Original Article

Investigation of Drug Release from a Biodegradable Biphasic Polymer System

Maryam Milani Fard* |**Amir Mohammad Milani Fard**

[1]*Researcher at the Anesthesia and Pain, Molecular and Cell Biology Research Center, Faculty of Medicine Department of Anatomy, Iran University of Medical Sciences, Tehran, Iran*
[2]*Graduate of nursing, School of Nursing and Medical Emergency, Alborz University of Medical Sciences, Researcher of Baqiyatallah Hospital Research Center, Tehran, Iran*

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ABSTRACT

In this study, a controlled drug delivery system was modeled to release the drug dissolved in a polymer matrix by polymer degradation. This system is in the form of a page. The drug is released into the environment by the mechanism of penetration and degradation of the polymer. What comes to mind when you first hear the name of the drug may be nothing more than pills, capsules or ampoules! While the world of medicine and the methods of its delivery to the body are not limited to these. Drugs usually enter the body in both digestive and non-digestive ways. The introduction of drugs from these methods has problems and limitations, and for this reason, researchers have been looking for ways that could solve the above problems to a large extent. Following these efforts, controlled drug delivery systems were introduced, which have many benefits. The most important of these advantages include the ability to maintain the drug concentration at a relatively constant level for a certain period of time, the ability to adjust the drug release rate depending on the drug delivery site, the ability to deliver the drug to a specific organ or tissue, and the ability to deliver multiple drugs with one formulation. These systems have revolutionized the treatment of many diseases and are evolving.

Introduction

Controlled Drug Release Systems (CDDS) are a new tool for drug delivery in the human body and have found many applications in the field of pharmaceutical science and technology [1]. These systems have many benefits such as creating positive effects of drug kinetics, reducing the frequency of drug use, regulating the level of fluctuations in the amount of drug in the blood, reducing side effects, reducing the accumulation of drug in the body, improving the bioavailability of some drugs and ultimately increasing treatment efficiency compared to conventional drug delivery systems. Disadvantages of these systems include reduced flexibility and dose adjustment, risk of rapid or sudden drug release, and defects in manufacturing technology. New drug delivery systems are divided into two main groups, which include:

1- Controlled release systems: In these systems, the rate of drug release from the drug

***Corresponding Author: Maryam Milani Fard** (maryammilani837@yahoo.com)*

form is controlled in various ways and is released from the drug form within a specified time frame and at a certain rate based on a predetermined mechanism [2].

2- Targeted drug delivery systems: In these systems, the drug is transferred to tissues that are pharmacodynamically desirable by various methods and exert their effect only in that area [3].

The difference between modern and traditional systems in the drug delivery system and traditional pills, the amount of drug in the blood follows a profile as shown in Figure 1 a), so that the amount of drug increases after each use and then decreases until the next use of the drug, an important point that in the methods. Traditional medicine sought to keep the amount of drug in the blood between the maximum state (indicating the toxic part) and the minimum state (below which the drug is ineffective). The purpose of designing controlled drug delivery systems is long-term drug use. As shown in Figure 1-1b), in CDDS, the amount of drug in the blood remains constant for a long period between the maximum and the optimal state [4-6].

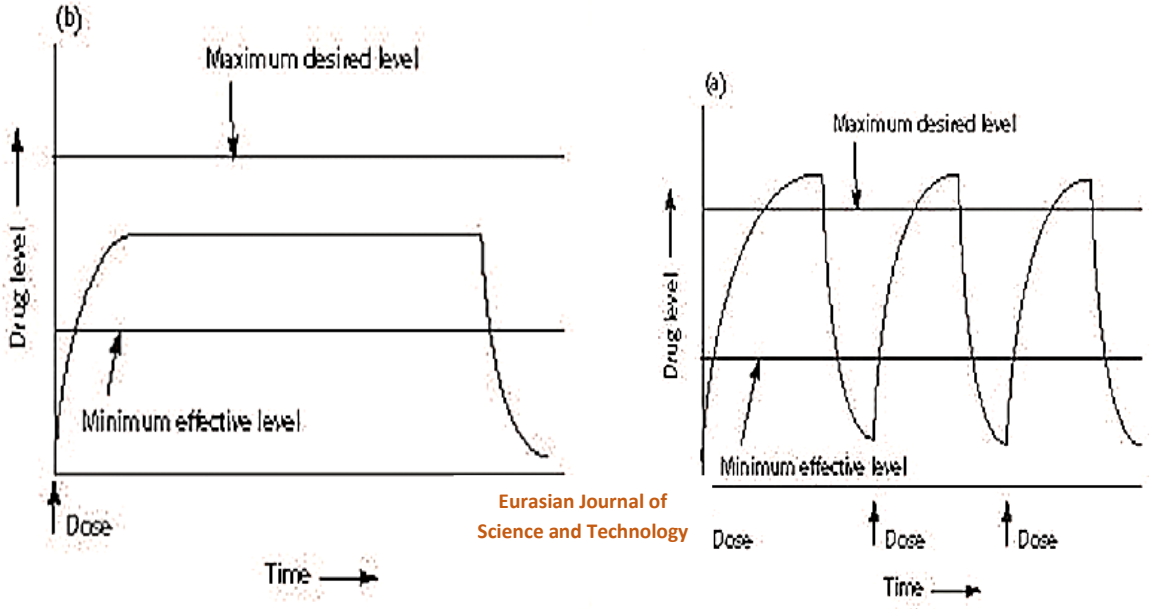

Figure 1 Drug levels in the blood a) Traditional drug delivery systems b) Modern drug delivery systems [1]

Release Mechanism

It describes the way in which drug molecules are transported or released and as a process or event that determines the rate of release. Another way of transfer through water-filled pores is through heat transfer, which is derived by a force such as osmotic pressure [7]. Osmotic pressure may be caused by the infiltration of water into an uninflated system, the transfer of the drug derived from this force is called osmotic pumping. Osmotic transmission depends only on length, but transmitted penetration depends on both length and area. The main methods of drug release include:

1- Penetration through water-filled pores;

2- Penetration through polymer;

3- Osmotic pressure;

4- Erosion the processes that control the release rate are called controlled rate release mechanisms. The actual release mechanisms are shown in Figure 2. Osmotic pressure is caused by the penetration of ambient fluid.

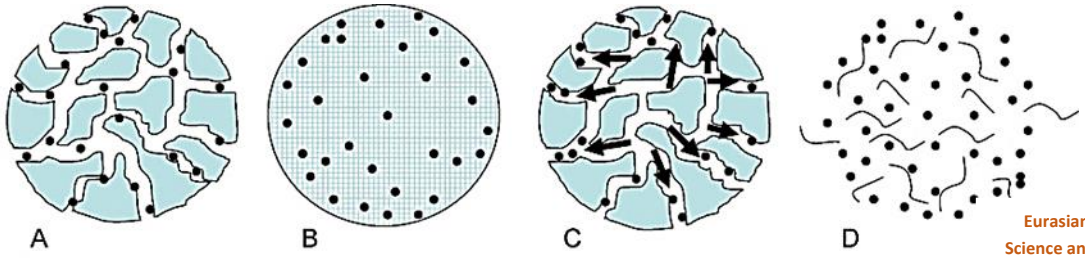

Figure 2 Real release mechanisms, (A) penetration through water-filled pores, (B) penetration through polymer, (C) osmotic pressure, and (D) erosion [4]

Promoting or Preventing Release Processes

Drug solubility, drug-drug reactions, drug-polymer reactions, hydrolysis, pore structure, and pore closure are all pH dependent, which is also dependent on the rate of hydrolysis; water uptake causes hydrolysis. Erosion as a controlled rate release mechanism leads to It forms a pore that increases the penetration rate. Disintegration is often the result of degradation and reduction in Tg. Hydrolysis causes erosion and pore formation, resulting in an increase in drug release. However, hydrolysis also results in lower Tg and the possibility of rearranging the polymer chains and closing the pore, thus possibly reducing the release of the drug [8-10].

Polymer in Pharmacy

Generally, natural and synthetic polymers are used as the infrastructure for controlled release and conventional drug delivery systems. These polymers may be swollen, non-swollen, porous, non-porous, semi-permeable, degradable, erodible and bio-adhesive. Polymers are widely used in pharmacy:

- As a tablet coating;
- As a binder such as gelatine;
- As a plasticizer such as polyethylene glycol;
- As a thickening agent in the manufacture of suspensions - such as tragacanth gum;
- In the manufacture of ocular solutions Colloids to stabilize the emulsion;
- To make an ointment base;

In controlling Drug Release

One of the easiest ways is to categorize them into two categories, natural and artificial. Since the biodegradability of polymers is one of the main factors in their use in drug delivery systems. In another classification, they are divided into two categories: Biodegradable and non-biodegradable. The hydrophilicity or hydrophobicity of polymers is another basis for their classification [11].

Biodegradable Polymers

In intrusion-controlled systems, the polymer only acts as a carrier and remains the same after the system expires. Sometimes it is necessary to degrade the polymer over time. The main application of this issue is in implant systems. In these systems, the device is surgically placed in place by a physician. Over time, the active agent (drug) is released in the body, which is the result of the breakdown of the polymer used in the system. After the end of the course, there will be no need for re-surgery to remove the system, because during the operation of the system, the polymer is completely decomposed. Polymers used in such systems are referred to as "biodegradable polymers", which form a broad branch of drug delivery control systems. Because we will no longer have the problem of accumulating particles and removing them from the body [1]. The active agent (drug) in these types of devices is physically fixed in the polymer and is released only by the degradation of the polymer. Polymer degradation Polymer degradation is the cutting of polymer chains into oligomers and monomers. Polymer degradation usually plays a very important role in drug delivery. Polyesters are degraded by the simple hydrolysis of ester bonds, which is an acidic process based on autocatalysis. Spatial order can also affect the degradation of the

polymer. Polymer properties such as molecular weight, crystallinity, and glass transition temperature control the rate of polymer degradation. Studies also show that the choice of dissolution conditions, physicochemical properties can affect the degradation process. Aliphatic (fatty) polyesters, such as poly (latic acid) and its glycolic acid copolymers, have gained considerable interest in controlled release formulations due to the biodegradability and biocompatibility of these synthetic polymers, which are bonded by hydrolytic binding to simple bonds [12-15].

The rate of degradation of the polymer strongly depends on the type of (main) functional groups of its composition. The most common types of reactive bonds of carboxylic acids are anhydrides, ester groups and ortho. However, the only type of bond that determines the rate of polymer degradation is not. The type of monomers, copolymerization, adjacent groups, and pH can indicate changes in hydrolysis rates [16-18].

Polymer Abrasion

Biodegradable polymers are widely used as carriers for drug release, as well as scaffolds for tissue engineering. The ability to model and predict erosion behavior can provide rational design and optimization of biomaterials for a variety of biomedical applications in the living environment. The polymer abrasion process is shown in (Figure 3) [19-21].

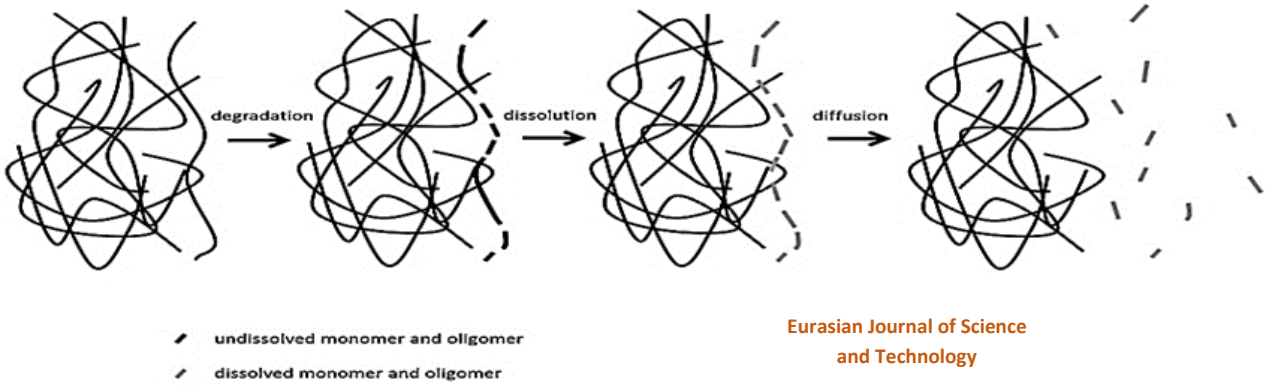

Figure 3 Polymer erosion process which is a combination of degradation, dissolution and diffusion [7]

Degradation is attributed to the occurrence of chain breakage, which in the case of biodegradable polymers is almost always due to hydrolysis (decomposition by water). Degraded oligomers and monomers are often more insoluble in water than the original polymer chains [22].

In semi-crystalline polymers, the bonds in the amorphous regions break easily relative to the crystalline region, causing shorter chains to move in the amorphous regions, which may lead to the development of crystallization along the degradation pathway. In some cases, polymer hydrolysis products contain acid monomers that accelerate the hydrolysis reaction and complicate the equations of velocity.

The chain length at important diffusion and dissolution stages, as well as the solubility and diffusion coefficient of polymers, can depend on the molecular weight. Solubility, diffusion coefficient and reaction rates can also depend on temperature and pH [23-25].

In addition, polymer abrasion can affect polymer swelling, pore makeup, and many other factors. Finally, erosion is the process of dissipating materials from the volume or surface of a polymer, and such materials may be monomers, oligomers, parts of the polymer structure, or even parts of the polymer mass.

Surface and Volumetric Erosion

Two different erosion mechanisms have been proposed for degradable polymers:

1- Heterogeneous or superficial erosion; and,

2- Volumetric or homogeneous erosion, the rules of these two mechanisms

In the case of polymeric matrices with surface abrasion, the degradation of the polymer is faster than the penetration of water into the polymer volume, so degradation occurs mainly from the ends of the outer layers of the polymer and erosion occurs only on the surface and not on the inner parts of the matrix (heterogeneous process). In volumetric erosion, water is loaded by the system much faster than polymer degradation.

Therefore, the integrated system hydrates faster and the polymer chains are separated and the erosion is not limited to the polymer surface (homogeneous process). According to the constitution, polymers made from highly reactive main groups are more prone to degradation for surface erosion (e.g., polyanhydrides), and as a result, polymers containing less reactive functional groups are more prone to volumetric erosion (e.g., polyesters) [26-28].

Classification of Biopolymers, Biodegradable, Synthetic Susceptible

The main classification of synthetic biodegradable polymers is shown in (Fig.4).

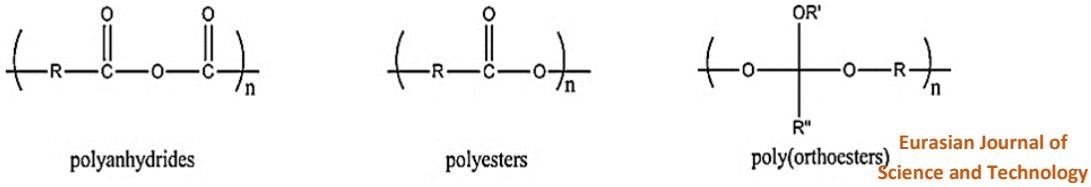

Figure 4 Chemical structure of synthetic biodegradable polymers [7]

Three types of polymers that have been extensively studied as drug carriers and most specific models cause degradation. They include: polyesters, polyarters and polyanhydrides as shown in Figure 4.

Polyesters

Polyesters are volumetric abrasion polymers with acid catalyzed degradation. The assumed truth is that their degradation products are acid monomers and they are prone to autocatalytic effects. Three very common polyesters include: Polyglycolic acid (PGA), polylactic acid (PLA) and poly-caprolactan (PCL), which polyglycolic acid has the lowest hydrophobicity and the highest and fastest hydrolysis, as well as a high degree of crystallinity. Polycaprolactone is degraded more slowly than the other two [9].

Like polyesters, Polyrthrosters are degraded by catalyzed acid hydrolysis, which depends on the relative rates of water penetration into the polymer. Polyorthoesters can withstand both surface and volumetric erosion. Under some conditions, polyorthostars can also exhibit autocatalytic degradation behavior [29-31].

Polyanidrides

Compared with polyesters, they have surface erosion which is mainly due to their hydrophobicity and prevents water from penetrating into the volume of the material until the surface is worn [11]. Polyanhydrides are catalyzed by hydrolysis. Some examples of monomers used for polyanhydrides are: Biomaterials containing aliphatic (fatty) groups such as sebacic acid (SA) and aromatic groups such as 1 and 3 bis (P-carboxy phenoxy) propene CPP, ...

Other Biodegradable Polymers

While there is a great variety of other biodegradable polymers such as poly

phosphatase and polyamides. For them, very low degradation models are directly applicable, perhaps due to the slow hydrolysis of these polymers [8]. Pure phase PCL degree of polymer degradation (Fig. 4) shows the graph of changes in the fraction of water concentration in terms of time. As can be seen, the system becomes hydrated after 40 days, and the water infiltration increases, respectively, along the element from the center to the outer layer, which according to results agrees with the volume degradation for this type of polymer.

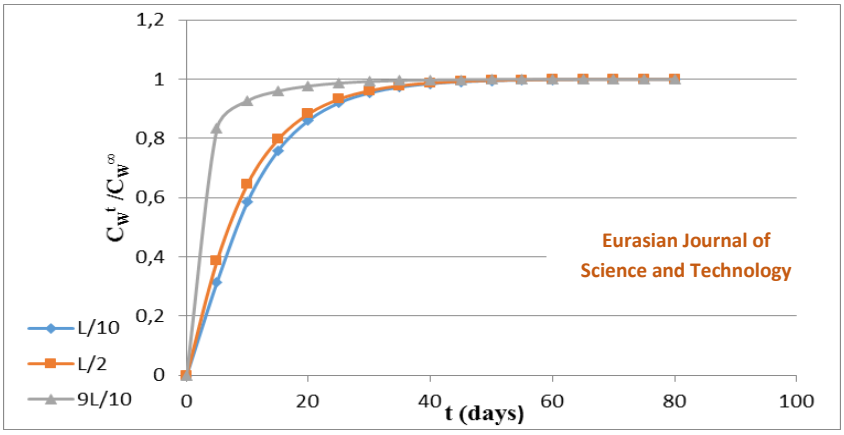

Figure 5 Graph of changes in water concentration fraction over time at different thicknesses for pure phase PCL

It can be stated that the transfer temperature of PCL glasses is equal to -60 degrees, so at the temperature of the culture medium (37 degrees), this chain is in the rubber state and the matrix has enough free volume to release the drug. Therefore, since the degradation of this polymer is very slow and it takes one year to completely degrade, as shown in Figure (6), the polymer is not degraded during this drug release period and according to the SEM image of this film after immersion.

The side in the culture medium is shown in Figure 7; it does not show any significant signs of degradation.

Therefore, in the study time frame for the above phase, the release process is not affected by destruction. The next section deals with the details of the release of the drug from this phase.

Drug release rate (Figure 8) shows the release rate of the drug. In the first 2 days or so, a sudden release period occurs for drug particles near or on the film surface, after which paclitaxel release is controlled by infiltration alone until complete release in about 40 days. The agreement between model and experimental data is clear.

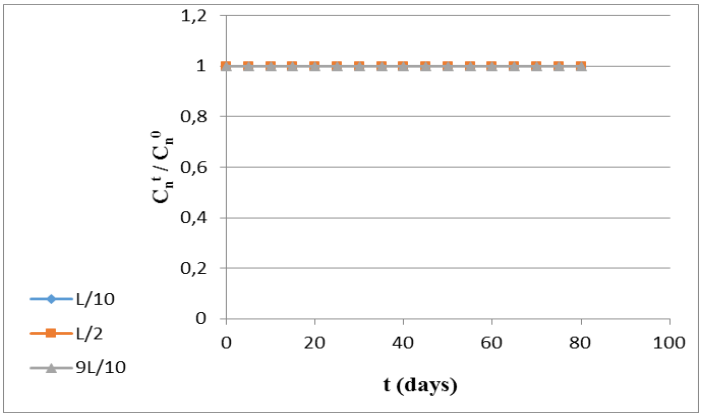

Figure 6 Graph of changes in PCL polymer concentration fraction over time at different thicknesses

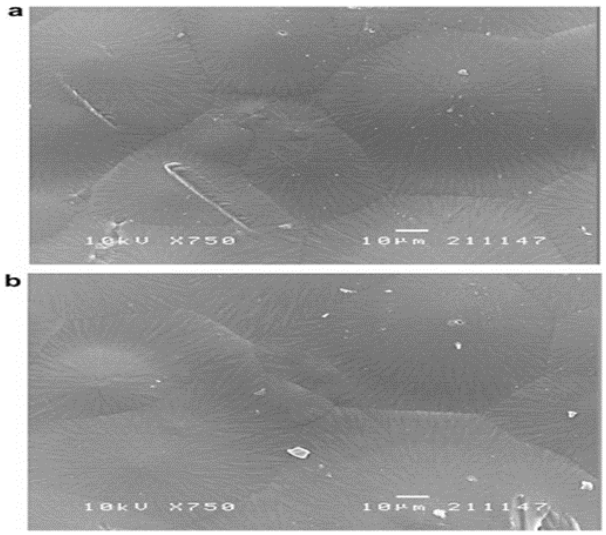

Figure 7 SEM images of poly caprolactan film (a) before immersion and (b) after 28 days of immersion in release medium [73]

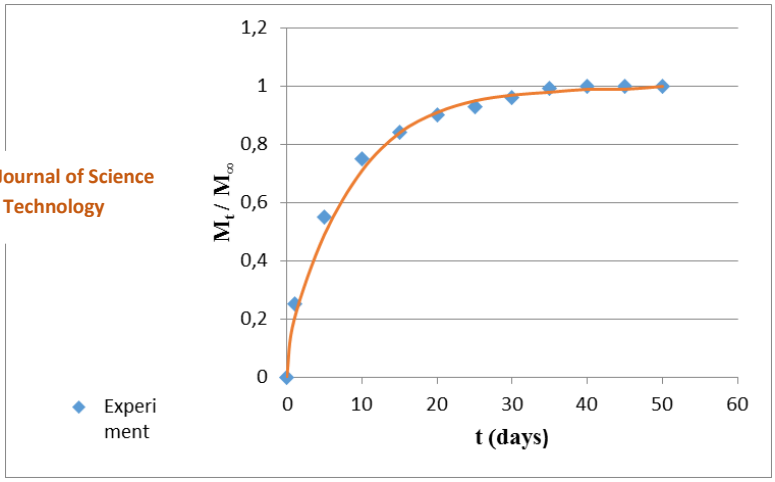

Figure 8 Drug release chart in terms of time and agreement between model and experimental data for pure phase PCL

Error calculation shows that the mathematical model cannot accurately predict numbers as experimental results, so there is always a difference between the experimental values and the model resulting from rounding numbers, shortening the series to solve the numerical differential equation, etc., which is misinterpreted.

According to the above data, the average relative error percentage for the above phase was calculated to be 4.1%.

Pure phase PLGA

Degree of polymer degradation (Figure 9) shows the graph of changes in the amount of molar concentration of water in terms of time. As can be seen, the system becomes hydrated after 30 days. The results agree with the view of volumetric degradation for this type of polymer and also due to the polyglycolic hydrophilicity, water penetrates into the system faster.

As stated, the transfer temperature of PLGA glasses is equal to 40-45 degrees, so at the temperature of the culture medium (37 degrees), this polymer is in the glass state and does not have enough free volume to release the drug and many knots. There are many in polymer chains. Therefore, the polymer must

be destroyed so that the chains are broken and enough free volume is created and part of the drug is released by the destruction of the polymer.

Table 1 Calculation of relative error of experimental values and model for pure PCL phase

Time (Day)	Experimental values	Model prediction value	Relative error	Absolute value of relative error	Relative error percentage
1	0/25	0/2	0/2	0/2	20
5	0/55	0/49	0/1090	0/1090	10/9
10	0/75	0/71	0/0533	0/0533	5/33
15	0/84	0/84	0	0	0
20	0/9	0/91	-0/0111	0/0111	1/11
25	0/93	0/95	-0/0215	0/0215	2/15
30	0/96	0/97	-0/01042	0.01042	1/042
35	0/99	0/99	0	0	0
40	1	0/99	0/01	0/01	1
45	1	1	0	0	0
50	1	1	0	0	0

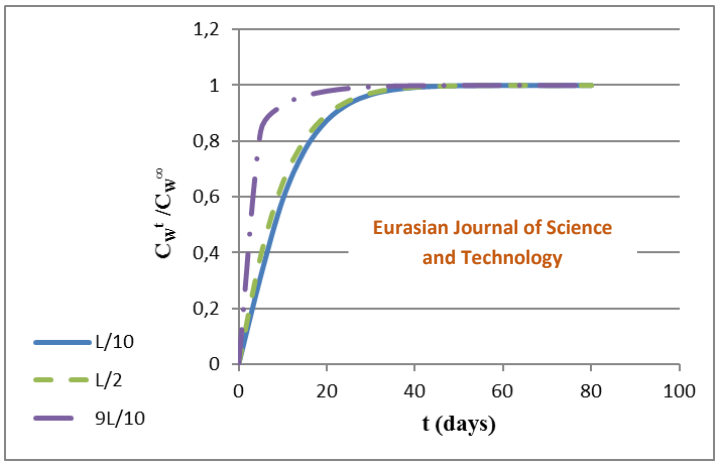

Figure 9 Graph of changes in water concentration fraction over time at different thicknesses for PLGA phase

Degradation therefore plays a vital role in creating more free volume and dissolving the drug and developing release. As can be seen in Figure (10), the polymer concentration is decreasing, indicating the degradation of the polymer. Also, short chains (oligomers) in the matrix are forced to open, and this process creates an open network in the system and the creation and growth of pores.

In addition, Figure (11) shows the SEM images of this film, which show that the polymer is degraded. The further the destruction continues, the more and more water penetrates into the matrix.

Drug release rate (Figure 12) shows the release rate of the drug from this phase and there is some agreement between the model and the experimental data. In the first 20 days we see the sudden release of the drug, then the release due to the destruction of the polymer and finally the penetration of the drug through the pores filled with water, and finally we see the completion of the release for up to 80 days.

Error calculation (Table 2) shows the relative error between the experimental values and the model for the pure PLGA phase.

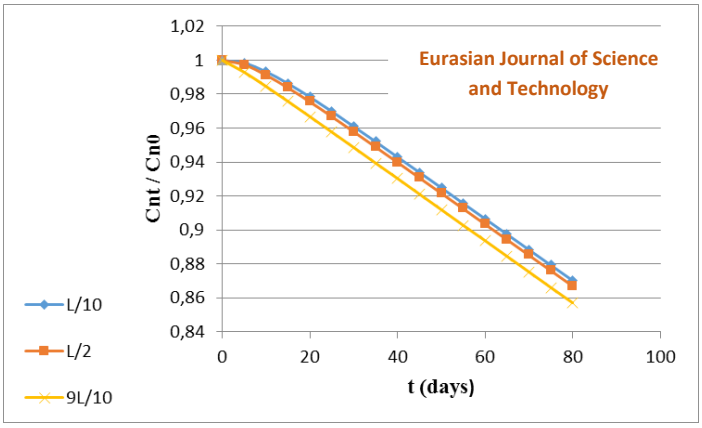

Figure 10 Graph of changes in the relative amount of PLGA polymer concentration over time at different thicknesses

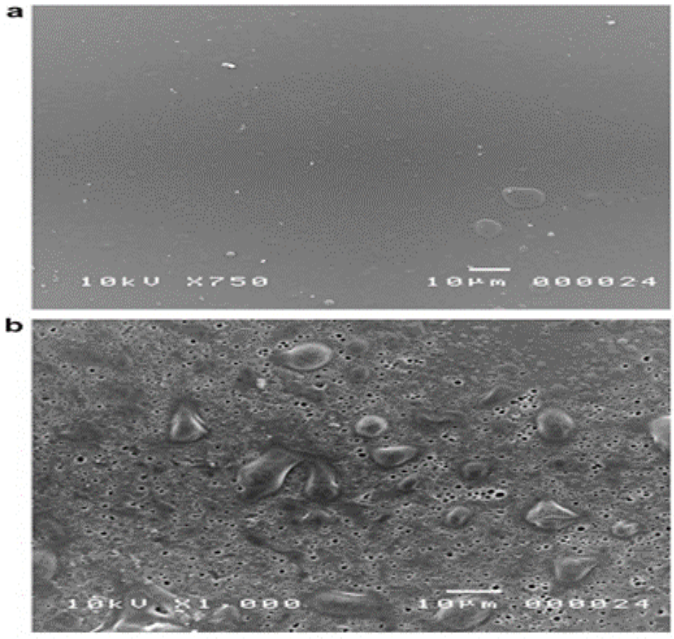

Figure 11 SEM images of co-glycolic acid polylactide films (a) before immersion and (b) after 28 days of immersion in release medium [73]

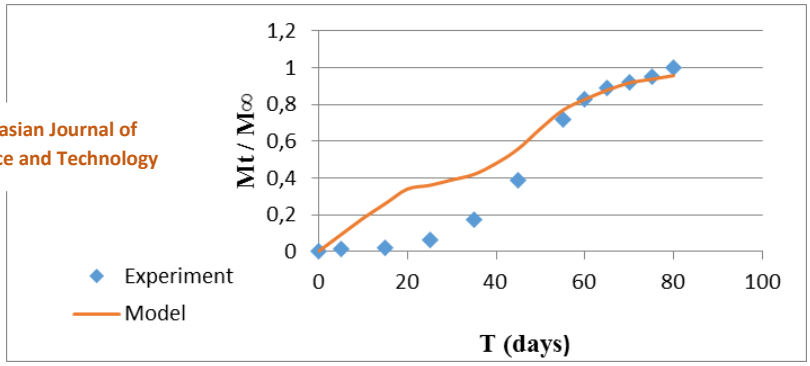

Figure 12 Drug release chart in terms of time and agreement between model and experimental data for pure PLGA phase

Table 2 Calculation of relative error of experimental values and model for pure PLGA phase

Time (Day)	Experimental Values	Model prediction Value	Relative Error	Absolute value of relative error	Relative error percentage
45	0/39	0/48	-0/231	0/231	23/1
55	0/72	0/77	-0/0694	0/0694	6/9
60	0/83	0/83	0	0	0
65	0/89	0/88	0/0112	0/0112	1/12
70	0/92	0/92	0	0	0
75	0/95	0/94	0/0105	0/0105	1/05
80	1	0/96	0/04	0/04	4

According to the above data, the average relative error percentage for the above phase after 35 days was calculated by 5.16%. The reason for the large difference between the experimental values and the model in the first 35 days could be a change in the culture medium conditions, an error in the measuring instrument [32-38].

Drug Release Rate

As can be seen from the release data for the pure phases, the emission from the pure PCL phase is unacceptably shorter than the continuous release phase, while the pure PLGA phase is longer. Therefore, a combination of these two phases provides an average and acceptable emission profile that reflects the effect of the two components. PCL leads to drug release in the first half (up to 20 days) while PLGA assists in drug release and distribution in the second half. Since these two types of polymers do not have any kind of interaction and fusion with each other and two separate phases are formed according to Figure (13) and the degradation of PLGA phase is faster. Therefore, the two-phase combination can be used as a combination of the obtained models.

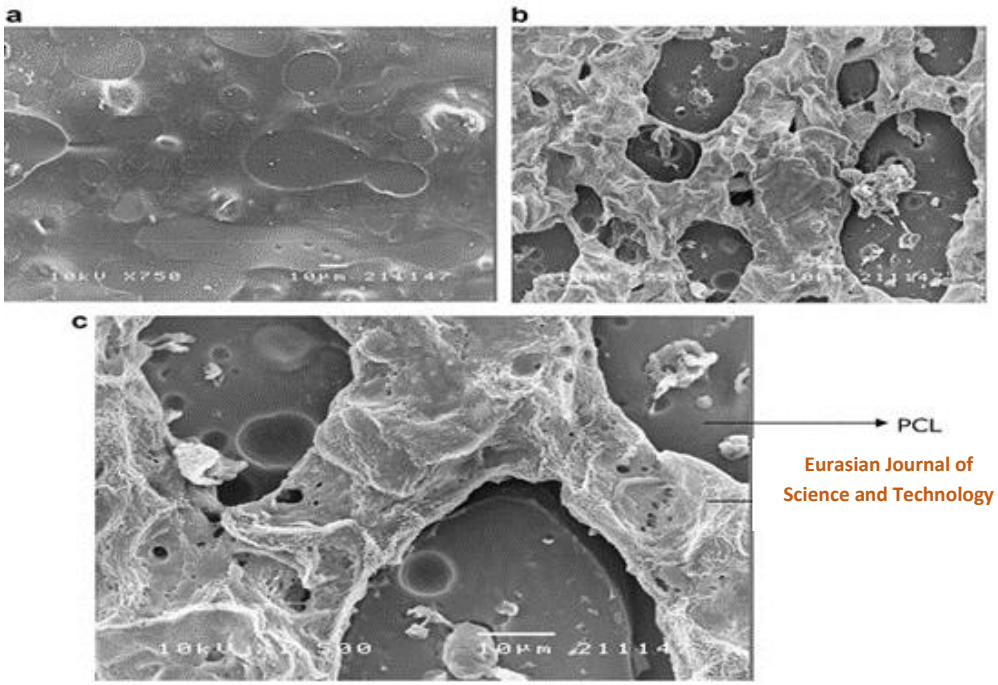

Figure 13 SEM images of the above film mixture (a) before immersion and (c, b) after 28 days of immersion in release culture medium [3]

Based on the release rate of the drug from the two-phase combination, it can be concluded that the release of the drug in a period of 20-45 days is due to the degradation of PLGA polymer. Therefore, in the general case, the release of the drug from the two-phase combination goes

through a three-step pattern and there is a good agreement between the model and the experimental data.

Error calculation (Table 3) shows the relative error between the experimental values and the model for the 50/50 two-phase combination.

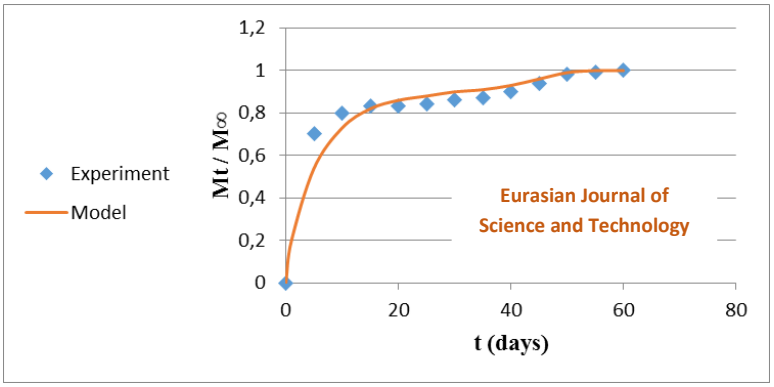

Figure 14 Drug release chart in terms of time and agreement between model and experimental data for two-phase composition

Table 3 Calculation of relative error of experimental values and model for 50/50 two-phase combination

Time (Day)	Experimental Values	Model prediction Value	Relative Error	Absolute value of relative error	Relative error percentage
5	0/7	0/54	0/2286	0/2286	22/86
10	0/8	0/73	0/0875	0/0875	8/75
15	0/83	0/82	0/0121	0/0121	1/21
20	0/83	0/86	-0/0361	0/0361	3/61
25	0/84	0/88	-0/0476	0/0476	76/4
30	0/86	0/90	-0/0465	0/0465	65/4
35	0/87	0/91	-0/0459	0/0459	59/4
40	0/9	0/93	-0/0333	0/0333	3/33
45	0/94	0/96	-0/0213	0/0213	2/13
50	0/98	0/99	-0/0102	0/0102	1/02
55	0/99	1	-0/0101	0/0101	1/01
60	1	1	0	0	0

According to the above data, the average relative error percentage for the above phase was calculated by 4.8%.

Conclusion

The results of this study can be presented as follows:

- For the pure phase, PCL is not destructive and drug release is based on two phases: sudden release and penetration. The results of comparing the experimental data and the model show an average error rate of 4.1%. In the pure PLGA phase, degradation is observed both in the polymer concentration diagram and in the release profile, so drug release is based on the three stages of abrupt release, release through polymer degradation and penetration. The results of comparing the experimental data and the model show an average error rate of 5.16%.
- For the two-phase combination, the polymer degradation for the PLGA phase was well visible in the release profile, and again we see three-step release. The results

of comparing the experimental data and the model show an average error rate of 4.8%. Factors such as drug type (hydrophilic / hydrophobic), polymer degradation rate, water permeability and drug-polymer interaction greatly affect the release profile. Finally, it can be said that the modeling of drug release from biodegradable polymers is followed by a three-step sequence:

1- Infiltration of solvent (water) into the matrix;

2- Degradation of the polymer to create more free volume for drug dissolution; and,

3- The drug is transferred to the culture medium, which is usually done by the process of penetration through pores filled with water.

ORCID

Maryam Milani Fard
https://orcid.org/0000-0002-0888-8847

Amir Mohammad Milani Fard
https://orcid.org/0000-0003-2635-2728

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