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Dedicated to Professor Bogdan C. Simionescu on the occasion of his 65th anniversary

MATHEMATICAL MODELLING OF THE RELEASE PROFILE OF ANTHRAQUINONE-DERIVED DRUGS ENCAPSULATED ON MAGNETITE NANOPARTICLES

Anamaria DURDUREANU-ANGHELUTA,[a] Simona BACAITA,[b,c] Viviana RADU, [d] Maricel AGOP,[c,e] Leonard IGNAT,[a] Cristina Mariana URITU,[a] Stelian Sergiu MAIER[f] and Mariana PINTEALA[a*]

[a] Centre of Advanced Research in Bionanoconjugates and Biopolymers, "Petru Poni" Institute of Macromolecular Chemistry, 41A Grigore Ghica Voda Alley, 700487 Iaşi, Roumania
[b] Department of Natural and Synthetic Polymers, Faculty of Chemical Engineering and Environmental Protection, "Gheorghe Asachi" Technical University, 73 Dimitrie Mangeron Road, 700050 Iaşi, Roumania
[c] Physics Department, Faculty of Machine Manufacturing and Industrial Management, "Gheorghe Asachi" Technical University, 73 Dimitrie Mangeron Road, 700050 Iaşi, Roumania
[d] Physics Department, Faculty of Physics, "Al. I. Cuza" University, 11 Carol I Road, 700506, Iaşi, Roumania
[e] Lasers, Atoms and Molecules Physics Laboratory, University of Science and Technology, Villeneuve d'Ascq, 59655 Lille, France
[f] Department of Textiles and Leather Chemical Engineering, "Gheorghe Asachi" Technical University, 73 Dimitrie Mangeron Road, 700050 Iaşi, Roumania

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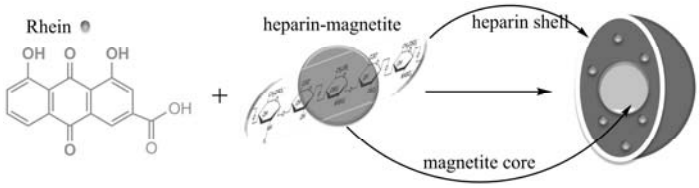
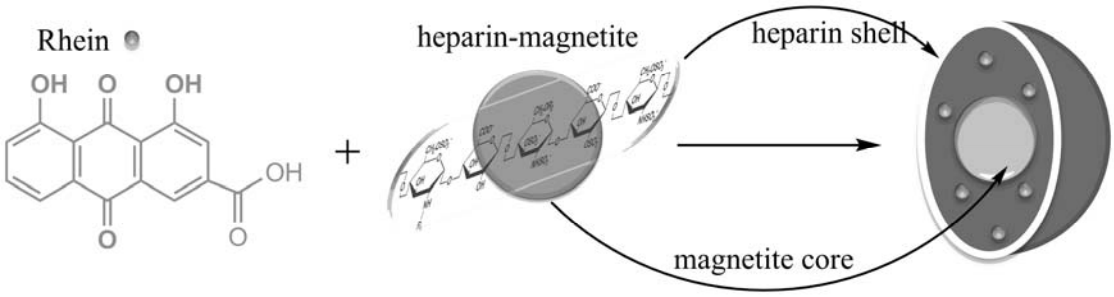
The paper describes the kinetics of rhein antitumor drug release from the heparin shell of magnetite nanoparticles, monitored by UV measurements and expressed through a fractal approximation based on Weibull model. A good correlation coefficient between the experimental curve and the Weibull fitted curve was found, pointing that the diffusion mechanism obeys a complex non-Fickian profile, with a large number of degrees of freedom in the phase space. The calculated parameters are in correlation with the fractal dimension, which depends on diffusion order. The chosen fractal mathematical pattern uses a reduced number of approximations with the purpose of simplifying mathematical modeling, which, otherwise, proves to be quite complex.



INTRODUCTION

Iron oxides are the most used magnetic materials. Among them, magnetite and maghemite are suitable for biomedical applications,[1] being extensively used as carriers for antitumor drugs. The vectors containing them are considered to represent the next generation of targeted delivery systems,[2] as a promising way to substitute the chemotherapy.[3] The drug delivery efficiency of such vectors is directly dependent on the magnetic properties of the nanoparticles, but also on their size.[1]

* Corresponding author: pinteala@icmpp.ro, tel: +40232-217454; fax: +40232-211299



Scheme 1 – Formation of bionanoconjugate rhein-heparinized magnetic particles.

The release of drugs from polymer matrices is a complex process conditioned by the high number of the involved structural entities, and by the interactions between them. Frequently, several accompanying phenomena (polymer swelling, drug dissolution and diffusion,[4,5] polymer degradation) take place simultaneously, negatively interfering with the releasing process (as examples, polymer swelling determine a faster diffusion of the drug, polymer degradation increase the surface porosity and, consequently, accelerates the diffusion). [6,7]

The complexity of nanoparticles mediated drug delivering process induces a nonlinear behavior of the entire system, consisting in the polymer matrix, the drug, and the release environment. As a result, the combined effect of the concurrent phenomena will determine inconvenient behaviours, which reflect all the supplemental interactions between the constituents, as well as their interdependence. These phenomena lead to unexpected states and events, such as the phase transitions,[8] the "pattern" occurrence, the irregular and unpredictable space and time processes evolutions.[9,10]

From a mathematical point of view, the mentioned phenomena can be analyzed in the fractal approximation of motion, described by Scale Relativity Theory (SRT).[11,12] According to this theory, the particles comprised in complex systems are moving on curves, determined by continuous and non-differentiable functions, named fractal functions.

This paper aims to describe the correlation between the drug delivery profile derived from experimental data, and the delivery profile theoretically obtained according to the fractal approximation. The magnetic particles involved in this study are of core-shell type, having a magnetite core, and heparin as shell. The obtaining of this kind of particles is described elsewhere.[13] Classically, magnetite particles are produced by a free-solvent technique, and are stabilized with oleic acid. In our study (see Scheme 1), the surfactant was replaced with aminopropyltriethoxysilane, in order to obtain hydrophilic magnetic particles. Heparin is a good candidate for coating these kind of particles because of its biocompatibility, and because it does not chemically interfere with rhein (Sigma-Aldrich R7269, CAS 478-43-3), the chosen antitumor drug.[14]

RESULTS AND DISCUSSION

Experimental drug release study

The kinetics of rhein desorption from the water soluble magnetic nanoparticles was carried out through UV-Vis spectrophotometric measurements. The calibration curve was determined using successive dilutions of a free rhein solution, by measuring the absorbance at 436 nm (see Fig. 1). The concentration of rhein released from magnetic nanoparticle conjugates was then calculated based on the regression line, starting from the time series of UV-Vis measurements.

In this respect, the nanoparticles loaded with rhein were dispersed in phosphate buffer solution (PBS, pH 7.4) and then incubated on a shaker, at 37°C. Aliquots samples of 3 ml were extracted after settled time intervals, and replaced with 3 ml of PBS. The concentration of released rhein, monitored at 436 nm, was plotted versus time (see Fig. 2). It was concluded that the particles slowly release the drug, the complete release being reached within approximately two days.

Mathematical modeling of drug release profile

The present theoretical approach considers the entire system as a "fluid". All interactions between solid particles are neglected, then complexity being devolved to fractality. This assumption leads to a generalized fractal "diffusion" equation, which can be analyzed in terms of two approximations: the dissipative and the dispersive ones. [15,16]

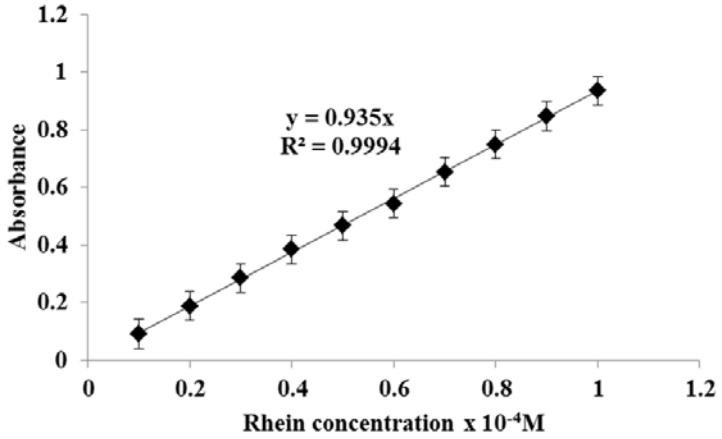


Fig. 1 – Calibration curve of rhein absorbance in aqueous buffered solution.

In the dissipative approximation, the fractal "diffusion" equation can be written as:

$$\frac{\hat{\partial} Q}{dt} = \frac{\partial Q}{\partial t} + \left(\hat{\boldsymbol{V}} \cdot \nabla\right) Q - i\mathcal{D}(dt)^{(2/D_F)-1} \Delta Q = 0 \quad (1)$$

where:

- Q represents the drug concentration field, mathematically defined by a fractal function;
- $\hat{\boldsymbol{V}} = \boldsymbol{V} - i\boldsymbol{U}$ is the complex speed (the real part, $\boldsymbol{V}$, represents the standard classical speed, independent of resolution, and the imaginary part, $\boldsymbol{U}$, arising from fractality, is resolution-dependent);
- $\mathcal{D}$ is considered to be a structure coefficient;
- D_F is the fractal dimension of the particle trajectories.

The fact that the right side of equation (1) has a null value means that system is in a stationary equilibrium state.[15,16]

An anomalous diffusion law may result from equation (1) under the following assumptions:

i) the diffusion paths have a fractal dimension $D_F \neq 2$;

ii) the dynamics at differentiable and non-differentiable scales are synchronous, *i.e.* $\boldsymbol{V} = \boldsymbol{U}$.

Based on the calculus described elsewhere, [15] the equation (1) subjected to the above constraints, (i) and (ii), has a solution of the form:

$$\frac{Q_t}{Q_\infty} = 1 - \exp\left[- \frac{m^2 \mathcal{D}}{\Gamma\left(\frac{2}{D_F} + 1\right)} t^{\frac{2}{D_F}} \right] \quad (2)$$

where Q_t and Q_∞ are cumulative amounts of drug released at time t and after an infinite time respectively, m is an integration constant dependent on diffusion order, and Γ is the Gamma function.

Equation (2) is similar to Weibull relation: $\frac{Q_t}{Q_\infty} = 1 - exp(-at^b)$, where a and b represents particular constants, specific for each system, defined by:

$$a = \frac{m^2 \mathcal{D}}{\Gamma\left(\frac{2}{D_F} + 1\right)}, b = \frac{2}{D_F} \quad (3a, b)$$

Both a and b constants are related to the fractal dimension of the drug particles trajectories, dimension that is a measure of its complexity. Moreover, the a constant also depends on the "diffusion" order.

When plotting the experimental data as a time variation of released drug concentration, a dependence on a specific form of high order polynomial functions appears. This fact results from a first fitting in the TableCurve 2D program carried out without any predefined functions, which showed the existence of more than 50 polynomial functions of orders between 3 and 10 that could track with good accuracy (at least 0.95) the experimental points (correlation coefficients between 0.98 and 0.995). These polynomial functions of different orders are actually particular forms of the Weibull relation, since the polynomial functions are power series expansions of the exponential function:

$$e^{\alpha x} = \sum_{n \geq 0} \frac{\alpha^n}{n!} x^n$$

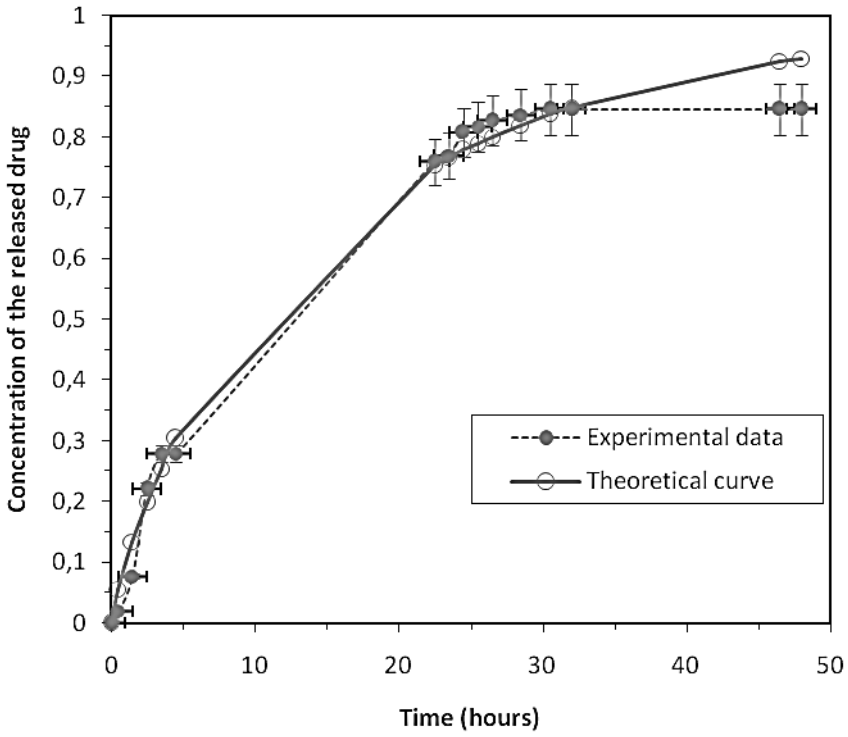


Fig. 2 – The experimental points and the fitted theoretical Weibull curve.

For this reason, as well as to reduce the number of system constants involved (polynomial functions have 4 to 11 coefficients, while Weibull relationship has only 2) a new fitting has been made with Mathematica 8 software application by using a predefined function of Weibull type (eq. 2). The Weibull constants were determined (a=0.075, and b=0.922), and a very good correlation coefficient was also obtained (0.99) for the delivery system comprised from rhein-heparinized magnetite particles. The experimental points and Weibull fittings are plotted in Fig. 2

The applicability of Weibull theoretical model for the current delivery system was confirmed, besides the appropriate correlation coefficient, by the value obtained (eq. 3b) for fractal dimension ($D_F = 2.17$), which is in a good agreement with the usually accepted values for fractal processes,[17] and by the value of constant b (between 0.75 and 1), frequently encountered in the release studies.[18] Moreover, the value of constant b also indicates a release mechanism based on diffusion in normal Euclidean space, with the contribution of other mechanisms.

The fact that the fractal dimension is higher than two indicates that a "super-diffusion" process occurs in the releasing system. In other words, during the release process, concurrent phenomena evolve (most probably polymer swelling and/or degradation, but also unwanted drug dissolution), whose cumulative effect is an increase in diffusion paths and, implicitly, a faster diffusion.

EXPERIMENTAL

Materials

To produce encapsulated rhein on heparinized magnetite particles, the following reagents were used: $FeCl_3 \cdot 6H_2O$ 97%, $FeCl_2 \cdot 4H_2O$ 99.99%, anhydrous NaOH ≥98% as pellets, oleic acid (OA), oleylamine, 3-aminopropyltriethoxysilane (APTES), toluene, triethylamine (TEA), heparin sodium salt from porcine intestinal mucosa, rhein (4,5-Dihydroxyanthraquinone-2-carboxylic acid) from Aldrich.

Experimental drug release studies

The drug release experiments were carried out in phosphate buffered aqueous medium (pH 7.4) at 37°C, by using the membrane diffusion technique,[19] and monitored by UV-Vis analysis on a Perkin Elmer Lambda 25 Spectrophotometer. The absorbance of standard solutions of rhein in PBS was measured (at a wavelength of 436 nm) and the calibration curve was calculated and statistically validated (see Fig. 1). The magnetic particles were dried and then dispersed in buffer solution using a Spectra/Por CE dialysis tube (100-500 MWCO) immersed into 10 ml of buffer solution, under gentle shaking. The rhein release was monitored during 48 hours, when, at selected times, 3 ml of release medium were withdrawn and absorbance measured.

Equal volumes of fresh phosphate buffered medium were immediately added each time to maintain the constant volume of 10 ml and similar sink conditions.[20-21] The amount of drug released from the magnetic particles suspension was calculated using the calibration curve.

Mathematical modeling of drug release profile

The algorithms used for calculation of correlation coefficients and data fitting against the Weibull law were performed with Mathematica 8 and TableCurve 2D software**.**

CONCLUSIONS

Experimental curve of rhein drug release from magnetite nanoparticles covered with heparin (having a twofold role of anticoagulant agent, and of drug carrier), was obtained by UV-Vis measurements. A complete release occurs within the first 32 hours. The release experimental data can be fitted with a very good correlation coefficient (0.9940), by using the fractal approximation Weibull model. The diffusion mechanism is complex, evolving a non-Fickian profile characterized by a large number of degrees of freedom in the phase space. The determined Weibull parameters prove the fractal dimension of the releasing process, and are depending on the diffusion order of the drug outside the heparin shell. The chosen fractal mathematical pattern which was used to model the release process is able to reduce the number of approximations needed to describe the system, otherwise quite difficult to solve.

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