Review Article

Modeling Drug Release

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Citation M. Milani Fard, A.M. Milani Fard, **Modeling Drug Release**. *Eurasian J. Sci. Technol.,* 2022, 2(1), 14-33.

https://doi.org/10.22034/EJST.2022.1.2

Article info:
Received: 06 April 2021
Accepted: 16 June 2021
Available Online: 16 June 2021
ID: JSTR-2106-1046
Checked for Plagiarism: Yes
Checked Language: Yes

Keywords:
Drug release, Degradable polymer, Model, Control system, Paclitaxel.

ABSTRACT

Due to the diversity of polymers as well as their complex behavior, research in this field is still widely developed. Because biodegradable polymers become decomposed in the human body after decomposition, they are more commonly used because surgery is not required to remove these polymers from the body after the drug is released. Understanding the mechanism, modeling and studies of drug release from homopolymers, copolymers and mixtures of this family of polyesters is the focus of this research. In this research, the release of drug from homo and biodegradable copolymer in pure form with drug and finally the mixture of the two with drug has been investigated to determine the differences. In the proposed model, the equations that represent the degradation of the polymer are used to be able to predict the degradation of the polymer. The drug used is paclitaxel, which is a very important drug for chemotherapy. Since this drug is administered every 3 weeks for 3 hours, it is necessary to use controlled systems. Therefore, the purpose of this study is to achieve a predictable model for controlled release of paclitaxel, so that this model responds to the release of paclitaxel at any time.

Introduction

Mathematical modeling of drug release was performed by Professor Higuchi in 1961 [1-3]. Numerous models have since been proposed, including experimental/ quasi-experimental models and mechanistic theories. Experimental/ quasi-experimental models are merely mathematical descriptions and are not based on physicochemical or biological phenomena.

However, they may be useful, for example, in describing the various stages of drug release. Mechanical theories are based on natural phenomena such as penetration, disintegration, swelling, erosion, deposition or degradation; these types of models are suitable for determining system-specific parameters and deeper insight into the basic mechanisms of drug release. The mechanistic models that describe drug release are often explained by the diffusion coefficient and by Fick's law.

Some models use a constant effective diffusion coefficient, while in other models the effective

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diffusion coefficient is a function of other parameters that include decomposition processes [4]. These models are the equations described based on real phenomena. For example, the transfer of mass by diffusion, the solubility of drug particles or excipients (a substance used to absorb or dilute drugs), or the transfer of a polymer from a glassy state to rubber, which are based on mathematical theory. Most of the partial differential equations in question are able to solve them; the boundary and initial conditions must be known. If drug release is controlled solely by influence, mathematical solutions may be more accurate.

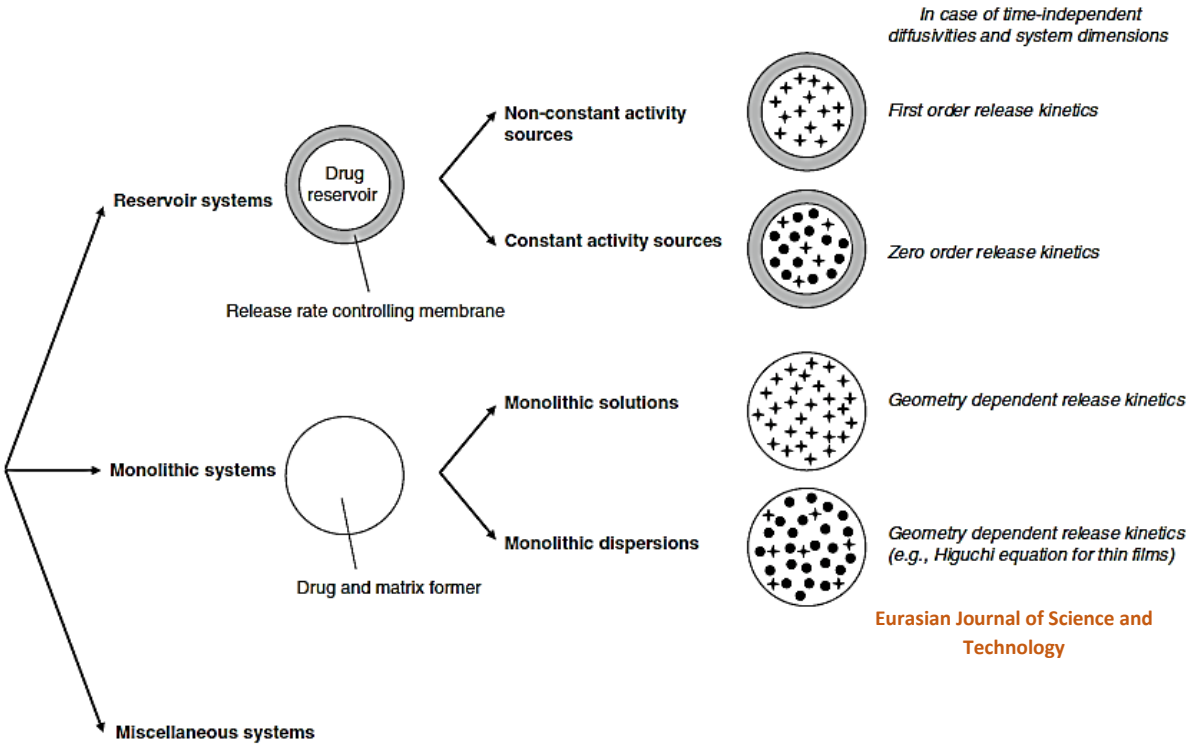

Figure 1 System classification for predominantly controlled drug delivery systems, star indicating single drug molecules, black circles of amorphous or crystalline drug masses, only spherical shapes are shown, but system classification is for each type of geometry [5]

Literature Review

Tamber and Himmelstein (1985) simulated the transfer-reaction model of catalyzed biodegradable polymer matrices for controlled drug release (numerical solution method) [6]. Ritter and Papas (1987) proposed a simple model to describe the release of dissolved objects from non-swollen devices in various forms [7]. Papas and Sahelin (1989) presented simple equations to describe the release of a dissolved body based on the composition of the polymer penetration and rest [8]. Joshi and Himmelstein (1991) proposed a mathematical model based on chemical diffusion-reaction to analyze the effective physicochemical parameters of biodegradable polymer matrices (polyarters) and showed that dynamic changes in the properties of the polymer matrix play a very important role in kinetic regulation. Method to solve the problem of penetrating controlled drug release for complex matrix systems that include complex geometry and composite structures with different boundary conditions, and concluded that it is a very suitable method for systems that can be solved [9]. Brazel and Pepas (2000) proposed a model for the release of drugs from volatile polymers [10]. In the same year, Tazfairi proposed a mathematical model of indirect release through diffusion for degraded volumetric matrices. Solving equations is numerical and finite element method [48]. Feng *et al*. (2002)

evaluated and synthesized the solubility of paclitaxel in water and concluded that it is a hydrophobic drug [11].

Lemeyer *et al*. (2003) worked on modeling of biodegradable porous matrices based on a combination of intrusion / erosion processes [12]. Wu *et al*. (2005) discussed mathematical modeling and laboratory studies of controlled release of drugs for polyethylene oxide polymer matrices with high molecular weight, high swelling, and degradability [13]. Mahadvan and Smith (2007) proposed a mechanistic model to describe the degradation of polymers [14]. Bertrand *et al*., modeled drug release from biodegradable globules using an automated cellular machine [14]. Lao and Wankatraman also used single-layer, double-layer, poly (DL-lactide-co-glycolide) / poly (L-lactide) films for biodegradable stents [15].

Lao *et al*. (2008) worked on the release of hydrophilic and hydrophobic agents from biodegradable polymers [16]. Rutstein *et al*. (2009) proposed an integrated mathematical model for surface-to-volume erosion systems, as well as matrices that conduct transition behavior from surface to volume erosion during demolition. The above model is based on destruction. And predicts destruction controlled by destruction [17]. Peral *et al*. proposed a new model for drug destruction and release based on one-dimensional penetration. The above model is based on the length of the polymer chain [18].

Han and Penn also presented a model to simulate the crystallization and biodegradability of biodegradable polymers [19]. Siriani *et al*. (2010) examined the release of paclitaxel (a hydrophobic drug) from a polymer coating (poly (styrene-isobutylene-styrene)) and performed mathematical modeling based on diffusion, mass dissolution, osmotic gradient and then comparison, which is a very interesting and efficient research. [20]. Suarez and Zunino worked on drug release from polydisperse polymer networks and proposed a hybrid model for water consumption, degradation and erosion [17].

Fu and Cao also succeeded in determining the release kinetics and transfer mechanisms of degradable and non-degradable polymer systems [21].

Rahimi and Kafroudi (2011) investigated the mechanism of degradation, the time of degradation and the factors affecting the degradation of polylactic acid, which is used as a support for broken bones, and numerically solved the governing equations and the reaction rate equation along with the boundary and initial conditions. Then they concluded that the rate of degradation of the above polymer is affected by factors such as the composition of the polymer, molecular structure, environmental conditions and the geometric shape of the polymer piece. The reaction rate depends on the thickness of the part, water penetration coefficient, monomer penetration coefficient [22]. In recent years, significant advances have been made in the use of water-swellable biomedical polymers as targeted carriers for drug, protein and growth factor release. Addressing and eliminating the clinical and pharmacological limitations of hydrogels makes their performance more specific and desirable. For this purpose, Khoei and Kordani (2012) examined these challenges and ways to deal with them based on methods of prolonging the process of drug release from hydrogels and also developing their function according to the nature of the drug. Finally, they concluded that copolymers with controlled hydrophilic and hydrophobic components could provide the desired release rates, especially if equipped with systems sensitive to environmental stimuli such as pH and temperature. The interesting use of these carriers in the treatment of cancer and diabetes or bone and cartilage repair has caused them to always receive special attention [23].

Giri *et al*. (2012) used a new method in drug-controlled release of the drug [24]. Versipt *et al*. (2013) described a mathematical modeling for drug delivery from PLGA autocatalytic degradable globules in a review article [65]. In the field of implants formed by fuzzy separation from PLGA, Parent *et al*. succeeded in determining critical physicochemical

parameters for estimating drug release [25]. Snoradottir *et al*. also numerically modeled drug release from layered silicon systems [26]. Recently, among the existing CDDS, advanced drug delivery systems have been proposed as release systems sensitive to environmental conditions or external stimuli, which have all the mentioned features in a desirable way. The basic premise of such systems is based on the use of the unique properties of hydrogels sensitive to external stimuli. Environmentally sensitive hydrogels are called smart hydrogels.

Husmann *et al*. 2002 [27] succeeded in presenting a model for drug release from this category of systems. The system releases the drug on-off only due to changes in ambient temperature, so that if the ambient temperature reaches a temperature higher than the desired temperature to start the release, the drug is released (on mode) and when the temperature drops below test, its release stops (off mode). The system in question is structurally composed of three completely separate parts, which are: the central drug core, the intermediate phase change layer and the outer polymer protective layer. The different parts of this system are located sequentially, one after the other, with a structure similar to the controlled release systems of a multi-layer tank.

On the effect of polymer concentration, Farrokhzad *et al*. (2009) investigated the effect of polymer concentration on a drug delivery system and compared at 22.5, 27 and 36% drug release concentrations based on the curves. The amount of sudden release is mostly related to the release of the drug from the surface due to the transfer of solvent with anti-solvent and along with it the initial ductility of the system. Increasing the polymer concentration increases the viscosity of the polymer solution. This increase in viscosity reduces the exit rate of the solvent and thus reduces the formation rate of the system, which in turn causes more compaction and reduction of the porosity of the underlying mass and the porosity of the surface of the membrane being formed. These two issues cause sudden release, as the polymer concentration increases sharply. To select the appropriate percentage composition, the results were compared with the results in the living ventricle.

An important and essential part of this system, which acts as a temperature sensor and provides the ability to respond to temperature changes, is the middle layer; this layer must be able to change the solid-liquid phase at Tset temperature. In other words, its melting temperature is equal to the set temperature to start the release (Tset). This layer must also be able to pass the drug in its liquid state and act as a barrier against its passage in the solid state. The main purpose of this study is to model the efficiency of the system with changes in ambient temperature. By solving the heat transfer equations in on mode, the important relationship of time delay of the system in responding to changes in ambient temperature was obtained and by solving the mass transfer equations in this case, the drug release kinetics of the system was obtained.

Also, by solving the mass transfer equations in the off state, the involuntary release kinetics of the drug in this state were determined. In general, the modeling of the desired system makes it possible to select the basic elements of the system optimized in practical cases, to achieve the desired and desired response systems quickly.

Polymer Equipment Can be classified into Two Main Categories

Integrated and reservoir equipment consists of integrated drug systems dissolved or distributed in an ineffective matrix, and reservoir systems comprise a core surrounded by a penetrating polymer membrane. Three types of equipment are provided by solvent casting techniques alone or combined by compression, integrated disks (SMD), multilayer disks with integrated central layer (MLDM) and multilayer disks with a central drug reservoir (MLDR) for highly water-soluble drug [28].

Controlling the release kinetics of integrated matrix systems is simpler and easier than other systems such as coated systems. In these systems, the drug is placed in the matrix in two ways.

1- A drug dissolved in a polymer;

2- Drug dispersed in the polymer

The governing equations of these systems and the governing lateral conditions are briefly discussed [29-31].

Dissolved Drug in Polymer

Polymers, in the form of cylinders, spheres, or plates, allow the drug to penetrate into the matrix, dissolve, and remain dissolved until the matrix is based on the second law of diffusion and applies only to drugs that penetrate into a dissolved and solvent matrix.

Drug Dispersed in the Polymer

If the solubility of the drug in the polymer is very slow, most drugs are evenly distributed within the polymer matrix and the rest are dissolved in the polymer. The release kinetics of material is dry. The drug combines with the polymer so much that the amount of drug is less than its solubility in the polymer. The solubility rate of the drug follows the penetration of the solvent through the polymer matrix. When a dry drug is placed on a polymer, the soaked and saturated drug in the polymer rapidly penetrates the solvent (due to its high solubility) and penetrates out of the polymer matrix. The mathematical expression governing the penetration of a dissolved body through a

this type of system follow the Higuchi model in which the concentration gradient between the drug receiving site and the drug solution is linear. Fick's first law governs this category if complete penetration conditions are provided throughout the release period and if the permeability of the drug through the membrane remains. The first-order release kinetics, regardless of the geometry of the device, are as follows:

$$\frac{dM_t}{dt} = \frac{ADKc_t}{L} = \frac{ADK}{L}\frac{M_0 - M_t}{V}$$

M_t: The absolute sum of the drug released at time t;

M_0: Initial amount of drug;

Ct: drug concentration in the release medium at the above time;

K: Drug partition coefficient between membrane and source;

v: drug tank volume;

A: The total surface area of the device;

L: Membrane thickness.

If the initial concentration of the drug is less than the solubility of the drug, the drug molecules are individually dissolved in the carriers (solid solution). Otherwise, the dissolved drug molecules coexist with the amorphous or crystalline masses of the drug (dispersed evenly). In the case of integrated solutions and in the absence of significant changes in the carrier matrices at the time of drug release (for example: Constant porosity, no swelling, time-independent permeability for the drug) and complete penetration conditions, the release results can be calculated as dependent on system geometry.

$$\frac{M_t}{M_0} = 1 - \frac{8}{\pi^2}\sum_{n=0}^{\infty}\frac{1}{(2n+1)^2}\exp\left(\frac{-D(2n+1)^2\pi^2 t}{L^2}\right)$$

$$\frac{M_t}{M_0} = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left(-\frac{Dn^2\pi^2 t}{R^2}\right)$$

$$\frac{M_t}{M_\infty} = 1 - \frac{32}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{q_n^2}\exp\left(-\frac{q_n^2}{R^2}Dt\right)\times\sum_{p=0}^{\infty}\frac{1}{(2p+1)^2}\exp\left(-\frac{(2p+1)^2\pi^2}{H^2}Dt\right)$$

q_n: The root of the Bessel function of the first type of zero order.

However, due to the complexity of setting the corresponding differential equations, an analytical solution cannot be chosen for this theory, but it can be solved if the model needs to be used [25].

$$\frac{M_t}{A} = \sqrt{DC_S t(2C_0 - C_S)}$$

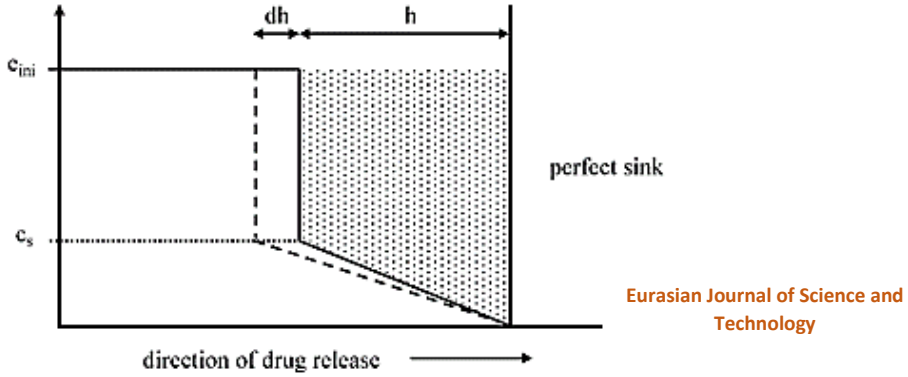

Figure 2 The quasi-steady state in agreement with the classical Higuchi equation [14]

The main premise of the theory described above is that the drug is distributed molecularly into the system. He later extended his theory to spherical geometry [26], a very similar method to quizumi. The advantage of their solution is that the approximate solution is simple in form and therefore easier to use than the relative Higuchi equation (fixed drug dispersion coefficient).

$$M_t = 4.\pi.r^2.[\sqrt{2.(c_0 - c_s).c_s.D.t} + \frac{4.c_s.D.t}{9.r}.\left(\frac{c_s}{2.c_0 - c_s} - 3\right)]$$

Different relationships for penetration:

- Effective time dependent coefficient and constant k polymer degradation rate.

$$D_{eff}(t) = D_0 \times e^{kt}$$

Relationship between Diffusion Coefficient and Molecular Weight of Polymer

In summary, for controlled release we have:

$$D(M_w) = D_0 + \frac{K}{M_w}$$

$$\ln(D) = -0.347x^3 + 10.394x^2 - 104.950x + 316.950 \qquad x = \ln(M_W)$$

Theories Related to Polymer Swelling

There are two very important consequences for polymer swelling in a controlled release matrix system:

1- Increasing the length of the penetration pathway leads to a decrease in drug concentration gradients (stimulus forces available for penetration) and, consequently, a potential drug release rate decrease.

2- Significant growth of macromolecule motility leads to increased drug motility, thus potential drug release rate increases. Depending on the type of polymer and the type of drug delivery system, one of these effects potentially overcomes and leads to a decrease

or increase in drug release rates. Figure 7 summarizes the physical phenomenon that can be involved in controlling drug release from an inflatable release system.

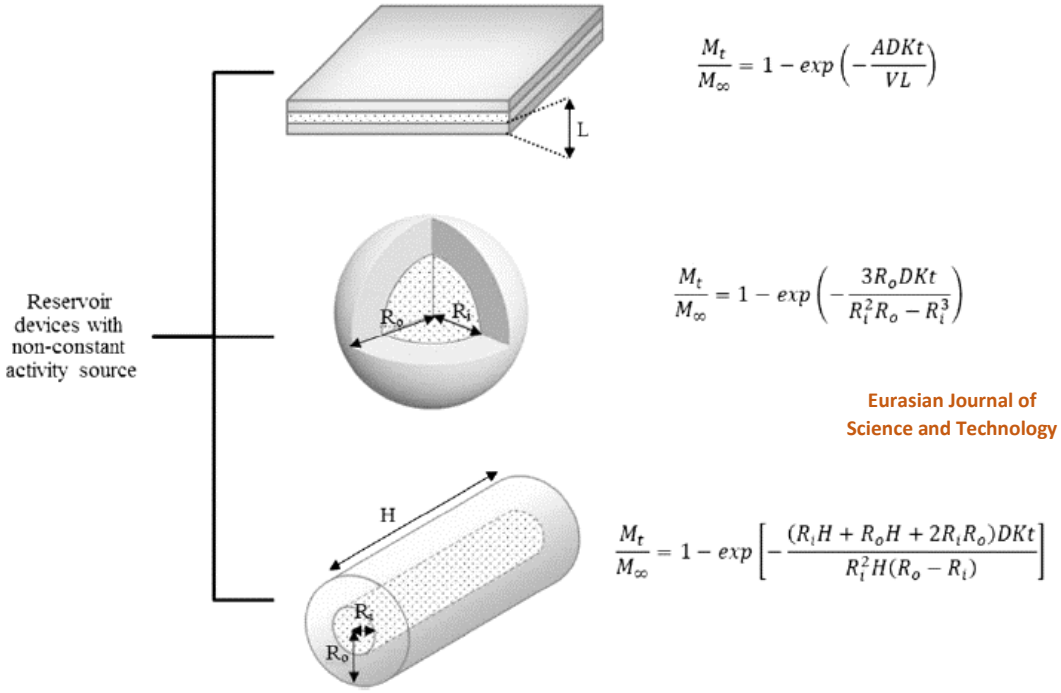

Figure 3 Mathematical equations for drug release from reservoir systems (initial drug concentration <drug solubility concentration) [24]

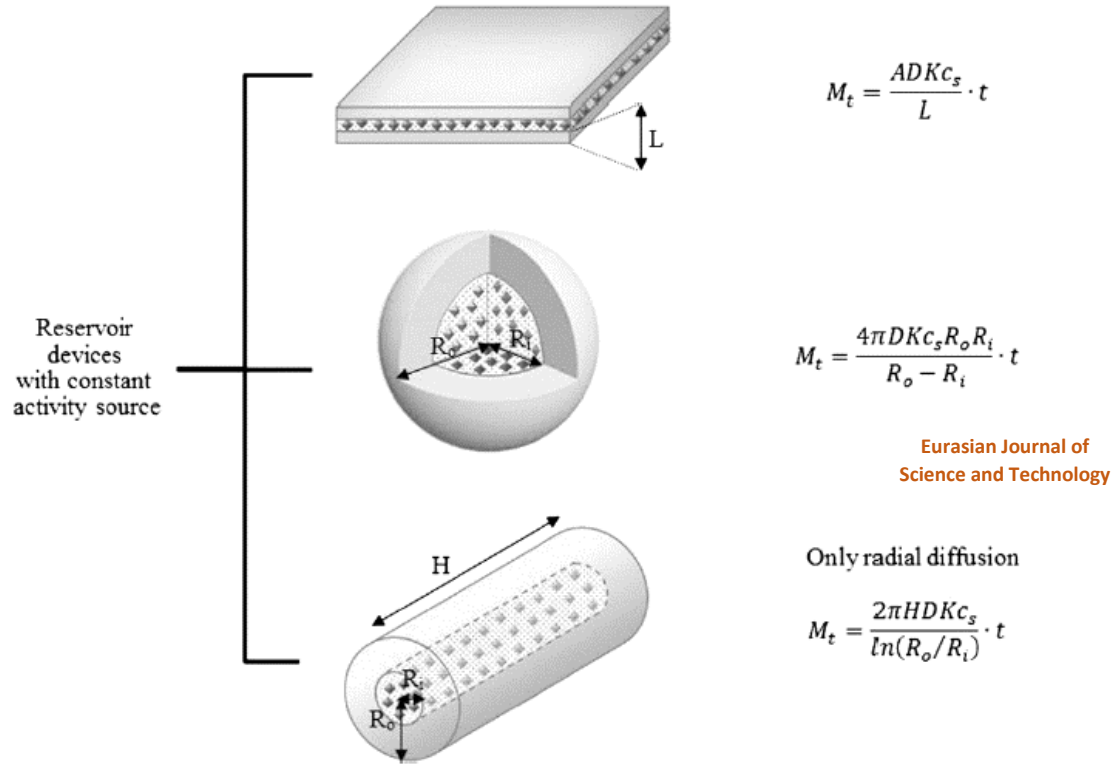

Figure 4 Mathematical equations related to drug release from reservoir systems (initial drug concentration> drug solubility concentration) [24]

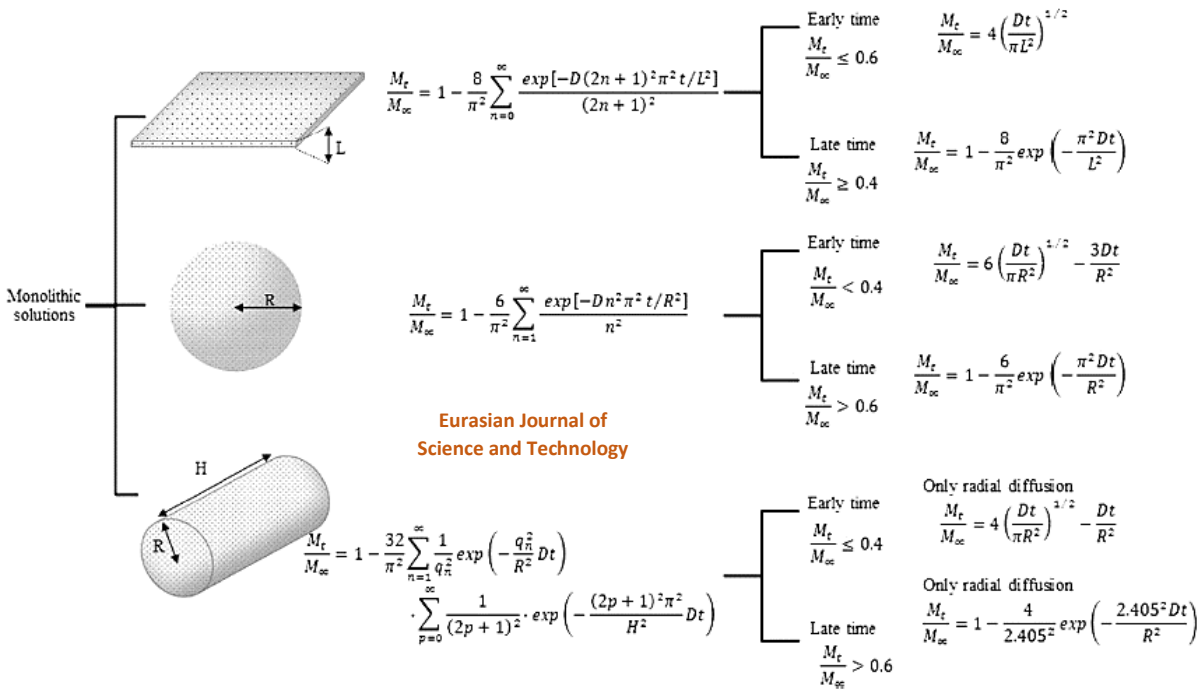

Figure 5 Mathematical equations for drug release from integrated solution systems (initial drug concentration <drug solubility concentration) [24]

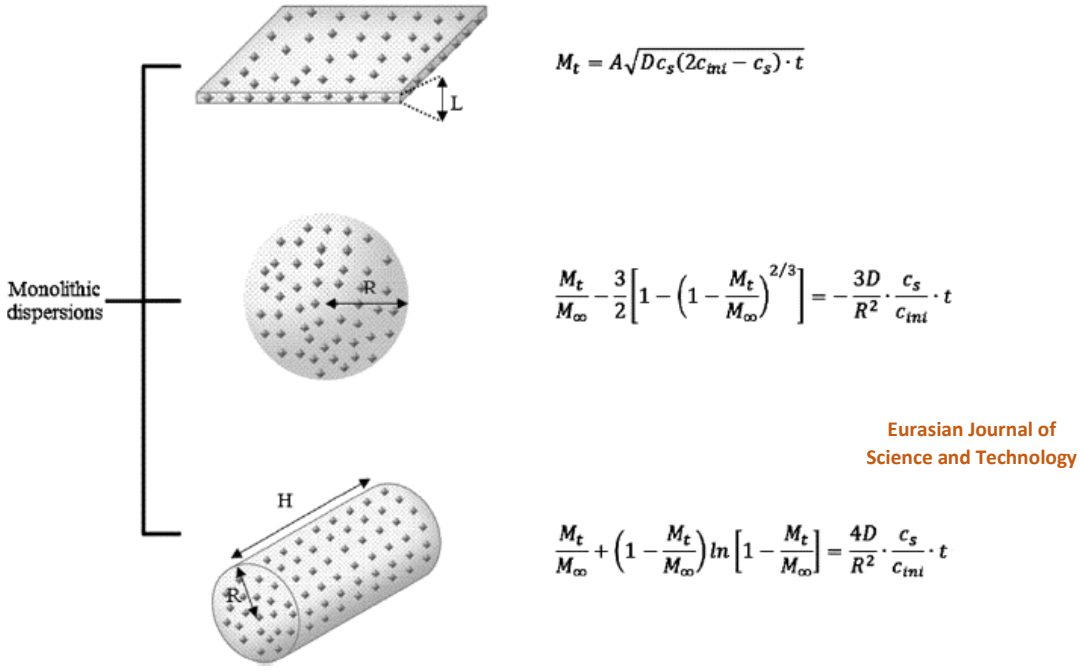

Figure 6 Mathematical equations for drug release from integrated solution systems (initial drug concentration> drug solubility concentration) [24]

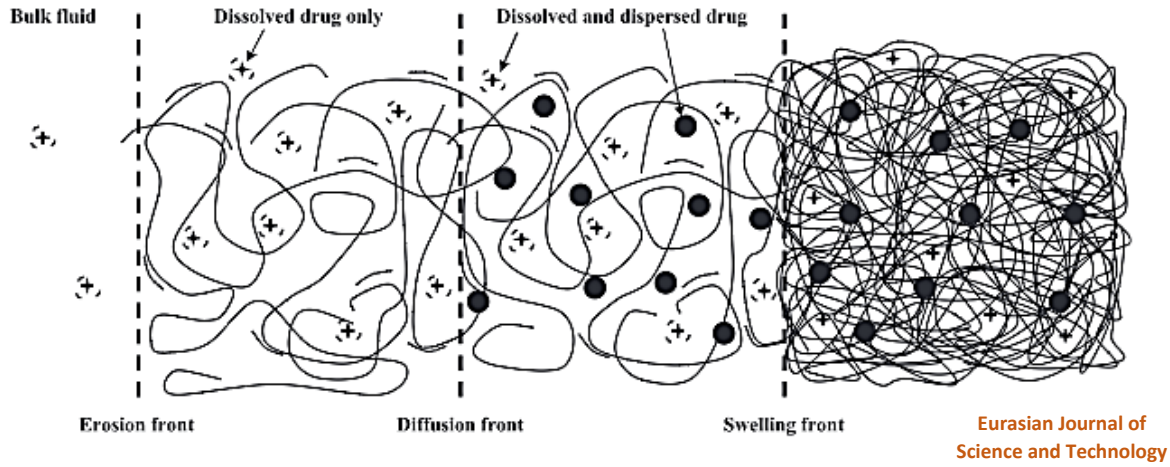

Figure 7 Schematic of a controlled swelling drug release system consisting of dissolved drug (star) and dispersed drug (black circles) according to boundary motion: 1) Erosion front that separates the fluid mass from the release system. 2) The diffusion front that separates the swollen matrix containing only the dissolved drug and the swollen matrix containing the dissolved and dispersed drug. 3) The inflation front that separates the swollen matrix from the non-swollen one [14]

If the initial concentration of the drug in the release system exceeds the solubility of the drug, the dissolved and insoluble drug are present together in the matrix. Due to the concentration gradients and increased mobility, the dissolved drug molecules penetrate out of the swollen matrix into the release medium provided that an additional unsolved drug is present.

The concentration of dissolved drug in this part of the system is constant. The equations are given in the relevant article [14].

Experimental and Quasi-experimental Mathematical Models

These models, like a descriptive mathematical analysis, can be used to compare different drug delivery profiles (for example, to design experimental studies).

Peppa's Equations

The model that is often used to describe and describe drug delivery is called the papas or powerline equations [25]:

$$\frac{M_t}{M_\infty} = Kt^n$$

n: Release determinant that may indicate the mechanism of drug release

For all device geometries and pure drug penetration control, different release values are obtained (Table 1).

Table 1. Exponential release values for different geometries [14]

Thin film	Exponent, n Cylinder	Sphere	Drug release mechanism
0.5	0.45	0.43	Fickian diffiusion
0.5 <n< 1.0	0.45< n <0.89	0.43 <n< 0.85	Anomalous transport
1.0	0.89	0.85	Polymer ewelling

Hoffenberg Model

An interesting quasi-experimental model to quantify drug release from degradable drug delivery systems. All mass transfer processes involved in drug release control are hypothesized to add to the zero-order process (described by a constant rate k0) that is

confined to the system surface area. This zero-order process must be related to a physical or chemical phenomenon, but it may also result from the adaptation of several processes such as dissolution, swelling or splitting of the polymer chain. The above model can be used as an example for polymeric matrices of erosion surface and its general equation is as follows [6]:

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{K_0 t}{C_0 a}\right)^n$$

a: The radius of the cylinder or sphere or half the thickness of the rod

n: The shape factor (spherical = 3, cylindrical = 2, piece = 1), the model ignores the end and edge effects

Cooney Model

More detailed analysis is provided for spheres and cylinders with surface erosion, as well as their model based on the assumption that it is a zero-order process trapped at the level of the drug delivery system. In the above model, the assumed release rate is proportional to the surface area of the device, which is time dependent. For a cylinder with an initial length of L0 and a diffusion coefficient of D0, the following equation was derived to quantify the drug release rate f as a function of time [27]:

$$f = \frac{(D_0 - 2Kt)^2 + 2(D_0 - 2kt)(L_0 - 2Kt)}{D_0^2 + 2D_0 L_0}$$

Artificial Neural Networks Artificial neural networks (ANNS) can also be used to model drug delivery [28].

Modeling Methods for Polymer Erosion and Degradation

These models are classified into three main methods, which are summarized in table (2) with a physical description. Mathematical modeling methods for erodible drug delivery systems are divided into two categories:

1- Experimental models that usually assume a single zero-order controlled process [7].

2- Theory of models of specific physico-chemical phenomena, such as intrusive mass transfer or chemical reactions [9].

Polymer degradation (simulated by Monte Carlo techniques). And intrusive mass transfer processes (described by Fick's second law of intrusion) are considered within the models developed by Gaffrich.

Phenomenological Models

Most models that account for polymer erosion are based on the mechanization phenomenon and based on studies of diffusion and dissolution reactions. Since this type of model is based on governing equations, there are a wide range of methods available for a variety of types, polymers, device geometries, and conditions that are sufficiently general and can be easily applied or extensively developed. In general, the penetration reaction (RD) method is used for erosion volume systems that show much more complex reaction behavior. These models are not limited to erosion volume systems and are also used to model the microstructural effects on the surface erosion of polyanhydride copolymers. A model was proposed by Burkersrodit [31] to provide a dimensionless parameter that describes the polymer's tendency to withstand surface and volumetric wear under critical conditions:

$$\varepsilon = \frac{\langle x \rangle^2 \lambda \pi}{4 D_{eff} \ln[\langle x \rangle] - \ln[\sqrt[3]{\overline{M_n}} / N_A (N-1)\rho]}$$

Deff: effective water diffusion coefficient;

φ: density;

λ: Destruction rate constant based on endurance factor

Mn: Numerical average of molecular weight;

NA: Avogadro number;

N: Medium degree of polymerization;

<X>: Average water movement

Possible Models

Possible distributions can be used to modify mechanistic theory in a system without an

equation that accurately describes the phenomenon and appears to be particularly suitable for polymer erosion because the polymers are combined in a distribution of molecular weights and their disintegration. They can be modeled:

Zygorakis: used the Monte-Carlo (MC) method for the erosion model. But the effects of intrusion into the calculations are not given.

Gaffrich: combined the possible Monte Carlo method with a model dependent on infiltration phenomenology for destruction.

Sipman: Decomposition of a Monter Carlo-modeled polymer with the intention of releasing a drug model from polymer microparticles.

The plates of symmetry inside the spherical geometry were divided into cells (Figure 8) with a random lifespan taken by:

$$t_{lifetime} = t_{average} + \frac{(-1)^{\varepsilon}}{\lambda} \ln\left(1 - \frac{\varepsilon}{100}\right)$$

λ: fixed for polymer;

ε: Random number between 0 and 99

Possible method for porosity by Rutstein for drug release kinetics from polymer matrices by pore growth in volume, porosity growth in polymer was modeled as a function of normal shrinkage distribution, and porosity ε is a function of time t.

$$\varepsilon(t) = \frac{1}{2}\left[erf\left(\frac{t-\bar{\tau}}{\sqrt{2\sigma^2}}\right)+1\right]$$

σ^2 variance

Table 2 Summary of applications and physical models of polymer erosion [7]

Modeling approach	Method	Physics accounted for by model	Degradable polymers
Probabilistic	CA	Bulk erosion	Polyesters
Probabilistic	CA	Crystallinity, surface erosion	Polyanhydrides
Probabilistic	MC	Crystallinity, bulk erosion	Polyesters
Probabilistic	MC	Surface erosion, porosity,monomer solubilit	Polyanhydrides
Probabilistic	MC	Monomer solubility and diffusion, porosity	Polyanhydrides
Phenomenological	RD	Copolymer microstructure and scission rate differences, crystallinity, surface erosion	Polyanhydrides
Phenomenological	RD	Polydispersity, chain length dependent diffusivity	Polyesters
Phenomenological	RD	Catalyzed hydrolysis, polydispersity, fraction of crystallinity and differences in copolymer scission rate (through degradation rate constants)	Polyesters
Phenomenological	RD	Crystallinity (through water partition coefficient), diffusivity dependent on extent of polymer hydrolysis, catalyzed hydrolysis, oligomer formation	Polyesters
Phenomenological	RD	Bulk erosion (“shrinking core”), polydispersity, catalyzed hydrolysis	Polyesters
Phenomenological	RD	Time-dependent crystallinity, catalyzed hydrolysis	Polyesters
Phenomenological	RD	Surface erosion, catalyzed hydrolysis	Poly(orthoesters)
Phenomenological	RD	Bulk erosion, time-dependent average molecular weight	Poly(orthoesters)
Phenomenological	RD	Surface and bulk erosion, time-dependent average molecular weight	Polyanhydrides, poly(orthoesters), and polyesters

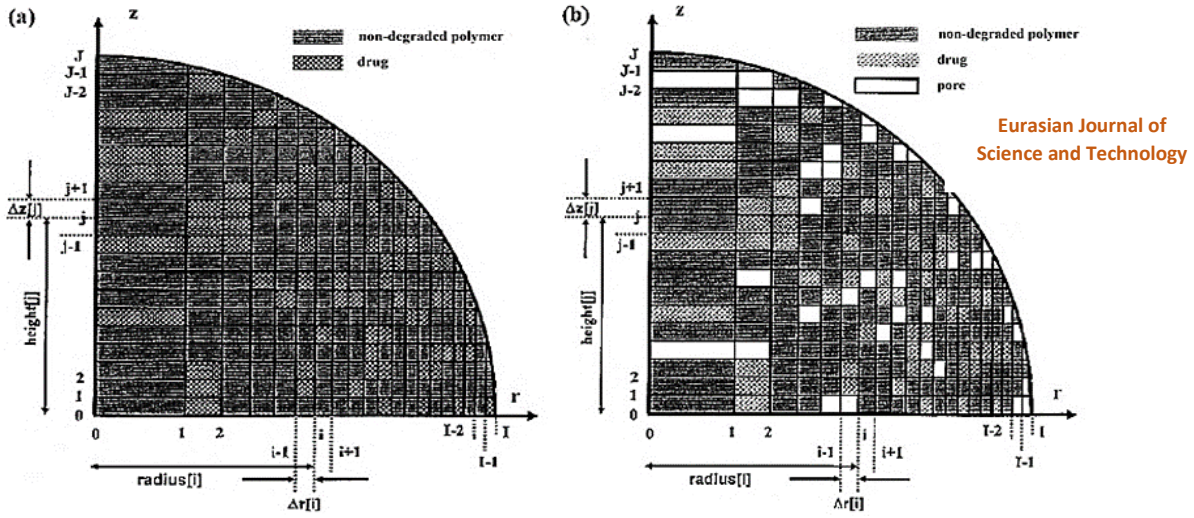

Figure 8 Monte Carlo method for modeling polymer erosion: (a) before and (b) during drug release

Models Based on Chemical Penetration and Reaction

Non-Monte Carlo Based Models

Heller and Becker (2018) developed mathematical models of drug dispersion of water-insoluble polymers that undergo hydraulic strength rupture. When polymer chains become the smallest number of water-soluble molecules. It was estimated that for polymeric matrices under volumetric abrasion, degradation could be described by first-order kinetics.

Examples of such systems include: PLGA, PLA. The starting point for their mathematical analysis was the classical Higuchi equation, and they assumed that the drug was initially homogeneously dispersed; the initial concentration of the drug was greater than the solubility of the drug in the matrix, integrated dispersion.

$$\frac{dM_t}{dt} = \frac{A}{2}.\sqrt{\frac{2.P.C_0}{t}}$$

M_t: net amount of drug released at time t;

A: The surface area of both sides of the film;

C_0: Initial concentration of drug within the system;

P: Drug permeability within the polymer matrix

Compared with Higucci's original model, Heller-Becker assumed that the permeability in the biodegradable polymer system was not constant and increased with time. For this issue, Heller and Becker hypothesized the following relationship between drug permeability at time t (p_t) and initial drug permeability (p_0) [30]:

$$\frac{P_t}{P_0} = \frac{N}{N-Z}$$

N: Number of initial links;

Z: Number of ruptures in time interval [0, t]

Assuming that the polymer bonds are discretized, we have the first-order kinetics:

$$\frac{dZ}{dt} = K.(N-Z)$$

K: First order speed constant

Integration and rearrangement lead to a phrase that calculates the amount of drug dispensing:

$$\frac{dM_t}{dt} = \frac{A}{2}.\sqrt{\frac{2.P_0.\exp(K.t).C_0}{t}}$$

Figure 9 shows the rate of drug release from the above equation and shows the difference between penetration and erosion compared with the completely controlled and calculated penetration release kinetics from the classical Higuchi equation.

The release rate clearly decreases with time in the controlled intrusion system due to the increase in longitudinal intrusion paths. However, according to the above model, after a

certain period of time, its effect is greatly enhanced by increasing the permeability of the drug in the polymer with progressive erosion; the rate of drug release decreases first and then increases.

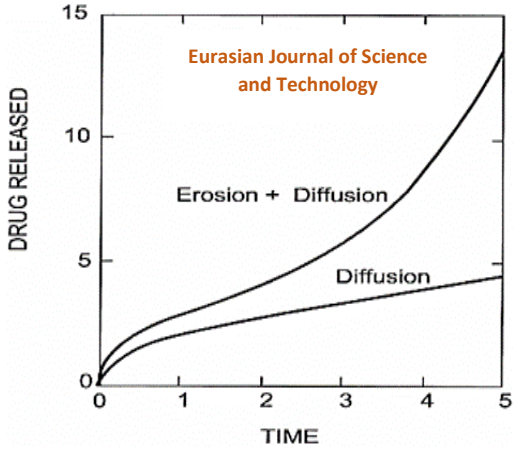

Figure 9 The Heller-Becker model is illustrated to describe drug release from films containing thin biodegradable polymers under volumetric erosion, as well as single-diffusion-controlled release kinetics calculated by the classical Higuchi equation (penetration curve)

In 1980, Lee [16] proposed an approximate analytical solution for drug dispersion on the thin surface of erodible polymer films that were reasonably available for different drug loading to drug solubility ratios in the matrix, a model based on two-sided motion, penetration and erosion. The conditions of complete penetration, the initial velocity of the fixed erosion front movements and the assumptions of the final effects are negligible. According to the following derivative phrase, a small amount of drug dispersion is obtained at different times:

$$\frac{M_t}{M_\infty} = \delta + \frac{B.a}{D}.\tau - \delta.\frac{C_S}{A}.(\frac{1}{2} + \frac{a_3}{6})$$

$$a_3 = \frac{A}{C_S} + \delta.h - \sqrt{-1 - 2.\delta.h + \left(\frac{A}{C_S} + \delta.h\right)^2}$$

$$h = \frac{1}{2}.\frac{B.a}{D}.\left(1 - \frac{A}{C_S}\right)$$

M_t, M_∞: Compression values of the drug released at the above times;

δ: Sign related to separation of intrusion and erosion fronts [δ = (S-R)/a];

B: Half the thickness of the film;

D: Injectable drug delivery coefficient;

τ: timeless dimension (τ= Dt/a²)

D: The ratio of erosion rate to matrix permeability measured for the erosion-dependent contribution of the drug;

A: The initial concentration of the drug inside the polymer system, which is greater than the solubility of the drug;

CS: drug solubility concentration;

Cb: The concentration of the drug in the solution was well stirred;

X: Position (zero center and x = a film surface)

The effect of the initial loading ratio of the drug on the drug solubility in the matrix (A/CS) on the results of drug dispersion kinetics has been shown and with increasing this ratio, the drug dispersion rate decreases. The model predicts zero-order kinetic methods of release when the initial loading of the drug exceeds the solubility of the drug in the matrix.

Kwaraz *et al*. [27] presented a mathematical model eligible for drug delivery from volumetric abrasion polymer films. Due to polymer degradation and drug penetration at the same time, theoretical calculations were compared. From a similarly stable method for initial drug loading and good solubility within the matrix, they also assumed that the polymer chain rupture followed the first-order kinetics

and that the diffusion coefficient increased exponentially with time.

$$D = D_0.\exp(K.t)$$

The equation represents the cumulative amount of drug released (Q) versus time derived:

$$Q = S.\sqrt{\frac{2.C_0.C_S.D_0.[\exp(k.t)-1]}{k}}$$

S: The surface area of the film is subject to moderate release

In addition, for the diffusion/ degradation model, they also calculated the release kinetics results based on the classical Higuchi equation and concluded that the Higuchi model only agrees with the experimental data released during the early stages of the drug. But the effect of polymer degradation on drug release is not known.

Models Based on Monte Carlo

About 80 or 90 years ago, Ziggoras proposed the first Monte Carlo model to simulate drug release from erosion surface polymer matrices [28]. Figure 10 summarizes the internal structure of the cylindrical devices during matrix erosion. The black areas of the unfired polymer, the white areas of the pores and pores of the monomers filled with aqueous solutions, and the gray areas of the crystalline particles of the monomers eventually lead to a series of partial differential equations and are solved numerically.

Release Profile

The release profile is sometimes used as a basis for evaluating the mechanism. Drug release is sometimes multistage. But three-stage profiles are more common. Large particles often show this three-step release profile due to heterogeneous degradation [29].

The first stage is a three-stage profile, commonly described as a sequential release; the second stage is often a slow-release stage as the drug penetrates slowly. The third stage is usually a faster release period, often attributed to the onset of erosion. The release profile may not show any consecutive release, some examples of different release profiles are given in Figure 11.

Hollow Squares

Release in a row and fast second stage. Solid circles: Three-step release with a short second step. Crosses: Release in a row and zero release.

Solid Lozenges

Three-step liberation. Lines: Two-stage liberation, similar to three stages without consecutive liberation [4].

Factors Affecting Liberation

The Effect of PVP on the Release Pattern

PVP Poly vinyl pyrrolidine is a hydrophilic polymer, used as a pore constituent to further achieve the porous polymer structure after contact with the release medium, resulting in an increase in drug release [30].

Glass Transfer Temperature

If the polymer is in the glass state (T <Tg), the mobility of the macromolecules is very weak, so the free volume available for penetration and consequently the rate of drug penetration through the polymer matrix is very small. In the rubber region (T> Tg) the macromolecules become more mobile, and as a result the diffusion coefficients of the drug in the direction of higher amplitudes become more regular than in the glass state. Figure 12 shows the evolution of the transfer temperature of polymer glass at PH = 7.4. Tg is determined by DSC for both dried and unwashed particles. For the undried ones below the system temperature, the polymer is in the rubber state and allows higher penetration rates through its matrix, in contrast to the dried particles, above the system temperature and determines that the polymer is in the glass state. This clearly shows the importance of water as an emollient.

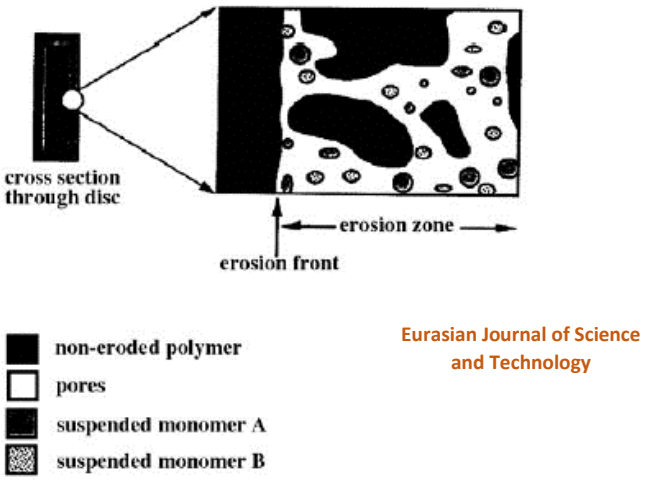

Figure 10 Model proposed by Gaffrich *et al*. To simulate polymer degradation and monomer release from polyhydride matrices by Monte Carlo. Schematic techniques known for the internal structure of cylindrical equipment during matrix erosion [8]

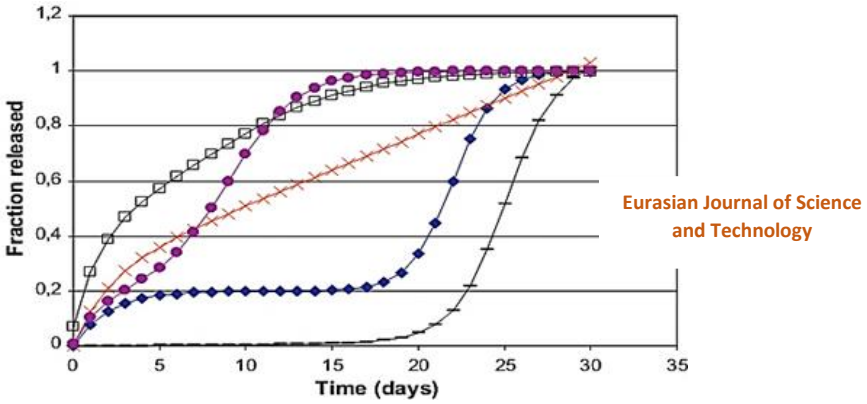

Figure 11 Release profiles include different phases

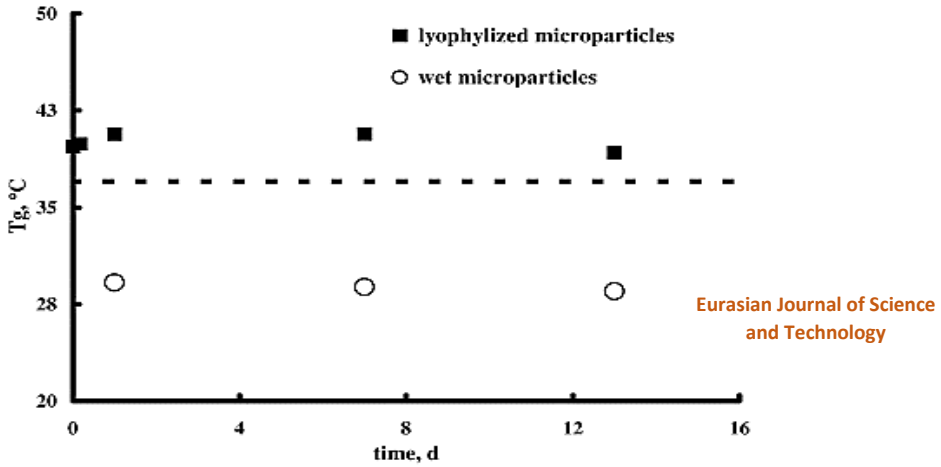

Figure 12 Glass transfer temperature estimated by DSC [21]

Table 3 summarizes some of the different release profiles [4]

Phase I	Phase II	Phase III
Burst	Slow diffusion-controlled release	Rapid erosion-controlled release
No burst	Slow diffusion-controlled release	On-set of degradation. Erosion-controlled release
Diffiusion-controlled release of drug molecules at the surface or in pores initially connected to the surface	Dependent on diffusion and erosion	Dependent on diffusion and erosion
Similar to the row above	Lag-phase, as the first and second phase did not overlap	Second phase, erosion-controlled
Similar to the row above	Slow and minimal release	Rapid release. Rapid water absorption associated with sudden mass loss
Similar to the row above	Degradation and erosion	Onset of bulk degradation
Burst. Drug molecules on or with access to the surface	Slow diffusion-controlled release	Erosion phase at which degradation occurs
Burst	Diffusion governed by water absorption and swelling	Faster diffusion due to erosion. The onset of this phase depends on the rate of hydration
Burst	Diffusion due to hydration	Faster diffusion due to erosion. The onset of this phase depends on the rate of hydration
Burst. Surface-bound and poorly encapsulated drugs may diffuse through pores and cracks	Slow diffusion, which may be attributed to binding of the drug to the polymer	Faster diffusion through the eroding matrix. Decrease in polymer Mw increases the gaps in the matrix
Burst. Solvent penetration and glass transition	Limited drug dissolution. Polymer degradation and relaxation	Diffusion through water-filled pores

Osmolality Release Culture Medium

The osmolarity of the culture medium can significantly affect the various processes involved in the controlled release of biodegradable systems. They are like the rate and amount of water penetration into the system. The rate of drug release decreases with increasing osmolarity of the culture medium and may be related to a decrease in water rate. In the system, as the volume of water decreases, the motility of the drug decreases and thus the rate of release decreases.

Based on these calculations, the initial penetration coefficient can be determined by an osmolarity factor of the release medium and the obvious culture, the amount of which decreases with increasing osmolarity. The following relation can be established (R2 = 0.98).

$$D_0 = \left(-0.0005 \times osmolarity[mosm/L] + 0.9395 \times 10^{-11} cm^2/s\right)$$

PH Release Culture Medium

By increasing the pH of the constant release medium, the degradation rate of the polymer decreases slightly. Reduction in the degradation rate constant causes less macromolecule mobility and therefore the drug release rate decreases; the lower the pH the higher the Tg, so the polymer is in the glassy state and the release rate is lower. But the higher it is, the lower the temperature and it is in a state of bondage, so the movements of the polymer chains and drug molecules become much larger, and as a result, the drug release rates increase. This fundamental difference in the physical state of the polymer explains the significant difference in the observed drug release behavior.

Release Culture Medium Temperature

The effect of temperature on the culture medium and the results of drug release kinetics from the microparticles studied are shown in Figure 13.

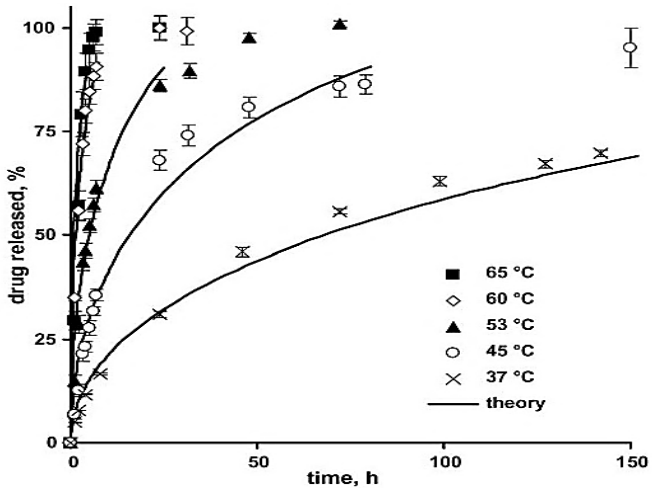

Figure 13 Release ambient temperature curves [39]

Clearly the release rate increases significantly when the temperature rises from 37 to 65 °C. Drug release profiles may all be single or two-step above 45 °C and can be attributed to increased mobility of polymer chains and molecules at high temperatures, which in turn leads to increased penetration rates. Based on these calculations, the initial drug diffusion coefficient in microparticles based on PLGA (D0) can be determined. Like a temperature function, the diffusion coefficient increases significantly with increasing temperature and the following exponential relationship can be established:

$$D_0 = 2.68 \times e^{0.1557T(^{\circ}C)} \times 10^{-14} cm^2 / s$$

The useful advantage of this equation is that it allows the drug diffusion coefficient to be calculated at optional temperatures (if the polymer is in bonded state).

The Effect of Latency Temperature on the Degradation of PLGA Particles

When the globules are exposed to different temperature conditions, it has been observed that the rate of polymer degradation increases with increasing time and the profile becomes multiphase. The K-rate constancy in the mass loss profile is calculated from equation and increases with increasing latency temperature. The effect of temperature on the reaction rate is obtained by the following proposed Arrhenius equation [31]:

$$K = Ae^{\frac{-Ea}{RT}}$$

Activation energy can be used to predict the effect of changes in latency temperature on the degradation rate and consequently on the release process. The rate of polymer degradation is faster for larger globules. Two stages of degradation were found to be the first stage, when polymer mass loss does not occur and does not depend on size. While the second stage was when we have mass loss and was founded for dependence on particle size. The rate of polymer degradation increases with increasing latency temperature at lower latency temperatures.

Severe Effect of pH on Polymer Degradation

Heller investigated the effect of pH on degradation and concluded that the rate of degradation could only be increased by decreasing the ambient pH, because hydroxide

ions were not able to attack the orthostatic bond carbon, so adding magnesium hydroxide to matrices was appropriate to reduce Accelerating their degradation, while the addition of carboxylic acid anhydrides is used for the opposite purpose [32-38].

Conclusion

New injectable drug delivery systems have made significant progress over the past few decades. This is due to the advantages that these systems have, such as simple application, effective topical drug delivery, long-term drug delivery, reducing the dose of the drug along with reducing the amount of side effects, increasing patient comfort and acceptance. Semi-perishable biodegradable injectable implant systems are made of biodegradable polymers that can be injected into the body with a syringe. These systems solidify as soon as they are injected to form a semi-solid storage. These systems are classified into four groups based on the mechanism of solidification in the living ventricle:

1- Thermoplastic pastes;

2- Systems that are networked at the injection site;

3- Systems that deposit at the injection site Solidification of organic gels at the injection site in the system formation method by deposition in solution, this sediment can be produced by leaving the solvent, change in temperature or change in pH.

Dan *et al*. (2009) introduced a drug delivery system of biodegradable polymers that can be used for humans and livestock. These injectable implant systems are composed of water-soluble biodegradable polymers such as poly (D, L-lactide), poly (-D, L-lactide-co-glycolide) and poly (D, L-lactide-co-1-caprolactone), which in the biocompatible solvent is physiologically soluble in water. By injecting this system into an aqueous medium, the solvent penetrates into the surrounding aqueous medium and water penetrates into the polymer medium. Because the polymer is insoluble in water, it precipitates in contact with water and forms a solid polymer implant system.

One of the problems of this system is the possibility of sudden release of the drug, especially in the first few hours after injection into the body. Because this injectable implant system is administered in liquid form, it is quite reasonable to assume that there is a delay between injection and solid implant formation. During the delay period, the sudden release of the drug may increase its concentration in the blood plasma compared with conventional implant systems. Sudden release of the drug causes tissue inflammation and in some cases systemic toxicity. Due to such unwanted phenomena, these systems are used only for specific treatments. In order to control the effects of sudden drug release, various factors have been studied. The four most important tested factors are: The concentration of the polymer in the solvent, the molecular weight of the polymer, the solvent used, and the addition of surfactants all affect the rate at which the polymer precipitates.

The results of this study show that the concentration of polymer is a determining factor in controlling the sudden release and release time of the drug. With increasing concentration at constant molecular weight, due to increasing viscosity and decreasing the rate of solvent exit, the membrane structure at the surface and mass of the system becomes denser, abrupt release decreases and total time increases.

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