THE EFFECTS OF MODIFIED CLAY ON CONTROLLED DRUG RELEASE SYSTEMS

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ABSTRACT

Recently, controlled drug release systems have been garnering a lot of attention, due to more targeted and effective approach for delivering drugs to a specific tissue. Because of a specific structure and natural abundance, clays are being added to those systems in order to increase its efficiency and minimize costs. In this study, controlled release kinetics of the drug active substance 5-Fluorouracil was studied, using halloysite clay/polymer drug carriers. For this purpose, the halloysite clay was initially modified with cetyltrimethyl ammonium bromide (CTAB). Drug carriers were prepared by adding modified halloysite clays in the mixtures of polyvinyl alcohol (PVA) and sodium alginate. Firstly, the swelling behaviour of the prepared substances was studied in buffer solutions at different pH. The drug release kinetics from the drug carriers, loaded with 5- Fluorouracil, was observed under a UV-spectrophotometer at 266 nm. Release profiles of the active substance were obtained by studying its release in buffer solutions at different pH. The results showed that the prepared drug carriers with modified halloysite clay were suitable for carrying and releasing of the 5-Fluorouracil.

Keywords: Controlled drug release, halloysite, 5- Fluorouracil, polymer, clay.

INTRODUCTION

Materials for controlled drug release and drug delivery systems are being intensively researched by scientists all over the world (Hua, Ma, Li, Yang, & Wang, 2010; Hua, Yang, Li, Zhang, & Wang, 2012). The production of new drug formulas is very difficult, costly and time-consuming process as long studies are required. The drug delivery system minimizes the side effects of the drug taken into the body while ensuring that the drug reaches the target directly. This system provides the effective use of the drug and minimizes the necessary drug doses (Prabha & Raj, 2017). Biopolymers are preferred to be used as the drug carrier materials. In order to improve

efficiency and lower costs of production, inorganic compounds with porous characteristics, such as alumina, silica etc are usually added to drug carrier materials (García-Villén et al., 2019; Ge et al., 2019). Due to biocompatibility and natural abundance, as well as possibility for surface modification and nontoxicity toward humans, silica has important role in production of drug carriers. Furthermore, drugs can be easily attached to silica particles. Halloysite, the most important member of the kaolinite group of clay minerals has tubular morphology. Between two layers of halloysites there are water molecules as a single layer. Such structure greatly affects the physical properties of alginate composite hydrogels (Huang, Liu, Long, Shen, & Zhou, 2017). Therefore it is commonly used in controlled drug delivery systems.

Alginates have wide range of applications and are one of the most versatile biopolymers. They are commonly used in cosmetic and food products when it is necessary to achieve gel-structure, thickening and stabilizing properties. Sodium Alginate is extracted from brown seaweed, and can play an important role in the design of a controlled-release scaffolds (García-Villén et al., 2019; Ge et al., 2019; Huang et al., 2017; Prabha & Raj, 2017; Tønnesen & Karlsen, 2002). Due to biocompatibility, polyvinyl alcohol (PVA) based nanocomposites are preferred for some biomedical applications such as wound closures, contact lenses and implants.

In this study, the controlled release kinetics of the drug active substance 5-Fluorouracil was studied using modified halloysite clay/polymer drug carriers. The effect of the modified and unmodified halloysite was assessed. The swelling behaviour of the prepared materials was investigated, and release profile of the modified halloysite/NaAlg/PVA system was obtained in different pH solutions. The release kinetics of the drug was studied by using 1st order kinetic model (Mulye & Turco, 1995), Higuchi model (Nochos, Douroumis, & Bouropoulos, 2008) and Korsmeyer-Peppas kinetic models (Ritger & Peppas, 1987; Siepmann & Peppas, 2001).

EXPERIMENTAL

Materials

Alginic acid, sodium salt (NaAlg) were supplied from Aldrich Chemical Company Inc. N,N′-Methylenebis (acrylamide) (MBA) as a cross linking agent used in gel preparation and Cetyltrimethyl ammonium bromide (CTAB) were obtained from Sigma-Aldrich. All other chemicals such as phosphoric acid and hydrochloric acid at analytical grade were obtained from Aldrich Chemical Company Inc. Potassium persulfate (PPS) (as initiator) and Polyvinyl alcohol (PVA) were purchased from Merck; 5-Fluorouracil (5-Fl) was supplied from Alfa Aesar company. Buffer solutions were prepared by using Merck products. Halloysite was obtained from Biga, Soğucak village, in Turkey.

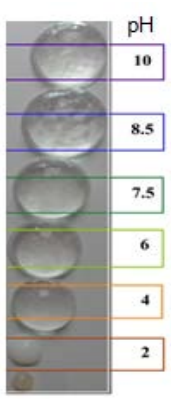
Methods

In this study, controlled release kinetics of the drug active substance 5-Fluorouracil was studied using halloysite/clay/polymer drug carriers. For this purpose, halloysite clay was initially modified with CTAB. Following the modification process, drug carriers were prepared by adding halloysite clays with different quantities in the mixtures of polyvinyl alcohol (PVA) and sodium alginate (1/1) (w/w) and mixed clay-polymer solution (1 and 5 wt % clay) using the ultrasonification technique. MBA (1 wt %) and PPS were added to this mixture. These crosslinked products were evaporated in the teflon petri dishes, until the concentrated gel was obtained. The resulting films were dried under reduced pressure at 80 °C until the films reached a constant weight. The swelling behaviour of the prepared substances was firstly studied in buffer solutions at different pH (2.0; 4.0; 6.0; 7.5; 8.5; 10) (Figure 1a). In order to compare the swelling behaviour of the samples prepared with modified clay, the swelling behaviour of the samples prepared from unmodified

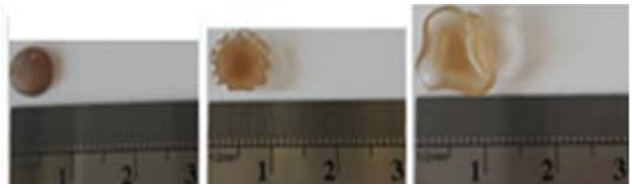
clay was investigated (Figure 2b). The swelling (%) values of clay/polymer hydrogels were calculated using the following equation.

$$\text{Swelling (\%)} = \frac{m_t - m_0}{m_0} * 100 \quad (1)$$

where m_0 and m_t are weight of hydrogel before and after swelling (at time t), respectively. Each measurement has been repeated three times and the average values have been reported. 5-Fluorouracil release in buffer solutions pH (4.0; 8.5) at 37 °C was determined spectrophotometrically using a UV–visible spectrophotometer: T80 Double Beam UV Visible Spectrophotometer PG Instruments at 266 nm.



a)



a)

Figure 1: a) Swelling behaviour of the prepared material using modified halloysite in different pH solutions b) Swelling behaviour of the prepared material using unmodified halloysite (at pH=8.5)

RESULTS

In this study, the swelling behaviour of the clay/polymer drug carriers prepared in buffer solutions was examined. The swelling curves of prepared hydrogels obtained by plotting wt % of swelling as a function of time at different pH are given in Figure 2.

Some of the prepared samples were then used as blanks whereas the rest were loaded with 5-Fluorouracil and their drug release kinetics was observed under a UV-spectrophotometer at 266 nm. Release profiles of the drug active substance were obtained by studying in buffer solutions at different pH (4,0; 8,5) values at 37 °C (Figure 3).

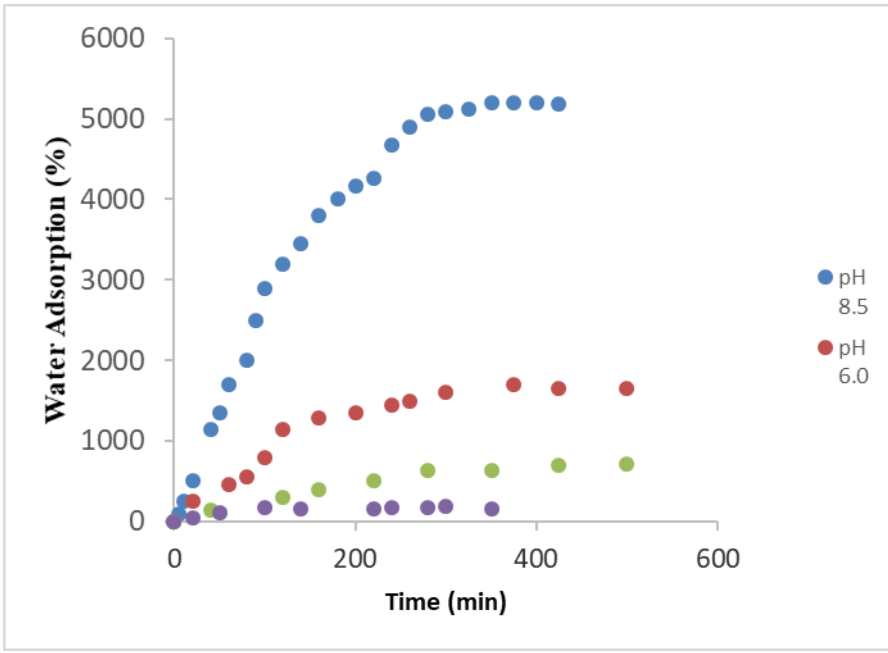


Figure 2: Swelling (wt %) of modified clay/polymer sample as a function of time at different pH

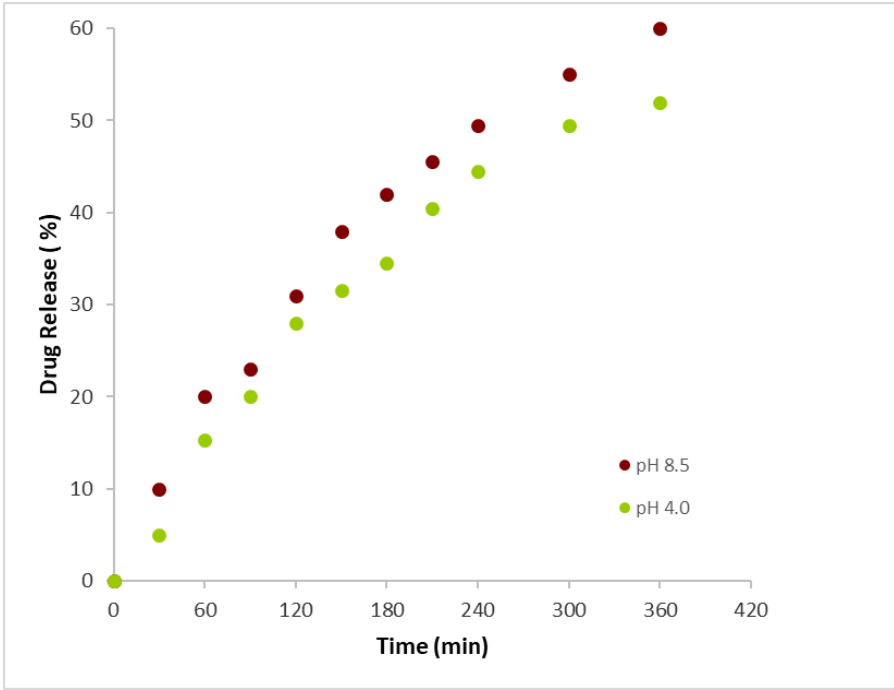


Figure 3: Release profiles of the 5- Fluorouracil in buffer solutions pH (4.0; 8.5) at 37 ^{0}C

To study the drug release kinetics, the experimental data were used for 1st order kinetic model, Higuchi model, and Korsmeyer-Peppas kinetic models. The formulas of these models are given below;

1st order kinetic model can be calculated by;

$$\ln Q_t = \ln Q_0 + k_1 t \quad (2)$$

Higuchi kinetic model can be calculated by;

$$f_t = K_H t^{1/2} \quad (3)$$

Korsmeyer-Peppas kinetic model can be calculated by;

$$\frac{M_t}{M_\infty} = k\, t^n \quad (4)$$

The symbols used in equations 2-4 are;

Q_o: the initial concentration of the drug solution (mg/L).

Q_t: the amount of cumulative drug released at time t.

k_1: first order rate constant.

K_H: Higuchi dissolution constant.

f_t: M_t / M_∞ = drug release rate.

n: coefficient due to drug release mechanism in Peppas model.

DISCUSION

In this study, swelling property of the drug holders prepared by modified halloysite and PVA/NaAlg polymers is more uniform and maximum swelling of sample was obtained at pH=8.5. The maximum swelling time was 5 hours. In the case of unmodified clay samples, the swelling at the same pH is not homogeneous and stable and the hydrogel disintegrates (or collapse) within the first 2 hours. The drug loading studies were completed in 6 hours. 50 % and 60% of drug released were observed at pH = 4.0 and pH = 8.5, respectively.

1st order kinetic model, Higuchi model, and Korsmeyer-Peppas kinetic models were applied to the experimental data. The best fitted model was selected from the adjusted correlation coefficient (R^2) obtained in each linear regression analysis. Comparison the R^2 values obtained from the linear regression analysis of the formulas show the applicability of the models. Drug release kinetics were found to be more appropriate to Higuchi kinetic model. R^2 values are higher output in this model comparing with the other kinetic models. This model showed that the release of the drug from the drug holder is controlled by diffusion and follows the Fick 1st law. This means that drug release occurs until a steady state and kinetic balance is reached between the drug concentration inside and outside the formulation. 1st order kinetic model also fits to the release behaviour of 5- Fluorouracil. This model shows the amount of drug released decreases over time.

CONCLUSION

Halloysite clay/polymer systems were prepared as drug carriers for controlled drug release. The swelling behaviour of the prepared clay/polymer drug carriers was examined in buffer solutions at different pH (2.0; 4.0; 6.0; 7.5; 8.5; 10). Swelling properties of the prepared drug carriers were

more uniform and maximum swelling of sample was obtained at pH=8.5. The maximum swelling time was 5 hours. In the case of unmodified clay samples, the swelling at the same pH is not homogeneous and stable and the hydrogel disintegrates (or collapse) within the first 2 hours. Drug release kinetics was observed under a UV-spectrophotometer, at 266 nm. Release profiles of the drug active substance were obtained by studying in buffer solutions at different pH (4.0; 8.5) values at 37 °C. Three mathematical models: 1st order kinetic model, Higuchi model, and Korsmeyer-Peppas kinetic models were applied to obtained experimental data. It was found that Higuchi kinetic model best describes drug release kinetics of obtained samples, which implies that drug release occurs until a steady state and kinetic balance is reached between the drug concentration inside and outside the formulation. From obtained results it was concluded that prepared drug carriers were suitable for carrying the 5-Fluorouracil drug active substance.

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