

Agar and Sesame Oil Based Organo-Hydrogels as a Pharmaceutical Excipient in Paracetamol/Carboplatin Release Systems

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Alpaslan *et al.*: Organo-Hydrogels in Emulsion Technique using Agar and Sesame Oil

Organo-hydrogels were synthesized by using free radical polymerization in the emulsion technique, using agar, glycerol, sesame oil, ammonium persulfate as initiator and N,N'-methylene bisacrylamide or glutaraldehyde as crosslinker. Swelling behaviors, blood compatibility, antioxidant and properties of the organo-hydrogels were investigated thoroughly. The highest swelling value was seen in organo-hydrogel synthesized with the N,N'-methylene bisacrylamide crosslinker containing 0.1 ml of sesame oil. Moreover, drug release behaviors of organo-hydrogels were studied as paracetamol and carboplatin used as model drugs. Release studies were shown that some basic parameters such as medium pH and composition of the polymer structure affect organo-hydrogels drug release behavior. As a result of drug release experiments, it was observed that the release values of organo-hydrogels changed depending on sesame oil and crosslinker content. The highest paracetamol release capacities for the p (AG-m-SO)² and p (AG-g-SO)² organo-hydrogels were calculated as 45.3 % and 79.8 %. When investigated carboplatin releases, the highest releases also were founded to be 100 % for p (AG-m-SO)² and 85 % for p (AG-g-SO)².

Key words: Organo-hydrogel, sesame oil, paracetamol, carboplatin, release system

The rapid development of technology in our age has led to the emergence of many innovations and new production models in various drug industries. One of the base reflections of these developments in the pharmaceutical industry is in the field of controlled drug delivery systems. These systems, which are the product of researches to solve some problems caused by classical drug forms and to resolve their deficiencies, have a history of approximately 20 y.

Synthesis or discovery of drugs with new biological effects for many years, It has been the focus of drug delivery research. Although this research area continues to be important, attention has been increasingly directed towards the way these drugs are administered. For a long time, it has been possible to develop release systems that can release the drug to certain areas of the body or control the long-term drug release rate^[1-5]. Some of these systems are liposomes, nano-associations, nanoparticles, active substance-polymer conjugates and polymers. In recent years, interest in organo-hydrogels has been increasing in these areas. The organogel-

hydrogels may consist of low molecular weight materials or polymeric materials. Polymeric organogel-hydrogels are classified as physical and chemical organogel-hydrogels. Chemical polymeric organogel-hydrogels are three-dimensional macromolecular structures that absorb water and organic solvents. Recently, organogel-hydrogels have been investigated in a wide range of fields including chemistry, biotechnology, drug delivery and pharmaceuticals.

In Sesame Oil (SO), it contains 7 %-12 % palmitic acid (C16:0), 0.3 %-6 % stearic acid (C18:0), 35 %-50 % oleic acid (C18:1), 35 %-50 % linoleic acid (C18:2), 0.3 %-0.8 % linolenic acid (C18:3), 2.6 % arachidonic acid (C20:4), respectively. In addition, SO is extremely resistant to oxidation due to secondary substances such

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as sesamine (0.5 %-1.5 %) and sesamol (0.3 %-0.5 %). Especially sesamin is very effective in lowering cholesterol levels in blood. One of the properties of SO is its tocopherol content. The total amount of tocopherol in SO ranges between 294-528 mg/kg. Tocopherols, the most powerful natural antioxidants that can be dissolved in fat, increase the nutritional value of the oil as vitamin E and fatty acids such as sesamine and sesamol was increased the antioxidant value^[6,7]. Because of these properties, sesame essential oils are used in the field of polymer and biomedical^[8-11].

Paracetamol (acetaminophen) is a drug active substance that is used as an alternative drug in aspirin-sensitive patients and has an antipyretic effect. Although its analgesic effect has been mild compared to the new generation analgesics, it's almost no side effects in the gastrointestinal tract, its reliability and its use in pregnant women ensure that paracetamol is always at the forefront and a classic analgesic^[12]. So far, although effective treatment or vaccine has not been produced for Coronavirus Disease-19 (COVID-19), has been reported in the literature used fever reducers, such as paracetamol, in primary care for fever in patients infected with the COVID-19 virus^[13-15].

Carboplatin (cis-diammine-[1,1-cyclobutanedicarboxylato]platinum(II)) is a 2nd generation platinum compound. It is designed to stop the growth of cancer cells and kill them. It is effective on carboplatin Deoxyribonucleic Acid (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^[16,17].

The synthesized gel, hydrogels and organo-hydrogels were investigated as an antioxidant, blood compatibility and drug release system. In this study, gels containing agar-based SO were synthesized using two different crosslinkers such as N,N'-methylene bisacrylamide (MBA) and Glutaraldehyde (GA) reagent. Characterization of synthesized gels; structural bonds are determined by Fourier Transform Infrared Spectroscopy (FTIR). The swelling properties of ethanol, acetone, ethanol/water, acetone/water, water

and tap water were investigated and the usability of the polymers as an effective sorbent was investigated. Organo-hydrogels were investigated for antioxidant, blood clotting, hemolysis properties and use in paracetamol and carboplatin drug delivery systems.

MATERIALS AND METHODS

Reagents:

Glycerol (Gly), agar (99 %), MBA (99 %), GA (25 % v/v), ethanol, acetone, Calcium Chloride (CaCl₂), 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. SO, gasoline, paracetamol and carboplatin were procured from local suppliers. Deionized (DI) water (18.2 MΩ cm; Human I) was also employed from the beginning to the end of this study. And the experimental procedures were as follows.

Agar-Glycerol (AG) based gels, hydrogels and organo-hydrogels synthesis:

Gel and hydrogels synthesized: AG 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.*^[18]. Gel and hydrogel compositions were given in Table 2.

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-Hydrogel	
poly (Agar-co-glycerol-co-sesame oil)/MBA-1	p (AG-m-SO) ¹
poly (Agar-co-glycerol-co-sesame oil)/MBA-2	p (AG-m-SO) ²
poly (Agar-co-glycerol-co-sesame oil)/MBA-3	p (AG-m-SO) ³
poly (Agar-co-glycerol-co-sesame oil)/GA-1	p (AG-g-SO) ¹
poly (Agar-co-glycerol-co-sesame oil)/GA-2	p (AG-g-SO) ²
poly (Agar-co-glycerol-co-sesame oil)/GA-3	p (AG-g-SO) ³

Note: AG: Agar-Glycerol; MBA: N,N'-Methylene Bisacrylamide; GA: Glutaraldehyde and SO: Sesame Oil

Organo-hydrogels synthesized: Free radical polymerization in emulsion media method was used to synthesis the AG-based organo-hydrogels given in Table 1. Briefly, first 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, of different amounts (0.1, 0.2 and 0.3 ml) SO 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 GA reagent was added as a crosslinker and further homogenized. Finally, the polymerization reaction was initiated by the addition of the initiator solution APS in 100 μ l DI water. Reaction temperatures were maintained at 25° with a temperature-controlled hot plate. Then, the solution was poured into a pipette with 6 mm diameter and was allowed to polymerize. These preparation steps were schematically given in fig. 1. Organo-hydrogel compositions were given in Table 2. 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-SO) and p (AG-g-SO) organo-hydrogels were dried in the oven at 40° until a constant weight was achieved and stored at 4° for further uses.

Organo-hydrogel synthesis containing paracetamol and carboplatin:

The synthesis of drug-loaded organo-hydrogels was synthesized as described by Alpaslan *et al.*^[18,19]. In addition to the reaction mixture mentioned above, 50 ppm 1ml paracetamol/carboplatin drug was added. Thus, drug-loaded organo-hydrogels were synthesized.

Characterization of organo-hydrogels:

Swelling analysis were performed with certain amounts of dried gel, hydrogels, organo-hydrogels placed in ethanol, water, ethanol/ID water (1:1), acetone, acetone/ID water (1:1), gasoline and different 2-12 pH for a day. Swelling tests were performed at 25°^[20-22].

The FT-IR spectra of organo-hydrogel was obtained from a Thermo Scientific Nicolet iS10 instrument using

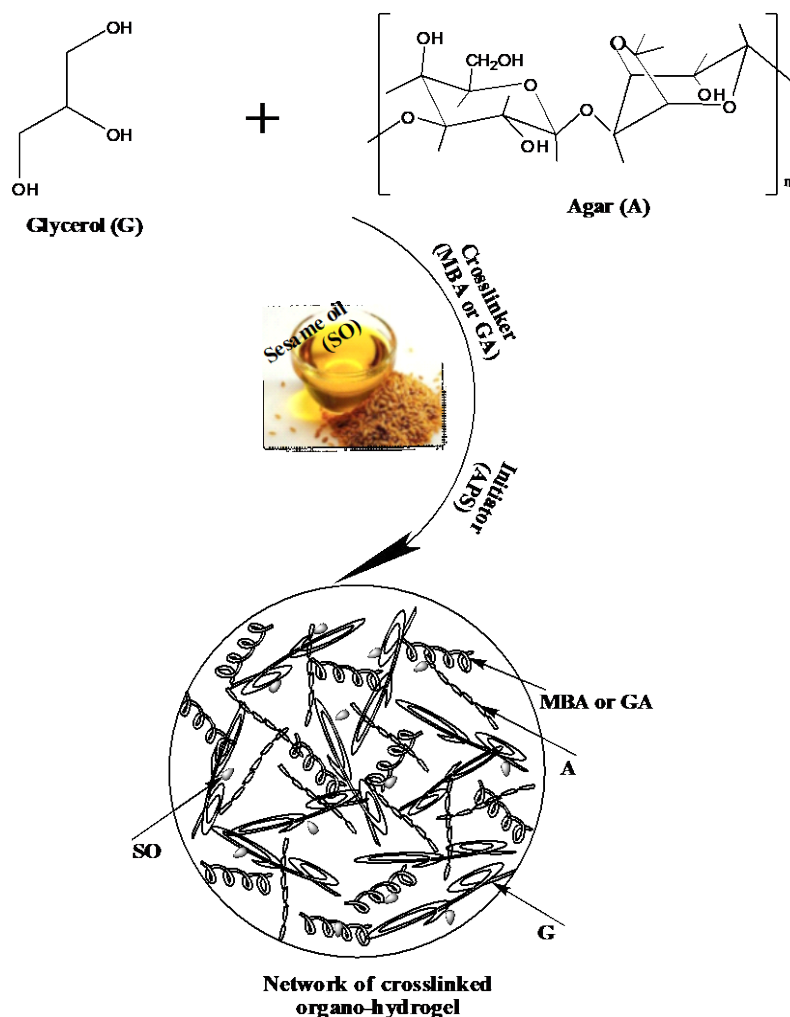


Fig. 1: Synthesis and schematic presentation of organo-hydrogels

Attenuated Total Reflectance (ATR) apparatus with 4 cm⁻¹ resolution between 4000-650 cm⁻¹.

Blood clotting and hemolysis analysis:

To evaluate the blood clotting^[23] and hemolysis analysis^[24] methods which were explained in the literature were applied.

Antioxidant analysis:

To evaluate the antioxidant activity, Folin-Ciocalteu (FC) assay^[25,26] and 2,2'-Azinobis-(3-Ethylbenzthiazolin-6-Sulfonic Acid (ABTS))^[21,26-28] methods which were explained in the literature were applied.

Paracetamol and carboplatin release studies:

Gel, hydrogels and organo-hydrogels loaded with a certain amount (50 ppm) of paracetamol, were used in 50 ml at four different pH values (2.0, 5.5 7.4 and 8.0 pH) for paracetamol (244 nm) release. Carboplatin (210 nm) release^[29] was performed in 50 ml 7.4 pH solution media. Each measurement was performed with 3 replicates and averaged with standard deviation values. The most common models, which are Zero order Model (ZoM)^[30,31], First order Model (FoM)^[32], Higuchi Model (HM)^[33] and Korsmeyer-Peppas Model (KPM) (the

power law), were used to identify the release kinetics. These equations are given in Table 3.

RESULTS AND DISCUSSION

FTIR analysis utilizes the fundamental physics principles infra-red to obtain a molecular fingerprint of synthesized gel, hydrogel and organo-hydrogel and to display for characterization of the functional groups. 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. 2. SO contained the band peak at 3401 cm⁻¹ belonging to the vibrations of the -OH groups, bands at 3007 cm⁻¹- 2896 cm⁻¹ and 2777 cm⁻¹ represented to -CH and -CH₂ vibrations. The peak in 1637 cm⁻¹- 1504 cm⁻¹ and 1471 cm⁻¹ belonged to the phenyl and -CH₂ groups and peak in 13 973 cm⁻¹ belonged to the methyl bands. The new bonds and structural diversity at organo-hydrogels were demonstrated the existence of hydrogen-bond interaction. After the SO got into the structure of the organo-hydrogel, the incoming bands from characteristic aromatic compounds (such as 3254 cm⁻¹, 3061 cm⁻¹ and 2922 cm⁻¹)^[7] exhibited high density and the peaks appear to be deepened or expanded. Considering the peaks in the organo-hydrogel, the peak at 1743 cm⁻¹, 1651 cm⁻¹ and 951 cm⁻¹ deepened, and the peak depth in the 1037 cm⁻¹ decreased. The change in these peaks indicated that SO entered the structure of the organo-hydrogel.

Since organo-hydrogels have the feature of swelling in different solvent environments, it is used as a water-retaining agent and artificial soil in agricultural applications, as well as personal care and hygienic products, in pharmacology controlled drug release applications.

The swelling ability of a polymeric gel determines by the interaction between the functional groups in its structure and the solvent. Push and pull between polymer chains are affected by non-covalent electrostatic, hydrophobic, van der Waals and hydrogen

TABLE 2: COMPOSITIONS AND CODES OF DIFFERENT ORGANO-HYDROGEL

Agar	Glycerol	SO	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-SO) ¹
2 %-2 ml	0.04 ml	0.2 ml	MBA	p (AG-m-SO) ²
2 %-2 ml	0.04 ml	0.3 ml	MBA	p (AG-m-SO) ³
2 %-2 ml	0.04 ml	0.1 ml	GA	p (AG-g-SO) ¹
2 %-2 ml	0.04 ml	0.2 ml	GA	p (AG-g-SO) ²
2 %-2 ml	0.04 ml	0.3 ml	GA	p (AG-g-SO) ³

Note: AG: Agar-Glycerol; MBA: N,N'-Methylene Bisacrylamide; GA: Glutaraldehyde and SO: Sesame Oil

TABLE 3: MATHEMATICAL MODELS FOR DRUG RELEASE

Model	Mathematical equation	Release mechanism	Codes
Zero order kinetic model	$C_r = C_0 - k_0 \cdot t$	Diffusion mechanism	ZoM
First order kinetic model	$\ln C_r = \ln C_0 - k_1 \cdot t$	Fick's first law, diffusion Mechanism	FoM
Higuchi model	$C_r / C_\infty = k_{H1} \cdot \sqrt{t}$	Diffusion medium based mechanism in Fick's first law	HM
Korsmeyer-Peppas model	$\ln C_r / C_\infty = \ln k_{KP} + n \cdot \ln t$	Semi empirical model, diffusion-based mechanism	KPM

Note: 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_{H1} is Higuchi release rate constant (1/√min); k_{KP} is Korsmeyer-Peppas release rate constant and n is release exponent which is indicative of the transport mechanism ($M_t/M_\infty < 0.6$ should only be used

bonding, hydrophobic interactions are such as physical crosslinker interactions and this affects the swelling behavior of the gel^[34].

The change in percent swelling of organo-hydrogels as a function of solvent concentration in water and organic solvent mixtures was shown in fig. 3. After the AG gel was crosslinked, the DI water absorption capacity increased in ratio 16 % for p (AG-m) and 27 % for p (AG-g), and the tap water absorption capacity increased in ratio 35 % for p (AG-g) and 68 % for p (AG-m)^[18]. When fig. 2. was examined, it has been determined that organo-hydrogels have absorption values close to each other with ethanol/DI water and acetone/water. When organo-hydrogels were compared among themselves, it was showed that p (AG-m-SO)³ organo-hydrogel has higher water absorption capacity than other organo-hydrogels *via* 110.8 % swelling value. Same time, it is seen that the organo-hydrogel swells up to 50 % in ethanol/DI water and acetone/DI water media. It was generally observed that the organo-hydrogels' S % value decreased with the increase of essential oil in the organo-hydrogel composition. Those observations were consistent with the literature^[35,36].

A small amount of swelling was observed in acetone

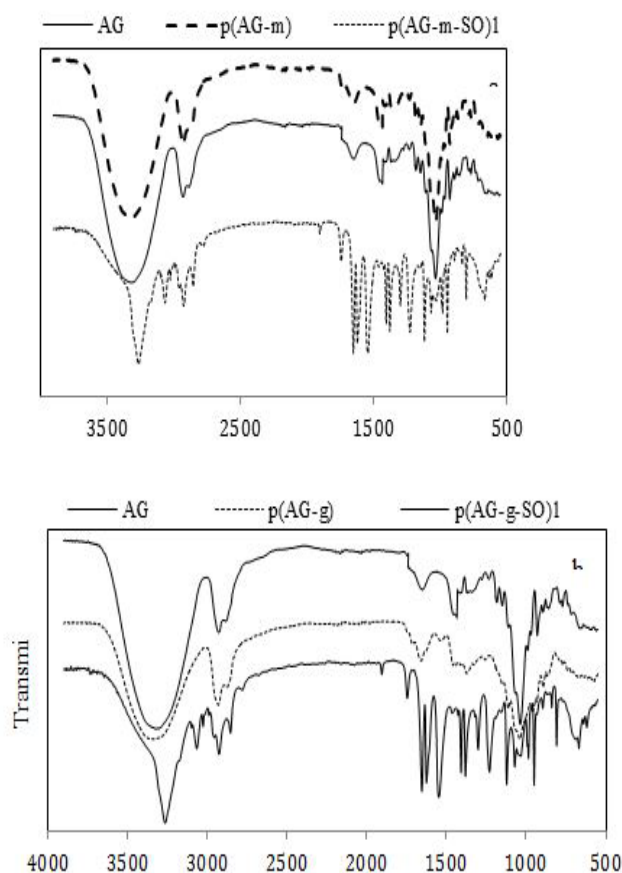


Fig. 2: FT-IR Spectra of (a) AG, p (AG-m) and p (AG-m-SO)¹; (b) AG, p (AG-g) and p (AG-g-SO)¹ organo-hydrogels

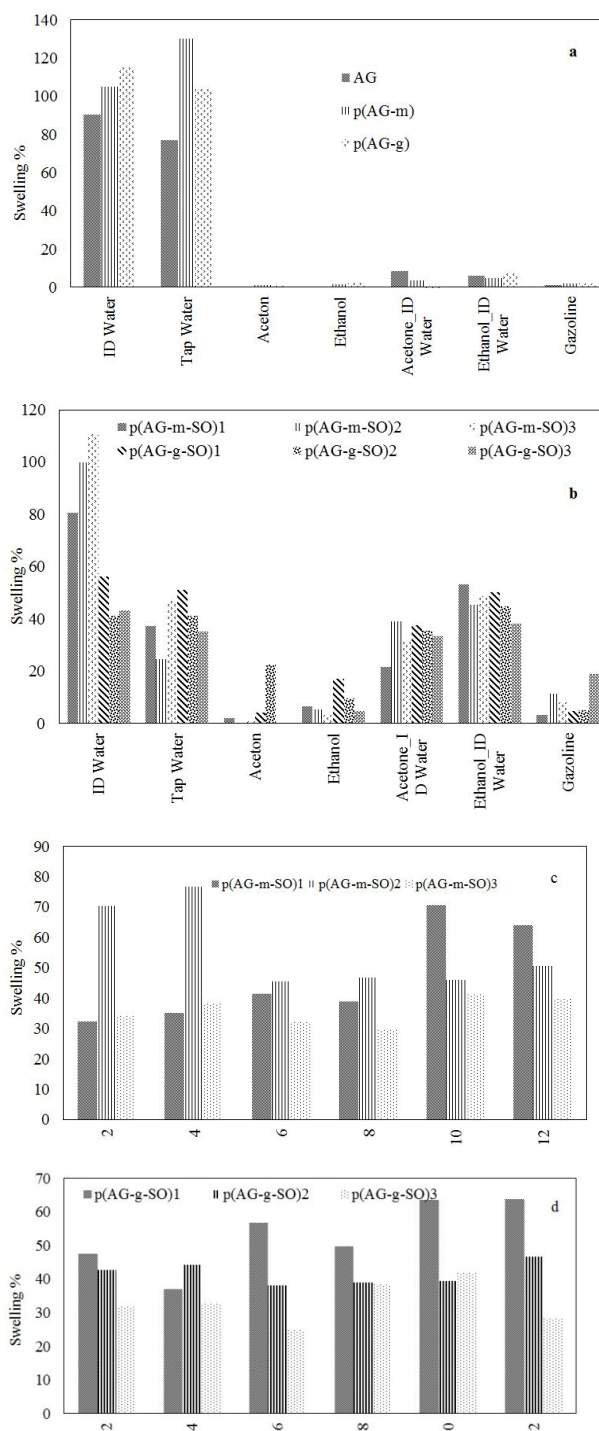


Fig. 3: Percent swelling degree of the (a) AG, p (AG-m), p (AG-g) and (b) Organo-hydrogels with time in DI water, tap water, ethanol, acetone, ethanol/DI water (1:1), acetone/DI water (1:1) and gasoline. Swelling percent of the (c) AG, p (AG-m), p (AG-g) and (d) Organo-hydrogels as a function of 2-12 pH (pH is adjusted by the addition of 0.1 M HCl, 0.1 M NaOH)

and ethanol media. 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^[37]. Therefore,

more hydrophobic groups in solvents reduce swelling of organo-hydrogels in water mixtures of ethanol, acetone and gasoline compositions.

If we evaluate organo-hydrogels in terms of crosslinkers; GA crosslinked organo-hydrogels and MBA crosslinked organo-hydrogels not seen a significant difference between the swelling values in solvent media. 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. The swelling of organo-hydrogels in different organic solvent-water mixtures can be controlled by the solvent composition.

The change in swelling properties in different types of media is due to the different ion mobility in the medium^[38,39]. 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 SO was added to the structure of the organo-hydrogels in different proportions, the number of ionizable groups in the structure of the organo-hydrogels increased and becomes sensitive to changes in different pH values. However, the anionic and cationic properties of the ionizable groups of organo-hydrogels increased and showed different swelling behaviors at different pH values.

Antioxidant can neutralize free radicals (harmful molecules), preventing them from harming a living cell. Antioxidant analysis is therefore of great importance in order to perform the drug release studies of newly synthesized organo-hydrogels. Unlike other vegetable oils, SO is highly resistant to oxidation due to its high content of oleic and linoleic acids, as well as secondary substances such as sesamine and sesamol. One of the properties of SO is its tocopherol content. Tocopherols, which are the most powerful natural antioxidants that can be dissolved in fat, increase both the nutritional value of the oil as vitamin E and the antioxidant value such as sesamine and sesamol^[6,10]. Antioxidant analyses were performed to determine the antioxidant properties of organo-hydrogel. The antioxidant activity of SO, p (AG-m), p (AG-g) and organo-hydrogels is given in Table 4 as the gallic acid equivalent value. The SO, p (AG-m), p (AG-g) and organo-hydrogels reduction capacity can determine it was antioxidant activity. When Table 4 is analyzed, as the concentration of the substance increases, the reduction power also

TABLE 4: TOTAL PHENOL CONTENT VALUES

Substance	Total phenol values (mg)
Organo-hydrogel	
p (AG-m-SO) ¹	438
p (AG-m-SO) ²	438
p (AG-m-SO) ³	375
p (AG-g-SO) ¹	203
p (AG-g-SO) ²	217
p (AG-g-SO) ³	212
Oil	
Sesame Oil	565

Note: AG: Agar-Glycerol and SO: Sesame Oil

increases due to the absorbents. When these values are considered, organo-hydrogels show higher antioxidant activity than other gels.

Organo-hydrogels must have a biocompatibility feature in order to be used in the release studies in the human body. In the long-term use of biomaterials in the biomedical field, as a result of the contact of blood with the biomaterial, many biological reactions occur on the surface of the biomaterial first. The purpose of the hemocompatibility; is to determine whether a toxic effect in the blood will occur as a result of a biomaterial coming into contact with blood. Therefore, blood compatibility properties of organo-hydrogels were determined by hemolysis and blood clotting tests hydrogel^[40,41]. Organo-hydrogels hemolysis analysis results were summarized in fig. 4. The hemolysis values AG, AG-m, AG-g, SO and organo-hydrogels were calculated at 5 mg/ml gel a concentration of 0.9 % for p (AG-m-SO)¹, 0.6 % for p (AG-m-SO)², 0.4 % for p (AG-m-SO)³, 0.9 % for p (AG-m-SO)¹, 0.4 % for p (AG-m-SO)², 0.5 % for p (AG-m-SO)³, respectively. It is stated that the hemolysis rate is not hemolytic up to 5 % hydrogel. Therefore, it can be said that organo-hydrogels were hemolysis at this rate. Another method of evaluating organo-hydrogel blood compatibility is to determine the organo-hydrogel Blood Clotting Index (BCI). The organo-hydrogel BCI values were shown in fig. 4b. In the fig, blood clotting indexes of organo-hydrogels were founded to be 5.9 % for p (AG-m-SO)¹, 6.8 % for p (AG-m-SO)², 4.8 % for p (AG-m-SO)³, 6.3 % for p (AG-m-SO)¹, 4.5 % for p (AG-m-SO)², 6.4 % for p (AG-m-SO)³. For these organo-hydrogels blood contact applications, the amount should be less than 5 mg/ml.

The main target of the studies in the field of medicine is to minimize the drug dose, to extend the dosing interval, to increase the quality of life by ensuring that the

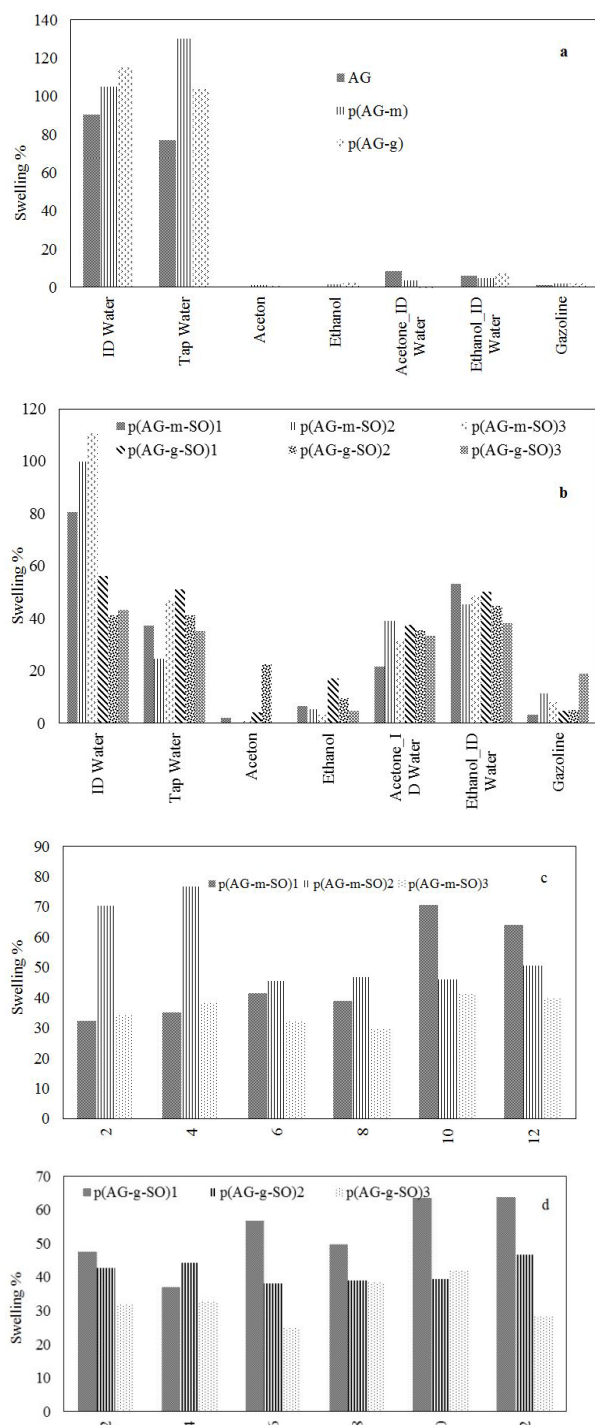


Fig. 4: Blood combability of the AG, p (AG-m), p (AG-g) and organo-hydrogels (a) Hemolysis and (b) Blood clotting

patient is not affected by the side and harmful effects. The systems that best respond to these expectations are “controlled release systems”. Recently, the use of organo-hydrogels in controlled release systems has been the focus. To perform a release of paracetamol and carboplatin, organo-hydrogels were imitated gastric, intestinal, oral, blood and skin media *in vitro*. For this, release analysis was done in different pH environments. All organo-hydrogels may not show the same behavior

in every pH environment^[42].

In this study, synthesized biocompatible gel, hydrogel and organo-hydrogels were utilized for their paracetamol and carboplatin release capacities. The amount of paracetamol and carboplatin loaded on gel, hydrogel and organo-hydrogels were determined as 50 ppm. Fig. 5 shows the paracetamol release behavior of organo-hydrogels at 37.5°. AG, p (AG-m) and p (AG-g) maximum paracetamol release were 8 % at pH 8.0, 7.8 % at pH 2.0 and 8.2 % at pH 2.0, respectively. Moreover, AG, p (AG-m) and p (AG-g) maximum carboplatin release were 1.8 %, 1.6 % and 2.6 % at pH 7.4, respectively. Due to the difference in concentration in the release event, while the solvent enters the organo-hydrogel structure, the loaded drug switches to the solvent medium. When fig. 5a- fig. 5d was examined, it was observed while all organo-hydrogels release paracetamol slowly, to release carboplatin rapidly. The amount of drugs released from the organo-hydrogel system was given in Table 5. As seen in the table, the highest paracetamol release is observed in p (AG-g-SO)² and p (AG-m-SO)³ organo-hydrogels, while the highest carboplatin release was found in p (AG-g-SO)² and p (AG-m-SO)² organo-hydrogels. When paracetamol release was compared between p (AG-m-SO) organo-hydrogels, it appeared that the minimum and maximum percent release was to be 23.9 % at pH 2.0 at the p (AG-m-SO)¹ and 45.3 % at pH 5.5 at the p (AG-m-SO)² organo-hydrogel. Compared between paracetamol release p (AG-g-SO) organo-hydrogels, the minimum percentage release was to be 42.6 % p (AG-g-SO)¹ at pH 2.0, while maximum percentage release was to be 79.8 % p (AG-g-SO)¹ organo-hydrogel was found to be at pH 2.0. The highest cumulative paracetamol release from organo-hydrogels was observed in organo-hydrogels synthesized by GA crosslinker. It was been seen from the results that paracetamol release can be controlled by changing the amount of SO in organo-hydrogels. When investigated carboplatin releases, the highest carboplatin releases were observed to be 100 % for p (AG-m-SO)² and 85 % for p (AG-g-SO)². Moreover some of the other reported material at literature was as p (AG-g-PmO) organo-hydrogels (72.3 % at pH 7.4) and p (AG-m-PmO) organo-hydrogels (69.8 % at pH 2.0)^[18], carboxylated lignin (70 % paracetamol), lignin tablet (70 % paracetamol) and non-lignin tablet (70 % paracetamol)^[43], 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)^[18], p (AG-g-GO)³ organo-hydrogels at (95.4 %, pH 7.4 carboplatin)^[44], pure drug

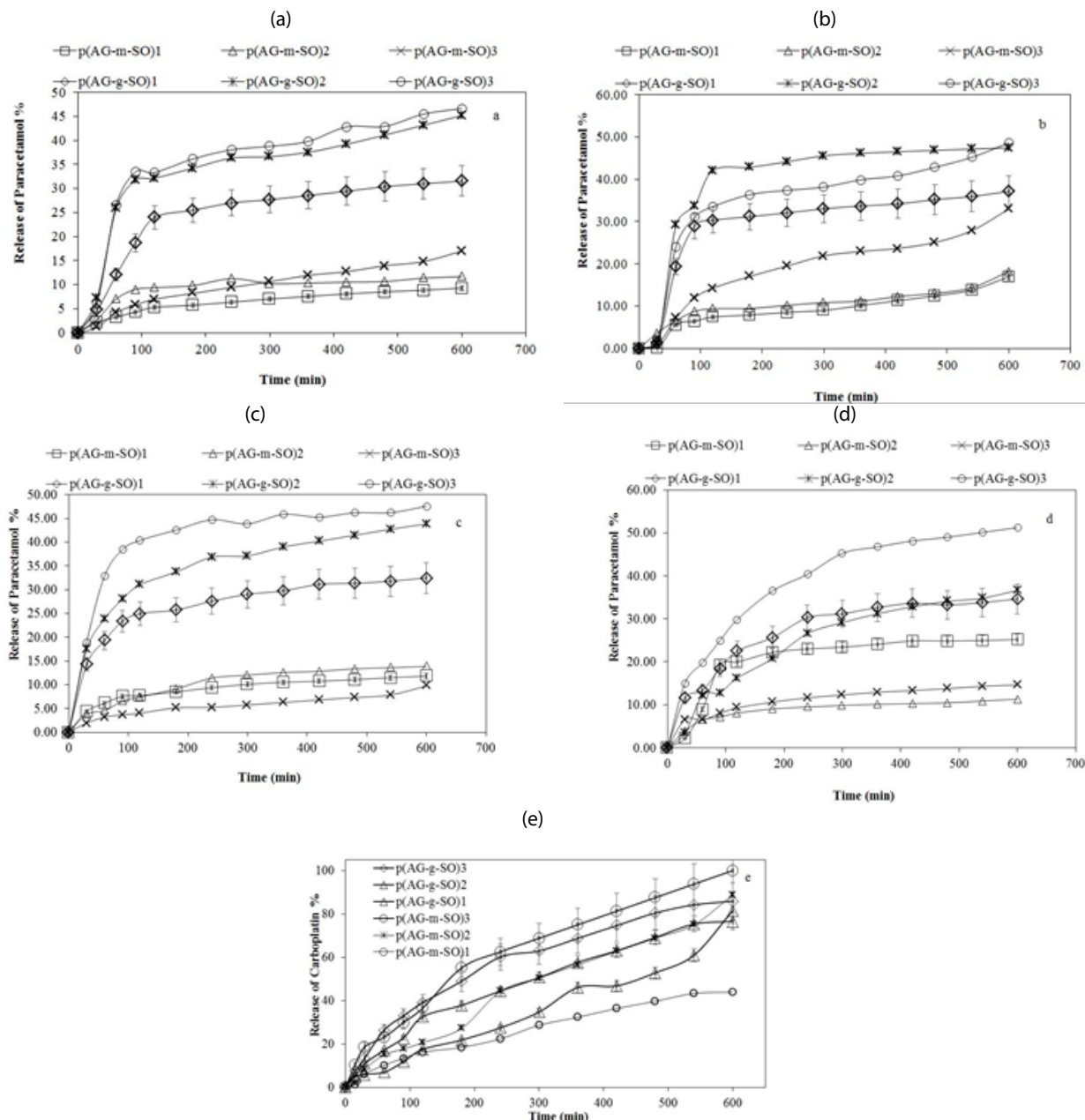


Fig. 5: Release behavior of paracetamol (a) 2.0 pH; (b) 5.5 pH; (c) 7.4 pH; (d) 8.0 pH from organo-hydrogels and carboplatin and (e) 7.4 pH organo-hydrogels (the first 600 min of paracetamol and carboplatin release were given in the graph)

TABLE 5: PARACETAMOL AND CARBOPLATIN PERCENTAGE RELEASE VALUES

	Paracetamol				Carboplatin
	pH 2.0	pH 5.5	pH 7.4	pH 8.0	pH 7.4
	Release %				Release %
AG	2.3	3.5	3.1	8.1	1.8
p (AG-m)	7.8	4.4	3.4	3.9	1.6
p (AG-g)	8.2	6.3	5.2	6.8	2.6
p (AG-m-SO) ¹	23.9	29.1	31.6	41	71.4
p (AG-m-SO) ²	34.3	33.8	33.3	27	100
p (AG-m-SO) ³	36.6	45.3	42.7	34.8	95.1
p (AG-g-SO) ¹	42.6	51.4	52.5	57.4	84.4
p (AG-g-SO) ²	79.8	71.9	69.5	61.2	85.2
p (AG-g-SO) ³	77.6	73.6	77.5	73.6	68.8

Note: AG: Agar-Glycerol and SO: Sesame Oil

(100 % carboplatin), carboplatin-loaded Polyethylene Glycol-Modified Multiwall Carbon Nanotube (PEGylated MWCNT) (95 % carboplatin) and enteric-coated PEGylated MWCNTs (95 % carboplatin)^[16] *so on*.

The analysis results were applied to the mathematical models shown in Table 6 to find the most suitable release model of organo-hydrogels. Paracetamol and carboplatin release data of organo-hydrogels were processed into these kinetic models to investigate release kinetics and systems. Given the best Correlation Coefficients (R^2) values, the most suitable model was chosen to symbolize paracetamol release behavior. The

TABLE 6: RELEASE KINETIC AND MECHANISM OF PARACETAMOL RELEASE

p (AG-m-SO) ¹		2	5.5	7.4	8	p (AG-g-SO) ¹		2	5.5	7.4	8
ZoM	Co	1.37	1.657	1.564	1.442	ZoM	Co	2.591	3.428	3.366	2.818
	ko	-0.002	-0.004	-0.004	-0.003		ko	-0.008	-0.009	-0.007	-0.009
	R ²	0.778	0.792	0.844	0.852		R ²	0.676	0.557	0.668	0.766
FoM	Co	1.045	1.726	5.222	3.819	FoM	Co	6.596	6.702	16.735	162.033
	k1	-0.001	-0.001	-0.003	-0.003		k1	0	-0.001	-0.006	-0.006
	R ²	0.044	0.546	0.826	0.901		R ²	0.783	0.718	0.907	0.745
HM	kh	0.033	0.02	0.031	0.031	HM	kh	0.046	0.864	0.037	0.038
	R ²	0.995	0.901	0.927	0.927		R ²	0.988	0.204	0.99	0.992
	n	0.452	0.457	0.521	0.462		n	0.252	0.168	0.29	0.254
KPM	kcp	0.036	30.009	44.8	35.677	KPM	kcp	0.176	3.104	8.223	6.697
	R ²	0.978	0.89	0.966	0.928		R ²	0.857	0.983	0.987	0.985
P (AG-m-SO) ²		2	5.5	7.4	8	p(AG-g-SO) ²		2	5.5	7.4	8
ZoM	Co	1.499	1.129	1.195	1.557	ZoM	Co	2.757	3.273	2.904	1.228
	ko	-0.003	-0.006	-0.005	-0.004		ko	-0.007	-0.008	-0.007	-0.008
	R ²	0.564	0.878	0.8	0.683		R ²	0.652	0.518	0.698	2.818
FoM	Co	2.666	1.996	3.754	8.892	FoM	Co	5.398	6.875	53.165	182.181
	k1	-0.001	-0.001	-0.004	-0.002		k1	-0.001	0	-0.004	-0.003
	R ²	0.593	0.827	0.983	0.902		R ²	0.783	0.459	0.904	0.753
HM	kh	0.039	0.019	0.032	0.035	HM	kh	0.036	0.792	0.038	0.038
	R ²	0.996	0.728	0.968	0.926		R ²	0.997	0.004	0.992	0.992
	n	0.094	0.202	0.361	0.174		n	0.277	0.164	0.165	0.165
KPM	kcp	0.438	7.043	16.224	3.902	KPM	kcp	0.114	2.937	3.499	3.499
	R ²	0.738	0.802	0.939	0.875		R ²	0.77	0.884	0.941	0.941
p (AG-m-SO) ³		2	5.5	7.4	8	p (AG-g-SO) ³		2	5.5	7.4	8
ZoM	Co	0.491	1.056	0.355	1.121	ZoM	Co	3.329	2.922	3.32	2.548
	ko	-0.005	-0.008	-0.002	-0.003		ko	-0.005	-0.004	-0.005	-0.005
	R ²	0.951	0.905	0.938	0.775		R ²	0.373	0.414	0.519	0.591
FoM	Co	1.144	1.595	1.693	4.046	FoM	Co	5.288	4.431	138.449	41.372
	k1	-0.002	-0.003	-0.002	-0.003		k1	0	0	-0.002	-0.002
	R ²	0.871	0.959	0.959	0.096		R ²	0.571	0.555	0.89	0.843
HM	kh	0.028	0.028	0.032	0.032	HM	kh	0.029	0.862	0.036	0.036
	R ²	0.97	0.891	0.978	0.978		R ²	0.982	0.007	0.994	0.994
	n	0.55	0.64	0.415	0.415		n	0.168	0.069	0.111	0.111
KPM	kcp	0.016	1	18.554	11.517	KPM	kcp	0.259	1.708	2.559	2.559
	R ²	0.993	0.858	0.989	0.979		R ²	0.937	0.739	0.92	0.92

Note: Fickian diffusion mechanism $n \leq 0.45$, non-Fickian (anomalous) diffusion mechanism $0.45 < n < 0.89$; AG: Agar-Glycerol; SO: Sesame Oil; ZoM: Zero order kinetic model; FoM: First order kinetic model; HM: Higuchi Model and KPM: Korsmeyer-Peppas Model

highest R^2 for all organo-hydrogels were seen in HM and KPM and it was determined that the paracetamol release occurred in accordance with these models. The n value expressed in the KPM gives information about whether the polymeric materials have the behavior that complies with Fick's law. As seen in Table 7, the diffusion exponentials of organo-hydrogels are generally < 0.45 and were found to behave in accordance with Fick's law. The carboplatin release of organo-hydrogels revealed a very high R^2 with the ZoM, HM and KPM. As seen in Table 7, diffusion exponents of carboplatin release

of organo-hydrogels, it has been found that it generally behaves according to non-Fick law. According to the Fick law, it was shown that the release was controlled by swelling and according to the non-Fick law, it was controlled by both swelling and relaxation.

The use of polymeric materials is more preferred in the preparation and development of controlled drug delivery systems. There are a few key factors to consider when developing these systems. The material to be applied which exhibits different swelling behavior

TABLE 7: RELEASE KINETIC AND MECHANISM OF CARBOPLATIN RELEASE

p (AG-m-SO) ¹		7.4	p (AG-g-SO) ¹		7.4
ZoM	Co	2.023	ZoM	Co	0.948
	ko	-0.031		ko	-0.039
	R ²	0.981		R ²	0.989
FoM	Co	2.102	FoM	Co	2.619
	k1	-0.006		k1	-0.005
	R ²	0.677		R ²	0.9
HM	kh	0.032	HM	kh	0.046
	R ²	0.995		R ²	0.993
	n	0.643		n	1.052
KPM	kkp	0.012	KPM	kkp	0.001
	R ²	0.99		R ²	0.932
p (AG-m-SO) ²		7.4	p (AG-g-SO) ²		7.4
ZoM	Co	1.31	ZoM	Co	3.486
	ko	-0.043		ko	-0.033
	R ²	0.983		R ²	0.978
FoM	Co	3.646	FoM	Co	4.467
	k1	-0.004		k1	-0.003
	R ²	0.895		R ²	0.85
HM	kh	0.037	HM	kh	0.034
	R ²	0.992		R ²	0.997
	n	0.85		n	0.644
KPM	kkp	0.004	KPM	kkp	0.016
	R ²	0.982		R ²	0.989
p (AG-m-SO) ³		7.4	p (AG-g-SO) ³		7.4
ZoM	Co	2.006	ZoM	Co	2.25
	ko	-0.028		ko	-0.024
	R ²	0.949		R ²	0.926
FoM	Co	3.102	FoM	Co	4.652
	k1	-0.004		k1	-0.002
	R ²	0.816		R ²	0.897
HM	kh	0.026	HM	kh	0.027
	R ²	0.98		R ²	0.967
	n	0.646		n	0.534
KPM	kkp	0.017	KPM	kkp	0.03
	R ²	0.992		R ²	0.995

Note: Fickian diffusion mechanism $n \leq 0.45$, non-Fickian (anomalous) diffusion mechanism $0.45 < n < 0.89$; AG: Agar-Glycerol; SO: Sesame Oil; ZoM: Zero order kinetic model; FoM: First order kinetic model; HM: Higuchi Model and KPM: Korsmeyer-Peppas Model

in different solvent and different pH environments; has biocompatible with the human body; is to ensure the controlled release of the drug substance into the target area. In the context of this study, we show that the organo-hydrogels we synthesized can be used as an alternative drug delivery system, thanks to the features mentioned above. Organo-hydrogels containing agar, glycerol and SO cross-linked with MBA and GA

reagents were synthesized by the free-radical emulsion polymerization method in the presence of the APS. Synthesized organo-hydrogels were characterized by swelling, FTIR, antioxidant and blood compatible analyses. According to the data obtained, the maximum balance swelling value was reached as 110.8 % in the p (AG-g-SO)³ organo-hydrogel water environment. Same time, it is seen that the organo-hydrogel swells up to 50 % in ethanol/DI water and acetone/DI water media. It can be said that organo-hydrogels were blood compatible and antioxidant properties. When paracetamol and carboplatin release were compared between organo-hydrogels, it appeared that the maximum percent release was to be 79.8 % at pH 2.0 at the p (AG-g-SO)² and 100 % at pH 7.4 at the p (AG-m-SO)² organo-hydrogel. Organo-hydrogels loaded with paracetamol showed very high correlations with KPM and HM release kinetics, while carboplatin loaded organo-hydrogels showed very high correlations with ZoM, KPM and HM release kinetics. Organo-hydrogels containing SO can potentially be used in biomedical, pharmaceutical and drug delivery systems due to their stated properties.

Conflict of interest:

The authors declared no conflict of interest.

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