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# Controlled release of donepezil hydrochloride from the ternary sodium alginate based hydrogels

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In the presented work, synthesis of the ternary sodium alginate based hydrogels as drug delivery systems having different properties and drug release experiments were performed. For this purpose, gelatine, α-cellulose, clinoptilolite, modified clinoptilolite and 4-acryloyl morpholine (4 AcM) were combined with sodium alginate (NaAlg). Hydrogels were characterized by Fourier transform infrared spectroscopy (FT-IR) and digital microscope. In vitro drug release studies have been performed for Donepezil hydrochloride loaded hydrogels at pH 1.2, 6.8 and 7.4. The results showed that these hydrogels can be used for drug delivery systems.

**Keywords:** The ternary sodium alginate based hydrogels, drug release, Donepezil hydrochloride**.**

## INTRODUCTION

Alzheimer's disease (AD) is an irreversible, progressive brain disorder which leads to deterioration of intellectual and social functions, memory loss, personality changes and inability for self-care. AD is the fourth leading cause of death in developed countries [1-2]. In 2013, Alzheimer's Disease International (ADI) reported the worldwide prevalence of dementia to be more than 44 million [3].

Drug delivery systems have been attracted a great deal of attention for the past few decades since it offers the effective and targeted drug delivery in the field of pharmaceutics [4-10]. Hydrogels are used control drug release because they change the gel structure in response to environmental situation [11]. The important physicochemical and biological characteristics of hydrogels, along with their huge diversity, collectively, have led to desirable attention to these polymeric materials as important candidates for delivery systems of therapeutic agents [12-18]. Donepezil Hydrochloride (DH) is a second-generation cholinesterase inhibitor (ChEI). It is used for the treatment of Alziemers disease (AD) having greater specificity for the brain acetyl cholinesterase enzyme (AchE) [19].

In this study; an Alzheimer drug donepezil hydrochloride (DH) which was encapsulated in to sodium alginate (NaAlg) hydrogels which were combined with gelatine, α-cellulose, clinoptilolite, modified clinoptilolite and 4-acryloyl morpholine. Fourier transform infrared (FT-IR) spectroscopy and digital microscope were used to characterize the hydrogels.

## EXPERIMENTAL

### *Materials*

Sodium alginate (Protonal LF 10/60) was purchased from FMC Biopolymer. Donepezil HCl was provided by Abdi İbrahim Company. Clinoptilolite was provided by Gordes Zeolit Company. Gelatine was provided by Carlo Erba, α-cellulose, and 4 Acryloyl morpholine were purchased from Sigma Aldrich. Calcium chloride, was provided by Merck.

### *Preparation and Characterization of Hydrogels*

Donepezil HCl 0.05 % (w/v) and 1% (w/v) NaAlg were dissolved in deionized water and mixed by using a magnetic stirrer at 40°C and 200 rpm. According to hydrogel type, 1% (w/v) gelatine, clinoptilolite, modified clinoptilolite, 4 AcM, α-cellulose were added. The solution was added drop wise into $CaCl_2$ solution (2 % (w/v) under constant stirring at 100 rpm. Hydrogels were washed and dried at room temperature.

Preparation of modified clinoptilolite: 50 g clinoptilolite was added in to 3M NaCl solution at 60°C for 30 sec in ultrasonic bath. This procedure was twice repeated. After that clinoptilolite washed with deionized water and dried for 24 h. Synthesis conditions of hydrogels are summerized in Table 1.

Diameter of hydrogels were calculated by using microscope photos (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 loadded hydrogels were used for swelling behaviour at 37°C. At predetermined time point, the hydrogels were taken out and weighed

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after removal of surface water. Swelling ratio was calculated as follows:

$$Swelling\ ratio = (W_s - W_i)/ W_i * 100$$

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

**Table 1**. Experimental synthesis conditions for the sodium alginate based composite

| Hydrogels | NaAlg | 4AcM | Clinoptilolite | Modified Clinoptilolite | Gelatine | α-cellulose |
|---|---|---|---|---|---|---|
| Hydrogel 1 (H1) | %1 | % 1 | - | - | - | - |
| Hydrogel 2 (H2) | %1 | %1 | %1 | - | - | - |
| Hydrogel 3 (H3) | %1 | %1 | - | %1 | | |
| Hydrogel 4 (H4) | %1 | %1 | - | - | %1 | - |
| Hydrogel 5 (H5) | %1 | %1 | - | - | - | %1 |
| Hydrogel 6 (H6) | %1 | - | %1 | - | %1 | - |
| Hydrogel 7 (H7) | %1 | - | %1 | - | - | %1 |
| Hydrogel 8 (H8) | %1 | - | - | %1 | %1 | - |
| Hydrogel 9 (H9) | %1 | - | - | %1 | - | %1 |
| Hydrogel 10 (H10) | %1 | - | - | - | %1 | %1 |

## 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. Figure 1 displays the FT-IR spectrum of hydrogels. As seen in Figure 1, the broad absorption band around 3388 $cm^{-1}$ is ascribed to the peaks of -OH groups. The absorption peaks at 1620 and 1416 $cm^{-1}$ is assigned to stretching characteristic of alginate.

Figure 1(a-b-c-d-e) illustrates the FT-IR spectra of the AcM based hydrogels. The band at 1615 $cm^{-1}$ displays the shift of C=O vibration of the AcM structure due to hydrogen bonding interactions. Also, the ring stretching vibration (mainly asymmetric ν(C-O-C)) in morpholine is observed at about 1112 $cm^{-1}$. As seen in Figure1(b) and (e), the FT-IR band connected with the internal Si–O(Si) and Si–O(Al) vibrations in tetrahedral or alumina- and silica oxygen bridges lies at 795 $cm^{-1}$. The band at 1268 $cm^{-1}$ representing amid groups in gelatine (c). The band at 1427 $cm^{-1}$ is ascribed to the OH groups which belonged to α-cellulose (d). Two different clinoptilolite was used in this study: clinoptilolite and modified clinoptilolite. When the difference spectrum of clinoptilolite and modified clinoptilolite was investigated, it was seen the presence of the same typical bands clinoptilolite and modified clinoptilolite. Figue 1(d-f-g-h), exhibits FT-IR analyses for gelatine based hydrogels. The band of gelatin centered at about 3400 $cm^{-1}$, which was the stretching vibration, broadened and coupled with –OH band of sodium alginate at 3450 $cm^{-1}$, included by the addition of sodium alginate to gelatin, implied the occurrence of hydrogen bonds between –OH groups of sodium alginate and –NH groups of gelatin molecules. Figure 1(e-g-i-j) shows the FT–IR spectra of α-cellulose based hydrogels modified by 4 AcM, gelatine, clinoptilolite and modified clinoptilolite, respectively.

The sizes of hydrogels were between 1.67 and 2.57 mm, which were obtained by digital microscope. Diameter of hydrogels are given in Table 2.

**Table 2.** Diameter of hydrogels

| Hydrogels | (mm) |
|---|---|
| H1 | 1,67 |
| H2 | 1,70 |
| H3 | 1,93 |
| H4 | 1,93 |
| H5 | 2,28 |
| H6 | 1,85 |
| H7 | 2,57 |
| H8 | 1,99 |
| H9 | 2,20 |
| H10 | 2,29 |

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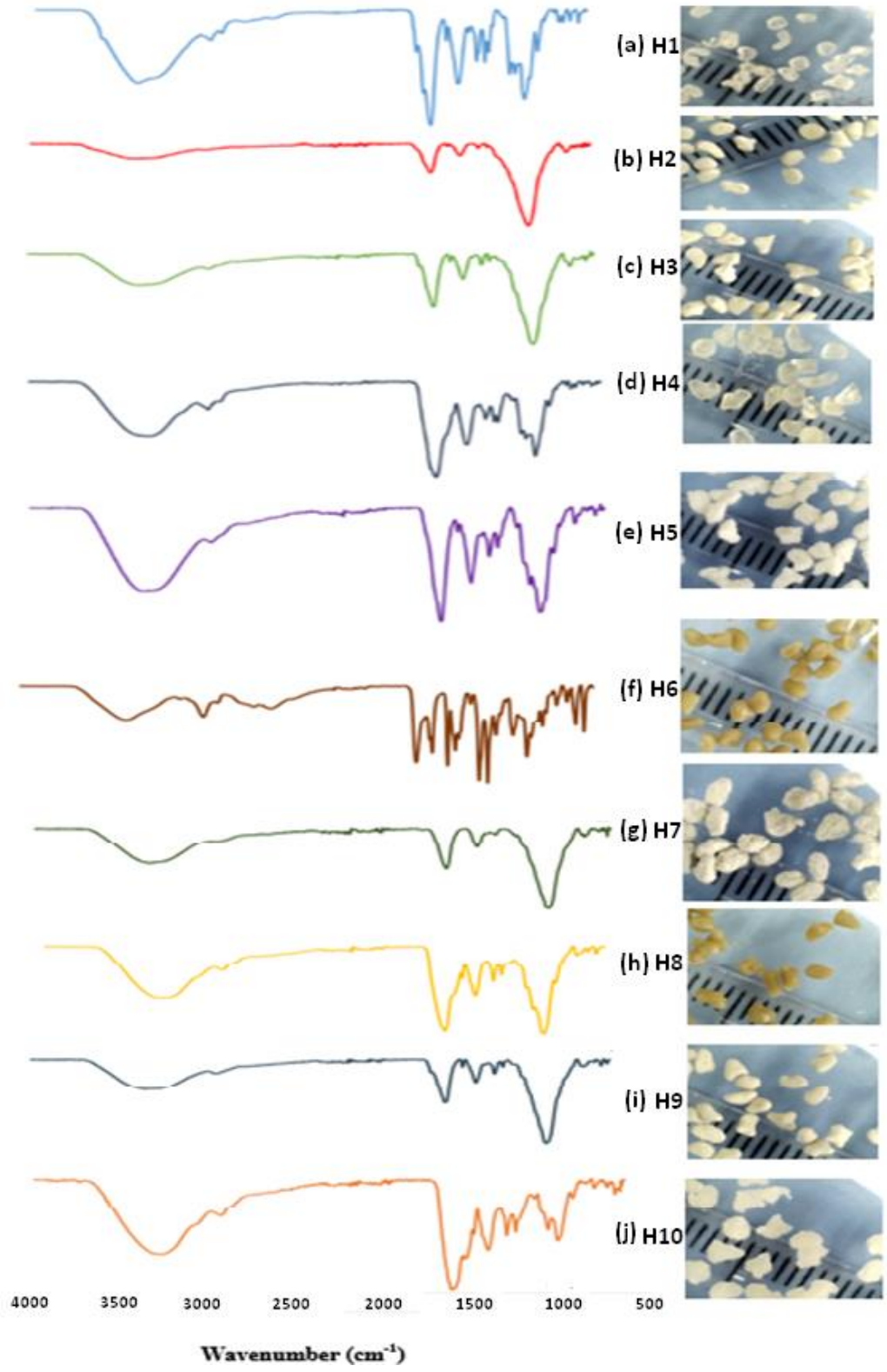


**Figure 1.** FT-IR analyses of hydrogels.

Two different clinoptilolite was used in this study: clinoptilolite and modified clinoptilolite. When the difference spectrum of clinoptilolite and modified clinoptilolite was investigated, it was seen the presence of the same typical bands clinoptilolite and modified clinoptilolite. Figue 1(d-f-g-h), exhibits FT-IR analyses for gelatine based hydrogels. The band of gelatin centered at about 3400 $cm^{-1}$, which was the stretching vibration, broadened and coupled with –OH band of sodium alginate at 3450 $cm^{-1}$, included by the addition of sodium alginate to gelatin, implied the occurrence of

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*Swelling properties of the hydrogels*

The swelling properties of hydrogels were studied as function of time and pH. Swelling curves and maximum equilibrium swelling of hydrogels in deionized water and in solutions with of pH 1.2, pH 6.8, pH 7.4 at 37°C were shown in Figure 2 and 3, respectively.

It has been well-known that the swelling–deswelling behavior is mainly due to the interaction between polymer and water molecules. It was observed that the swelling of hydrogels are depended on medium. As shown in Figures 2 and 3, for all hydrogels, maximum swelling was obtained at pH 6.8 and minimum at pH 1.2. Hydrogels presented a very low swelling ratio at pH 1.2, due to the protonation of carboxylate group in sodium alginate lowering the electrostatic repulsion. Three hours later, it was observed that hydrogels started to break into pieces at pH 6.8 and 7.4. Also, hydrogels which content gelatine presented the best swelling capacities. The percentage of swelling of H4 (NaAlg/4AcM/Gelatine) reached up 84 % within 24 h in pH 1.2, 104% within 24 h in deionized water, 424 % within 3h in pH 7.4 and 1309 % within 3 h in pH 6.8.

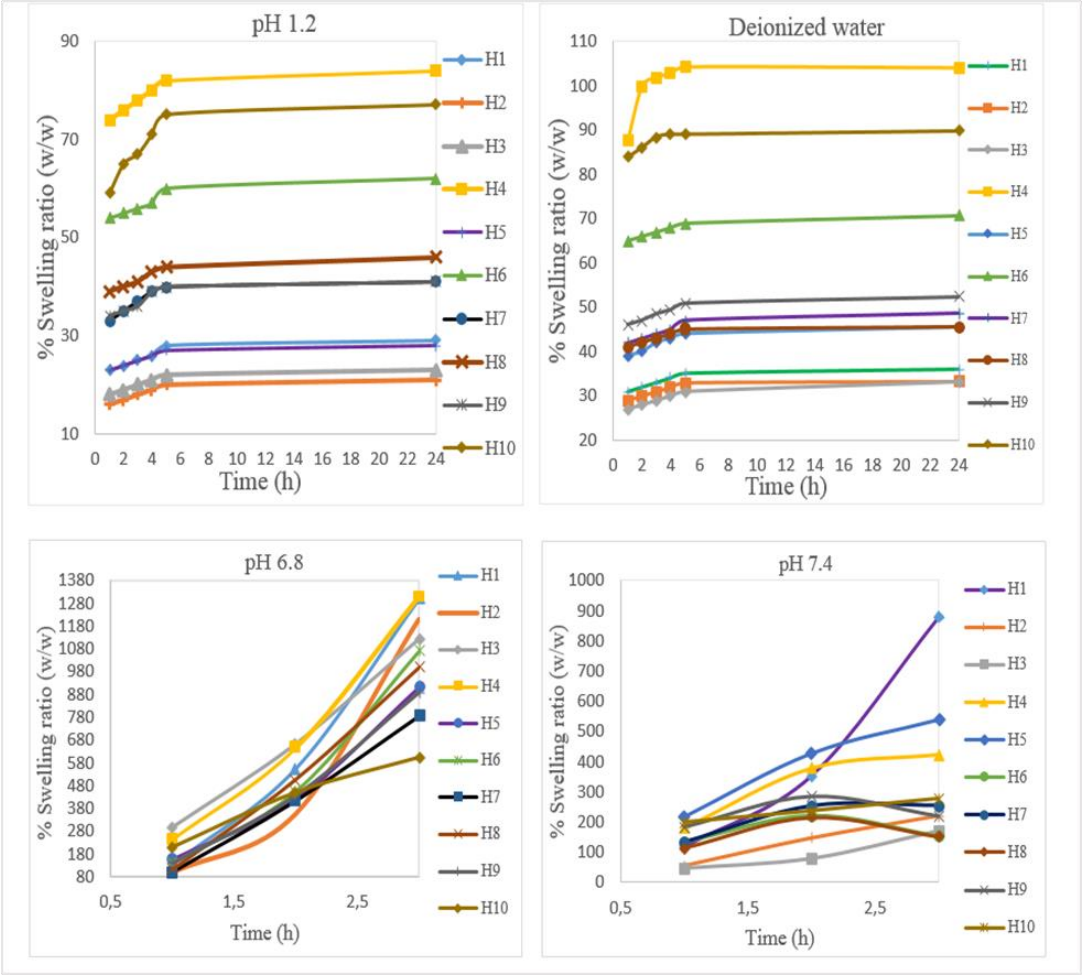


**Figure 2.** Swelling rate curves of hydrogels

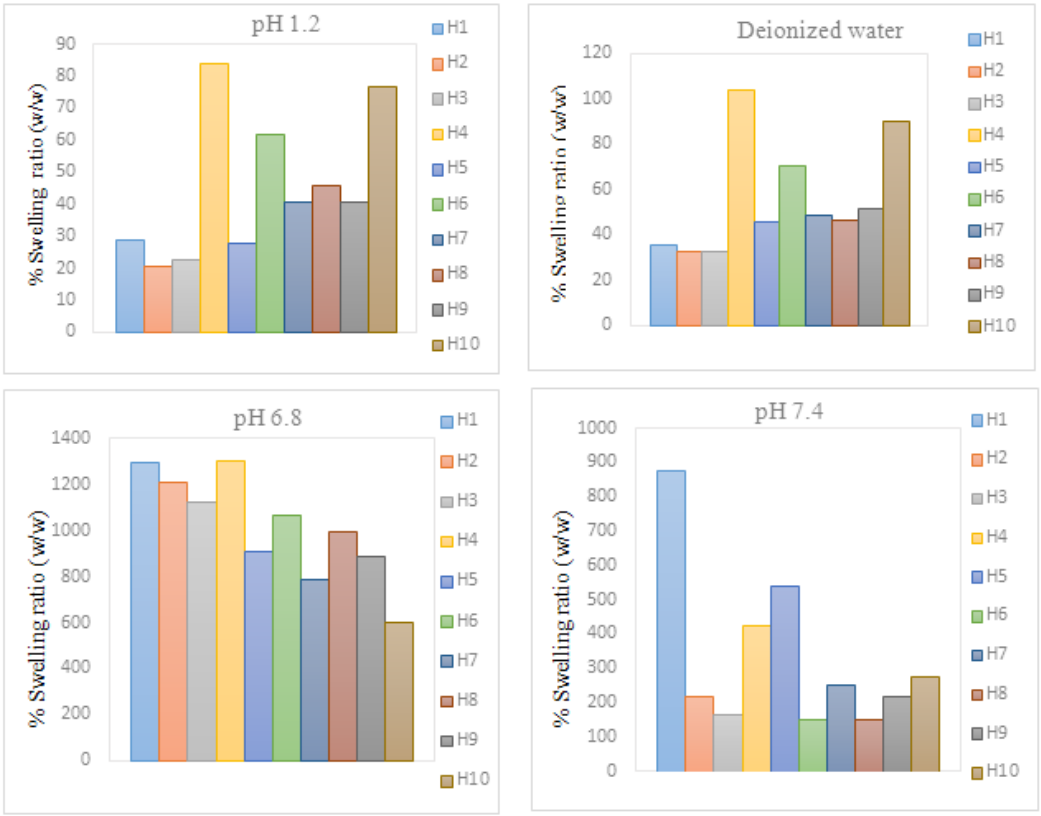


**Figure 3.** Swelling ratio of hydrogels.

*Donepezil HCl release studies*

In this section the interaction of the hydrogels with donepezil hydrochloride was studied. pH 1.2, pH 6.8 and pH 7.4 were selected as mediums for the study of the hydrogels interaction with donepezil hydrochloride. Figure 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.

It has been found that the hydrogels of NaAlg/α-cellulose/Clinoptilolite show the highest release ratio in all mediums. While the gelatine based hydrogels showed prolonged release profiles, the AcM based hydrogels did not. When compared the release of clinoptilolite, modified clinoptilolite, there is not significant difference between them. Also the release behavior of donepezil hydrochloride from the hydrogel was very sensitive to pH. It has been determined that release duration of Donepezil Hydrochloride at pH 1.2 was longer than pH 6.8 and pH 7.4. Since extending the time of release of hydrogels were obtained at pH 1.2, hydrogels can lead to a successful application for localized drug delivery used for gastric medium. The percentage cumulative release of donepezil HCl from AcM based hydrogels was lower in all medium pH.

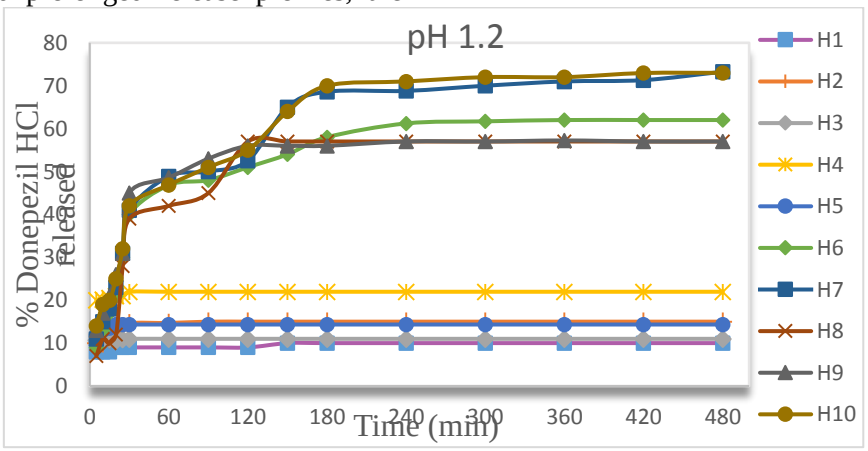


**Figure 4**. Donepezil HCl release of hydrogels in pH 1.2 media.

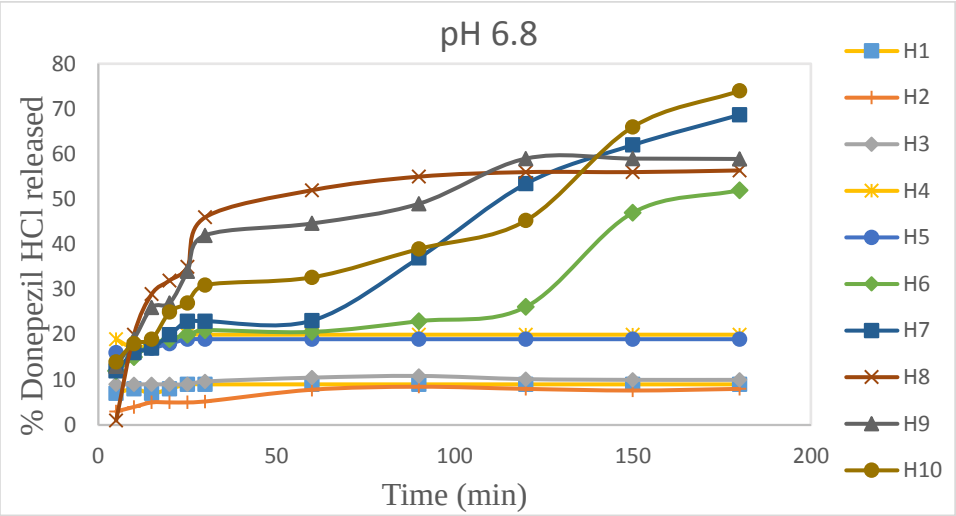


**Figure 5.** Donepezil HCl release of hydrogels in pH 6.8 media.

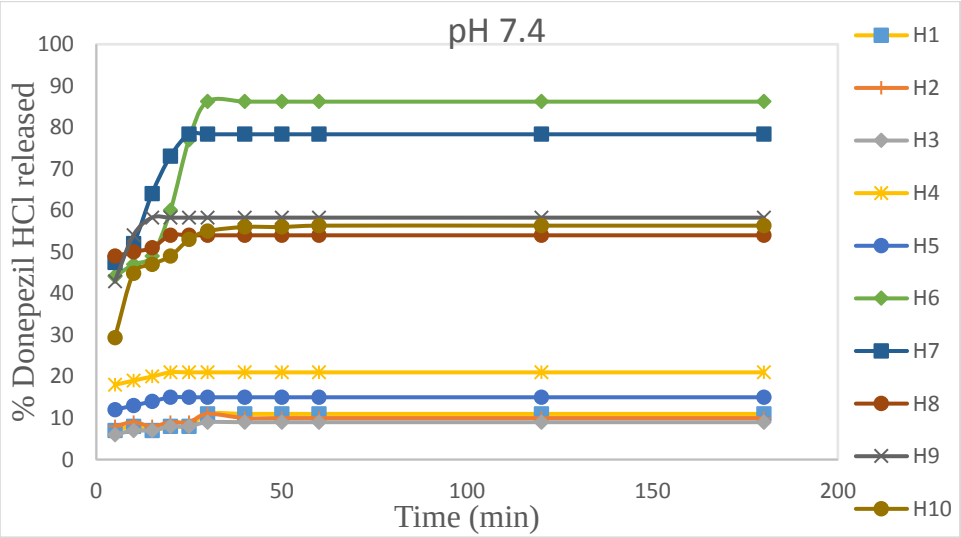


**Figure 6.** Donepezil HCl release of hydrogels in pH 7.4 media.

## CONCLUSIONS

In this study, the ternary sodium alginate based hydrogels were prepared successfully with gelatine, α-cellulose, clinoptilolite, modified clinoptilolite and 4-acryloyl morpholine. It has been found that the hydrogels content gelatine show the highest degree of swelling and release rate. Also the release behavior of donepezil hydrochloride from the hydrogels was very sensitive with the medium pH. It was seen that the time of release of hydrogels was very high at pH 1.2. These results suggest that the sodium alginate based composite hydrogels may be appropriate for use in the controlled release of drugs.

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