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Study on the Preparation and Drug Release Property of Modified PEG-DA Based Hydrogels

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Abstract: The aim of the present study is to develop hydroxyapatite-modified PEG-DA and PEG-DA/HEMA based hydrogels for release of Donepezil HCl for potential treatment of Alzheimer's disease. [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 used as photo-initiators in the synthesis of hydrogels and hydroxyapatite was used for modifying hydrogels. Fourier transform infrared spectroscopy (FT-IR), scanning electron microscope (SEM) and digital microscope were utilized to investigate the characteristic properties of hydrogels. Photopolymerization technique was selected for the synthesis of hydrogels. Swelling and drug release studies have been performed under different pH conditions.

Keywords: Alzheimer's Disease, Hydrogels, Photopolymerization, Donepezil HCl, Polyethylene diacrylate, 2-Hydroxyethyl methacrylate.

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INTRODUCTION

Many new classes of materials have been used to improve different innovative applications. Hydrogels, being cross-linked three-dimensional polymeric materials, have the ability to absorb large amounts of water. In recent years, hydrogels have an increasing demand for drug delivery systems. The purpose of the drug delivery systems is to maintain drug concentration in the blood or in target tissues at prolonging drug-release times (1-6).

Polyethylene glycol diacrylates (PEG-DA) based polymers possess highly attractive properties that cause widely using in variety of applications

such as tissue engineering, controlled drug delivery, and medicine areas. Polyethylene glycol diacrylate is non-volatile, non-toxic, environmentally friendly, and also tailor-made into various shapes. Polyethylene glycol diacrylate acts as potential stabilizers and matrices for the formation of functional hydrogels (7-10).

Poly(2-hydroxyethyl methacrylate) (pHEMA), one of the synthetic water-soluble polymer, has been largely preferred, especially in various biomedical applications due to its chemical stability (11-12).

Hydroxyapatite (HAp), $Ca_{10}(PO_4)_6(OH)_2$, is a double salt of tri-calcium phosphate and calcium hydroxide, and it is the main inorganic component of human bones and teeth. However, hydroxyapatite has an excellent biocompatibility and tissue bioactivity (13-16).

UV light polymerization is one of the main methods used in the synthesis of hydrogels in biomedical field. Considerable attention has been focused on photopolymerization method due to its broad applications. Nowadays, free radical polymerization with UV light is utilized in different applications such as coatings, information storage systems, films, contact lenses, and biomaterials. In the photopolymerization, the primary radicals were generated from light absorption of photoinitiator at a suitable wavelength thus polymerization and into highly cross-linked structures of multifunctional acrylates occurs (17-18).

Alzheimer's disease (AD) is the most common type of dementia that cause cognitive impairment and memory loss (19). The number of patients with AD is projected to more than double by 2050. Although the etiology of AD has been elucidated, multiple questions remain unanswered (20-21).

Donepezil is a piperidine-based, reversible acetylcholinesterase (Ach) inhibitor generally used in the treatment of Alzheimer patients. Donepezil prevents the hydrolysis of the residual Ach in the brain so it is the best pharmacological tool to decrease cognitive deficits in AD patients. Donepezil has been investigated to be sufficient for enhancing of cognitive impairment and memory loss in patients with Alzheimer's disease. It is well efficient when 5 mg of the drug is used once daily (22-27).

In this study, we aimed to develop prolonged drug release systems enhanced with HAp. We synthesized PEG-DA/HEMA based hydrogels with modified Hap via photopolymerization. Fourier transform infrared spectroscopy (FT-IR), scanning electron microscope (SEM) and digital microscope were utilized to investigate the characteristic properties of hydrogels. Modified PEG-Da/HEMA hydrogels were used for prolonging the release time.

EXPERIMENTAL

Materials

2-Hydroxylethyl methacrylate (HEMA), polyethylene glycol diacrylates M_n=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), hydroxyapatite (powder, 5 μm and surface area ≥ 100 m^2/g), were supplied by Sigma-Aldrich. 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 supplied from J.T Baker. All chemicals were used as received without further purification.

Preparation and characterization of PEG-DA/HEMA hydrogels

PEG-DA/HEMA based hydrogels were prepared in the presence of a photo-initiator (Irg 184, Irg 651, Irg 2959) and a crosslinking agent (ethylene glycol dimethacrylate), as shown in Table 1. The reactant mixtures were added to petri plates which consist of olive oil, using a micropipette. The reactant mixtures were deaerated by bubbling nitrogen gas during the reaction. Photopolymerization was performed at 365 nm under UV irradiation for a short time.

According to hydrogel type, 50% (w/v) PEG-DA, 25% (w/v) PEG-DA- 25% (w/v) HEMA and predetermined ratios of photo-initiators were mixed by using a magnetic stirrer at 50 rpm. Then, 0.07% (w/v) Donepezil HCl and deionized water were added. 0.5% ethylene glycol dimethacrylate was then introduced. After photopolymerization, hydrogels were washed with n-hexane and dried at room temperature.

Table 1: Synthesis conditions for the PEG-DA/HEMA based hydrogels.

Hydrogels	PEG-DA	HEMA	EGDMA	Irg 651	Irg 184	Irg 2959	HAp
Hydrogel 1 (H1)	50%	-	0.5%	1%	-	-	1%
Hydrogel 2 (H2)	50%	-	0.5%	-	1%	-	1%
Hydrogel 3 (H3)	50%	-	0.5%	-	-	1%	1%
Hydrogel 4 (H4)	25%	25%	0.5%	1%	-	-	1%
Hydrogel 5 (H5)	25%	25%	0.5%	-	1%	-	1%
Hydrogel 6 (H6)	25%	25%	0.5%	-	-	1%	1%

The equilibrium swelling ratios of the swollen hydrogels were measured using a gravimetric method in deionized water, pH 1.2, 6.8, and 7.4. Drug loaded hydrogels were used for swelling behavior at 37 °C. At predetermined time points, the hydrogels were taken out and weighed after removal of surface water. Swelling and release analyses were repeated three times. A UV–Vis spectrophotometer (Analytikjena Specord 200/Plus) at 270 nm was used for release studies.

The determination of swelling ratio and preperation of buffer solution procedure has been reported previously in detail (4,28).

RESULTS AND DISCUSSIONS

FT-IR Analyses of Hydrogels

For the imaging of photo-crosslinked PEGDA-based hydrogels, the attenuated total reflectance-FTIR (ATR-FTIR) scan was performed with a Perkin Elmer Spectrum 100 FTIR spectrometer. For each sample, a spectrum is obtained using the ATR utilizing a diamond internal reflection element mounted on a holder at a resolution of 4 cm^{-1} in the range 4000-400 cm^{-1} for a total of 16 scans.

FT-IR spectra of the hydrogels are shown in Figure 1. In the PEG-DA spectrum, there was an –OH at 3600 cm^{-1}, a CH_2 at 2853 cm^{-1}, a C=O at 1728 cm^{-1}, and a C=C at 1628 cm^{-1}. For the PEG-DA/HEMA based hydrogels, there was an –OH bond at 3500 cm^{-1}, a CH_2 at 2853 and 2956 cm^{-1} , a C=O at 1730 cm^{-1} , a C=C at

1610 cm^{-1}, a C–OH at 1059 cm^{-1}. The bands at 1090 and 960 cm^{-1} are used for the characterization of phosphate stretching vibration and the bands observed at 598 and 559 and at 1020 cm^{-1} are due to the phosphate being in vibration. FT-IR analyses results confirm the combination of PEG-DA and HEMA.

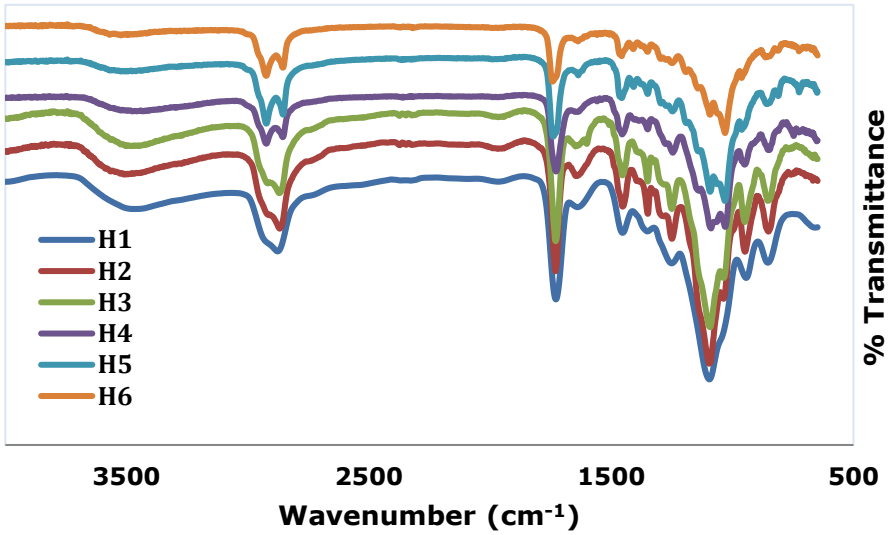

Figure 1. FT-IR spectra of the hydrogels.

SEM Analysis of Hydrogels

The sizes of hydrogels were obtained by digital microscope (Veho, VMS- 004 USB) Microscope (Figure 4). The textures of the hydrogels were examined by a conventional scanning electron microscopy (JEOL JSM 6335F). Figure 2 shows the SEM micrographs of PEG-DA based hydrogels using HAp as modified. The SEM morphology of H1 hydrogel showed a surface devoid of pores and cracks. Figure 3 shows the effect of incorporation of HEMA and PEG-DA on structure of hydrogels. While microparticles were formed in the presence of PEG-DA, the presence of HEMA revealed a spherical structure. The hydroxyapatite modified PEG-DA hydrogels were very different from and PEG-DA/HEMA based hydrogels.

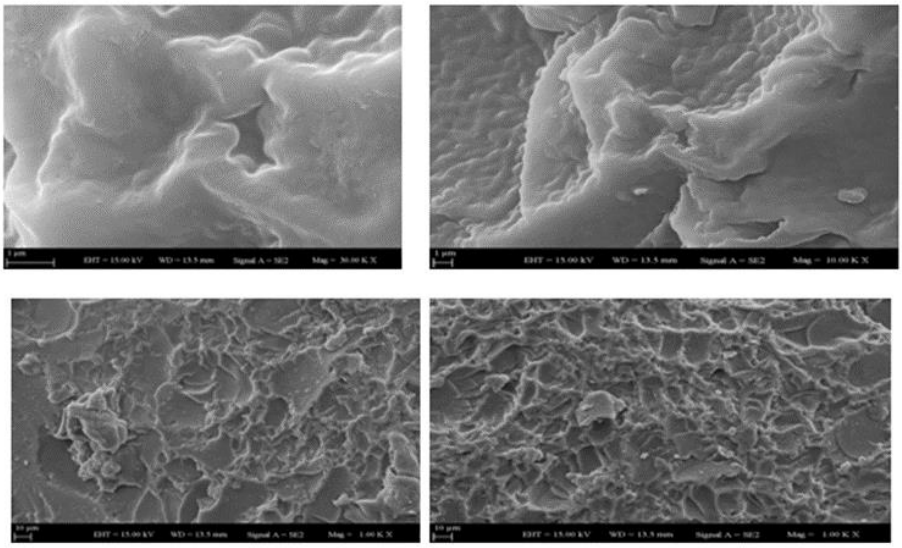

Figure 2: Scanning electron micrographs of H1 hydrogel.

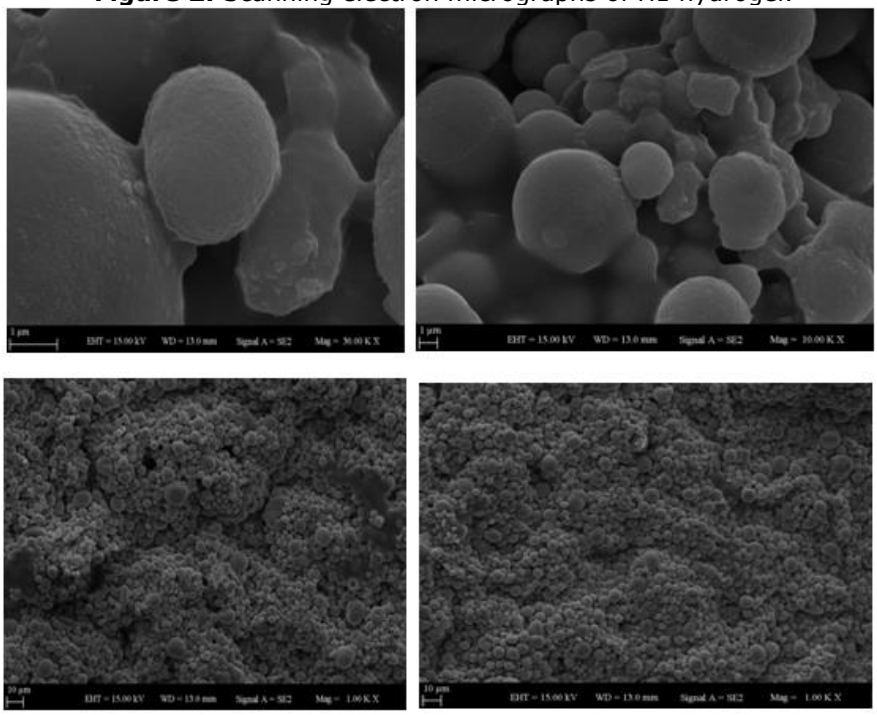

Figure 3: Scanning electron micrographs of H6 hydrogel.

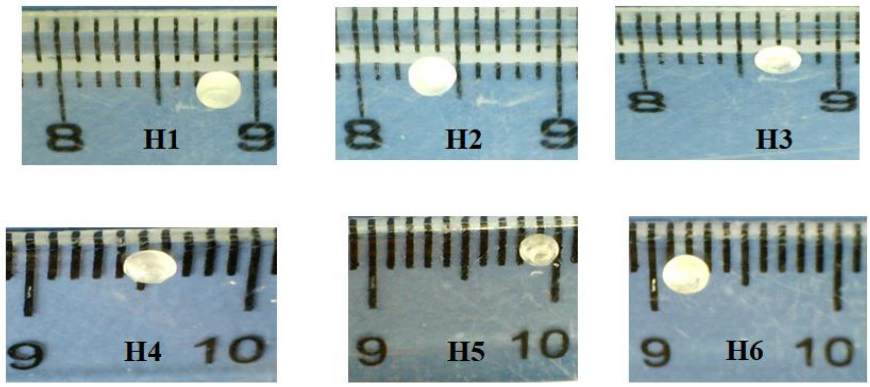

Figure 4: Digital microscope photos of synthesized hydrogels.

Swelling tests

In order to investigate the influence of the presence of HAp and pH, swelling kinetics of PEG-DA and PEG-DA/HEMA based hydrogels were studied. Swelling ratios of the studied hydrogels after 240 minutes of immersion in water and solutions with of pH 1.2, pH 6.8 and pH 7.4 at 37 °C were summarized in Figures 5-8. As seen in the figures, higher swelling ratios were observed for PEG-DA hydrogels according to PEG-DA/HEMA 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 hydrogels were ranged between 80 and 86%, swelling percentage of PEG-DA/HEMA hydrogels were ranged between 43 and 49%. 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.

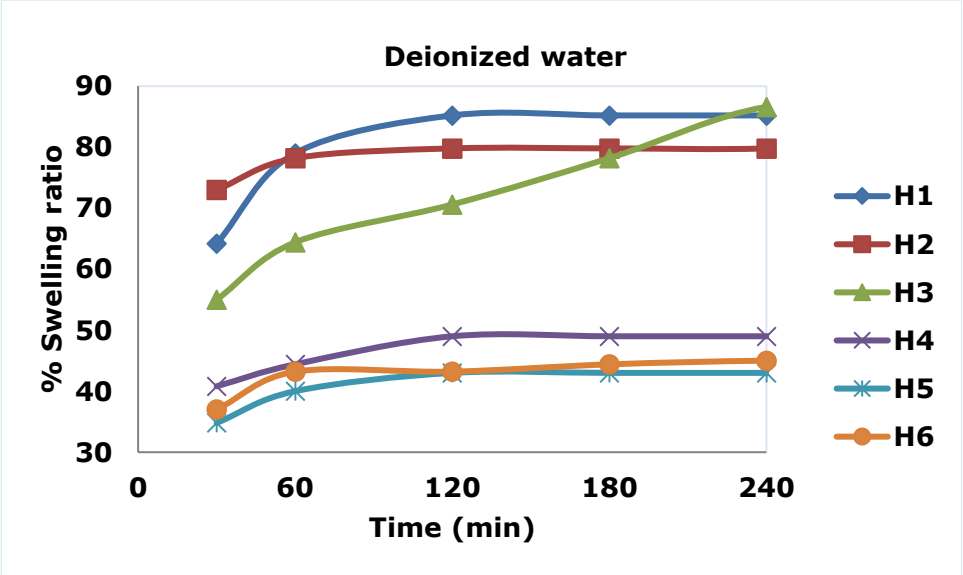

Figure 5: Swelling weight ratio of the studied hydrogels in deionized water.

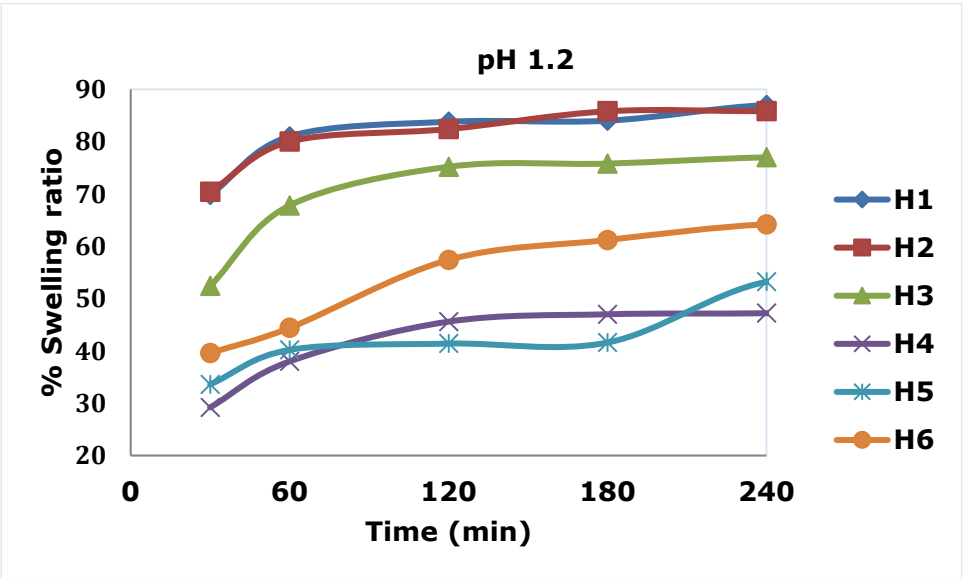

Figure 6: Swelling weight ratio of the studied hydrogels in pH 1.2.

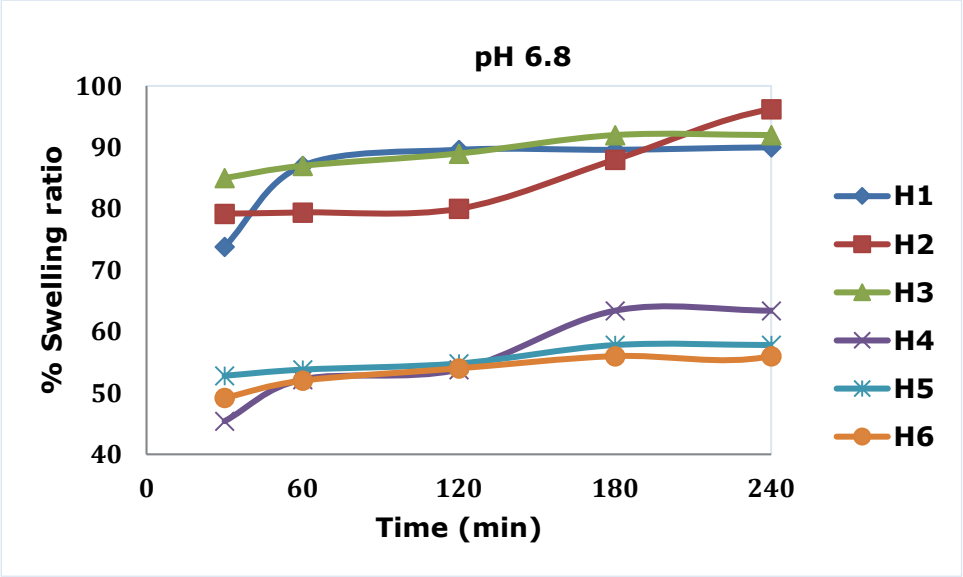

Figure 7: Swelling weight ratio of the studied hydrogels in pH 6.8.

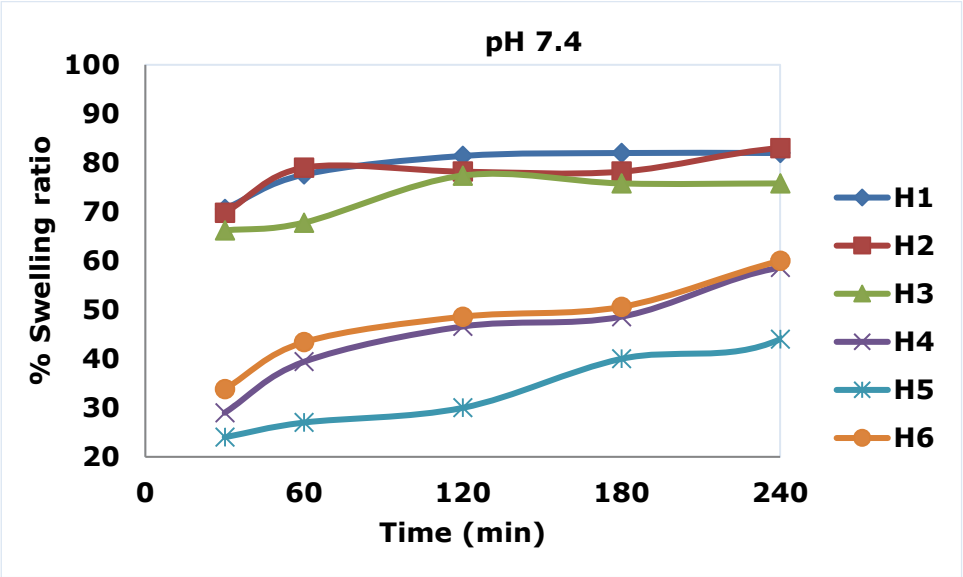

Figure 8: Swelling weight ratio of the studied hydrogels in pH 7.4.

Donepezil HCl release analyses

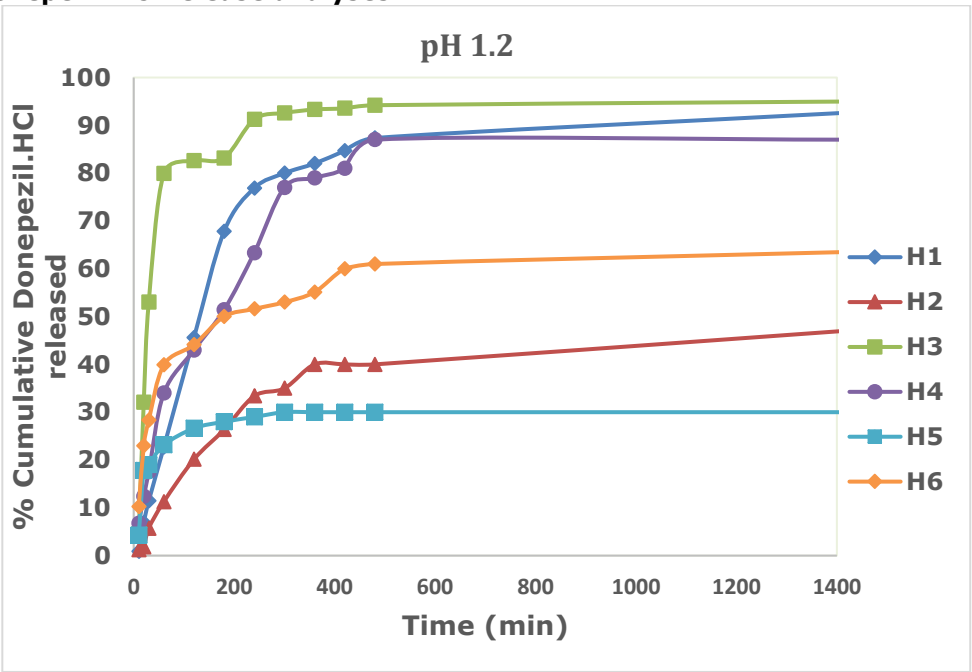

Figure 9: Release ratio of hydrogels in pH 1.2.

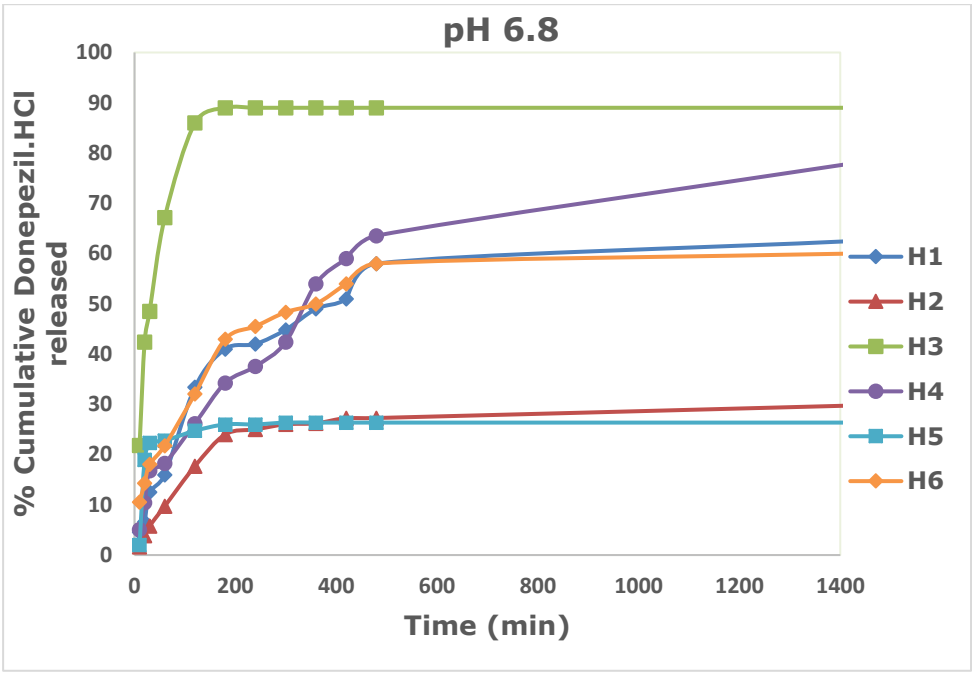

Figure 10: Release ratio of hydrogels in pH 6.8.

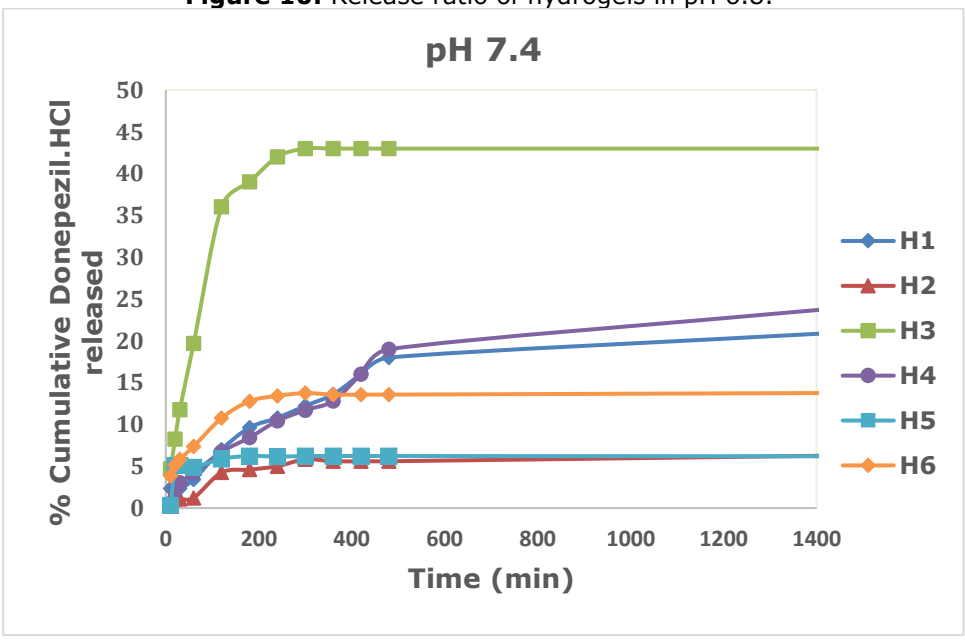

Figure 11: Release ratio of hydrogels in pH 7.4.

Figures 9, 10 and 11 show the percent cumulative release of the pharmaceutical ingredient from synthesized hydrogels at simulated media, at 37 °C. It has been found that H3 hydrogel (hydroxyapatite modified PEG-DA, in the presence of Irgacure 2959 as a photo-initiator shows the highest release. The results demonstrated that synthesized hydrogels using Irg 184 released the minimum amount of donepezil

hydrochloride. Also, PEG-DA/HEMA hydrogels were very pH sensitive. The amount of drug released increased with increasing pH. Similar results obtained from our previous studies (4,29).

CONCLUSION

In the presented study, the synthesis of PEG-DA/HAp and PEG-DA-HEMA/HAp hydrogels was achieved by UV photopolymerization. According to swelling and release analysis of hydrogels in different pH environments, the synthesized hydrogels exhibited a pH sensitive behavior. The release was slower when the pH was lower. Morever, both swelling and release behavior of hydrogels were highly influenced by the type and amount of photo-initiators. The results in the present investigation confirm the controlled release of Donepezil HCl. These data suggested that, this kind of hydrogels may be useful for utilization in the release of drug.

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