Application of poly (Agar-co-Glycerol-co-Sweet Almond Oil) based organohydrogels 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 organohydrogels containing pH-sensitive Agar (A), Glycerol (G), Sweet Almond oil (SAO). Organohydrogels, 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 organohydrogels were examined. In addition, Organohydrogels which loaded with Ceftriaxone (antibiotic) and Oxaliplatin (an anti-cancer agent), 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), skin surface (pH 5.5), blood fluid (pH 7.4) and intestinal fluid (pH 8), 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 organohydrogels and values consistent with release results were found.

1. 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 organohydrogels 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 organohydrogels, 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 gruop 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].

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 organohydrogels 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 organohydrogels drug-release studies have been investigated in vitro conditions Organohydrogels systems have been prepared using the free radical polymerization technique in the emulsion media method. The drug-loaded organohydrogels release kinetics at different pH were interpreted to investigate the release behaviors. Organohydrogels release behaviors were compared to investigate the effect of ceftriaxone and carboplatin drugs on release kinetics.

2. Materials And Methods

Agar-Glycerol-based gels and 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[16]. Gel and hydrogel compositions were given in Table 2. For the preparation of organohydrogels above given method was used (Table 1). Shortly; agar solution (2 mL), glycerol (0.04 mL), and Sweet Almond oil (0.1, 0.2 and 0.3 mL) were added to the 21 mL vial and made homogeneous by vortex (at 25 00 rpm for 1 5 min) until the formation of a clear homogeneous solution emulsion. Crosslinker reagent was added and further homogenized. Organohydrogel compositions were showed in Table 2. The polymerization reaction was initiated by the addition of the initiator solution APS in 0.1 mL DI water. Reaction were maintained at 25°C with a temperature-controlled hot plate. These preparation steps are schematically given in Figure 1. The gel, hydrogels and organohydrogels were kept in DI water. Finally, the synthesized materials were dried until a constant weight was achieved and stored at 4ºC for further uses.

Organohydrogel synthesis containing Ceftriaxone and Oxaliplatin

Ceftriaxone or Oxaliplatin drugs were directly synthesized with organohydrogel [17]. The synthesis of Ceftriaxone/Oxaliplatin-loaded organohydrogels was the same as the synthesis procedure of the organohydrogels described above. In addition to only the reaction mixture mentioned above, Ceftriaxone or Oxaliplatin (50 ppm 1mL) were added.

Characterization of organohydrogels

Swelling analysis were performed with certain amounts of dried materials placed in ethanol, water, acetone, ethanol/IDwater (1:1), gasoline and acetone/IDwater (1:1) different 2-12 pHs for a day. Swelling tests were performed at 25ºC [18, 19].

The FT-IR spectra of organohydrogel was obtained from a Thermo Scientific Nicolet iS10 instrument using ATR apparats with 4 cm^{-1} resolution between 4000-650 cm^{-1}

To evaluate the blood clotting [16] and hemolysis analysis [20] methods which were explained in the literature were applied.

To evaluate the antioxidant activity, FC [21-23] and ABTS [22, 24] methods which were emphases in the literature were applied.

Ceftriaxone and Oxaliplatin release studies

Synthesized drug-loaded gel, hydrogels and organohydrogels were used as controlled release systems for Ceftriaxone (antibiotic) and Oxaliplatin (an anti-cancer agent), which are frequently used in the medical field The release methods [16] [20] which were explained in the literature were applied. Released Ceftriaxone and Oxaliplatin quantities were calculated on the calibration curves prepared at 244 nm and 210 nm amount were calculated on the calibration curves measurement in the UVVis-spectrophotometer, respectively. The most prevalent models was used. Those equations were showed in Table 3.

3. Results And Discussion

Swelling properties of the Organohydrogels

Swelling work carried out in polar and apolar environments is a widely used technique for characterizing gel, hydrogel and organohydrogels. 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 organohydrogels 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 Figure 2. After the AG gel was crosslinked, the IDwater absorption capacity increased in ratio[16, 20]. On the contrary, after the hydrogel added SAO, the IDwater absorption capacity approximately decreased in 40-52% for p(AG-m) and 27-60% for p(AG-g) the tapwater absorption capacity decreased in 37-57% for p(AG-g) and 47-73% for p(AG-m). p(AG-g-SAO)^1 organohydrogel 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 organohydrogel in acetone and gasoline media were approximately 7.6% and 2.4%. In this situation; organohydrogels are associated with functional gruops in their structure and these gruops are; very prone to hydrogen bonding with water molecules. As a result of

the said gruops forming hydrogen bonds with water molecules, more water molecules enter the organohydrogel structure and as a result, the organohydrogel swells more. On the other hand, swelling behavior in the polar environment; relates to protonation of functional gruops. Functional gruops formed in organohydrogel repel each other and cause organohydrogel pores to grow. Hereat; more solvent molecules enter the growing pores of organohydrogels, causing it to swell [25].

If we evaluate organohydrogels in terms of cross-linkers; GA cross-linked organohydrogels 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 organohydrogels; 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 organohydrogels is pH-sensitive. This behavior; was an important feature of organohydrogels that release controlled drugs to be used especially in the stomach, intestine, skin and blood systems.

Fourier Transform Infrared Spectroscopy (FT-IR) analysis

Organohydrogels, AG, p(AG-m), p(AG-g) were prepared by free radical polymerization in emulsion media and the FTIR spectra were shown in Figure 3 and explain in the literature [16, 20]. Sweet almond oil contained the band peak at 3600-3000 cm^{-1} belonging to the vibrtions of the -OH gruops, 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 [26, 27]. The new bonds and structural diversity at organohydrogels were demonstrated the existence of hydrogen-bond interaction. After the SAO got into the structure of the organohydrogel, the incoming bands from characteristic aromatic compounds (such as 2922 cm^{-1} -2853, cm^{-1}, 1640 cm^{-1} and 1532 cm^{-1}) exhibited high density, and the peaks appear to be deepened or expanded. Considering the peaks in the organohydrogel, 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 organohydrogel.

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 organohydrogels was given in table 4 as the gallic acid equivalent value. The SAO, AG, p (AG-m), p (AG-g) and organohydrogels 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 organohydrogels 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, organohydrogels shown higher antioxidant activity than the others.

Blood clotting and hemolysis tests

Organohydrogels must meet certain criteria in order to be used in medical applications. Therefore, primary measures to determine the blood compatibility of organohydrogels 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 organohydrogel are coagulation (BCI) and hemolysis tests. Organohydrogels blood compatibility analysis results were summarized in Figure 4. Hemolysis and blood coagulation analysis of gel, hydrogels and organohydrogels were performed and calculated. It was stated that the hemolysis rate was not hemolytic up to 5%. Therefore, it can be said that organohydrogels were blood compatible at this rate. Hemolysis and blood clotting (BCI) analysis of AG, AG-m, AG-g, SAO and organohydrogels (at a concentration of 5 mg / mL) were performed, calculated and was given in Figure 4a,b.

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. Organohydrogels are very suitable for such applications with their wide range of mechanical, physical and chemical properties. The structure of organohydrogels 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 organohydrogels 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 equilibrium in four different pH environments and results. It were given in Figure 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 organohydrogels were compared in terms of release amounts, the maximum release was obtained in the p(AG-g-SAO) organohydrogels. It was observed that p(AG-g-SAO) organohydrogel released 29% of Ceftriaxone and 100% of Oxaliplatin at 7.4 pH. It was found that the release of organohydrogels containing ceftriaxone was slow, and the total amount of drug released after 8 hours was low. These findings were interpreted as that Ceftriaxone in the organohydrogel structure can not only prolong the release but also protect Ceftriaxone from hydrolysis. As seen in Figure5 , the amount of Oxaliplatin in the environment increased in the first 60 minutes, but then began to decrease over time. And almost all organohydrogels was observed to release 100% of Oxaliplatin in its structure within 10 hours. Unlike Ceftriaxone release from organohydrogels, 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)[28], Citrus-Pectin (CP) (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) [29], chitosan 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)[30], 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 organohydrogels.

When the Ceftriaxone release kinetics of the organohydrogels were examined, it was determined that the Ceftriaxone release of the organohydrogels synthesized with both types of crosslinkers conforms to the HM and KPM release kinetic model, given in Table 6. When Oxaliplatin release kinetics of organohydrogels 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 seen that the drug release of organohydrogels complies with Fick's law. For all organohydrogels, n values were in the range of 0.1 to 0.5. It was observed that all organohydrogels 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 organohydrogels loaded synthesized with different cross-linkers (glutaraldehyde (G) or methylene bis acrylamide (MBA)) and release studies of different drugs such as ceftriaxone and Oxaliplatin were examined in vitro conditions.

Organohydrogels A more useful drug-organohydrogel 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 organohydrogels; 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 organohydrogels 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 organohydrogels 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, organohydrogels release behaviors were founded to be sensitive to pH.

As a result; It can be suggested that all organohydrogels 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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Tables

Table 1 Codes of different organohydrogel

Gel	Code
Agar-Glycerol	AG
Hydrogel	**Code**
poly (Agar-co-Glycerol)/MBA	p(AG-m)
poly (Agar-co-Glycerol)/GA	p(AG-g)
Organo-ydrogel	Code
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 organohydrogel

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-m-SAO)^1
2% -2 mL	0.04 mL	0.2 mL	MBA	p(AG-m-SAO)^2
2% -2 mL	0.04 mL	0.3 mL	MBA	p(AG-m-SAO)^3
2% -2 mL	0.04 mL	0.1 mL	GA	p(AG-g-SAO)^1
2% -2 mL	0.04 mL	0.2 mL	GA	p(AG-g-SAO)^2
2% -2 mL	0.04 mL	0.3 mL	GA	p(AG-g-SAO)^3

3. Mathematical models for drug release.

Model	Mathematical Equation	Release Mechanism	Codes
Zero order kinetic model		Diffusion Mechanism	ZoM
First order kinetic model		Fick's first law, diffusion Mechanism	FoM
Higuchi Model		Diffusion medium based Mechanism in Fick's first law	HM
Korsemeyer-Peppas Model		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/); 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.

4 Total phenol content values.

Substance	Total phenol (mg)
Organohydrogel	
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

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

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]		2.0	5.5	7.4	8.0	p(AG-g-SAO)[2]		2.0	5.5	7.4	8.0
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]		2.0	5.5	7.4	8.0	p(AG-g-SAO)[3]		2.0	5.5	7.4	8.0
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

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

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]		7.4	p(AG-g-SAO)[2]		7.4
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]		7.4	p(AG-g-SAO)[3]		7.4
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

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

Figures

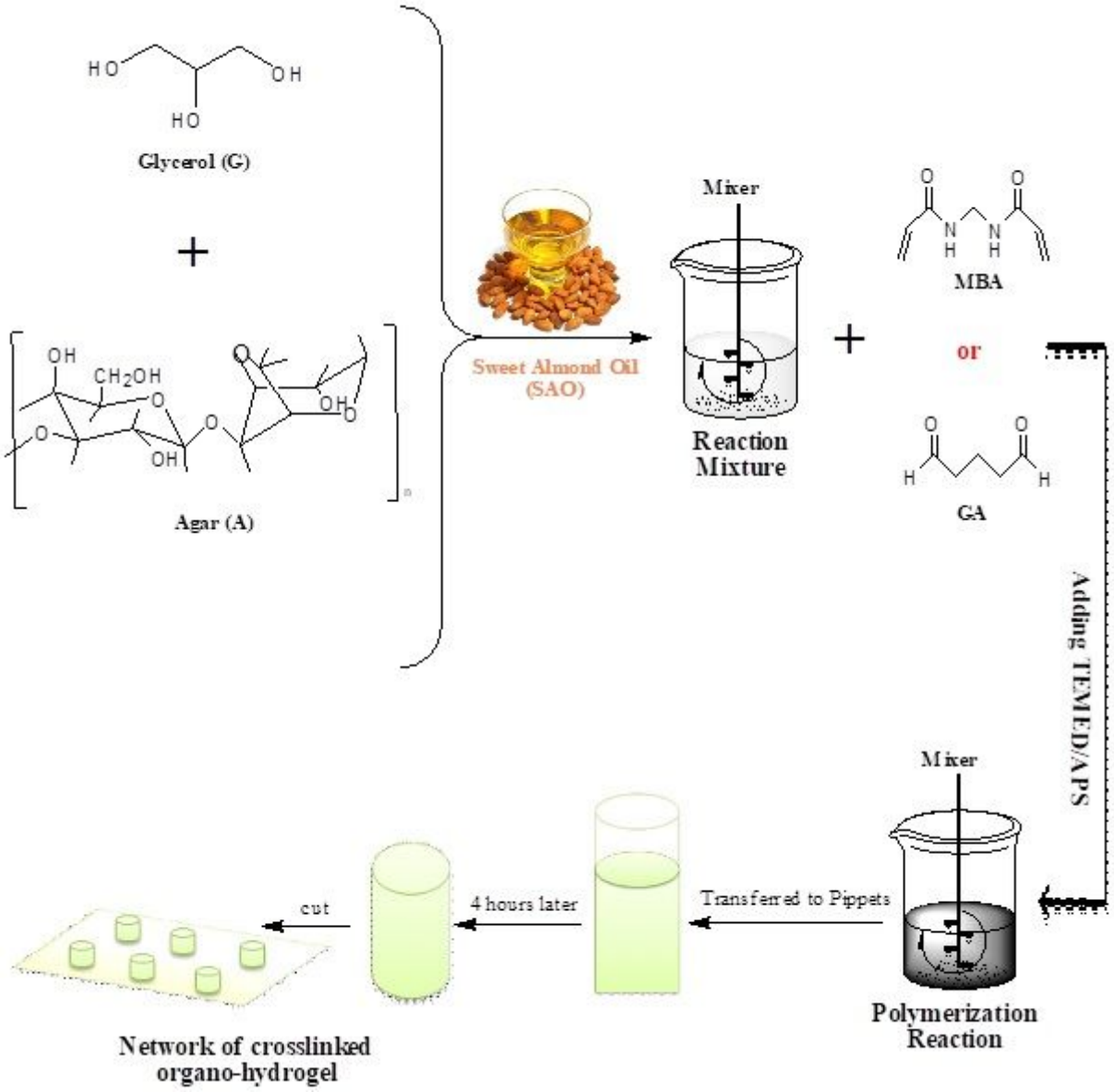

Figure 1

Synthesis and schematic presentation of organohydrogels.

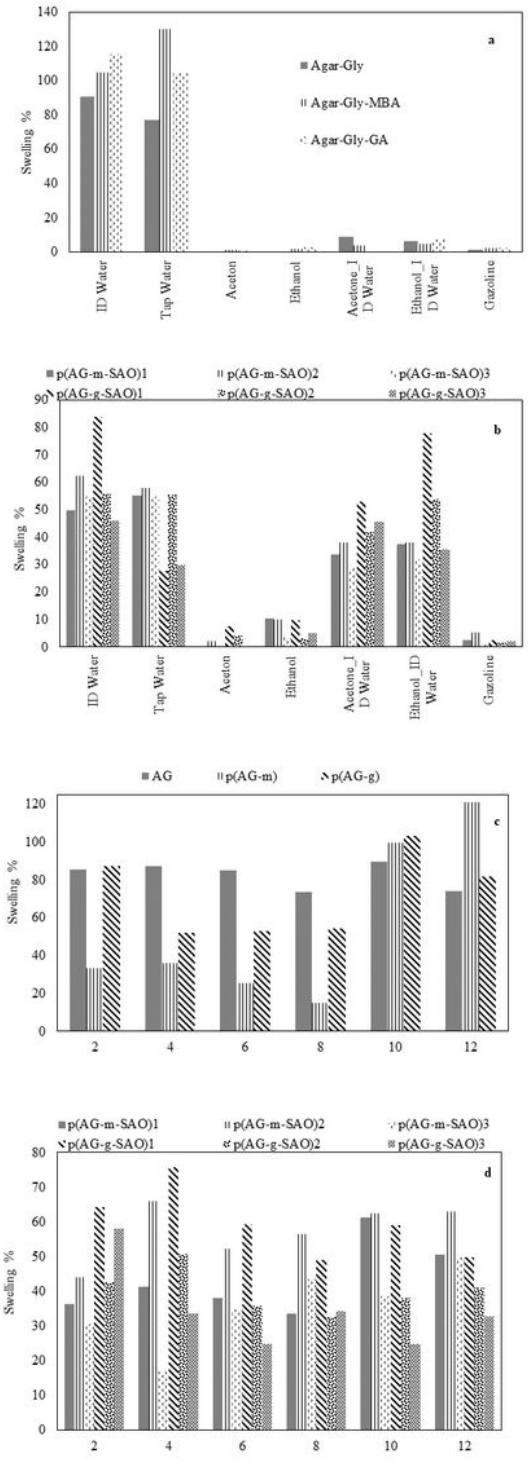

Figure 2

Percent swelling degree of the (a)AG, p(AG-m), p(AG-g) and (b) organohydrogels with time in ID water, tap water, ethanol, acetone, ethanol/ID water (1:1), acetone/ID water (1:1) and gasoline. Swelling % of the (c) AG, p(AG-m), p(AG-g) and (d) organohydrogels as a function of 2.0-12 pH (pH is adjusted by the addition of 0.1 M HCl, 0.1 M NaOH).

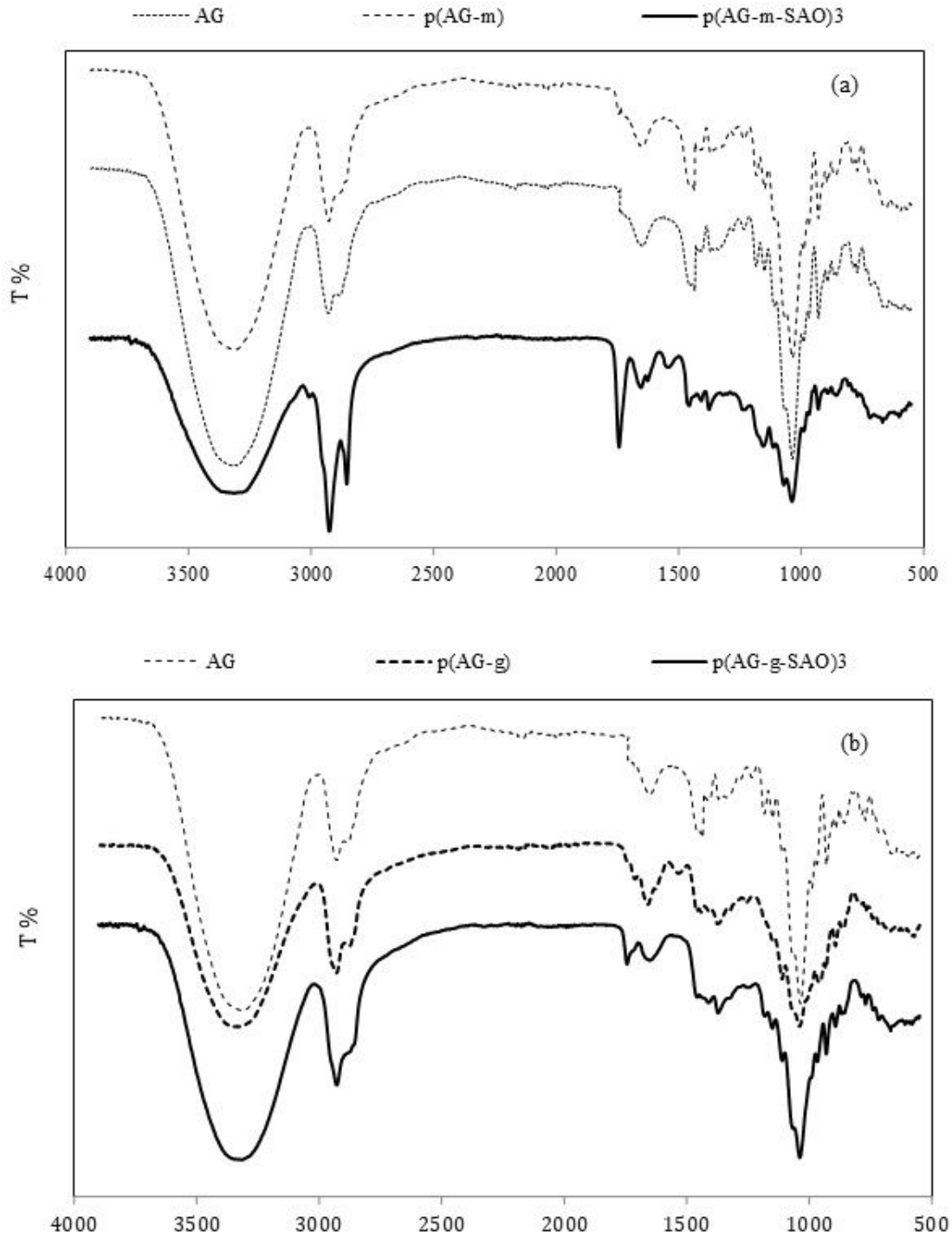

Figure 3

FT-IR Spectra of (a) AG, p(AG-m), and p(AG-m-SAO)3, (b) AG, p(AG-g) and p(AG-g-SAO)3 organohydrogels

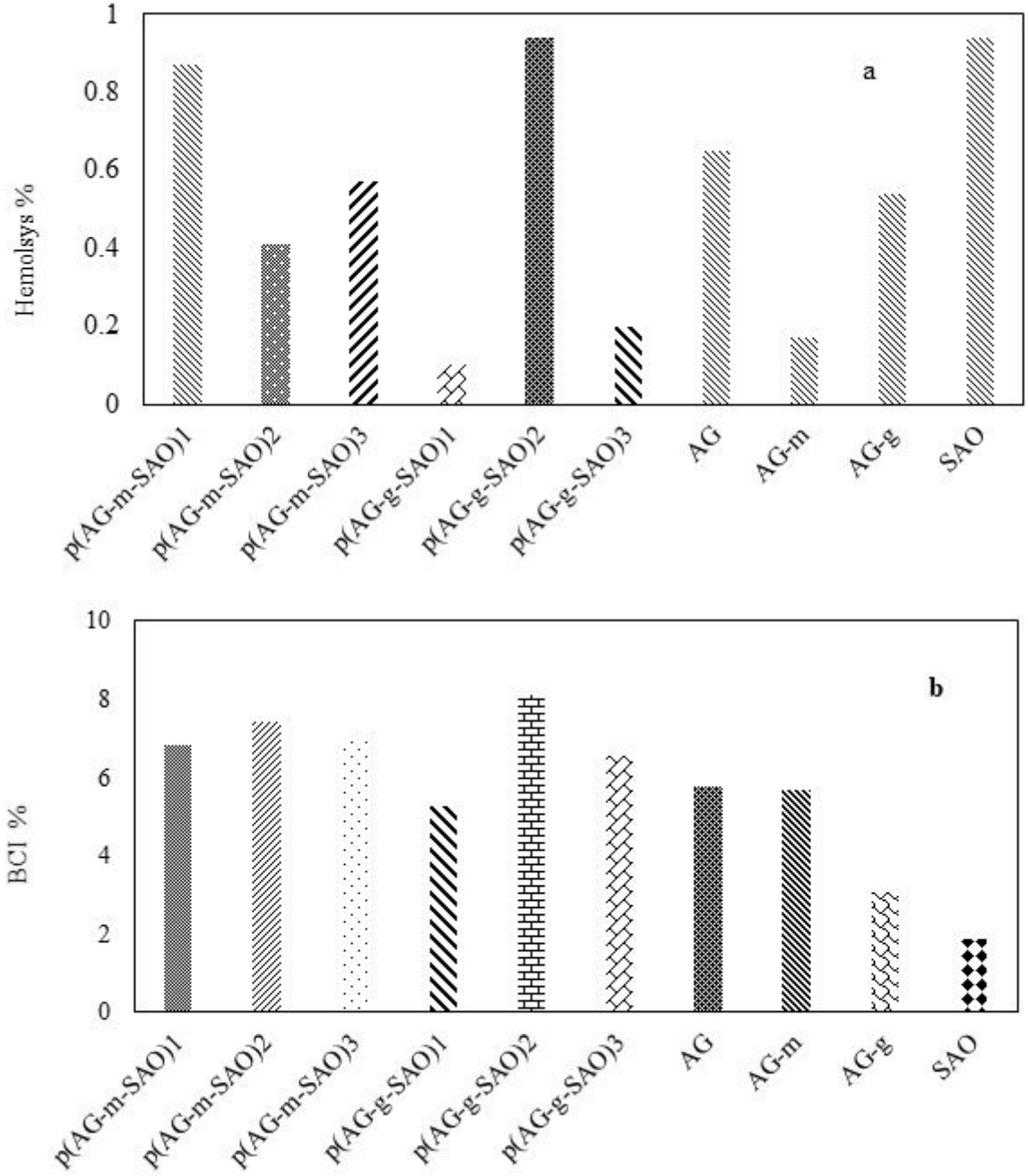

Figure 4

Blood combability of the AG, p(AG-m), p(AG-g) and organohydrogels (a) hemolysis (b) blood clotting.

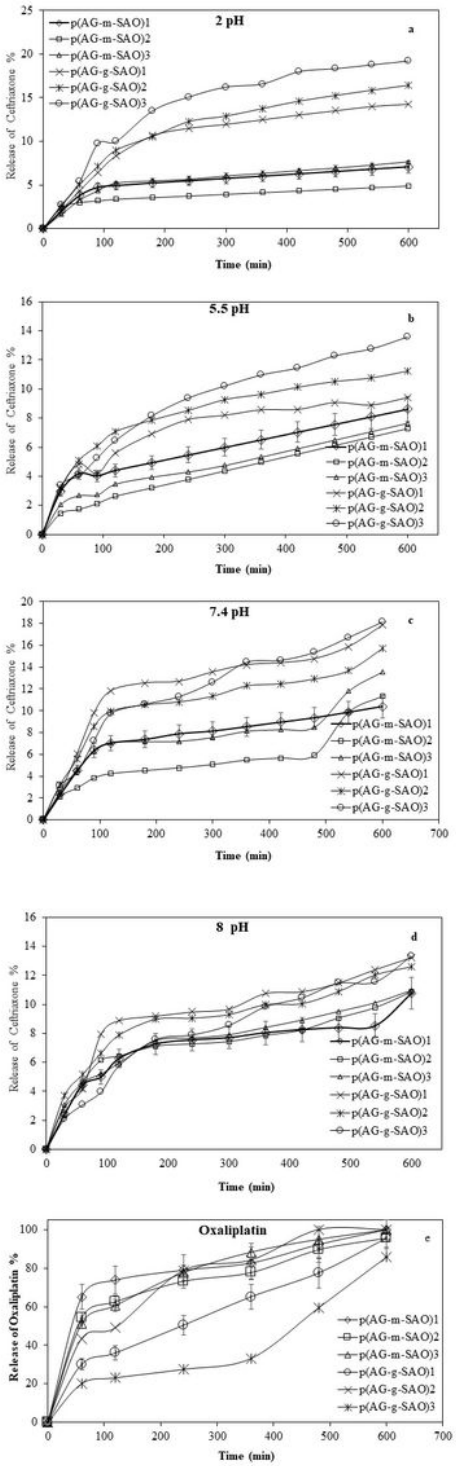

Figure 5

Release behavior of Ceftriaxone (a) 2.0 pHs (b) 5.5 pHs (c) 7.4 pHs (d) 8.0 pHs from organohydrogels and (e) Oxaliplatin 7.4 pHs organohydrogels. (The first 600 min of Ceftriaxone and Oxaliplatin release were given in the graph).