



Research Paper / Makale

Preparation of Photopolymerizable HEMA/PEG-DA Based Hydrogels Filled with Low Concentrations of Nanoparticle Titanium Dioxide for Release of Donepezil HCl

Şebnem ŞENOL^{1a}, Emel AKYOL^{1b}

¹Department of Chemical Engineering, Yıldız Technical University, İstanbul, Turkey
sebnemsenol_@hotmail.com

Received/Geliş: 28.02.2021

Accepted/Kabul: 04.05.2021

Abstract: 2-hydroxyl ethyl methacrylate/poly(ethylene glycol) diacrylate (HEMA/PEG-DA) based hydrogels are attractive drug carriers due to their appealing properties such as biodegradability and sustained release. The scope of this study was to investigate the swelling and release behaviors of HEMA/PEG-DA-based hydrogels filled with low concentrations of nanoparticle titanium dioxide (TiO₂). Hydrogels have been synthesized successfully by photopolymerization. 2,2-dimethoxy-2-phenyl-acetophenone (Irgacure 651), 1-hydroxycyclohexyl phenyl ketone (Irgacure 184) and 2-hydroxy-4'-(2-hydroxyethoxy)-2 methylpropiophenone (Irgacure 2959) were selected for photopolymerization. Fourier Transform Infrared Spectroscopy (FT-IR) had been used in confirming the functional group of hydrogels. A digital microscope and Scanning Electron Microscope (SEM) were used for characterizing synthesized hydrogels. This study revealed that the content of hydrogels, the kind of photo-initiators and pH have a significant effect on the swelling and releasing of Donepezil Hydrochloride (active pharmaceutical ingredient (API) for Alzheimer disease) behaviours.

Keywords: HEMA/PEG-DA based hydrogels, nanoparticle titanium dioxide, Donepezil HCl, Swelling, Releasing

Donepezil HCl Salımı İçin Düşük Konsantrasyonlarda Titanyum Dioksit Nanopartikülü İçeren Fotopolimerize Edilebilir HEMA/PEG-DA Tabanlı Hidrojellerin Hazırlanması

Öz: 2-hidroksil etil metakrilat/poli (etilen glikol) diakrilat (HEMA / PEG-DA) tabanlı hidrojeller, biyobozunur olma ve sürekli salım gibi özellikleri nedeniyle ilgi çekici ilaç taşıyıcılarıdır. Bu çalışmanın kapsamı, düşük konsantrasyonlarda titanyum dioksit (TiO₂) nanopartikülü içeren HEMA / PEG-DA tabanlı hidrojellerin şişme ve salım davranışlarını araştırmaktır. Hidrojeller, fotopolimerizasyon ile başarılı bir şekilde sentezlenmiştir. Fotopolimerizasyon için 2,2-dimetoksi-2-fenil-asetofenon (Irgacure 651), 1-hidroksisikloheksil fenil keton (Irgacure 184) ve 2-hidroksi-4'-(2-hidroksietoksi)-2 metilpropiyofenon (Irgacure 2959) seçilmiştir. Fourier Dönüşümlü Kızılötesi Spektroskopisi (FT-IR), hidrojellerin fonksiyonel grubunu doğrulamak için kullanılmıştır. Dijital mikroskop ve taramalı elektron mikroskopu hidrojellerin karakterizasyonu için kullanılmıştır. Bu çalışma, hidrojel içeriğinin, fotobaşlatıcıların türünün ve pH'nın, Donepezil Hidroklorür'ün (Alzheimer hastalığı için ilaç etken maddesi (Active Pharmaceutical Ingredient (API)) şişme ve salım davranışlarının üzerinde önemli bir etkiye sahip olduğunu göstermiştir.

Anahtar Kelimeler: HEMA/PEG-DA tabanlı hidrojeller, titanyum dioksit nanopartikülü, Donepezil HCl, Şişme, Salım

How to cite this article

Senol, S., Akyol, E. "Preparation of Photopolymerizable HEMA/PEG-DA Based Hydrogels Filled With Low Concentrations of Nanoparticle Titanium Dioxide For Release Of Donepezil HCl" El-Cezeri Journal of Science and Engineering, 2021, 8 (2); 887-896.

Bu makaleye atıf yapmak için

Senol, S., Akyol, E. "Preparation of Photopolymerizable HEMA/PEG-DA Based Hydrogels Filled With Low Concentrations of Nanoparticle Titanium Dioxide For Release Of Donepezil HCl" El-Cezeri Fen ve Mühendislik Dergisi 2021, 8 (2); 887-896.

ORCID ID: *0000-0002-3341-4731; *0000-0002-6420-995X

1. Introduction

Controlled release is one of the effective methods, which is used for releasing active pharmaceutical ingredients into the simulated media at desired intervals, quantity and shorten the treatment period. The main target of researchers to increase drug dosage and inhibit side effects on patients. Controlled release provides no continuous daily usage [1].

Conventional using drug doses lead to a non-treating, unnecessary toxic level. Controlled drug delivery is the best option to overwhelm this side effect and provide stable drug concentration in the blood. Natural or synthetic polymers are utilized for drug delivery because of high bioavailability and stability. Many researchers have given their attention to hydrogels, microspheres, polymeric micelles and smart materials for drug delivery systems [2-4].

Hydrogels are selected by researchers in pharmaceutical and medicine as biomaterials due to their ability to respond to changes in their environment like as temperature, pH, heat, light, magnetic and electrical field, etc. These properties of hydrogel allow them to utilize releasing of active substances [5-9].

Poly(hydroxyethyl methacrylate) is hydrophilic but not water-soluble. Hydroxyethyl methacrylate based hydrogels are highly biocompatible and less harmful than the other polymers so it is used in contact lenses, drug delivery application, and tissue and biomedical engineering [10-12].

Poly(ethylene glycol) (PEG)-based hydrogels have high sorption, biocompatibility, low immunogenicity, and ease of use in drug delivery and biomedical fields. These properties allows them to use photopolymerizable-curing technique [13-15]. (PEG) based hydrogels are the most commonly applied nonionic polymers in the area of polymer-based drug delivery systems. Due to high aqueous solubility, hydrogels are considered as versatile candidates for the prodrug conjugation. However, more efforts are expected for designing PEG-based prodrug conjugates [16]. We have previously reported that PEG-DA, HEMA hydrogels have a favorable behaviour for controlled release of Donepezil HCL [1, 6, 7]. Although promising results have been achieved in our studies, further studies are needed.

In the biomedical field, UV light polymerization is a method to produce hydrogels. Free radical polymerization with UV light is applied in wide variety of areas such as coatings, films, lenses and biomaterials. This type of polymerization is not harmful to the human body. Temperatures and pH near physiological values can provide hydrogel production and temporary control of the processing time [17-20].

Inorganic nanoparticles have been used in biomedical applications, drug delivery, imaging diagnosis, adsorption, and disease therapeutics. Polymer/TiO₂ nanocomposites have been gained attention in many applications because the composite materials can solve the recycling problem of TiO₂ nanoparticles (NPs) while they improve the stability of hydrogels [21-23].

Alzheimer disease (AD) is one of the most widely neurodegenerative diseases and most of the patients with AD are suffered from loss of synapses and disability of memory, learning [24-26]. Donepezil is a piperidine-based, reversible and inhibitor of acetylcholinesterase (AChE) [27].

In the current study, we investigated the synthesis and utility of PEG-DA and PEG-DA/HEMA hydrogels filled with low concentrations of nanoparticle TiO₂ for the controlled Donepezil HCl. Previous work has shown that addition of metals, metal oxide nanoparticles such as titanium dioxide into hydrogels develops the antimicrobial properties of hydrogels and mechanical

characteristics [28-29]. The swelling degree and release capacities of the hydrogel systems and the influence of the pH medium and type of photoinitiator on the release properties were also examined.

2. Experimental Methods

2.1. Materials

2-hydroxyl ethyl metacrylate (HEMA), polyethylene glycol diacrylates Mn=700 (PEG-DA), ethylene glycol dimethacrylate, 2,2-dimethoxy-2-phenyl-acetophenone (Irgacure 651, 99% purity), 1-hydroxycyclohexyl phenyl ketone (Irgacure 184, 99% purity), 2-hydroxy-4'-(2-hydroxyethoxy)-2-methylpropiophenone (Irgacure 2959, 98% purity) were supplied from Sigma-Aldrich. Titanium powder was ordered from Alfa Aesar. The complete experimental procedure of TiO₂ synthesis was reported previously in detail [29]. Donepezil HCl was a kind gift by Abdi İbrahim Company. Sodium chloride and hydrochloric acid were purchased from Merck. Sodium hydroxide and monobasic potassium phosphate were provided from J.T Baker. All chemicals were used as received without purification.

2.2. Methods

PEG-DA and HEMA/PEG-DA based hydrogels were used in the presence of a photo-initiators (Irg 184, Irg 651, Irg 2959) and crosslinking agent (ethylene glycol dimethacrylate), as shown in Table 1. The reactant ingredients were added to petri plates which consist of olive oil, using micropipette under nitrogen gas during the chemical reaction. Photopolymerization process was occurred at 365 nm under UV irradiation for 50 seconds.

According to desired hydrogel type, 50 % (w/v) PEG-DA, 25 % (w/v) PEG-DA-25 % (w/v) HEMA, 1% TiO₂ and photo-initiators were added with the help of magnetic stirrer at 50 rpm. Donepezil HCl (0.07 % (w/v)) and deionized water were also mixed. Predetermined ratio of ethylene glycol dimethacrylate was added. After UV light polymerization, hydrogels were washed with n-hexane and later, they were dried at room temperature.

Table 1. Content of HEMA/PEG-DA Based Hydrogels.

Hydrogels	PEG-DA	HEMA	EGDMA	Irg 651	Irg 184	Irg 2959	TiO ₂
H1	50%	-	0.5%	1%	-	-	1%
H2	50%	-	0.5%	-	1%	-	1%
H3	50%	-	0.5%	-	-	1%	1%
H4	25%	25%	0.5%	1%	-	-	1%
H5	25%	25%	0.5%	-	1%	-	1%
H6	25%	25%	0.5%	-	-	1%	1%

Swelling studies, calculation of swelling ratio and preparation of buffer solution procedure has been reported previously in detail [7].

3. Results and Discussion

3.1. FT-IR Analyses of Hydrogels

For the imaging photo-crosslinked PEG-DA based hydrogels, the attenuated total reflectance-FTIR (ATR-FTIR) scan was performed with FTIR Perkin Elmer Spectrum 100. For each

sample, a spectrum was obtained using the ATR utilizing a diamond internal reflection element mounted on a holder at a resolution of 4 cm^{-1} in the range $4000\text{--}400\text{ cm}^{-1}$ for a total of 16 scans.

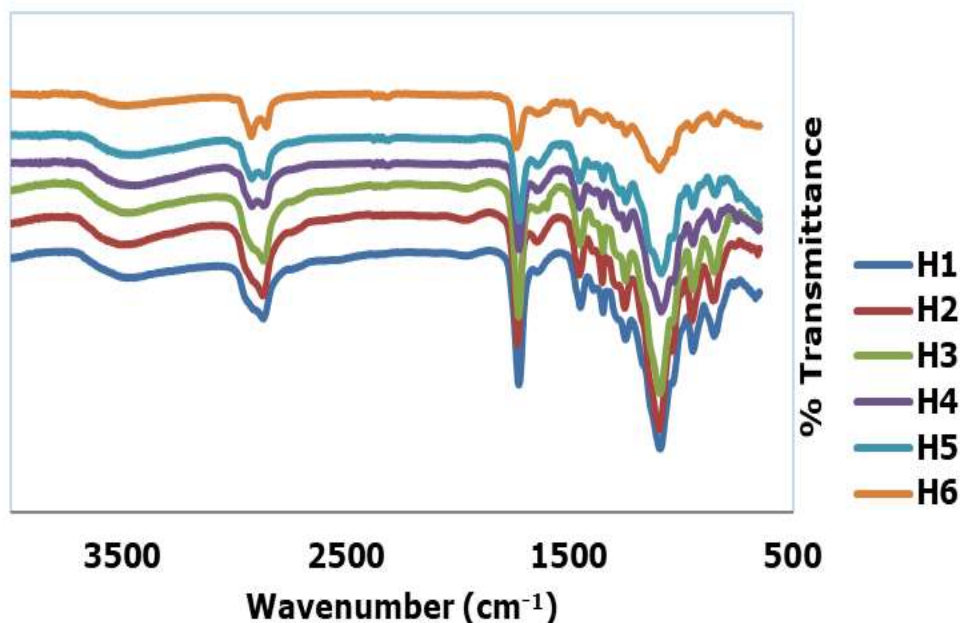


Figure 1. FT-IR Analyses of Hydrogels.

Absorption of the C=C bonds occurs at $\sim 1630\text{ cm}^{-1}$ and the carbonyl groups at 1724 cm^{-1} . In the spectrum of monomer (Fig. 1) the -OH peak is broad in the range of $3400\text{--}3700\text{ cm}^{-1}$ indicating hydrogen bonding. -C=C- bonds of PEG-DA and HEMA at 933 and 816 cm^{-1} disappeared after UV crosslinking, which showed hydrogel formation by consuming -C=C- bonds. The results showed (Fig.1) that with HEMA content increasing in PEG-DA based hydrogels, equilibrium water content raised and the contact angle lessened which resulted from the strong H-bonding interactions of HEMA between the polymer and water (for H4, H5 and H6). The peak at 620 cm^{-1} is perceived for all possible transform structures with Ti-O composition. Therefore, the FTIR spectroscopy results confirmed the incorporation of PEG-DA, HEMA and TiO_2 in hydrogel.

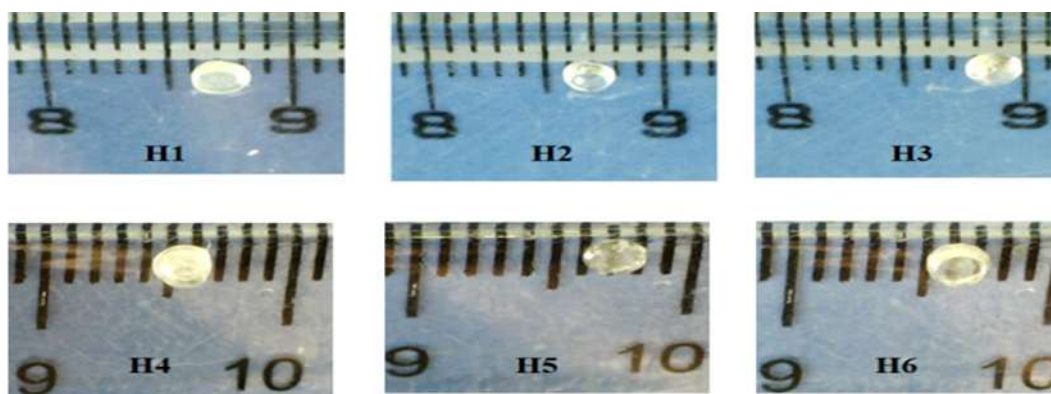


Figure 2. Image of Hydrogels.

The sizes of hydrogels were about 2 mm , which were obtained by digital microscope. SEM micrographs of the surface of PEG-DA with 1% of TiO_2 is shown in Figure 3. As seen the Figure 3, PEG-DA hydrogels exhibited a pore size of $5\text{--}15\text{ }\mu\text{m}$ and TiO_2 nanoparticles were dispersed uniformly on the surface.

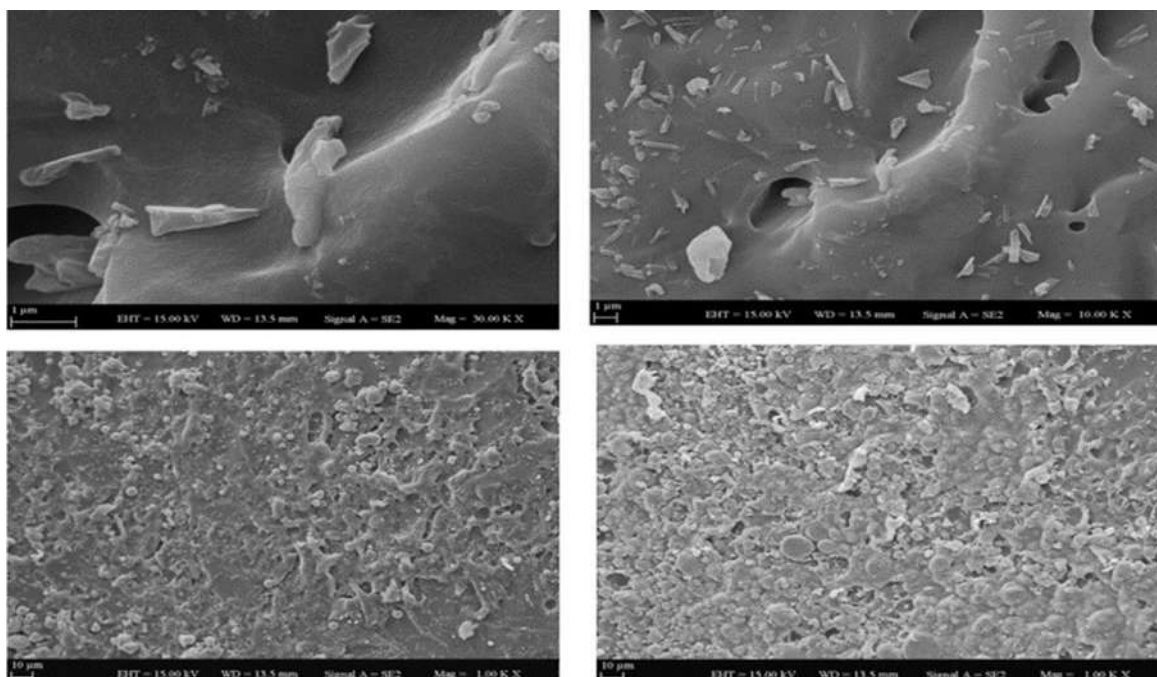


Figure 3. SEM Image of H1 Hydrogel

Figure 4 shows HEMA/PEG-DA hydrogels. Hydrogels have gained a spherical form, when poly(ethylene glycol) diacrylate was combined with composed 2- hydroxyethyl methacrylate.

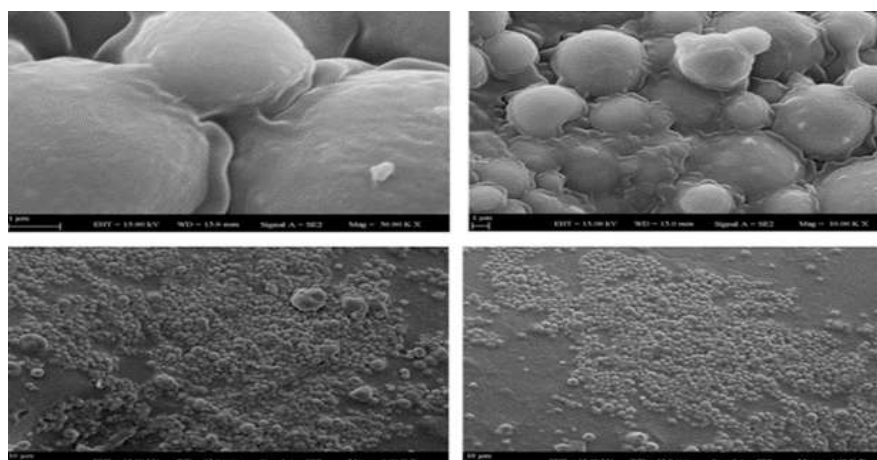


Figure 4. SEM Image of H4 Hydrogel

3.2. Swelling Tests

The swelling analyses were applied to determinate the effect of the presence of HEMA and type of photoinitiators on hydrogels. Swelling ratio of prepared hydrogels in deionized water and in different pH medium at 37°C were indicated in Figure 5-8. As seen in Figures, higher swelling ratios were observed for PEG-DA hydrogels according to HEMA/PEG-DA based hydrogels. The swelling ratio of hydrogel decreased significantly with the incorporation of HEMA to PEG-DA. While the values of swelling percentage of PEG-DA based hydrogels were ranged between 66 and 88%, swelling percentage of HEMA/PEG-DA based hydrogels were ranged between 57 and 78 %. The swelling of hydrogels usually depends on the pH. As illustrated in these figures, at pH 6.8 has the highest swelling ratio for all hydrogels.

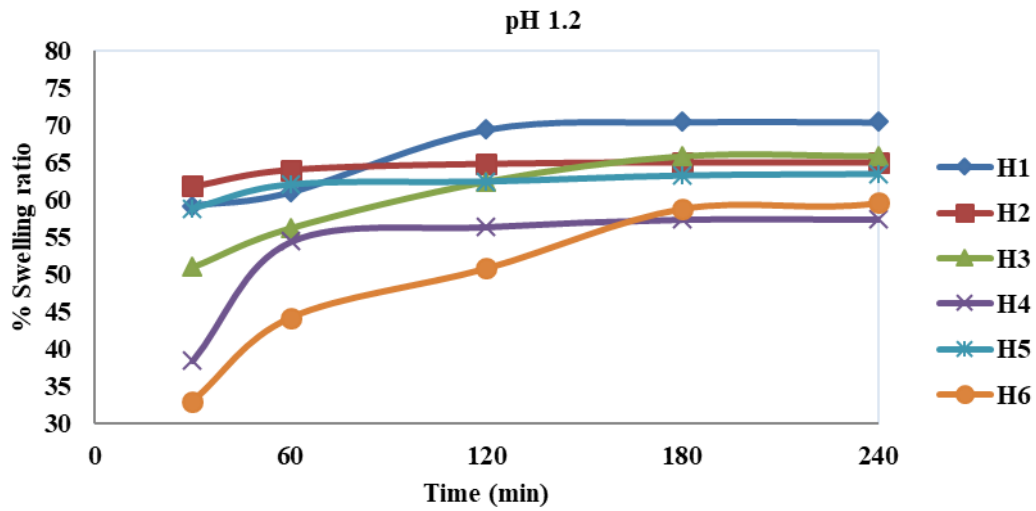


Figure 5. Swelling degree of hydrogels in pH 1.2

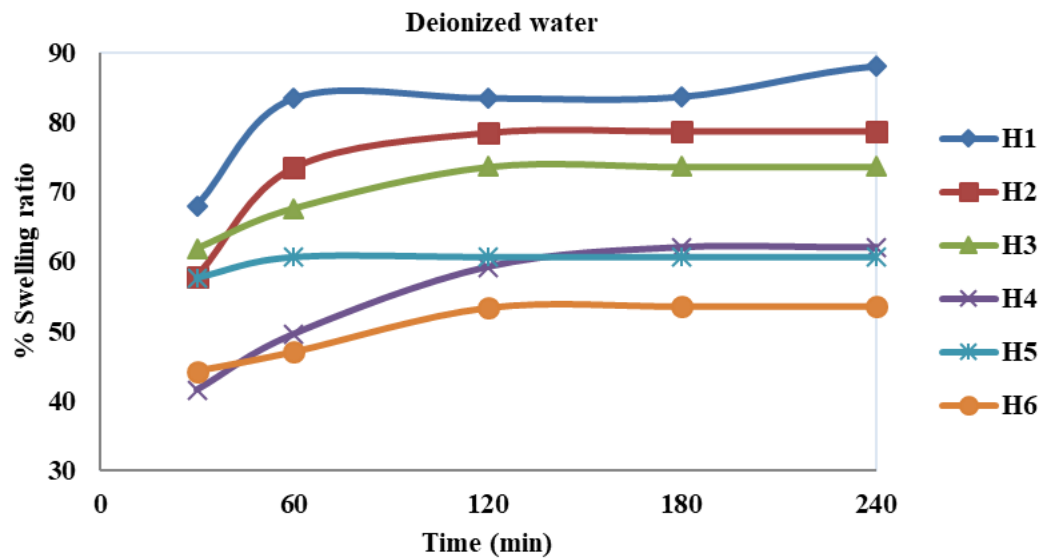


Figure 6. Swelling degree of hydrogels in deionized water.

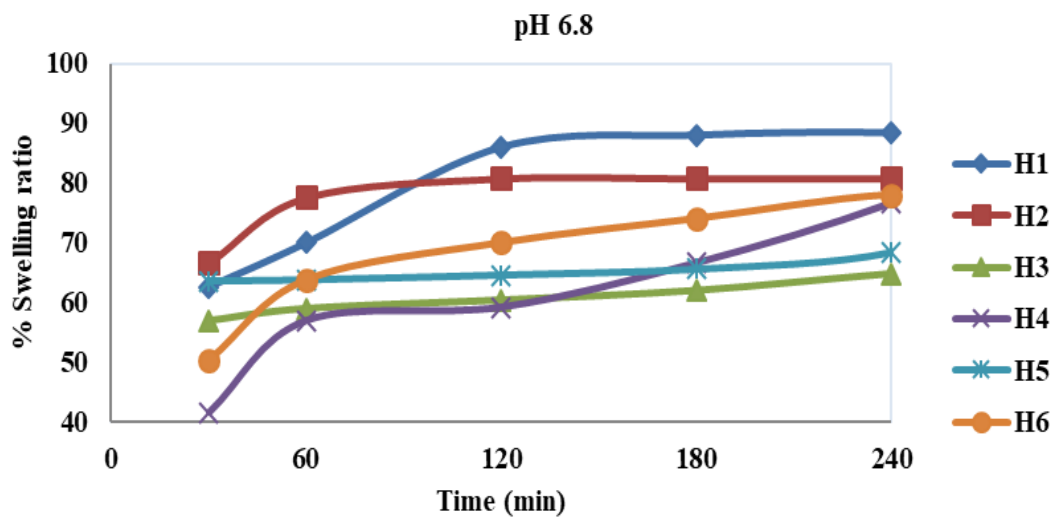


Figure 7. Swelling degree of hydrogels in pH 6.8

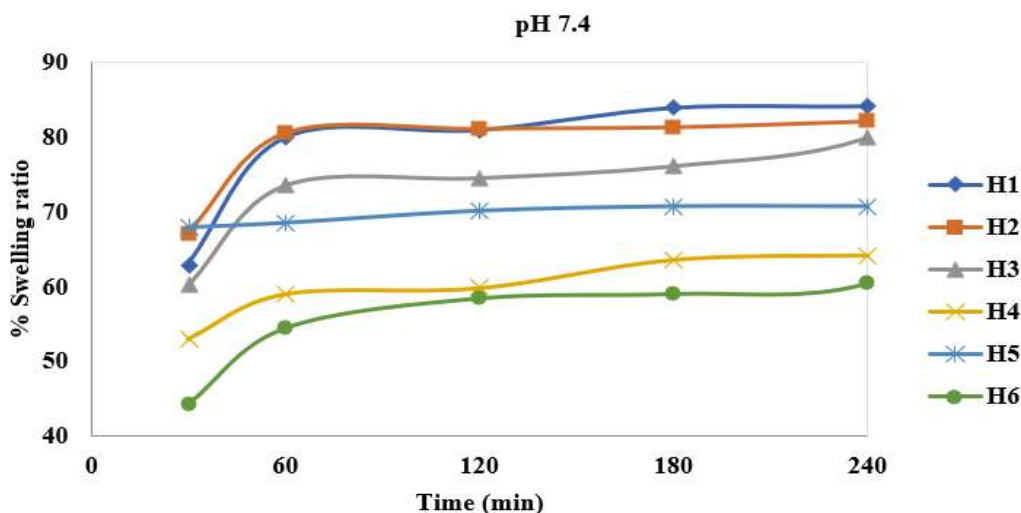


Figure 8. Swelling degree of hydrogels in pH 7.4.

Figure 9, 10 and 11 show the cumulative release of drug from prepared hydrogels at simulated media, at 37°C. It has found that H1 hydrogel (in the presence of TiO₂, with Irgacure 651) shows the highest release.

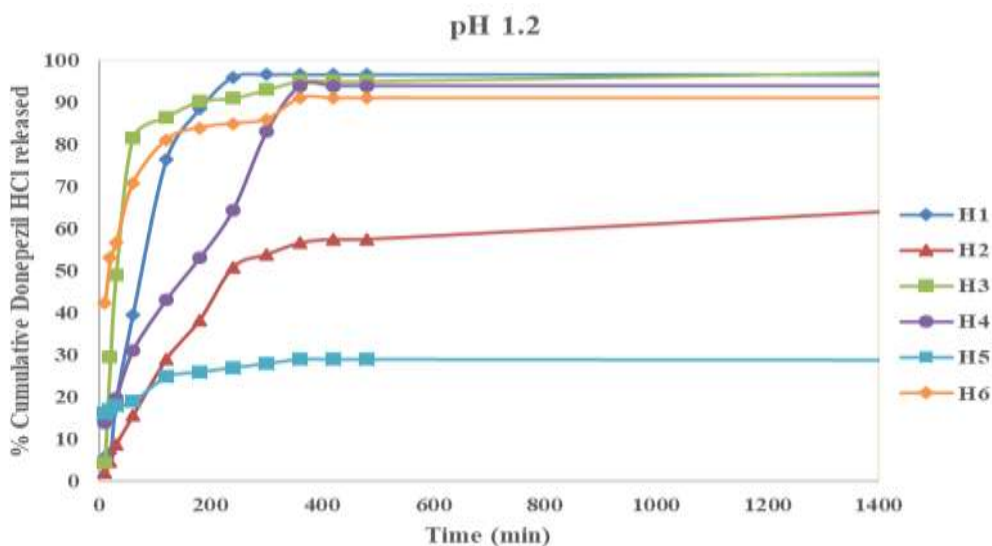


Figure 9. Release ratio of hydrogels in pH 1.2

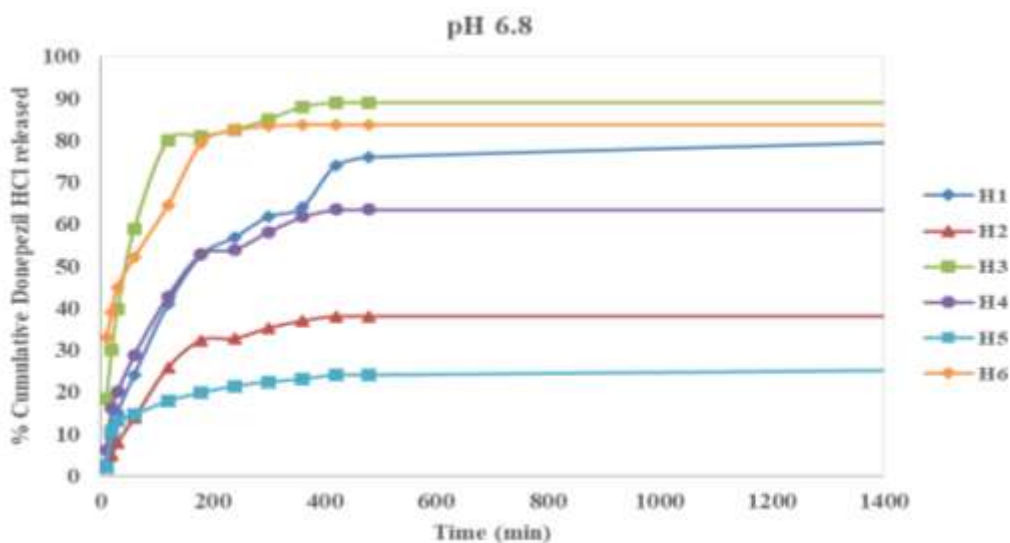


Figure 10. Release ratio of hydrogels in pH 6.8

The results demonstrated that synthesized H5 hydrogels released the minimum amount of Donepezil Hydrochloride. PEG-DA and HEMA/PEG-DA hydrogels were very pH sensitive. The amount of drug released increased with increasing pH.

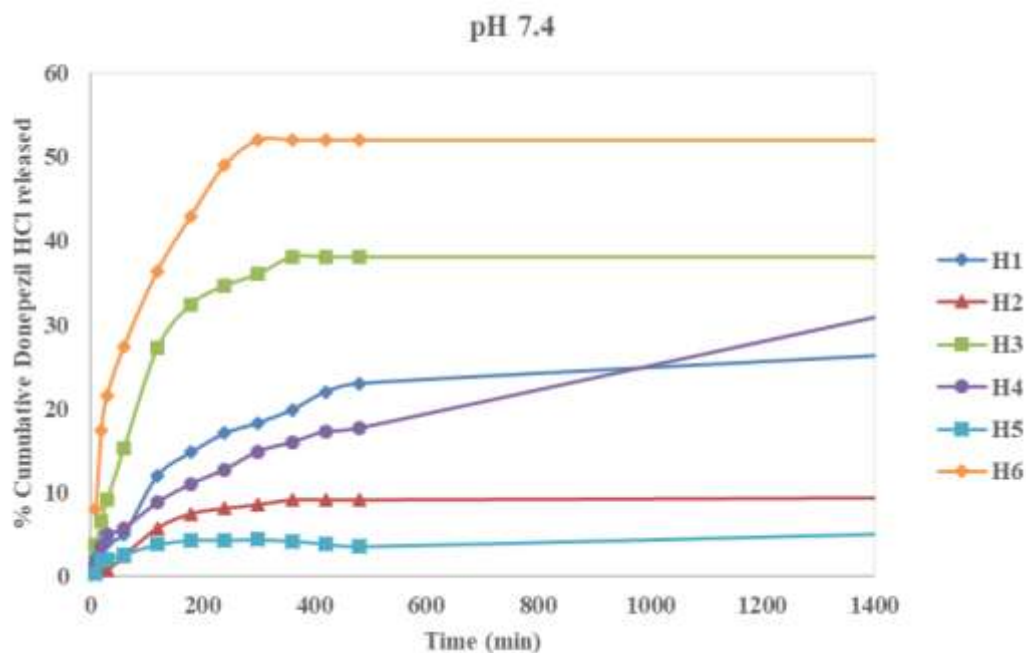


Figure 11. Release ratio of hydrogels in pH 7.4

4. Conclusions

In presented study, synthesis of PEG-DA/TiO₂ and HEMA-PEG-DA/TiO₂ hydrogels were achieved by UV photopolymerization and their release profiles in varying pH medium were examined. Swelling behavior of hydrogels in different pH medium demonstrated that they are pH sensitive. In addition, type of the photo-initiators influenced swelling and release behaviors. In vitro drug release from, PEG-DA/TiO₂ and HEMA-PEG-DA/TiO₂ hydrogels showed a controlled Donepezil HCl release profile. Results depicts the drug release of hydrogel increased by rising pH. Synthesized hydrogels in presence of Irgacure 2959 showed the highest release. In conclusion, these hydrogels may have a potential as drug carriers.

Authors' Contributions

EA and SS designed the experimental procedure. SS carried out the experimental work the theoretical calculations, in collaboration with EA. EA and SS wrote up the article. Both authors read and approved the final manuscript.

Competing Interests

The authors declare that they have no competing interests.

Refereneces

- [1]. Senol, S., Akyol, E., Study on the Preparation and Drug Release Property of Modified PEG-DA Based Hydrogels. Journal of The Turkish Chemical Society: Chemistry A, 2019, 6, 1-14.

- [2]. Taşdemir, T., Başaran, H.B. Removal of Suspended Particles from Wastewater by Conventional Flotation and Floc-flotation. *El-Cezerî Journal of Science and Engineering*, 2021, 8, 421-431.
- [3]. Yuan, X., Praphakar, R., Munsamy, M., Alarfaj, A., Kumar, S., Rajan, M., Mucoadhesive Guar gum Hydrogel Inter-connected Chitosan-g-polycaprolactone Micelles for Rifampicin Delivery, *Carbohydrate Polymers*, 2019, 206, 1-10.
- [4]. Liang, Y., Zhao, X., Ma, P., Guo, B., Du, Y., Han, X., pH-responsive Injectable with Mucosal Adhesiveness Based on Chitosan-grafted-di hydrocaffeic Acid and Oxidized Pullulan for Localized Drug Delivery, *Journal of Colloid and Interface Science*, 2019, 536, 224–234.
- [5]. Aycan, D., Alemdar, N., Development of pH-Responsive Chitosan-based Hydrogel Modified with Bone Ash for Controlled Release of Amoxicillin, *Carbohydrate Polymers*, 2018, 184, 401-417.
- [6]. Senol, S., Akyol, E., Controlled Release of Donepezil Hydrochloride From PEG-DA Hydrogels, *Bulgarian Chemical Communications*, 2018, 1, 12-17.
- [7]. Senol S., Akyol, E., Synthesis and Characterization of Hydrogels Based on poly (2-hydroxyethyl methacrylate) for Drug Delivery Under UV Irradiation, *Journal of Materials Science*, 2018, 53, 14953-14963.
- [8]. Sinani, G., Sessevmez, M., Gök, K., Özgümüş, S., Okyar, A., Alpar, O., Cevher, E., Nasal Vaccination with poly(aminoester)-poly(D,L-lactide-co-glycolide) Hybrid Nanoparticles, *International Journal of Pharmaceutics*, 2017, 529, 1-14.
- [9]. Demir S, Hahraman M.V, Bora N, Kayaman Apohan N, Ogan A. Preparation, Characterization, and Drug Release Properties of Poly(2-hydroxyethyl methacrylate) Hydrogels Having β -Cyclodextrin Functionality, *Journal of Applied Polymer Science*, 2008, 109, 1360–1368.
- [10]. Bounabi, L., Mokhnachi, N-B., Haddadine, N., Ouazib, F., Barille, R., Development of poly(2-Hydroxyethyl Methacrylate)/Clay Composites as Drug Delivery Systems of Paracetamol, *Journal of Drug Delivery Science and Technology*, 2016, 33, 58-65.
- [11]. Kamoun, E., Menzel, H., Crosslinking Behavior of Dextran Modified with Hydroxyethyl Methacrylate upon Irradiation with Visible Light-Effect of Concentration, Coinitiator Type and Solvent, *Journal of Applied Polymer Science*, 2010, 117, 3128–3138.
- [12]. Sadeghi, M., Synthesis of Starch-g-poly(acrylic acid-co-2-hydroxy ethyl methacrylate) as a Potential pH-sensitive Hydrogel-based Drug Delivery System, *Turk J Chem*, 2011, 35, 723-733.
- [13]. Lv, Chao., Xia, H., Shi, Q., Wang, G., Wang, Y-S., Chen, Q-D., Zhang, Y-L., Liu, L-Q., Sun, H-B., Sensitively Humidity-Driven Actuator Based on Photopolymerizable PEG-DA Films, *Advanced Materials Interfaces*, 2017, 4, 1601002-10.
- [14]. Tan, G., Liao, J., Ning, C., Zhang, L., Preparation, Characterization and Drug-Release Properties of PEG-DA-Based Copolymer Hydrogel Microspheres. *Journal of Applied Polymer Science*, 2011, 125, 3509–16.
- [15]. Kocabay, G-O., Ismail, O., Synthesis And Characterization of Poly(ϵ -Caprolactone)–Poly(Ethylene Glycol)–Poly(ϵ -Caprolactone) Copolymers: Investigation of the Effect of Blocks On Micellization, *Revue Roumaine de Chimie*, 2018, 63(12), 1165-75.
- [16]. Shashwat, S.B., Naval, A., Rajesh, P., Jayant, K., Poly(ethylene glycol)-Prodrug Conjugates: oncept, Design, and Applications, *Journal of Drug Delivery*, 2012, 1-17. (doi:10.1155/2012/103973).
- [17]. Onuki, Y., Hasegawa, N., Kida, C., Obata, Y., Takayama, K., Study of the Contribution of the State of Water to the Gel Properties of a Photocrosslinked Polyacrylic Acid Hydrogel Using Magnetic Resonance Imaging, *Journal Of Pharmaceutical Sciences*, 2014, 103, 3532–3541.

- [18]. Akyol, E., Senol, S., Dogan, O., Controlled Release of Donepezil Hydrochloride from the Ternary Sodium Alginate Based Hydrogels. *Bulgarian Chemical Communications*, 2017, 49, 57-63.
- [19]. Ayhan, H., Ayhan, F., Photocrosslinked poly(ethylen glycol) Hydrogels for Controlled Drug Delivery, *Turk J Biochem*, 2014, 39, 403-415.
- [20]. Kazemi, F., Mohamadnia, Z., Kaboudin, B., Karimi, Z., Photodegradation of Methylene Blue with a Titanium dioxide/polyacrylamide Photocatalyst Under Sunlight, *Journal of Applied Polymer Science*, 2016, 133, 43386–43395.
- [21]. Wang, Di., Tan, Y., Xu, H., Wang, X., Yu, L., Xiao, Z., Wang, J., Xu, S., A Tough and Fluorescent Dual Nanocomposite Hydrogel Based On SiO₂@TiO₂ Core-Shell Nanoparticles, *Applied Surface Science*, 2019, 467, 588–595.
- [22]. Dogan, O., Bodur, B., Investigation of Hydroxyapatite Morphology at Different Experimental Conditions, *Bulgarian Chemical Communications*, 2017, 49, 122-127.
- [23]. Zhang, H., Shi, R., Xie A, Li J, Chen L, Chen P, Li S, Huang F, Shen Y. Novel TiO₂/PEG-DA Hybrid Hydrogel Prepared in Situ on Tumor Cells for Effective Photodynamic Therapy, *Applied Material&Interfaces*, 2013, 5, 12317-12322.
- [24]. Li, Q., Chu, T-T., Chen, Y-X., Li ,Y-M., Tau Protein Associated Inhibitors in Alzheimer Disease, *Chinese Journal of Chemistry*, 2014, 32, 964-968.
- [25]. Lasagna-Reeves, C.A., Kaye R., Astrocytes Contain Amyloid- β Annular Protofibrils in Alzheimer's Disease Brains, *FEBS Letters*, 2011, 585, 3052–57.
- [26]. Asil, T., Uzuner, N., Differentiation of Vascular Dementia and Alzheimer Disease, *J. Ultrasound Med*, 2005, 24, 1065–107.
- [27]. Jackson, S., Ham, R., Wilkinson, D., The Safety and Tolerability of Donepezil In Patients with Alzheimer's Disease, *British Journal of Clinical Pharmacology*, 2004, 58, 1-8.
- [28]. Amir, Oleyaei S., Razavi, S.M. A., Mikkonen, K.S., Physicochemical and Rheo-mechanical Properties of Titanium Dioxide Reinforced Sage Seed Gum Nanohybrid Hydrogel, *International Journal of Biological Macromolecules*, 2018, 118, 661-670.
- [29]. Senol, S., Akyol, E., Preparation and characterization of pH-sensitive hydrogels from photo-crosslinked poly(ethylene glycol) diacrylate incorporating titanium dioxide, *Materials Science-Poland*, 2020, 38, 443-449.