Preparation and characterization of pH-sensitive hydrogels from photo-crosslinked poly(ethylene glycol) diacrylate incorporating titanium dioxide

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The purpose of the present investigation was to prepare pH-sensitive hydrogels from photo-crosslinked poly(ethylene glycol) diacrylate (PEG-DA). Rutile titanium dioxide (TiO₂) was employed to modify the PEG-DA hydrogels. The rutile titanium dioxide (TiO₂) nanoparticles were prepared by direct oxidation of titanium in the presence of polyethylene glycol (PEG) at high temperature. The nanoparticles were characterized by FT-IR, XRD and SEM. The influence of experimental conditions, such as pH, type and amount of photoinitiators on the release profiles of donepezil hydrochloride (active pharmaceutical ingredient for Alzheimer disease) from modified PEG-DA hydrogels, was investigated. The drug release processes were analyzed kinetically using zero-order, first-order, Hixson-Crowell and Peppas models.

Keywords: PEG-DA based hydrogels; rutile titanium oxide; release profiles; kinetic models

1. Introduction

Alzheimer's disease (AD) is one of the cognitive dysfunctions. AD patients are affected by several factors, including forgetfulness, high caregiver burden, high pill burden, complex medication regimens, and swallowing difficulties. In the treatment of Alzheimer's disease, donepezil is used for treating. Donepezil hydrochloride therapeutic effect causes an increase in the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase [1–6].

Many geriatric patients find it difficult to swallow the tablets or capsules. In recent years, wide variety of novel drug delivery systems have been developed to increase patient's comfort [4]. Controlled drug delivery using nanostructured functional materials is gaining an increasing attention [7]. Drug delivery systems improve bioavailability, selectivity, and release profile of therapeutic agents. These systems can maintain precise control over drug concentration within the therapeutic window [8, 9]. Also, controlled drug delivery has

a robust structure and large loading capacity of hydrophilic drugs [10–12].

Hydrogel is one of the smart materials which are used in biological and medical science, drug encapsulation and release, organ tissue engineering and microrobots [13]. Poly(ethylene glycol) (PEG)-based materials are widely used for biomedical applications because of their biocompatibility, non-immunogenicity and ease of use. PEG based materials have high humidity adsorption due to the presence of hydrogen bond between the PEG chain and water molecule. Poly(ethylene glycol) diacrylate (PEG-DA) hydrogel doped with photoinitiators is used to fabricate scaffolds and topographical patterns via polymerization by intense light irradiation. Acrylate groups of PEG-DA monomers can be cross-linked with each other to form a solid-state polymer [14–18].

UV light triggers photoinitiators to activate and generate free radicals, thus initiating the process of photopolymerization to form a crosslinked network [19, 20]. A photopolymerization-curing technique provides an easy preparation of the films based on the PEG-based materials. Also, photopolymerization is efficient, energy saving, and environmentally friendly technology due to easily

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controlled process parameters and a rapid curing rate. This method is widely used for coatings, dental restorative materials, lenticular lenses, and photolithography [21–25].

Titanium dioxide (TiO_2) is one of the best biocompatible and hydrophilic inorganic nanoparticles. The incorporation of metals and metal oxide nanoparticles, such as titanium dioxide into hydrogels enhances the antimicrobial activity of hydrogels and improves their mechanical characteristics [26, 27]. TiO_2 has rutile, anatase, and brookite phases [28]. Titanium dioxide or titanium oxide based materials have powerful photocatalysis and chemical stability, biocompatibility, resistance to corrosion, nontoxicity, low-cost, and high reactivity. They absorb UV light. Titanium dioxide is a highly photostable and highly effective material. Also, TiO_2 provides long lasting release in several diseases [27–36].

Donepezil hydrochloride (DH), studied in this work, was encapsulated in PEG-DA hydrogels which were combined with modified TiO_2 via photopolymerization. TiO_2 was chosen as a biomaterial for hydrogel preparation due to its interesting characteristics, including favorable mechanical properties [25]. Fourier transform infrared (FT-IR) spectroscopy, XRD, SEM analyses and digital microscope were used to characterize the hydrogels.

2. Experimental

2.1. 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) were purchased from Sigma-Aldrich. Donepezil hydrochloride was 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. Titanium powder (–325 mesh, 99.5 %) was provided by Alfa Aesar. All chemicals

were used as received without further purification.

2.2. Preparation and characterization of TiO_2

2.38 g PEG and 7.28 (d) deionized water were mixed at 650 rpm. Then, 0.467 g titanium powder was added and mixed for 24 h. After that, the mixture was put into Petri dishes for drying. Then, the mixture in an alumina crucible was fed into a muffle furnace (Protherm), heated to a temperature of 900 °C and burned for 30 min. The samples were characterized by XRD, FT-IR and SEM. The XRD patterns of the crystals were recorded on a diffractometer (Panalytical X'Pert Pro PW 3040/60) with nickel filtered $\text{CuK}\alpha$ ($\lambda = 1.54 \text{ \AA}$) as a radiation source and at a 2θ scan speed of $1^\circ/\text{min}$ at 30 kV and 20 mA. For FT-IR spectral analysis, PerkinElmer Spectrum 100 was used in the 4000 cm^{-1} to 400 cm^{-1} region at a resolution of 4 cm^{-1} . SEM studies were carried out using a JEOL JSM 6335F.

2.3. Preparation and characterization of hydrogels

According to the synthesized hydrogel type, 50 % (w/v) PEG-DA and 0.5 % (w/v) photoinitiators (Irg 184, Irg 651, Irg 2959) were mixed by using a magnetic stirrer at 50 rpm. 0.07 % (w/v) donepezil hydrochloride (API) powder and deionized water were added. Predetermined amount of ethylene glycol dimethacrylate (crosslinker) was then introduced. After UV irradiation, the hydrogels were washed in n-hexane and dried at room temperature. TiO_2 nanoparticles were mixed with the pre-formed hydrogels.

PEG-DA based hydrogels were prepared in the presence of a photoinitiators (Irg 184, Irg 651, Irg 2959) and crosslinking agent (ethylene glycol dimethacrylate), as shown in Table 1. Diameters of the hydrogels were calculated by using microscope photos (Veho, VMS-004 USB microscope). Characterization of functional groups present in the hydrogels was performed by FT-IR spectroscopy (PerkinElmer Spectrum 100). Swelling behavior was studied by the gravimetric method. Drug loaded hydrogels were used for swelling

Table 1. Synthesis conditions for the PEG-DA based composite hydrogels.

Hydrogels	PEG-DA Mn = 700	EGDMA	Irg 651	Irg 184	Irg 2959	TiO ₂
Hydrogel 1 (H1)	50 %	1 %	0.5 %	—	—	0.05 %
Hydrogel 2 (H2)	50 %	3 %	0.5 %	—	—	0.05 %
Hydrogel 3 (H3)	50 %	1 %	—	0.5 %	—	0.05 %
Hydrogel 4 (H4)	50 %	3 %	—	0.5 %	—	0.05 %
Hydrogel 5 (H5)	50 %	1 %	—	—	0.5 %	0.05 %
Hydrogel 6 (H6)	50 %	3 %	—	—	0.5 %	0.05 %
Hydrogel 7 (H7)	50 %	1 %	0.5 %	—	—	—
Hydrogel 8 (H8)	50 %	1 %	—	0.5 %	—	—
Hydrogel 9 (H9)	50 %	1 %	—	—	0.5 %	—

behavior studies at 37 °C in distilled water, pH 1.2, pH 6.8 and pH 7.4. The pH 1.2 solution was prepared according to United States of Pharmacopia (USP) standards. Preparation of buffer solutions with various pH values (pH 6.8 and pH 7.4) has been reported in detail [12, 37]. pH 1.2 and pH 6.8 were used for simulating gastric media and intestinal fluid, respectively. At predetermined time point, the hydrogels were taken out and weighed after removal of surface water.

Swelling ratio was calculated as follows:

$$\text{Swelling ratio} = (W_s - W_i) / W_i \cdot 100 \quad (1)$$

where W_i is the initial weight of the prepared hydrogel and W_s is the weight of the hydrogel in a swollen state. The analyses were repeated three times. Determination of swelling ratio and preparation procedure of buffer solution have been reported previously in detail [12].

Donepezil hydrochloride release studies were performed by using UV-Vis spectrophotometer (Analytik Jena Specord 200/Plus) at 270 nm. The experiments were performed in triplicate and repeated three times with similar results. The reproducibility of this approach is 2 % to 3 %.

3. Results and discussion

3.1. Characterization of the prepared TiO₂

Diffraction data presented in Fig. 1 show some prominent peaks, indicating crystallinity of the deposited thin film. The peak indexing was done

Fig. 1. XRD spectra of TiO₂ R: rutile TiO₂.

using JCPDS standard data. According to X-ray diffraction patterns, all diffraction lines could be indexed to the rutile structure of TiO₂.

Fig. 2. FT-IR spectrum of TiO₂ R: Rutile TiO₂.

Fig. 2 shows FT-IR absorption spectrum of TiO₂ powders. The peaks at 496 cm⁻¹ and 620 cm⁻¹ are perceived for all possible structures containing Ti–O, and seem to be dominant in rutile TiO₂ phase.

Fig. 3. SEM image of TiO₂ powder.

Scanning electron microscopic images of the synthesized TiO₂ powders are shown in Fig. 3. All the particles are of nanocrystalline size.

3.2. Characterization of the prepared hydrogels

The sizes of hydrogel particles observed by a digital microscope were between 1.3 and 1.4 mm.

Fig. 4. PEG-DA/TiO₂ based hydrogels.

FT-IR spectrum of PEG-DA is shown in Fig. 4 and the identified functional groups are collected in Table 2. Characterization of hydrogels by FT-IR was carried out to determine the chemical structure of obtained compounds. Absorption of the C=C bonds occurs at 1633 cm⁻¹ and the carbonyl groups at 1724 cm⁻¹. Absorption of the Ti-O metal oxygen band occurs at 620 cm⁻¹.

3.3. Swelling properties of the hydrogels

Swelling properties of the hydrogels were studied as function of time and pH. Swelling ratio of

the hydrogels in deionized water and in solutions with pH 1.2, pH 6.8, pH 7.4 at 37 °C are shown in Fig. 5. All the hydrogel samples show a similar swelling kinetic behavior. Initially, swelling capacity of the hydrogel samples increases considerably and then it increases with a slow rate until the equilibrium swelling capacity is reached.

Fig. 5. Swelling ratio of hydrogels in simulated media.

It was observed that swelling ratio of the hydrogel decreased with increasing the concentration of crosslinking agent (ethylene glycol dimethacrylate) in presence of Irgacure 184 and Irgacure 651 as photoinitiators for all media. It can be explained by the fact that there are more chain ends in the networks when the M_n becomes smaller, and this also means that the networks with more chain ends have higher swelling capacity according to Flory's report [38]. But swelling ratio of hydrogel increased by increasing the concentration of ethylene glycol dimethacrylate in presence of Irgacure 2959 at high pH. Also the results demonstrated that the incorporation of TiO₂ to hydrogels increased the swelling capacity. Previous research has shown that titanium binders are characterized by a higher swelling ratio [39, 40].

3.4. Donepezil hydrochloride release studies

The interaction of the hydrogels with donepezil hydrochloride was studied. pH 1.2, pH 6.8 and pH 7.4 were selected for the release of donepezil hydrochloride.

Fig. 6 depicts the percentage cumulative release of donepezil hydrochloride from the hydrogels at pH 1.2, pH 6.8 and pH 7.4, respectively, at 37 °C.

Table 2. Functional groups of hydrogels.

Wavenumber [cm^{-1}]	Functional group
2700 – 3300	C–H
3000 – 3700	O–H
900 – 1300	C–O
1600 – 1700	C=C
1600 – 1900	C=O
620	Ti–O metal oxygen band
1630 – 2919	H–O–H bending vibrations of coordinated water
3432	Asymmetric and symmetric stretching vibrations of O–H group

It was observed that *in vitro* drug release from PEG-DA hydrogels which were combined with modified TiO_2 showed a controlled release profile. As illustrated in these figures, at pH 7.4 the highest drug release values have been achieved. At lower pH values, the hydrogels swell less than at pH 7.4. The hydrogel swelling increased which resulted in increased API release. Also, the type of photoinitiators changed the release behavior. Hydrogels, prepared in the presence of Irg 651, showed the highest drug release values and the steadier release rates. It is known that the chemical nature of the photoinitiator affects the light resistance and the stability of the hydrogels [41]. Irg 651 is more hydrophobic and generates more free radicals than Irg 184 and Irg 2959 [42]. We hypothesize that Irg 651 may selectively incorporate into the acrylate core in PEG-DA solutions to a greater extent than the others.

Zero-order, first-order, Hixson-Crowell and Peppas kinetic models were used [43]. Kinetics models of hydrogels are shown in Table 3. Drug-release kinetics for the H1 and H2 hydrogels best corresponds to the first-order model showing good correlation of the data with R^2 values varying between 0.993 and 0.996 while the H5 and H6 hydrogel complies with the zero order kinetic model. According to Peppas model, H3 and H4 hydrogels show good linearity with R^2 values ranging from 0.827 to 0.991, indicating that diffusion is the predominant mechanism of drug release from these formulations.

Fig. 6. Donepezil hydrochloride release of hydrogels in simulated media.

4. Conclusions

In this study, PEG-DA hydrogels were prepared by photopolymerization method with different photoinitiators in the presence of rutile TiO_2 and *in*

Table 3. Kinetic models of hydrogels.

	pH	Zero order		First order		Hixson-Crowell		Peppas		
		R ²	K ₀ [mg/h]	R ²	K ₁ [h ⁻¹]	R ²	K _s	R ²	n	k
H1	1.2	0.983	2.73×10^{-3}	0.993	0.003	0.989	0.00015	–	–	–
	6.8	0.575	5.25×10^{-4}	0.929	1.023	0.466	0.0084	0.616	0.2904	0.508
	7.4	0.914	1.00×10^{-3}	0.996	1.039	0.961	0.014	0.901	0.409	0.669
H2	1.2	0.874	9.58×10^{-4}	0.988	1.514	0.750	0.047	0.929	0.607	0.538
	6.8	0.847	5.64×10^{-4}	0.979	1.436	0.977	0.031	0.923	0.358	0.416
	7.4	0.904	1.14×10^{-3}	0.994	0.006	0.842	0.00008	0.946	0.3443	0.52
H3	1.2	0.993	1.17×10^{-3}	0.950	1.633	0.971	0.028	0.995	0.6071	0.548
	6.8	0.442	2.30×10^{-4}	0.649	1.498	0.656	0.020	0.857	0.3321	0.407
	7.4	0.719	5.53×10^{-4}	0.459	0.611	0.652	0.007	0.827	0.1997	0.772
H4	1.2	0.810	1.34×10^{-3}	0.536	1.901	0.594	0.023	0.856	0.9907	0.616
	6.8	0.755	4.24×10^{-4}	0.734	1.617	0.646	0.009	0.907	0.3575	0.341
	7.4	0.969	6.68×10^{-4}	0.912	1.186	0.849	0.011	0.991	0.3282	0.513
H5	1.2	0.583	3.98×10^{-4}	0.563	0.704	0.573	0.022	0.510	0.2995	0.838
	6.8	0.951	5.42×10^{-4}	0.770	0.994	0.758	0.007	0.956	0.2465	0.517
	7.4	0.953	4.13×10^{-4}	0.942	1.181	0.602	0.024	0.831	0.3319	0.787
H6	1.2	0.829	1.52×10^{-4}	0.750	0.390	0.750	0.026	0.634	0.309	0.910
	6.8	0.937	3.0×10^{-3}	0.914	0.004	0.906	0.00018	0.599	0.3648	1.77
	7.4	0.942	7.89×10^{-4}	0.536	1.020	0.574	0.018	0.931	0.6074	0.813

vitro release of donepezil hydrochloride from the PEG-DA hydrogels at 37 °C was performed. Rutile phase TiO₂ was successfully synthesized by direct oxidation of titanium in the presence of PEG at 900 °C. The XRD patterns showed that the TiO₂ nanocrystals were predominantly composed of rutile crystal phase. The controlled drug release experiments carried out with the hydrogels demonstrated that the pH of swelling medium, EGDMA content and kind and amount of photoinitiators influence the drug-release profile. It was found that API release was considerably higher at pH 7.4, suggesting that the release system has a potential for intestinal drug delivery. In addition, kinetic data were fitted with zero and first kinetic model. PEG-DA hydrogels with TiO₂ presented a controlled release behavior with significantly slower release rate compared to PEG-DA hydrogels without TiO₂. The results indicate that the combination of PEG-DA and TiO₂ could be useful in drug-release systems.

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