Modeling and quantifying drug release

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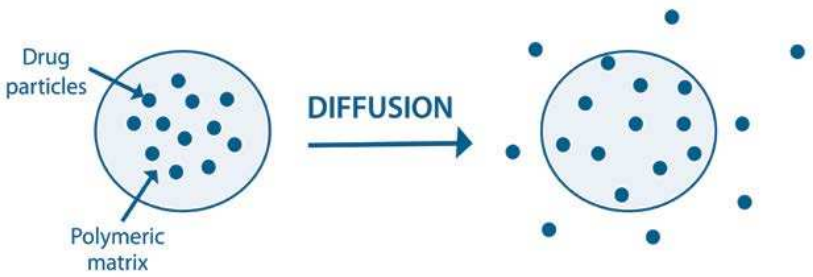
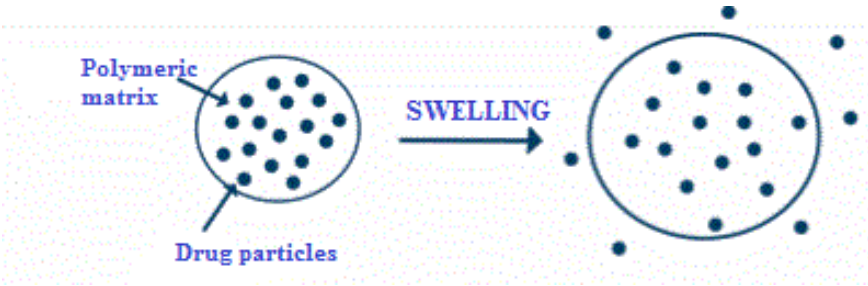
Main drug release mechanisms

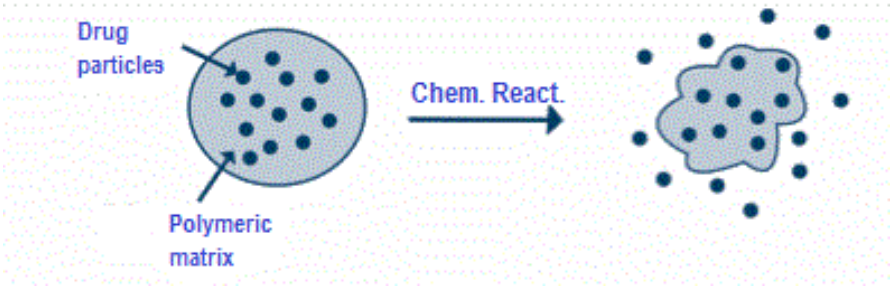
- Diffusion



- Swelling



- Chemical reactions (degradation, erosion, dissolution, etc.)



Often more than one mechanism is involved in the release process.
Different mechanisms may dominate at different stages of the release

Lin and Metters, *Adv. Drug Deliv. Rev.* **58**, 1379 (2006)
Siepmann and Siepmann, *Int. J. Pharm.* **364**, 328 (2008)
Peppas and Narasimhan, *J. Control. Release* **190**, 75 (2014)
Fundamentals and Applications of Controlled Release Drug Delivery, Springer (2012)

Quantifying drug release profiles

Dependence of the release profiles on the device characteristics

Diffusion controlled release from:

spheres,
composite spheres,
and slabs

Numerical simulations (Monte Carlo) and analytical solutions of diffusion equation

Numerical procedure (Monte Carlo simulations)

To simulate diffusion from a sphere of radius R, we consider a 3D cubic lattice and then define a spherical region inside it.

A number of drug particles is randomly placed in lattice cells *inside* the sphere, avoiding double occupancy, until a fixed initial particle concentration is reached in the sphere.

Diffusion is simulated by randomly selecting a particle at each Monte Carlo step and trying to move it to a *randomly selected* nearest neighbor site. The move is allowed if the site is empty but rejected if already occupied, assuming excluded volume interactions.

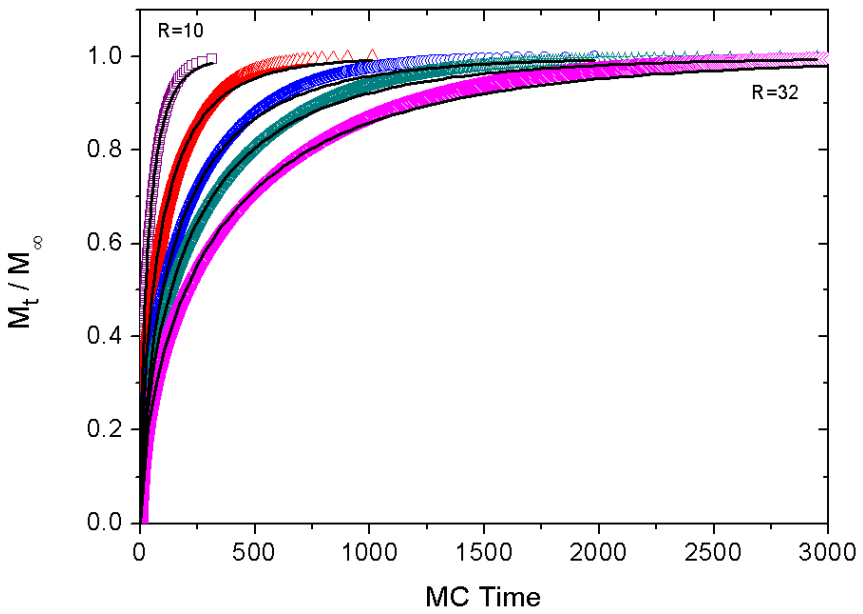
As soon as a particle migrates to a site lying outside of the sphere it is removed from our simulation.

To simulate processes with different diffusion coefficients ($D \leq D_0$) we introduce an additional parameter, q ($0 \leq q < 1$), that can be directly linked to the relative diffusion coefficient, $D_r = D/D_0$, as $q = 1 - D_r$. At each MC step, the randomly chosen particle may stay immobile with a probability q, or try to move with a probability $1-q$.

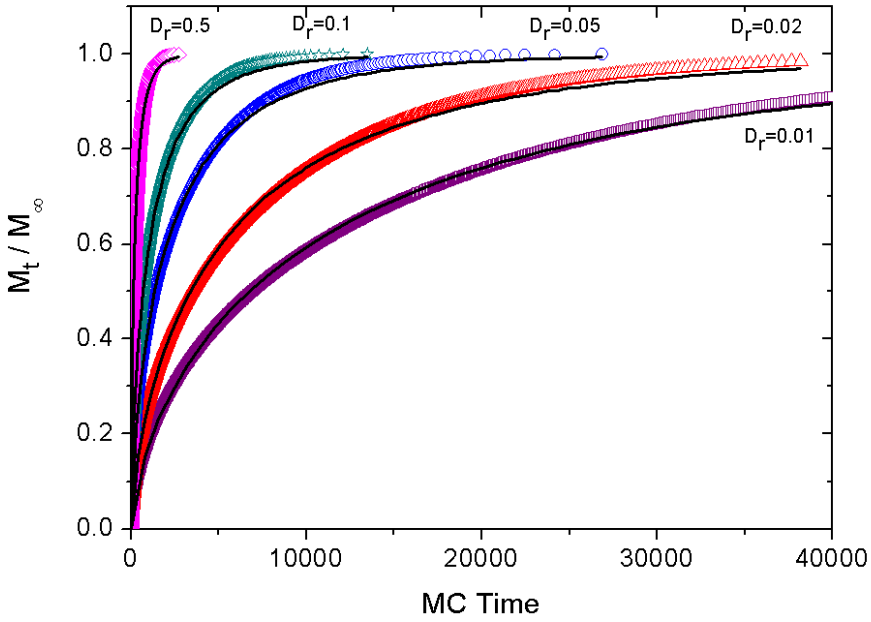
After each MC step, time is incremented by $1/N(t)$, $N(t)$ being the number of particles still remaining in the system.
We follow the number of remaining particles inside the sphere as a function of time, until the sphere is completely empty.
The results are statistically averaged over a number of realizations (~100), using the same problem parameters.

Kosmidis, Argyrakis, Macheras, *Pharm. Res.* **20**, 988 (2003)

Drug release from simple spherical devices



Fractional release from spheres of radii:
R=10, 16, 22, 26, 32 ($D_r=D/D_0$=1)



Fractional release from spheres of different diffusion coefficients D_r (R=18)

A stretched exponential function accurately fits the numerically obtained results

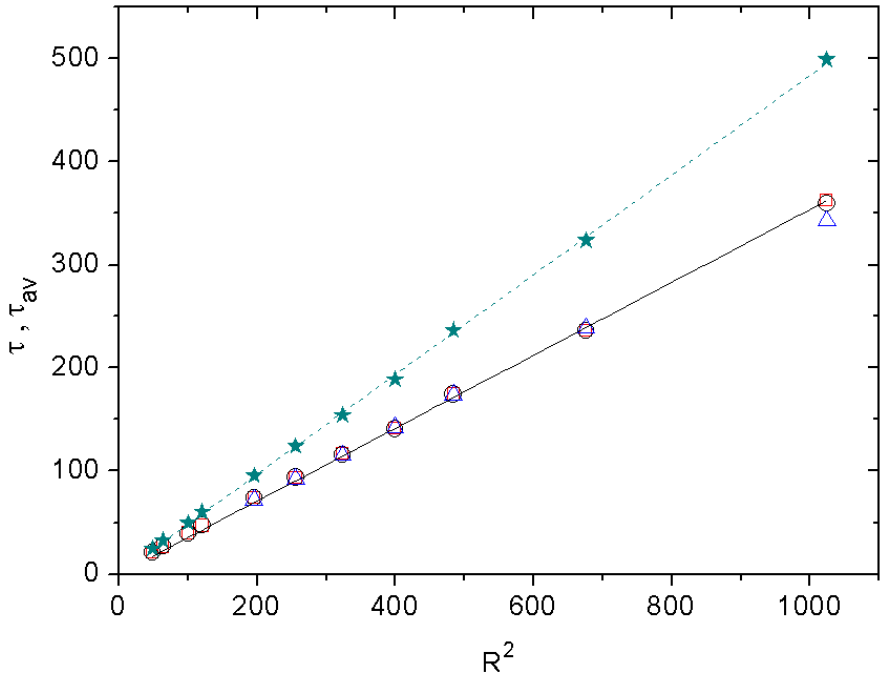
$$\frac{M_t}{M_\infty} = 1 - e^{-\left(\frac{t}{\tau}\right)^b}$$

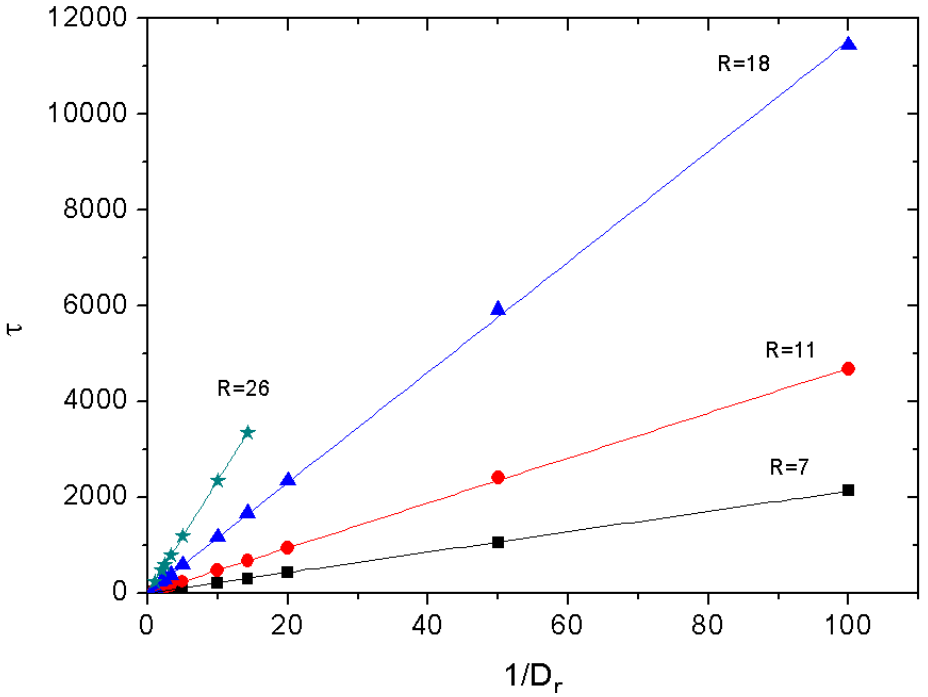
Quantitative description: what is the dependence of parameters b and τ on the device characteristics (R,D,C_0)?

Hadjitheodorou, Kalosakas, *Mater. Sci. Eng. C* **33**, 763 (2013)

Drug release from simple spherical devices

Dependence of stretched exponential time parameter τ





$\tau(R^2)$ for initial drug concentrations: 0.9 (red squares), 0.5 (black circles), 0.01 (blue triangles). $D_r=D/D_0=1$

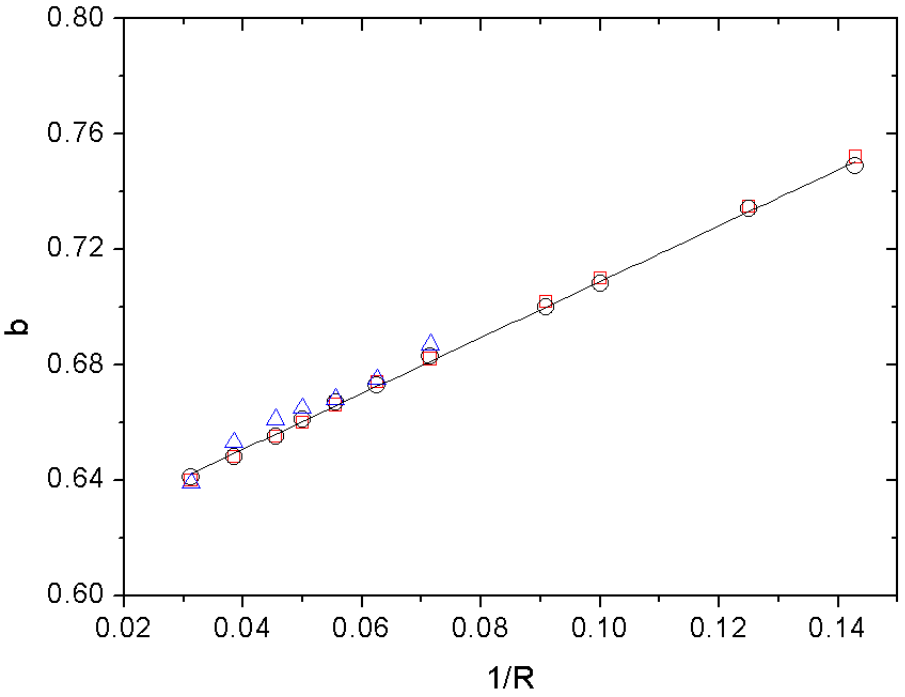
$\tau(1/D_r)$ for different sphere radii R

The numerical simulations result in

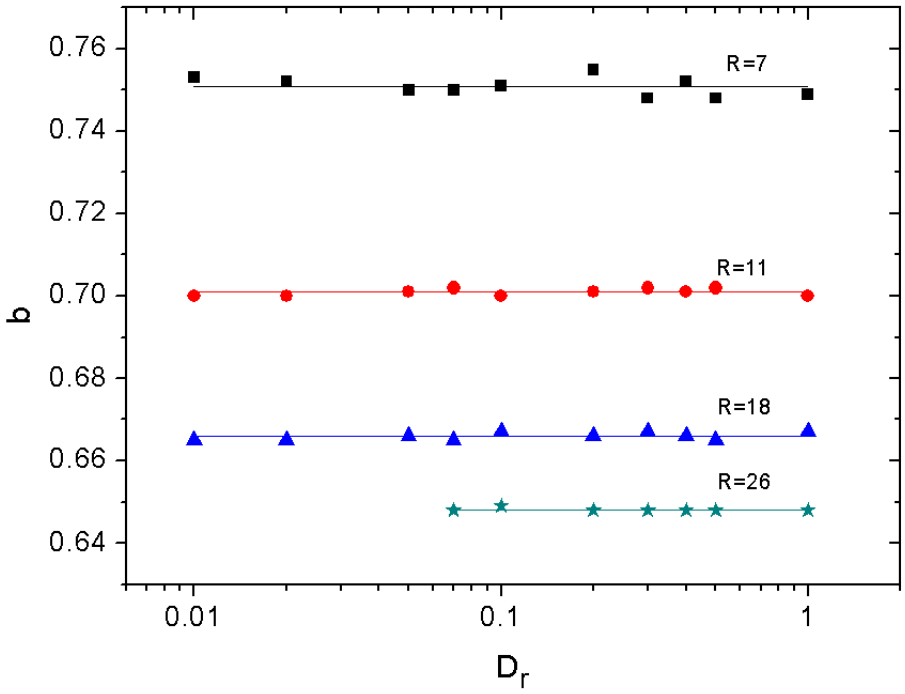
$$\tau = 0.058\,\frac{R^2}{D}$$

Drug release from simple spherical devices

Dependence of stretched exponential exponent b



b(1/*R*) for initial drug concentrations: 0.9 (red squares), 0.5 (black circles), 0.01 (blue triangles). $D_r=D/D_0=1$



b(D_r) for different sphere radii *R*

The numerical simulations result in

$$b = \frac{1.0}{R/l_u} + 0.61$$

Drug release from simple spherical devices

Analytical estimates from the solution of diffusion equation

Solution of diffusion eq. for drug molecules with density *C* in a spherical matrix of radius *R*, with homogeneously distributed drug particles as initial condition and sink boundary conditions:

$$\frac{\partial C}{\partial t} = D\,\nabla^2 C \qquad C(\vec{r}, t=0) = C_0 = \frac{M_\infty}{(4/3)\pi R^3} \qquad C(r=R,t)=0$$

Writing diffusion eq. in spherical coordinates and taking into account the symmetry of the problem, i.e. *C=C(r,t)*, we get

$$\frac{\partial C}{\partial t} = \frac{1}{r} D \frac{\partial^2 (rC)}{\partial r^2}$$

$$C(r,t) = \frac{3M_\infty}{2\pi^2 R^2 r} \sum_{n=1}^{\infty} \frac{(-1)^{n+1}}{n} \sin\left(\frac{n\pi r}{R}\right) e^{-n^2\pi^2 \frac{D}{R^2} t}$$

This equation can be solved, for $U = r\,C$, with the separation of variables method

The mass $M_{in}(t)$ of drug molecules inside the spherical matrix, at time *t*, equals to

$$M_{in}(t) = 4\pi \int_0^R C r^2 dr = \frac{6M_\infty}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} e^{-n^2\pi^2 \frac{D}{R^2} t}$$

The released drug: $M_t = M_\infty - M_{in}(t)$ ➔

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} e^{-n^2\pi^2 \frac{D}{R^2} t}$$

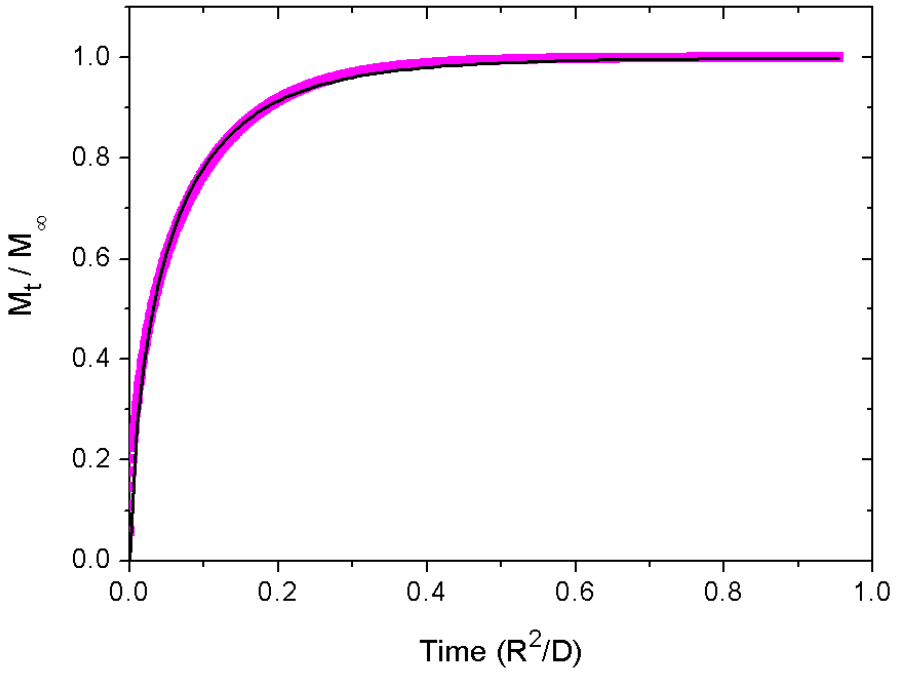
Drug release from simple spherical devices

Analytical estimates from the solution of diffusion equation

Analytical solution:

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}e^{-n^2\pi^2\frac{D}{R^2}t} = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}e^{-n^2\pi^2 t_d}$$

$t_d = t\,D/R^2$
dimensionless time



Analytically obtained fractional release and fitting with a stretched exponential (b=0.68, τ_d=0.054)

Analytical estimates:

$$\tau = 0.054\frac{R^2}{D}$$ independent of C_0

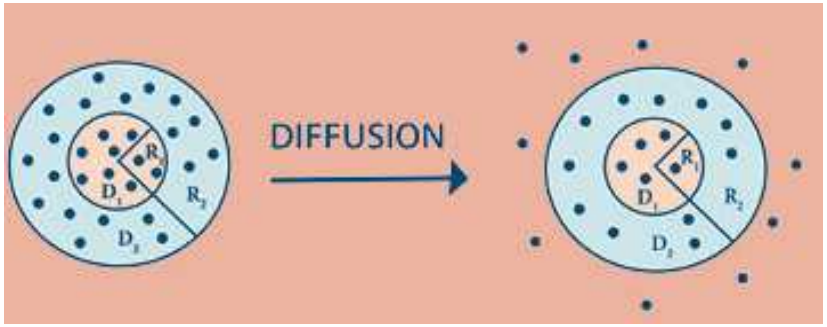
$$b = 0.68$$ independent of R, D, C_0

Numerical estimates:

$$\tau = 0.058\frac{R^2}{D} \qquad b = \frac{1.0}{R/l_u} + 0.61$$

Drug release from composite spherical devices

Solution of diffusion eq. for a composite spherical matrix with homogeneously distributed drug particles as initial condition and sink boundary conditions:



$$\frac{M_t}{M_\infty} = 1 - \frac{6}{R_r^2}\sum_{n=1}^{\infty}\frac{\varphi_1(y_n)}{\varphi_2(y_n)}e^{-y_n^2\frac{D_1}{R_1^2}t}$$

$R_r = R_2/R_1$, $k=\sqrt{D_1/D_2}$, and

the sum is over the positive roots y_n of

$$ky\cot[ky(R_r-1)] + k^2 y\cot(y) + (1-k^2) = 0$$

$$\varphi_1(x) = \frac{1}{x}\left(\sin^2(x) - \frac{x}{2}\sin(2x)\right)\sin[kx(R_r-1)] + \frac{1}{k}\left\{R_r - \frac{1}{kx}\sin[kx(R_r-1)] - \cos[kx(R_r-1)]\right\}\sin^2(x)$$

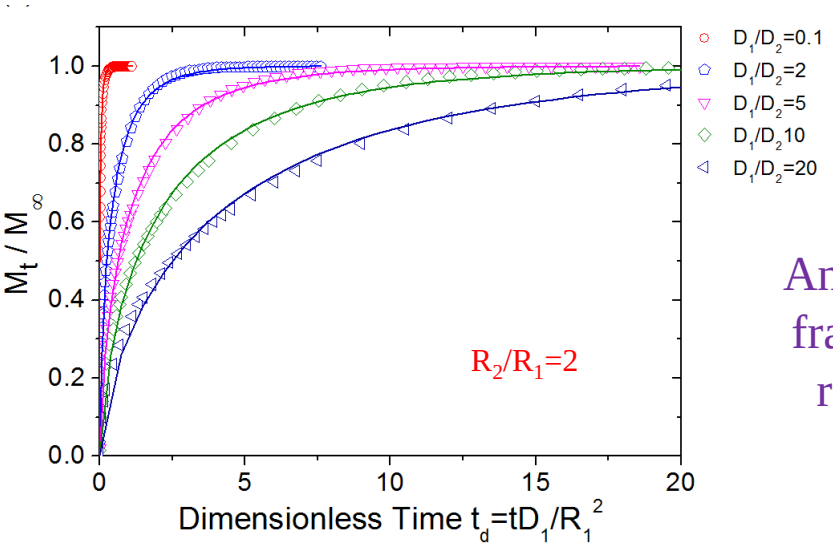
$$\varphi_2(x) = kx^2\sin^2[kx(R_r-1)] + kx^2(R_r-1)\sin^2(x) + \frac{1-k^2}{k}\sin^2(x)\sin^2[kx(R_r-1)]$$

If $k(R_r\text{-}1)$ is rational ($=l/m$) the solution acquires an additional term:

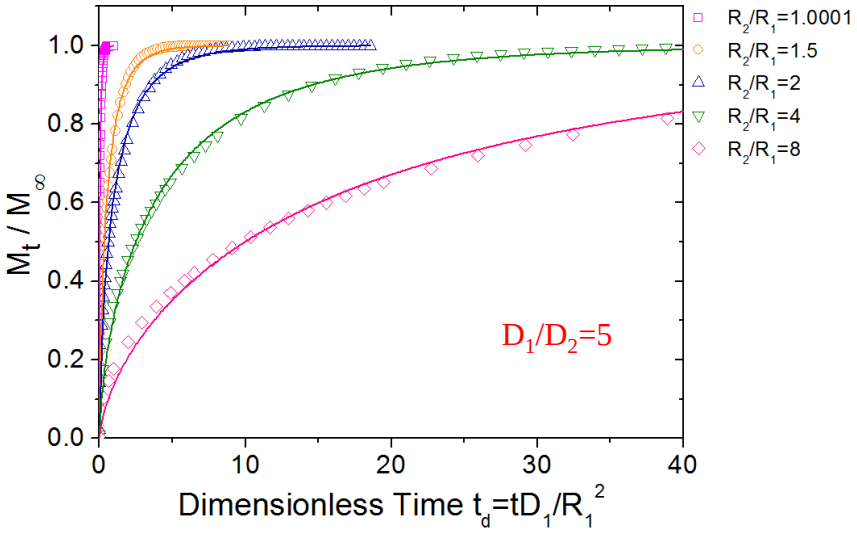
$$-\frac{6}{\pi^2 R_r^2(lk+m)}\sum_{n=1}^{\infty}\frac{1}{n^2}\left\{\frac{(-1)^{mn+(l+m)^n}}{m} + \frac{k(R_r-1)\left[R_r-(-1)^{nl}\right]}{l}\right\}\cdot e^{-n^2\pi^2 m^2\frac{D_1}{R_1^2}t}$$

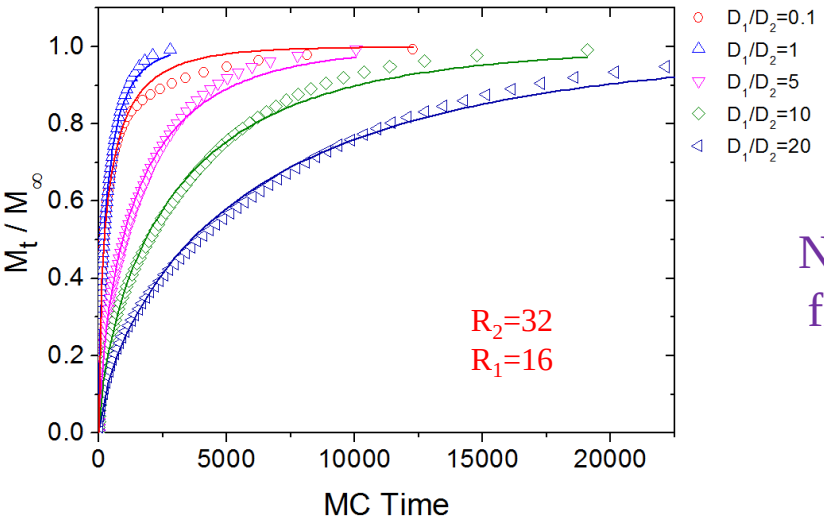
Considering the dimensionless time $t_d = tD_1/R_1^2$, the solution depends only on k and R_r

Drug release from composite spherical devices: Results

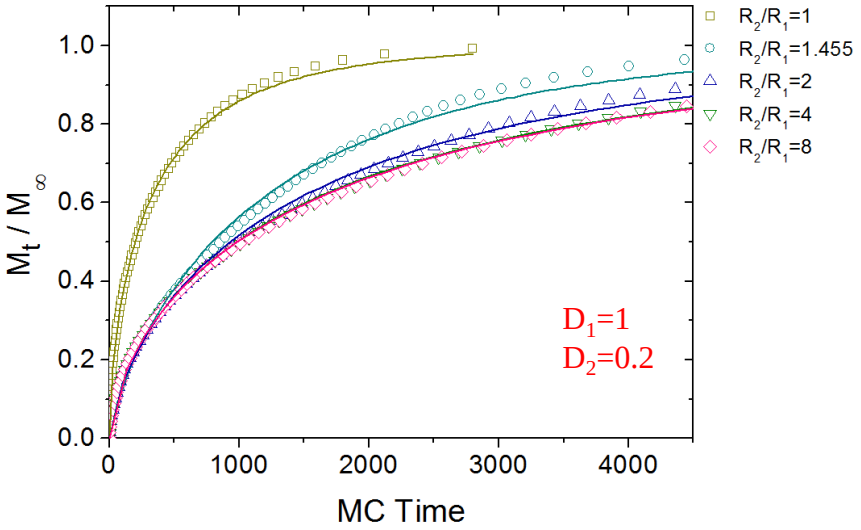


Analytical fractional release





Numerical fractional release

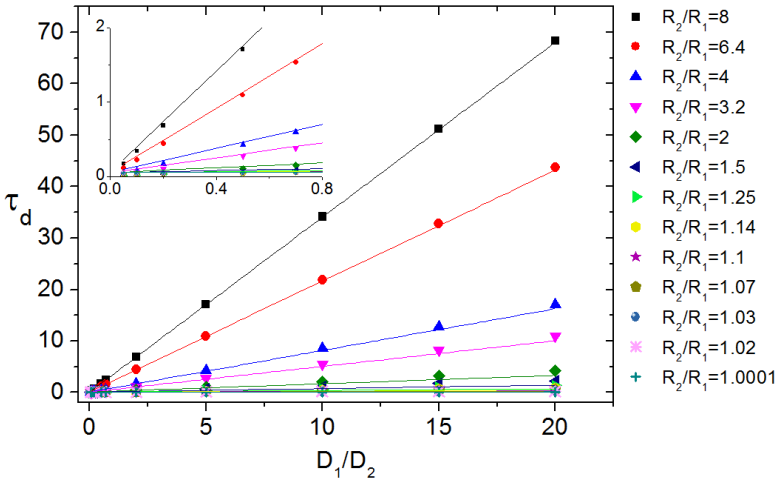


Continuous lines: fitting with stretched exponential

Hadjitheodorou, Kalosakas, *Mater. Sci. Eng. C* **42**, 681 (2014)

Drug release from composite spherical devices

Dependence of stretched exponential parameters

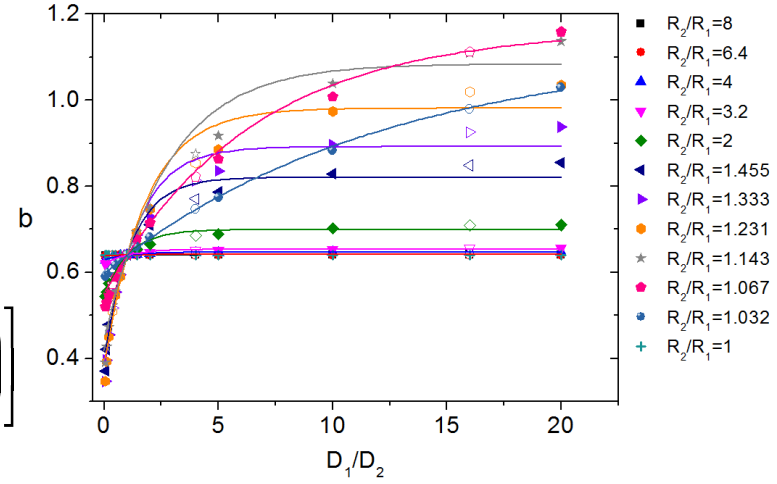


$\tau_d(D_1/D_2)$ for different radii ratios R_2/R_1, obtained from analytical results

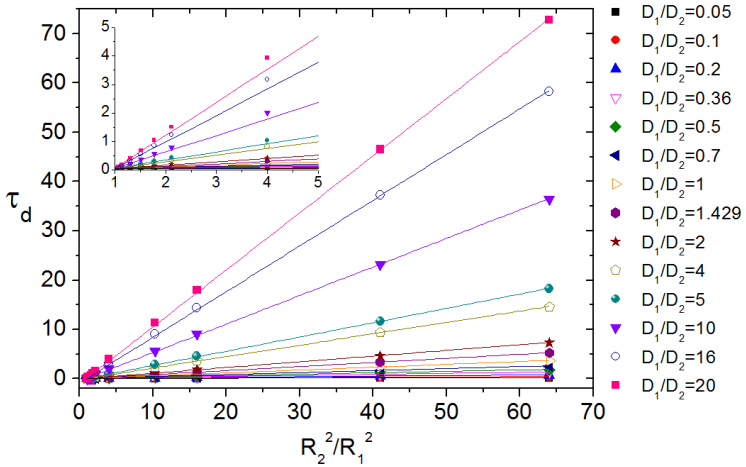
$$\tau_d = c\left[1 + \frac{D_1}{D_2}\left(\frac{R_2^2}{R_1^2} - 1\right)\right]$$

$$c_{analyt.} = 0.054$$

$$c_{numeric.} = 0.058$$

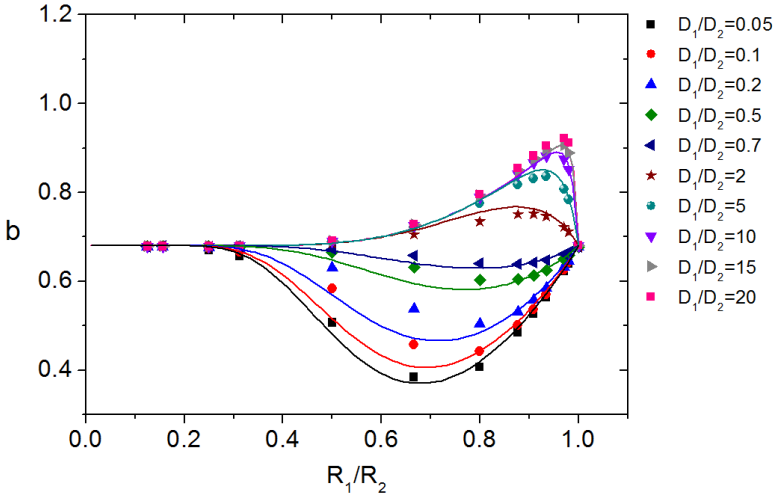


b(D_1/D_2) for different radii ratios R_2/R_1, obtained from numerical results



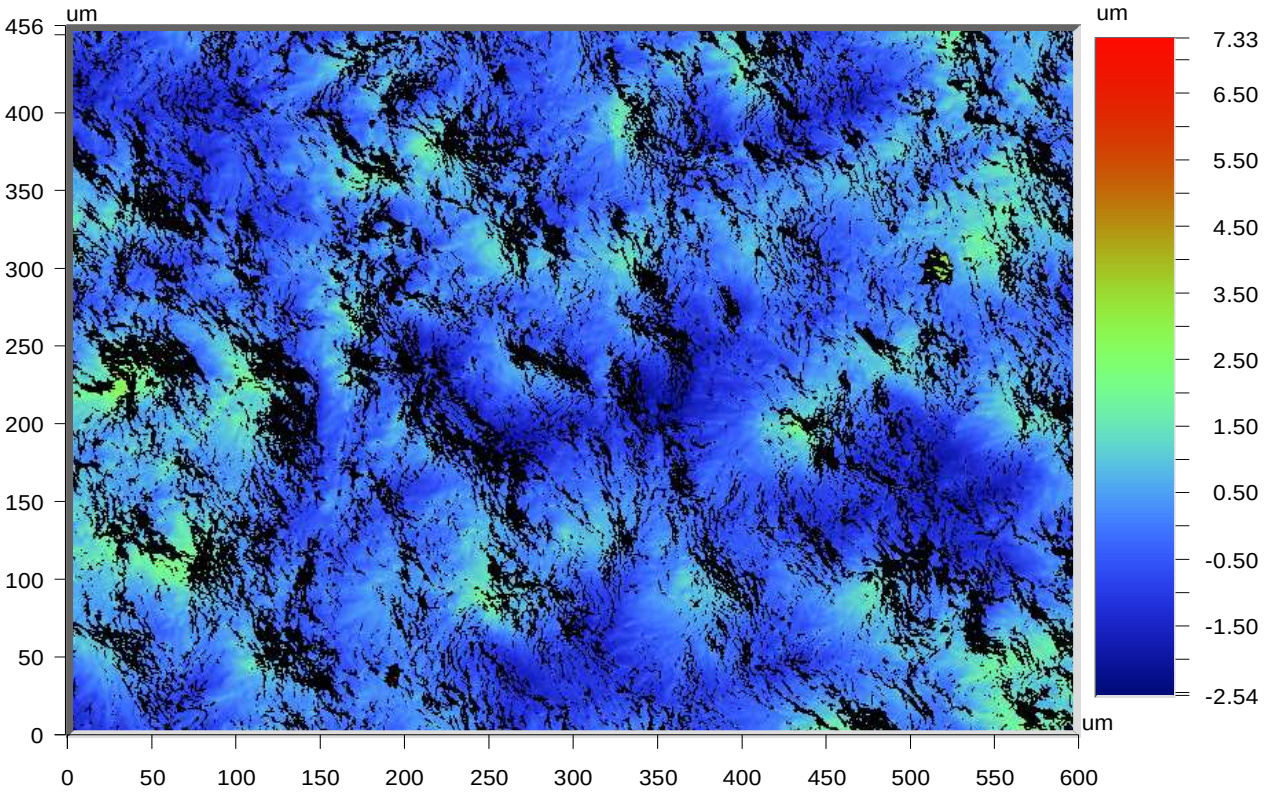
$\tau_d(R_2^2/R_1^2)$ for different ratios D_1/D_2, obtained from numerical results

$$\tau = c\left[\frac{R_1^2}{D_1} + \frac{R_2^2 - R_1^2}{D_2}\right]$$



b(R_1/R_2) for different ratios D_1/D_2, obtained from analytiical results

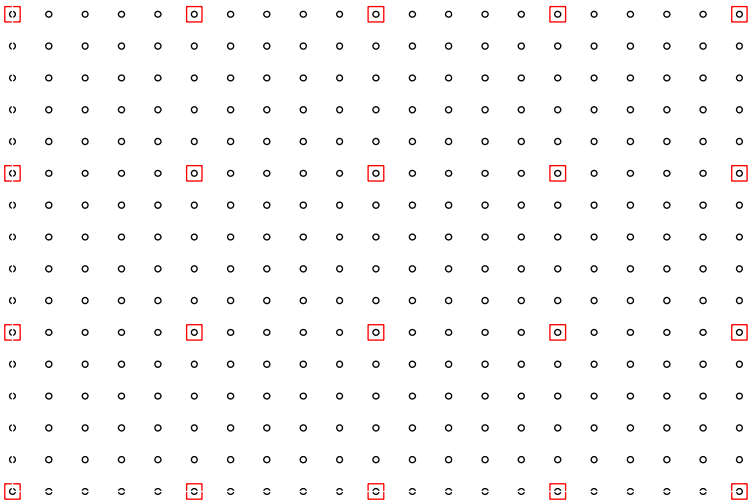
Drug release from slabs of non-uniform thickness



Optical profilometer image of a thin poly(ε-caprolactone) membrane loaded with 0.2% Verapamil Hydrochloride.
A surface region with dimensions around 600x450 μm is shown.
The colorbar at the right displays the fluctuations of the surface roughness.
The average thickness is around 2.7 mm in this case.

Kontopoulou, Bouropoulos, *unpublished.*
Kontopoulou, *Diploma Thesis*, Patras Univ. (2013)

ɒm slabs of non-uniform thickness



Construction of rough slab surfaces

(considering a slab of average thickness *L* and degree of surface roughness, *w*)

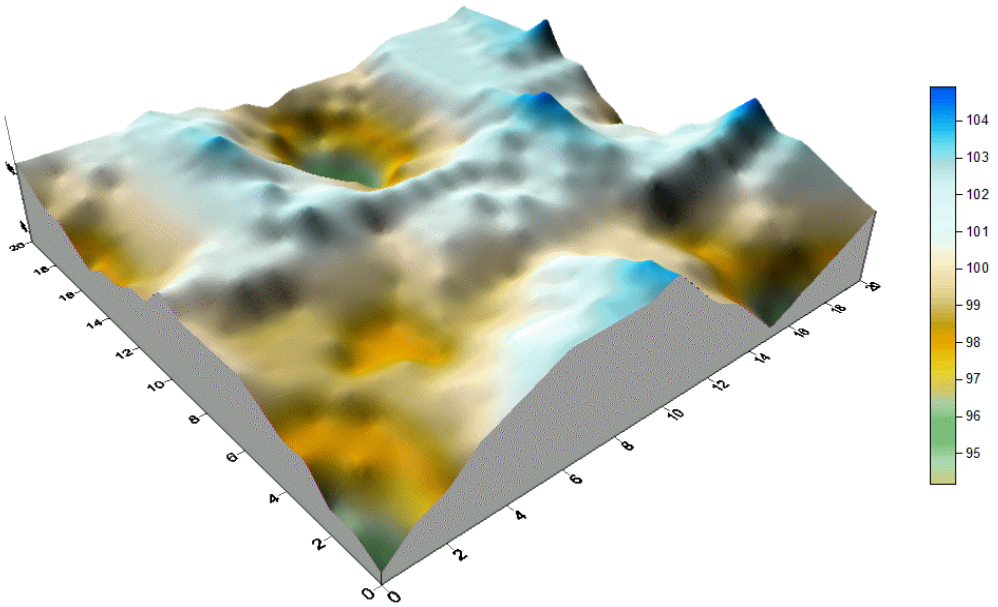
A sub-grid (red squares) is considered in the *xy* grid (black circles).

For the lower (upper) irregular surface, random numbers in the region 0+/-*w* (*L*+/-*w*) are given at each point of the subgrid.

Bilinear interpolation is used to obtain the values at the other points of the grid.

The position of each surface at the grid varies in a range of 2*w*.

The thickness of the slab varies in a range of 4*w* (*L*+/-2*w*)

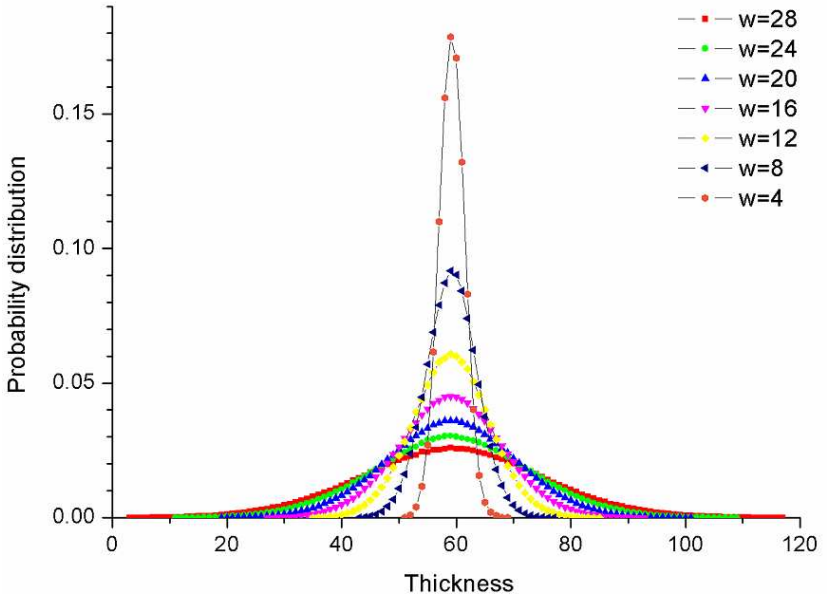


Upper surface of a non-uniform thickness slab with *L*=100 and *w*=4, constructed with this method

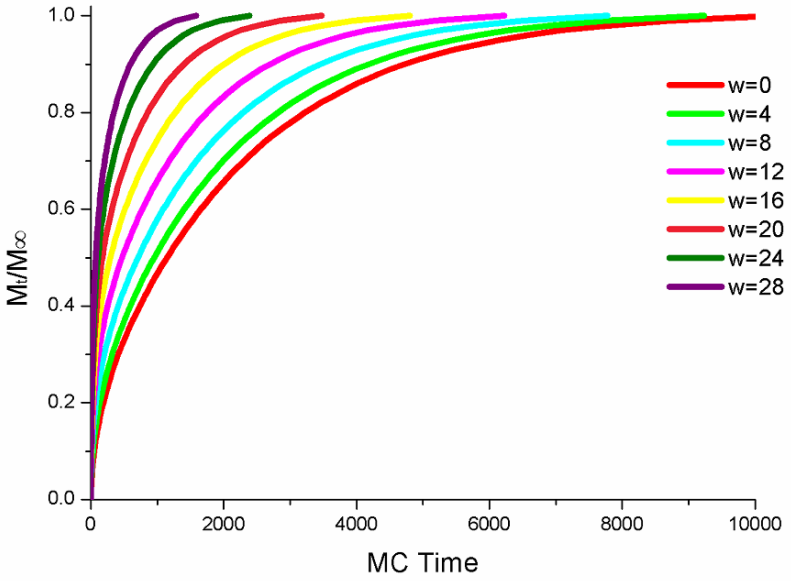
Kalosakas, Martini, *Int. J. Pharm.* **496**, 291 (2015)

Drug release from slabs of non-uniform thickness

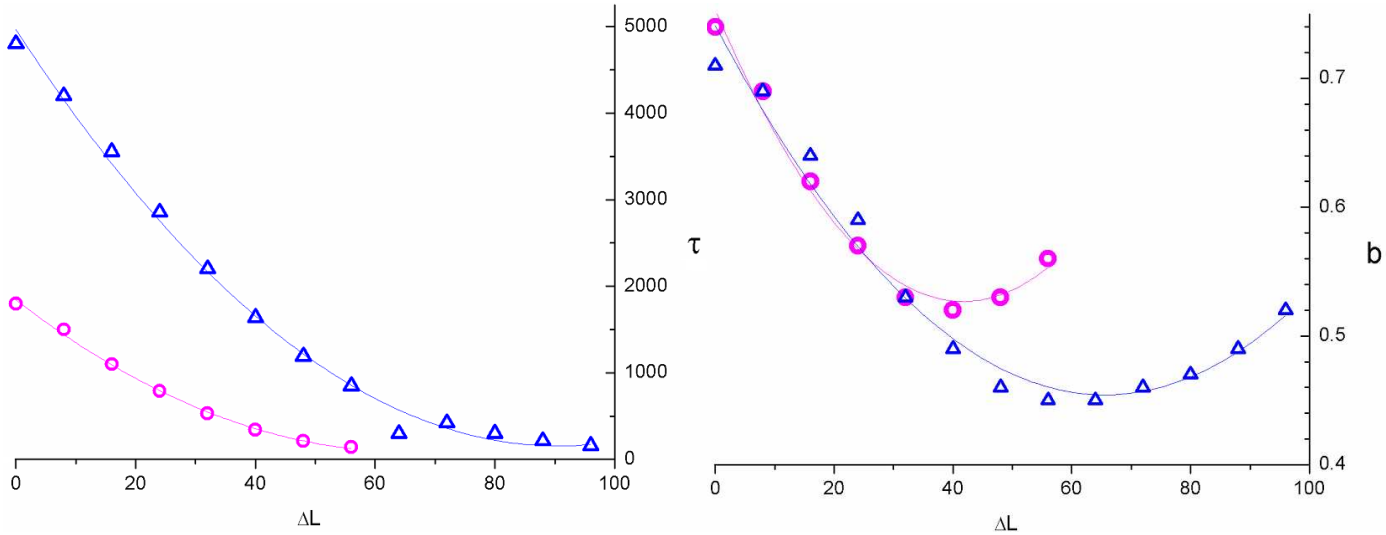
Results from a slab of dimensions (20pbc, 20pbc, 60+/-2w)



Thickness distribution for different values of the degree of surface roughness *w*



Fractional release for different values of the degree of surface roughness *w*



The numerical release results are fitted by a stretched exponential function.

Dependence of the stretched exponential parameters on the degree of surface roughness ($\Delta L=2w$)