# Poly (Ethylene Glycol) / Gelatin Composite Hydrogels for Drug Delivery

Fatma Ayhan*, Sabiha Demirci and Hakan Ayhan

*Muğla Sıtkı Koçman University, Faculty of Science, Department of Chemistry, Biochemistry & Biomaterials Research Laboratory, Muğla, Turkey*

**Abstract:** Hydrogels are three dimentional, hydrophilic, and polymeric networks that have been designed and fabricated to fulfill the needs of the pharmaceutical and medical fields. Many biomedical applications including controlled drug delivery have developed based on hydrogel technologies. Various composite hydrogels including synthetic and natural materials can be produced to create controllable systems in drug delivery applications. In this study, poly(ethylene glycol) (PEG-DA) based composite hydrogels were prepared by photopolymerization method and 2,2-dimethoxy-2-phenylacetophenone (DMPA) was used as photoinitiator. Macromer mixtures were prepared by mixing 30 % PEG-DA and 0.5 % DMPA. Photocuring was achieved by cross-linking with 3 % ethylene glycol diacrylate (EGDMA) after addition of drug and gelatin solutions under mild conditions. The effect of gelatin concentration and molecular weight on the gentamicin release was studied with 75, 100, 225, and 300 bloom gelatin for 0.1, 0.5, and 1.0 w/w ratios. Drug release kinetics from loaded composite hydrogels were tested by spectrophotometric method in phosphate (pH 7.4) and citrate buffer (pH 1.2) representing small intestine and stomach media, respectively. New biopolymer containing composite hydrogels enhanced drug release rates for all compositions and gentamicin release was found to be adversely effected by concentration and molecular weight. Hydrogels were morphologically characterized by SEM images which indicated the presence of pinholes like structures with smaller sizes for larger molecular weights.

**Keywords:** Poly(ethylene glycol)-diacrylate (PEG-DA), Gelatin, Composite hydrogel, Photopolymerization, Drug delivery, Gentamicin.

## INTRODUCTION

Hydrogels are hydrophilic polymer networks which may absorb large quantities of water while remaining insoluble in aqueous solutions due to chemical or physical crosslinking of individual polymer chains [1,2]. They can be prepared from natural or synthetic polymers. Although hydrogels made from natural polymers may not provide sufficient mechanical properties and may contain pathogens or evoke immune and/or inflammatory responses, they do offer several advantageous properties such as inherent biocompatibility, biodegradability, and biologically recognizable moieties that support cellular activities. Synthetic hydrogels do not possess inherent bioactive properties but usually have well-defined structures that can be modified to yield tailorable degradability and functionality. Because of those characteristics, hydrogels have been extensively used in the biomedical and pharmaceutical industries for making contact lenses, biosensors, membranes, artificial organs, and carriers for controlled drug delivery [2,3]. Commonly used natural polymers are chitosan, alginate, fibrin, collagen, gelatin, hyaluronic acid, and desxtran while hydroxyethyl methacrylate (HEMA), N-(2-hydroxypropyl) methacrylate (HPMA), N-vinyl-2-pyrrolidone (NVP), vinyl acetate (VAc), acrylic acid (AA), methacrylic acid (MAA), polyethylene glycol acrylate/methacrylate (PEGA/PEGMA), and polyethylene glycol diacrylate/dimethacrylate (PEGDA/PEGDMA) are some of the most studied synthetic monomers [1,4].

Gelatin is the commercial protein, derived from denatured collagen that is present in animal skin and bone, and is an important gelling biopolymer widely used in foods to provide elasticity, viscosity, and stability. The gelatin possesses excellent bio-compatibility and form a firm gel at ambient temperature [5]. The gelatin manufacture is typically carried out by acid pre-treatment (Type-A) or alkali pretreatment (Type-B) from bovine or porcine skin or bone. Gelatin extractions has different physical and chemical properties due to hydrolytic degradation during process. Due to its interest for edible, pharmaceutical and photographic uses and for medical applications, this biomaterial has focussed much scientific interest [7-10].

Various composite hydrogels have been synthesized as organic (polymer)/inorganic (clay) nanocomposite [11], hydroyapatite/gelatin nanocomposites [12], highly ionic gelatin- poly-L-lysine (PLL) or poly-L-glutamic acid (PLG) hydrogel scaffolds [13], and porous chitosan-gelatin scaffold containing plasmid DNA [14] to develop composite biomaterials for the controlled release of different therapeutic factors.

*Address correspondence to this author at the Muğla Sıtkı Koçman University, Faculty of Science, Department of Chemistry, Biochemistry&Biomaterials Research Laboratory, Muğla, Turkey; E-mail: fayhan@mu.edu.tr

E-ISSN: 2311-8717/14 

In the research investigated by Seki et al., the nasal absorption of insulin was examined in rats by a sperminated gelatin which was prepared as a candidate absorption enhancer by the addition of spermine to gelatin. Immuno-reactive insulin levels in the plasma after nasal administration of insulin were increased 5.3-fold by addition of 0.2 % SG, and the plasma glucose levels fell in a manner dependent on the insulin levels. So, sperminated gelatin was reported as a good candidate for a safe absorption enhancer to produce a slight modification of the permeability of the paracellular pathway of mucosal membranes, while retaining the sieving property of the epithelial membranes [15].

A gelatin/montmorillonite-chitosan (Gel/MMT-CS) nanocomposite scaffold was prepared via the intercalation process and the freeze-drying technique, using the ice particulates as the porogen materials. It was demonstrated that the introduced intercalation structure endowed the Gel/MMT-CS scaVold with good mechanical properties and a controllable degradation rate. The mitochondrial activity assay provided good evidences of cells viability on the Gel/MMT-CS membranes, giving an indication of possible application as a matrix for tissue engineering [16].

Gelatin was used in Poly(ethylene glycol) (PEG)-modified thiolated gelatin (PEG-SHGel) nanoparticles to enhance DNA delivery and transfection. Reporter plasmid expressing enhanced green fluorescent protein (EGFP-N1) was encapsulated in the nanoparticles. The size of DNA-containing gelatin (Gel) and thiolated gelatin (SHGel) nanoparticles after surface modification with PEG were found to be in the range of 310 to 350 nm. The highest transfection efficiency of the reporter plasmid was obtained from the qualitative and quantitative results of *in vitro* transfection studies in murine fibroblast cells (NIH3T3), PEG-Gel and PEG-SHGel nanoparticles [17].

A biodegradable gelatin hydrogel formulation was used to increase the circulation time of PEG-catalase to test the inhibiting effect of reactive oxygen species (ROS)-mediated acceleration of tumor metastasis. Implantation of $^{111}$In-PEG-catalase/gelatin hydrogel into subcutaneous tissues maintained the radioactivity in plasma for more than 14 days. In the study, the effect of each treatment on spontaneous pulmonary metastasis of B16-BL6/Luc cells from subcutaneous tumors was examined by measuring luciferase activity in the lung. The results revealed that the PEG-catalase/hydrogel significantly inhibited the pulmonary metastasis compared with PEG-catalase solution [18].

In recent studies, gelatin containing interpenetrating polymer network (IPN) and semi-IPN hydrogels were prepared from photo-reactive polyethylene glycol diacrylate (PEG-DA), gelatin, and poly(lactic-ethylene oxide fumarate). Mucin adsorption possessed greatest mucoadhesion properties and the release of anti-fungal reagent, nystatin showed slow release from the sIPN gelatin nanofiber scaffold [19]. Preserving gelatin in the hydrogel structure provides cell motif sites for a longer period of time, which is desirable for uniform cell proliferation [20].

We present results on the synthesis and gentamicin release from photopolymerized PEG/Gelatin composite hydrogels. The dependence of drug release on gelatin composition and molecular weight was measured as a function of time for pH 7.4 and 1.2. The morphology of hydrogel network structure was characterized by SEM images. Drug release behaviours were investigated on proposed five kinetic models.

## MATERIALS AND METHODS

### 1. Materials

Gelatin (G6650, 75 bloom; G6144, 100 bloom; G9382, 225 bloom; G1890, 300 bloom, Poly ethylene glycol diacrylate (PEG-DA, Mn: 700), Ethylene glycol dimethacrylate (EGDMA, 98%,), 2,2-dimethoxy-2-phenylacetophenone (DMPA, 99 %), $Na_2HPO_4.2H_2O$, $NaH_2PO_4.2H_2O$ Sodium sitrate were purchased from Sigma-Aldrich. NaCl and HCl (30 %) were purchased from Merck. Gentamicin® 80mg I.M/I.V (Deva Holding A.Ş, Turkey) ampoule which contains gentamicin sulphate equivalent to 80 mg gentamicin in each 2 ml ampoule was used. Ultra-pure water was produced by a Human power I water purification system.

### 2. Composite Hydrogel Synthesis

The optimum hydrogel synthesis conditions were obtained previously by our group's research studies and used for the synthesis of hydrogels [21,22]. Briefly, a precursor solution was prepared by mixing PEG-DA and DMPA in dark media for two hours with slow magnetic stirring. The predetermined amount of solution containing Gentamicin sulphate and gelatin was then added. The final total volume was adjusted to 400µl with cross-linking agent, EGDMA. The experiments were conducted in cylindrical glass molds with the size of 12 mm diameter and 10 mm height. The solution was polymerized by exposure to 365 nm UV light with 10 mW/cm$^2$ intensity for ~ 10 min following nitrogen treatment. The same method was used to

prepare hydrogels without gelatin by adding drug solution for control group experiments. The amount of PEG-DA, cross-linker (EDGMA) and photoinitiator (DMPA) were 30, 3, and 0.5 weight percent based on the macromer weight, respectively. The concentrations of biopolymer were tested at 0.1, 0.5, and 1 % wt/wt for each bloom. Figure **1** shows the chemical structures of macromer, cross-linker, and photoinitiator while molecular weight values with corresponding bloom numbers were given in Table **1**.

**Table 1. Average Molecular Weight Values of Different Bloom Numbers**

| Number of Bloom | Type of Bloom | Average Molecular Weight |
|---|---|---|
| 50-125 | Low | 20,000-25,000 |
| 175-225 | Medium | 40,000-50,000 |
| 225-325 | High | 50,000-100,000 |

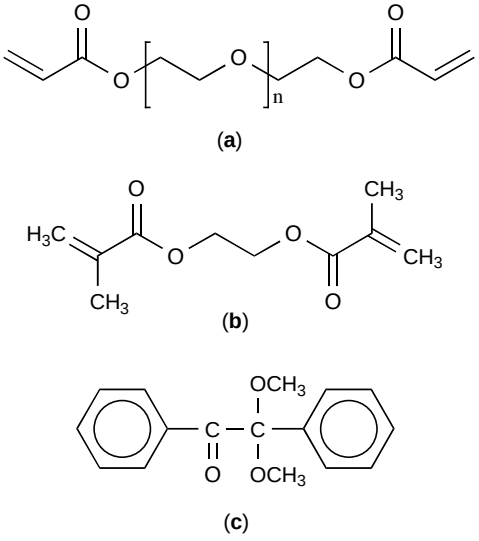
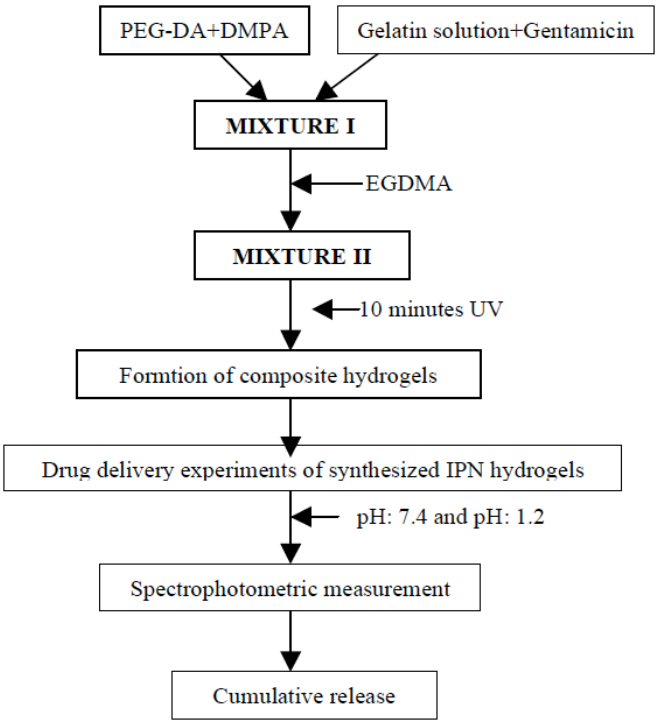



**Figure 1:** Chemical structures of the compounds used in the research experiments: **a**) Poly(ethylene glycol) diacrylate (PEG-DA macromolecule); **b**) Cross-linker, Ethylene glycol dimethacrylate (EGDMA); **c**) Photoinitiator, 2,2-dimethoxy-2-phenylacetophenone (DMPA).

## 3. Evaluation of Drug Release

For the conduction of release experiments, a gentamicin loaded disk was placed in a vial containing 10 ml buffer solution and the release characteristics of the 0.8 mg gentamicin loaded samples were determined in phosphate buffer (pH 7.4) and in citrate/HCl buffer (pH 1.2). The ionic strength of all buffers was adjusted to 0.13 M by the addition of KCl. The temperature and stirring speed were maintained at 37°C and the amount of gentamicin sulphate released at predetermined time points was monitored using UV-Visible spectrophotometer at the $\lambda_{max}$ value of 255 nm, and cumulative fractional release at time t was then calculated.

**Table 2. Schematic Representation of the Experimental Process**




The drug release experiments were followed up to 400 min. The experimental method which is practised at study environment is presented in Table **2** with flow chart in details.

## 4. Morphological Studies

The morphology of control and drug loaded sample was investigated using JEOL (Japan) model JSM-840A scanning electron microscope. The samples were mounted on the base plate and coated with gold using vapor deposition techniques. The hydrogel surfaces were then scanned by using 5 000 X magnification to investigate the hydrogel structure.

## 5. Drug Release Kinetics

Kinetics of drug release from composite hydrogels is tested using zero-order, first-order, Higuchian and Hixson-Crowell's models (Equation **1**-**4**). Constant release rates can be achieved with zero-order kinetics which shows linear relationship between amount released and time. When the release of drug is proportional to the amount of drug remaining to be

released, first-order kinetics describes the system. The square root time dependent expression based on Fick's law was derived by Higuchi and Hixson-Crowell model assumes the release rate to be limited by the drug particle dissolution rate [23].

$$Q_t = K_0 t \quad (1)$$

$$\ln Q_t = \ln Q_\alpha + K_1 t \quad (2)$$

$$Q_t = K_H t^{1/2} \quad (3)$$

$$Q_\alpha^{1/3} - Q_t^{1/3} = K_{HC} t \quad (4)$$

$$\frac{M_t}{M_\infty} = kt^n \quad (5)$$

Here $Q_t$ is the amount of drug released in time t, $Q_\infty$ is the initial amount of drug and $K_0$, $K_1$, $K_H$ and $K_{HC}$ are release rate constants for zero-order, first-order, Higuchi and Hixson-Crowell equation, respectively. Another empirical equation defined by Korsmeyer-Peppas in 1983 [2, 24-26] was used to and the rate constant, k and the exponent n that represents the type of transport mode of the Fickian and non-Fickian diffusional behavior (Equation **5**).

All drug release experiments were repeated three times and the results were reported as average values.

## RESULTS

### 1. Hydrogel Synthesis

Previous work indicated that hydrogels containing 30%(w) PEG-DA had mass swelling ratio (weight swollen divided by weight dry) of 120 having 3%(w/w) cross-linker and 0.5 % (wt/wt) photoinitiator [27].

In this study, gentamicin loaded cylindirical PEG-DA/Gelatin composite hydrogels were synthesized (Figure **2**) and drug delivery experiments from PEG-DA/Gelatin hydrogels were practised. Release experiments were tested with structures including model drug gentamicin at pH 7.4 and pH 1.2 at 37ºC and calculated values of cumulative release commensally calibration chart.

### 2. Drug Release

The cumulative release of gentamicin sulphate from PEG-DA/Gelatin composite hydrogels in phosphate (pH 7.4) and citrate/HCl (pH 1.2) buffers, respectively, are depicted in Figures **3** and **4**. Studies were carried out for 4 hours or less. Drug release profiles were drawn as a function of time for each gelatin concentration and four bloom values studied. Control grup experiments were performed with photopolimerized composite hydrogel without gelatin.

When the graphics were analysed, quite different results were observed according to release media pH. In general, addition of a bio-molecule to the structure of hydrogel leads to an increased gentamicin release compared with control group results. The cumulative gentamicin release was measured about 18 % for 300 bloom gelatin and higher (32 % to 36 %) for 75, 100, and 225 bloom values when gelatin concentration was kept in 0.1 % (Figure **3a**). In the case of 0.5 % gelatin concentration again drug release is higher more than 2 fold for that of control group results and almost 24 % release rate was observed for 0.5 % gelatin concentration as can be seen in Figure **3b**. High drug

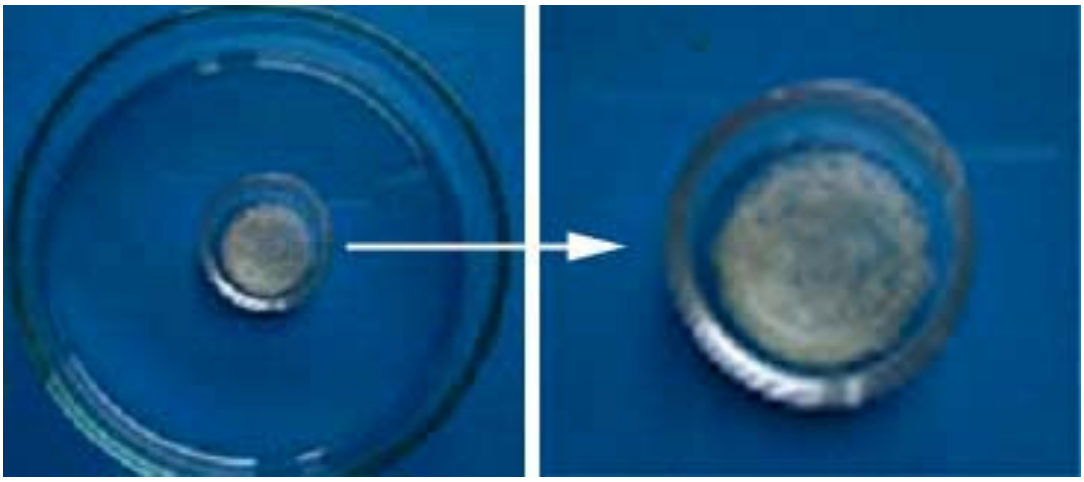


**Figure 2:** Synthesized PEG-DA/Gelatin composite hydrogel.

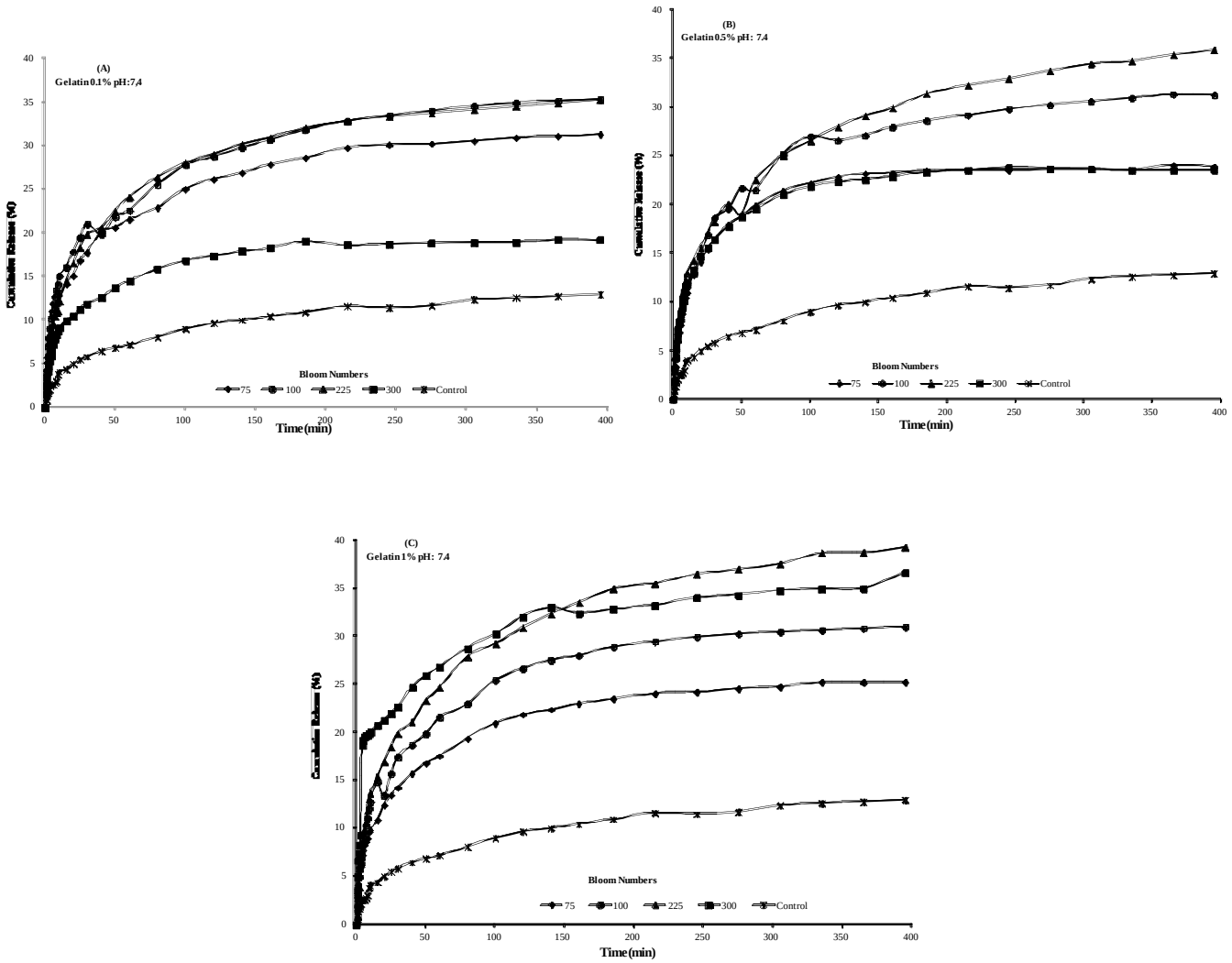



**Figure 3:** Release graphics of PEG-DA/Gelatin composite hydrogels synthesized with different molecular weight and concentrations of gelatin at pH 7.4: (**a**) 0.1 %, (**b**) 0.5 %, (**c**) 1 % gelatin.

release rates were obtained for 100 and 225 bloom numbers when gelatin concentration was 0.5 %. The highest gelatin concentration in hydrogels resulted with 24 %, 31 %, and 36-39 % drug release which are again more than 2 times greater than control experiments which gave 12 % release after 400 min. Cumulative release was higher in PEG-DA/Gelatin composite hydrogels with molecular weight (225 and 300 bloom) gelatin than smaller molecular weight (75 and 100) gelatins in which drug release has been realized nearly 40 % at 400 minutes (Figure **3c**). It must be noted that a small burst effect appeared for high release rates in each Figure at pH 7.4. Drug release was followed up to 60 days and complete drug release was observed after 35 days for 75 and 100 bloom number when gelatin concentration was 0.1%. It was measured as 45 days for 225 bloom number and 50 days for 300 bloom number gelatin containing hydrogels. Drug release ended up with little longer period of time when gelatin concentration was adjusted to 0.5 and 1 % ratios.

In order to analyze the behaviour of hydrogels in high acidic media, drug release experiments were conducted at pH 1.2. Gelatin concentrations were adjusted to be 0.1%, 0.5%, and 1% as shown in Figure **4**. Gentamicin release was completed within 200 min for each gelatin concentration value. But control group cumulative release values were approximately 75% after 400 min treatment time in pH 1.2 buffer condition. When gelatin concentration was kept as 0.1 % drug was released within 200 min for 75 bloom number gelatin. But the presence of 0.5 % gelatin concentration resulted complete gentamicin release for 300 bloom number gelatin. Drug release reached to 100 % slowly then 100 and 300 bloom numbers compared to bloom numbers of 75 and 225 ones. Controlled grup drug

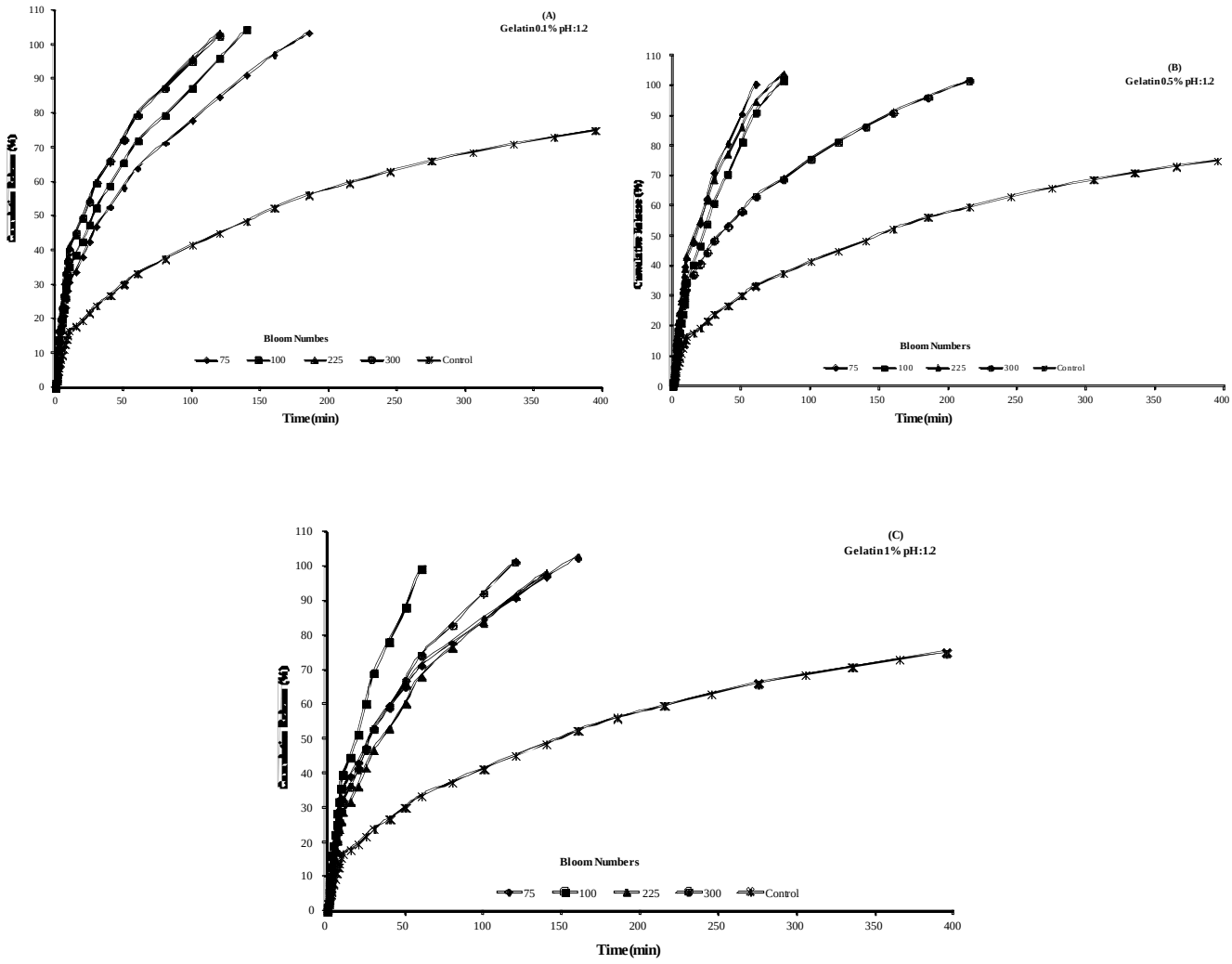



**Figure 4:** Release graphics of PEG-DA/Gelatin composite hydrogels synthesized with different molecular weight and concentrations of gelatin at pH 1.2: (**a**) % 0.1, (**b**) % 0.5, (**c**) % 1 gelatin.

release was completed after three days for all types of gelation concentration and bloom types.

### 3. Hydrogel Morphology

The morphology of cross-linked composite hydrogel structures for different bloom numbers was also studied. Figure **4** depicts the hydrogel structural changes for 75, 100, 225, and 300 bloom number when gelatin concentration was adjusted to 1%. Figure **5e** shows that control group PEG-DA hydrogels are relatively homogeneous and have a smooth morphology and lacunas. Combination with gelatin appeared to alter the homogenity and cause to disappear the lacunas.

Incorporation of gelatin to the hydrogel structure cause the lacunes to become smaller for bigger gelatin bloom values which can be seen in Figure **5a-c**. The hydrogel structure shown in Figure **5d** do not contain any pinhole like formations as in previous micrographs, and a homogenious structure was obtained.

### 4. Drug Release Kinetics

Release profiles in buffers pH 7.4 and 1.2 when 1% gelatin used was tested to zero-order, first-order, Higuchi and Hixson-Crowell drug release kinetic models and the results were given in Table 3. We have also fitted the release data to another empirical equation defined by Ritger & Peppas in 1987 [2,24] and the rate constant, k and the exponent n that represents the type of transport mode were calculated and given in Table **3**. It is of paramount importance that this equation can be applied only to the first 60% of the total amount of drug released. Release profiles in buffers reasonably fitted to Hixson-Crowell model for 75 bloom number gelatin containing hydrogel and

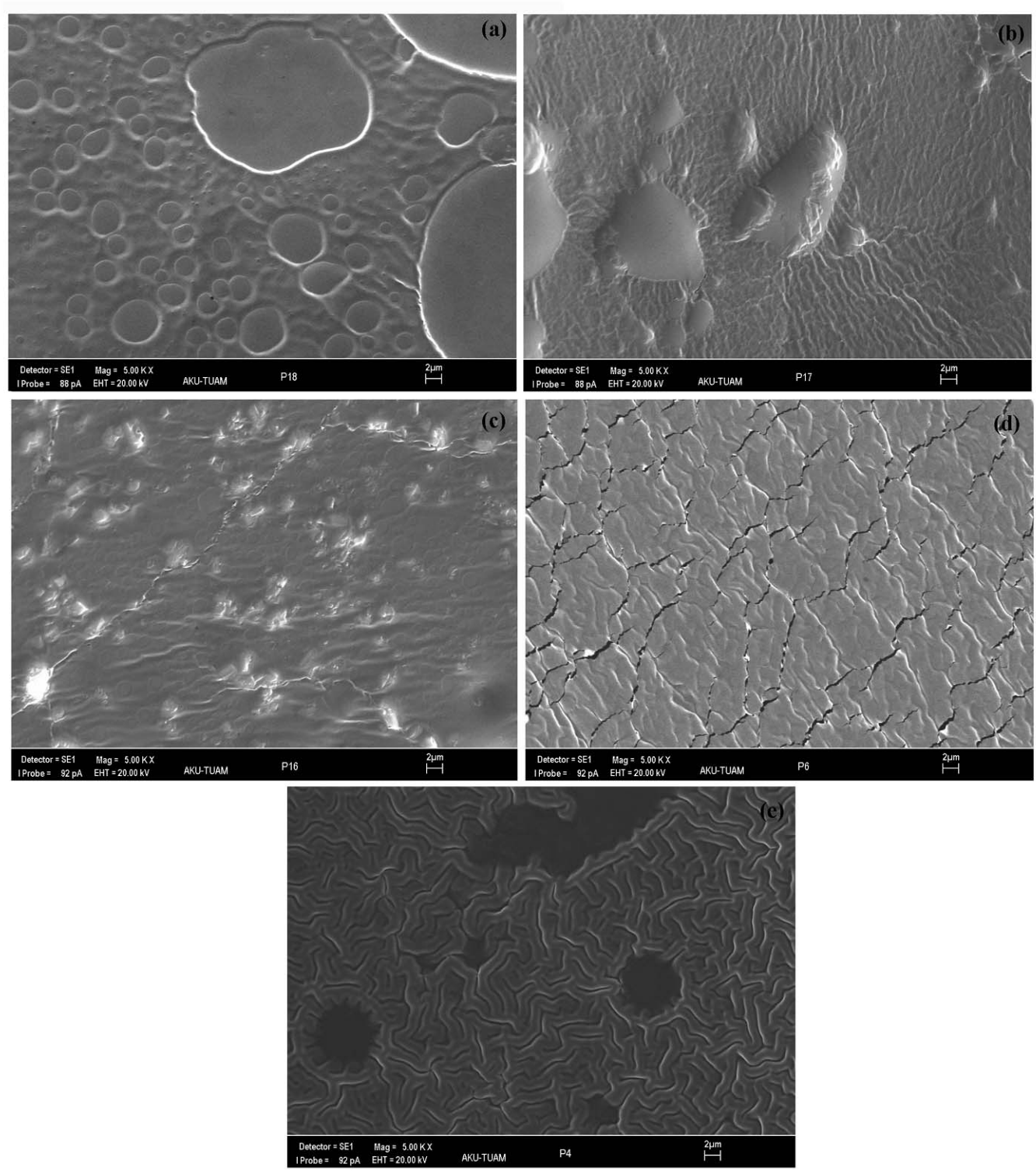



**Figure 5:** SEM images of PEG-DA/Gelatin composite hydrogels with 1 % gelatin (5000x zoom) (**a**) 75 bloom; (**b**) 100 bloom; (**c**) 225 bloom; (**d**) 300 bloom; (**e**) Without gelatin.

Korsmeyer-Peppas model when 100, 225, and 300 bloom numbers was used at pH 7.4 buffer (Table **3**). First-order drug release model describes the release behaviour at pH 1.2 with the best correlation coefficients which were also given in Table **3**.

## DISCUSSION

The drug release behavior of any polymer network depends upon the nature of the polymer, solvent compatibility, and the degree of cross-linking. The addition of gelatin increased the hydrophilic nature of

**Table 3. Effect of Bloom Number and pH on the Drug Release Kinetics of Gentamicin from PEG-DA/Gelatin Composite Hydrogels**

| Blomm | Zero-order | | First-order | | Higuchi | | Hixson-Crowell | | Krosmeyer&Peppas | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Number | $K_0(h^{-1})$ | $R^2$ | $K_1(h^{-1})$ | $R^2$ | $K_H(h^{-1/2})$ | $R^2$ | $K_{HC}$ | $R^2$ | k | n | $R^2$ |
| ***pH: 7.4*** | | | | | | | | | | | |
| 75 | 0.7927 | 0.8944 | -0.0085 | 0.9002 | 0.6049 | 0.9458 | -0.0045 | 0.9941 | 0.283 | 0.8138 | 0.9458 |
| 100 | 1.0842 | 0.9765 | -0.0118 | 0.9810 | 0.6242 | 0.9962 | -0.0058 | 0.9432 | 0.243 | 0.6695 | 0.9966 |
| 225 | 1.3455 | 0.9753 | -0.0146 | 0.9805 | 0.9247 | 0.9832 | -0.0071 | 0.9359 | 0.126 | 1.1796 | 0.9832 |
| 300 | 1.9244 | 0.8062 | -0.0221 | 0.8088 | 0.6614 | 0.9334 | -0.0115 | 0.8666 | 0.246 | 0.5939 | 0.9374 |
| ***pH: 1.2*** | | | | | | | | | | | |
| 75 | 3.0523 | 0.9796 | -0.0368 | 0.9902 | 1.0480 | 0.9711 | -0.0178 | 0.9169 | 0.099 | 1.3783 | 0.9711 |
| 100 | 3.5536 | 0.9859 | -0.0440 | 0.9950 | 1.1409 | 0.9667 | -0.0210 | 0.8985 | 0.081 | 1.5537 | 0.9667 |
| 225 | 4.0774 | 0.9823 | -0.0531 | 0.9950 | 1.0005 | 0.9802 | -0.0254 | 0.9024 | 0.110 | 1.2180 | 0.9802 |
| 300 | 3.0903 | 0.9904 | -0.0374 | 0.9952 | 0.9597 | 0.9903 | -0.0177 | 0.8865 | 0.104 | 1.2158 | 0.9903 |

$R^2$: correlation coefficient; K: release rate constant for respective models; Drug release kinetics were not colculated when more then 60 %,

the hydrogels. The release data indicates that the bloom number of gelatin needs to be specified in drug release studies due to lower drug release rate in high bloom numbers which may be the result of dense structure. Drug release rate profiles seems to be not effected by gelatin concentrations of 0.1 to 1 % in pH 7.4. The formulations containing the greatest amount of gelatin resulted with the highest gentamicin release rate which may come from the increased amount of hydrophilic molecule. It was thought that hydrophilic gelatin interacts directly with the surrounding solution, and allow them to penetrate within the network and facilitate drug diffusion. The release of hydrophylic antibiotic, gentamicin was strongly dependent on the pH value. The high hydrophilicity level of water-soluble antibiotic, gentamicin sulphate also may contribute to this process.

In the work conducted by Kommareddy & Amiji, the release profiles of EGFP-N1 plasmid DNA from gelatin, thiolated gelatin, poly(ethylene glycol)-modified gelatin, and PEG-modified thiolated gelatin nanoparticles were obtained. The thiolated gelatin nanoparticles were formed by solvent composition change and cross-linked with glyoxal. PEG-modified manoparticle (40 % to 45 %) show a greater fraction of the DNA being released when compared to the unmodified nanoparticles (25 % to 30 %). In the presence of glutathione (0.1 mM and 5mM) the reease of plasmid DNA from the thiolated nanoparticle, both modified and unmodified, has been enhanced with almost 60 % over a peried of 5 hours in the case of PEG-modified thiolated gelatin nanoparticles. They use methoxy-PEG-succinimidyl glutarate of molecular weight 2000 Da and 225 bloom strength gelatin. The DNA-encapsulated nanoparticles were prepared by using a 1% (w/v) solution of the gelatin or thiolated gelatin adjusted to pH 7.0, followed by the addition of plasmid DNA (EGFP-N1) at a final concentration of 0.5 % (w/w) of the polymer and formed into nanoparticles by the desolvation process as described before.

In a study, the properties of biopolymer composite nanoparticles, based on the encapsulation of the anticancer drug 5-fluorouracil (5-FU) with the HYL enzyme and chitosan/polyethylene glycol/gelatin (CS/PEG/G), were investigated. Increasing drug release times were observed after the addition of complexes containing PEG and gelatin as a consequence of the high polymeric chain, leading to slow water entry. The release of 5-FU was strongly dependent on the pH value. Their results of drug release rates were slower at pH 1.2 than at pH 6.8 due to the very high degree of interaction between the polymers. It contains a large amount of free positive charges, possibly due to the pH-dependent interaction between 5-FU and the composites. Hence, the drug diffusion inside the composites is retarded and the release of 5-Fu is suppressed [28].

In the presented study the variables and obtained results are in agreement with literature. We incorporated gelatin to the hydrogel structure without crosslinking either with PEG-DA or itself and this process leads to a kind of assistance to enhance drug release due to hydrophilic structure of this biopolymer. The molecular interactions were greatly affected by gelatin concentration and bloom numbers so increased

drug release rates were estimated for higher gelatin concentration. Drug release was retarded for 300 bloom number compared with other bloom values greatly as a result of dense structure. Drug release kinetics were also in agreement with the result which shows super case II transport mechanism and the hydrophilic molecular nature of biopolymer contribute hydrogel to relaxation and increase drug release rates either at neutral or highly acidic pH environment.

In conclusion, PEG-DA/Gelatin composite hydrogels were synthesized and drug release was performed at pH 7.4 and 1.2 at 37°C to simulate physiological conditions. Photopolymerized PEG-DA/Gelatin composite hydrogels containing different molecular weight (bloom) and different values of gelatin are suitable for long-time drug release in neutral pH and physiological temperature. Synthesized PEG-DA/Gelatin composite hydrogel structure characterized with scanning Electron Microscope (SEM) clearly indicates the presence of gelatin.

## REFECENCES


[1] Hoffman AS. Hydrogels for biomedical applications. Adv Drug Deliv Rev 2012; 64: 18-23. http://dx.doi.org/10.1016/j.addr.2012.09.010

[2] Peppas NA, Bures P, Leobandung W, Ichikawa H. Hydrogels in pharmaceutical formulations. Eur J Pharm Biopharm 2000; 50:27-46. http://dx.doi.org/10.1016/S0939-6411(00)00090-4

[3] Li L, Lee LJ. Photopolymerization of HEMA/DEGDMA hydrogels in solution. Polymer 2005; 46: 11540-11547. http://dx.doi.org/10.1016/j.polymer.2005.10.051

[4] Lin C-C, Metters AT. Hydrogels in controlled release formulations: Network design and mathematical modeling. Adv Drug Deliv Rev 2006; 58: 1379-1408. http://dx.doi.org/10.1016/j.addr.2006.09.004

[5] Chang S-T, Chen L-C, Lin S-B, Chen H-H. Nano-biomaterials application: Morphology and physical properties of bacterial cellulose/gelatin composites via crosslinking Food Hydrocoll 2012; 27: 137-144. http://dx.doi.org/10.1016/j.foodhyd.2011.08.004

[6] Gaspard S, Oujja M, Nalda R, Abrusci C, Catalina F, Bañares L, Castillej M. Submicron foaming in gelatine by nanosecond and femtosecond pulsed laser irradiation Appl Surf Sci 2007; 253: 6420-6424. http://dx.doi.org/10.1016/j.apsusc.2007.01.083

[7] Laymana H, Spigab M-G, Brooksa T, Phamc S, Websterb KA, Andreopoulos FM. The effect of the controlled release of basic fibroblast growth factor from ionic gelatin-based hydrogels on angiogenesis in a murine critical limb ischemic model. Biomaterials 2007; 28: 2646-2654. http://dx.doi.org/10.1016/j.biomaterials.2007.01.044

[8] Chen K-Y, Yao C-H. Repair of bone defects with gelatin-based composites: A review. BioMedicin I 2011; 29-32.

[9] Zhang YZ, Venugopal J, Huang Z-M, Lim CT, Ramakrishna S. Crosslinking of the electrospun gelatin nanofibers. Polymer 2006; 47: 2911-2917. http://dx.doi.org/10.1016/j.polymer.2006.02.046

[10] Olsen D, Yanga C, Bodoa M, Changa R, Leigha S, Baeza J, Carmichaela D, Perälä M, Hämäläinen E-R, Jarvinen M, Polarek J. Recombinant collagen and gelatin for drug delivery. Adv Drug Deliv Rev 2003; 55: 1547- 1567. http://dx.doi.org/10.1016/j.addr.2003.08.008

[11] Haraguchi K & Takehisa T. Nanocomposite hydrogels: A unique organik-ınorganic network structure with Extraordinary mechanical, optical, and swelling/de-swelling propertie. Adv Materials 2002; 14(16): 1120-1124. http://dx.doi.org/10.1002/1521-4095(20020816)14:16<1120::AID-ADMA1120>3.0.CO;2-9

[12] Teng S, Shi J, Peng B, Chen L. The effect of alginate addition on the structure and morphology of hydroxyapatite/gelatin nanocomposites. Compos Sci Technol 2006; 66: 1532-1538. http://dx.doi.org/10.1016/j.compscitech.2005.11.021

[13] Laymana H, Spigab M-G, Brooks T, Pham, S, Webster KA, Andreopoulos FM. The effect of the controlled release of basic fibroblast growth factor from ionic gelatin-based hydrogels on angiogenesis in a murine critical limb ischemic model. Biomaterials 2007; 28: 2646-2654. http://dx.doi.org/10.1016/j.biomaterials.2007.01.044

[14] Guo T, Zhaob J, Changa J, Dinga Z, Honga H, Chena J, Zhang J. Porous chitosan-gelatin scaffold containing plasmid DNA encoding transforming growth factor-b1 for chondrocytes proliferation. Biomaterials 2006; 27: 1095-1103. http://dx.doi.org/10.1016/j.biomaterials.2005.08.015

[15] Seki T, Kanbayashi H, Chono S, Tabata Y, Morimoto K, Effects of a sperminated gelatin on the nasal absorption of insulin. Int J Pharm 2007; 338(1-2): 213-8. http://dx.doi.org/10.1016/j.ijpharm.2007.02.004

[16] Zheng JP, Wang CZ, Wang XX, Wang HY, Zhuang H, Yao KD. Preparation of biomimetic three-dimensional gelatin/montmorillonite-chitosan scaVold for tissue engineering. React Funct Polym 2006; 67(9): 780-788. http://dx.doi.org/10.1016/j.reactfunctpolym.2006.12.002

[17] Kommareddy S, Amiji M. Poly(ethylene glycol)-modified thiolated gelatin nanoparticles for glutathione-responsive intracellular DNA delivery. Nanomedicine 2007; 32- 42. http://dx.doi.org/10.1016/j.nano.2006.11.005

[18] Hyoudou K, Nishikawa M, Ikemura M, Kobayashi Y, Mendelsohn A, Miyazaki N, Tabata Y, Yamashita F, Hashida M. Prevention of pulmonary metastasis from subcutaneous tumors by binary system-based sustained delivery of catalase. J Controlled Release 2009; 137: 110-115. http://dx.doi.org/10.1016/j.jconrel.2009.04.005

[19] Aduba DC, Hammer JA, Yuan Q, Yeudall WA, Bowlin GL, Yang H. Semi-interpenetrating network (sIPN) gelatin nanofiber scaffolds for oral mucosal drug delivery. Acta Biomater 2013; 9: 6576-6584. http://dx.doi.org/10.1016/j.actbio.2013.02.006

[20] Fathi A, Lee S, Zhong X, Hon N, Valtchev P, Dehghani F, Fabrication of interpenetrating polymer network to enhance the biological activity of synthetic hydrogels. Polymer 2013; 54(21): 5534-5542. http://dx.doi.org/10.1016/j.polymer.2013.08.052

[21] Ayhan F, Ozkan S. Gentamicin release from photopolymerized PEG Diacrylate and pHEMA hydrogel discs and their in-vitro antimicrobial activities. Drug Deliv 2007; 14(7): 433-439. http://dx.doi.org/10.1080/10717540701202911

[22] Sökmen N, Bican F, Ayhan F, Ayhan H. Chelating Agent Effect on the Release of Gentamicin from PEG-DA Hydrogels, Hacettepe J Biol Chem 2008, 36(4): 347-352.

[23] Modi S, Jain JP Domb AJ, Kumar N. Copolymers of pharmaceutical grade lactic acid and sebacic acid: Drug release behavior and biocompatibility European J Pharm Biopharm 2006; 64: 277-286. http://dx.doi.org/10.1016/j.ejpb.2006.05.013

[24] Rokhade AP, Agnihotri SA, Patil SA, Mallikarjuna NN, Kulkarni PV, Aminabhavi TM. Semi-interpenetrating polymer network microspheres of gelatin and sodium carboxymethyl cellulose for controlled release of ketorolac tromethamine Carbohydr Polym 2006; 65: 243-252. http://dx.doi.org/10.1016/j.carbpol.2006.01.013

[25] Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems Acta Poloniae Pharm Drug Res 67; 3: 217-223, 2010.

[26] Ramakrishna S, Mihira V, Tabitha K. Design and evaluatıon of drug release kinetics of diltiazem hydrochloride sustained release tablets Intern J Medical Pharm Sci 2011; 1(4): 1-13.

[27] Arslan A. Akrilat Bazlı Hidrojellerin Fotopolimerizasyon Yöntemi ile Hazırlanması, Karakterizasyonu ve Kontrollu İlaç Salım Sistemlerinde Kullanımının Araştırılması PhD Thesis; co-Adviser: Hacettepe Universitesity, Department of Bioengineering, 2006; A0278572.

[28] Rajan M, Raj V, Al-Arfaj AA. Murugan AM. Hyaluronidase enzyme core-5-fluorouracil-loaded chitosan-PEG-gelatin polymer nanocomposites as targeted and controlled drug delivery vehicles. Int J Pharm 2013; 453: 514-522. http://dx.doi.org/10.1016/j.ijpharm.2013.06.030

Received on 13-10-2013 Accepted on 11-11-2013 Published on 24-09-2014

DOI: http://dx.doi.org/10.12974/2311-8717.2014.02.01.5