 4 was analyzed, it was observed that the power reduction due to the absorbents increased as the concentration of the substance increased. When these values were considered, organo-hydrogels shown higher antioxidant activity than the others.

Blood Clotting and Hemolysis Tests

Organo-hydrogels must meet certain criteria in order to be used in medical applications. Therefore, primary measures to determine the blood compatibility of organo-hydrogels are to determine the coagulation and destruction of red blood cells with the first adsorbed protein molecules on the surface. For this reason, the primary procedures to determine blood compatibility of an organo-hydrogel are coagulation (BCI) and hemolysis tests. Organo-hydrogels blood compatibility analysis results were summarized in Fig. 4. Hemolysis and blood coagulation analysis of gel, hydrogels and organo-hydrogels were performed and calculated. It was stated that the hemolysis rate was not hemolytic up to 5%. Therefore, it can be said that organo-hydrogels were blood compatible at this rate. Hemolysis and blood clotting (BCI) analysis of AG, AG-m, AG-g, SAO and organo-hydrogels (at a concentration of 5 mg/mL) were performed, calculated and was given in Fig. 4a,b.

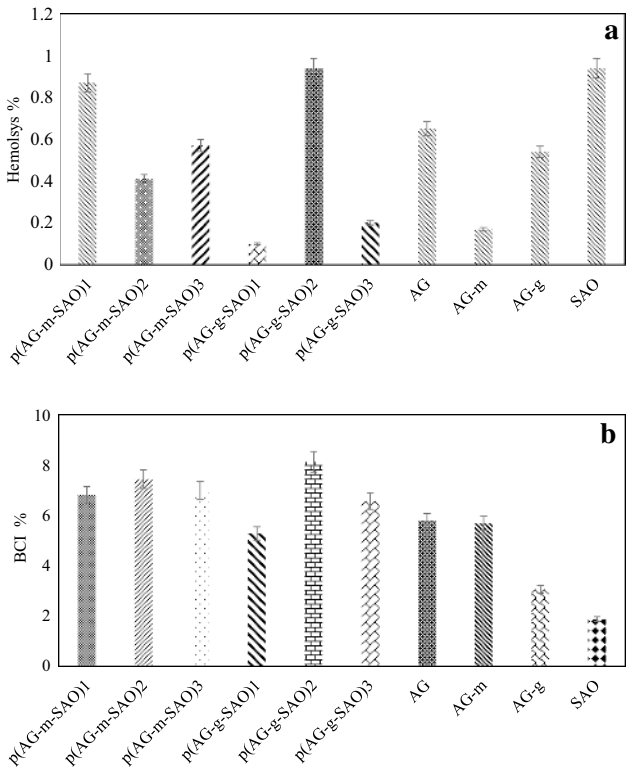

Fig. 4 Blood combability of the AG, p(AG-m), p(AG-g) and organo-hydrogels **a** hemolysis **b** blood clotting

Table 4 Total phenol content values

Substance	Total phenol (mg)
Organo-hydrogel	
p(AG-m-SAO)[1]	463
p(AG-m-SAO)[2]	462
p(AG-m-SAO)[3]	527
p(AG-g-SAO)[1]	594
p(AG-g-SAO)[2]	918
p(AG-g-SAO)[3]	941
Oil	
Sweet Almond Oil	959

Ceftriaxone and Oxaliplatin Release Studies

One of the most important issues in drug transportation systems research and development is the development of controlled drug release matrices. Controlled drug release matrices are the means by which a therapeutic agent is released over time in a certain area of the body and/or over a period of time. Organo-hydrogels are very suitable for such applications with their wide range of mechanical, physical and chemical properties. The structure of organo-hydrogels to be used for controlled drug release studies is a very important parameter. The surface on which the drug will retention and release will significantly affect the amount of attachment and rate of release.

The gel, hydrogel and organo-hydrogels loaded with Ceftriaxone and Oxaliplatin drugs were used in controlled drug release trials at 37.5 C with four different pH media. Measurements were carried out at certain intervals until

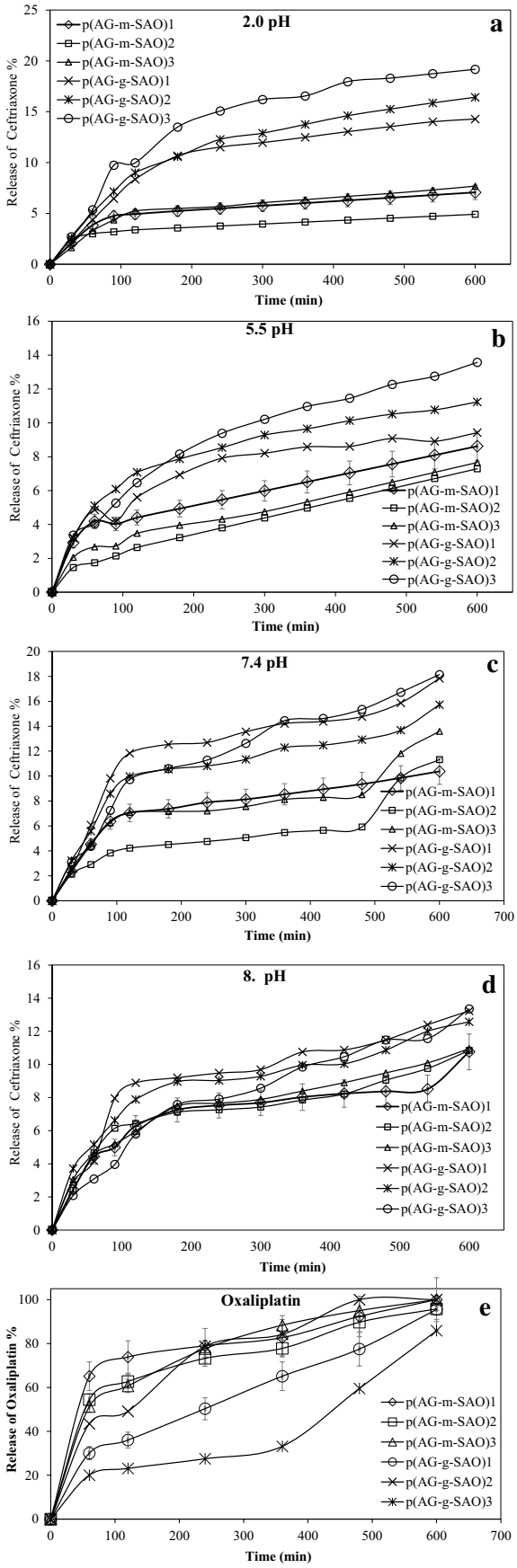

Fig. 5 Release behavior of Ceftriaxone **a** 2.0 pHs, **b** 5.5 pHs, **c** 7.4 pHs, **d** 8.0 pHs from organo-hydrogels and Oxaliplatin, **e** 7.4 pHs p(AG-m-SAO) and p(AG-g-SAO) organo-hydrogels (The first 600 min of Ceftriaxone and Oxaliplatin release were given in the graph)

Table 5 Ceftriaxone Oxaliplatin % release values

	Ceftriaxone				Oxaliplatin
	pH 2.0	pH 5 .5	pH 7.4	pH 8.0	pH 7.4
	Release %				Release %
p(AG-m-SAO)[1]	8.43	14.00	20.00	17.01	100
p(AG-m-SAO)[2]	8.51	15.96	20.57	16.50	100
p(AG-m-SAO)[3]	9.83	13.03	19.60	15.97	100
p(AG-g-SAO)[1]	16.92	12.68	26.07	21.22	100
p(AG-g-SAO)[2]	21.29	15.59	24.73	20.22	100
p(AG-g-SAO)[3]	21.67	17.09	29.34	24.58	100
AG	2.74	2.97	3.54	2.87	7.94
p(AG-m)	9.52	8.71	8.88	12.59	10.91
p(AG-g)	11.03	9.69	13.67	12.79	11.66

equilibrium in four different pH environments and results. It were given in Fig. 5 and Table 5. AG, p(AG-m) and p(AG-g) maximum Ceftriaxone release were 3.54% at pH 7.4, 12.59% at pH 8 and 13.67% at pH 7.4, respectively. Moreover AG, p(AG-m) and p(AG-g) maximum Oxaliplatin release were 7.94%, 10.91%, and 11.66% at pH 7.4, respectively. When the organo-hydrogels were compared in terms of release amounts, the maximum release was obtained in the p(AG-g-SAO) organo-hydrogels. It was observed that p(AG-g-SAO) organo-hydrogel released 29.34% of Ceftriaxone and 100% of Oxaliplatin at 7.4 pH. It was found that the release of organo-hydrogels containing ceftriaxone was slow, and the total amount of drug released after 8 h was low. These findings were interpreted as that Ceftriaxone in the organo-hydrogel structure can not only prolong the release but also protect Ceftriaxone from hydrolysis. As seen in Fig. 5, the amount of Oxaliplatin in the environment increased in the first 60 min, but then began to decrease over time. And almost all organo-hydrogels was observed to release 100% of Oxaliplatin in its structure within 10 h. Unlike Ceftriaxone release from organo-hydrogels, Oxaliplatin release reached 100% release rate within 1 day. Moreover some of the other reported material at literature was HAP-2 (porosity of 2% Hydroxyapatite) (34.78% Ceftriaxone), HAP-4 (49.65% Ceftriaxone), HAP-6 (64.65% Ceftriaxone), HAP-8 (75.01% Ceftriaxone) and HAP-10 (92.61% Ceftriaxone) [34], Citrus-Pectin [35] (97.2% Ceftriaxone), CP:PVA 1:02 (97.7% Ceftriaxone, 7 days), CP:PVA 1:04 (79.2% Ceftriaxone, 7 days), CP:PVA 1:06 (69.2% Ceftriaxone, 7 days) [35], chitosan

Table 6 Release kinetic and mechanism of Ceftriaxone release

p(AG-m-SAO)[1]		2.0	5.5	7.4	8.0	p(AG-g-SAO)[1]		2.0	5.5	7.4	8.0
ZoM	C_o	1.785	1.612	2.235	2.066	**ZoM**	C_o	1.802	1.602	2.616	2.019
	k_o	− 0.003	− 0.005	− 0.006	− 0.005		k_o	− 0.008	− 0.004	− 0.008	− 0.006
	R^2	0.800	0.985	0.779	0.817		R^2	0.823	0.847	0.711	0.762
FoM	C_o	2.080	1.886	15.007	11.057	**FoM**	C_o	1.186	0.803	3.909	2.909
	k_1	− 0.001	− 0.001	− 0.004	− 0.004		k_1	− 0.001	− 0.001	− 0.004	− 0.003
	R^2	0.732	0.635	0.900	0.851		R^2	0.800	0.770	0.909	0.963
HM	k_h	0.034	0.017	0.028	0.028	**HM**	k_h	0.048	0.025	0.022	0.245
	R^2	0.997	0.918	0.959	0.959		R^2	0.990	0.909	0.991	0.993
KPM	n	0.219	0.286	0.239	0.267	**KPM**	n	0.414	0.394	0.338	0.359
	kkp	4.850	9.640	7.475	8.909		kkp	14.701	14.644	10.514	13.194
	R^2	0.947	0.923	0.940	0.934		R^2	0.923	0.899	0.937	0.927
p(AG-m-SAO)[2]						**p(AG-m-SAO)[2]**					
ZoM	C_o	1.287	0.593	1.319	2.133	**ZoM**	C_o	1.930	1.723	2.210	1.817
	k_o	− 0.002	− 0.005	− 0.003	− 0.005		k_o	− 0.006	− 0.003	− 0.004	− 0.004
	R^2	0.940	0.997	0.870	0.809		R^2	0.908	0.930	0.867	2.019
FoM	C_o	1.408	1.140	2.620	11.844	**FoM**	C_o	0.716	0.665	2.210	1.996
	k_1	− 0.001	− 0.003	− 0.006	− 0.005		k_1	− 0.002	− 0.001	− 0.004	− 0.003
	R^2	0.980	0.946	0.885	0.932		R^2	0.800	0.908	0.867	0.942
HM	k_h	0.039	0.012	0.024	0.028	**HM**	k_h	0.036	0.021	0.219	0.219
	R^2	0.996	0.986	0.952	0.959		R^2	0.997	0.976	0.992	0.992
KPM	n	0.234	0.632	0.374	0.229	**KPM**	n	0.294	0.307	0.235	0.216
	kkp	6.399	80.310	20.545	5.936		kkp	9.101	9.740	6.352	5.645
	R^2	0.971	0.996	0.717	0.912		R^2	0.940	0.993	0.970	0.944
p(AG-m-SAO)[3]						**p(AG-m-SAO)[3]**					
ZoM	C_o	0.948	0.614	1.265	1.236	**ZoM**	C_o	1.582	1.011	1.223	0.713
	k_o	− 0.004	− 0.004	− 0.006	− 0.006		k_o	− 0.009	− 0.006	− 0.008	− 0.006
	R^2	0.755	0.923	0.746	0.814		R^2	0.828	0.902	0.895	0.931
FoM	C_o	1.553	1.068	4.593	6.132	**FoM**	C_o	1.146	0.583	2.178	1.440
	k_1	− 0.001	− 0.002	− 0.005	− 0.004		k_1	− 0.001	− 0.002	− 0.003	− 0.005
	R^2	0.814	0.946	0.825	0.953		R^2	0.840	0.882	0.968	0.977
HM	k_h	0.025	0.017	0.025	0.025	**HM**	k_h	0.022	0.027	− 0.130	− 0.130
	R^2	0.944	0.969	0.953	0.953		R^2	0.915	0.982	0.994	0.994
KPM	n	0.229	0.418	0.328	0.328	**KPM**	n	0.392	0.479	0.427	0.554
	kkp	5.848	1.000	12.569	10.251		kkp	13.005	26.441	20.164	51.172
	R^2	0.943	0.952	0.841	0.959		R^2	0.964	0.985	0.968	0.960

Bold represents the oscillation model and parameters

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

nanoparticles (98.4%, pH4.5, Oxaliplatin) and chitosan nanoparticles (15.7%, pH7.4, Oxaliplatin) [14], poly-lactic-co-glycolic acid-oxaliplatin microspheres (100%, Oxaliplatin) [13], RG-503 (PLAGApolymer) (100%, Oxaliplatin), 10% PLAGAoligomer RG503 (90%, Oxaliplatin), RG503 (80%) and RG502 (20%, Oxaliplatin)[15], MWCNTPEGOxaliplatin (80%, Oxaliplatin, 7 days), MWCNTOxaliplatin (89% Oxaliplatin, 5 days)[36], so on. The highest cumulative ceftriaxone release from organogels was observed in organogels synthesized by GA crosslinker. It was been seen from the results that ceftriaxone release can be controlled by changing the amount of sweet almond oil in organo-hydrogels.

When the Ceftriaxone release kinetics of the organo-hydrogels were examined, it was determined that the Ceftriaxone release of the organo-hydrogels synthesized with both types of crosslinkers conforms to the HM and KPM release kinetic model, given in Table 6. When Oxaliplatin release kinetics of organo-hydrogels were examined, it was observed that they fit the ZoM, HM and KPM release kinetics model, given in Table 7. When the results were examined, it was

Table 7 Release kinetic and mechanism of Oxaliplatin release

p(AG-m-SAO)[1]		7.4	p(AG-g-SAO)[1]		7.4
ZoM	C_o	1.512	**ZoM**	C_o	2.113
	k_o	− 0.006		k_o	− 0.007
	R^2	0.713		R^2	0.658
FoM	C_o	1.640	**FoM**	C_o	2.004
	k_1	− 0.018		k_1	− 0.008
	R^2	0.784		R^2	0.718
HM	k_h	0.008	**HM**	k_h	0.022
	R^2	0.955		R^2	0.991
KPM	n	0.392	**KPM**	n	− 2.255
	kkp	0.091		kkp	− 0.313
	R^2	0.841		R^2	0.872
p(AG-m-SAO)[2]			**p(AG-g-SAO)[2]**		
ZoM	C_o	1.494	**ZoM**	C_o	2.143
	k_o	− 0.003		k_o	− 0.004
	R^2	0.728		R^2	0.831
FoM	C_o	1.975	**FoM**	C_o	2.143
	k_1	− 0.001		k_1	− 0.004
	R^2	0.885		R^2	0.831
HM	k_h	0.024	**HM**	k_h	0.219
	R^2	0.952		R^2	0.992
KPM	n	0.378	**KPM**	n	− 1.835
	kkp	0.071		kkp	− 0.238
	R^2	0.929		R^2	0.969
p(AG-m-SAO)[3]			**p(AG-g-SAO)[3]**		
ZoM	C_o	0.842	**ZoM**	C_o	0.496
	k_o	− 0.006		k_o	− 0.006
	R^2	0.839		R^2	0.953
FoM	C_o	3.453	**FoM**	C_o	3.437
	k_1	− 0.009		k_1	− 0.003
	R^2	0.945		R^2	0.884
HM	k_h	0.025	**HM**	k_h	− 0.130
	R^2	0.953		R^2	0.994
KPM	n	0.371	**KPM**	n	− 1.498
	kkp	0.057		kkp	− 0.199
	R^2	0.954		R^2	0.905

Bold represents the oscillation model and parameters

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

seen that the drug release of organo-hydrogels complies with Fick's law. For all organo-hydrogels, n values were in the range of 0.1 to 0.5. It was observed that all organo-hydrogels have decreased release values and n values.

Conclusion

The results achieved in the study were summarized as follows:

Within the scope of the presented study, preparation of Agar, Glycerol and Sweet almond oil-based organo-hydrogels loaded synthesized with different cross-linkers (glutaraldehyde (G) or methylene bis acrylamide [37]) and release studies of different drugs such as ceftriaxone and Oxaliplatin were examined in vitro conditions.

Organo-hydrogels A more useful drug-organo-hydrogel system was developed which is prepared in the form of cylindrical geometry and film and thus could release drugs in the stomach, intestine, skin and blood fluid system.

The synthesized organo-hydrogels; As a result of balance swelling studies in physiological solutions (2.0–12 pH) compared to body fluids, it has been observed that there are organo-hydrogels sensitive to pH, which can be applied in gastric, intestinal, skin and blood fluid drug delivery systems.

Release studies of drug active molecules from Gel, hydrogels, and all organo-hydrogels which were loaded Ceftriaxone as a broad-spectrum antibiotic, and Oxaliplatin as drug component commonly used in cancer treatment were investigated 2.0, 5.5, 7.4 and 8.0 pH environments. as a result, organo-hydrogels release behaviors were founded to be sensitive to pH.

As a result; It can be suggested that all organo-hydrogels Ceftriaxone, Oxaliplatin and similar active substance molecules prepared as part of this study may be drug support materials that can be used in controlled release.

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