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Development of a Controlled Released System Based on IPN Types Hydrogel for Cartilage Repair

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Highlights

- This paper focuses on controlled released system based on IPN types hydrogel for cartilage repair.
- The hydrogels were synthesized via free radical polymerization by using gelatin polymer and HEMA.
- The release studies of Fluconazole and Naproxen from the hydrogels were studied.

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Abstract

The purpose of this study is to develop a controlled Fluconazole and Naproxen releasing system for cartilage repair. Interpenetrating polymer network (IPN) type of hydrogels were prepared by using different ratios of 2-Hydroxyethyl methacrylate (HEMA) and gelatin. The hydrogels were synthesized by using ammonium persulfate (APS) and sodium metabisulfite (SBS) as initiator pair and ethylene glycol dimethacrylate (EGDMA) and glutaraldehyde (GA) as cross linkers. The prepared hydrogels were characterized via hydrogel formation and swelling/degradation measurements, Fourier Transform Infrared Spectroscopy (FT-IR) and Scanning Electron Microscope (SEM) analysis. From swelling tests, it is observed that semi-IPN hydrogels swell much more than full-IPNs which crosslinked by two agents, EGDMA and GA. The higher ratios of HEMA/gelatin negatively affect swelling values. In general, the IPN hydrogel discs were not affected by the variation of temperature. The release studies of Fluconazole and Naproxen were performed at 37 ºC and it is found that the swelling and releasing profiles were similar to each other. The releases of drugs increase rapidly at first and then complies nearly 36 h-48 h. Because of the looser and porous structure, semi-IPN hydrogels have higher release values than full-IPNs.

1. INTRODUCTION

Hydrogels are 3D hydrophilic crosslinked polymer networks having high water absorption capacity. There are too many medical studies about hydrogel application such as biomedical and drug delivery devices, implants, and tissue engineering [1]. Interpenetrating polymer networks (IPNs) are combinations of two hydrogel structure. IPN's could be prepared in two form called semi or full-IPN. If one of the polymers is crosslinked to each other and the other placed into these structure as guest polymer, this hydrogel is called as semi-IPN. Full-IPN hydrogels are synthesized by crosslinking of both polymers. IPN hydrogels have superior properties in terms of stability, mechanical properties, swelling capacity, and biocompatibility. Due to the combination of different polymer properties in one structure, they can be used in a wide range of areas from soft to hard tissues such as blood vessels, bone, and cartilage. In addition, IPNs are used for adjusting hydrogel hydrophilicity and controlled release kinetic [2].

Controlled release is a system which delivers an active agent at a predetermined rate and period for locally or systematically. There are several mechanisms to control the release in this system like diffusion, erosion, swelling, magnetic and mechanic-controlled release systems. Hydrogels are often used as controlled release material in matrix or encapsulation form. The two important properties to control the drug release are pore

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size and hydrophilicity of hydrogel. Consequently, the release behavior could be arranged by changing the polymer/crosslinker ratios [3].

Poly(2-hydroxyethyl methacrylate) (PHEMA) is an optically transparent, strength, biocompatible, non-toxic, and non-degradable polymer which one of the derivatives of methacrylate. Because of its superior properties, PHEMA have commonly usage in medical applications like contact lenses, tissue engineering, drug releasing, and so on [4, 5]. Because of its crosslinking ability and hydrophilicity, it is convenient to be used in hydrogel preparing processes [6]. The diffusion and physical properties of PHEMA hydrogels can be adjusted by changing crosslinking density or various combination techniques of the polymers [7, 8].

Gelatin is a natural biopolymer in protein structure and obtained from animal source collagen. Due to its excellent properties like biocompatibility, swelling capacity and low cost, it is used in the field of medicine and the food industry. To improve its mechanical strength, gelatin can be combined with polysaccharides, synthetic polymers, additives, and various biological materials by physically mixing, crosslinking, in-situ synthesis, and others [9, 10]. The hydrogel forms of gelatin are especially preferred because of its functional side groups and crosslinking capacity. In the literature, there are release studies from hydrogels consisting of gelatin and PHEMA for different usages [11-13].

Cartilage is a durable and flexible connective tissue that protects our bones. Three kinds of cartilage are hyaline, fibrocartilage, and elastic cartilage are present in the body. Hyaline, named articular cartilage, is usually located at the ends of the bones. It is a supportive tissue found in joints that reduces the friction between the ends of bones [14]. Extracellular matrix (ECM) of articular cartilage is composed from the slow-dividing chondrocytes, collagens, proteoglycans and matrix proteins [15]. The hydration of ECM reduces by aging and injure [16]. Therefore, this unique and complex structure begin to deteriorate and the articular cartilage loss its functions. So, the most common disorders like osteoarthritis (OA) and rheumatoid arthritis (RA) occur over many years [17]. The surgery, physical therapy and drug therapies can help to delay, stop or reverse the disease progression. The hydrogels containing various supplements, drugs, growth factors or enzymes widely used for treatment of the damaged cartilage [18].

Fungal arthritis is swelling and inflammation of a joint by a fungal infection. Many organs such as the lungs and tissue can be affected from fungal activity through the blood circulation. Likewise, any fungal activity into the body could be transfer to the joint systems. Articular cartilage can also be infected during a surgery. The symptoms of fungal arthritis are fever, joint pain, joint stiffness, swelling of the ankles, feet, legs or joint. Amphotericin B or azole family drugs such as ketoconazole, fluconazole, or itraconazole are commonly used for fungal arthritis treatment [19, 20]. Fluconazole is a triazole antifungal drug that inhibits the fungal dispersion by disrupting of fungal membranes [21]. Naproxen is a non-steroidal anti-inflammatory drug (NSAIDs) commonly preferred in human or veterinary medicine to reduce pain and inflammation due to its anti-inflammatory analgesic and antipyretic properties [22]. It is also used to treat the fungal arthritis.

In our study, it is aimed to develop a series of IPN hydrogel based on PHEMA/Gelatin for cartilage repair. These materials were designed to be placed into the damaged area and release the drugs by contacting the cartilage. Fluconazole and Naproxen were chosen to reduce pain and prevent fungal infections. These drugs were loaded into the hydrogel structure and release studies were followed. The kinetic parameters of release were also calculated.

2. MATERIAL METHOD

2.1. Materials

HEMA (97%), EGDMA, gelatin, GA (25% aqueous solution), $(NH_4)_2S_2O_8$, $Na_2S_2O_5$, Fluconazole and Naproxen were provided from Sigma-Aldrich. The preparation of Britton-Robinson Buffer (BRB) solution is as reported in the literature [23]. The combination of H_3BO_3 (Merck), H_3PO_4 and CH_3COOH (Sigma-Aldrich) has been titrated to targeted pH with 0.2 M NaOH.

2.2. Synthesis of the IPN Hydrogels

In this section the synthesis of semi-IPN and full-IPN type hydrogels were given by composing in different ratio synthetic monomer HEMA and natural polymer gelatin. All hydrogels were obtained by radical polymerization method of HEMA monomer chains using of $(NH_4)_2S_2O_8/Na_2S_2O_5$ as redox initiator pair and the presence of different ratio of gelatin solution. The predetermined amounts of all reactants are given in Table 1. Gelatin and aqueous HEMA solution were transferred with different volumes into glass tubes. All types of hydrogels were synthesized in the presence of 96 μL EGDMA as the crosslinker of HEMA. Full-IPN hydrogel discs were synthesized with GA, the crosslinker of gelatin, in addition to EGDMA. The reactions were continued for 24 h at room temperature. The wet obtained hydrogel was slices into disk and washed with distilled water to remove unreacted components. The hydrogel discs were dried at room temperature, and then in an oven at 37°C. They were weighed at certain time intervals until constant weight was reached.

2.3. Characterization

Yield of Hydrogel Formation

Yields of hydrogel formation (HF) of the discs were gravimetrically performed. The obtained hydrogel discs were dried until constant weight was reached. Then they were washed in water bath for 48 h to remove the unreacted components. After the extracted hydrogel discs were removed from the bath, dried at room temperature and then at 37°C. The yields of HF of discs were determined by below formula:

$$\text{HF } (\%) = \frac{m}{m_0} \tag{1}$$

where m and m_0 are the weight of the dried hydrogel disc after and before extraction, respectively. The results were obtained at the end of the triplicate measuring.

Table 1. *Amount of the reactants used to synthesize the hydrogel discs and the HF*

Samples	HEMA, 5M (mL)	Gelatin, 5% (mL)	GA, 25% (μL)	HF (%)
$(H_5G)_S$-9	9	1	-	96.40
$(H_5G)_F$-9	9	1	50	96.77
$(H_5G)_S$ -7	7	3	-	95.84
$(H_5G)_F$-7	7	3	50	97.15
$(H_5G)_S$ -5	5	5	-	91.24
$(H_5G)_F$-5	5	5	50	97.92
$(H_5G)_S$-3	3	7	-	86.95
$(H_5G)_F$-3	3	7	50	98.06
$(H_5G)_S$-1	1	9	-	82.18
$(H_5G)_F$-1	1	9	50	99.30

FT-IR Measurements

FT-IR spectra of homopolymer PHEMA, pure gelatin, a semi-IPN and full-IPN hydrogel disc were investigated using a Thermo Scientific Nicolet İS5 spectrometer. The spectra were formed at a resolution of 4 cm^{-1} after 128 scans were collected.

Swelling Tests

Swelling test of the hydrogel samples were gravimetrically conducted at three stages. At the first stage, dehydrated samples were put to swell in BRB (pH=7.4) at 37°C. Swollen hydrogels taken from the buffer at predetermined intervals were weighed and replaced into the bath. The tests were continued to reaching constant weight for each hydrogel. The swelling rates (S%) were determined by using the Equation (2):

$$S(\%) = \frac{M_w - M_d}{M_d} \text{ x } 100. \quad (2)$$

M_w is the hydrated weight of the disc and M_d is the dehydrated weight of the disc before swollen state. For all hydrogels, this process takes approximately 24 hours.

The second stage is investigation of effect of temperature to swelling profiles of the hydrogels. In this stage, the dried samples were left to swell at different temperatures changing from 4°C to 60°C. At the end of 24 h, the swollen discs were taken from the BRB solution, dried and weighed. Swelling values were determined with Equation (2).

The third stage is about effect of pH to swelling profiles of the hydrogels. While time and temperature of swelling were 24h and 37°C, dried samples were left to swell at various pH changing from 2 to 12. After 24 h, with the same procedure, the samples were taken from the BRB solution, dried, weighed and the swelling rates were determined with Equation (2).

Degradation Tests

Degradation tests of samples were performed at 37°C and pH=7.4. Hydrogel discs dried to constant weight were swelled in BRB medium. The swollen hydrogels were taken from the medium at the 24 h, dried and weighed. This weight (M_m) was noted as the most swollen situation of hydrogel discs. After that the samples were left into the swelling medium and weighed at determined intervals for 60 days. The values of degradation (%) were calculated by the Equation (3):

$$\text{Degradation (\%)} = \frac{M_m - M_t}{M_m} \text{ X } 100 \quad (3)$$

where M_m and M_t is the weight of hydrogel disc at the maximum swollen state and at the time t, respectively. The measurements were replicated three times.

SEM Observations

The samples were left to swell to equilibrium in BRB at 37°C. They were placed in a deep freezer at -20°C for 24 h and then replaced into a freeze dryer at −85°C for 24 h (Christ-Alfa 2–4 Model, Martin Christ GmbH). The samples were coated with 200 Å Au. The images of surfaces belonging to hydrogel discs were obtained via SEM (JEOL JSM 6060 LV).

Loading and Release Studies

From swelling/degradation tests, $(H_5G)_S$-3 and $(H_5G)_F$-3 hydrogel discs were chosen for drug release studies. Fluconazole and Naproxen loaded IPN hydrogel discs were prepared by directly adding of Fluconazole (50 mg per disc) and Naproxen (10 mg per disc) into the glass tubes during crosslinking reaction. Similar to our standard hydrogel forming process mentioned above, the wet hydrogel bulk was taken from glass tube and then cut into 0.5 cm-long slices. Drug loaded hydrogels were dried at 30°C.

The release of Fluconazole and Naproxen from the hydrogel discs were investigated in 100 mL of BRB solution by a spectrophotometer (Unicam UV-2100 Haverhill, MA). The specific wavelength of both drugs

was observed at λmax = 260 nm. At various intervals, aliquots of 0.5 mL were drawn from the solution and replaced with an equivalent volume of BRB. By this way sink conditions were maintained during drug release [24]. The results were obtained by repeating the measurements triplicate. The percentage of cumulative release of the drugs was determined by the Equation (4):

$$\text{Cumulative Release (\%)} = \frac{W_t}{W_{total}} \text{ X } 100 \quad (4)$$

where W_t and W_{total} is the weight of the released Fluconazole or Naproxen at any time and the initial total weight of drug loaded into the hydrogel matrix, respectively.

3. RESULTS AND DISCUSSION

3.1. Hydrogel Formation

As a cartilage repair material, the IPN hydrogels were synthesized via incorporation of PHEMA and gelatin and in situ crosslinking. Polymerization reaction was initiated with $Na_2S_2O_5$ and $(NH_4)_2S_2O_8$ redox pair. Gelatin, GA and EGDMA crosslinkers were directly added into reaction medium. It can be though that PHEMA is host and gelatin is guest polymer in this prepared semi-IPN hydrogel. The proposed schematic mechanism of hydrogel formation is given in Figure 1. While EGDMA cross-links PHEMA molecules, GA bonds the gelatin chains. By this way, the IPN hydrogel structures were obtained.

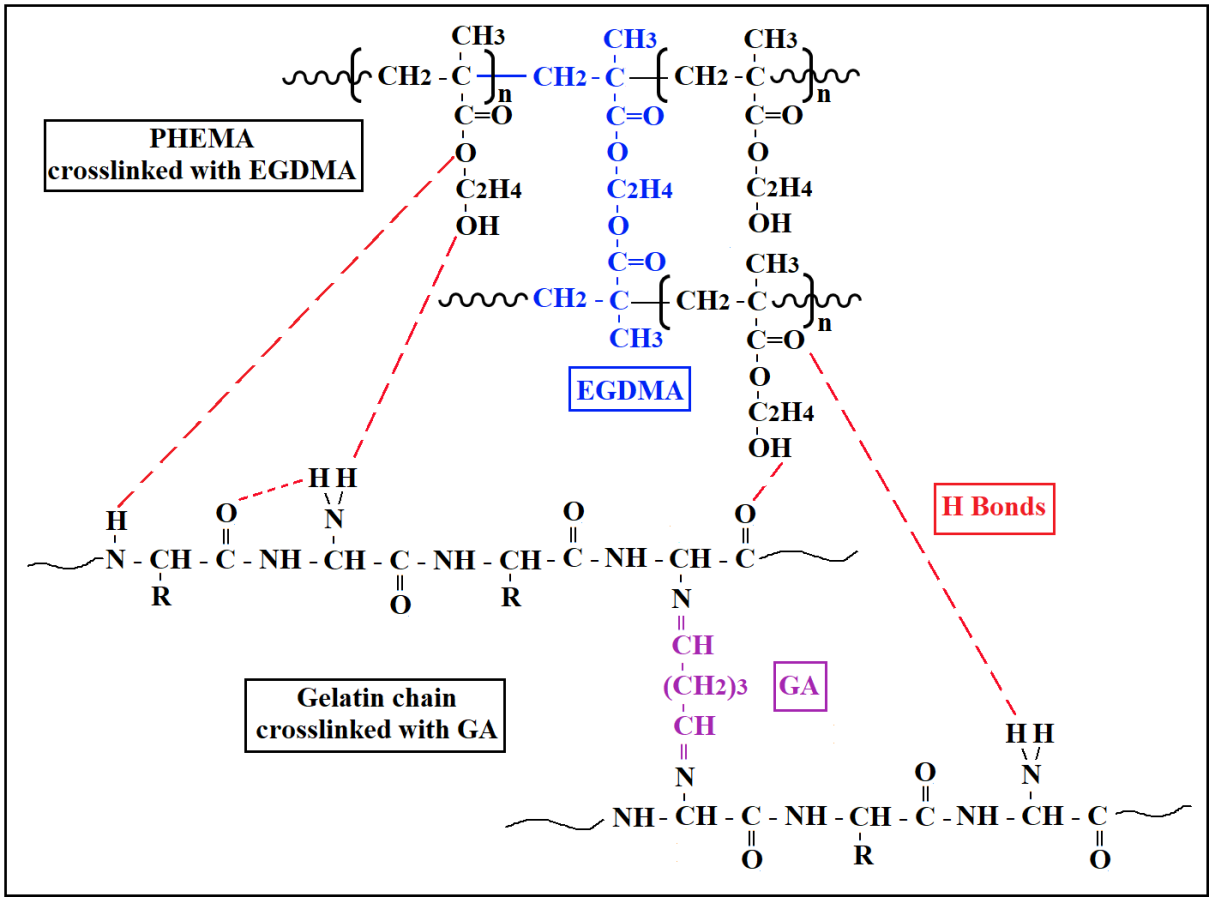

Figure 1. *Mechanism of the IPN hydrogels*

The color changing of gelatin hydrogels from yellow to brownish indicates successful crosslinking process with GA between the amino acid of gelatin [25]. The procedure was also evaluated by determining the HF (%) values via Equation (1) and they were given in Table 1. It is observed that nearly 100% values were

reached for full-IPN hydrogels due to using of two different crosslinkers in matrix. The lower HF values for semi-IPN discs were obtained as HEMA/gelatin ratio decreases. These results depend on the crosslinking of only PHEMA polymer chains. The gradually diminishing of the amounts of PHEMA into the bulk causes the less crosslinked matrix system. So, the more flexible and loose hydrogel structures were obtained.

3.2. FT-IR Spectra

The FT-IR spectra of PHEMA and gelatin homopolymer, semi and full-IPN hydrogels are given in Figure 2. The curve given at Figure 2a shows the two broad bands belongs to PHEMA at ~3300 cm^{-1} and at 2926 cm^{-1} due to O-H and the aliphatic –CH stretching vibrations, respectively. The band at 1709 cm^{-1} is assigned to C=O stretching vibration peaks of PHEMA. In addition, it is observed the specific peaks at 1152 cm^{-1} (asymmetric stretching of the C-O-C bridge), 1070 cm^{-1} and 1022 cm^{-1} (skeletal vibrations including C-O stretching) that indicates the existence of PHEMA [11]. The similar bonds were also detected in the curves (b) and (c) that belongs to the hydrogels including PHEMA. As expected, these peaks disappear in the curve (d) belongs to gelatin hydrogel.

At the curve (d), the broad peaks at 3292 cm^{-1} indicates to N-H stretching. Also, there are aliphatic C-H stretching and bending vibrations at 3074 cm^{-1}, 2935 cm^{-1} and 1446 cm^{-1}, 1404 cm^{-1}, respectively. The peak at 1627 cm^{-1} is related to N-H stretching being in amide I groups. This specific peak did not exist in the curve of pure PHEMA hydrogel (Figure 2a). In the hydrogels including gelatin, Schiff base linkage was expected between the amino groups of the gelatin and aldehyde groups of glutaraldehyde. The specific peak at 1531 cm^{-1} indicates -HC=N stretching vibrations attributed to amide II band in Schiff bases [26]. The same peak was weakly occurred at the curve (c) which is belongs to full-IPN hydrogel.

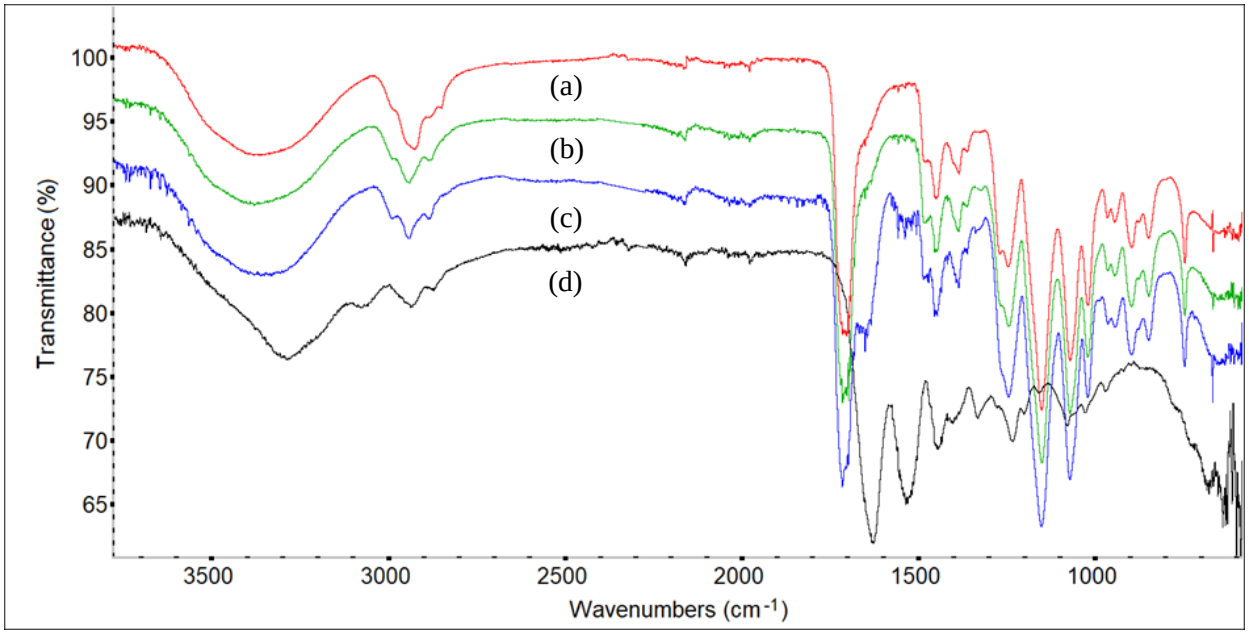

Figure 2*. FTIR spectrum of a) PHEMA; b) $(H_5G)_S$-3; c) $(H_5G)_F$-3 and d) gelatin hydrogels*

3.3. Swelling Behavior of the Hydrogels

Figure 3 presents the changing of swelling percentages with time at 37°C and pH=7.4. Swelling values increased at first and then remained constant at nearly 24 h. The swelling values were indicated to 250% for the most swollen hydrogel $(H_5G)_S$-1, and 46% for the least swollen hydrogel $(H_5G)_F$–9. As seen, semi-

IPN hydrogels swell more than full-IPNs which crosslinked by two agents, EGDMA and GA. The tighter hydrogel network of full-IPN inhibits the mobility of polymer chains and causes fewer water molecules to penetrate, and so suppressed swelling [27]. It is observed that the higher ratios of HEMA/gelatin negatively affect the S% values. As the hydrophilicity of HEMA lower than gelatin molecules, HEMA content in the structure decreases the swelling values.

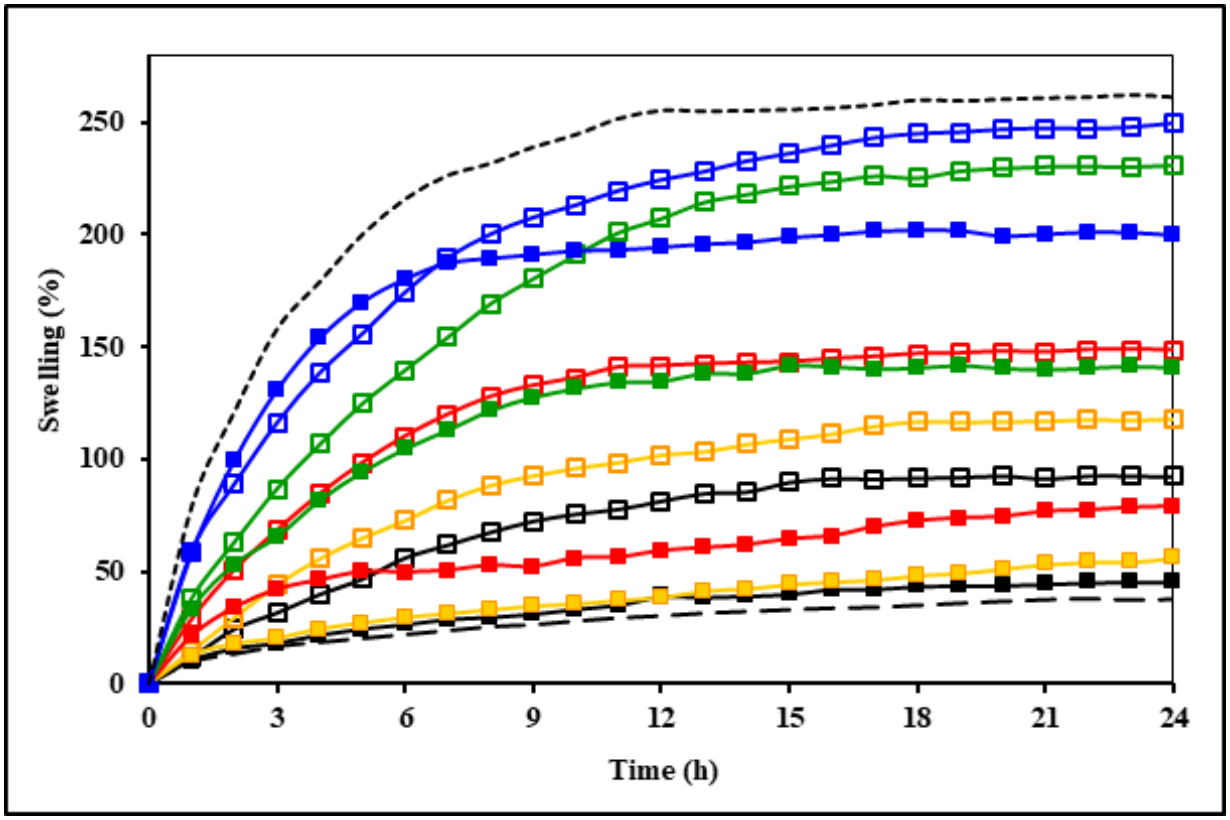

Figure 3. *The change of S% with time for semi and full IPN hydrogel discs*

(-■- $(H_5G)_F$-9; -□- $(H_5G)_S$-9; -■- $(H_5G)_F$-7; -□- $(H_5G)_S$-7; -■- $(H_5G)_F$-5; -□- $(H_5G)_S$-5; -■- $(H_5G)_F$-3; -□- $(H_5G)_S$-3; -■- $(H_5G)_F$-1; -□- $(H_5G)_S$-1; ▬ ▬ PHEMA; - - - Gelatin)

Figure 4 shows the change of swelling with temperature at pH=7.4 for 24 h. In general, the IPN hydrogel discs were not affected by the variation of temperature. Temperature-S% profiles like time-S% variations. Semi-IPN swell much more than full-IPN hydrogels. The less swelling value belongs to PHEMA, and gelatin has the highest value of S%. S% values gradually increase as the ratio of gelatin in the mixture increased.

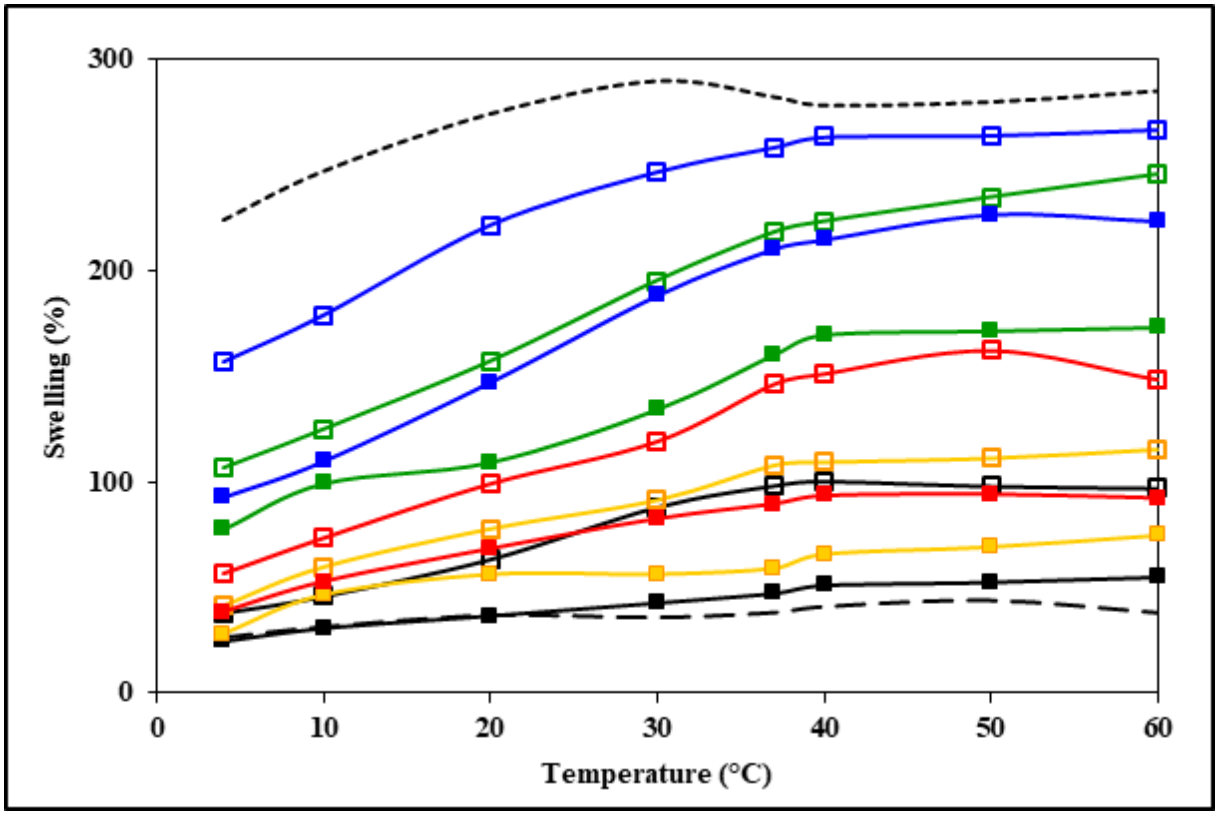

Figure 4. *The change of S% with temperature for semi and full-IPN hydrogel discs*

(-■- $(H_5G)_F$-9; -□- $(H_5G)_S$-9; -■- $(H_5G)_F$-7; -□- $(H_5G)_S$-7; -■- $(H_5G)_F$-5; -□- $(H_5G)_S$-5; -■- $(H_5G)_F$-3; -□- $(H_5G)_S$-3; -■- $(H_5G)_F$-1; -□- $(H_5G)_S$-1; ▬ ▬ PHEMA; - - - Gelatin)

The change of S% values with pH at 37°C for 24 h is shown in Figure 5. It is observed that the changes of swelling profiles with temperature and time are compatible with each other. Semi-IPN discs have higher %S values than full-IPNs and the swellings are negatively affected from the ratio of HEMA/gelatin. Because of the non-ionic structure of HEMA molecules, the swelling of its hydrogels was not influenced from pH changes. Unlike PHEMA, gelatin hydrogel has pH sensitivity due to its amphoteric groups. Negative and positive charges of proteins are equalized at a specific pH value which is called as isoelectric point (pI). pI value of gelatin is between 4.68–5.26 [28]. As seen from the graph, the swelling profile of gelatin hydrogel with pH is parabolic depending on its pI. Like other protein structures, the carboxylic and amino groups of gelatin are sensitive to pH changes. At below pI, amino groups ($-NH_2$) of gelatin chains can protonate and formed ammonium groups ($-NH_3^+$). The repulsive electrostatic interactions occur between these positively charged ammonium groups of the gelatin network. Thus, the swelling of IPN structure increases. Carboxyl groups (-COOH) of gelatin chains at pH above pI, can ionize to carboxylate groups ($-COO^-$). In this case, the negatively charged carboxyl groups repulse each other and then swelling is supported again. Near pI, negative and positive charges belonging gelatin become coequal. The attractive electrostatic forces between these groups caused to collapse the network [29]. So, swelling value of the gelatin hydrogel decreases when the pH value is close to pI, then minimum at pI and increases due to interacting more water molecules far from the pI. According to this unique property, while the amount of gelatin into the mixture increases, the swelling profiles of the PHEMA-gelatin hydrogels became more like gelatin hydrogel.

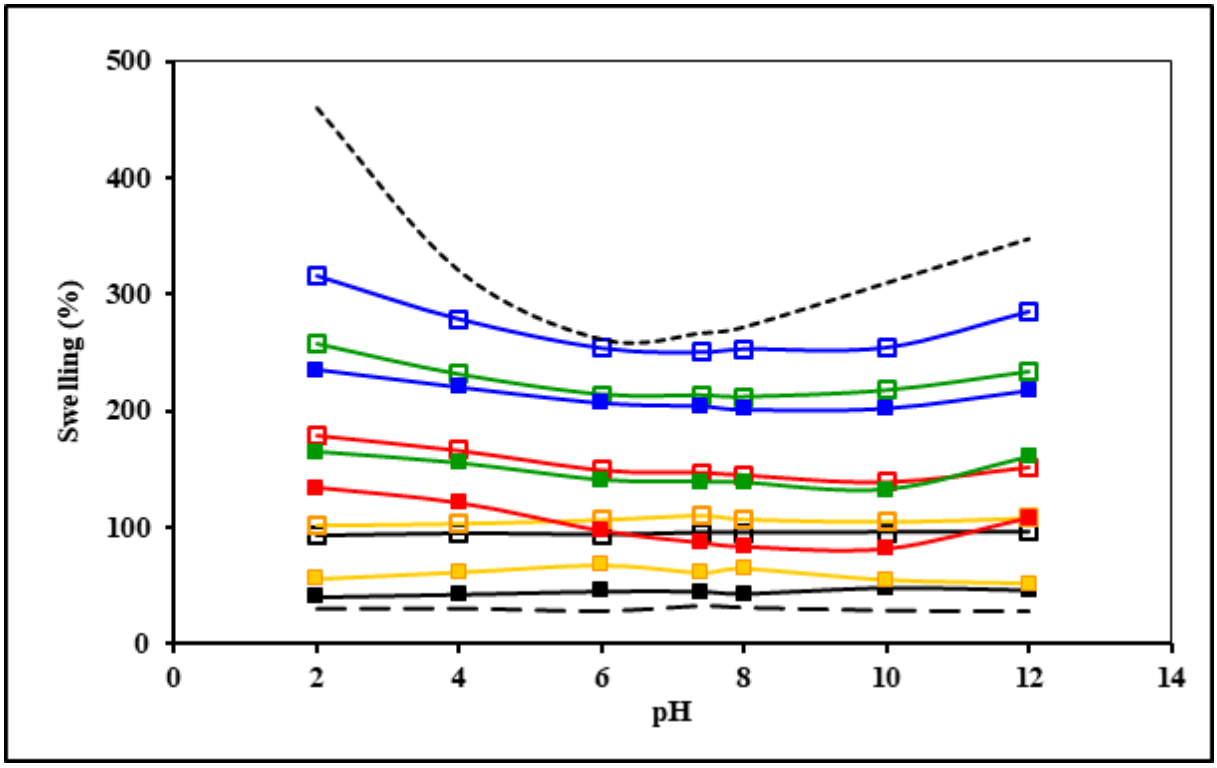

Figure 5. *The change of S% with pH for semi and full-IPN hydrogel discs*

(-■- $(H_5G)_F$-9; -□- $(H_5G)_S$-9; -■- $(H_5G)_F$-7; -□- $(H_5G)_S$-7; -■- $(H_5G)_F$-5; -□- $(H_5G)_S$-5; -■- $(H_5G)_F$-3; -□- $(H_5G)_S$-3; -■- $(H_5G)_F$-1; -□- $(H_5G)_S$-1; ▬ ▬ PHEMA; - - - Gelatin)

3.4. Degradation Behavior of the Hydrogels

The degradation of hydrogel discs was performed in BRB medium for 60 days. The degradation variations were presented in Figure 6. In general, a slight degradation was observed for all of the hydrogels except gelatin. It is seen that the fastest degraded hydrogel is gelatin and PHEMA hydrogel nearly didn't lost their mass [30]. While the presence of PHEMA in hydrogels increases, their resistance to degradation also increases. Semi-IPN hydrogels began to degrade in a shorter time. In these groups of hydrogels, gelatin have been as a guest polymer without crosslinking. Therefore, with the increasing ratio of gelatin, the difficulty of being trapped in the network structure occurs and consequently gelatin chains may be separated more easily from the hydrogel structure.

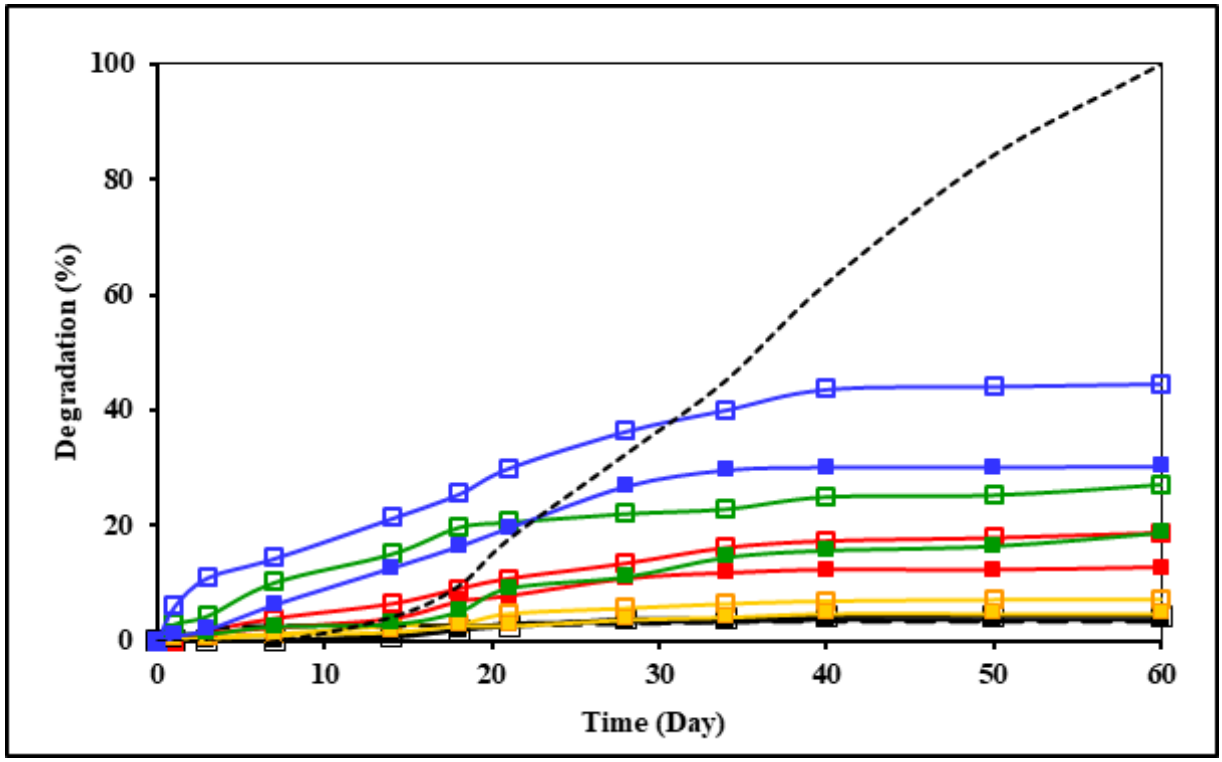

Figure 6. *Degradation profiles of the hydrogel discs at 37°C and pH=7.4*

(-■- $(H_5G)_F$-9; -□- $(H_5G)_S$-9; -■- $(H_5G)_F$-7; -□- $(H_5G)_S$-7; -■- $(H_5G)_F$-5; -□- $(H_5G)_S$-5; -■- $(H_5G)_F$-3; -□- $(H_5G)_S$-3; -■- $(H_5G)_F$-1; -□- $(H_5G)_S$-1; ▬ ▬ PHEMA; - - - Gelatin)

3.5. SEM Observation

SEM images of $(H_5G)_S$-3 and $(H_5G)_F$-3 hydrogels which is selected for releasing studies are presented in Figure 7. Pure gelatin and PHEMA images were also taken to compare the matrix structures. It is seen that all of the hydrogels, except PHEMA have highly porous morphology. As is known, porous structure affects mechanical, swelling and releasing properties. The least swollen hydrogel, PHEMA, has smooth and nonporous structure. Conversely, the pure gelatin sample which is the most swollen hydrogel has the largest pore sizes.

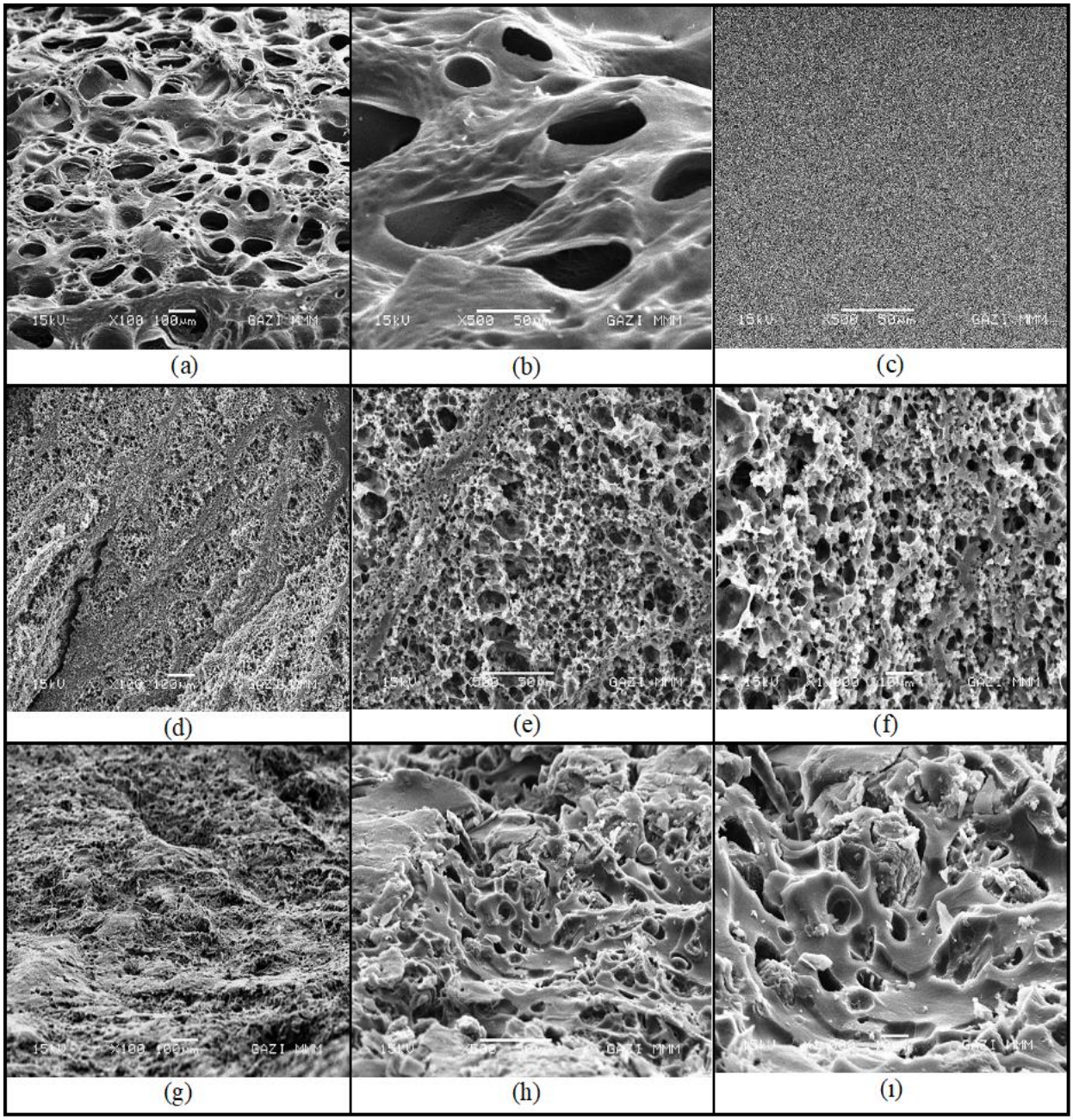

Figure 7. *SEM micrographs of the hydrogel a) gelatin (X100) b) gelatin (X500) c) PHEMA (X500) d) $(H_5G)_S$-3 (X100) e) $(H_5G)_S$-3 (X500) f) $(H_5G)_S$-3 (X1000) g) $(H_5G)_F$-3 (X100) h) $(H_5G)_F$-3 (X500) ı) $(H_5G)_F$-3 (X1000)*

Both semi and full-IPN hydrogels are also presents porous structure. But, the less swollen hydrogel, $(H_5G)_F$-3 displays the lower pore density then $(H_5G)_S$-3. As is known, double crosslinking causes the compact and tight bulk structure. That's why the most porous images were obtained for $(H_5G)_S$-3 hydrogel. SEM micrographs are consistent with the swelling behaviors.

3.6. Fluconazole and Naproxen Release Kinetics

Considering the data that obtained from swelling and degradation tests, $(H_5G)_S$-3 and $(H_5G)_F$-3 discs were chosen for drug loading and release studies. The cumulative release profiles of Fluconazole and Naproxen through semi and full-IPN hydrogel were presented in Figures 8-9. As seen from the figures, releases of drugs increase rapidly at initial and then continues after 36 h and 48 h, respectively. Semi-IPN hydrogels have high values of release than full-IPNs because of having looser matrix. As observed that the swelling

behavior of the hydrogels is similar to that of their releasing behaviors. Because the swelling behaviors of the hydrogel discs directly affect the release behaviors.

The values of Fluconazole release for hydrogel discs were determined in between 70-88%. The serum levels of Fluconazole at daily dose of 200 mg have been reported in the literature as 7.5-33.4 μg/mL [31]. Moreover, a susceptibility breakpoint for 400 mg Fluconazole/day doses is stated as MIC 16 mg/L or more [32]. The drug release from the IPN discs have founded this range at 1 h for Fluconazole for this study.

The values of Naproxen release for hydrogel discs were also determined in between 65-80%. The therapeutic range of Naproxen has been reported to 3-9 μg/mL in the literature [33]. Drug release from the IPN discs reached this range at 1 h for Naproxen.

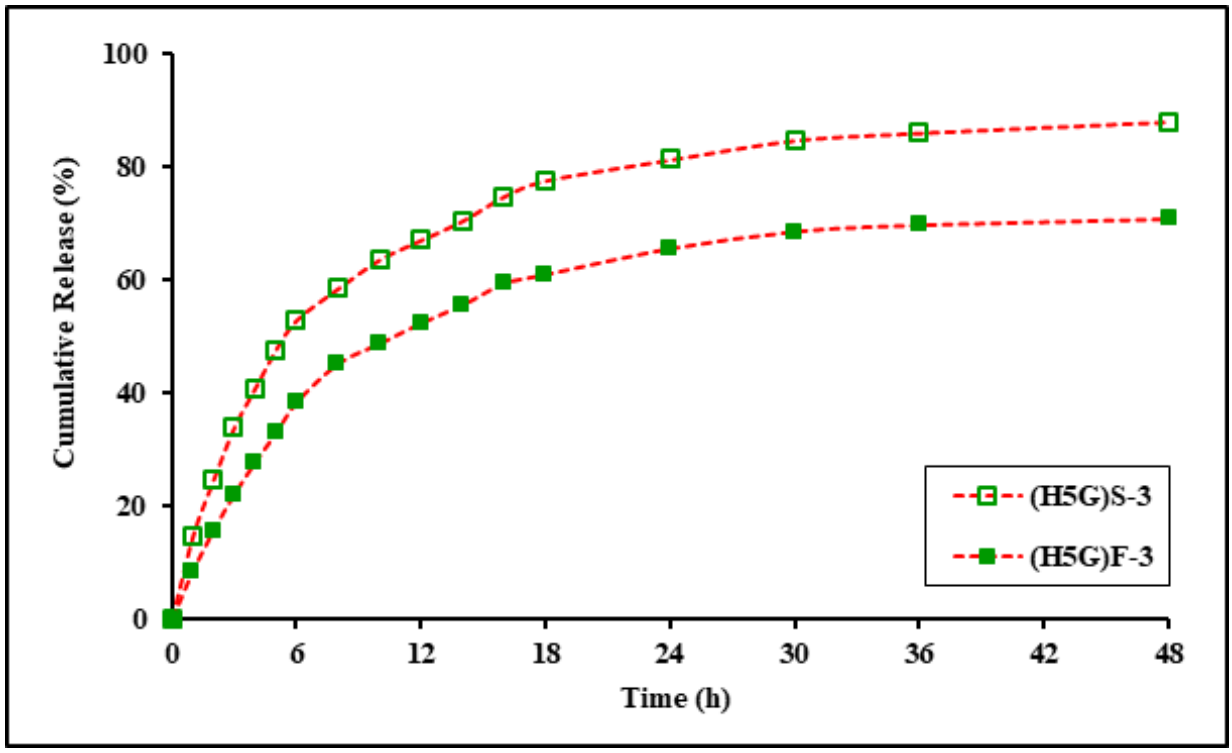

Figure 8. *Release profiles of Fluconazole from the $(H_5G)_S$-3 and $(H_5G)_F$-3 discs*

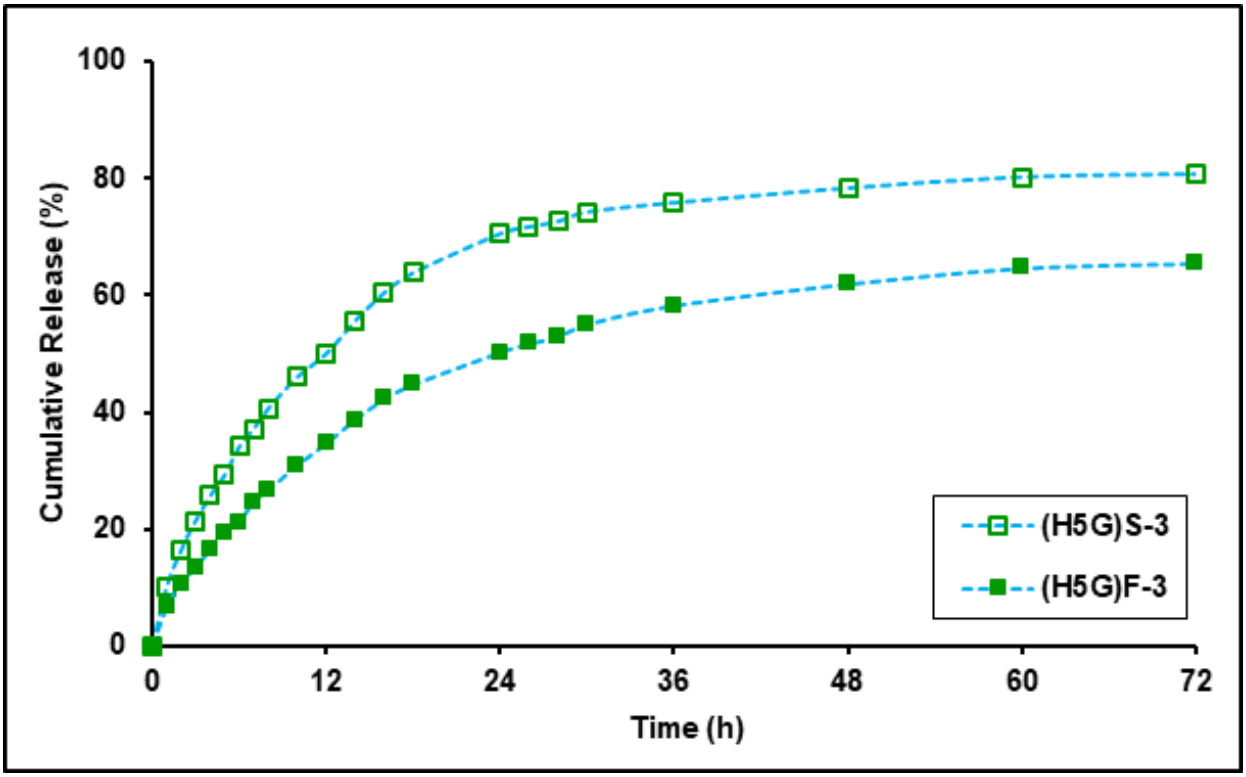

Figure 9. *Release profiles of Naproxen from the $(H_5G)_S$-3 and $(H_5G)_F$-3 discs*

It is needed the kinetic parameters of drug release to determine the diffusion type of the system. We chose the Ritger-Peppas Model among empirical mathematical models in Equation (5) to express drug release kinetics [34]

$$\frac{M_t}{M_\infty} = k.t^n \quad . \tag{5}$$

This simple exponential relation describes the solute release behavior of controlled release polymer systems. Where Mt is the amount of released drug at time t and M∞ is the maximum amount of released drug. k is a characteristic constant correlated to the structure of the matrix, and n is the diffusional exponent characteristic of the release mechanism. It has been stated that the release of the solutes from spheres, cylinders, and discs can define by this equation, disregarding the release mechanism. For cylindrical samples n=0.45 corresponds to the Fickian diffusion while 0.45<n<1.00 indicates the anomalous or non-Fickian transport, n=1.00 implies Zero-order release. The n and k values of $(H_5G)_S$-3 and $(H_5G)_F$-3 discs were defined by Equation (5) and presented in Table 2. When n values of Fluconazole and Naproxen were calculated which presented below, it can be said that these discs have release kinetics by non-Fickian diffusion.

Table 2. *Release parameters of drugs through the hydrogels (R^2: Deterministice coefficient)*

Samples	**Release of Fluconazole**			**Release of Naproxen**		
	n	k	R^2	n	k	R^2
$(H_5G)_S$-3	0.71	9.50×10^{-3}	0.9977	0.65	8.64×10^{-3}	0.9995
$(H_5G)_F$-3	0.80	4.73×10^{-3}	0.9971	0.66	6.79×10^{-3}	0.9985

4. RESULTS

In our study, ten types of hydrogels were synthesized by using the various ratio of HEMA/gelatin. Two types of crosslinkers, EGDMA and GA, were used to obtain semi and full-IPN hydrogels. The hydrogels were investigated by FTIR, SEM and the swelling and degradation analysis. This crosslinking process was affirmed by FTIR analysis. The yields of HF were calculated and high values were found for all samples. The swelling behaviors were determined by change of time, pH and temperature. It is observed that the swelling percentages changed in the range of 45-250%. The swelling capacity of PHEMA was stated as between 566% and 988% in the literature [35, 36]. Gelatin's has reported between 300% and %450 [11]. Generally, full-IPNs swell less than semi-IPNs because of the high crosslinking density. The slower degradation rates were obtained for all full-IPN samples. Porosity properties of the hydrogels were defined via SEM analysis. Semi-IPN hydrogel have smaller but numerous pores than full-IPN. SEM analysis are compatible with the swelling results. The drug releasing studies were carried out by using $(H_5G)_S$-3 and $(H_5G)_F$-3 discs to compare the crosslinking effect. Fluconazole and Naproxen were chosen as active reagents. The release parameters were calculated and a non-Fickian release diffusion kinetic was observed. Consequently, it could be concluded that the synthesized IPN discs are a promising controlled release material for cartilage repair.

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CONFLICTS OF INTEREST

No conflict of interest was declared by the authors.

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