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Controlled release of donepezil hydrochloride from PEG-DA hydrogels

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Aim of the research work is to create a controlled-release system through the preparation and characterization of hydrogels based on polyethylene glycol diacrylate (PEG-DA). To determine the influence of photo-initiators on the drug release behavior of the resulting hydrogels, three different photo-initiators 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. In addition, hydroxyapatite (Hap) was employed to modify PEG-DA hydrogels. Fourier transform infrared (FT-IR) spectroscopy and digital microscopy were used for characterizing the prepared hydrogels. Swelling ratios and release behaviors of the prepared hydrogels under different conditions were investigated. Drug release studies were performed at pH 1.2, 6.8 and 7.4.

Keywords: PEG-DA based hydrogels, Controlled-release, Hydroxyapatite.

INTRODUCTION

Polyethylene glycol diacrylate (PEG-DA) hydrogels are very useful materials with a wide variety of applications such as controlled release, biomedical applications and pharmaceutical applications because of their low toxicity, biocompatibility, and increased mechanical stability [1-8].

Photo-crosslinking is a type of chemical crosslinking which is performed in the presence of UV radiation, crosslinking agents and chemical photo-initiator [9]. Hydrogels are prepared through photopolymerization on relevant time scales of seconds to several minutes. Photopolymerization has the ability to prepare hydrogels under mild and physiological conditions [10].

Hydroxyapatite (HAp) is a known calcium ion supply with a slow-release pattern, which has been gradually attracting significant attention due to its excellent bioactivity, biocompatibility and desirable biologic properties. Mixtures of hydroxyapatite and polymers show good biological properties and biocompatibility [11-16]. In order to improve the mechanical properties of the hydrogels, hydroxyapatite particles have been encapsulated in them to control drug release for drug delivery applications [17].

Alzheimer's disease (AD) is a type of dementia and irreversible brain disorder that affects patient's memory, thinking, and social life [18].

Donepezil is the most effective agent which is a potent and selective acetylcholinesterase inhibitor developed and used for the treatment of AD [19,20].

In this study, donepezil hydrochloride (DH) which was encapsulated in PEG-DA hydrogels was combined with HAp *via* photopolymerization. Fourier transform infrared (FT-IR) spectroscopy and digital microscopy were used to characterize the hydrogels.

EXPERIMENTAL

Materials

Polyethylene glycol diacrylate (PEG-DA, M_n=700) was purchased from Sigma Aldrich. 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, surface area≥100m^2/g), were purchased from Sigma-Aldrich. Donepezil HCl was generously gifted by Abdi İbrahim Company. Sodium chloride and hydrochloric acid were provided by 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 Hydrogels

PEG-DA 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 placed into glass molds (diameter of 15 mm, depth of 1 mm), and deaerated by bubbling with nitrogen gas during the reaction. Photopolymerization was performed at 365 nm under UV irradiation for 40 s.

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Table 1. Experimental conditions for the synthesis of PEG-DA based composite hydrogels

Hydrogels	PEG-DA Mn=700	EGDMA	Irg 651	Irg 184	Irg 2959	HAp
Hydrogel 1 (H1)	50 %	3 %	0.5 %	-	-	-
Hydrogel 2 (H2)	50 %	3 %	-	0.5 %	-	-
Hydrogel 3 (H3)	50 %	3 %	-	-	0.5 %	-
Hydrogel 4 (H4)	50 %	3 %	0.5 %	-	-	0.05 %
Hydrogel 5 (H5)	50 %	3 %	-	0.5 %	-	0.05 %
Hydrogel 6 (H6)	50 %	3 %	-	-	0.5 %	0.05 %

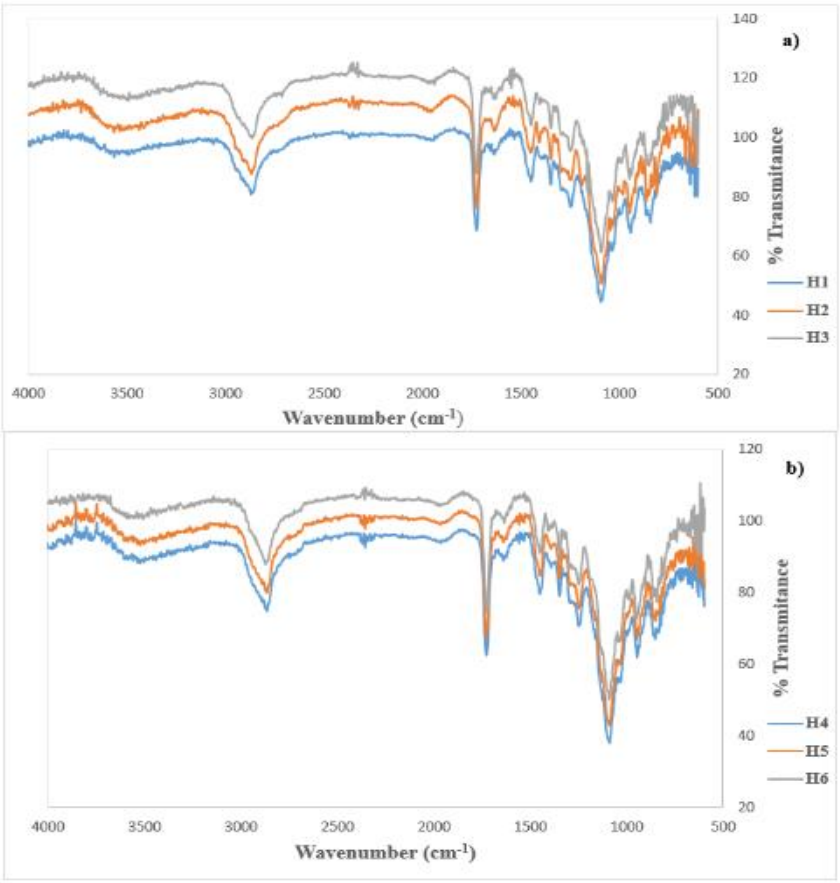

Figure 1. FT-IR analyses of PEG-DA hydrogels (a) and PEG-DA/HAp hydrogels (b)

Diameters of hydrogels were calculated by usng micro photographs (Veho, VMS- 004 USB Microscope). Characterization of functional groups present in the hydrogels were performed by FT-IR spectroscopy (Perkin Elmer Spectrum 100). Swelling behavior was studied by a gravimetric method. Drug-loaded hydrogels were used for studying the swelling behavior at 37°C. At a predetermined time point, the hydrogels were taken out and weighed after removal of surface water. Swelling ratio was calculated as follows:

$$\text{Swelling ratio} = (W_s - W_i)/ W_i \times 100$$

where W_i is the initial weight of the prepared hydrogel and W_s is the weight of the hydrogel in swollen state.

RESULTS AND DISCUSSION

Characterization of the Prepared Hydrogels

Characterization of hydrogels by FT-IR was carried out to determine the chemical structure and to confirm the combination.

The FT-IR spectrum of PEG-DA is shown in Figure 1 and Table 2. Absorption of the C=C bonds occurs at 1633 $cm^{-1}$and of the carbonyl groups at 1724 cm^{-1}. Absorption of the C=C bonds occurs at 1633 $cm^{-1}$and of the carbonyl groups at 1724 cm^{-1}.

The results demonstrated the existence of characteristic bands of HAp at 598 and 559 and at 1020 cm^{-1} attributed to $P^{3-}{}_4$ and $PO_3{}^{-4}$ groups vibrations, respectively.

Table 2. Functional groups of hydrogels [21-23].

	Wavenumber (cm^{-1})	Functional group
PEG-DA		
	2700 - 3300	C-H
	3000 – 3700	O-H
	900 - 1300	C-O
	1600 - 1700	C=C
	1600 - 1900	C=O
HAp		
	561	ν_4 vibrations normally associated with O-P-O modes
	600	
	631	
	832	CO_3^{2-}
	963	ν_1 symmetric stretching vibrations normally associated with P-O mode
	1027	PO_4^{3-}
	1091	
	1374	CO_3^{2-}
	1644	CO_3^{2-}
	3215	water
	3570	OH^-

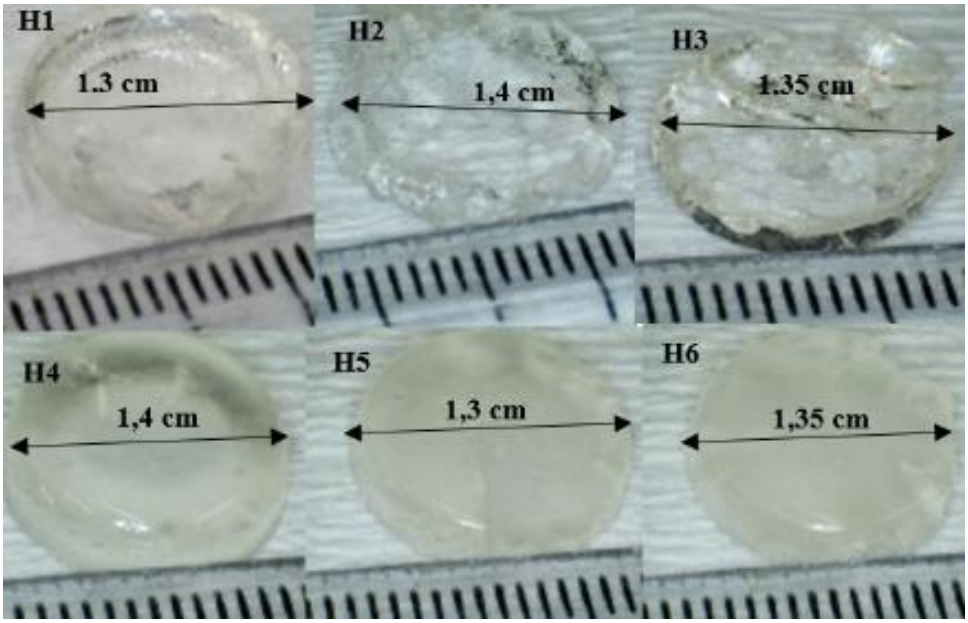

Figure 2. Samples of hydrogels

The sizes of hydrogels were between 1.3 and 1.4 mm, which were determined by digital microscopy.

Swelling properties of the hydrogels

The swelling properties of hydrogels were studied as functions of time and pH. Swelling ratios of hydrogels in deionized water and in solutions with pH 1.2, pH 6.8, pH 7.4 at 37°C are shown in Figure 3. An increase in the swelling degree was observed with the decrease in pH values for all synthesized formulations.

The percentage of swelling of H1 reached up 88 % within 24 h in deionized water, the percentage of swelling of H4 - 76 % within 24 h at pH 1.2, the percentage of swelling of H4 - 80 % within 24 h at pH 6.8 and the percentage of swelling of H4 - 75 % within 24 h at pH 7.4.

Donepezil HCl release studies

The interaction of the hydrogels with donepezil hydrochloride was studied. pH 1.2, pH 6.8 and pH 7.4 were selected as media for the study of the hydrogels interaction with donepezil hydrochloride. Figures 4, 5 and 6 depict the percent cumulative release of donepezil hydrochloride from hydrogels at pH 1.2, pH 6.8 and pH 7.4, respectively, at 37°C.

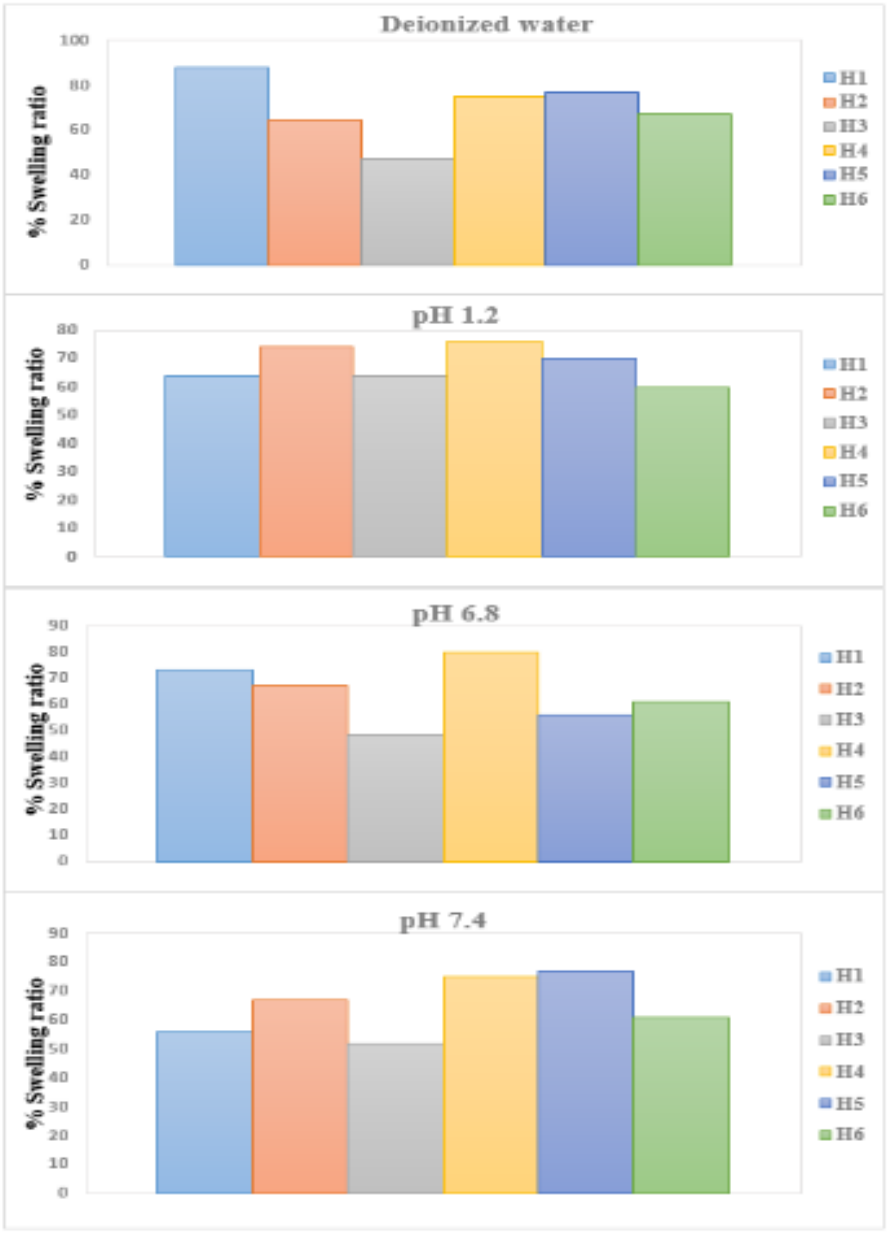

Figure 3. Swelling ratios of hydrogels

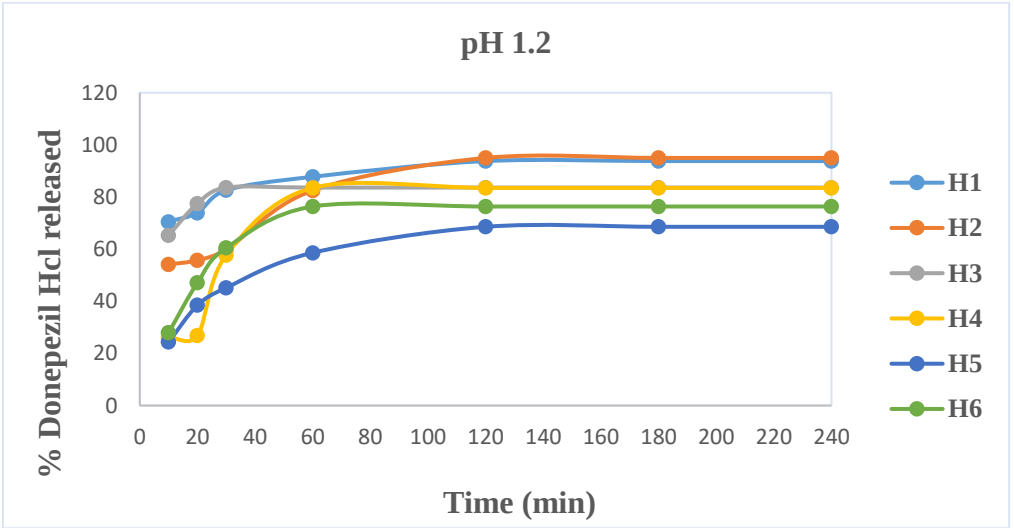

Figure 4. Donepezil HCl release of hydrogels in pH 1.2 media

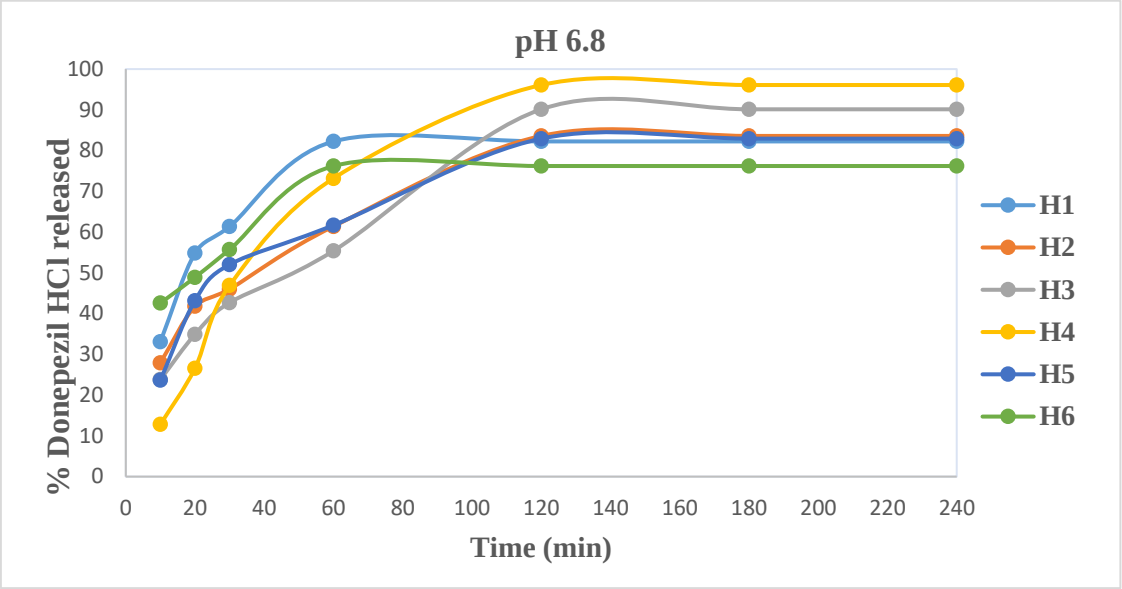

Figure 5. Donepezil HCl release of hydrogels in pH 6.8 media

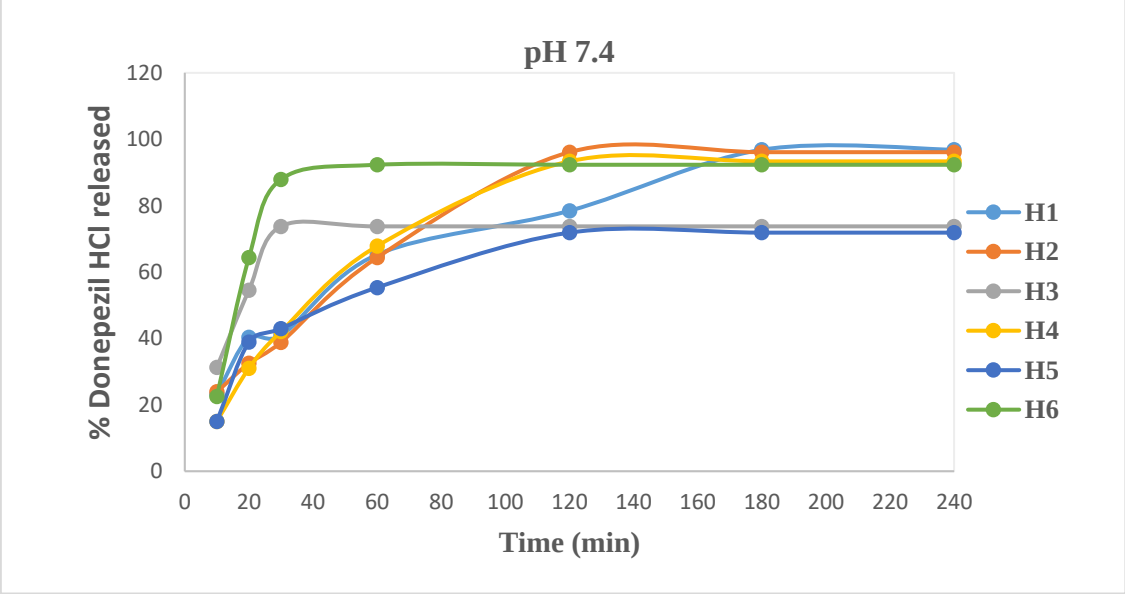

Figure 6. Donepezil HCl release of hydrogels in pH 7.4 media

It was found that in simulated gastric fluids (pH 1.2), the hydrogels showed a slower and steadier release rate. The drug release increased with the increase in pH of the medium. Also, the results indicated that the type and amount of photo-initiators changed the release behavior. The incorporation of hydroxyapatite into the hydrogel reduced donepezil hydrochloride release rate.

CONCLUSIONS

In summary, hydrogels containing various concentrations of HAp intended for oral administration were prepared and evaluated. Incorporation of HAp into the hydrogels improved the release behavior. These results indicated that PEG-DA-based hydrogels had a favorable behavior for drug delivery. The combination between PEG-DA and HAp could delay the degradation rate of the hydrogels in simulated gastrointestinal fluid. The obtained results showed that the prepared hydrogels could be potentially beneficial for drug delivery applications.

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КОНТРОЛИРАНО ОСВОБОЖДАВАНЕ НА ДОНЕПЕЗИЛ ХИДРОХЛОРИД ОТ PEG-DA ХИДРОГЕЛОВЕ

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(Резюме)

Целта на настоящата работа е да се създаде система за контролирано освобождаване на лекарства чрез получаване и охарактеризиране на хидрогелове на базата на полиетиленгликол диакрилат (PEG-DA). За определяне влиянието на фотоинициатори върху освобождаването на лекарства от получените хидрогелове са използвани три фотоинициатора: 2,2-диметокси-2-фенилацетофенон (Irgacure 651), 1-хидроксициклохексилфенил кетон (Irgacure 184) и 2-хидрокси-4'-(2-хидроксиетокси)-2-метилпропиофенон (Irgacure 2959). За модифициране на PEG-DA е използван хидроксиапатит. FT-IR спектроскопия и дигитална микроскопия са използвани за охарактеризиране на получените хидрогелове. Съотношенията на набъбване на хидрогеловете и поведението им при освобождаване са изследвани при различни условия. Освобождаването на лекарствата е изследвано при pH 1.2, 6.8 и 7.4.