Study of the Release Kinetic and the Diffusion Coefficient of Doxorubicin-Chrysin Coated with Fe_3O_4 and Polycaprolactone-Polyethylene glycol Copolymers

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ABSTRACT: *Recent advances in the development of magnetic nanoparticles modified with biodegradable polymers have shown promise in the improvement of therapeutic approaches for the clinical management of cancer patients. In this study, polycaprolactone -polyethylene glycol – polycaprolactone (PCL-PEG-PCL) copolymers modified with magnetic nanoparticles were used for encapsulation of doxorubicin (DOX) and chrysin (Chr) anticancer drugs by dual emulsion (W / O / W). The effect of temperature and pH on drug release was investigated. The release of the doxorubicin drug in pH 7.4 and 5.8 were 26.5% and 30.6%, respectively after 144 h. In chrysin drug, the release of drug in pH 7.4 and 5.8 was equal to 45% and 49%, respectively after 144 h. The kinetics of the drug's release was also studied based on zero-order, first-order, Higuchi, and Korsmeyer-Peppas models. From the kinetic models, based on the correlation coefficient, Higuchi (R^2=0.9017) and Korsmeyer-Peppas (R^2=0.9639) models were found to be the best models for doxorubicin and chrysin, respectively. After performing kinetic studies, the diffusion coefficient of drug release was also studied. The drug distribution was considered uniform, and the system was investigated in Cartesian and spherical coordinates. The results showed that the diffusion coefficient of drug release followed Fick's law. The diffusion coefficient decreased with increasing time due to decreasing the concentration difference.*

KEYWORDS: *Magnetic nanoparticles; Doxorubicin; Chrysin; Diffusion coefficient; Drug release.*

INTRODUCTION

In recent years, several novel technologies reported for the development of an effective drug delivery system. Nanotechnologies could be employed as novel solutions for the handling of many diseases. The invention of tools with the nanoscale has opened wide horizons to treat and distinguish diseases. Especially, this event has been a vital case for the diagnosis of cancer and its control, the preparation of medicinal carriers, imaging devices, and bio-sensor [1-3]. These systems can easily intercommunicate with the biological molecule in the cells level and their inside and also access to the spot of the body that already was not imaginable [4]. In the last 25 years, more methods

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have been used to treat cancer. New treatments have been aimed such as the function of blood globules that cause to feed cancerous cells and the use of purposive medicinal compounds that have very accurate functions [5-8].

Different types of polymers are the most important materials for preparing compatible compounds in a biological environment. Among them, synthetic copolymers are being considered most in nanotechnology that has controlled structures and adjusted physical and chemical features. The main aim in designing the effective delivery system of the drug is being purposive drugs in cells or special tissues of the body that have caused to increase in the treatment effects of drugs, decrease the side effects of drugs, and the treatment dose of drugs, and finally to improve the physical and chemical features. Magnetic nanoparticles and synthetic copolymers have been able to access these aims and satisfy limitations such as lower absorption, low solubility, low stability, explosive drug release, and deformed encapsulation of drugs [9, 10]. Furthermore, the problems related to the poor solubility and absorption of drug systems have been removed increasingly, because the improvements in structures in dual hydrated copolymers that are composed of hydrophobic and hydrophilic monomers have developed. It can be said that putting the particular ligands on the surface of nanoparticles is used to connect them to particular cellular receivers and purposive delivery of drugs in cells [11,12].

Smart polymer systems have a significant change in properties with small changes in the environment. The most important of these systems from a biomedical point are those that are sensitive to pH or temperature. The human body has different pH throughout the digestive system. This change in pH is also observed in other tissues (for example, in tumors) and intracellular components. Thermosensitive polymers with transition temperatures close to physiological values offer many possibilities in the biomedical field [13,14]. The main role of the copolymer in these systems is the regulation of drug release kinetics to achieve a sustained and controlled release. This is made possible due to the ability to modify the biodegradability of the copolymer by altering its chemistry, molecular weight, stoichiometry, functionalization of the terminal groups, and changing its size, shape, and porosity. The drug release of medicinal nanoparticles is the main determinant of biological effect. Therefore, the kinetic assessment of drug release has exclusive importance in this area. Almost the use of kinetic models is helpful to explain the diffusion mechanism that in turn it can be used to control the drug release. Another advantage is that information about releasing is shown with one or two parameters. In addition, one kinetic parameter can be used to study the effects of formulation factors on drug release for the optimized and controlled release [15-19].

Doxorubicin is known as a potent anticancer agent against a wide range of cancers that has been related to the production of reactive oxygen species (ROS). Particularly, detoxification of DOX is related to reactions with GSH in order to the formation of DOX specific GS-X conjugates. On the other hand, the overexpression of Glutathione transferases (GSTs) is observed in various tumor cells. Thus, the conjugation of DOX to GSH is considered as a significant detoxification process that can be facilitated by glutathione transferases GSTs. However, metabolites of DOX is readily eliminated by different multi-drug resistance proteins (MRPs) from the cell. The investigations demonstrated that the flavonoid-induced glutathione (GSH) efflux in the presence of MRPs and following intracellular GSH level reduction is a sustainable approach to sensitize tumor cells toward chemotherapy [20, 21]. Chrysin (Chr), as a natural flavonoid is known as a biologically active compound. Glucuronide and chrysin sulfate as main metabolites of chrysin are substrates for MRPs. However, the low solubility of this drug in water has limited its application. Some of these limitations can be overcome by using polymeric nanoparticles [22,23].

Magnetic nanoparticles account for a large part of nanomaterials and are used in diagnosis and clinical treatments due to their magnetic properties and very little toxicity in the body compared to other nanoparticles [24]. They are easily converted and removed from the body. The other advantage of magnetic nanoparticles is their use in targeted drug delivery, which is precisely directed to the cancer cell by applying an external magnetic field [13].

There are various methods for preparing magnetic nanoparticles such as co-precipitation method, thermal decomposition, microemulsion, hydrothermal synthesis, and sonochemical synthesis. The co-precipitation method has more advantages than other methods because it takes a little time to do it, the distribution size of the particles is less,

the chemicals used are cheap and accessible, the reaction temperature is low and the reaction yield is high [25, 26]. To increase the therapeutic and diagnostic power of magnetic nanoparticles, they should usually be coated with different polymers. These coatings must be biocompatible with the ability to be transformed in the biochemical environment of the body with minimal toxicity [13, 27, 28].

In recent years, several studies have been conducted on the encapsulation of chrysin and doxorubicin drugs, but the dual encapsulation of chrysin and doxorubicin in PCL-PEG-PCL magnetic nanoparticles has not been reported [27, 29, 30].

In this research, magnetic nanoparticles coated with PCL-PEG-PCL have been reported as a successful delivery system for the drug. Kinetic studies of the drug release were carried out to study the release of anti-cancerous drugs of doxorubicin and chrysin capsulated in polycaprolactone polyethylene glycol copolymer that had been modified by magnetic nanoparticles and then mass transfer and changes of the diffusion coefficient of drug release were studied.

EXPERIMENTAL SECTION

Materials and methods

Caprolactone, polyethylene glycol, stannous octoate, polyvinyl alcohol (PVA), chrysin, and doxorubicin hydrochloride were prepared from Sigma-Aldrich (USA). Ferrous chloride tetrahydrate, ferric chloride hexahydrate, and ammonium hydroxide (32 wt%) were purchased from Fluka. The pore structure and particle morphology were characterized by scanning electron microscopy (SEM, KYKY-EM3200). Dynamic light scattering (DLS) was used to measure the particle size distributions of dispersed supports (Nano Series, Malvern Instrument, UK). The magnetic properties were studied by a vibrating sample magnetometer (VSM, Meghnatis Daghigh Kavir). The drug-loading capacity was measured using an ultraviolet-visible spectrometer (Shimadzu).

Encapsulating the drugs

In this research, magnetic nanoparticles were prepared by the conventional co-precipitation method. The synthesis steps are shown in Fig. 1.

The ring-opening polymerization method was used to synthesize biodegradable copolymer of polycaprolactone-polyethylene glycol. Ethylene glycol (1.5 g) and -caprolactone (3.7 g) in a dry three-necked flask were heated at 130ºC under the nitrogen atmosphere to complete melting. Then, the polymerization was completed by adding $Sn(Oct)_2$ (0.05% (w/w)) at 180ºC for 6 h. Subsequently, the product was dissolved in dichloromethane and precipitated in cold diethyl ether, and the copolymer was dried under the vacuum for 48 h at 50ºC.

The anti-cancerous drugs were obtained with the dual emulsion method (W/O/W) that consisted of magnetic nanoparticles copolymer. In the one step, Doxorubicin (11.2 mg), Chrysin (11.2 mg), and Fe_3O_4 nanoparticles (10 mg) were added to 200 mg copolymer in 15 mL dichloromethane. The obtained mixture was sonicated (20,000 rpm, 48.15 s) for the formation of the emulsion (w/o). Then, the mixture of containing of the emulsion (w/o) and PVA (polyvinyl alcohol) (50 mL, 0.5%) was sonicated (70,000 rpm, 2 min) to obtained the emulsion (w/o/w).

After the evaporation of the organic solvent of emulsion (w/o/w), the nanoparticles were centrifuged at least for three times at 12000 rpm for 15 minutes in the each of cycles. Next, the participated nanoparticles were freeze-dried. Finally, the filtration of nanoparticles was achieved by using of a 1.2 mm filter (Millipore, Bedford, MA). The concentration of drugs was determined by spectrophotometer at 484, 348 nm for DOX and Chr respectively. More details about the synthesis method, optimization of most important parameters on encapsulation efficiency, and features of synthesized samples are explained in previous studies [28].

The release tests of drugs

At first, 3mg of lyophilized nanoparticles containing doxorubicin-chrysin was suspended in 3.0 mL of phosphate buffer solution (0.5 molars) (0.35% moles of disodium hydrogen phosphate with pH 7.4). The solution was placed on a shaker incubator at 37ºC. 3.0 mL of transparent solution was sampled for 7 days at certain periods and at the same time, 3.0 mL of phosphate buffer solution was replaced with it. Finally, after 7 days, 20 samples were prepared and then samples were collected and the doses of chrysin and doxorubicin were measured by spectrophotometer UV and calibration curve. This test

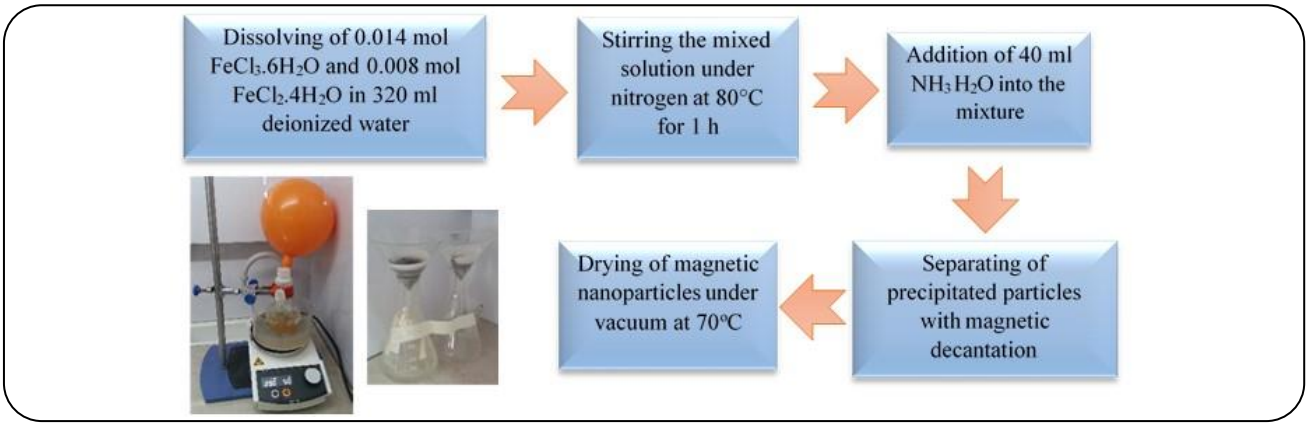

Fig. 1: Synthesis steps of Fe_3O_4 magnetic nanoparticles.

was repeated to study the effect of pH on the released drug in an acid acetate buffer solution at pH 5.8 and 40ºC [28].

Kinetic studies of the release drugs

The kinetic studies about releasing encapsulated drugs were carried out based on four models of zero order model, first order model, higuchi model, and Korsmeyer-Peppas model.

Zero order model is an ideal model in the release drugs and it is expected that this model can be suitable for drugs that their levels must be fixed on blood. For example, cardiac drugs and controller drugs of blood pressure comply with this model. In this model, the amount of resolved drug is independent of the initial amount of drug:

$$Q_t = k_o t + Q_o \quad (1)$$

In this relationship, Q_t is the amount of resolve drug for time t, k_o is the constant of the drug rate. And Q_o is the initial amount of drug in buffer that almost is equal to zero.

First order model describes the absorption or excretion kinetic of some drugs. The drug release that is accordance with first order model, is explained as follow:

$$dC/dt = -kC \quad (2)$$

In this relationship, K is the constant of first-order rate that is expressed in the time unit. This expression can be defined as C_o showing the initial concentration of the drug.

$$\log C = \log C_o - k_t/2.303 \quad (3)$$

The Higuchi model uses homogeneous matrixes to describe the drug release. In this state, the drug release is checked and controlled by the diffusion of solutions in the matrix and follows the releasing mechanism from diffusion. In this model, there is a relationship between the amount of resolved drug and the square root of time that Q_t is the amount of released drug at the moment t, and k is the constant of Higuchi rate. In this model, there is a relationship between the amount of resolved drug and the square root of time [31]:

$$Q_t = kt^{0.5} \quad (4)$$

Korsmeyer-Peppas model is the most comprehensive and semi-experimental equation to describe the release of drugs. This model is accorded to power law that was designed by *Korsmeyer et al.* (1983). Due to determining the drug release mechanism, 60% of the initial release data must be accorded to this model. Korsmeyer-Peppas Equation is expressed as equation 5 [32]:

$$\log(M_t/M_\infty) = \log k + n \log t \quad (5)$$

where M_t, is defined as the mass of drug released at time t, and M_∞, is the mass of drug released as time approaches infinity. M_t/M_∞ is the fraction of the drug release until t.

Diffusion coefficient

Mathematical modeling of drug release can be very helpful to understand the mechanisms controlling drug release. Diffusion is defined as the grid removal of molecules through the concentration gradient that Fick's law of diffusion was used to study [33].

Fick's second law of diffusion in Cartesian and spherical coordinate systems is expressed as relations 6 and 7, respectively.

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} \quad (6)$$

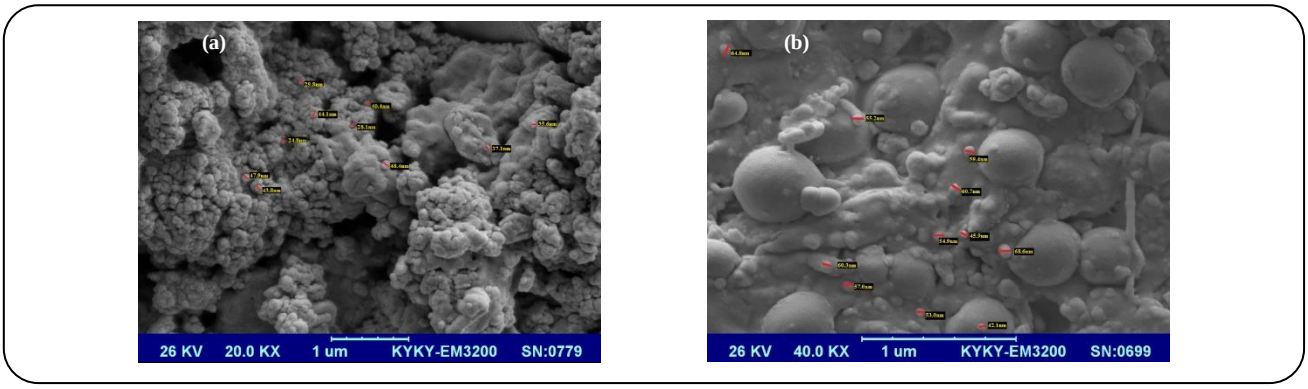

Fig. 2: SEM image of (a) pure magnetic nanoparticles and (b) drugs loaded with magnetic-copolymer nanoparticles.

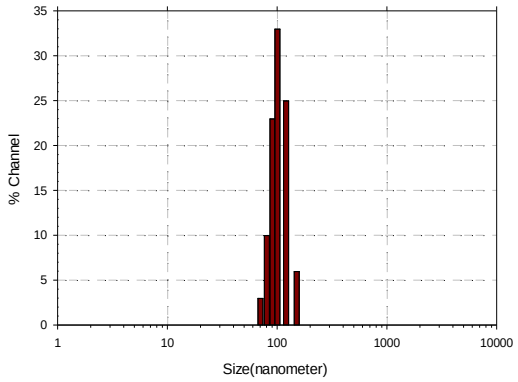

Fig. 3: The size distribution of magnetic-copolymer nanoparticles.

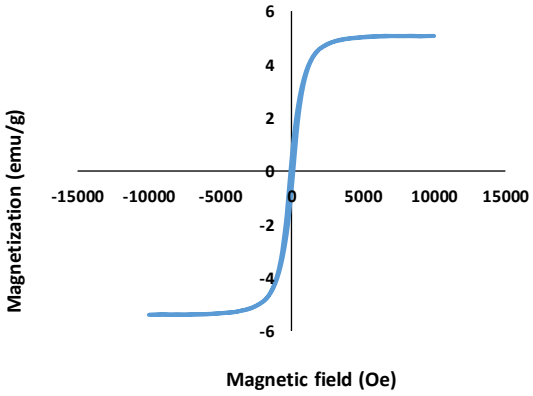

Fig. 4: Room temperature (298K) magnetization curve for Fe_3O_4/PCL-PEG/Drug.

$$\frac{\partial c}{\partial t} = \frac{D}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c}{\partial r}\right) \quad (7)$$

In this equation, c shows the drug concentration and D shows the diffusion coefficient [34].

RESULTS AND DISCUSSIONS

Characterization

SEM image of pure magnetic nanoparticles and drugs loaded with magnetic-copolymer nanoparticles are shown in Fig. 2. The SEM results revealed that the particle size of the drug-encapsulated magnetic modified nanoparticles was less than 100 nm.

Fig. 3 shows the DLS results of magnetic-copolymer nanoparticles. As shown in this picture the average size of particles was 100 nm with narrow size distribution. This result is in agreement with SEM images.

The magnetization curve of the synthesized sample at room temperature (298 K) was obtained by the use of a vibrating sample magnetometer (VSM) (Fig. 4). The saturation magnetization of drugs encapsulated with the copolymer, was found to be 5 emu/g, that is, less than for the pure Fe_3O_4 nanoparticles (61 emu/g). This difference suggests that a large amount of polymer encapsulated the Fe_3O_4 nanoparticles and drugs. With such saturation magnetization, drug-encapsulated Fe_3O_4 modified with PCL–PEG copolymer could be separated from the reaction medium in a magnetic field.

Drug release

pH measurement of extracellular liquids of solid tumors has shown that acidic pH is suitable for the growth of solid tumors. In according to this truth, nanoparticles sensitive to pH contained of anticancer drugs have been obtained and prepared. Since the release of doxorubicin-chrysin of Fe_3O_4-PCL_{1000}-PEG_{4000}-PCL_{1000}-Dox-Chr in pH 5.8 happens more than pH 7.4, it can be expected that drug release percent in acidic environment of extracellular

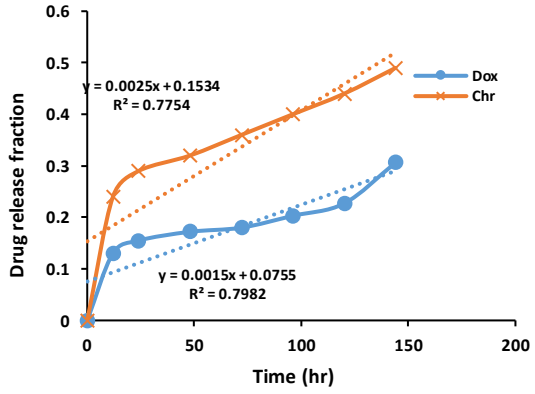

Fig.5: Drugs release kinetics for zero-order model.

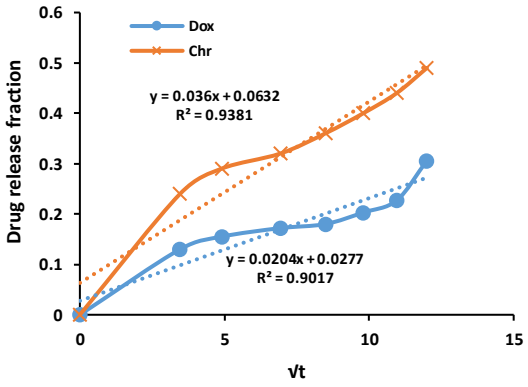

Fig.7: Drugs release kinetics for Higuchi model.

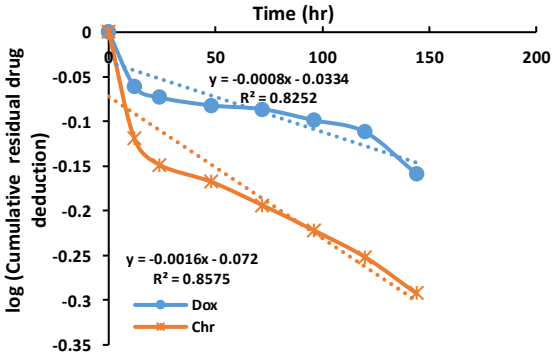

Fig.6: Drugs release kinetics for first-order model.

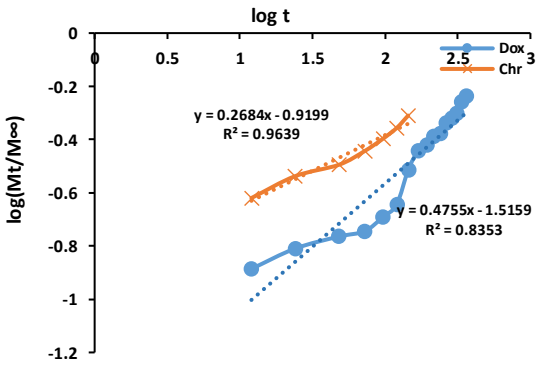

Fig. 8: Drugs release kinetics for Korsmeyer-Peppas model.

liquid of the tumor has been better than other cells. The release of doxorubicin drug in pH 7.4 and 5.8 was obtained as 26.5% and 30.6%, respectively after 144 h. in chrysin drug, the release of drug in pH 7.4 and 5.8 was equal to 45% and 49%, respectively after 144 h.

Kinetic studies of the drug release

Kinetic studies about the release of the capsulated drugs were conducted in pH 5.8, based on four models zero-order model, first-order model, Higuchi model, and Korsmeyer-Peppas model, and were been shown in Figs. 5 to 8. The obtained data from mentioned models were fitted and evaluated according to the correlation coefficient R^2 in Table 1. In the case of doxorubicin, the correlation coefficient number of the Higuchi model was higher than other models (R^2=0.9017) and the data fit better with this model. Therefore, it can be concluded that the release of the doxorubicin drug follows the Higuchi model and shows a controlled intruded delivery. When the value of R^2 is higher and closer to one, the data fits better with the model, and the most suitable model can be. In this research, according to the correlation coefficient, the release of chrysin drug from polymer magnetic nanoparticles followed the Korsmeyer-Peppas model (R^2=0.9639). For determining drug release mechanism, 60% of basic release data must be accorded to this model that there is this correspondence. In this model, if n <0.45, we will have a Fick diffusion. According to the value reported for the constant n, which is the slope of the Korsmeyer-Peppas diagram in Table 1 (n=0.2684), it can be seen that the mechanism of drug delivery from the nanoparticle system follows Fick's law of diffusion [31].

Calculating the diffusion coefficients for the drug release in Cartesian system

Diffusion is called a network displacement of molecules due to gradient concentration for its studying,

Table 1: Results of Different Models in Terms of R^2, Slope and Intercept.

Model Name	Slope		Intercept		R^2	
	Doxorubicin	Chrysin	Doxorubicin	Chrysin	Doxorubicin	Chrysin
Zero order	0.0015	0.0025	0.0755	0.1534	0.7982	0.7754
First order	-0.0008	-0.0016	-0.0334	-0.072	0.8252	0.8575
Higuchi	0.0204	0.036	0.0277	0.0632	0.9017	0.9381
Korsmeyer-Peppas	0.4755	0.2684	-1.5159	-0.9199	0.8353	0.9639

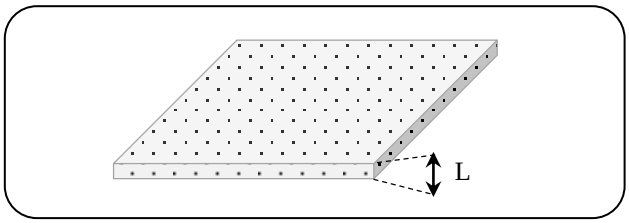

Fig. 9: Scheme of thin polymer slab of thickness L (The dots represent dissolved drug molecules)

Fick's law of diffusion was used. In this part, drug distribution was considered uniform and the release happened from a one-dimensional and isothermal thin polymer slab of thickness L (Fig. 9). The system is initially maintained at a constant uniform drug concentration, C_1, and its surfaces are kept at a constant drug concentration, C_0. So the appropriate initial and boundary conditions for Fick's second law of diffusion in the x direction (equation 6), may be written as equations 8 and 9. [34, 35]

$$t = 0 \qquad -\frac{L}{2} < x < \frac{L}{2} \qquad C = C_1 \tag{8}$$

$$t > 0 \qquad x = \pm\frac{L}{2} \qquad C = C_0 \tag{9}$$

The solution to Fick's law in the form of a trigonometric series under the above conditions is equation 10. M_t/M_∞ is the drug release fraction and D is the drug diffusion coefficient in the system and L is total thickness. [32, 33].

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2}\sum_{n=0}^{\infty}\frac{\exp\left(-\frac{D(2n+1)^2\pi^2 t}{L^2}\right)}{(2n+1)^2} \tag{10}$$

For small times, equation 10 can be approximated with equation 11. The short-time approximation is valid for the first 60% of the total released drug.

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\pi L^2}\right)^{\frac{1}{2}} \qquad \frac{M_t}{M_\infty} \leq 0 \cdot 6 \tag{11}$$

The size distribution of encapsulated drug particles was between 70 and 150 nm. To study the changes in the diffusion coefficient for different thicknesses, the diffusion coefficient was obtained by the placement of the release drug fraction into equation 11 in different thicknesses of 70, 100, and 150 nm.

In Fig. 10 (a, b, and c), the diffusion coefficient changes according to time were been shown for drugs of doxorubicin and chrysin in different thicknesses. Always the current moves from one area with a higher concentration to an area with a lower concentration. In the early times, because the concentration difference of the drugs is high, the diffusion coefficients is higher, but with the passage of time and with the decrease of the concentration difference, the diffusion coefficients decreases and remains constant [34].

Calculating the diffusion coefficients for the drug release in spherical system

In this part, drug distribution was considered uniform and the system was assumed to be a one-dimensional radial release from a sphere of radius R (Fig. 11). The system is initially maintained at a constant uniform drug concentration, C_1, and its surfaces are kept at a constant drug concentration, C_0. So the appropriate initial and boundary conditions for Fick's second law of diffusion in the r direction (equation 7), may be written as equations 12 and 13 [34, 35].

$$t = 0 \qquad 0 < r < R \qquad C = C_1 \tag{12}$$

$$t > 0 \qquad r = R \qquad C = C_0 \tag{13}$$

The solution to Fick's law under the above specified conditions is equation 14. In early times for release fraction less than 0.4, the approximate solution was obtained with equation 15. Then diffusion coefficient was obtained by the placement of the release drug fraction into equation 15 in radius 50 nm.

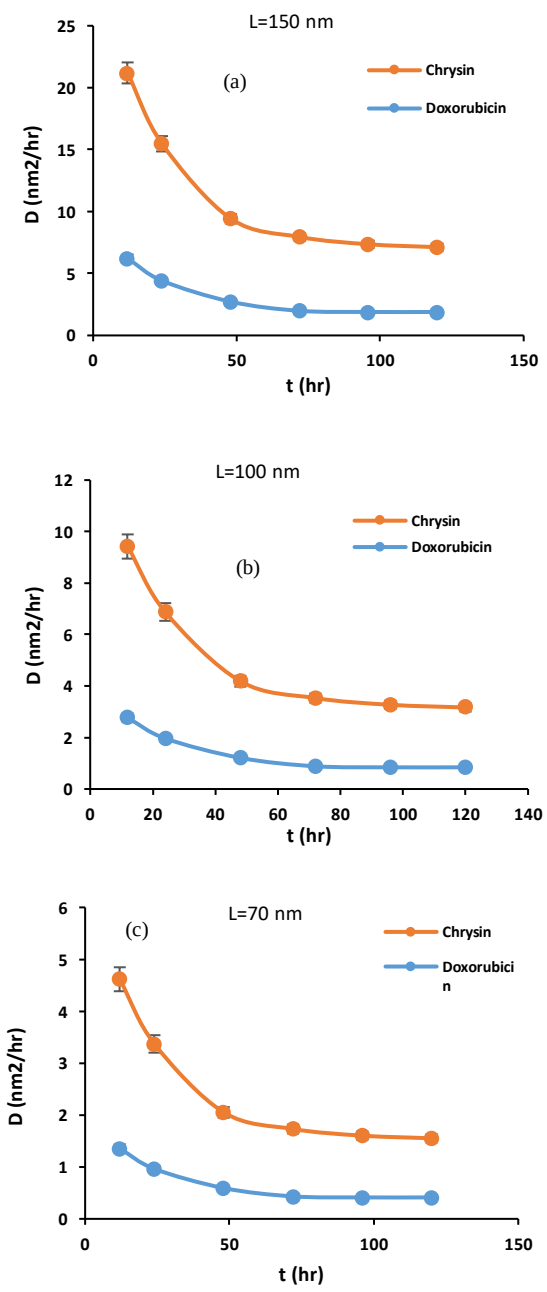

Fig. 10: Time-varying diffusion coefficients for doxorubicin and chrysin (a) L=150 nm (b) L=100nm (c) L=70 nm.

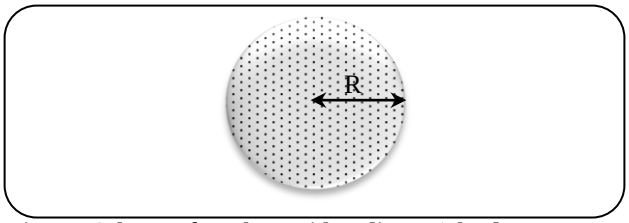

Fig. 11: Scheme of a sphere with radius R (The dots represent dissolved drug molecules).

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{\exp\left(-Dn^2\pi^2 t/R^2\right)}{n^2} \qquad (14)$$

$$\frac{M_t}{M_\infty} = 6\left(\frac{Dt}{\pi R^2}\right)^{\frac{1}{2}} - \frac{3Dt}{R^2} \qquad \frac{M_t}{M_\infty} < 0\cdot 4 \qquad (15)$$

In Fig. 12, the diffusion coefficient changes according to time were been shown for drugs of doxorubicin and chrysin in radius 50 nm.

CONCLUSIONS

Considering the importance and application of magnetic nanoparticles in drug delivery, in this research work, Fe_3O_4 nanoparticles were prepared by use of the co-precipitation method. Copolymer nanoparticles of PCL-PEG-PCL were synthesized through ring-opening polymerization. Then, the process of dual drug encapsulation of DOX and Chr in PCL-PEG-PCL magnetic nanoparticles was followed by the double emulsion method (w/o/w). After studying and approving the synthesized structures, in-vitro (drug release) investigations were accomplished. The amount of drug dislodgement was studied in different pHs. In acidic pH (pH=5.8), this amount is more than neutral and base. Its main reason is that these nanoparticles are easily transformed in an acidic environment. Meanwhile, since the extracellular liquid of the tumor has an acidic environment, then drug release is achieved very well in this environment.

The kinetics of the drug's release was studied based on zero-order, first-order, Higuchi, and Korsmeyer-Peppas models. From the kinetic models, Higuchi and Korsmeyer-Peppas models were found to be the best models for doxorubicin and chrysin respectively based on the correlation coefficient (R^2 = 0.9017 for doxorubicin and R^2 = 0.9639 for chrysin). The study of diffusion coefficient changes was done based on Fick's law of diffusion. The drug distribution was considered a uniform and the system was assumed in Cartesian and spherical coordinates. At first, the diffusion coefficient of the two drugs was more because of the high concentration difference of drugs in early times but after passing time, the diffusion coefficient was decreased and fixed.

Application of nano drugs, especially magnetic nanoparticles coated with biocompatible polymers could be considered a sure and very convenient and low-cost method instead of the traditional and accepted

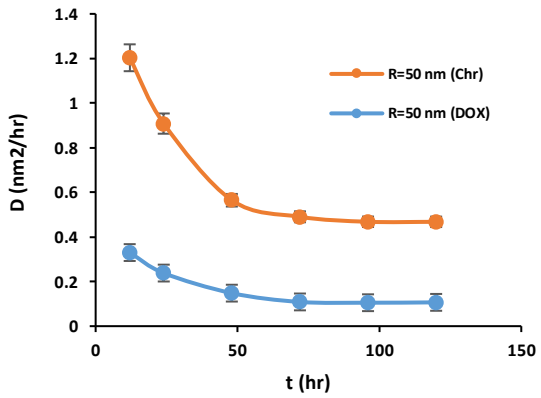

Fig. 12: Time-varying diffusion coefficients for doxorubicin and chrysin from a sphere of radius R=50 nm.

chemotherapy methods. The feature of desire toward the magnetic field in magnetic nanoparticles leads to the product of the purposive drugs attached to these particles in the body. Applying an external magnetic field causes the conduction of magnetic nanoparticles to tumor tissue and helps to treat cancer tumors effectively.

In this research, it was limited to two drugs, but it can be expanded, and use the combination of more anti-cancer drugs such as cisplatin, paclitaxel, and silibinin and a combination of chrysin with other anti-cancer drugs are suggested. Also, in-vivo studies of Fe_3O_4-PCL-PEG-PCL-Dox-Chr nanoparticles on cancer cells, are proposed in the next research.

Nomenclatures

PCL	Polycaprolactone
PEG	Polyethylene glycol
DOX	Doxorubicin
Chr	Chrysin
W/O/W	Water-in-Oil-in-Water (Dual emulsion method)
R^2	Coefficient of correlation
GSH	Glutathione
ROS	Reactive oxygen species
GSTs	Glutathione S-transferases
MRPs	Multi-drug resistance proteins
PVA	Polyvinyl alcohol
SEM	Scanning electron microscopy
DLS	Dynamic light scattering
VSM	Vibrating sample magnetometer
Q_t	Amount of resolve drug for time t
Q_o	Initial amount of drug in buffer at time t=0
D	Diffusion coefficient
c	Drug concentration
M_t/M_∞	Drug release fraction
L	Total thickness

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