Abstract: Description of the kinetics of drug release from hydrogels is a domain of steadily increasing academic and industrial importance. The aim of this paper is to review mathematical approaches to drug release from hydrogel matrix devices. In the first section the parameters of hydrogel structure are described. Than the phenomena that influencing resulting drug release are discussed. Finally, mechanisms of physical release and release with chemical reaction are studied. In this section mathematical expression that predicting drug release profiles are described.

Keywords: hydrogel, mathematical modelling, controlled release, drug delivery, diffusion, swelling, erosion

Introduction

Hydrogel is a hydrophilic mixture which has the properties of both solid and liquid [1, 2]. Hydrogel structure consists of networks that are formed from randomly cross-linked macromolecules [3]. It contains three phases:
1) polymeric-network matrix solid phase,
2) interstitial fluid phase,
3) ionic phase.

The solid phase includes a network of cross-linked polymeric chains. Polymeric chains create a three-dimensional matrix with interstitial space filled up with water and often biological fluids. The cross-linked polymeric network can be formed physico-chemically, for example by van der Waals interactions, hydrogen bonding, electrostatic interactions and physical entanglements as well as by covalent bonds. The fluid phase fills in the pores of the polymeric matrix and makes that hydrogel has wet and elastic properties. Due to these properties structure of hydrogel resembles to living tissue. The ionic phase consists of the ionisable groups that are bounded to the polymer chains and the mobile ions (counter-ions and co-ions). This phase exists due to the presence of electrolytic solvent.

Hydrogels can be formed from both natural and synthetic polymers [4-6]. Hydrogels based on natural polymers can have insufficient mechanical properties, contain pathogens...
and evoke immune responses. On the other hand, they have numerous advantageous properties like inherent biocompatibility, biodegradability, bacteriostatic and wound-healing properties. Synthetic hydrogels do not have these inherent bioactive properties.

Drugs can be incorporated into hydrogel matrices by two ways [4]:
1) post-loading,
2) in-situ loading.

In the post-loading method a hydrogel matrix is formed and than the drug is absorbed to this matrix. For an inert hydrogel system diffusion is the major force for drug uptake. Drug release will be determined by diffusion and/or gel swelling. For hydrogel containing drug-binding ligands the release will be determined by a drug-polymer interaction and drug diffusion. In the in-situ loading a polymer precursor solution is mixed with drugs or drug-polymer conjugates. Hydrogel network formulation and drug encapsulation are accomplished simultaneously. The drug release will be determined by diffusion, hydrogel swelling, reversible drug-polymer interactions or degradation of labile covalent bonds.

The device geometry significantly influences the resulting drug release kinetics [1, 7]. The delivery device can be in the shape of:
1) thin film,
2) sphere,
3) cylinder,
4) irregular solid.

The nanostructure of hydrogel can be described by three parameters [4, 8]:
1) \( v_{2s} \), - polymer volume fraction in the swollen state of hydrogel,
2) \( M_c \), - average molecular weight between crosslinks,
3) \( \xi \), - network mesh size.

The mobility of molecules and their rates of diffusion in swollen non-porous hydrogels are determined by the amount of liquid which is retained in the hydrogel, the distance between polymer chains and flexibility of those chains.

The polymer volume fraction in the swollen state is the amount of fluid which can be absorbed and retained in the hydrogel matrix. It is expressed as a ratio of the polymer volume (\( V_p \)) to the swollen gel volume (\( V_g \)):

\[
v_{2s} = \frac{V_p}{V_g}
\]

The average molecular weight between two consecutive cross-links (\( M_c \)) is a measure of the degree of hydrogel cross-linking. The cross-links can be both chemical and physical in nature. Due to the random nature of the polymerization process only an average value of molecular weight is calculated. It can be described by the Flory-Rehner equation:

\[
\frac{1}{M_g} = \frac{2}{M_n} - \left( \frac{V}{V_j} \right) \left[ \ln(1-v_{2s}) + v_{2s} + \chi_{12} v_{2s}^2 \right]
\]

where:
\( M_n \) - average molecular weight of the polymer chains,
\( \nabla \) - specific volume of the polymer,
\( V_1 \) - molar volume of water,
\( \chi_{12} \) - parameter of polymer-water interaction.

The network mesh size is a measure of space accessible between the macromolecular chains (e.g., for the drug diffusion). This space is considered as molecular mesh or pores. Hydrogels can be classified as:
1) macroporous,
2) microporous,
3) nonporous.

The size of pores is described by correlation length \( \xi \). This structural parameter is defined as a linear distance between two neighbouring crosslinks. It can be expressed by the following equation:

\[
\xi = \frac{1}{\sqrt{v_2}} \left( \frac{\rho_1}{\rho} \right)^{\frac{1}{2}}
\]

In this expression \( \left( \frac{\rho_1}{\rho} \right)^{\frac{1}{2}} \) is the root-mean-squared end-to-end distance of network chains between two neighbouring crosslinks in the swollen state.

![Diagram](image)

**Fig. 1.** Schematic illustration of mesh size in hydrogel at (A) swollen state and (B) deswollen state (adapted from [4]).

The mesh size in the swollen and deswollen state is shown in Figure 1. This parameter depends on several factors like the degree of gel cross-linking, chemical structure of the composing monomers and external stimuli (temperature, pH and ionic strength).

These three parameters \((v_2, \bar{M}_c, \xi)\) can be determined theoretically or through experimental techniques.

**The mechanism of release**

Depending on the composition of hydrogel (type of polymer, type of drug and additives), geometry (size and shape), preparation technique and environmental conditions during drug release, one or more of the following physical and chemical phenomena affect the drug release kinetics [7, 9]:
1) Wetting of the drug delivery device surface with release medium (water).
2) Release medium (water) penetration into the drug delivery device (e.g., via pores).
3) Creation of pores filled with water.
4) Degradation of drug and/or polymer.
5) Diffusion of drug and/or products of polymer degradation inside the hydrogel matrix.
6) Diffusion of drug and/or products of polymer degradation in the fluid.
7) Dissolution and/or precipitation of drug and/or degradation products.
8) Microenvironmental pH changes inside the hydrogel matrix caused by the degradation of polymer.
9) Autocatalytic effects during hydrogel matrix degradation.
10) Swelling of polymer.
11) Closing of pores caused by polymer swelling.
12) Osmotic effects caused by creation of significant hydrostatic pressure in the drug delivery device.
13) Creation of acidic or basic microenvironments in the dosage forms caused by degradation products.
14) Physical drug-products of polymer degradation interactions (e.g., ion-ion attraction/repulsion and van der Waals forces) which can significantly vary with time and position caused by changes in microenvironmental conditions.
15) Chemical reactions between the drugs and products of polymer degradation and/or water.
16) Convection processes caused by significant hydrostatic pressure created in drug delivery device.
17) Adsorption and/or desorption processes.
18) Changes in the drug delivery device geometry and/or dimensions caused by shear forces.

It is not reasonable to take all the mentioned phenomena into account. It is crucial for a mathematical model to take into account only dominating physical and chemical processes. Moreover, these phenomena concern only drug transport in the model system, not in the living organism. To describe the mechanism of drug transport in the living body various additional phenomena must be taken into account, e.g., enzymatic degradation, protein binding, active and passive drug uptake into cells, interactions with compounds in extra- and intracellular space [7].

From the process engineering point of view, the mechanism of release consists of the following phenomena:
1) exterior diffusion,
2) interior diffusion,
3) desorption,
4) chemical reactions.

Moreover, the processes of shape change (e.g., heterogeneous and homogeneous erosion) and processes of surface change (desorption, reconstruction and reaction) can overlap to above phenomena. These processes (diffusion, desorption, chemical reactions and matrix erosion) are studied below.

**Exterior diffusion**

The mechanism of release consists of exterior and interior processes of diffusion [10]. Exterior diffusion takes place when drug molecules diffuse from surface of the hydrogel...
Drug release from hydrogel matrices

Matrix to bulk of the liquid phase (Fig. 2). The rate of mass transfer can be described by the following expressions:

\[ N_A = k_L (C_{AL}^* - C_{AL}^b) \]  \hspace{1cm} (4)

or

\[ G_A = k_L A (C_{AL}^* - C_{AL}^b) \]  \hspace{1cm} (5)

where:

- \( N_A \) - flux of the drug,
- \( G_A \) - mass transfer rate,
- \( k_L \) - mass transfer coefficient,
- \( C_{AL}^* \) - surface concentration of the drug,
- \( C_{AL}^b \) - bulk concentration of the drug,
- \( A \) - area of mass transfer.

The mass transfer coefficient \( (k_L) \) is expressed as:

\[ k_L = \frac{(D_{AB})_L}{\delta_L} \]  \hspace{1cm} (6)

where \( (D_{AB})_L \) - drug diffusion coefficient.

Fig. 2. Exterior diffusion: line - model concentration profile of drug, dotted line - real concentration profile of drug.
Drug concentration is the highest close to the surface of the hydrogel matrix and it decreases with the length. When the bulk of liquid is well stirred the value of drug concentration is constant. Exterior diffusion can control the rate of drug release only in exceptional cases. In general, the rate of drug release depends on interior phenomena, especially on interior diffusion.

**Interior diffusion**

In general, the rate of drug release is controlled by interior diffusion (Fig. 3).

![Interior diffusion of drug molecules](image1)

Theories which are based on Fick’s law of diffusion distinguish two types of systems (1) reservoir and (2) monolithic devices (Fig. 4).

![Reservoir device and Matrix device](image2)
In the reservoir system a polymer membrane surrounds inner bulk of dissolved, suspended or neat drug [11, 12]. Diffusion of an encapsulated drug through the membrane is the rate-limiting step in this delivery system. A constant concentration gradient across the polymer membrane is achieved by saturated concentration of the drug core. Drug is absorbed from inner bulk by the membrane. Then it diffuses through the membrane and is desorbed from the membrane to the fluid which surrounds the reservoir device.

The drug release in a reservoir system where a polymeric hydrogel membrane surrounds the drug bulk can be described by Fick’s first law of diffusion [1, 4]:

\[ N_A = -D \frac{dC_A}{dx} \]  

where:

- \( N_A \) - flux of the drug,
- \( D \) - drug diffusion coefficient,
- \( C_A \) - drug concentration.

For the reservoir device with initial drug concentration smaller than drug solubility, the drug concentration at inner surface of the membrane decreases with time. The process runs at the unsteady state conditions and the exact solution can be obtained by solving the equations of mass balance for the membrane and bulk of the liquid. For a short time in the case of non-swelling or dissolving membrane and perfect sink conditions of release, the drug release can be described by the first order kinetics. The drug release kinetics is not dependent on the device geometry [7]:

\[ \frac{dM_t}{dt} = ADKC_t \frac{M_0 - M_t}{V} \]  

where:

- \( M_t \) - absolute cumulative amount of drug released at time \( t \),
- \( C_t \) - concentration of drug in the release medium at time \( t \),
- \( M_0 \) - initial amount of drug in the device,
- \( V \) - volume of drug reservoir,
- \( A \) - total surface area of the device,
- \( l \) - thickness of the membrane,
- \( K \) - partition coefficient of the drug between the membrane and the reservoir,
- \( D \) - diffusion coefficient of the drug within the membrane.

In the case of a system with initial drug concentration much bigger than the drug solubility in the reservoir device, the released molecules are replaced by the dissolution molecules of drug crystals/amorphous aggregates. The inner membrane surface concentration of drug is constant. If the membrane thickness and drug permeability are constant and perfect sink conditions are maintained during the release, the drug release may be described by zero order release kinetics. It is independent on the drug delivery device geometry [7]:

\[ \frac{dM_t}{dt} = \frac{A J_{lin}}{l} = \frac{ADKC_t}{l} \]  

where:

- \( \frac{dM_t}{dt} \) - steady state release rate at time \( t \),
J_{lim} - membrane-limiting flux,
C_s - solubility of the drug in the reservoir.

In the matrix system the drug is equally dissolved or dispersed in the polymer matrix [11, 12]. A disadvantage of this system is the release with a continuously decreasing release rate. This is caused by an increase of diffusion way length and decrease of drug area in the polymer matrix as the drug release proceeds.

For a matrix system in which the drug is equally dispersed throughout the polymeric matrix, unsteady-state drug diffusion in a one-dimensional slap-shaped matrix can be described by Fick’s second law of diffusion [4, 13]:

\[
\frac{dC_A}{dx} = D \frac{d^2 C_A}{dx^2}
\]  (10)

In this equation the drug diffusion coefficient is assumed to be constant. In the case in which diffusivity is concentration-dependent the following equation can be used:

\[
\frac{\partial C_A}{\partial t} = \frac{\partial}{\partial x} \left( D(C_s) \frac{\partial C_A}{\partial x} \right)
\]  (11)

For monolithic devices the system geometry strongly affects the resulting drug release profile. In the case of the device with the initial drug concentration below drug solubility, the drug molecules are dissolved in the hydrogel (monolithic solution). Otherwise, the drug molecules coexist with amorphous aggregates and/or drug crystals (monolithic dispersion). For monolithic solution with the following release conditions:
1) the absence of significant changes in the hydrogel matrix during the release,
2) perfect sink conditions during the release,
3) the release of drug is mostly controlled by diffusion through the hydrogel matrix,
different equations are used to calculate a resulting release profile, depending on the system geometry.

For example, an analytical solution of Eq. (10) can be obtained using separation of variable technique [1]:
1) thin film with negligible edge effects:

\[
\frac{M_t}{M_0} = 1 - \sum_{n=1}^{\infty} \frac{1}{(2n+1)^2} \exp \left( - \frac{D(2n+1)^2 \pi^2 t}{L^2} \right)
\]  (12)

where:
- n - dummy variable,
- L - thickness of the film.
2) spherical delivery device:

\[
\frac{M_s}{M_0} = 1 - \sum_{n=0}^{\infty} \frac{1}{n^2} \exp \left( - \frac{Dn^2 \pi^2 t}{R^2} \right)
\]  (13)

where R - sphere radius.
3) cylinders delivery device:

\[
\frac{M_c}{M_0} = 1 - \sum_{n=1}^{\infty} \frac{1}{(2n)^4} \exp \left( - \frac{q^2 Ds}{R^2} \right) \times \sum_{p=0}^{\infty} \frac{1}{(2p+1)^2} \exp \left( - \frac{D(2p+1) \pi^2 t}{H^2} \right)
\]  (14)
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where:
\( p \) - dummy variable,
\( q_n \) - the roots of the Bessel function of the first kind of zero order,
\( R \) - cylinder radius,
\( H \) - cylinder height.

For monolithic dispersion the mathematical model is more complicated. Higuchi developed a mathematical equation to predict drug release from a monolithic matrix system with the simplest geometry of thin films with negligible edge effects [1, 7, 14, 15]:

\[
\frac{M_t}{A} = \sqrt{D(2C_0 - C_s)C_s t} \quad \text{for} \quad C_0 \gg C_s
\]

(15)

where:
\( M_t \) - cumulative absolute amount of drug released at time \( t \),
\( A \) - surface area of the controlled release device exposed to the release medium,
\( D \) - drug diffusivity in the polymer,
\( C_0 \) - initial drug concentration,
\( C_s \) - drug solubility in the polymer.

Equation (15) can be simplified to the following equation:

\[
\frac{M_t}{M_\infty} = K\sqrt{t}
\]

(16)

where:
\( M_\infty \) - absolute cumulative amount of drug released at time \( t \) that should be equal to the initial amount of drug in the system at time \( t = 0 \),
\( K \) - system constant.

Higuchi developed this model using the pseudo-steady state assumptions. A controlled drug delivery system must fulfil the following conditions:

1) The initial drug concentration must be much higher than the solubility of the drug \((C_0 \gg C_s)\).
2) The release is one-dimensional and thus the edge effects can be neglected.
3) The drug particles are much smaller than the thickness of drug delivery device.
4) The polymer matrix does not swell or dissolve.
5) The drug diffusivity is constant with the time and position.
6) Perfect sink conditions are maintained in the system.

The simplicity of Higuchi’s model is its important advantage.

Peppas and co-workers developed another empirical equation which assumes a time-dependent power low function [8]:

\[
\frac{M_t}{M_\infty} = k \cdot t^n
\]

(17)

where:
\( M_t \) - fractional release,
\( M_\infty \) - structural/geometric constant for a particular system,
\( k \) - release exponent representing the release mechanism.

Table 1 gives values of \( n \) for delivery matrices with different geometries and release mechanisms.
Table 1

<table>
<thead>
<tr>
<th>Exponent, n</th>
<th>Slab</th>
<th>Cylinder</th>
<th>Sphere</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0.45</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>0.5 &lt; n &lt; 1.0</td>
<td>0.45 &lt; n &lt; 0.89</td>
<td>0.43 &lt; n &lt; 0.85</td>
<td>Anomalous transport</td>
</tr>
<tr>
<td>1.0</td>
<td>0.89</td>
<td>0.85</td>
<td>Controlled swelling</td>
</tr>
</tbody>
</table>

Fick’s law equations cannot be solved analytically when more complex geometries or non-constant drug diffusivities are incorporated into the model. Moreover, in the case of swelling polymers diffusivities of encapsulated molecules will be strongly affected by the degree of swelling and cross-linking density of the gel. Thus D will be sensitive to environmental changes or degradation polymer matrix and might vary over the time-scale of release. Theoretical models for calculation of molecule diffusion coefficients can be described by the following general form [4]:

\[
\frac{D_g}{D_0} = f(r, v_{2,s}, \xi) \tag{18}
\]

where:

- \( D_g \) - drug diffusion coefficient in the swollen hydrogel network,
- \( D_0 \) - drug diffusion coefficient in pure solvent,
- \( r_s \) - size of the drug to be delivered.

This expression takes into account factors which affect drug release, like the gel structure, the polymer composition, water content, and the size of molecules. In the case of degradable polymer \( D_g \) changes with the degradation of polymer network due to an increase in hydrogel mesh size and decrease in polymer volume fraction over time.

Several expressions have been developed to describe the relationship between drug diffusivity in the hydrogels and in the solution. For example, Lustig and Peppas proposed the following equation to correlate the relationship between drug diffusivity and network structure [4]:

\[
\frac{D_g}{D_0} = \left(1 - \frac{r_s}{\xi} \right) \exp \left( -Y \left( \frac{v_{2,s}}{1-v_{2,s}} \right) \right) \tag{19}
\]

where \( Y \) - ratio of the critical volume required for translation movement of the encapsulated drug molecule and the average free volume per solvent molecule.

Finally [10], the influence of pore size on diffusion coefficients should be mentioned. If:

1) pore diameter is much bigger than average free length of molecules - effective diffusion coefficient (\( D_e \)) can be calculated from the formula:

\[
D_e = D \frac{v_{2,s}}{1} \tag{20}
\]

\[
N_A = -D_e \frac{dC_A}{dx} \tag{21}
\]

2) pore diameter is lower than average free length of molecules - Knudsen’s diffusion coefficient (\( D_k \)) govern the law:
Simultaneous diffusion and desorption of drug

Drug molecules can be adsorbed either chemically or physically on the pore surface [16]. In chemisorptions, the electronic structure (electronic density) of adsorbate molecule is strongly modified. In physical adsorption the adsorbate is weakly adherent by secondary interactions (eg van der Waals forces).

The rate of mass transfer can be controlled by physical adsorption if the rate of desorption is finite (or is comparable to the rate of diffusion). In literature, a description of such processes is lacking. A simple model of drug release with desorption is described in the work [17]. The drug is desorbed from the hydrogel pore surface and then diffuses within the pore (Fig. 5). In the system with following conditions:

1) distribution of pores in the hydrogel is homogeneous,
2) movement of molecules is described by first Fick’s law of diffusion,
3) diffusion coefficient is constant,
4) the release medium is ideally mixed - without exterior resistance,
the drug release can be described (Fig. 5) by the following equation:

$$\frac{dV}{dt} = [(N_A + dN_A) - N_A] \tau_a - r_a dV$$

(24)

This equation describes the differential volume of the medium that is in the pore between x and x+dx. The final results of the model can be found in the paper [17].

**Chemical reactions**

In the case of release with a chemical reaction drugs and/or products of polymer degradation can react with the released medium inside its pores. The released medium molecules diffuse to hydrogel medium pores. During the contact with drugs or products of polymer degradation they undergo a chemical reaction. This reaction can be reversible or irreversible, simple or complex and slow or fast. Then, the products of chemical reactions undergo interior and exterior processes of diffusion.

**Change of shape**

Hydrogel matrix can change of its shape during the release. Change of shape can be caused by following phenomena:
1) chain cleavage,
2) matrix swelling,
3) matrix erosion.

These processes are discussed below.

**Chain cleavage**

In the case of systems with pendant chain (prodrugs), the drug is covalently linked to the polymer network and its release depends on the rate of bond splitting [4]. The drug release is not mediated by diffusion in this system.

The prodrugs system is used to improve the therapeutic efficiency of the drug. In general, the release of covalently bound drugs depends by the degradation rate of the polymer-drug link. Most of these links are hydrolytically degradable. This causes that the rate of drug release is absolutely characterized by simple first-order kinetics.

Göpferich formulated [18-20] a theory of polymer degradation and erosion. He assumed that the rate of polymer degradation is identical in the whole polymer matrix. When the polymer is initially insoluble in water and hydrolysis is the only mechanism of polymer erosion, then erosion is controlled by:
1) rate of water diffusion into the bulk of polymer ($t_{diff}$),
2) rate of the polymer backbone degradation by water ($t_c$).

Water velocity inside hydrogel matrix pores can be described by diffusion. The rate of water diffusion into the polymer matrix can be expressed by the following equation:

$$t_{diff} = \frac{(x)^2 \Pi}{4D_{eff}}$$

(25)

where:
- $x$ - mean distance,
- $D_{eff}$ - effective diffusion coefficient of water inside the polymer matrix.
The rate of chain cleavage by water can be expressed by the following equation:

$$t_c(n) = \frac{1}{\lambda} \ln\left(\frac{M_A}{N \rho (N-1)}\right)$$

(26)

where:
- $n$ - number of polymer bonds,
- $\lambda$ - rate constant that takes into account differences in the reactivity of hydrogel functional groups,
- $M_A$ - average molecular weight number,
- $N_A$ - Avogadro’s number,
- $N$ - average degree of polymerization (the number of monomers per polymer chain),
- $\rho$ - polymer density.

Erosion number is used to predict the erosion mechanism. It is a dimensionless number expressed by the ratio of the rate of water diffusion to the rate of chain cleavage by water:

$$\varepsilon = \frac{t_{\text{diff}}}{t_c(n)}$$

(27)

The values of erosion number can be divided into three ranges. For $\varepsilon \gg 1$ water reacts with a polymer faster than the water diffuses. This system is controlled by surface erosion. For $\varepsilon \sim 1$ the erosion mechanism is changed. For $\varepsilon \ll 1$ water diffuses faster than it can react with the polymer. This system is controlled by bulk erosion.

Matrix swelling

The mechanism of hydrogel swelling is one of the most important factors in drug release phenomena. This mechanism of drug release occurs when diffusion of an active agent is faster than hydrogel swelling [4, 15 and 21]. In swelling-controlled system hydrogels may undergo a swelling-driven phase transition from a glassy state to rubbery state (Fig. 6). This transition occurs when the characteristic glass-rubber polymer transition temperature is lower than temperature of fluid which surrounds the drug delivery matrix. In the glassy state, entrapped molecules remain immobile. In the rubbery state dissolved drug molecules rapidly diffuse to the fluid through the swollen layer of polymer. Released fluid molecules contact the external layer of hydrogel. This forms a moving front that divides hydrogel matrix into a glassy and swollen region. In these systems the rate of molecule release depends on the rate of gel swelling.

In the swelling-controlled delivery system following phenomena take places [7]:
1) The length of drug diffusion way increases. This causes a decrease of drug concentration gradient (driving force of diffusion) and a decrease of drug release rates.
2) The mobility of drug molecules increases. This causes an increase of drug release rates.

Drug diffusion time and polymer chain relaxation time are two main parameters that determine drug delivery from swelling polymeric matrices. In this system the time-scale for polymer relaxation ($\lambda$) is the rate-limiting step. In the diffusion-controlled delivery system, the time-scale of drug diffusion ($t$) is the rate limiting step. The Deborah number (De) is applied to compare these two time-scales:
where $\delta(t)$ - time-dependent thickness of the swollen phase.

\[
\text{De} = \frac{\lambda}{t} = \frac{\lambda D}{\delta(t)^2} \tag{28}
\]

Fig. 6. Schematic illustration of drug delivery device in glassy and rubbery state matrix (adapted from [4])

In the case of diffusion-controlled systems (De<<1) Fickian diffusion dominates the molecule release process. In the case of swelling-controlled systems (De>>1) the rate of molecule release depends on the swelling rate of polymer networks.

In the swelling-controlled delivery systems to describe molecule release a modified empirical power law can be used. Peppas and Sahlin developed such a model taking into account the drug diffusion and polymer relaxation [22]:

\[
\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \tag{29}
\]

where:
- $k_1$ - constant that corresponds to the release rate of diffusion,
- $k_2$ - constant that corresponds to the release rate of polymer relaxation,
- $m$ - constant.

The first term on the right-hand side represents the diffusion and the second term represents polymer relaxation.

This empirical expression does not take into account „moving-boundary” conditions in which the gel expands heterogeneously as water penetrates and swells the gels. For this case Krosmeyer and Peppas introduced an equation to correlate the moving boundary phenomena with hydrogel swelling:

\[
S_w = \frac{V \delta(t)}{D} \tag{30}
\]

where:
- $S_w$ - swelling interface number,
- $V$ - velocity of the hydrogel swelling front,
- $D$ - drug diffusion coefficient in the swollen state.

In a slab system with $S_w<<1$ drug diffusion is much faster than the movement of glassy-rubbery interface and a drug release has a zero-order release profile.

Siepmann and Peppas [23-25] developed a more rigorous method to predict molecule release from SCDS, the so-called sequential layer model. This model takes into account...
drug diffusion, polymer relaxation and dilution. For example, in the system with cylindrical geometry and concentration-dependent diffusion coefficients the following equation should be solved:

$$\frac{\partial C_k}{\partial t} = \frac{\partial}{\partial t} \left( D_k \frac{\partial C_k}{\partial t} \right) + \frac{D_k}{r} \frac{\partial C_k}{\partial r} + \frac{\partial}{\partial z} \left( D_k \frac{\partial C_k}{\partial z} \right)$$

(31)

where $C_k$ and $D_k$ are the concentration and diffusivity of the diffusible species, respectively.

Matrix erosion
Surface erosion

In systems with surface erosion (heterogeneous erosion) drug release is caused by degradation of the polymer surface (Fig. 7).

Fig. 7. Schematic illustration of surface and bulk erosion (adapted from [9])

The rate of bond hydrolysis of hydrophobic polymer networks is much faster than the rate of water transport into the polymer bulk. Erosion occurs mostly in the external layers of the polymer matrix. The degradation takes place only on the surface (heterogeneous process). This system of drug release occurs only in enzymatic-degrading systems in which the rate of enzymatic degradation is much faster than the transport of enzyme into the hydrogel [9, 15].
Most of the models with surface-erosion are based on hydrolytic- and enzymatic-degrading polymers.

Hopfenberg proposed a model for theoretical prediction of the molecule release from surface-eroding matrix in which the release depends only on matrix erosion rates [1, 13]:

\[
\frac{M(t)}{M_\infty} = 1 \left(1 - \frac{k_a t}{C_0 a_0}\right)^n
\]

(32)

In this equation \(k_a\) is the erosion-rate constant, \(a_0\) is the initial dimension of drug delivery device (radius for a spherical or cylindrical geometry and half-thickness for slab geometry) and \(C_0\) is the initial concentration of drug in the polymer matrix. \(n\) is the geometric shape factor (1 for a slab, 2 for a cylinder and 3 for a sphere). In the case of slab \((n = 1)\) drug release has a zero-order profile.

Katzhendler, Hoffman and co-workers described a general mathematical model for heterogeneous eroding networks [26]. In this model it is assumed that swelling of the polymer matrix is slower than its erosion. It can be applied for the hydrogel tablets with different rates of erosion in the radial and axial directions. The kinetics of drug release from erodible polymer matrix with two coordinates \(a\) in radial and \(b\) in axial directions can be described by the following equation:

\[
\frac{M(t)}{M_\infty} = 1 \left(1 - \frac{k_a t}{C_0 a_0}\right)^2 \left(1 - \frac{2k_b t}{C_0 b_0}\right)
\]

(33)

In this equation:
- \(k_a\) - radial erosion-rate constant,
- \(k_b\) - axial erosion-rate constant,
- \(a_0\) - initial radius of the tablet,
- \(b_0\) - initial thickness of the tablet.

Lee proposed another mathematical theory for surface-eroding hydrogel systems [7]. This model can be applied to film geometry devices with different “drug loading/drug solubility” ratios. Lee considered movements of the diffusion front and erosion front (Fig. 8). This model assumes that the front of erosion moves at constant velocity, edge effects can be neglected and there are perfect sink conditions throughout the test. The drug release can be expressed by the following equation:

\[
\frac{M(t)}{M_\infty} = \frac{\delta + B a}{D} \tau - \frac{\delta}{\tau} \frac{C_s}{A} \left(1 + \frac{a_3}{6}\right)
\]

(34)

\[
a_3 = \frac{A}{C_s} + \delta h - \sqrt{\left(\frac{A}{C_s} + \delta h\right)^2 - 1 - 2\delta h}
\]

(35)

\[
h = \frac{1}{2} \frac{B a}{D} \left(1 - \frac{A}{C_s}\right)
\]

(36)

In the above equations:
- \(\delta\) - relative separation between the diffusion and erosion fronts,
- \(B\) - constant of surface erosion front,
- \(a\) - half-thickness of the film,
**Drug release from hydrogel matrices**

- Drug diffusivity in the system, \( D \)
- Dimensionless time, \( \tau \)
- Measure of relative contribution of erosion and diffusion to drug release, \( B_a / D \)

**Fig. 8. Scheme of the drug concentration in the surface-eroding system (adapted from [7])**

**Bulk erosion**

In bulk degrading systems the drug release is governed by degradation of the network and molecule diffusion (Fig. 7). Bulk eroding polymers degrade slowly and water infusion into the system is much faster than the degradation of polymer [4, 9, 15]. Thus, the whole drug delivery device is rapidly hydrated and polymer chains break off throughout the system. Erosion takes place in the entire system (homogeneous process).

Heller and Baker developed a mathematical theory predicting drug release from waterinsoluble polymers that can be hydrolytically converted in water-soluble molecules [9]. This model assumes that the degradation of bulk eroding polymers can be described by first-order kinetics. Heller and Baker modified the classical Higuchi equation (Eq. (15)). They assumed that permeability of the drug in the biodegradable polymeric matrix is not constant and increases with time. In their model they applied the following ratio of the drug permeability at time \( t \) (\( P_t \)) to the initial permeability (\( P_0 \)):

\[
\frac{P_t}{P_0} = \frac{\text{initial number of bonds}}{\text{remaining number of bonds}} = \frac{N}{N-Z} \tag{37}
\]

where:
- \( N \) - initial number of bonds,
- \( Z \) - number of cleavage during time interval \([0,t]\).

Polymer bonds are split with the first-order kinetics:

\[
\frac{dZ}{dt} = K(N-Z) \tag{38}
\]

where \( K \) - the first order rate constant.
After integration and rearrangement one can get the following equation which describes the drug release from thin slab with initial drug concentration above the drug solubility in hydrogel:

\[
\frac{dM_t}{dt} = \frac{A}{2} \sqrt{\frac{2P_0 \exp(\frac{Kt}{2})C_0}{t}}
\]  \hspace{1cm} (39)

Charlier and his co-workers described another mathematical model predicting drug release from bulk eroding polymer films [27]. They assumed that the polymer degradation and the drug diffusion are simultaneous. Experimental results of mifepristone release from poly(lactic-co-glycolic) (PLGA) matrices were compared with model predictions. They developed this model by the pseudo-steady state assumptions, similar to classical Higuchi equation (Eq. 15). Moreover, the model assumes that polymer chains split with first-order kinetics and drug diffusion coefficients are exponential functions of time:

\[
D = D_0 \exp(kt)
\]  \hspace{1cm} (40)

In this equation:

- \(D_0\) - drug diffusion coefficient at time \(t = 0\),
- \(k\) - polymer degradation rate.

They got the following expression for the cumulative amount of drug release as a function of time:

\[
Q = S\sqrt{\frac{2C_0 C_s D_0 \exp(kt) - 1}{k}}
\]  \hspace{1cm} (41)

where:

- \(S\) - surface area of film contacted with the release fluid,
- \(C_0\) - initial drug concentration,
- \(C_s\) - solubility of drug in the polymer.

Surface phenomena

The rate of drug delivery can be affected by surface phenomena. Different surface phenomena can be distinguished:

1) desorption of species from surface,
2) surface reconstruction,
3) surface reactions.

The above phenomena significantly influence the resulting drug release kinetics. The species can be desorbed from the hydrogel surface. It is related to surface erosion and has been discussed above.

In surface reconstruction atomic or molecular rearrangement occurs on the surface of the device, thus the surface/interfacial tension is reduced. Surface reactions take place when drug molecules react with the release medium and new substances are formed.

Conclusions

Mathematical modeling of drug release from the polymeric matrix has big academic and industrial importance. It is very difficult to accurately predict the mechanism of drug release from the hydrogel device in living organisms. The drug transport in various organs and in different cells should be described by different models. In the future mathematical
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theories will attempt to take into account differences between in vitro and in vivo conditions.

References


Słowa kluczowe: hydrożel, modelowanie matematyczne, kontrolowane uwalnianie, podawanie leków, dyfuzja, pęcznienie, erozja