SYNTHESIS AND DETERMINATION OF DRUG RELEASE BEHAVIORS OF SHAPE MEMORY MAGNETIC NANOCOMPOSITE FILMS

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ABSTRACT

Developing efficient drug delivery systems ensure that the drug reaches the target tissue at the highest rate without damaging other tissues. Since magnetic nanoparticles can be controlled externally by magnets, and shape memory polymers can be adapted to any tissue, they are both often used in drug delivery systems. In this study, γ-Fe2O3 nanoparticles and a PVA/regenerated cellulose-cotton solution were combined to develop a more advantageous system that is aimed to be effective to use in target-oriented release of cancer drugs.

Keywords : *Magnetic nanoparticle, Shape memory polymer, Drug release*

1. Introduction

1.1. Polymers

Polymers, also known as macromolecules, are large molecules that are formed by the repetition of one or a group of small chemical units called monomers. The word polymer is formed by the combination of the Latin words “poly” meaning numerous and “meros” meaning piece [22, 23] .

Polymers are divided into three groups according to their chain forms: thermoplastics, elastomers and thermosettings (Fig. 1). Thermoplastics, by means of the linear or branched chains in their structure, can be softened, melted and reshaped by the application of heat. They can be easily dissolved with the use of an appropriate solvent.

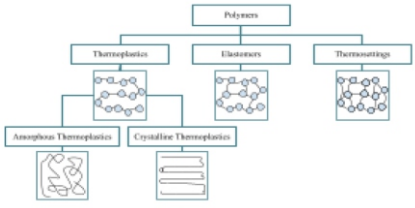


Fig. 1: Classification of polymers depending on the chain structure

The second type of polymers, elastomers which are also known as rubbers, are highly flexible and elastic. Due to the small number of crosslinks between the polymer chains, they can temporarily elongate at a high rate with the tensile effect. The tensile effect causes the polymer chains to slide over each other, but the crosslinks prevent permanent flow, so the molecules return to their original positions when the force is removed.

The third and last type of polymers, thermosettings, are defined as three-dimensional rigid polymers that contain a lot of crosslinks in their structure (network polymers). At high temperatures, they cannot be melted or reshaped, they break down and decompose by breaking the chains and bonds in their structure [19].

Polymeric composites, which are generally obtained from petroleum-derived materials, are materials with a high loading capacity per unit mass, corrosion resistant, easy to process and shape, and suitable for long-term use. There are two types of polymeric composites, the first being thermoset and the second being thermoplastic matrix composites. Thermoset matrix composites are found in liquid form and are first gelled by adding a solidifier and then solidified in order to be shaped. They are frequently used in fibre-reinforced composite making, and during this process, it is often required for them to have a low viscosity. With the effect of heat, can be melted, cooled and solidified, thereby obtaining the ability to be remodeled [11, 12, 16].

1.2. Magnetic Nanoparticles

The word nano means “dwarf” in Greek and denotes one billionth of a unit. Therefore, a nanometer corresponds to one billionth of a meter. Nanostructures are systems consisting of 10-100 atoms, and nanoparticles are nanostructures that are generally between 1-100 nanometers in length [20]. It can be said that there are many subgroups of nanostructures such as nanotubes, nanocrystals, nanowires, nanorods, nanoparticles, and nanofilms. It is seen that nanoparticle production is of great importance for new developments in the field of nanotechnology, owing to its wide application area and superior properties [5, 15].

Nanoparticles could contain materials with different chemical structures such as metals, metal oxides, silicates, organic and carbon materials and biomolecules [17]. The fact that their movements can be easily controlled externally using a magnetic field and their high surface area/volume ratio make magnetic nanoparticles suitable for use in biology, medicine and many more fields, including diagnosis and treatment of numerous diseases, drug delivery, bio-labelling, separation or purification of biomolecules, and medical imaging [3, 24].

Essentially, two approaches are followed for the production of nanoparticles, namely top-down and bottom-up. The top-down approach is based on the separation of the material into nano-sized pieces by energising the volumetric material from the outside by mechanical, chemical or different processes (Fig.2). The bottom-up approach, on the other hand, is the opposite of the top-down approach, aiming to create particles by growing atomic or molecular structures through chemical

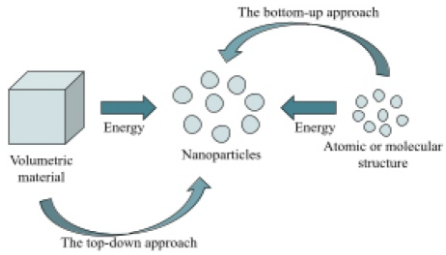


Fig. 2: Procedures used in the production of nanoparticles

One of the main contents of nanoparticles, iron oxides are formed as a result of the chemical combination of iron and oxygen, and approximately 16 types of iron oxide have been identified to date [4]. Since iron oxides, which can be found in many geological and biological processes, are not very sensitive to oxidation, they can maintain the stability of their magnetic effects [20]. Fe_3O_4, α-Fe_2O_3 and γ-Fe_2O_3 are the most common forms of iron oxides in nature. Among these three forms, Fe_3O_4 and γ-Fe_2O_3 nanoparticles have attracted more attention with their superparamagnetic properties, low toxicity, and high surface area/volume ratios. Iron oxide nanoparticles can be used in various biomedical applications such as drug delivery, magnetic resonance imaging (MRI), and protein immobilization, as well as in coating, concrete and paint production [1, 13].

1.3. Smart Materials

Such as diodes and photovoltaics colour or phase-changing, light-emitting piezo materials are defined as smart materials. There are also smart materials that are designed to respond to a stimulating source or that provide optimum interaction by changing the geometry, electromagnetic character and mechanical/physical properties of the molecule [21]. With the current technology, it is possible to produce polymer-based smart materials with different properties that are sensitive to various conditions such as humidity, pH, temperature, light, magnetic field and solvent in the environment [6, 8].

Shape memory polymers, which have the ability to change shape depending on various variables in the environment and then return to their permanent shape, are one of the most frequently used smart polymer types. In recent years, thermosensitive shape memory polymers have been given importance in studies on shape memory polymers due to their wide application area, especially in materials engineering, textile and biomedical devices. In the structure of thermosensitive shape memory polymers, there are often physical or chemical cross-linked points such as various crystals, intertwined chains or amorphous hard segments, which allow their permanent shape to be retained in memory [9].

In addition to their shape memory properties, smart polymers also have the ability to carry about a thousand times their weight. This is due to the high energy released during some property changes. The usability of these polymers, which can easily return to their original shape at body temperature, in the biomedical field is an important research topic. Smart polymers are especially preferred in different biomedical applications such as artificial skin, surgical sutures and drug release. One of the areas where smart biomaterials are frequently used is drug release systems that enable the active substance to be delivered to the target in the body. The sensitivity of smart polymers to properties such as temperature and pH allows the desired change to be made in the desired area of the body, even when a slight difference occurs [21].

2. Method

2.1. Synthesis of Iron (III) Nanoparticles

For this method, after weighing 6.06 and 11.75 grams of ferrous sulfate heptahydrate ($FeSO_4.7H_2O$) and non-hydrated ferric chloride ($FeCl_3$), they were first mixed in 100 mL of distilled water in an ultrasonic environment and then in the ultrasonic water bath without applying heat. 25 mL of 25% ammonium hydroxide solution was added dropwise to the clear solution obtained, and then the resulting precipitated solution was stirred and heated in an ultrasonic environment for 60 minutes. After the resulting brown precipitate was filtered, it was washed with distilled water until pH=7. Afterwards, the precipitate was dried at 70°C for 12 hours and prepared for the analysis [10].

2.2. Preparation of Shape Memory Polymers

In order to prepare the RC-C (regenerated cellulose-cotton) solution, necessary amounts of NaOH, urea and distilled water with a weight ratio of 7:12:81 were used to obtain an aqueous solution in a 250 mL beaker and the resulting solution was cooled. After the cotton, which was previously decomposed in H2SO4, was added to this solution, the solution was mixed vigorously. Then, this solution was centrifuged to remove bubbles and insoluble substances and was taken to a 4°C environment [7, 14] (Fig. 3).

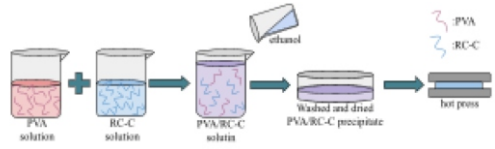


Fig. 3: Preparation of PVA/RC-C composites

The solution consisting of 8 g PVA and 92 g distilled water was heated to 98°C and mixed to obtain 8% by weight PVA solution. Afterwards, the PVA and RC-C solutions were mixed for 30 minutes, and the resulting solution was co-precipitated by adding more ethanol. The precipitate was washed with water, then soaked and dried for several days at 60°C for 4 hours to remove any remaining NaOH and urea. After drying, the PVA/RC-C precipitates were hot pressed at 110°C for 3 minutes [7]. At the end of these processes, γ-Fe_2O_3 nanoparticles were placed into the shape memory polymer at 1%, 2.5% and 5% ratios, and the preparation of shape memory nanocomposite film samples was completed.

2.3. Characterisation of Nanocomposite Films

At this stage, the determination of morphological characteristics of shape memory magnetic nanoparticles were carried out by examining the samples containing 1%, 2.5% and 5% γ-Fe_2O_3 nanoparticles and no nanoparticles with a light microscope.

After that, a dynamic mechanical analyzer was used to analyze the mechanical properties of shape memory magnetic nanocomposites. The tensile strengths of each sample under a force of 1N were calculated.

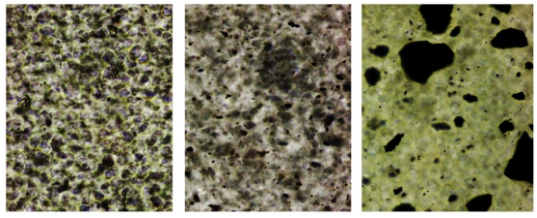
In order to examine the drug release behaviour of nanocomposite films, a certain amount of samples were transferred into 50 mL buffer solutions, then the solutions were placed in a shaking water bath. Drug release tests lasted for 120 hours in pH=1.2 HCl acid solution and pH=7

phosphate buffer. To determine the amount of clarithromycin released from the nanocomposites, 0.5 mL samples were taken from the solutions per hour and to calculate the concentrations of the samples, absorbance values at 760 nm wavelength were determined and the calibration chart was used [18].

3 Conclusion and Discussion

3.1. Determination of Morphological Characteristics of Shape Memory Magnetic Nanocomposite Films

As a result of the investigations to determine the morphological properties of the prepared nanocomposite films, as shown above, it was seen that the magnetic γ-Fe_2O_3 nanoparticles showed a homogeneous distribution in the shape memory polymer (Fig. 4a-c).



a b c

Fig. 4: Microscopic image of nanocomposite film samples containing a) 1 , b) 2 and c)5 % magnetic nanoparticles, respectively

3.2. Determination of Mechanical Endurance of Shape Memory Magnetic Nanocomposite Films

It is seen that the mechanical endurance of the samples containing nanoparticles is prominently higher than the mechanical endurance of the control sample without magnetic nanoparticles (Table 1). Additionally, it was determined that among the nanocomposite films containing nanoparticles, the sample with the highest mechanical endurance was the sample with 5% nanoparticles, and the sample with the lowest mechanical endurance was the sample with 1% nanoparticles.When the table is examined, it can be seen that the mechanical endurance of the sample with the least amount of nanoparticles increased by 173%, and the sample with the highest amount of nanoparticles increased by 227% compared to the sample without nanoparticles. It was observed that the mechanical endurance of the sample containing 5% nanoparticles reached approximately 3.5 times that of the sample without nanoparticles. The high mechanical endurance ensures that the drug delivery system is not damaged until the drug is delivered to the required tissue, therefore significantly increasing the efficiency of the drug delivery system.

Table 1: The mechanical endurance increase percentage of the samples containing nanoparticles compared to the control sample

Sample	Mechanical Endurance (MPa)	Mechanical Endurance Increase (%)
control	18.38	-
1%	50.15	173%
2.5%	55.86	204%
5%	60.15	227%

3.3. Determination of Drug Release Behaviors of Synthesized Shape Memory Magnetic Nanocomposite Films

It can be easily seen that samples containing nanoparticles have much higher drug loading capacities than the control sample. It was determined that the drug loading capacities of nanoparticle-containing samples are twice the sample without nanoparticles (Table 2) (Fig. 5).

Table 2: Drug loading rates for nanocomposite films with 1%, 2.5% and 5% magnetic nanoparticles

Sample	Drug Loading Rates
control (0%)	48.75%
1%	97.15%
2.5%	99.8%
5%	95.6%

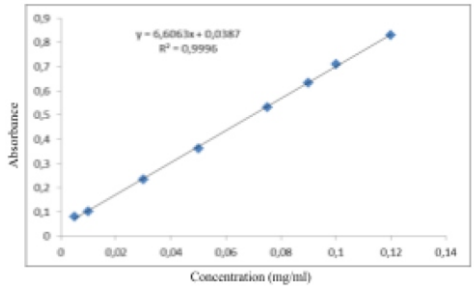


Fig. 5: The standard calibration chart prepared for clarithromycin

In figures (6-9), the drug release amounts of nanocomposite films in the first 10 and 120 hours in environments with pH levels of 1.5 and 7 are given. In both graphs, it is seen that the drug release rates of the samples containing nanoparticles are higher than the samples that do not contain them. Considering that the drug release amounts of the samples containing 5% nanoparticles reached 100% at the end of the 120th hour, it was revealed that the prepared drug release system was more efficient in terms of drug release amount from the shape memory polymer. The fact that the samples containing nanoparticles released at high rates and close to each other in both environments with different pH levels indicate that the synthesised nanocomposite films are compatible with different environments. When the samples containing nanoparticles are compared with each other, it can be concluded that the increase in the nanoparticle ratio will positively affect the drug release, based on the fact that the highest release rate is observed in the sample containing 5% nanoparticles in both samples.

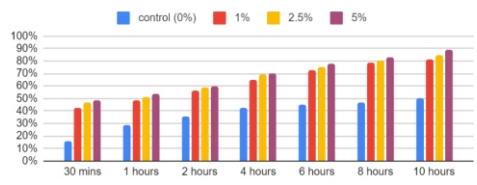


Fig. 6: First 10-hour release graph for pH=1.5

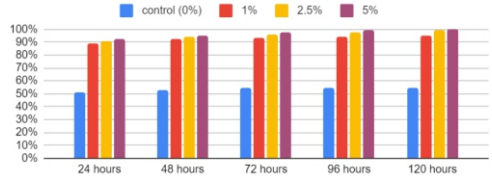


Fig. 7: First 120-hour release graph for pH=1.5

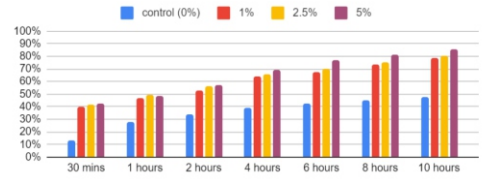


Fig. 8: First 10-hour release graph for pH=7

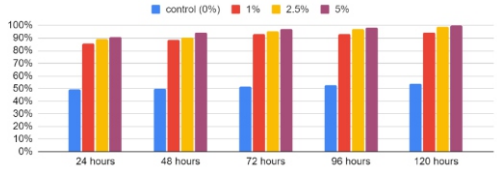


Fig. 9: First 120-hour release graph for pH=7

4. Conclusions

In this study, shape memory magnetic nanocomposite drug carrier polymeric systems, which have not been encountered before in the literature, have been developed. Since it is a fairly new field of study in the scientific world, our study has been very promising in terms of developing new generation drug delivery systems after its biocompatibility has been proven by testing it in cells and tissues in the next stages. Besides, it is known that magnetic nanoparticles have the advantage of being able to control with magnets. It is predicted that the nanocomposite films that we have synthesized using this advantage will be very successful, especially in the controlled and target-oriented direction of cancer drugs. Likewise, since these magnetic nanoparticles are excellent heat conductors after they are delivered to the target tissue, they can be brought to the desired temperature from the outside and used to release the drug at the desired temperature.

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