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Application of guar gum in electrospun nanofibers as mebendazole drug release controller: a kinetic study and thermodynamics analysis

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Abstract

The current study aimed at *in vitro* investigating the kinetic study and thermodynamic analysis of mebendazole drug released from electrospun cellulose nanofiber in which guar gum is used as a release controller. The nanofibers were fabricated by electrospinning technique. The fibers were boosted by different controller guar gum 10 at 50, 250, and 500 ppm concentrations. The drug release was investigated on each fiber at 25 °C, 31 °C, 37 °C, and 43 °C for 72 h. The results showed that guar gum can be used as a drug controlling agent in nanofiber. The drug release becomes more difficult where the concentration of guar gum in the nanofiber is higher. Various models for kinetic modeling were investigated, among which the Sahlin-Peppas model fitted the experimental data efficiently. Kinetic studies have shown that both diffusion and swelling mechanisms contribute to the drug release process. This is due to the hydrophilic nature of guar gum. If the value of the controller is greater, the diffusion mechanism dominates the process. Thermodynamic analysis showed that drug release at all controlling concentrations is not spontaneous ($\Delta G>0$) and is an endothermic process ($\Delta H>0$), leading to increased disorder ($\Delta S<0$). Activation energy increases with the increase in the amount of guar gum controller, which means that more energy is needed to release the drug.

Keywords: Drug delivery system; electrospinning; mebendazole; guar gum; thermodynamics; kinetic.

Introduction

The drug delivery system is a process in which the drug releases into the body at the right time and place. This method is very important because, in addition to reducing the side effects of the drug and the overall cost of treatment, it also increases the effectiveness of the treatment. [1-5]

Guar gum is a non-ionic polysaccharide natural polymer which has convenient properties that make it widely used in food, pharmaceutical, paper, textile and cosmetics industries. In recent years, various studies have been published on the use of guar gum in the drug delivery systems. Guar gum is

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naturally hydrophilic and has swelling properties in aqueous media [6].

Echinococcus granalus is a common disease between humans, dogs and domestic animals [7]. It causes the formation of hydatid cysts in different parts of the infected patient's body [8,9]. Surgery and use of The PAIR (puncture-aspiration-injection-reaspiration) procedure are among the most important and best ways to treat this disease. Rupture and release of hydatid fluid containing protoscoleces during surgery is not impossible. This is the most important cause of the recurrence of this highly dangerous disease that can lead to the patient's death [9]. One of the ways to treat and kill the larvae of this disease is to use mebendazole [10]. Drug delivery at the right time and place can be effective in the treatment [11].

One of the drug carriers that are widely used in drug delivery systems is electrospun nanofibers [12,13]. This method has been in use for more than a century and a variety of equipment has been developed for its application [14-16]. Electrospun nanofibers have a continuous porous structure and their surface-to-volume ratio is higher. The basic principle of using an electrospinning method in a drug delivery system is that the drug and its release controller are embedded in the nanoscale pores during nanofiber fabrication [13,15,17,18]. These nanofibers are produced by electrospinning under high voltage different conditions [13].

Kinetic study of drug release and determining its mechanism is one of the most important tasks that must be done to design a predictable and repeatable drug delivery system [19]. Various models have been proposed to explain the kinetics of drug release. Each of these models is based on a release mechanism and relates the amount of drug release, time, and temperature [20,21]. Zero-order and first-order models are merely a mathematical model that do not cover a specific mechanism and not related to biological or physicochemical phenomena, but only linearly quantify its release value over time. The Higuchi model describes the solubility of drug in solvent media based on the diffusion mechanism. This model is based on Fick's first law. In this model, it is assumed that the drug diffuses only in one dimension with constant rate and drug particles much smaller than system thickness. Swelling of matrices and dissolution is negligible. Diffusion of solvent into the matrices, swelling of matrices as solvent enter, formation of gel, diffusion of drug and controller out of the matrices, and dissolution of fiber were considered in Korsemeyer-Peppas model (power law model) [22]. Like the aforementioned models, the Hixson-Crowell model (Erosion release mechanism), Weibull model (empirical model, life-time distribution function), Baker-Lonsdale model (Release of drug from spherical matrices), Hopfenberg model (erosion mechanism), Gompertz model (dissolution model), the Courraze model (assuming polymer degradation), the Sahlin-Peppas model (contribution of each mechanism), and Sequential model (swelling mechanism) are kinetic models that each has been achieved with assumptions and limitations [19,20,22,23]. The choice of the best kinetic model depends on the research conditions and assumptions.

In this study, cellulose nanofibers containing mebendazole and various amounts of guar gum controller were fabricated using electrospinning technique. The release of mebendazole from nanofibers has been investigated and the effect of controlling of guar gum has been considered. Kinetic and thermodynamic studies of drug release were performed and finally equations for predicting drug release rate were obtained. It should be noted that there are no published articles on the use of guar gum as a drug release controller in electrospun nanofibers containing the drug mebendazole.

Materials and methods

Mebendazole was obtained from Unichem laboratories (Goa, India), and Guar gum was purchased from S.D. Fine Chem Ltd (India). Ethyl cellulose was obtained from Signet chemical (Mumbai, India). Ethanol (100% purity) was purchased from Merck (Germany).

Electrospinning the aluminum foil and needle were exposed to a 10-kV voltage by a high-voltage generator (model DW-P403-1AC; Dongwen Factory, China). There was a 12-cm distance between the aluminum foil and needle tip. A TCI-I syringe pump (SLGO, Beijing, China) was used to control the syringe movement rate. For the precursor solution, the feed rate was set at 1.0 $mL.h^{-1}$. On the aluminum foil, a compact fiber web was collected. For examining the nanofibers, an SEM microscope (S-3000N, Hitachi, Japan) was used. For spectrophotometry, Hewlett-Packard 8453 diode array spectrometer was controlled by a computer. Ultrasonic devices with specification with device model MP and with device code 18128 Switzerland were prepared.

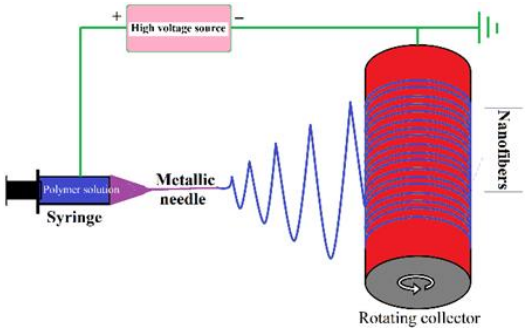

Figure 1. Schematic setup of Electrospinning

Experimental

Preparation of nanofibers

A process to fabricate Guar gum fibers by electrospinning technique is as follows: first of all, 0.5 g of Ethyl cellulose with 4.5 mL Ethanol and 0.002 g of mebendazole drug were added and placed into an ultrasonic apparatus for a period of 15 minutes. Next, 0.5cc of Guar gum controller with a concentration of 10 ppm was transferred to the container. Then, after 10 minutes, it was placed again into the ultrasonic apparatus and the completely uniform solution was generated. After that, the Guar gum solutions (10 ppm, 50 ppm, 250 ppm, and 500 ppm) were prepared respectively.

Scanning electron microscopy (SEM)

The current study provided an SEM image from fibers prepared by adding 5 mg of ethyl cellulose and 4500 mg of ethanol, and it was ensured that the fiber had no controllers and nodes; the controllers were mounted on it (Figure 2).

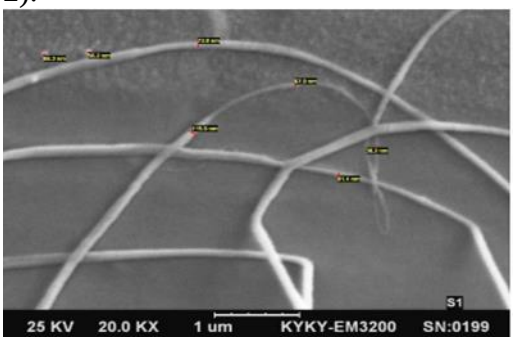

Figure 2. SEM image of electrospun nanofiber collected using a patterned collector

Evaluation of the mebendazole content in the system

Drug-free and controller-free nanofibers were placed in physiological serum and UV testing was performed at different times. This was done to investigate the solubility of nanofiber in physiological serum. There was no evidence of solubilization of the nanofiber. Also, no chemical interactions were observed between the compounds of guar gum, mebendazole and cellulose nanofiber and no new material was added or decreased in the system.

The absorption test was performed on each fiber within 72 h. The corresponding absorptions were determined in the calibration equation, which indicates the concentration of the drug released. According to the total amount of drug used in fibers, the drug release percentage in the medium could be measured.

$$\text{percentage of drug release} = \frac{C_t}{C_\infty} * 100\% \quad (1)$$

Results and discussion

According to the preparation process of ethyl cellulose fiber, 10, 50, 250, and 500 ppm of Guar gum fiber and 0.01 g were used and mixed with 10 mL of physiological serum, and then placed in a Bain-marie circulatory system at 25 ˚C, 31 ˚C, 37 ˚C, and 43 °C, and the absorption rate was measured for each fiber after 72 h. Based on the results of the absorption tests, the drug concentration released into the medium at different temperatures were determined.

The contour release rate of mebendazole from Nano-fibers containing zero ppm guar gum is shown in Figure 3. In this case, drug release begins at an early time and the least resistance to drug release is observed. As time goes on and the temperature rises, the rate of release increases and reaches above 80% at a temperature of 28.5 °C and 50 h. However, at 43 °C, this amount of release can be achieved within 31 h. As shown in the Figure 3, the area greater than 80 % of drug release in the contour indicates that this fiber is not capable of controlling drug release rates.

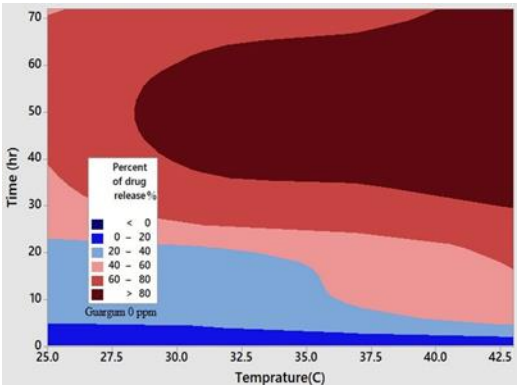

Figure 3. Mebendazole drug released contour from nanofiber with 0 ppm of guar gum

The contour release rate of mebendazole from Nano-fibers containing 10 ppm guar gum is shown in Figure 4. In this case, the effect of guar gum on resistance to drug release is observed. Compared to nanofiber without Guar gum controller, it takes more time and temperature to achieve a certain amount of release. For this fiber, the rate of release increases with time and with increasing temperature. In contour, the largest area is about 15% to 75% percent of drug release. As shown in Figure 4, area greater than 75% of drug release in contour shows that this fiber has some ability to control drug release rates.

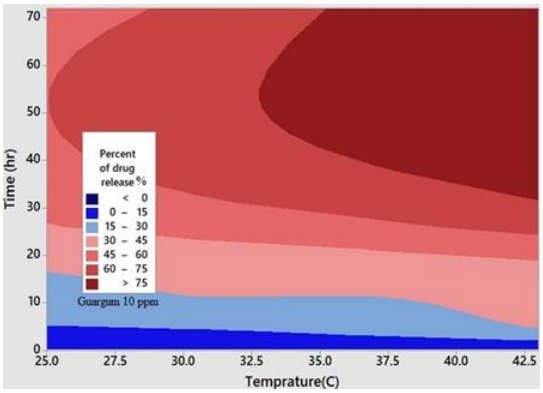

Figure 4. Mebendazole drug released contour from nanofiber with 10 ppm of guar gum

The contour release rate of mebendazole from Nano-fibers containing 50 ppm guar gum is shown in Figure 5. In this case, the presence of 50 ppm guar gum provides greater resistance to drug release. In this case, the presence of 50 ppm guar gum provides greater resistance to drug release. In the time and temperature range of the experiment, the amount of release eventually reaches 72.5%, and the area of release is between 60% to 70% percent of a remarkable extent.

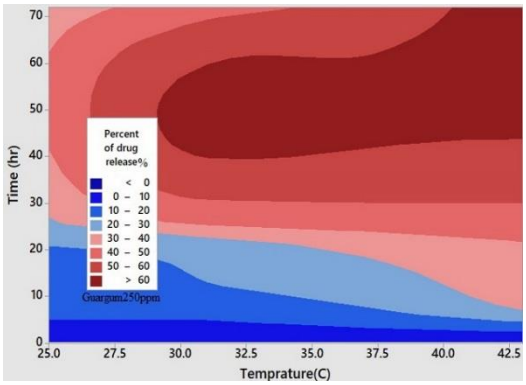

Figure 6. Mebendazole drug released contour from nanofiber with 250 ppm of guar gum

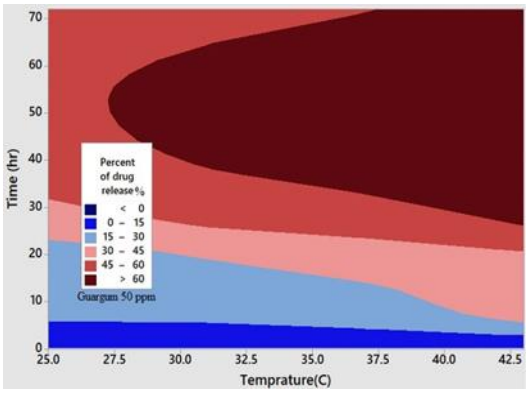

Figure 5. Mebendazole drug released contour from nanofiber with 50 ppm of guar gum

The contour of mebendazole release from Nano-fibers containing 250 ppm guar gum is shown in Figure 6. When 250 ppm guar gum is applied to nanofiber, resistance to drug release will be increased. As gum concentration increases, its effect on release is more pronounced. According to Figures 5 and 6, at a given temperature, the amount of release shows a symmetric trend. This is because both diffusion and swelling mechanisms contribute to drug release process. At the beginning of the process, the diffusion mechanism is dominant and over time, due to the hydrophilicity of the guar gum, the swelling mechanism begins to control the process and eventually the structure of the guar gum is destroyed and its controlling properties are lost and the drug release reaches its maximum.

The contour release of mebendazole from Nano-fibers containing 500 ppm guar gum is shown in Figure 7. In this study, the maximum concentration considered as a gum controller is 500 ppm. This level of nanofiber controller greatly increases the resistance to drug release. According to Figure 7, at a certain temperature, the release value does not show a symmetric trend. The reason is that at this concentration of the controller and at the time tested, the diffusion mechanism controls the release of the drug. Figure 7 shows that as the

amount of guar gum in the nanofibers increases, the structural degradation of the guar gum is delayed and its controlling property is retained.

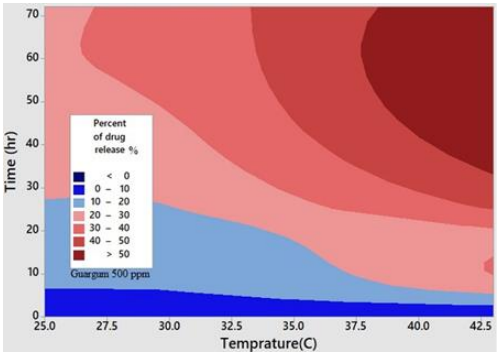

Figure 7. Mebendazole drug released contour from nanofiber with 500 ppm of guar gum

As shown in the results, due to the hydrophilic properties of guar gum, the mechanisms of drug release are dominant by diffusion and swelling mechanism simultaneously. On this basis, a kinetic model that can describe both diffusion and swelling mechanisms should be selected for mathematical modeling. Higuchi model, Korsemeyer-Peppas model or Peppas-Sahlin model can be used in this modeling. These models are shown in Table 1.

Table 1. Kinetic models and their equation [22]

Kinetic model	Equation
Higuchi	$C_t/C_\infty = K_H * t^{0.5}$
Korsmeyer–Peppas	$C_t/C_\infty = K_{KP} * t^n$
Peppas–Sahlin	$C_t/C_\infty = k_1 * t^n + k_2 * t^{2n}$

As it is shown, K_H, K_{KP}, k_1, and k_2 are the constant of kinetic equations, the 'n' is order of equations, the 't' is time base on hour (hr), C_t and C_∞ is released drug and entire of drug in nanofiber, respectively. Kinetic constants were temperature-dependent, using the Arrhenius equation:

$$K = K_0 \exp\left(\frac{-E_a}{R_g T}\right) \qquad (2)$$

Activation energy (E_a) can be obtained after obtaining kinetic constants at different temperatures. After the activation energy is obtained, the pre-exponential factor of Arrhenius equation (K_0) is obtained. By studying the kinetics of drug release, thermodynamic analysis of drug release is possible. kinetic constants link to thermodynamic parameters with Eyring equation:

$$\ln\left(\frac{K}{T}\right) = \left[\ln\frac{K_b}{h} + \frac{\Delta S}{R_g}\right] - \frac{\Delta H}{R_g} \times \frac{1}{T} \qquad \textbf{(3)}$$

where K is a kinetic equation constant, K_b is the Boltzman constant, h is the Plank constant, R_g is the universal gas constant and T is the temperature. ΔS and ΔH are entropy and enthalpy change of drug released process, respectively. After the enthalpy and entropy of the process are obtained, Gibbs free energy is obtained:

$$\Delta G = \Delta H - T \times \Delta S \qquad (4)$$

Curve fitting of kinetic models was performed by least squares method using the MATLAB 2016b. The drug release experimental data were fitted along with the respective equations and parameters. The percentage of the drug released was considered as a function of time. The adjusted coefficient of determination (R^2- Adjusted) was used to compare the adjustment of the kinetic models to the experimental data. The Root Mean Squared Error (RMSE) determine the difference between the experimental data and kinetic model output. The quality and accuracy of fitting the experimental data is measured with the RMSE and R2-Adjusted. If the RMSE is closer to zero, the fitting error is low and if R2-Adjusted is closer to one, the fitting quality is higher. On this basis, the appropriate kinetic model is determined. Thus, the model that better describes the experimental data will be the one that presents. The results are reflected in Table 2.

Based on the results, Peppas-Sahlin's kinetic model describes the data more accurately. This model encompasses both release mechanisms including diffusion and swelling. k_1 is the diffusion coefficient and k_2 is the coefficient of the swelling mechanism, each of which has a physical meaning. In the Peppas-Sahlin model n=0.5-1. If n is close to 0.5, it means that diffusion mechanism is dominant. If "n" is close to 1, it means that swelling mechanism is dominant. The results show that n is about 0.5 and k_2 is close to zero. Physically, this means that the drug release from the studied nanofibers is based on the mechanism of diffusion.

Table 2. Adjustment of the kinetic model to the experimental data

Release controller	Kinetic Model	Equation	Constants		Adjusted R^2	RMSE
Guar gum 50 ppm 25 °C	korsmeyer-peppas	$k_{kp}t^n$	K_{kp} = 0.06051		0.9426	0.0439
	peppas-sahlin	$k_1t^n+k_2t^{2n}$	k_1 = 0.03152	k_2 = -0.000512	0.9547	0.0309
	higuchi	$K_Ht^{0.5}$	K_H = 0.06267		0.9218	0.0409
Guar gum 50 ppm 31 °C	korsmeyer-peppas	$k_{kp}t^n$	K_{kp} = 0.08322		0.9307	0.055
	peppas-sahlin	$k_1t^n+k_2t^{2n}$	k_1 = 0.03523	k_2 =-0.0005559	0.9769	0.0317
	higuchi	$K_Ht^{0.5}$	K_H = 0.06962		0.9394	0.0514
Guar gum 50 ppm 37 °C	korsmeyer-peppas	$k_{kp}t^n$	K_{kp} = 0.1062		0.9349	0.0588
	peppas-sahlin	$k_1t^n+k_2t^{2n}$	k_1 = 0.04809	k_2 =-0.0009354	0.988	0.0253
	higuchi	$K_Ht^{0.5}$	K_H = 0.07898		0.9325	0.0599
Guar gum 50 ppm 43 °C	korsmeyer-peppas	$k_{kp}t^n$	K_{kp} = 0.1591		0.9624	0.0511
	peppas-sahlin	$k_1t^n+k_2t^{2n}$	k_1= 0.1149	k_2= -0.004522	0.9701	0.0456
	higuchi	$K_Ht^{0.5}$	K_H = 0.09688		0.9204	0.0746
Guar gum 250 ppm 25 °C	korsmeyer-peppas	$k_{kp}t^n$	K_{kp} = 0.05974		0.9299	0.0349
	peppas-sahlin	$k_1t^n+k_2t^{2n}$	k_1= 0.03353	k_2=-0.0008057	0.9467	0.0305
	higuchi	$K_Ht^{0.5}$	K_H = 0.04516		0.9306	0.0347
Guar gum 250 ppm 31 °C	korsmeyer-peppas	$k_{kp}t^n$	K_{kp} = 0.06574		0.8792	0.065
	peppas-sahlin	$k_1t^n+k_2t^{2n}$	k_1 = 0.02014	k_2=-0.0002002	0.9331	0.0484
	higuchi	$K_Ht^{0.5}$	K_H= 0.05962		0.902	0.0586
Guar gum 250 ppm 37 °C	korsmeyer-peppas	$k_{kp}t^n$	K_{kp} = 0.08992		0.9422	0.0489
	peppas-sahlin	$k_1t^n+k_2t^{2n}$	k_1 = 0.04369	k_2 =-0.0008781	0.9812	0.0279
	higuchi	$K_Ht^{0.5}$	K_H = 0.06958		0.9426	0.0488
Guar gum 250 ppm 43 °C	korsmeyer-peppas	$k_{kp}t^n$	K_{kp} = 0.1161		0.9889	0.0246
	peppas-sahlin	$k_1t^n+k_2t^{2n}$	k_1= 0.1086	k_2 = -0.002682	0.9901	0.0215
	higuchi	$K_Ht^{0.5}$	K_H = 0.08389		0.9726	0.0386
Guar gum 500 ppm 25 °C	korsmeyer-peppas	$k_{kp}t^n$	K_{kp} = 0.03533		0.9807	0.0139
	peppas-sahlin	$k_1t^n+k_2t^{2n}$	k_1 = 0.03159	k_2= -0.000564	0.9954	0.0127
	higuchi	$K_Ht^{0.5}$	K_H = 0.03376		0.9843	0.0125
Guar gum 500 ppm 31 °C	korsmeyer-peppas	$k_{kp}t^n$	K_{kp} = 0.03654		0.9939	0.0097
	peppas-sahlin	$k_1t^n+k_2t^{2n}$	k_1 = 0.03776	k_2 =0.0004719	0.9943	0.0871
	higuchi	$K_Ht^{0.5}$	K_H = 0.04091		0.9935	0.01
Guar gum 500 ppm 37 °C	korsmeyer-peppas	$k_{kp}t^n$	K_{kp} = 0.06181		0.9909	0.016
	peppas-sahlin	$k_1t^n+k_2t^{2n}$	k_1= 0.05911	k_2= 0.0006904	0.9921	0.0114
	higuchi	$K_Ht^{0.5}$	K_H = 0.05746		0.992	0.0151
Guar gum 500 ppm 43 °C	korsmeyer-peppas	$k_{kp}t^n$	K_{kp} = 0.1015		0.9683	0.0343
	peppas-sahlin	$k_1t^n+k_2t^{2n}$	k_1= 0.08309	k_2=-0.002909	0.9742	0.0315
	higuchi	$K_Ht^{0.5}$	K_H = 0.06939		0.9481	0.0439

The thermodynamic parameters are obtained after obtaining the kinetic constants, by using Eyring's equation. This equation links the enthalpy and entropy changes to the kinetic constant. Activation energy was obtained from Arrhenius equation. The values of the Gibbs free energy, enthalpy and entropy changes are shown in Table 3.

The results show that E_a *(Guar gum 500ppm)*> E_a *(Guar gum 250ppm)*> E_a *(Guar gum 50ppm)* > E_a *(Guar gum 10ppm).* More activation energy means that more energy will be needed for the drug release process to occur. In all cases, the enthalpy changes are positive *(ΔH>0)* that indicate the drug release process is endothermic. As shown in the figure, the release rate increases with increasing temperature. The entropy of the system is negative *(ΔS<0)*, which indicates an increase in system disorder during drug release. Gibbs free energy changes are the most important.

Table 3. Activation energy and thermodynamic parameters of release drug from nanofiber containing 10, 50, 250, 500 ppm of Guar gum

System	Temperature (°C)	Gibbs Free Energy (ΔG) [kJ/mol]	Enthalpy ΔH [kJ/mol]	Entropy ΔS [kJ/mol.K]	Activation Energy Ea[kJ/mol]
Guar gum 10 ppm	25	79.058	19.1970	-0.201	21.748
	31	80.325			
	37	81.591			
	43	82.858			
Guar gum 50 ppm	25	79.591	30.264	-0.166	32.816
	31	78.302			
	37	76.912			
	43	75.423			
Guar gum 250 ppm	25	80.197	23.975	-0.188	36.527
	31	81.279			
	37	82.362			
	43	83.445			
Guar gum 500 ppm	25	85.059	40.297	-0.138	42.851
	31	86.141			
	37	87.224			
	43	88.307			

Thermodynamic parameters were associated with the drug release process. If the Gibbs free energy changes are negative *(ΔG<0)*, the process is spontaneous. But for all the nanofibers containing Guar gum, the Gibbs free energy changes are positive *(ΔG>0)*, which means that the drug release process from these nanofibers is not spontaneous. In comparison to nanofibers containing guar gum, the largest Gibbs free energy changes are at Guar gum 500 ppm, which is thermodynamically more resistant to spontaneous drug release.

Conclusion

The current study analyzed the mebendazole drug release kinetics from cellulose nanofiber containing guar gum controller. In this study, nanofibers were fabricated by electrospinning. The results showed that in controlling the release process of mebendazole from nanofiber, guar gum can be used as an effective controller. The results of the kinetics study showed that when guar gum is used as a release controller, the mechanism of diffusion and swelling can dominate the process. By increasing the concentration of guar gum, the mechanism of diffusion is superior to the mechanism of swelling. According to the

results of kinetic modeling, the Peppas-Sahlin model fits the experimental data with less error and greater accuracy. The activation energy value indicated that as the concentration of guar gum increases, the energy required to release the drug increases. Based on the thermodynamic analysis, it was found that the enthalpy changes ($\Delta H>0$) of the drug release process are positive, indicating that the process is endothermic, that is to say, as the temperature increases, its release rate increases. The entropy changes ($\Delta S<0$) in the drug release process were negative, indicating an increase in system irregularity. Gibbs free energy changes were positive ($\Delta G>0$), which negates the spontaneous release process. Also, as the concentration of the controller increases, the amount of Gibbs free energy changes becomes more positive and distances itself from being spontaneous.

This research has the potential to extend the study on live larvae of hydatid cysts and ultimately experiment on live animals and is a starting point for further work.

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Conflicts of Interest: The authors declare no conflict of interest.

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