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# Multiscale mechanism of drug release from polymeric matrices: a confirmation through a nonlinear theoretical model

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In this paper we propose a new approach for the dynamic of drug delivery systems, assimilated to complex systems, approach based on concepts like fractality, non-differentiability, multiscale evolution. The main advantage of using these concepts is the possibility to eliminate the approximations used in the standard approach by replacing complexity with fractality, that impose, in mathematical terms, the mandatory use of non-differential character of defined physical quantities. The theoretical model presented, validated for other physical systems, demonstrates its functionality also for drug delivery systems, highlighting, in addition, new insights in the complexity of this system. The spatio-temporal scales of system evolution are characterized through fractality degree, as a measure of the complexity of the phenomena occurring at each scale. The numerical analysis of the experimental showed that the overall drug release kinetic can be obtained by composing "smaller release kinetics" occurring at scales appropriate for each phase of the drug release mechanism, phases whose expansion depends on system density. Moreover, the uncertainties in establishing the exact limits of the phases were removed by applying the principle of scales superposition, resulting a global fractality degree corresponding to the entire release kinetics. Even if the theoretical model is perfectible by identifying constants specific to each delivery system, this paper is intended to be the beginning of an alternative approach of drug delivery mechanism.

## 1. Introduction

Drug delivery systems (DDS) are *complex systems*, due to the large number of particles among which multiple and interrelated interactions occur; moreover, the complexity degree increases when DDS releases the encapsulated drug, due to the additional interactions with the environment.

Complex systems are very favourable medium for the appearance of instabilities that imply both chaos and self-structuring through generation of ordered complex structures.[1] In the classical concepts, the theoretical models are build on the assumption that the dynamics of system particles occur on continuous and differentiable curves, so that they can be described in terms of continuous and differentiable motion variables (energy, momentum, density, etc.), exclusively dependent on the spatial coordinates and time. In reality, the complex system dynamics proves to be much more complicated and the classical theoretical models failed in the attempt to explain all of the aspects of the complex system dynamics, as illustrated by experimental observation. These difficulties can be overcome in a complementary approach, using fractal concepts, defined for the first time by Mandelbrot.[2] He introduced the term "fractal" to describe "exotic" shapes that did not fit the patterns of Euclidian geometry, such as irregular geometrical objects, cells of living organisms, human arterial, neural network, convoluted surface of the brain, etc. Such structures often possess invariance under changes of the scale of the magnification, which can be captured well by the fractal geometry, an extension of the conventional Euclidean geometry that allows the measures to change in a non-integer or fractional way when the unit of measurements changes. Fractal analysis has proven to be a useful tool in describing different systems from physics[3,4], chemistry[5,6], biology[7,8], medicine[9,10]. Moreover, depth analysis of different systems evolution showed that most of the phenomena are nonlinear and, therefore, new mathematical tools to describe and explain their evolution and properties were required. These have been provided by the Scale Relativity Theory (SRT)[11] and by the Extended Scale Relativity Theory (ESRT).

These new concepts resulted in new ways of approaching different phenomena, including in the science and technology of drug delivery from polymeric matrices. The results of the increasingly more studies made in the last decade, on different DDS types: particles[12,13], hydrogels[14-16], liposomes[17,18] proved the fractal

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approach to be a successful one in the field of pharmaceucetical nanotechnology and pharmacokinetics[19].

The purpose of this study is to apply a non-linear theoretical model to a drug release phenomena having in view a confirmation of the multi-scale evolution and of the "scales superposition principle" in complex systems.

## 2. Theoretical considerations

### 2.1. Non-linear theoretical model

The evolution patterns in complex systems can be characterized by to various degrees of freedom associated to different time resolution scales. Such an assumption can be sustained by a typical example, i.e. the collision processes in complex system: between two successive collisions the trajectory of the complex system particle is a straight line, but all the collision impact points form an uncountable set of points, that defines a fractured line, whose non-linearity level depends on the time taken into consideration.

From the above example, emerged the assumption that the motions of the complex systems particles take place on continuous, but non-differentiable curves, named fractal curves. Since the non-differentiability, assimilated with fractality, appeared as a fundamental property of the complex system dynamics, a corresponding non-differentiable physics was necessary and it was systematically developed using Nottale's scale relativity theories[11] or Extended Scale Relativity Theory, i.e. the Scale Relativity Theory (SRT) with an arbitrary constant fractal dimension[20]. Therefore, a Euclidean dynamics of a complex system with external constraints was replaced with the fractal dynamics of a complex system free of any external constrains. Practically, the motion with constrains in the Euclidean space, i.e. on continuous and differentiable curves, was replaced by a motion free of constrains in the fractal space, i.e. on continuous, but non-differentiable curves. To do this, the correspondence between the interaction processes and the "fractality" of the motion trajectories was admitted.[21-23]

The non-linear theoretical model proposed in this work is based on the assumption that all the motions of complex system particles take place on continuous, but non-differentiable curves (fractal curves). In this hypothesis, some consequences of non-differentiability are evident:

i) any continuous, but non-differentiable curve of the complex system particles (fractal curve) is explicitly scale resolution $\delta t$ dependent, i.e., its length tends to infinity when $\delta t$ tends to zero;[2]

ii) the physics of the complex system phenomena is related to the behavior of a set of functions during the zoom operation of the scale $\delta t$; then, through the substitution principle, $\delta t$ will be identified with $dt$, i.e., $\delta t \equiv dt$ and, consequently, it will be considered as an independent variable[11];

iii) the complex system dynamics is described through fractal variables, i.e., functions dependent on both the space-time coordinates and the scale resolution since the differential time reflection invariance of any dynamical variable is broken;[11]

iv) the differential of the spatial coordinate field is expresses as the sum of the two differentials, one of them being scale resolution independent (differential part), and the other one being scale resolution dependent (fractal part);[11]

v) the fractal part of the spatial coordinate field satisfies the fractal equation $d_{\pm}\xi^i(t,dt) = \lambda_{\pm}^i (dt)^{1/D_F}$, where $\lambda_{\pm}^i$ are constant coefficients through which the fractalisation type is specified and $D_F$ defines the fractal dimension of the fractal motion curve;[23]

vi) the complex velocity field can written as $\hat{V}^i = V_D^i - iV_F^i$, where he real part $V_D^i$ is differentiable and scale resolution independent (differentiable velocity field), while the imaginary one $V_F^i$ is non-differentiable and scale resolution dependent (fractal velocity field);[11]

vii) in the absence of any external constrains, an infinite number of fractal curves can be found relating any pair of points, and this is true on all scales. Then, in the fractal space, all complex system particles are substitutes with the fractal curves and any external constraint is interpreted as a selection of fractal curves. The infinity of fractal curves in the bundle, their non-differentiability, and the two values of the derivative imply a generalized statistical fluid like description (fractal fluid);[11]

viii) the complex system dynamics can be described through a covariant derivative:

$$\frac{\hat{d}}{dt} = \partial_t + \hat{V}^i \partial_i \pm \frac{1}{4}(dt)^{(2/D_F)-1} D^{lk} \partial_l \partial_k \qquad (1)$$

where $D^{lk}$ are compounds like $\lambda_+^l \lambda_+^k$, $\lambda_-^l \lambda_-^k$, etc..[23]

Considering the functionality of a scale covariance principle (the complex system physics laws are invariant with respect to scale transformations), the transition from the dynamics of the classical complex system physics to the dynamics of the non-differentiable (fractal) complex system physics can be implemented by replacing the standard time derivative $d/dt$ by the non-differentiable operator $\hat{d}/dt$.[21-23] Thus, this operator plays the role of the covariant derivative, namely, it is used to write the fundamental equations of complex system dynamics in the same form as in the classic (differentiable) case. Under these conditions, applying the operator (1) to the complex velocity field, in the absence of any external constraint and for motions more complex than the Brownian one, i.e. motions on Levy curves, the fractal curves of the motion have the form:

$$\frac{\hat{d}\hat{V}^i}{dt} = \partial_t \hat{V}^i + \hat{V}^l \partial_l \hat{V}^i - i\lambda (dt)^{(2/D_F)-1} \partial_l \partial_k \hat{V}^i = 0 \qquad (2)$$

Previous result shows that the local acceleration, the convection and the dissipation make their balance in any point of the non-differentiable curve [21-23]. Moreover, the presence of the complex coefficient of viscosity-type indicates that the complex system is a rheological medium, so it has memory, as a datum, by its own structure.

For irrotational motions, the complex velocity field $\hat{V}^i$ was chosen in the form $\hat{V}^i = -2i\lambda(dt)^{(2/D_F)-1}\partial^i \ln\Psi$ and the standard equation of motion for the "one body problem" in ESRT can be written as:

$$\lambda^2(dt)^{(4/D_F)-2}\partial^l\partial_l\Psi + i\lambda(dt)^{(2/D_F)-1}\partial_t\Psi - \frac{U}{2}\Psi = 0 \qquad (3)$$

where $\ln\Psi$ defines the scalar potential of the complex velocity field, $U$ is an external scalar potential and $\lambda$ is the coefficient of the fractal-non fractal transition.[23]

If $\Psi = \sqrt{\rho}\exp(iS)$ with $\sqrt{\rho}$ the amplitude and $S$ the phase of $\Psi$, the complex velocity field takes the form $\hat{V}^i = 2i\lambda(dt)^{(2/D_F)-1}\partial^i \ln\Psi$ with the real part ($V_D^i = 2\lambda(dt)^{(2/D_F)-1}\partial^i S$) and the imaginary one ($V_F^i = \lambda(dt)^{(2/D_F)-1}\partial^i \ln\rho$). Substituting (3) in (2) and separating the real and the imaginary parts, up to an arbitrary phase factor which may be set to zero by suitable choice of the phase of $\Psi$, we obtained:

$$\partial_t V_D^i + (V_D^l\partial_l)V_D^i = -\partial^i(Q+U) \qquad (4)$$

$$\partial_t\rho + \partial^i(\rho V_D^i) = 0 \qquad (5)$$

with $Q$ the specific non-differentiable (fractal) potential:[23]

$$Q = -2\lambda^2(dt)^{(4/D_F)-2}\frac{\partial^l\partial_l\sqrt{\rho}}{\sqrt{\rho}} = -\frac{V_F^l V_{Fl}}{2} - \lambda(dt)^{(2/D_F)-1}\partial_i V_F^i \qquad (6)$$

Equation (4) represents the specific momentum conservation law, while equation (5) represents the states density conservation law. Equations (4)-(6) define the fractal hydrodynamic model in ESRT and imply the followings:

i) any complex system particle is in a permanent interaction with a fractal medium through the specific non-differentiable potential (6);

ii) the complex system can be identified with a fractal fluid (non-differentiable fluid), the dynamics of which is described by the fractal hydrodynamic model;

iii) the fractal velocity field $V_F^i$ does not represent actual motion, but contributes to the transfer of the specific momentum and to the energy focus; this may be seen clearly from the absence of $V_F^i$ from the states density conservation law and from its role in the variational principle.

iv) any interpretation of the specific fractal potential should take cognizance of the "self" nature of the specific momentum transfer. While the fractal energy is stored in the form of the mass motion and fractal energy is stored in the form of the mass motion and fractal potential energy, some is available elsewhere and only the total is conserved. It is the conservation of the fractal energy and the fractal momentum that ensures fractal reversibility and the existence of fractal eigenstates, but denies a Levy motion fractal force of interaction with an external medium.[23]

The fractal hydrodynamic solution for the free particle was obtained in the one-dimensional case of equations (4) - (6), in the absence of any external constraint ($U = 0$) and led, by an adequate dimensioning, both to the states density:

$$N(\xi,\tau) = \left[1+\mu\ \tau^2\right]^{-1/2}\exp\left[-\left(\frac{(\xi-\tau)^2}{1+\mu\tau^2}\right)\right] \qquad (7)$$

and velocity:

$$V(\xi,\tau) = \frac{1+\mu\xi\tau}{1+\mu\tau^2} \qquad (8)$$

where $\xi$, $\tau$ are "extrinsic" variables, involving in "coordinates space" ($\xi$ of space type and $\tau$ of temporal type) and $\mu = (dt)^{4/D_F-2}$ an "intrinsic" variable, of fractal type, named fractality degree, which implies "diffusion" type processes in scale space.[11] We present in Fig. 1 the three (alongside with the contour curves) and two dimensional dependences of states density of "extrinsic" variables $\xi$ and $\tau$ for a constant value of the "intrinsic" fractal variable $\mu$ ($\mu = const.$); basically, we are talking about a spatio-temporal "diffusion" on curves of equal fractality (same degree of self-interaction at constant scale resolution).

It can be noted that in the point of coordinates $(\xi,t) = (0,0)$ the states density has a maximum value with a similar decreasing evolution both in space and in time

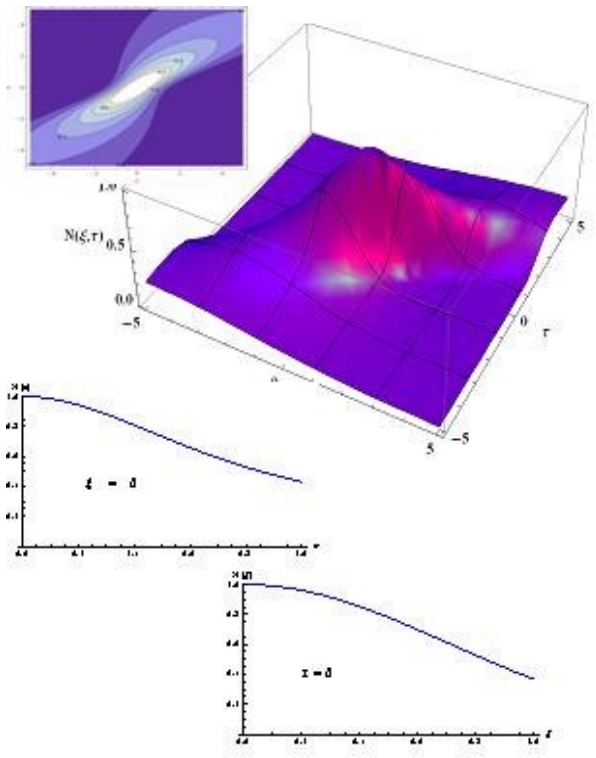



Fig. 1. Three (alongside with the contour curves) and two dimensional dependences of states density on "extrinsic" variables $\xi$ and $\tau$ for a constant value of the fractality degree $\mu = 1$

In Fig. 2 the three (alongside with the contour curves) and two dimensional dependences of states density of the "extrinsic" temporal variable $\tau$ and of the "intrinsic" fractal variable $\mu$, for a constant value of the "extrinsic" spatial variable $\xi$ ($\xi = const.$) are represented; basically, we are talking about a mixed "diffusion", of temporal-fractal type, on curves of equal position. It can be noted that, in a given point, a higher value of fractality degree, determined by the greater complexity of the phenomena involved, implies a decrease in the maximum density of states, characteristic to the equilibrium state, through self-organization. Moreover, it appears faster at higher fractality degree.

### 2.2. Model validation

The drug delivery systems used for the validation of the theoretical model are chitosan based hydrogels: chitosan-gelatin and chitosan-poly(vinyl alcohol)(PVA) cross-linked with sodium sulphate (Na2SO4) and sodium tripolyphosphate (TPP), for which the polymer mass ratios and the ionic cross-linking agent amount were modified for the optimization of their properties, i.e. high mechanical stability and prolonged drug release.

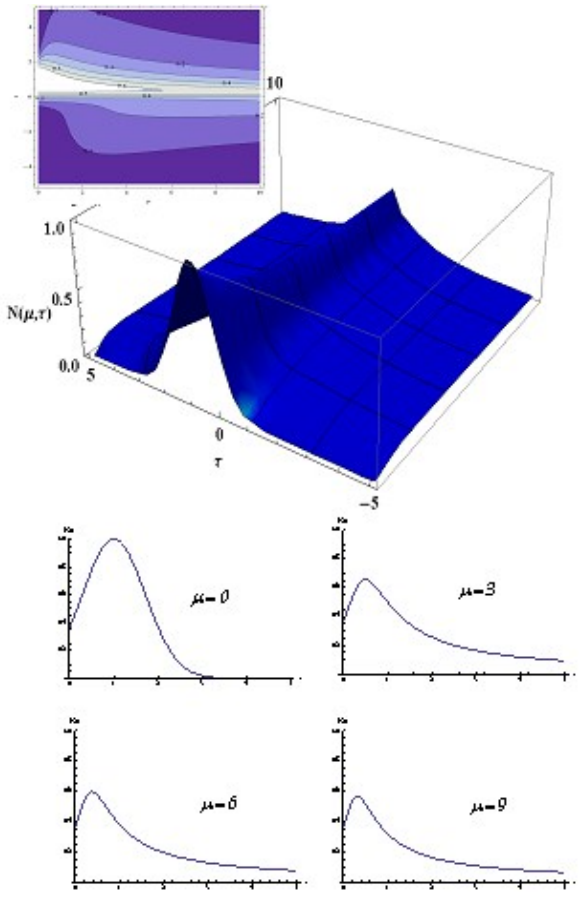



Fig. 2. Three (alongside with the contour curves) and two dimensional dependences of states density on "extrinsic" variable $\tau$ and the "intrinsic" fractal variable $\mu$ in a given point $\xi = 1$

The hydrogels were loaded with calcein and the release kinetics were analyzed. The procedure applied for obtaining the hydrogels and for studying the drug release is not the subject of this paper, but is described in a previous work.[24]

Since, for one group, all of the samples show similar evolution, regardless of the polymers ratio and cross-linker type, for each group, one sample was chosen to illustrate the experimental release kinetics (Fig. 3).

The analysis of all release kinetics showed that:

i) hydrogels with PVA (CP group) have similar evolution to that of hydrogels with gelatin (CG group), for the same ionic cross-linker, with differences in time intervals for each of phase of evolution, (see, in Fig. 3, CG-S1 vs. CP-S4 and CG-T2 vs. CP-T4); this was attributed to the fact that on the one hand, PVA does not participate in ionic crosslinking and, on the other hand, gelatin cross-linking degree is low, so that the main component that participate at cross-linking, and therefore, cause hydrogel density, is chitosan;

ii) samples cross-linked with TPP have lower release efficiency compared to those cross-linked with $Na_2SO_4$, because TPP is a stronger cross-linker than $Na_2SO_4$, and, therefore, hydrogels with TPP have a more dense network (see, in Fig. 2, CG-S1, CP-S4 vs. CG-T2, CP-T4).[15]

Four consecutive phases were identified in the drug release mechanism (for a better understanding, the phases were delineated by the surrounding areas in Fig. 4):

i) *burst effect phase* (I) in which a fast drug release occurs in a very short time, induced by the concentration gradient;

ii) *swelling phase* (II), with a moderate drug release rate, up to the constant plateau;

iii) *equilibrium phase* (III), for which concentration of released drug is constant;

iv) *degradation phase* (IV), characterized by a decrease of released calcein, determined by a reverse process: released calcein bonding to the polymer fragments resulted from hydrogel degradation.[15]

The time threshold for each of the phases were determined by following the inflection points from the release kinetics and the time intervals for each phase are presented in Table 1.

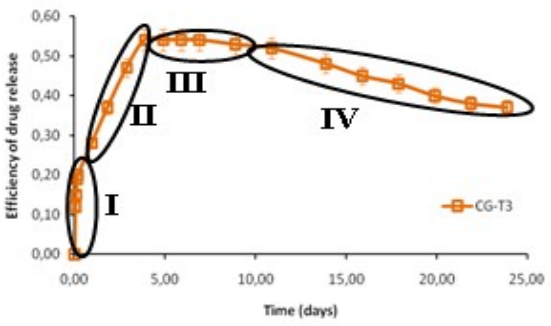



Fig. 3. Phases demarcation in drug release mechanism

| Sample group | Phase I | Phase II | Phase III | Phase IV |
|---|---|---|---|---|
| CG-S | 0 …..130 min. | 130 min. … 3 days | 3 ….. 6 days | 6 ….. 24 days |
| CG-T | | 130 min. … 4 days | 4 ….. 9 days | 9 ….. 24 days |
| CP-S | | 130 min. … 2 days | 2 ….. 4 days | 4 …. 24 days |
| CP-T | | 130 min. … 3 days | 3 ……6 days | 6 …..24 days |

Table 1. Time intervals for the phases of drug release mechanism

Considering that the system (hydrogel in the fluid release medium) is a complex one, we will regard it as a fractal fluid and the complexity induced by the multitude of concurrent and interrelated interactions between components, that makes their outcome very difficult, almost impossible, to quantify, will be replaced by fractality. In other words, the drug particle will be considered a free particle (with no external constraint) in a fractal fluid, and its evolution must be analyzed using the tools of continuous, but non-differentiable physics presented in Section 2.

To apply the fractal hydrodynamic solution for the free particle (7), to our systems, we set the following correspondences:

i) the normalization will be carried out in relation to the maximum possible value, for each of the variables;

ii) $\xi$, the non-dimensional space coordinate, will be set to its maximum value $\xi = 1$, assuming sampling for measuring the amount of drug released is done at the farthest point from the loaded hydrogel;

iii) $\tau$, the non-dimensional time coordinate, will be evaluated in relation to the maximum time of determinations, i.e., in our case $\tau = t/t_{max}$, with $t_{max}$= *24 days*;

iv) $N(\xi,\tau)$, the states density, is equivalent, in our opinion, to efficiency of drug release, $N(\xi,\tau) = M_t/M_\infty$, where $M_t$ is the amount of drug released at time $t$ and $M_\infty$ the amount of drug released as time approaches infinity, i.e. the maximum possible value;

The fractality degree, $\mu = (dt)^{4/D_F - 2}$, is a measure of self-interaction between structural units of the complex system, whose positioning compared with a value equal to 2 of the fractal dimension of the motion curve can indicate the type of dominant process taking place in the system. Thus:

- if $\mu < 1$, that is for $D_F > 2$, non-correlative type processes, local, which manifests at the small spatial scales;
- if $\mu = 1$, that is for $D_F = 2$, quantum type processes, that depend on previous dynamic states of the system;
- if $\mu > 1$, that is for $D_F < 2$, correlative type, which is manifested in large spatial scales throughout the system.[2,25]

Therefore, through the fractality degree, as a measure of self-interaction between structural units of the complex system, at a given resolution scale, will be reflected only its local properties. Each of the phases previously mentioned can be associated to a different fractality degree, each induced by the complexity of the phenomena that evolves within it. A short review of the succession of phenomena involved in drug release shows that polymer swelling is the most important one and present in all phases, besides others, such as drug dissolution and diffusion (in the burst effect, swelling and equilibrium phases), polymer erosion and chemical reactions (in degradation phase). System self-organization by establishing a balance in the ratio between these phenomena determines the values of fractality degree.

In order to determine the fractality degree for each phase, the experimental data were fitted to equation (7), separately for each time interval from Table 1, and the values for which the correlation coefficients had the highest value were selected and presented in Table 2.

The theoretical graphics (obtained by composing the curves given by (7) for each phase, i.e. for the fractalities from Table 2) are represented in Figs. 4. The correlation coefficients with the experimental data are higher than 0.9 and for a better comparison, the experimental release kinetics are also illustrated in Figs. 4. We mention that the continuity of the theoretical graphics was assured by a convenient choice of normalization factors for each phase.

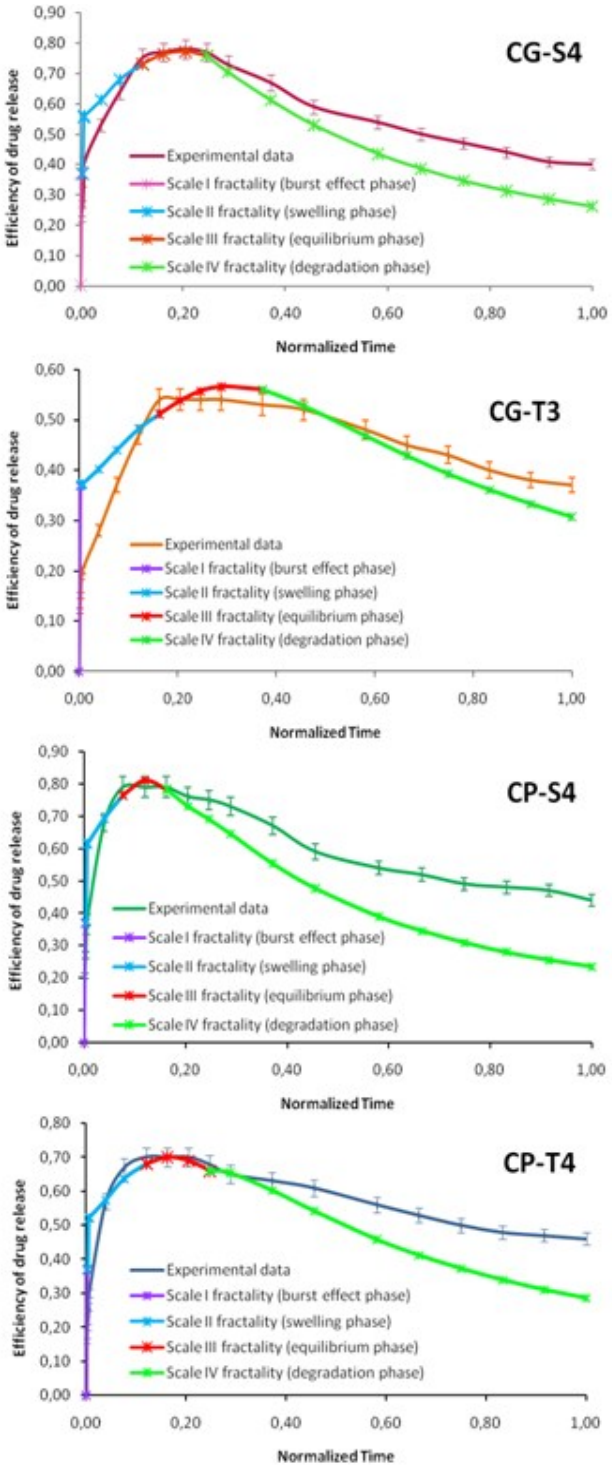
**a)**

| Sample code | Fractality degree I | Fractality degree II | Fractality degree III | Fractality degree IV |
|---|---|---|---|---|
| CG-S1 | 5 | 45 | 25 | 58 |
| CG-S2 | 4 | 45 | 25 | 46 |
| CG-S3 | 6 | 46 | 25 | 64 |
| CG-S4 | 3 | 45 | 24 | 36 |
| CG-T1 | 2 | 26 | 13 | 13 |
| CG-T2 | 2 | 24 | 13 | 11 |
| CG-T3 | 2 | 18 | 9 | 10 |
| CG-T4 | 3 | 18 | 10 | 16 |

**b)**

| Sample code | Fractality degree I | Fractality degree II | Fractality degree III | Fractality degree IV |
|---|---|---|---|---|
| CP-S1 | 4 | 100 | 71 | 45 |
| CP-S2 | 4 | 100 | 50 | 45 |
| CP-S3 | 3 | 100 | 60 | 41 |
| CP-S4 | 3 | 100 | 70 | 41 |
| CP-T1 | 5 | 70 | 41 | 40 |
| CP-T2 | 3 | 80 | 41 | 25 |
| CP-T3 | 3 | 60 | 37 | 24 |
| CP-T4 | 2 | 50 | 35 | 19 |

Table 2. The values of fractality degree for each phase of drug release for CG samples (a) and CP samples (b)




Figs. 4. Experimental release kinetics and theoretical graphics, obtained by composing the plots for different fractality degrees, i.e. for different local scales

An analysis of the values from Table 2 shows that the samples cross-linked with TPP, the stronger crosslinker, (CG-T and CP-T samples) manifest fractalities smaller than those cross-linked with $Na_2SO_4$ (CG-S and CP-S samples), an expected result because the first ones have more denser, compact networks and their evolution (swelling rate and capacity, degradation rate) is slower, and therefore the complexity, equivalent to fractality degree, induced by these, is lower. The same cause can explain the smaller values for CG samples compared to CP samples, since at first ones both chitosan and gelatin participates at croslinking, while at the last only chitosan, and therefore the network is less compact. Within a sample group, the values are not very different because of the small differences in sample composition, that does not influence the global system evolution, but overall, the same reasoning is available.

Since in scale space the functionality of the expansion/contraction operator $\partial/\partial \ln \mu$ is admitted, the intrisec resolution variable (the fractality degree), i.e the function that operates in scales space will not be $\mu$, but $\ln \mu$. Therefore, it must be chosen in the form $\mu_1 = \frac{\mu_{s_1}}{\mu_0}, \mu_2 = \frac{\mu_{s_2}}{\mu_{s_1}}, \ldots\ldots$[11]. By means of such procedure, the acceptance of the "scales superposition principle"[2, 11] implies the functionality of the relation:

$$\ln \mu_t = \sum_{i=1}^{n} \ln \mu_i = \ln \frac{\mu_{S_1}}{\mu_0} + \ln \frac{\mu_{S_2}}{\mu_{S_1}} + \ldots + \ln \frac{\mu_{S_n}}{\mu_{S_{n-1}}} = \ln \frac{\mu_{S_n}}{\mu_0}.$$

where $\mu_0$ is the absolute fractality degree (reference scale)[11].

In our case, the global scale fractality degree for the entire drug release mechanism, considering as reference the scale of the first phase, can be determined by the relation $\mu_t = \frac{\mu_{S_4}}{\mu_{S_1}}$.

By means of such procedure, the particular values, determined from the values of fractality degree for each phase, from Table 2, are given in Table 3.

**a)**

| Sample code | Global fractality degree |
|---|---|
| CG-S1 | 11,6 |
| CG-S2 | 11,5 |
| CG-S3 | 10,7 |
| CG-S4 | 12,0 |
| CG-T1 | 6,5 |
| CG-T2 | 5,5 |
| CG-T3 | 5,0 |
| CG-T4 | 5,3 |

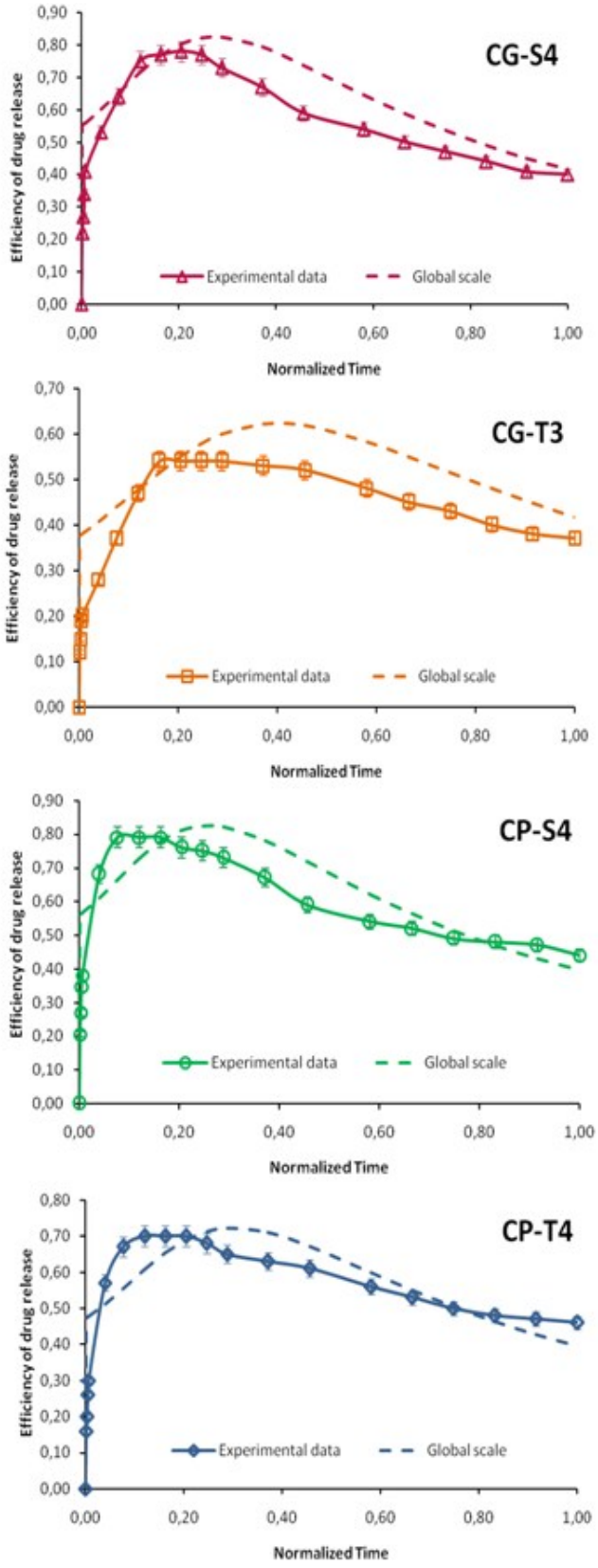
**b)**

| Sample code | Global fractality degree |
|---|---|
| CP-S1 | 11,3 |
| CP-S2 | 11,3 |
| CP-S3 | 13,7 |
| CP-S4 | 13,7 |
| CP-T1 | 8,0 |
| CP-T2 | 8,3 |
| CP-T3 | 8,0 |
| CP-T4 | 9,5 |

Table 3. The values of global fractality degree for the drug relese for CG samples (a) and CP samples (b)

The validity of the superposition principle is demonstrated by the correlation between the theoretical graphics, given by (7) for global scales from Table 3, and experimental kinetics, shown in Figs. 5, with correlation factors between 0,8 and 0,9.

All the above confirm the validity of the theoretical model and of the scales superposition principle.




Figs. 5. Experimental release kinetics and theoretical graphics, obtained for the global fractality degree values

**3. Comparison with the existing models. Advantages and disavantages**

Mathematical modelling of drug release kinetics aims to provide a basis for the study of mass transport mechanisms that are involved in drug release. In general, diffusion, erosion, and degradation are the most important mechanisms and should be considered in developing the mathematical models.

In spite of the complexity of the phenomena involved in drug release mechanisms, most of the mathematical expressions used in pharmaceutics to describe the kinetics of drug release from a large variety of devices are rather simple: power laws (Higuchi[26], Korsmeyer and Peppas[27], Peppas–Sahlin[28]) or exponential laws (Weibull[29]). These are empirical models, easy to use, but limited by certain approximations. For example, in order to apply Higuchi relation, one must impose that the diffusivity coefficient is constant, there is perfect sink at the interface and no swelling and erosion of the matrix takes place[26]. In addition to these, for Korsmeyer and Peppas equation, swelling rates are assumed constant in all direction and possible transition from the glassy to the rubbery state of the polymer are not considered[27]. Moreover, any of the models don't consider the erosion of the polymer.

The present theoretical model overcomes these limitation by eliminating the approximations and taking into considerations all the phenomena involved in drug release mechanism (diffusion, swelling, dissolution, erosion), generating thus a high degree of complexity. In order to manage this, the complexity degree was replaced with fractality degree and the concepts from SRT were applied. Althrough the mathematics seems complicated, this model can open new perspectives on the release mechanisms. One example, for this particular system, the global system evolution can be considered the result of the superposition of „paralel" evolutions at different spatio-temporal scales.

Moreover, the extensively used empirical models can be deducted as consequences of the fractal type dependences for dynamics variables, such as energy, density, momentum, mass. Thus, if we operate only in scale space, then an usual fractal denpendence of the type: $Q^i = \lambda^i \varepsilon^{1/D_F}$, where $Q^i$ is the dynamic variable, $\varepsilon$ este the resolution scale, $D_F$ is the fractal dimension and $\lambda^i$ are constant coefficients whose explicit form is given by the fractalization type[2, 11], can led to power laws. For example, if we consider: $Q^i = M(t)$, $\lambda^i = M_\infty$, $\varepsilon = t$, $\alpha = 1/D_F$, the general form of the simple power laws, i.e. Higuchi, Korsmeyer and Peppas equations, $\frac{M(t)}{M_\infty} = t^\alpha$, can be obtained ($M_t$ is defined as the amount of drug released at time *t*, $M_\infty$ the amount of drug released as time approaches infinity, α a constant). Moreover, by admiting the superposition scales principle, the cumulative power laws as Peppas-Sahlin, Alfrey can be deducted.

A Weibull type law is the result of a dynamic in space scale of the drug release phenomen, admitting a simultaneous functionality

of covariance scale principle and of an action-reaction type principle. But this aspect requires a more elaborate demonstration, which is beyond the scope of this work and will be documented in a forthcoming paper.

Therefore, we consider this model a step forward in the theory of drug release mechanism, due to its high degree of generality and its possibility to discover new insights on the drug release mechanism.

**Conclusions**

Depending on the characteristics of drug delivery system, the spatio-temporal expansion of the phases varies, resulting in decreasing or increasing drug release rates. But, for all types of drug delivery systems, the succession of phenomena is similar:

(i) upon contact with the release medium, suddenly, water diffuses into drug delivery system and the drug molecules into release medium. This the burst effect phase, that takes place at a small spatio-temporal scale, and, as consequences, characterized by small fractality degree;

(ii) with increasing water content, the mobility of polymer chains and, also, drug molecules, increases. This is the swelling phase and its spatio-temporal scale depends on the speed of the "swelling front", which separates the swollen from non-swollen polymer matrix, strongly influenced by its density. Its degree of fractality is considerably higher than that of the first phase, and, moreover, the highest of all, indicating a high complexity of the phenomena;

(iii) after the polymer matrix is completely swollen, the equilibrium phase is achieved, for which the drug concentration in the release environment is constant, i.e. release rate is zero; in this case, the fractality degree has an approximate average value compared to the other ones;

(iv) when the front which separates the drug delivery system from the release medium, called "erosion front", starts moving, the degradation phase begins. As in the swelling phase, its spatio-temporal scale depends on the "erosion front" movement and is strongly influenced by its polymer matrix density, and, in addition to it, by the number of bonds formed between polymer fragments and drug molecules.

(v) the moving fronts, swelling and erosion, are those that determine the spatio-temporal expansion of each phase. This delimitation of phases can be considered rough, since, at least, in the transition intervals, the phases can overlap. To overcame this aspect, difficult to predict, the scales superposition principle, proved its functionality.

(vi) the global system evolution can be considered the result of the superposition of „paralel" evolutions at different spatio-temporal scales.

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