Fractal Hydrodynamic Model for Drug Release Processes from Starch Based Hydrogels

VIVIANA RADU1, SIMONA BACAITA2,3*, ANCUȚA ULINIUC2, MARCEL POPA2, SIDONIA SUSANU4
1 Al. I. Cuza” University Iasi, Department of Physics, Carol I Blv., 70050, Iasi, Romania
2 “Gheorghe Asachi” Technical University of Iasi, Faculty of Chemical Engineering and Environmental Protection, Department of Natural and Synthetic Polymers, 73 Prof. dr. docent Dimitrie Mangeron Rd., 70050, Iasi, Romania
3 “Gheorghe Asachi” Technical University of Iasi, Physics Department, Faculty of Machine Manufacturing and Industrial Management, 59A Prof. dr. docent Dimitrie Mangeron Rd., 70050, Iasi, Romania
4 University for Medicine and Pharmacy „Gr. T. Popa” Iasi, Department of Ophthalmology, 16 Universitii Str., 700115, Iasi, Romania

Assuming that the “structural” elements of a multiphase fluid (hydrogel, drug or fluid particles) move on continuous and non-differentiable curves (fractal curves), a new theoretical model that describes the drug release processes from polymeric hydrogels is established. This model, namely fractal hydrodynamic model, is based on two equations: the momentum and probability density conservation laws. The fractal potential, from the momentum conservation law, is a measure of the non-differentiability of the movement curves and controls the drug release processes. The model allows us to evaluate some characteristics of the hydrogel network, such as a distribution parameter for drug particle inside hydrogel. The novelty of this approach is that the system complexity is replaced by fractality, eliminating thus the whole classical “arsenal” of quantities from the standard physics based on the assumption of continuity and differentiability of physical quantities (differentiable physics).

Keywords: fractal hydrodynamic, drug release, polymer, hydrogel

Controlled release systems have been developed to improve the temporal and spatial release of drug in the body, to protect drug from physiological degradation or elimination, to improve patient compliance, and to enhance quality control in manufacturing of drug products. When designing controlled-release systems, it is important to identify and understand particular mechanisms involved in the release process. Often, more than one mechanism is involved at a given time or different mechanisms may dominate at different stages of the drug delivery process [1].

Hydrogels are one of the most used controlled release systems, due to the large variety in chemical structure and cross linking methods. They are cross linked polymers with the ability to swell in an aqueous medium.

The main controlled-release mechanisms from hydrogels include dissolution, partitioning, diffusion, swelling, erosion and targeting. Of these, diffusion is considered, not always accurate, the predominant phenomena and the release theories are based on the analyze of diffusion phenomena.

While it may be natural to think of hydrogel as a static solid, it is actually a dynamic fluctuating structure and the diffusion coefficient may be thought of as a measure of the degree that these fluctuations accommodate random motion of the diffusing molecule. For a molecule diffusing through a water-swollen hydrogel, diffusivity of the drug is affected by the viscosity of the water space and also by obstructions placed in the drug molecule path by the hydrogel chains. Many models of diffusion in hydrogels, therefore, combine elements of Stokes-Einstein and free volume theories. In this case, the size of water-filled spaces between hydrogels chains is assumed to fluctuate, making room for movement of the drug diffusing molecule. The characteristic distance between points of chain crossing in the hydrogel is called the correlation length and the ratio of the molecular radius of drug to the correlation length is considered to be the primary structural parameter governing the drug diffusion coefficient in the hydrogel [2].

However, the molecular basis of the diffusion consists in the fact that all molecules constantly undergo random collisions with other molecules; at any step, the direction of motion of a molecule is random, and it repeatedly changes due to collisions with other molecules. Over time, the displacement of the molecule from its point of origin is the result of a multitude of such random steps. Microscopically, their trajectories can be described by continuous and non-differentiable curves (fractal curves): between two successive elastic collisions the particles trajectories are straight lines and the trajectories become non-differentiable in the impact point (there are left and right derivatives in this point). Macroscopically, the independent random walks taken by large number of drug molecules lead them, finally, from regions of higher concentration to regions of lower concentration [3].

Thus, by considering drug particle trajectories as fractal curves, the complexity of the systems can be replaced by non-differentiability/fractality and it will be no longer necessary to use the whole classical “arsenal” of quantities from the standard physics (differentiable physics) [4].

This approach was applied for the case of polymeric microparticles, at small time scale [5, 6] and large time scale [7]. The good correlation factors between the theoretical model and experimental data validated this theory. We must mention that until this attempt, they were some fractal approaches for polymer physics [8, 9], some of them fractal [10], but only in the case of some local and structural analysis of polymers. Also, the fractal approach...
proved to have very good results in related fields as biology [11] and medicine [12].

The novelty of our model is that, based on the arguments presented above, we will particularize this theory for the drug release process from hydrogels (a particular type of polymeric matrices). These physical systems will be considered as a special interaction-less "fluid", called fractal fluid [13-15], in which transport phenomena takes place [ref transport phenomena 16-18].

This paper is structurated as follows: in Section 2, using the hydrodynamic fractal model, expressions for the probability density and speed field of drug particles are obtained, with a particular discussion for the one-dimensional case. Experimental results, that we used in our analyze are presented in Section 3. Section 4 contains the results and discussions arised from this new approach. In Section 5, the conclusions are given.

Theoretical considerations

We assume that our system, consisting of hydrogel, drug and the fluid release environment, is a complex system that can be assimilated with a multiphase fluid those "structural" elements (either hydrogel or drug or fluid particles) move on continuous and non-differentiable curves (fractal curves). Next, in our paper, by fluid particle we will mean any "structural" element of the system.

Fractal hydrodynamics

In the hydrodynamic fractal model [19-21], assuming that the fluid particle movements take place fractal curves (for details see [22-24]), the fluid particle dynamics are described by a Navier-Stokes type equation:

$$\frac{\partial \hat{\mathbf{v}}}{\partial t} + (\mathbf{v} \cdot \nabla) \hat{\mathbf{v}} - \nu \nabla^2 \mathbf{v} + \mathbf{f} = 0$$

where \(\hat{\mathbf{v}}\) is the complex velocity field of the fluid particle:

$$\hat{\mathbf{v}} = \mathbf{v} - i \mathbf{u},$$

\(\mathbf{v}\) is the standard classical speed, which is independent of scale resolution, \(\mathbf{u}\) is a new quantity arising from non-differentiability, which is dependent on resolution, \(D\) a coefficient, that characterize the fractal-non-fractal transition, dependent on the resolution scale and fractal dimension \(D_F\) [25-28].

The equation (1) means that at any point of a fractal path, the local temporal term, \(\hat{\mathbf{v}}\), the non-linearly (convective) term, \(\mathbf{v} \cdot \nabla \mathbf{v}\), and the dissipative one, \(\nabla^2 \mathbf{v}\), make their balance.

If the fluid particle motion is irrotational, i.e. \(\nabla \times \mathbf{v} = 0\), we can choose \(\hat{\mathbf{v}}\) of the form:

$$\hat{\mathbf{v}} = -2i \overline{n} S \nabla \ln n$$

where \(\psi\) is a new complex scalar function, called speed potential.

For

$$\psi = \sqrt{n} e^{i\theta},$$

with \(\sqrt{n}\) the amplitude and \(S\) the phase of \(\psi\), the complex speed field (2) takes the explicit form:

$$\mathbf{v} = 2\overline{n} S \nabla \ln n \quad \text{and} \quad \mathbf{u} = \overline{n} S \nabla \ln n$$

$$\mathbf{f} = 2\overline{n} S \nabla \ln n$$

By substituting (5a-c) in (1) and separating the real and the imaginary parts, up to an arbitrary phase factor which may be set at zero by a suitable choice of the phase of \(\psi\), we obtain:

$$m_0 \left( \frac{\partial \hat{\mathbf{v}}}{\partial t} + (\mathbf{v} \cdot \nabla) \hat{\mathbf{v}} \right) = -\nabla Q$$

$$\text{with } Q \text{ the fractal potential} [28]:$$

$$Q = -2m_0 \overline{n}^{2/3} \frac{1}{\sqrt{n}} \frac{\partial \psi}{\partial n}$$

The fractal potential (7) comes from the non-differentiability and must be treated as a kinetic term and not as a potential one [29].

The equation (6a) is the law of momentum conservation, the equation (6b) is the law of mass conservation and \(m_0\) is the rest mass of the fluid particle. These equations define the fractal hydrodynamics.

Fractal hydrodynamics in one-dimensional case

In the one-dimensional case, the fractal hydrodynamic equations (6a,b) with (7), for Peano’s type curves and fractal dimension \(D_F = 2\) take the form:

$$m_0 \left( \frac{\partial \hat{\mathbf{v}}}{\partial t} + (\mathbf{v} \cdot \nabla) \hat{\mathbf{v}} \right) = -\frac{\partial}{\partial x} \left[ 2m_0 \overline{n}^{2/3} \frac{1}{\sqrt{n}} \frac{\partial \psi}{\partial n} \right]$$

Using the substitutions:

$$\mathbf{f} = \tau, \quad kx = \xi, \quad \mathbf{v}/v_0 = V,$$

with:

$$n/\overline{\overline{n}} = N, \quad \mu^2/2 = 2\sqrt{\overline{n}} \kappa^3/\omega_0,$$

the equations (8a,b) became:

$$\left( \frac{\partial V}{\partial \tau} + V \frac{\partial V}{\partial \xi} \right) = \frac{\partial}{\partial \xi} \left[ \frac{\mu^2}{2} \frac{\partial^2 V}{\partial \xi^2} \right]$$

$$\frac{\partial N}{\partial \tau} + \frac{\partial}{\partial \xi} (NV) = 0$$

Considering that the initial state of the fluid particle is specified by the normalized speed:

$$V(\xi, \tau = 0) = V_i$$

and by a Gaussian normalized position distribution of the fluid particle that is related to a normalized distribution parameter \(\alpha\) [24]:

$$N(\xi, \tau = 0) = \frac{1}{\sqrt{4\pi \alpha}} e^{-\frac{\xi^2}{4\alpha}}$$

This means that at \(\tau = 0\), the center of the distribution \(N(\xi)\) is at \(\langle \xi \rangle_o = 0\) and has the speed \(\langle V \rangle_o = V_o\). The boundary conditions are:

$$V(\xi = +\infty, \tau) = V_o, \quad N(\xi = -\infty, \tau) = 0$$

Since \(\langle \xi \rangle = V_0 \tau\) in the absence of external forces, this suggests that, equation (10a), can be separated into:

$$\frac{\partial}{\partial \xi} \left( \frac{1}{\sqrt{N}} \frac{\partial N}{\partial \xi} \right) = \frac{2}{\alpha} (\xi - V_0 \tau)$$
Integration of equation (14a) gives, under consideration of the boundary conditions (13a,b), a quadratic solution in $(\xi - V_0 \tau)$, i.e.

$$N(\xi, \tau) = \frac{1}{\sqrt{\pi a(\tau)}} \exp \left[ -\frac{(\xi - V_0 \tau)^2}{a(\tau)} \right]$$ \hspace{1cm} (15)

This function indeed satisfies the initial condition (12), if the initial value of $a(\tau)$ is chosen as

$$a(\tau = 0) = \alpha^2$$ \hspace{1cm} (16)

Introducing equation (15) into the continuity equation (10b) indicates that for $\xi = V_0 \tau$

$$\frac{1}{2a} \frac{d a}{d \tau} \left[ \frac{\partial V}{\partial \xi} \right]_{\xi = V_0 \tau}$$ \hspace{1cm} (17)

Then, the differential equation for $a(\tau)$ is obtained by performing the operation $\left( \frac{\partial}{\partial \xi} \right)_{\xi = V_0 \tau}$ on equation (14b),

$$\frac{d^2 a}{d \tau^2} - \frac{1}{2} \left( \frac{da}{d \tau} \right)^2 = 2 \mu^2$$ \hspace{1cm} (18)

The solution of equation (18) with the initial condition (16) (satisfying the requirement $N(\xi, \tau)$ to be real, which is met by the symmetry condition $a(\tau) = a(-\tau)$) is:

$$a(\tau) = \alpha^2 + \left( \frac{\mu}{\alpha} \right)^2 \tau^2$$ \hspace{1cm} (19)

According to equations (15) and (19), the probability density is a Gaussian in a form with a time-dependent distribution parameter $a(\tau)$, and spreads with the “classical” normalized particle speed $V_0$.

$$N(\xi, \tau) = \frac{1}{\sqrt{\pi \left( \alpha^2 + \left( \frac{\mu}{\alpha} \right)^2 \tau^2 \right)}} \exp \left[ -\frac{(\xi - V_0 \tau)^2}{\alpha^2 + \left( \frac{\mu}{\alpha} \right)^2 \tau^2} \right]$$ \hspace{1cm} (20)

Similarly, integration of equation (14b) with the initial condition (11), and the boundary one (13a), gives the normalized speed field of the fluid particle:

$$V(\xi, \tau) = \frac{V_0 \alpha^2 + \left( \frac{\mu}{\alpha} \right)^2 \xi \tau}{\alpha^2 + \left( \frac{\mu}{\alpha} \right)^2 \tau^2}$$ \hspace{1cm} (21)

The relations (20) and (21) represent the normalized fractal-hydrodynamic solution for the motion of a fluid particle.

Next, we will apply this model to the drug release process from polymeric hydrogel, following the determination of a qualitative dependence between some “structure” parameters of the hydrogel network (distribution and diffusion parameters) on the crosslinking time.

**Experimental part**

New hydrogels, with variable hydrophilicity, based on chemically modified starch and cross linked with citric acid were obtained. The terminology used is as follows: HS- unmodified starch based hydrogel, HSCP- hydrogel based on modified starch with palmitoyl chloride, HSPCL- hydrogel based on modified starch with PCL (poly(Î´-caprolactone)). The effect of various cross linking time used in the experimental program and the changes in the morphology and/or stability of the hydrogels in water have been studied [30].

The samples codes indicates the crosslinking time (e.g. HS4 represents the sample of unmodified starch based hydrogel with 4h crosslinking time, HSCPL6 – the sample of hydrogel based on starch modified with PCL with 6h crosslinking time).

**Results and discussions**

We particularize the theoretical results from Section 2 for the above presented drug loaded hydrogels.

We assume that when the drug loaded hydrogel is introduced into a liquid in which the drug release occurs, the fluid, tending to reduce the perturbation induced by the drug concentration gradient will interact with drug particles and induces them a dynamic similar to that of fluid particles through fractal potential (7).

Moreover, in the initial state, we assume that the drug particles are in rest ($V_0 = 0$) and the density probability profile, which in our case can be assimilated with the drug concentration one inside the hydrogel, is a Gaussian type distribution, similar with relation (12). With these assumptions, from (20) results that the normalized probability density for drug particles inside hydrogen varies in time, in a certain point $\xi$ equal with unit length, according to relation:

$$N(\tau) = \frac{1}{\sqrt{\pi \left( \alpha^2 + \left( \frac{\mu}{\alpha} \right)^2 \right)}} \exp \left[ -\frac{1}{\alpha^2 + \left( \frac{\mu}{\alpha} \right)^2} \right]$$ \hspace{1cm} (22)
and, from (21), the speed of drug particle inside hydrogel is:

$$v_i(\tau) = \frac{\mu_i}{\alpha^2 + \left(\frac{\mu_i}{\alpha}\right)^2}$$  \hspace{1cm} (23)

Now, by means of relation (22), the normalized probability density of drug particle in the release environment, outside hydrogel, at the normalized moment $\tau$, is:

$$N_i(\tau) = N_i - N_0 = N_i \left[1 - \frac{1}{\left(1 + \frac{\mu_i}{\alpha^2}\right)^2} \exp\left(-\frac{1}{\left(1 + \frac{\mu_i}{\alpha^2}\right)^2}\right)\right]$$  \hspace{1cm} (24)

where

$$N(\tau = \infty) = N_0 = \frac{1}{\alpha \sqrt{\pi}}$$  \hspace{1cm} (25)

is the normalized probability density of drug released at equilibrium (stationary state). Since, in the usual theories of the release kinetics of a drug from polymeric materials, based on random processes [10], the normalized probability density identifies with normalized concentration, expressed as a mass ratio between released drug and loaded hydrogel.

From (25) and from the experimental data, results the values from table 1 for distribution parameter for drug particle inside hydrogel $\alpha$.

We note that these values increases with the crosslinking time, so we can consider this as measure of the network density. The fact that the network is denser when the crosslinking time increases is confirmed by the fact that the amount of the loaded drug decreases with crosslinking time [30].

By means the above assumption, through which we identify the normalized probability density with normalized concentration, the equation (24) was fitted to experimentally determined levofloxacin release kinetics and, based on these fittings, the “structural parameter” $\mu$ was estimated. The obtained values are shown in table 2.

According to relation (9e), in non-normalized coordinates, this “structural parameter” can be identified with the diffusion coefficient. Its decrease when the drug particle is moving through a denser network is conform with the kinetic theory of diffusion (diffusion is much faster in media with low density due a higher diffusion pathways determined by the small number of collisions between drug particle and hydrogel network).

The correlation factors ($R^2$) between data resulted from (24), with the above values for the structure parameters $\alpha$ and $\mu$, and the experimental data, were very good, as seen in figure 2.

These values lead to the following speed field, shown in figure 3. These microscopic evolutions of drug particle will determine, at macroscopic level, the release characteristics (the initial “burst effect”, the time on which the release can sustained). The speed evolutions have a similar trend as the release kinetics: a strong increase and then levels off to reach a plateau that corresponds to the equilibrium stationary state.

For all the samples, the drug particle speed inside hydrogels exhibits, at first, strong variations corresponding to the macroscopic “burst effect”, due to the initial high concentration gradient between the drug loaded hydrogel and release environment; the samples with higher crosslinking time have smaller variations for speed, as a result of the movement through a denser network.

Regarding the release time, it is determined by the release speed: a small value for particle speed implies a slower movement of particle through the hydrogel network and, in consequence, a longer release time for the drug. This theoretical result is validated by the experimental

<table>
<thead>
<tr>
<th>Crosslinking time (h)</th>
<th>HS</th>
<th>HSCP</th>
<th>HSPLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>2.191</td>
<td>6.839</td>
<td>3.407</td>
</tr>
<tr>
<td>5</td>
<td>2.526</td>
<td>7.341</td>
<td>3.637</td>
</tr>
<tr>
<td>6</td>
<td>2.861</td>
<td>9.703</td>
<td>5.019</td>
</tr>
</tbody>
</table>

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Table 1

VALUES OF DISTRIBUTION PARAMETER $\alpha$

<table>
<thead>
<tr>
<th>Crosslinking time (h)</th>
<th>HS</th>
<th>HSCP</th>
<th>HSPLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>1.064</td>
<td>12.45</td>
<td>1.102</td>
</tr>
<tr>
<td>5</td>
<td>0.616</td>
<td>11.816</td>
<td>0.554</td>
</tr>
<tr>
<td>6</td>
<td>0.504</td>
<td>8.760</td>
<td>0.496</td>
</tr>
</tbody>
</table>

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Table 2

VALUES OF THE “STRUCTURAL PARAMETER” $\mu$

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Fig. 2 Experimental and theoretical release kinetics of levofloxacin from starch based hydrogels: HS(a), HSCP(b), HSPLC(c)
results [30] that revealed that samples with higher cross linking time have longer release time, according to the theoretical fact that for these samples the drug speed has the smaller values.

One common feature of all mentioned parameters is that, after some time intervals, specific for each polymeric system, their values reach a constant limit, the corresponding states being stationary and independent on the preparation procedure [31].

Conclusions

This approach of the drug release process from hydrogels allows the determination of a qualitative dependence between some “structural” parameters of the hydrogel network (distribution and diffusion parameters) on the cross linking time. Their variation with experimental protocol parameters (the cross-linking time) is consistent with the experimental data. The great advantage of this approach, in which complex systems dynamics are replaced by fractality, is that it offers an alternative to the classical mathematical modeling, based on the assumption of continuity and differentiability of physical quantities, in which is very difficult to take into considerations all phenomena, so that approximations are required.

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