Non-differentiability at Mesoscopic Scale in Drug Release Processes from Polymer Microparticles

DANIELA MAGOP[1], SIMONA BACAITA[2, 3], CATALINA PEPTU[2], MARCEL POPA[2], MARICEL AGOP[3,*]

[1] "Al. I. Cuza" University, Physics Department, 11 Carol I Road, 700506, Iasi, Romania

[2] "Gheorghe Asachi" Technical University, Faculty of Chemical Engineering and Environmental Protection, Department of Natural and Synthetic Polymers, 73 Dimitrie Mangeron Road, 700050, Iasi, Romania

[3] "Gheorghe Asachi" Technical University, Physics Department, 59A Dimitrie Mangeron Road, 700050, Iasi, Romania

The fundamental assumptions of the traditional deterministic linear models are those of continuous and differentiability of physical quantities involved in drug release processes. However, these assumptions are in reality contrary to the evidence given by the complexity of the drug release process. Thus, we will consider that, at mesoscopic scale, the drug release mechanisms are based on the assumption that the drug particle movements take place on continuous, but non-differentiable curves (fractal curves), for which a Weibull type equation results. In this approach, analyzing some experimental data, information on the drug release mechanism and system complexity are obtained.

Keywords: fractal, drug release mechanism, polymers microparticles, mesoscopic scale

To use in investigations only Euclidean geometry, which describes objects with integer dimensions, restricts the possibility of adequate description of real, natural and artificial objects, because it leaves numerous objects with non-integer dimensions, like plants, galaxies, population patterns, crystal growth, beyond the scope of consideration. The properties of such objects can be described using fractal geometry [1,2]. In this category have been included, also, natural and synthetic polymers as fractal objects, whose main structural unit, the macromolecular coil, is known to be a fractal, and whose behaviour manifests fractal characteristics at mesoscopic scale [3-8].

In this paper, we will consider that a process in which polymer fractality manifests is drug release from polymer microparticles. The arguments that allow us to make this assumption are presented next.

Analyzing the experimental drug release kinetics results that these structures (drug + polymer microparticle) are thermodynamically unstable, evolving to an equilibrium state. Depending on specific parameters of each structure (the drugs type, incorporated drug dose(s), types and amounts of excipients, preparation technique, environmental conditions during drug release as well as geometry and dimensions of drug delivery system), each will "find" its own evolution path, consequence of the internal collective processes. Thermodynamically nonequilibrium processes result in the formation of mesoscopic fractal structures [5, 9], so, also, the released drug trajectories are continuous and non-differentiable curves (fractal curves) [1, 10-12].

But, in spite of the complexity of the phenomena involved in drug release mechanism (water penetration into the device, drug dissolution, phase transitions, drug and/or polymer degradation, polymer swelling, physical drug-excipient interactions, chemical reactions between drug and polymer and/or water), the mathematical expressions used in pharmaceutics to describe the kinetics of drug release from a variety of structures are rather simple, namely power laws type: Higuchi, Ritger-Peppas, Peppas-Sahlin, Alfrey [13]. Knowing the fact that the structure whose dynamics is ruled by power laws manifests critical self-structuring [14], property specific for fractals, we can affirm that these structures (drug loaded polymer matrix) manifests a mesoscopic fractal behaviour.

Thus, the question of whether or not the fractal analysis should be used to describe the structure and evolution of such a structure, drug loaded polymer matrix, is not a matter of researcher's choice, but is dictated by the requirements of a correct approach of this issue.

In this context, we will analyze this process in the fractal approach considering that the complexity of the physical processes is replaced by fractality and it is no longer necessary to use the whole classical "arsenal" of quantities from the standard physics (differentiable physics); the physical systems will behave as a special interaction-less "fluid". In this way, we introduce the fractal approximation of motion in the study of this complex physical systems dynamics, considering that the drug trajectories are continuous, but non-differentiable curves, named fractal curves. The physical model which treats the interactions in the previously mentioned manner is the Scale Relativity Theory (SRT) [10-12]. In this theory, we shall obtain a generalized "diffusion" type equation that describes better than the power laws the entire experimental release curves [15], eliminating thus the criticisms based on the lack of a kinetic basis for its use and the non-physical nature of its parameters [16].

This paper is structurated as follows: in Section 2, using the fractal approximation of motion, a generalized "diffusion" type equation, which implies Fickian and non-Fickian drug release mechanisms, is obtained. Experimental results, which validates our model, are presented in Section 3. In Section 4, the conclusions are given.

*email: m.agop@yahoo.com

Experimental part

Theoretical considerations

Taking into account the complexity of the phenomena involved in drug release processes from polymer microparticles, we shall assume that this processes occurs on continuous, but non-differentiable curves (fractal curves).

If such an assumption works, then, according to [11, 12], the dynamics of the fractal released drug concentration field at mesoscopic scale are described by the equation:

$$\frac{\hat{\partial} Q}{\partial t} = \frac{\partial Q}{\partial t} + \left(\hat{\mathbf{V}} \cdot \nabla\right) Q - iD(dt)^{(2/D_F)-1} \Delta Q = 0 \qquad (1)$$

where $\hat{V}$ is the complex speed field

$$\hat{V} = V - iU \qquad (2)$$

V is the standard classical speed, which is independent of scale resolution (dt), whiles the imaginary part, U, is a new quantity arising from non-differentiability, which is resolution-dependent. D is a structure coefficient, characteristic to the fractal-non-fractal transition, scale resolution and fractal dimension D_F dependent [1, 10-12].

This means that at any point of a release curve (released drug trajectories) the local temporal term, ∂, Q, the non-linearly "convective" term, $\left(\hat{V} \cdot \nabla\right) Q$ and the dissipative one, Δ Q, make their balance.

Separating the real and imaginary parts in equation (1), we obtain

$$\frac{\partial Q}{\partial t} + V \cdot \nabla Q = 0$$
$$- U \cdot \nabla Q = D(dt)^{(2/D_F)-1} \Delta Q \qquad (3a, b)$$

and, moreover, by adding these two equations, a generalized "diffusion" type law results:

$$\frac{\partial Q}{\partial t} + (V - U) \cdot \nabla Q = D(dt)^{(2/D_F)-1} \Delta Q \qquad (4)$$

Generalized "diffusion" type equation

This "diffusion" law results from (4) on the following assumptions:

- the "diffusion" path are fractal curves with fractal dimension $D_F \neq 2$;
- the time resolution, δt, is identified with the differential element dt, i.e. the substitution principle can be applied also, in this case (see Appendix);
- the movements at differentiable and non-differentiable scales are "synchronous"

(the same drug release mechanisms at fractal scale manifests, also, at differentiable scale), i.e. **V**=**U**.

Then, the equation (4) can be written:

$$\frac{\partial Q}{\partial t} = D(dt)^{(2/D_F)-1} \Delta Q \qquad (5)$$

In one-dimensional case, applying the variable separation method [17]

$$Q(t, x) = T(t) \cdot X(x) \qquad (6)$$

with the standard initial and boundary conditions:

$$Q(t,0) = 0,\ Q(t, L) = 0,\ Q(0, x) = F(x),\ 0 \le x \le L \qquad (7)$$

implies:

$$\frac{1}{D(dt)^{(2/D_F)-1}} \frac{1}{T(t)} \frac{dT(t)}{dt} = \frac{1}{X(x)} \frac{d^2 X(x)}{dx^2} = -l^2 = -\left(\frac{m\pi}{L}\right)^2,\ m = 1, 2 \qquad (8a,b)$$

where L is a system characteristic length, l a separation constant, dependent on diffusion order m.

Accepting the viability of the substitution principle [11, 12], from (8a, b), through integration, results:

$$\ln T = -l^2 D \int (dt)^{2/D_F} \qquad (9)$$

Taking into consideration some results of the fractional integro-differential calculus [18, 19], (9) becomes:

$$\ln T = -\frac{l^2 D}{\Gamma\left(\frac{2}{D_F} + 1\right)} t^{\frac{2}{D_F}}, \qquad \Gamma\left(\frac{2}{D_F}\right) = \int_0^\infty x^{\left(\frac{2}{D_F}\right)-1} e^{-x} dx \qquad (10a, b)$$

Moreover, (10a,b) can be written under the form:

$$T(t) = \exp\left[-\frac{l^2 D}{\Gamma\left(\frac{2}{D_F} + 1\right)} t^{\frac{2}{D_F}}\right] \qquad (11)$$

The relative variation of non-differentiable released drug concentrations, time dependent, is defined as:

$$T(t) = \frac{Q_\infty - Q}{Q_\infty} \qquad (12)$$

where Q and Q_∞ are cumulative amounts of drug released at time t and infinite time. From (11) and (12) results:

$$\frac{Q}{Q_\infty} = 1 - \exp\left[-\frac{l^2 D}{\Gamma\left(\frac{2}{D_F} + 1\right)} t^{\frac{2}{D_F}}\right] \qquad (13)$$

equation similar to the well-known Weibull relation:

$$\frac{Q}{Q_\infty} = 1 - \exp(-at^b) \qquad (14)$$

a and b representing constant specific for each system that are defined by:

$$a = \frac{l^2 D}{\Gamma\left(\frac{2}{D_F} + 1\right)} = \left(\frac{m\pi}{L}\right)^2 \frac{D}{\Gamma\left(\frac{2}{D_F} + 1\right)}$$
$$b = \frac{2}{D_F} \qquad (15a, b)$$

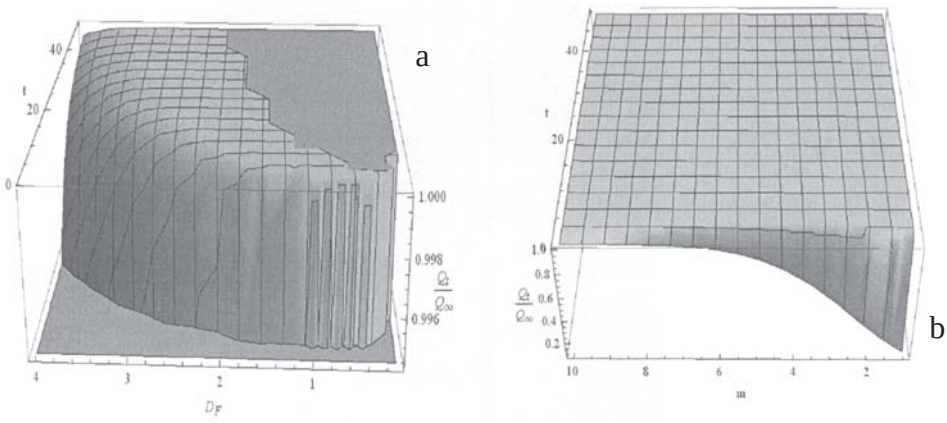

Fig. 1(a, b). Theoretical dependence of (13) on the variables time t and fractal dimension D_F, for a given diffusion order m (a) and on the variables time t and order diffusion m, for a given fractal dimension D_F (b)

We observe that both constants, a and b, are functions of the fractal dimension of the curves on which drug release mechanism take place, dimension that is a measure of the complexity and nonlinear dynamics of the system. Moreover, constant a depends, also, on the "diffusion" order m.

In figures 1, we present the theoretical dependence (13) on the variables time t and fractal dimension D_F, for a given diffusion order m (fig. 1a) and on the variables time t and order diffusion m, for a given fractal dimension D_F (fig. 1b).

Let's note that the fractal processes [1, 10-12, 20-22] given by the equation (4) with $D_F \neq 2$ are known as "anomalous diffusion" (sub-diffusion for $D_F < 2$ and super-diffusion for $D_F > 2$).

Particular cases

For different values of a and/or b parameters, the following cases can be distinguished.

i) For $b=1$, that implies $D_F = 2$, we can affirm that the release is compatible with first-order release, whereas the concentration gradient in the dissolution medium drives the rate of release. Also, this condition implies the next considerations:

-the diffusion paths are the fractal curves of Peano's type. This means that the fractal dimension of the fractal curves is $D_F = 2$. Moreover, the average values (A.19 from Appendix) are defined through Wiener's stochastic processes [1, 10-12, 20-22], *i.e.*:

$$\left\langle d_{\pm}\xi^{i} d_{\pm}\xi^{j} \right\rangle = 2\mathrm{D}\, dt \qquad (16)$$

- the movements at differentiable and non-differentiable scales are synchronous, i.e. $\mathbf{V=U}$;

- the structure coefficient $\mathbf{D}$ is identified with the diffusion coefficient, i.e. $\mathrm{D} \equiv D$.

and the "diffusion" law can be written in the form:

$$\frac{\partial Q}{\partial t} = D\,\Delta Q \qquad (17)$$

- If in the relation (14) we consider the restriction on time $t << 1/a^b$ (that will allow short time approximations for exponential function), with $a<1$, this can be reduced to a well-known law in drug release studies, the Peppas law [15]:

$$\frac{Q}{Q_\infty} = kt^n, \qquad (18)$$

where

$$k = a = \left(\frac{m\pi}{L}\right)^2 \frac{D}{\Gamma\left(\frac{2}{D_F}+1\right)},\ n = b = \frac{2}{D_F}. \qquad (19a,b)$$

Depending on the values of parameter b, i.e. the fractal dimension D_F of the released drug fractal curves (released drug trajectories), one can identify the release mechanism of drug from different kind of polymer matrixes, release environments, drug type [23]. In such context, for $b=1/2$ it is a Fickian release type mechanism (Higuchi's law), while for $0.5\langle b\langle 1$ manifests a non-Fickian release type mechanism [15].

Experimental considerations

In this paragraph we will present some experimental results, for polymer microparticles, followed by some observations, in the context of this new theoretical approach.

Gelatin and poly(vinyl alcohol) (GEL-PVA) microparticles cross-linked with glutaraldehide (GA), for samples prepared by using different amount of cross-linking agent (2, 6, 8, 10% - the sample code indicate the crosslinking amount: for example, GA2 represents a sample with 2% crosslinking amount), loaded with chloramphenicol, were studied (details regarding materials and experimental protocol can be found in [24]).

The experimental points of release kinetics are represented in figure 2.

Results and discussions

All the above drug carriers represents polymer micro particles, but with different structure characteristics, as a result of different experimental parameters. Despite this, they have similar behaviour in time, from a qualitative point of view. In order to analyze quantitatively, we must take into account the loaded drug amount that is direct proportional with the released drug amount, issue that is not the subject of this paper.

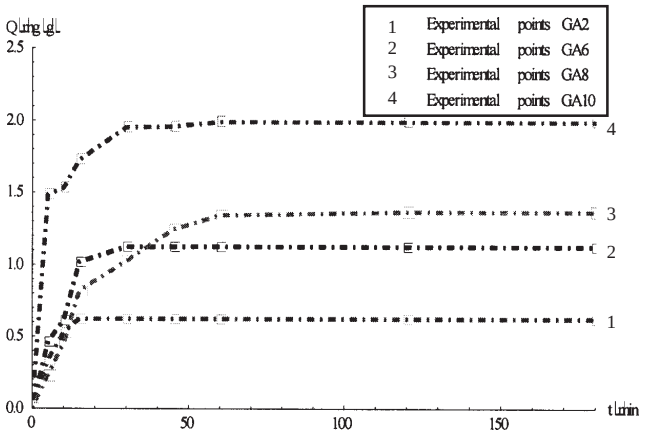

Fig. 2. Chloramphenicol release kinetics from GEL-PVA microparticles

Sample	Weibul			Fractal dimension	Release mechanism—remarks
	a	*b*	Correlation coefficient		
GA2	0,0782	1.4069	0.9994	1.42	Non-Fickian "sub-diffusion"
GA6	0.0577	1.2602	0,9902	1.59	Non-Fickian "sub-diffusion"
GA8	0,0348	1.121	0,9953	1.78	Non-Fickian "sub-diffusion"
GA10	0.5711	0.4816	0,9966	4.15	Non-Fickian "super-diffusion" - high degree of system complexity

Table 1
WEIBULL PARAMETERS VALUES AND REMARKS

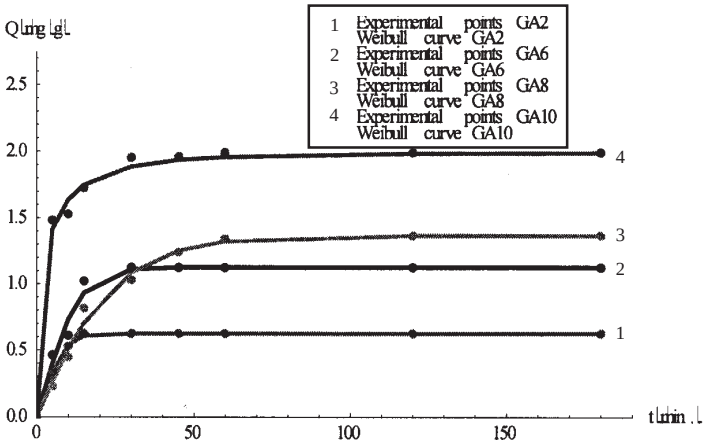

Fig. 3. Experimental and Weibull curves for GEL-PVA microparticles

We analyzed these results fitting the experimental data with a Weibull type law, demonstrated in the above paragraph. As a result, we obtained parameters *a* and *b*, the correlation factors and release kinetics fractal dimension for each of the samples that indicates some information on the drug release mechanisms at mesoscopic scale (table 1).

The first observation is that the correlation coefficient between the experimental curves and Weibull fitted curve are very good, better that than for Peppas curve (data not shown in this paper), this allowing us to affirm that this entire release process can be described better by the Weibull type law instead of Peppas law, showing the wide applicability of a Weibull type law. For illustration, we plot in figure3 the experimental and Weibull type curves.

Also, the values for *n*, from the Peppas law, namely no value of 0.5, indicate that in all these cases the diffusion mechanism is a non-Fickian one, the diffusion not being the predominant phenomena, others having, also, an important contribution: physical interactions between drug, polymer micro particles and release environment, chemical reactions and drug/polymer degradation.

Consequently, this complexity of the phenomena determines, also, naturally, a complex trajectory for the drug particles. It is known that a measure of the trajectory complexity is the fractal dimension of the trajectory, named, in this case, the fractal dimension of the release curve. This reasoning is confirmed by the fractal dimension values, determined according to (15b). The values between 1 and 3 are in agreement with the values usually accepted for fractal process [25]; the higher values denotes the fact that, either fractal dimension must be redefined as function of structure "classes", or the drug release process is complex, involving many freedom degrees in the phase space [26, 27]. Another observation that can be made based on this results is that the samples with $D_F < 2$ manifests a "sub-diffusion" and, in the other, with $D_F > 2$, the release process is of "super-diffusion" (table 1), classification in concordance with the experimental observation that these samples exhibit a "faster" diffusion, with a higher diffusion rate, with respect to the other samples [28-30].

Conclusions

In this paper, we have replaced the complexity of the physical processes that determines drug release from polymer micro particles with fractality, case for which it is no longer necessary to use the whole classical "arsenal" of quantities from the standard physics (differentiable physics). In this way, we introduce the fractal approximation of motion in the study of this complex physical and chemical system dynamics. Using fractional calculus, the fractal "diffusion" equation give rise to a Weibull type relation, a statistical distribution function of wide applicability, inclusively in drug release studies. In this approach, we consider all the simultaneous phenomena involved, equivalent with complexity and fractality, offering, in this way, a physical base to this equation and for its parameters. They are functions of fractal dimension of the curves on which drug release mechanism takes place, dimension that is a measure of the complexity and nonlinear dynamics of the system, dependent on the diffusion order.

This approach is confirmed as viability by some experimental results, from whose analyze results that experimental curves can be fitted, with very good correlation factors, better that that for the power type laws, by a Weibull type relation and that the fractal dimension of a drug release curve offers information on the drug release mechanisms.

Acknowledgement: This paper was supported by the project PERFORM-ERA "Postdoctoral Performance for Integration in the European Research Area" (ID-57649), financed by the European Social Fund and the Romanian Government and by the project POSDRU/88/1.5/S/47646 of The European Social Fund.

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Manuscript received: 28.03.2012