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Kinetic Modeling on Mitoxantrone Release from Hyaluronic MNP as a Drug Delivery System

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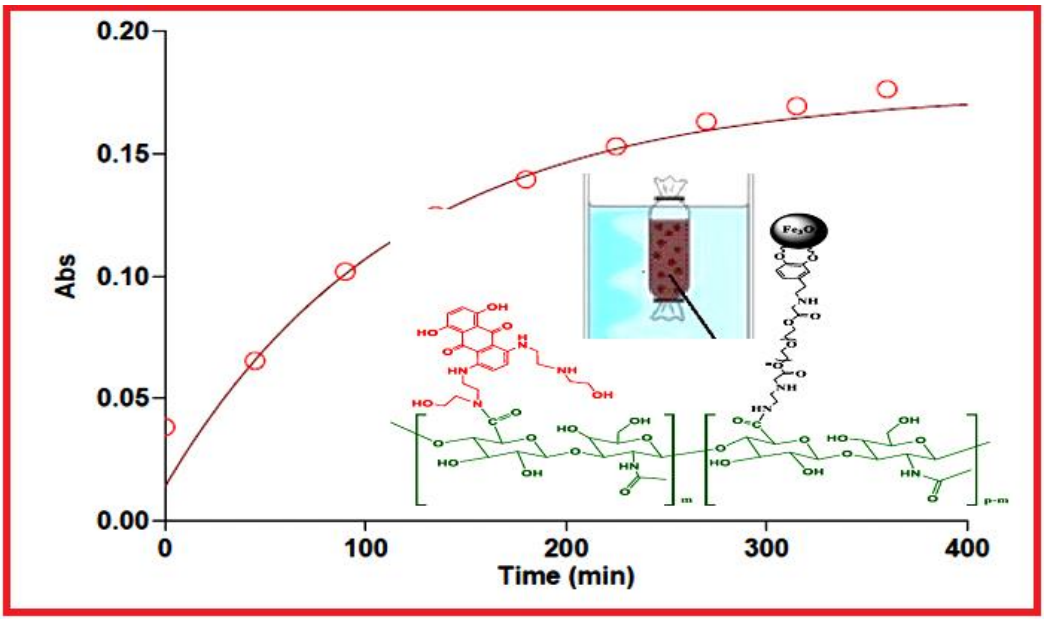
ABSTRACT

This study evaluated the kinetics of mitoxantrone (MTX) releases from Fe_3O_4-PEG-HA NPs as a drug delivery system in the presence of sodium citrate buffer (pH=5.0) into a dialysis bags at 37 °C using both the UV-vis spectrophotometry technique and statistical patterns. The formal empirical absorbance plot (dotted line) against time was properly fitted by the first-order fitting plot. To ascertain the best fitted model recognition of character in drug liberation, we calculated several statistical quantities as error standard functions. The release of MTX from the titled was considered with respect to the statistical kinetic patterns of Ritger-Peppas, Sahlin-Peppas, first-order kinetics, Higuchi, and Hixson-Crowell equations. According to the correlation constraint R^2 value that emerged from statistical patterns, the first-order model was found as a more comprehensive description than the other patterns for chemical kinetics in drug liberation and the rate of drug release depends on drug concentration.

GRAPHICAL ABSTRACT



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Introduction

Mitoxantrone (MTX) as a class of developed anthraquinone is a usual drug applied in the therapy of breast and prostate cancers as the most common cause of death in the world, lymphomas, and acute leukemia [1, 2]. MTX interact with biological macromolecules[3] covalently and non-covalently, deter the mitochondrial pathway and inhibit topoisomerase II, making cell death or apoptosis in DNA single and double-strand breaks in both healthy and cancer cells [3, 4]. Nowadays, magnetic nanoparticles carriers (MNPs) as a drug delivery system (DDS) have an extremely significant role in the treatment of special tumor cells and directed at the target by means of an external magnetic field [5]. They create at least adverse side effects on non-target tissues in the flow of release of the drug locally [6]. Superparamagnetic iron oxide nanoparticles are most commonly utilized for magnetic drug delivery that can release drugs in a target tumor.

In cancer therapy, after a good nano-carrier choice for transport, drug release, and accumulation in the target site are important. To gain the most effectiveness of it, drug release from nanoparticles must be sluggish sufficient to elude notable drug loss before the carrier attains the target [7, 8]. Hence, optimizing results will require tunable rate to liberate a drug in an especial target [9-11]. Chemical kinetics in drug liberation of a nanoparticle base should be an important project to present models for drug formulation [12]. Dialysis bag is one of the best methods for investigation in chemical kinetics and the mechanism of drug liberation of nanoparticles [12, 13]. A UV–vis spectrum analysis revealed that the absorption specification of liposomal MTX created with NiSO4 gradient procedure was noticeably different from that of liposomal MTX gathered with pH gradient procedure and that of free MTX. Tran's membrane NiSO4 gradient could intercede successfully MTX loading and the formulation made with fluid lipid had a fast release rate and better yield in the L1210 ascitic tumor model [14]. Also, the loading and release of mitoxantrone from unmodified ordered mesoporous carbon films was observed using UV-vis spectroscopy. The results showed that release of mitoxantrone was free of film thickness, proposing diffusion restrictions in pore filling [15]. Wang (2017) reported that mitoxantrone hydrochloride (MAH) joined GCS7.5-CM3-7β-CD polymers in an acidic medium could be released from the carrier and kill the cancer cells [16].

Previously, the kinetics of a wide variety of organic reactions involving C-H, S-H, N-H acids have been published for providing a mechanism of the reaction, rate law, reaction order, and the detection of the reactive intermediate by UV-vis spectrophotometry technique [17-21]. Herein, we evaluated the release kinetics of Fe_3O_4-PEG-HA-MTX NPs [22] (Figure 1) for MTX delivery using five kinetic models with a dialysis bag and the UV-vis spectrophotometry technique. Moreover, error analysis equations were applied to identify the best model.

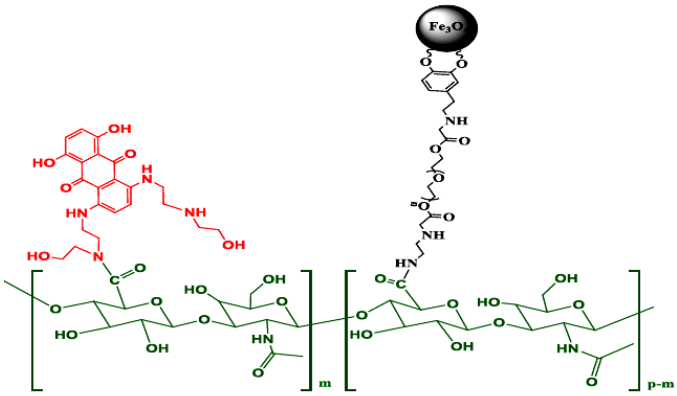

Figure 1: Schematic illustration of the Fe_3O_4-PEG-HA-MTX NPs [14]

Material and methods

The procedure of preparation and in-vitro cellular cytotoxic effects of Fe_3O_4-PEG-HA-MTX NPs was published in our previous work.[14] Herein, the value of MTX liberation into the liquid phase was kinetically specified using UV-vis spectrophotometry apparatus; model Cary Bio-300 with a 10 mm light-path quartz cell in a

maximum wavelength of 608 nm at 37 °C. Fitting and calculating model parameters were performed in the MATLAB (version 7.8, Math Works, Natick, Massachusetts). Fitting kinetic models were executed with "*lsqcurvefit*" function (using Levenberg-Marquardt algorithm) applying the MATLAB fitting curve toolbox.

Error analysis

The experimental results of drug liberation required proper interpretations of error standard to confirm a suitable and precise model.[15] In this work, six error functions were employed expressed as follows [15,16]:

Residual root mean square error (RMSE):

$$RMSE=\sqrt{\frac{1}{n-2}}\sum_{i-1}^{n}(q_{exp}-q_{cal})^2 \quad (1)$$

Where n is the number of empirical data points and q expresses the ratio C_t/ C_0.

a. Determining coefficient (R^2):

$$R2=\frac{(q_{exp}-\overline{q_{cal}})^2}{\sum_{i-1}^{n}(q_{exp}-\overline{q_{cal}})^2+(q_{exp}-q_{cal})^2} \quad (2)$$

Is the average of qcal.

b. Sum of the square error (SSE):

$$SSE=\sum_{i-1}^{n}(q_{exp}-q_{cal})^2 \quad (3)$$

c. Sum of the absolute error (SAE):

$$SAE=\sum_{i-1}^{n}\left|q_{cal}-q_{exp}\right|_i \quad (4)$$

d. Average relative error (ARE):

$$ARE=\frac{1}{n}\sum_{i-1}^{n}\left|\frac{Y_{cal}-Y_{exp}}{Y_{exp}}\right| \quad (5)$$

e. Average relative standard error (ARS):

$$ARS=100\times\sqrt{\sum_{i-1}^{n}\frac{(\frac{y_{cal}-y_{exp}}{y_{exp}})^2}{n-1}} \quad (6)$$

Result and Discussions

Kinetic modeling

Kinetic measurement of MTX released on HA-PEGylated MNPs was performed by monitoring absorbance changes in UV-vis spectrophotometry double beam in 608 nm, in the presence of sodium citrate buffer (pH=5.0) into a dialysis bags at 37 °C [14]. The changes in absorbance of the drug release was considered as a function of wavelengths (550-700 nm) during 72 h (Figure 2A). Then, the drug release was undertaken under the same conditions for recording the experimental absorbance curve versus time (Figure 2B).

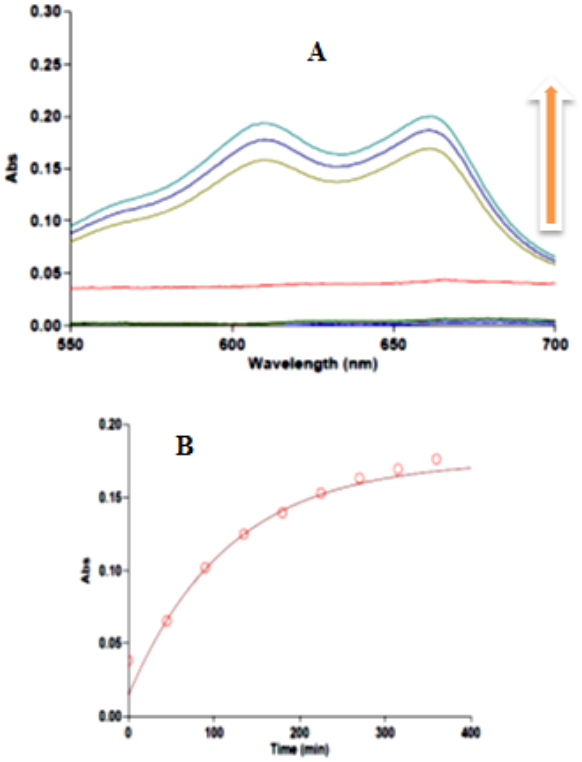

Figure 2 A: Change in absorption spectra vs. wavelength at 37 °C for the MTX release. The upward direction of the arrow indicates the progress of the reaction. Over time, drug releases from nano particle and its amount increases in the buffer, so does absorption. **Figure 2 B:** First-fitting plot (solid line) on the formal empirical absorbance plot (dotted line) *vs.* time at a selected wavelength of 608 nm

As can be seen in Figure 2B, the formal experimental absorbance plot (dotted line) against time is properly fitted by the first-order fitting plot (solid line); therefore, MTX release on Fe_3O_4-PEG-HA NPs followed the first-order kinetics. Nevertheless, to confirm these results, five mathematical kinetic models with consideration of error equations by MATLAB program were employed to obtain the best model of fit for more understanding of the mechanism of drug liberation.

The statistical kinetic pattern of the drug release had the main role in the controlled growth of drug release as it appoints the profile of it. This gave some significant physical quantities, such as the drug diffusion constant, resorting to fitting model on experimental data and identification of more details in providing reliable deliverer [17]. Also, a kinetic model can predict new systems by applying favorable geometry, route of synthesis, and its size.

In this study, fitting and calculating model parameters were performed in MATLAB (version 7.8, Math Works, Natick, Massachusetts). Fitting kinetic models were executed with "*lsqcurvefit*" function (using Levenberg-Marquardt algorithm) applying MATLAB curve fitting toolbox.

Linear and non-linear least-squares derivation can be used to estimate linear and non-linear factors. Of course, linear factors can be estimated using ordinary least squares. On the other hand, non-linear derivation algorithms were specially designed to handle non-linear factors. The parameters can be considered as non-linear when the correlation of the factors and the residuals is not linear. The non-linear factors to be fitted here were the rate constants of the reaction mechanism and constants of the considered mechanism. Besides, several non-linear derivation algorithms exist. One of the most commonly chosen methods of non-linear regression is the Newton–Gauss–Levenberg/Marquardt (NGL/M) considered which was used in this work.

As shown in Table 1, the release of MTX from Fe_3O_4-PEG-HA-MTX NPs was considered with reference to the statistical kinetic patterns of Ritger-Peppas [18], Sahlin-Peppas [19], first-order kinetics, Higuchi [20], and Hixson-Crowell [21] equations. The correlation constant (R^2) and the relevant quantities were obtained from linear and non-linear least-square derivation analyses. The quality of fit and projection of the drug release profile was evaluated by R^2 and error analysis functions (SSE, SAE, ARE, and ARS) were applied (Table 1). As can be seen, all models such as the Ritger-Peppas, Sahlin-Peppas, Higuchi, and Hixson-Crowell show inappropriate fitting curves with relative values. It appeared that the mechanism of MTX release from Fe_3O_4-PEG-HA-MTX NPs followed mainly the first-order model since it had a higher "R^2" value (0.8970) and fewer values of SSE, SAE, ARE and ARS (0.0186, 0.3540, 0.4949, and 67.25) respectively, than other patterns. The results from the statistical kinetic pattern (first-order) had a considerable agreement with that of the UV-vis spectrophotometry technique.

Table 1: Results of fitting drug release data from statistical kinetic patterns

Model	equation	R^2	K_1	K_2	M	n	SSE	SAE	ARE	ARS
Ritger-Peppas	$\frac{M_t}{M_\infty}= kt^n$	0.6642	0.0157	-----	---	0.3801	0.7553	2.371	0.6246	76.73
Sahlin-Peppas	$\frac{M_t}{M_\infty}=k_1t^m+k_2t^{2m}$	0.7285	-20.917	18.87	0.0136	-----	0.5608	1.962	0.7131	94.88
First-order	$\ln Q_t=-kt+\ln Q_0$	0.8970	0.0001	-----	---	-----	0.0186	0.3540	0.4949	67.25
Higuchi	$\frac{M_t}{M_\infty}= kt^{0.5}$	0.6779	0.0044	-------	---	-----	0.8217	2.456	0.7319	87.72
Hixson-Crowel	$(1-\frac{M_t}{M_\infty})^{1/3}=1-k_t$	0.7090	1.37e-05	-----	---	-----	0.4360	1.434	0.3049	47.61

Conclusion

The kinetics mechanism interpretation of MTX liberation as the anticancer drug was undertaken by both the UV-vis spectrophotometry method and the mathematical pattern of Ritger-Peppas, Sahlin-Peppas, first-order kinetics, Higuchi, and Hixson-Crowell equations. The behavior of fit and the estimate of the drug liberation profile was

determined by the error standard functions and correlation constant. The results from both the UV-vis spectrophotometry method and statistical patterns revealed that the first-order model was better than the other patterns for chemical kinetics in drug liberation. The first-order kinetic described that the rate of drug release depends on drug concentration.

Conflict of Interest

We have no conflicts of interest to disclose.

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