

Properties, Bioactivity, *In vitro* Drug Release and Functionality as a Biomaterial of Poly(Apigenin) Hydrogel

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Abstract Controlled release systems used in the biomedical industry or still in the animal testing phase generally use various chemicals, especially natural or artificial polymers. In recent years, there has been increasing interest in plant-based products as controlled release materials. For the first time in the literature, poly(apigenin) hydrogel was synthesized from apigenin, an important flavonoid. Swelling percentages and biodegradation percentages of poly(apigenin) hydrogel at different pH values were investigated. Structural analyses of poly(apigenin) hydrogel were performed using FT-IR (Fourier Transform Infrared Spectroscopy). To examine drug release amounts and kinetics, different drug active ingredients (paracetamol, ceftriaxone, and 5-Fluorouracil(5-fu)) were loaded into the poly(apigenin) hydrogel. The release of paracetamol, ceftriaxone, and 5-fu from the synthesized poly(apigenin) hydrogel was determined as 95%, 58% and 96%, (pH 7.4) respectively. For kinetic studies, zero-order, first-order, Higuchi, and Korsmeyer-Peppas, models were used. When the correlation coefficients (R^2) were compared, it was seen that the drug release kinetics fit better with the Korsmeyer-Peppas model. It was observed that the poly(apigenin) hydrogel synthesized in this study was a suitable material for the release systems of paracetamol, ceftriaxone, and 5-Fluorouracil.

Keywords Apigenin, poly(Apigenin), Hydrogel,

Drug Release

1. Introduction

Flavonoids, naturally found in the stems, leaves, bark, roots, and especially flowers of plants, are one of the largest groups of naturally occurring polyphenols. They have anti-oxidant, anti-cancer, anti-microbial, anti-viral, and anti-bacterial properties. Since flavonoids are found in most green plants, they are used in most studies with plant extracts [1, 2].

Many positive effects of flavonoids on human health have been determined. It has anti-oxidant, antiviral, anti-mutagenic, anti-inflammatory, anti-cancer, cholesterol-lowering, anti-bacterial, and anti-allergic properties. It prevents cardiovascular disease and reduces the risk of a heart attack. It has been stated that these effects are generally due to the anti-oxidant properties of flavonoids. Many flavonoids are used in biomedical fields as support materials for anti-cancer, anti-ulcer, anti-oxidant, anti-allergic, anti-tumor, and hemostatic drugs, and controlled drug release is included in wound healing products.

Apigenin is called 4', 5, 7-trihydroxyflavone, or 5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-

one. It is a flavonoid belonging to the flavone subclass. It is a trihydroxyflavone with the 'OH' functional group at the '4, 5 and 7' positions. It has the chemical formula $C_{15}H_{10}O_5$ and a molecular weight of 270.24 g/mol. It is lipophilic in nature and survives in the gastrointestinal tract in a low-acid environment. Apigenin has been used as a traditional medicine for many years. For example, plants containing high levels of apigenin have also been used to treat persistent asthma, Parkinson's disease, neuralgia, shingles, insomnia, and anxiety [2-6]. Features such as bioavailability, chemical activity, easy availability, and low price make Apigenin interesting.

The swelling, porosity, pHpzc point, and bioavailable properties of the synthesized poly(apigenin) hydrogel and the release mechanisms of the drug paracetamol, ceftriaxone, and 5-Fluorouracil of the poly(apigenin) hydrogel were examined. The drugs used in the release were selected as the most commonly used painkiller paracetamol during the pandemic, ceftriaxone as a broad-spectrum antibiotic, and 5-fu as an anticancer drug. It is thought that the poly(apigenin) hydrogel we synthesized will be a new and effective material that can serve as a modular platform for a predictable functional release system for use in the biomedical field.

2. Material and Method

2.1. Materials

Apigenin was procured from local suppliers. Ethyleneglycoldimethacrylate (EGDMA), APS, and TEMED were used as a crosslinking, accelerator and initiator.

2.2. Preparation of Poly(Apigenin) Hydrogels

0.05 g of apigenin and 1 mL of 0.01 M NaOH were added to the 20 mL vial and mixed at 700 rpm. Then, 9 mL of DI water was added and stirred at room temperature for 1 hour. When apigenin was completely dissolved, a yellow, transparent solution was obtained. 2 mL of the prepared apigenin solution was taken and transferred to another vial. 0.1 mL of cross-linker (EGDMA), 0.01 mL of the accelerator (TEMED), and 0.1 mL of initiator (APS) were added to the same vial, vortexed, transferred to the petri dish, and the reaction was started. At the end of the 4-hour reaction period, the poly(apigenin) hydrogel was washed with pure water and dried in the oven until it reached a constant weight.

2.3. Swelling Degree

To determine the degree of swelling of the poly(apigenin) hydrogel, the hydrogels were cut into equal weights and kept in a 37 °C oven for dehydration overnight. The samples were placed in a beaker containing 50 mL of DI

water solution at room temperature and taken at a certain time interval, weighed and then placed back into pure water. Before each weighing, excess moisture on the sample surfaces was carefully removed by placing it between two filter papers. The swelling ratio of hydrogels was calculated by the following equation.

$$\text{Swelling degree or ratio} = (W_w - W_d) / W_d$$

W_d : Initial weight of the sample

W_w : Final weight of the sample

2.4. Swelling Degree at Different pH Values

To determine the degree of swelling of the poly(apigenin) hydrogel at different pH values, the poly(apigenin) hydrogels were cut into equal weights and kept in a 37 °C oven for dehydration overnight. The samples were placed in 50 mL of 12 different pH solutions ranging from pH 1.0 to pH 12, and were taken out at a certain time interval, weighed, and then placed back into the different pH solutions. Before each weighing, excess moisture on the sample surfaces was carefully removed by placing it between two filter papers. The swelling ratio of poly(apigenin) hydrogels at different pH values is calculated using the equation below.

$$\text{Swelling degree or ratio at different pH values} = (W_w - W_d) / W_d$$

W_d : Initial weight of the sample

W_w : Final weight of the sample

2.5. *In vitro* Biodegradability Test

In vitro hydrolytic degradation experiments of the prepared poly(apigenin) hydrogel were performed at room temperature and in 12 different pH solutions. After weighing the dry weight (W_d) of the prepared poly(apigenin) hydrogel, it was placed in 50 mL of different pH solution medium. Poly(apigenin) hydrogel samples were taken every day for the first 15 days, and twice a week after the 15th day. The solution was removed with the help of filter paper and the poly(apigenin) hydrogel samples were weighed (W_1) and the values were recorded. Thus, mass losses of the prepared poly(apigenin) hydrogels were analyzed over 40 days. At the end of the 40th day, the samples were dried at room temperature. Completely dried samples were weighed again. Mass losses were determined using the equation below.

$$WL (\%) = [(W_d - W_w) / W_w] 100$$

WL: Weight loss

W_d : Initial weight of the sample

W_w : Final weight of the sample

2.6. pH Value

Poly(apigenin) hydrogels were placed in deionized

water at a ratio of 1:100 (w v⁻¹) and kept at room temperature for 24 hours. The solution pH value was measured with a pH meter. It was determined at the 3rd and 24th hours.

2.7. Bioactivity Test

The literature included descriptions of the techniques used to assess the bioactivity of the poly(apigenin) hydrogel, including H₂O₂ scavenging capacity [7], antioxidant (Folin-Ciocalteu [8]), blood coagulation analysis, and hemolysis analysis [9].

2.8. Drug Loading and *In vitro* Release Studies

Paracetamol, ceftriaxone, and 5-Fluorouracil were chosen as drugs. Synthesis of drugs with poly(apigenin) hydrogel was carried out using the method reported in the literature [9]. Drug release studies were carried out at 37 °C in solutions with 4 different pH values (2.0, 5.4, 7.4, and 8.0) using poly(apigenin) hydrogels containing paracetamol, ceftriaxone, and 5-Fluorouracil (50 ppm). The amount of the drugs paracetamol, ceftriaxone, and 5-fluorouracil in each pH solution was determined from the calibration curve created using a UV-Vis spectrophotometer [10]. To determine the release kinetics, the most often employed models were zeroorder (ZoM), firstorder (FoM), Higuci (HM), and Korsmeyer-Peppas (KPM).

3. Results and Discussion

One of the main challenges in using natural materials was hydrogels *in vitro* biodegradability and stability during use. To evaluate the biodegradability of the synthesized poly(apigenin) hydrogel, the hydrogels were stored at ambient temperature (25 °C) for 40 days for solutions at different pH values, and their weights were measured every day for the first 15 days and every 5 days after that. As shown in Figure 1, they showed good stability during 40 days of use, but their weight increased slightly. This slight increase was due to water absorption and swelling of the poly(apigenin) hydrogel. Despite some fluctuations in hydrogel weights, biodegradability was within the

acceptable range. The results showed that the poly(apigenin) hydrogel could remain stable in the solution phase for at least 40 days at room temperature. The degree of swelling (water-holding) was related to the water absorption of poly(apigenin) hydrogel. The prepared poly(apigenin) hydrogels had water-holding capacity results as shown in Figure 1. The water retention percentage of cross-linked poly(apigenin) hydrogels was 409 % at pH 7.4 at 5 days.

The swelling behavior of poly(apigenin) hydrogel was examined in 13 different environments, including distilled water and at different pH (1-12) values, and the results were compared with each other. The maximum swelling degree of the poly(apigenin) hydrogel was measured as 483.98% at pH 11.0 and the minimum swelling degree was 360.73 % at pH 6.0. This shows that storage conditions and duration do not affect the degradation of poly(apigenin) hydrogel and as a result, storage time may increase. The porosity value for poly(apigenin) hydrogel was calculated as 85 ± 0.5%. This value shows that the overall porosity of the poly(apigenin) hydrogel has a high and advantageous ratio. Poly(apigenin) hydrogels kept in solutions with different pH values for 24 hours occurred in an acidic environment, shown in Figure 2. The acidic environment was thought to be a good barrier against bacteria in the wound environment [11].

Figure 3 shows the FTIR spectrum of the synthesized poly(apigenin) hydrogel. When the FTIR spectra of pure apigenin were examined in the literature, it was observed that the -OH stretching vibration peak observed at 3400-3200 cm⁻¹ and the C-H peak observed at 3330 cm⁻¹ decreased in the FTIR spectrum of the synthesized poly(apigenin) hydrogel. At the same time, when the FTIR spectra of apigenin in the literature [6, 12, 13] were examined, it was determined that there was no peak at approximately 2866 cm⁻¹ wavelength. However, a new peak belonging to a sharp C-H bond was formed at 2866 cm⁻¹ in the structure of the p(apigenin) hydrogel synthesized by the polymerization reaction. Additionally, it was observed that the intensity of the peaks observed at 1608 cm⁻¹, 1354 cm⁻¹ and 1091 cm⁻¹ in the literature changed significantly after the polymerization reaction. The strong band observed at 1722 cm⁻¹ corresponds to the C=O stretching vibrations of EGDMA.

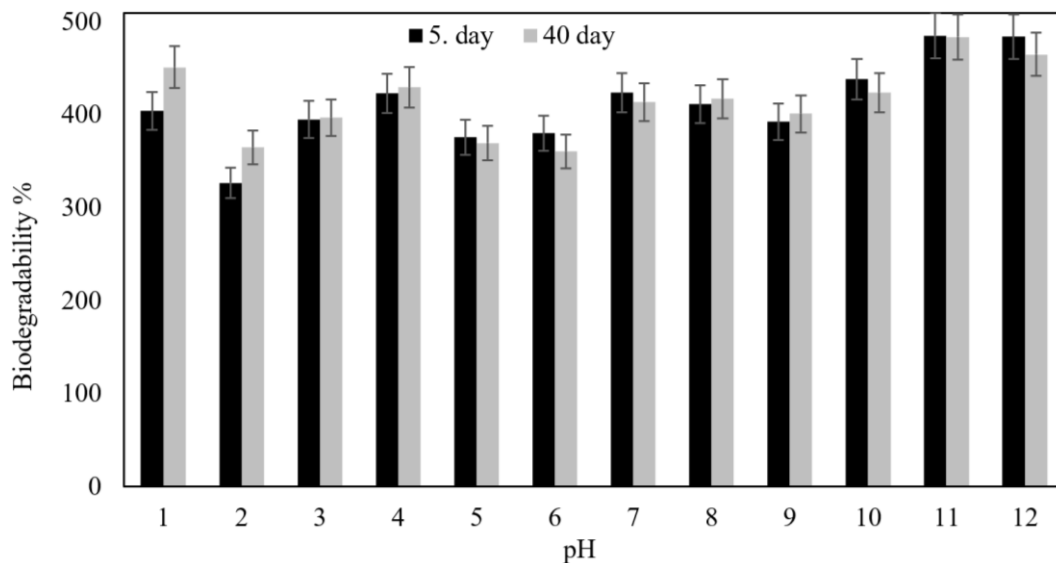


Figure 1. Biodegradability results at different pHs of poly(apigenin) hydrogel

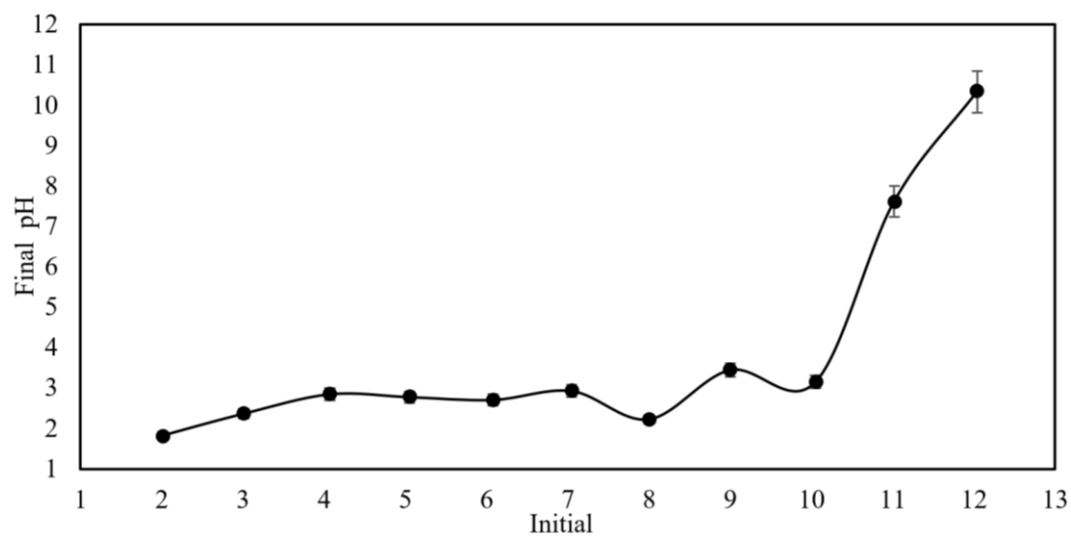


Figure 2. pH value poly(apigenin) hydrogel

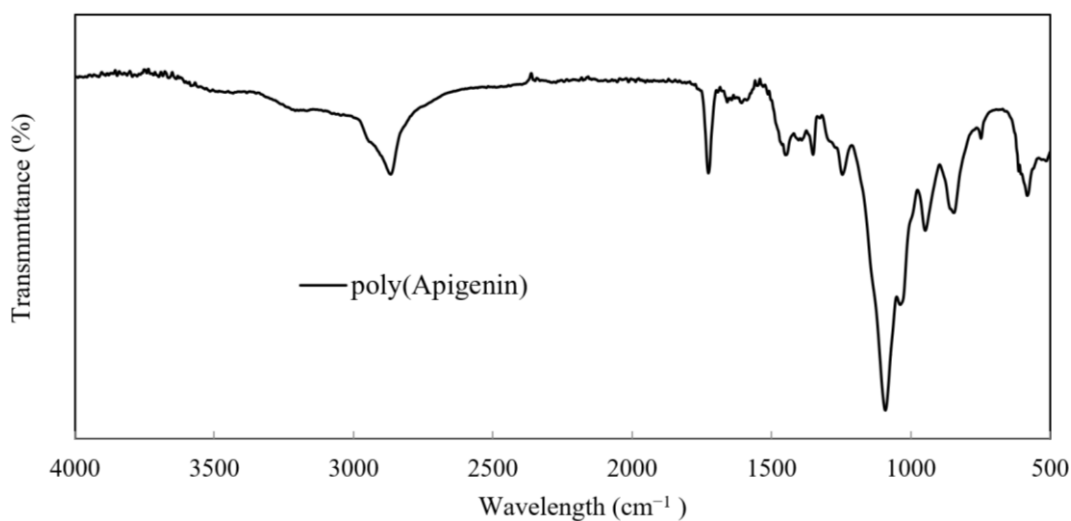


Figure 3. FT-IR spectra of poly(apigenin) hydrogel

As can be seen (Table 1) from the total phenol values of the synthesized poly(apigenin) hydrogel and apigenin solution it is observed that the poly(apigenin) hydrogel synthesized from apigenin solution preserves the antioxidant property of Apigenin and the structural change increases this property. The antioxidant potential of poly(apigenin) hydrogel was investigated according to its H₂O₂ scavenging ability. Poly(apigenin) hydrogel potently scavenged hydrogen peroxide. It showed that the inhibition of poly(apigenin) hydrogel and apigenin was almost the same in the applied dose range. The total antioxidant effect potential of poly(apigenin) hydrogel showed its effect in a concentration-dependent manner. It was stated that the antioxidant properties of flavonoids were very important due to the number of phenolic substituents, high molecular weight and proximity of the aromatic ring and hydroxyl group. The strong scavenging potential of poly(apigenin) hydrogel against free radicals, even in the hydrogel, was attributed to the formation of a high concentration of phenolic moieties in the molecules.

Table 1. Total phenol and H₂O₂ scavenging values

Total phenol (gallic acid) (mg g ⁻¹)			
Substance	Amount (mg)	poly(Apigenin)	Apigenin
p(Apigenin)	2	464±0.14	39.2±0.03
p(Apigenin)	4	843.6±0.08	100.3±0.03
p(Apigenin)	8	1179.2±0.14	174.34±0.01
H ₂ O ₂ scavenging			
Substance	Amount (mg)	poly(Apigenin)	Apigenin
p(Apigenin)	2	178.1±0.01	2115±0.03
p(Apigenin)	4	199.4±0.03	213.5±0.03
p(Apigenin)	8	227.5±0.03	230.2±0.03

Depending on the amount of poly(apigenin) hydrogel used, the % hemolysis rate after contact with blood was calculated at 51%, 41%, and 42%, respectively. The hemolysis value is expressed as >5% hemolytic [14, 15]. In line with these data (Figure 4), it can be said that poly(apigenin) hydrogel is hemolytic. BC index varies

between 42-48% depending on the amount of poly(apigenin) hydrogel used. The BC index is compared to the blood clotting index value of 100% to show that the material prevents blood clotting. In line with these data, poly(apigenin) hydrogel does not pose a significant problem for blood clotting. It has been observed that poly(apigenin) hydrogel can be applied in biomedical application areas that may require contact with blood.

From the slopes of the drug release graph of poly(apigenin) hydrogel in 4 different pH environments, it was observed that paracetamol releases were approximately 50% or "initial burst release" in the first hour, increased by more than 80% in the fourth hour, and were released continuously throughout the process. It was observed that 5-fu releases in 4 different pH environments varied between approximately 13-24% in the first hour and were released continuously throughout the process. It was observed that the release varied between approximately 96-60% within 10 hours. It was observed that ceftriaxone releases varied between approximately 10-20% in the first hour in 4 different pH environments, increased by more than 80% in the fourth hour, and were released continuously throughout the process. In studies on the development of materials for wound healing, it has been stated that drug release may be more than 50% in the first hours [16, 17] and that there will be up to 80% release within 6 hours [18]. The results of this study showed that poly(apigenin) hydrogel rapidly released the drug from the matrix within the first hour at pH 8.0 and 7.4.

Drug release information from poly(apigenin) hydrogel was used to predict the nature of the release profile and the type of diffusion of the drug by fitting it to the data for drug release kinetic models (zero-order, first-order, Higuchi, and Korsmeyer-Peppas). The correlation coefficient values and graphs of these kinetic models were given in Table 2. This study was carried out by taking measurements from the formed poly(apigenin) hydrogel at pH 2.0, 5.4, 7.4, and 8.0 and 37 °C at specified times. Among the kinetic models used in this study, the better correlation coefficient values in the Korsmeyer-Peppas model indicate that the release of the drug is a diffusion-mediated process. From the data obtained, the parameters of the kinetic modeling used for the poly(apigenin) hydrogel were given in Table 2.

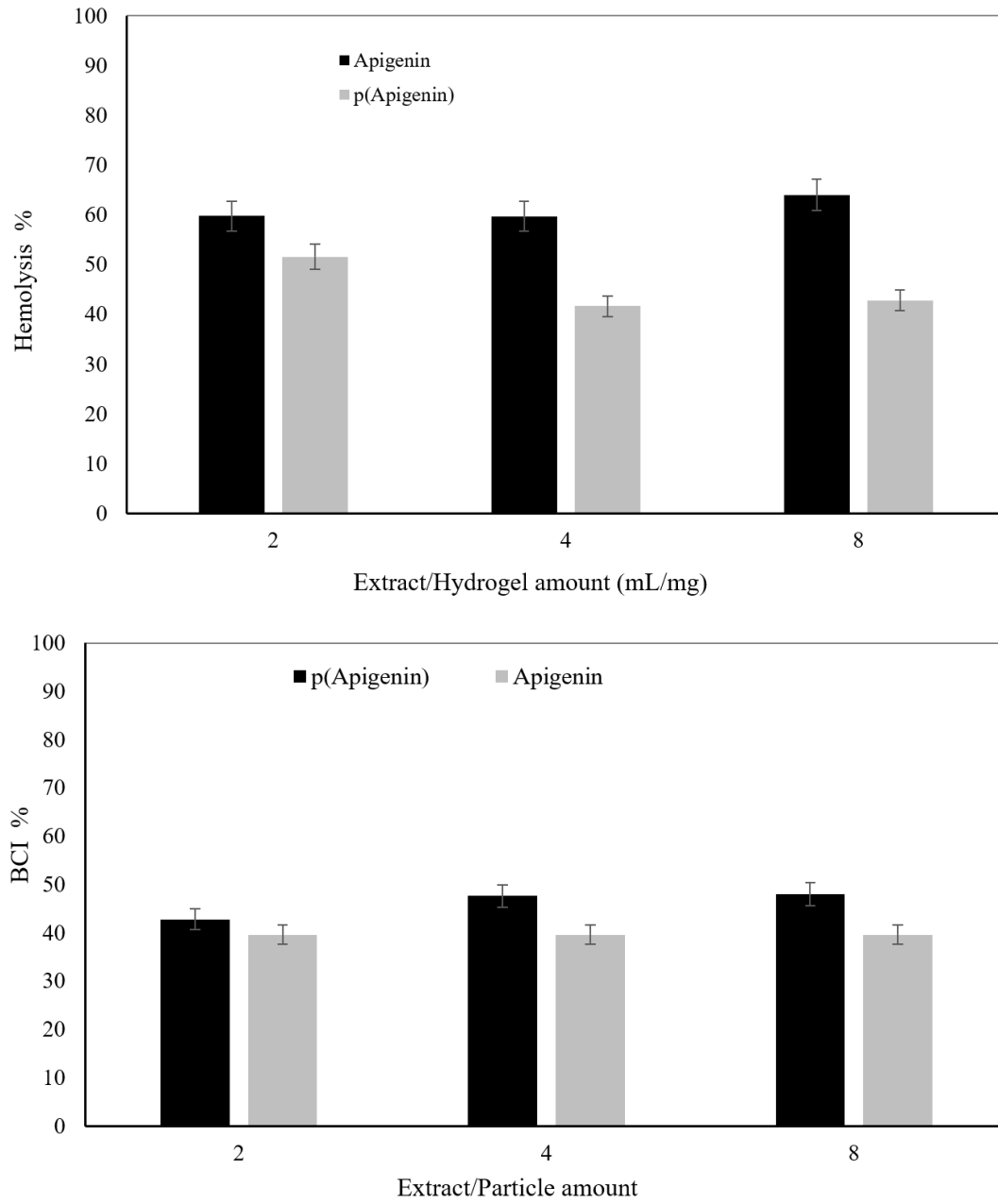


Figure 4. Hemolysis value and BC index of poly(apigenin) hydrogel

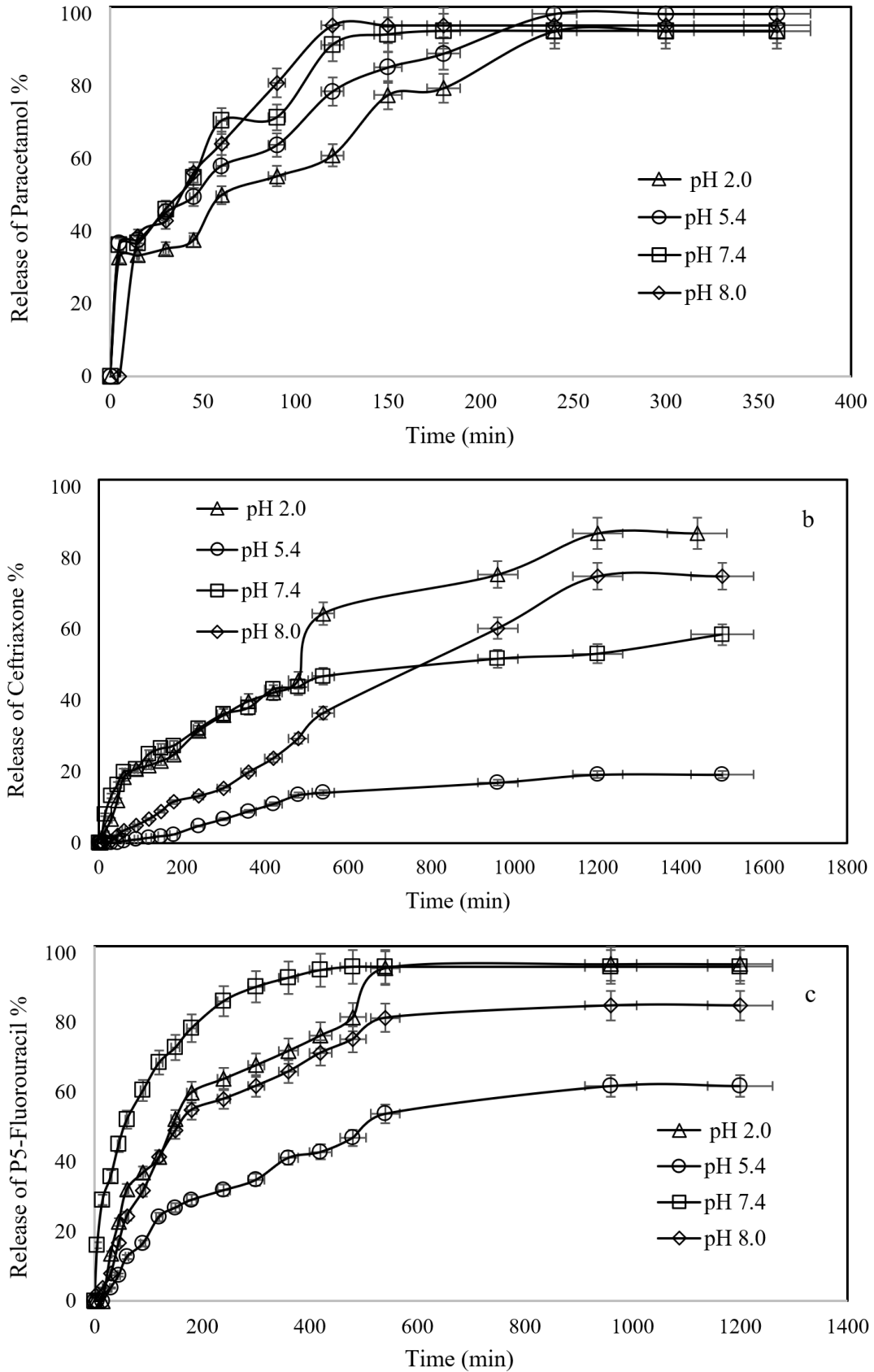


Table 2. Release kinetic models of drugs release

		poly(apigenin)			
Paracetamol		2.0	5.4	7.4	8.0
ZoM	Co	0.671	0.856	0.982	1.197
	ko	-0.0051	-0.0050	-0.0046	-0.0004
	R²	0.945	0.924	0.757	0.613
FoM	Co	2.478	2.373	2.021	1.777
	k1	-0.319	-0.119	-0.036	-0.136
	R²	0.908	0.864	0.704	0.575
HM	kh	0.056	0.049	0.050	0.005
	R²	0.968	0.974	0.889	0.794
KPM	n	0.406	0.359	0.350	0.284
	kkp	0.099	0.135	0.157	0.231
	R²	0.945	0.983	0.932	0.856
Ceftriaxone		2.0	5.5	7.4	8.0
ZoM	Co	0.115	0.017	0.190	0.004
	ko	-0.0023	-0.0005	-0.0021	-0.0012
	R²	0.888	0.943	0.852	0.980
FoM	Co	4.299	3.381	2.875	21.046
	k1	-0.004	-0.007	-0.003	-0.007
	R²	0.284	0.162	0.269	0.238
HM	kh	0.024	0.004	0.023	0.012
	R²	0.966	0.813	0.959	0.963
KPM	n	0.751	1.619	0.467	1.291
	kkp	0.006	0.000	0.027	0.000
	R²	0.921	0.992	0.973	0.938
5-Fu		2.0	5.5	7.4	8.0
ZoM	Co	0.159	0.047	0.559	0.128
	ko	-0.0042	-0.0023	-0.0042	-0.0002
	R²	0.883	0.902	0.880	0.902
FoM	Co	1.858	3.427	1.813	8.282
	k1	-0.003	-0.003	-0.005	-0.010
	R²	0.312	0.085	0.595	0.670
HM	kh	0.030	0.043	0.052	0.004
	R²	0.809	0.945	0.981	0.971
KPM	n	0.629	3.656	2.272	5.458
	kkp	0.022	0.026	0.103	0.004
	R²	0.929	0.945	0.992	0.948

The n diffusion exponent of poly(apigenin) hydrogel in paracetamol release was around 0.406 for pH 2.0, 0.359 for pH 5.4, 0.350 for pH 7.4, and 0.204 at pH 8.0, although it has decreased slightly, it was less than 0.45 values. These recorded values show that the release of paracetamol from the poly(apigenin) hydrogel occurs by Fick-type diffusion at all four pH values. The n diffusion exponent of poly(apigenin) hydrogel in ceftriaxone release was around 0.751, 1.156, 0.467 and 0.1291 for pH 2.0, pH 5.4, pH 7.4, and pH 8.0, respectively. According to these values, the ceftriaxone release of the poly(apigenin) hydrogel occurs by non-Fick type diffusion at pH 2 and 7.4, and by super-case II diffusion at pH 5.4 and 8. The 5-fu drug release n diffusion exponent was around 0.629, 3.656, 2.272, and 5.458 for pH 2.0, pH 5.4, pH 7.4, and pH 8.0, respectively. According to these values, non-Fick-type diffusion was observed at pH 2.0. It was understood that super-case II diffusion occurs in the release of 5-fu drug from poly(apigenin) hydrogel at pH 5.4, 7.4, and 8.0.

Poly(apigenin) hydrogel, synthesized mainly using Apigenin, was synthesized for the first time in this study. When looking at the literature, it can be seen that there have been several studies on microgels, and hydrogels synthesized by loading Apigenin. In the literature, it was seen that Apigenin-loaded hydrogen and nanogels were synthesized. In these studies, Samadian and Hashemi [19] found that apigenin-loaded nanogel significantly suppressed the growth of K562 cells and may attract interest as a new strategy in cancer treatment. Zhao and Wang [20] stated that apigenin-loaded API-Me-hydrogels can control drug release at pH 1.2 and pH 7.4 and that pH-sensitive API-Me-hydrogels can be a pH-controlled release system for oral hydrophobic drug delivery. Shukla and colleagues in their study [21] concluded that apigenin-loaded API-Me-hydrogels can control drug release at pH 1.2 and pH 7.4 synthesized gellan gum-chitosan hydrogel (GGCH-HGs). They observed that the apigenin-loaded hydrogel they synthesized effectively stimulated wound contraction and significantly increased the collagen content in diabetic and normal wound tissues. They suggested that the data they obtained was since apigenin plays a role in diabetic wound healing with its free radical scavenging effect [21]. To increase the bioavailability of apigenin, apigenin was loaded onto Cs/Gel membranes. It has been reported that apigenin-loaded membranes degrade more slowly *in vitro* and that low doses of apigenin-loaded Cs/Gel have a better effect on calcium accumulation and osteoblast maturation [22].

4. Conclusions

The results showed that poly(apigenin) hydrogel showed better results than many materials reported for its application as a biomedical material. In addition to the improved drug release feature, swelling capacity and

release feature in different pH environments are also effective factors in reducing the effect of wound dehydration. Its use as a biomedical material is also supported by its good antioxidant activity and free radical scavenging effect. With these features, biodegradable polymer-based hydrogels will have a significant impact on the regeneration phase by positively affecting the wound-healing process. It was thought that it would be appropriate to plan future studies to fully elucidate the mechanisms of these positive effects of poly(apigenin) hydrogel, and that poly(apigenin) could be an alternative treatment material for drug release, anticancer agent, and wound healing.

Conflict of Interest

The authors declare that they have no conflict of interest. This research did not receive any specific funding.

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