EXPERIMENTAL AND THEORETICAL INSIGHT INTO FORMULATIONS BASED ON POLY(VINYL ALCOHOL BORIC ACID) AND DICLOFENAC SODIUM SALT

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A series of three formulations were prepared in view of experimental and theoretical investigation of their drug release potential. The morphology of the film formulations, in terms of distribution of drug into the polymeric matrix and the nature of the drug was investigated by scanning electron microscopy and polarized light microscopy techniques. The in vitro drug release has been studied in a medium mimicking the physiological medium. It was established that the drug release is in close correlation with the mass ratio. Assuming that the dynamics of polymer-drug system's structural units take place on continuous and nondifferentiable curves (multifractal curves), we show that in a one-dimensional hydrodynamic formalism of multifractal variables the drug release mechanism (Fickian diffusion, non-Fickian diffusion, etc) are given through synchronous dynamics at a differentiable and non-differentiable scale resolutions. Finally, the model is confirmed by the empirical data.

Keywords: Poly(vinyl alcohol boric acid), diclofenac, drug release, multifractal model

1. Introduction

Poly(vinyl alcohol boric acid) (PVAB) is a poly(vinyl alcohol) (PVA) derivative resulted by reaction with boric acid [1-3]. The combination of the water soluble PVA with boric acid results in an improved hydrophilic polymer with

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antimicrobial and chiral activity, and unique ability to anchor a large variety of low molecular weight molecules due to the presence of electron deficient boron atom [4-9]. Latest studies realized on PVAB demonstrated its capacity to act as excellent matrix for low molecular weight molecules resulting into a large variety of composites with valuable properties for bio-applications. PVAB can easily accommodate liquid crystals to give polymer dispersed liquid crystals or drugs to give new formulations with slow drug release [4, 5, 8, 9]. In this line of thought, PVAB was used as polymer matrix for encapsulation of diclofenac sodium salt as drug model, and it proved to be a versatile matrix, which can assure a controlled modulation of the properties by simple variation of the polymer/drug mass ratio [9]. This promising result encouraged us to further investigate the system by a theoretical approach to gain a deeper view on the forces which governs the anchoring and release of the drug.

On another hand, the homogeneity assumption in its various forms (homogenous kinetic space, law of mass etc.) has become almost dogmatic in Pharmacokinetics (PK).The functionality of such a hypothesis allowed the development of a class of differentiable models in the description of dynamics of biological systems (i.e. "compartmental" analysis) and mainly, of drug release dynamics in such systems. However, biological systems are nowadays understood as inherently non-differential (fractal). Specifically, the microenvironments where any drug molecules with membrane interface, metabolic enzymes or pharmacological receptors are unanimously recognized as unstirred, space-restricted, heterogeneous and geometrically fractal. It is thus necessary to define a new class of models, this time non-differentiable, in describing biological system dynamics and particularly drug release dynamics in such systems.

In the present paper a novel approach for describing drug release dynamics in polymer-drug systems, considering that drug release dynamics can be described through continuous but non-differentiable curves (multifractal curves) is proposed.

The theoretical model is confirmed by the empirical date related to the diclofenac sodium salt and polyvinyl alcohol boric acid release.

2. Experimental setup

2.1. Materials and methods

Diclofenac sodium salt (DCF) and polyvinyl alcohol boric acid (PVAB, Mw=54 000) were purchased from Sigma Aldrich and used as received.

2.2. Formulation preparation

The formulations were prepared by mixin PVAB and DCF in different mass ratios, after the prior solubilizing of PVAB in bidistilled water at 90 ^{o}C. Shortly,

into a 7.5 % PVAB solution was slowly dropped a 5% DCF solution in ethanol under vigorous magnetic stirred. The mixture was further vortexed and then casted into petri dishes and allowed to dry at room temperature. The as obtained films were dried under vacuum before analysis. The mass ratio of the two components was PVAB/DCF = 70/30; 80/20; 90/10. They were coded P3, P2 and P1, function of the drug content.

2.3. Methods

The morphology of the film formulations was analyzed by a field emission Scanning Electron Microscope (SEM) EDAX – Quanta 200 at accelerated electron energy of 20 KeV. The nature of the DCF drug into the PVAB matrix was observed by polarized light microscopy (POM) with a Leica DM 2500 microscope.

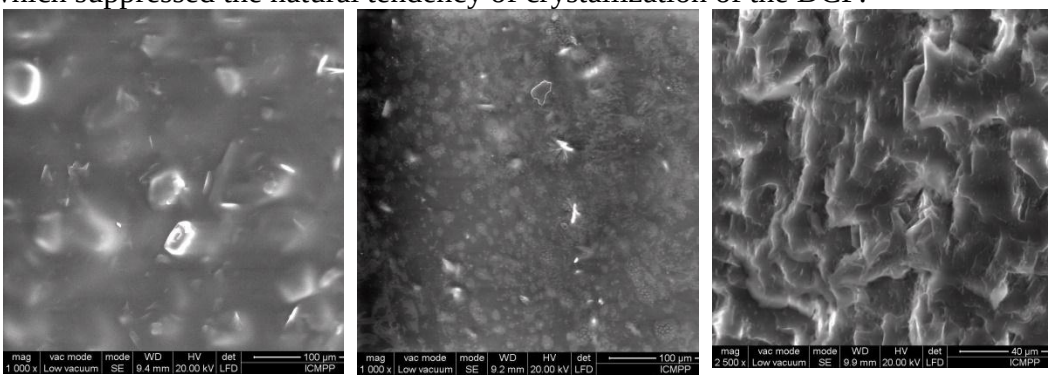
The in vitro DCF release was monitored into a medium mimicking the physiological environment, by fitting the concentration of the supernatant to a previous drawn calibration curve. Shortly, pieces of formulations films of 14 mg were immersed into 10 mL phosphate buffer and 2 mL supernatant was extracted at certain times and replaced with fresh PBS. The extracted supernatant was subjected to UV spectra measurements, monitoring the absorption of the characteristic DCF band at 275 nm on a Perkin Elmer Lambda.

3. Results

The film morphology was investigated by SEM which showed a granular topography, with uniform dispersed grains (Figure 1 a, b) with size around 40 μm for the P1 formulation and around 20 μm for P3 one. In cross-section, the films showed a highly rough topography. This is in agreement with the dispersion of the drug mainly as crystals [10, 11]. The increase of the drug crystals along with the decrease of its content into the PVAB matrix is related to the viscosity of the solution, as also observed in other investigations [12, 13]. The lower viscosity of the P3 formulation favored a better mixing of the two components and consequently the growth of crystals of lower dimension. On the contrary, the higher viscosity of the P1 solution hindered the mixing of the components and forced their rapid segregation.

To have an insight on the nature of the drug into the PVAB matrix, the formulation films were observed by POM. As can be seen in Figure 2, the films presented clear birefringent spots, attributed to the crystalline nature of the DCF [14, 15]. On the other hand, it could be observed that the crystals had different shape compared to the pure DCF crystals, signature of the influence of the PVAB matrix on the crystallization. Considering the presence of the strong electron deficient boron site of the PVAB matrix and the presence of the electron donor sites of the

DCF, it can be anticipated strong electrostatic forces between the two components which suppressed the natural tendency of crystallization of the DCF.



a) b) c)

Fig. 1. Representative images of the formulation films, a, b) at surface and c) in cross-section

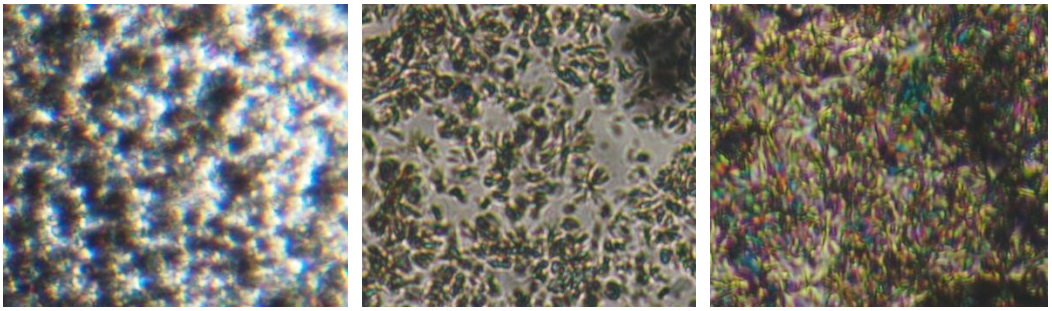


Fig. 2. Representative POM images of the film formulations

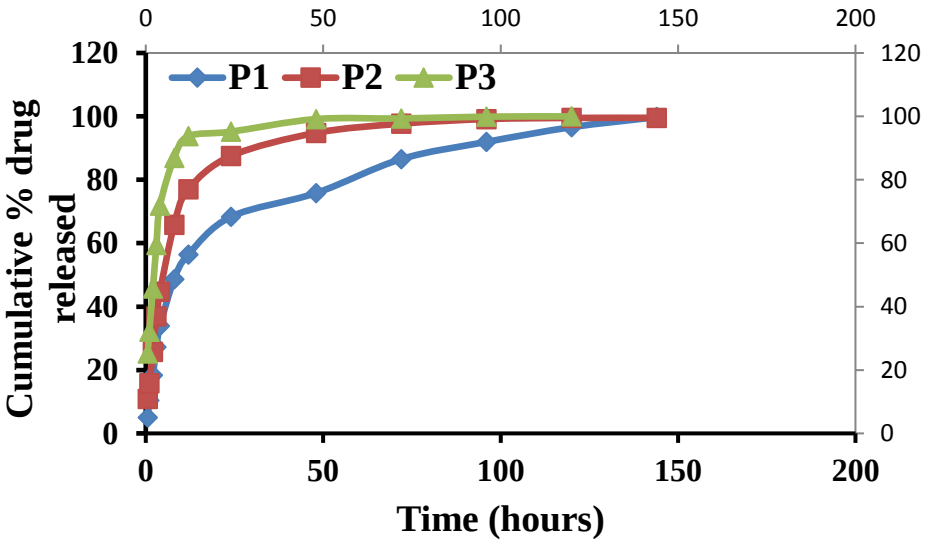


Fig. 3. In vitro release curves of the DCF from PVAB based formulations

In vitro release of the DCF showed different release rates, in close correlation with the DCF content. Thus, while P3 containing the highest amount of DCF presented a high burst effect, releasing almost all the drug in first 10 hours, the drug release slow down as the content of drug diminished, reaching a release lower than 60% for P1, in the same time (Figure 3). This behavior was in agreement with the higher hydrophilicity of the system containing higher amount of the drug, which favored a rapid swelling of the matrix, which favored the rapid diffusion of the drug [16]. It should be highlighted the high amount of drug which was successfully encapsulated into the PVAB matrix.

4. Theoretical Model

Let it be considered the one-dimensional multifractal hydrodynamic-type equations [17-21], in the form:

$$\partial_t V_D + V_D \partial_x V_D = -\partial_x \left[-2\lambda (dt)^{\left[\frac{4}{f(\alpha)}\right]-2} \frac{\partial_x \partial_x \sqrt{\rho}}{\sqrt{\rho}} \right] \tag{1}$$

$$\partial_t \rho + \partial_x (\rho V_D) = 0 \tag{2}$$

The equation (1) corresponds to the specific momentum conservation law of multifractal type, while equation (2) corresponds to the state density conservation law of multifractal type. In (1, 2) V_D is the differentiable velocity of the polymer-drug system independent on the resolution scale *dt*, ρ is the state density of multifractal type, *x* is the spatial coordinate of multifractal type, *t* is the temporal coordinate of non-multifractal type which is also affine parameter of the movement curves, λ is a parameter associated with the multifractal-non-multifractal scale transitions, $f(\alpha)$ is the singularity spectra of α order of the fractal dimension D_F and α is the singularity index of the fractal dimension [21, 22].

There are many modes, and thus a varied selection of definitions of fractal dimensions, the fractal dimension in the sense of Kolmogorov, the fractal dimension in the sense of Hausdorff – Besikovich [22] etc. Selecting one of these definitions and operating in the polymer-drug dynamics, the value of the fractal dimension must be constant and arbitrary for the entirety of the dynamical analysis. For example, it is regularly found $D_F<2$ for correlative processes, $D_F>2$ for non – correlative processes etc. In such a conjecture operating with the singularity spectrum *f(α)* it is possible to identify not only the "areas" of the polymer-drug dynamics that are characterized by a certain fractal dimension, but also the number of "areas" whose fractal dimensions are situated in an interval of values. Moreover, through the singularity spectrum *f(α)* it is possible to identify classes of universality

in the complex fluid dynamics laws, even when regular or strange attractors have different aspects [22].

These equations for the initial and boundary conditions:

$$V_D(x, t=0) = V_0, \qquad \rho(x, t=0) = \frac{1}{\sqrt{\pi}\alpha} exp\left[-\left(\frac{x}{\alpha}\right)^2\right] \tag{3}$$

$$V_D(x = V_0 t) = V_0, \qquad \rho(x = -\infty, t) = \rho(x = +\infty, t) = 0 \tag{4}$$

with V_0 the initial velocity and α the parameter of Gaussian distribution of positions, using the mathematical procedures from [22-27], admit the solution:

$$V_D(x, t, \sigma, \alpha) = \frac{V_0\alpha^2 + \left(\frac{\sigma}{\alpha}\right)^2 xt}{\alpha^2 + \left(\frac{\sigma}{\alpha}\right)^2 t^2} \tag{5}$$

$$\rho(x, t, \sigma, \alpha) = \frac{\pi^{-1/2}}{\left(\alpha^2 + \left(\frac{\sigma}{\alpha}\right)^2 t^2\right)^{1/2}} \exp\left[-\frac{(x - V_0 t)^2}{\alpha^2 + \left(\frac{\sigma}{\alpha}\right)^2 t^2}\right] \tag{6}$$

with

$$\sigma = \lambda(dt)^{\left[\frac{2}{f(\alpha)}\right]-1} \tag{7}$$

the multifractal degree. From here, the non-differentiable velocity V_F takes the form:

$$V_F(x, t, \sigma, \alpha) = \sigma \frac{(x - V_0 t)}{\alpha^2 + \left(\frac{\sigma}{\alpha}\right)^2 t^2} \tag{8}$$

Introducing the non-dimensional variables:

$$\xi = \frac{x}{V_0\tau_0}, \qquad \eta = \frac{t}{\tau_0} \tag{9}$$

and non-dimensional parameters

$$\mu = \frac{\sigma\tau_0}{\alpha^2}, \qquad \phi = \frac{\alpha}{V_0\tau_0} \tag{10}$$

with τ_0 the specific time, (5), (6) and (8) become:

$$V \equiv V_D(\xi,\eta,\mu) = \frac{V_D(x,t,\sigma,\alpha)}{V_0} = \frac{1+\mu^2\xi\eta}{1+\mu^2\eta^2} \tag{11}$$

$$\begin{aligned}\rho(\xi,\eta,\mu,\phi) &= \pi^{\frac{1}{2}}\alpha\rho(x,t,\sigma,\alpha)\\ &= (1+\mu^2\eta^2)^{-\frac{1}{2}}exp\left[-\frac{(\xi-\eta)^2}{\phi^2(1+\mu^2\eta^2)}\right]\end{aligned} \tag{12}$$

$$U \equiv V_F(\xi,\eta,\mu) = \frac{V_F(x,t,\sigma,\alpha)}{V_0} = \mu\frac{(\xi-\eta)}{1+\mu^2\eta^2} \tag{13}$$

Now taking out the quadratic term in η between (11) and (13), it results that for $\xi = const.$ the ratio $\frac{V}{U}$ is homographic dependent of ξ by the form:

$$\frac{U}{V} = \frac{\mu(\xi-\eta)}{1+\mu^2\xi\eta} \tag{14}$$

From here, the condition (dynamical simultaneity):

$$d\left(\frac{U}{V}\right) = 0 \Leftrightarrow V = constU \tag{15}$$

(i.e. the extension of the first principle of Newton to any scale resolution, or equivalently, "synchronizations" of drug release dynamics at differentiable scale with drug release dynamics at non-differentiable scale), implies correlations between phase and amplitude of the shape function, by the form:

$$\ln\rho = \rho_0 exp[const(s-s_0)] \tag{16}$$

where ρ_0 and s_0 are integration constants. Thus, it is stated that various "mechanisms" involved in the drug release process can be mimed through period doubling, quasi-periodicity, intermittences etc. (for details see [28]).

Because through the restriction (15) given, for example, by $V = -U$, the multifractal type conservation laws (1) and (2) take the form of the multifractal type "diffusion" equation:

$$\partial_t\rho = \lambda(dt)^{\left[\frac{2}{f(\alpha)}\right]-1}\partial_l\partial^l\rho = \sigma\partial_l\partial^l\rho \tag{17}$$

it results that these "mechanisms" "manifest"/are "perceived" as diffusions at various scale resolutions in a multifractal space (Fickian-type diffusion, non-Fickian-type diffusion etc.) To explain such a situation: the one-dimensional drug

diffusion of multifractal type from a controlled-release polymeric system with the form of a plane shut, of thickness δ. If drug release of multifractal type occurs under perfect sink condition, the following initial and boundary conditions can be assumed:

$$\begin{aligned} t = 0, \qquad & -\frac{\alpha}{2} < x < \frac{\alpha}{2}, \qquad \rho = \rho_0 \\ t > 0, \qquad & x = \pm\frac{\alpha}{2}, \qquad \rho = \rho_1 \end{aligned} \tag{18}$$

where ρ_0 is the initial drug states density of the multifractal type in the "device" of multifractal type and ρ_1 is the drug states density at the "polymer-fluid" interface of multifractal type. This solution equation under these conditions can take the following form (for details in the classical case see [28]). In Figure 4 there are represented the

$$f = \frac{\rho_t}{\rho_\infty} = 2\left(\frac{\sigma t}{\delta^2}\right)^{\frac{1}{2}} = \left\{\pi^{-1/2} + \sum_{n=1}^{\infty}(-1)^n erfc\left[\frac{n\delta}{2(\sigma t)^{\frac{1}{2}}}\right]\right\} \tag{19}$$

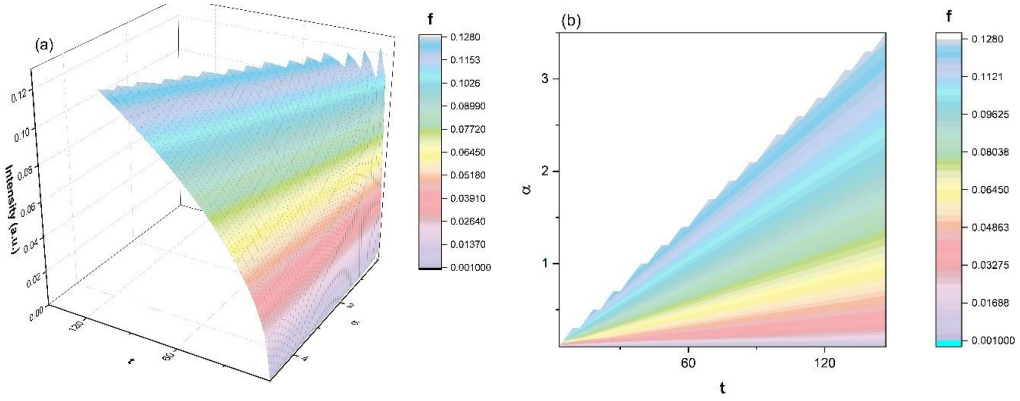


Fig. 4. 3D (left-side) and contour plot (right-side) representations of our multifractal function use for drug release mechanism analysis

An accurate expression can be obtained for small values of t since the second term of (20) disappears and then it becomes:

$$\frac{\rho_t}{\rho_\infty} = 2\left(\frac{\sigma t}{\delta^2}\right)^{\frac{1}{2}} = const(t)^{\frac{1}{2}} \tag{20}$$

In such a context, $\frac{\rho_t}{\rho_\infty}$ can be assimilated to the fraction of dissolved drug i.e. $\frac{M_t}{M_\infty} \equiv \frac{\rho_t}{\rho_\infty}$, where M_t is the amount of drug dissolved in time t and M_∞ is the total amount of time dissolved when the pharmaceutical dosage form is exhausted [21,

28]. A verification of our model is presented in Figure 5, for the drug release of diclofenac sodium salt and polyvinyl alcohol boric acid from. The empirical data was fitted with the mathematical function [29], and in terms of fractal analysis, fitted by the multifractal theoretical model [30, 31]. The figure shows that the model is well equipped to predict the drug-release dynamics.

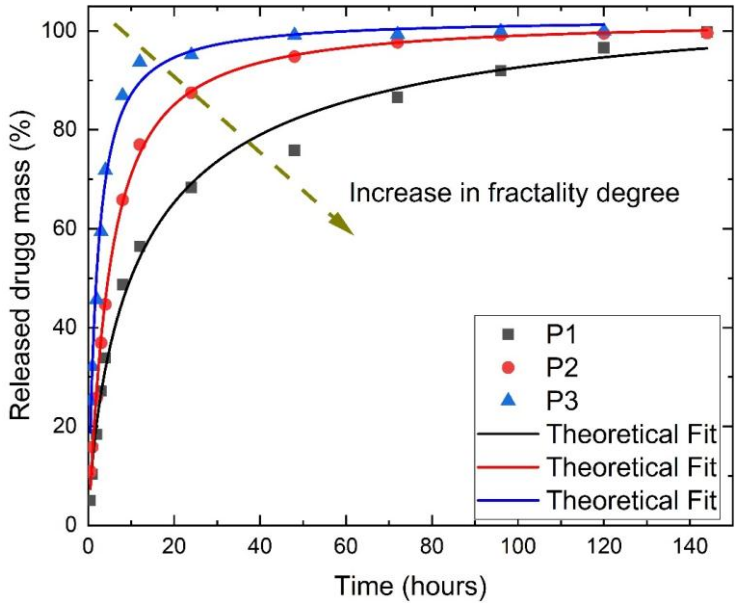


Fig. 5. Experimental showcase of the diclofenac sodium salt and polyvinyl alcohol boric acid release from the formulations fitted by the multifractal theoretical model

5. Conclusions

Formulations based on PVAB matrix and DCF drug were investigated as a promising strategy for drug release applications. It was highlighted that the presence of the electron deficient boron site favors accommodation of large amounts of drug by electrostatic anchoring and its slow release. This enlarge the possibility to further design new formulations which release properties can be modulated at demand, function of the targeted application. Assuming that the dynamics of polymer-drug system's structural units take place on multifractal curves, we have shown that in a one-dimensional hydrodynamic formalism of multifractal variables the drug release mechanism are given through synchronous dynamics at a differentiable and non-differentiable scale resolutions. Predictions given by our model are confirmed by the empirical data.

Authors' contributions:

All authors have equally contributed to this paper.

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