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| RESEARCH ARTICLE

Design and Optimization of Elanzapine Drug Release with Polyoxazoline Based Hydrogel

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| ABSTRACT
Due to the fact that Elanzapine is prescribed orally and by injection for psychotic and schizophrenic disorders, and depending on the type of disease, these people are prevented from swallowing the drug; therefore, checking the injectable form of the drug with controlled release, which increases the release of the drug to one week with a single injection, is important. On the other hand, one of the most important biodegradable polymers that have the adhesive property of Elanzapine is Polyoxazoline, so the aim of this study is to design a slow release system, considering the short half-life of this drug and the need for a large number of doses and the patient's lack of cooperation for treatment. The drug is based on Polyoxazoline, which can reduce the consumption and, consequently, the toxicity and accumulation of the drug in the body. Mathematical heart direction, the forecast of different conditions will be presented, and also obtaining the optimal conditions and the final formulation is one of the main goals of this study. In this research, the release of olanzapine on the matrix loaded with olanzapine, the morphological characteristics of the matrix, the thermal characteristics of the matrix and the rheological characteristics of the matrix have been investigated. The release of olanzapine in the examined gels lasted for more than 168 hours, which was a sign of the slow release system, which is the main goal of this project. Several models were used to investigate the release kinetics of olanzapine, and among them, the Higuchi equation showed the best degree of regression with experimental data. By increasing the percentage of Elanzapine, the process of changes in viscosity goes out of the linear state; on the other hand, the difference between the optimum matrix viscosity of 3 and 4% of Elanzapine is small.

| KEYWORDS
Matrix, Optimization, Slow release system, Elanzapine, Polyoxazoline

| ARTICLE INFORMATION
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1. Introduction

Elanzapine is used to treat schizophrenia and similar mental disorders and belongs to the second generation of antipsychotic agents. Elanzapine is insoluble in water and has only 60% food bioavailability, and its half-life in humans is 30 hours, and the side effects of Elanzapine are less than other common antipsychotics (J. S. Soares, 2010). When the drug is consumed in the old ways that are based on food or injection, it may cause problems such as instability or adverse side effects and narrow therapeutic windows, high solubility, sensitization, etc. It is possible to improve the efficiency of the old methods. It faces limitations. Destruction of sensitive drugs in the stomach and intestines, rapid metabolism and removal of the drug immediately after injection, as well as the need for long-term consumption in chronic diseases and the need to inject the drug at a specific point (therapeutic chemistry), low solubility and no Stability of new drugs Because peptides, vaccines, growth hormones and antibodies, the need to design controlled drug release systems and the increasing importance of these issues become clearer. By using drug release control systems, it is possible to keep the drug concentration in the blood at its maximum therapeutic limit and to reduce the amount of drug consumption to the lowest amount (M. Korber, 2010). It also protects the drugs that are quickly destroyed in the body's cycle to prevent excessive consumption (J. Siepmann, 2011). Today, slow release drug systems are among the most important issues in

the field of pharmaceuticals and biotechnology because in these systems, the amount of drug consumption can be significantly reduced, and as a result, their side effects and toxicity. Caused by long-term consumption due to drug accumulation in the body (Y. Fu, 2010). And it also prevents the unnecessary disposal of medicines. Almost all bio adhesive materials used for drug delivery systems are polymers or pseudo polymers with high molecular weight, but Polyoxazoline has a very low molecular weight with low solubility in water and is unsaturated and a waxy substance (T. K. Giri, 2012). The shape of the room temperature is that in the research of Has It is used for slow drug release (A. N. F. Versypt, 2013). Therefore, the aim of this study is to design a slow drug release system based on Polyoxazoline, considering the short half-life of this drug and the need for a large number of users and the patient's non-cooperation for treatment, which can reduce the number of users and, as a result, the toxicity and accumulation of the drug in the body. gave a hash. In order to achieve this goal, the effect of each of the independent parameters on the drug loading percentage and its release rate has been investigated, and finally, a mathematical model will be presented to predict different conditions and also achieve The optimal system, and the final formulation are among the most important activities of this study. It will be.

2. Materials and Methods

In this research the main goal of the research is to design and optimize the release of the Elanzapine drug. But in this direction, efforts are being made to use polymers with different atomic weights and Polyoxazoline agents.

1) Investigating the thermal characteristics of the matrix: thermos gravimetric analysis is one of the thermal techniques that records the weight changes of the material as a function of temperature or time in a controlled atmosphere. In the thermal weighing test, if the temperature of two thermal events are close to each other, it will be difficult to separate them in the weight change curve in terms of temperature.
2) Investigating the rheological characteristics of the matrix: the rheological characteristics of the prepared matrices are a function of their formulation, and all samples are pseudo-plastic and shear reducing. The yield stress is the lowest stress under which gel samples maintain their fluidity.

Glycerol monolete was obtained from Danesco company in Denmark, Polyoxazoline 5000 was obtained from Sigma company in Germany, and anzapine was obtained from Sabhan company in Iran. 0.2-micrometer syringe filter and 1 kilodalton dialysis bag were purchased from Sigma, Germany, and the rest of the chemicals were prepared with high purity.

2.1 Experiment design:

The response surface methodology is a set of mathematical methods that determine the relationship between one or more response variables with several independent variables (case of study) (M. Parent, 2013).

This method was introduced by Box and Wilson in 1951, and it is still used as one of the experimental design tools. Although many consider this method as a pseudo-model (A. T. Balter, 2013). studies such as Kerami et al.'s study have shown the response surface method as an acceptable method compared to traditional modeling methods (B. S. Snorradottir, 2013). In engineering sciences, many phenomena are modeled based on their own theories. This is while many phenomena do not have the ability to have a suitable mathematical model due to the large number of controlling factors, unknown mechanisms or computational complexity. In such cases, the use of experimental modeling methods is effective; The response level method is considered one of the experimental modeling methods (L. L. Lao, 2008). The response level method is one of the research approaches in the design of experiments and related sciences. In the response surface method, an attempt is made to find a way to estimate interactions, quadratic effects, and even the local shape of the studied response surface by using a suitable experimental design. In the meantime, certain goals are seriously pursued, the most important of which is to improve the process by finding optimal inputs, fixing the problems and weak points of the process, and stabilizing it. Here, stabilization is an important concept in quality statistics that implies minimizing the effects of secondary or uncontrolled variables (confounding). Carrying out the response surface method without having information about the process and the variables affecting it can be misleading. It is more common that before performing the steps of the response surface method, the process under study is well investigated, and a screening test plan is used to identify the effect of inputs on the process under study. As it was stated, the design of the experiment is a very effective method for conducting experiments so that the obtained data can be analyzed and statistically analyzed, and the results are presented at a significant confidence level. The response surface method is an experimental design that is obtained from the combination of mathematical and statistical techniques and obtains the best mathematical model according to statistical parameters such as P-Value and F-Test and the way dependent variables change with independent variables. It evaluates the goal. The box design method is a suitable option for experimental design.

Bax-Bakin statistical design using Design Expert software with three independent variables: Elanzapine amount in the range of 4-2%, water/GMO weight ratio in the range of 4-2% and POZ/GMO weight ratio in the range of 2-6% became a slave. The dependent variable of the research was loading efficiency and release percentage in the 12th and 168th hours. According to the box design - not with 3 factors, 17 experiments were needed to examine the effects of 3 independent factors on one response.

2.2 Preparation of matrix loaded with Elanzapine

One gram of glycerol monolete with Polyoxazoline in different weight ratios (0.2, 0.4, and 0.6 w/w) was mixed by vortex, and then Elanzapine was added to them with different weight percentages (2, 3, and 4%) and the pH of the solutions It was measured. The pH of all the samples was determined below 4, and considering that Elanzapine is a fat-loving drug, therefore, at low PHs, the rate of loading and mixing of the matrix increased. Then water was added in three proportions (0.2, 0.3 and 0.4 w/w) to the prepared solution and, mixed by vortex for 10 minutes and kept for 48 hours at room temperature to reach equilibrium.

2.3 The Amount of Drug loading in the matrix

A) standard Curve of Drug absorption

A solution of 2 ml of water and 1 ml of 2% acetic acid was prepared and used as a control. Then, the witness was placed in the analysis cell along with the drug Elanzapine, and the absorption spectrum of the drug was obtained in the range of 200-600 nanometers. Gharbal-Gray determined by the device that the drug Elanzapine has the maximum absorption rate at the wavelength of 265 nanometers. In order to make sure that there is no interference between the absorption between the polymer and the drug, solutions of glycerol monolete and Polyoxazoline with a specific concentration were prepared, and their absorbance was read at a wavelength of 265 nanometers, and it was observed that in this wavelength C. The mentioned polymers had no absorption. For drawing the standard curve, 10 mg of the drug was weighed using a balance and made up to volume in a 100 ml volumetric flask with water and acetic acid solvents. The concentration of the obtained stock solution was 100 micrograms per milliliter. The stock solution, solutions with dilutions of 25, 30, 20, 10, 15 micrograms per milliliter of the drug, were prepared by taking the appropriate volume from the original solution and diluting it with solvents, and the absorption rate of each of them was 265 nanometers. Notre was read, and This order of the standard absorption curve and its equation were determined.

B) Determining the amount of Drug loaded in the matrix

The drug content in the gel system was determined by diluting 10 mg of the gel in 10 ml of ethanol, and then the solution was filtered using a 0.2-micrometer syringe filter, and the absorbance of the solution was measured by a spectrophotometer at 265 nm. It will be measured **using the standard absorption** curve and the obtained equations; the concentration of the solution and the drug present in it was calculated. Considering that the amount of the primary drug in the solution is known from the difference between these two values, the amount of the drug contained in the matrix was obtained. Then, using the obtained information and using the following formula, the percentage of loaded drugs was calculated.

$$\mathrm{EE\%} = \frac{\mathrm{A}}{\mathrm{B}} * 100$$

The concentration of Elanzapine in the gel and B: the initial concentration of Elanzapine in the system.

C) Measuring the rate of Controlled Drug release in vitro

The extracorporeal release of Elanzapine from the gel system was evaluated by the dialysis bag method reported by Yang. The amount of gel placed in the dialysis bag was measured according to the solubility of the drug in the buffer environment and the creation of completely sink conditions. For this purpose, 10 mg of the obtained polymer-drug matrix in different concentrations, together with 2 ml of phosphate buffer, was poured into a 1 kg Dalton dialysis bag that was soaked in deionized water the night before. The solution was immersed in 100 ml of phosphate buffer (the amount of gel) placed in the dialysis bag was measured according to the solubility of the drug in the buffer environment and the creation of sink conditions. The human body containing the phosphate buffer and the dialysis bag was placed in a vibrating incubator at a temperature of 37 ºC. One milliliter of the medium inside the dialysis bag was replaced at the specified times (2, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, and 168 hours) with an equal volume of fresh buffer. The samples were filtered with a 0.2 micrometer syringe filter and then analyzed with a spectrophotometer at 265 nm, and the percentage of drug release was measured. By using the standard absorbance value, the concentration of the drug and, as a result, the amount of drug released in the phosphate buffer solution was obtained. The measurement of the released drug continued until there was no change in the concentration of the solution. For accuracy, all experiments were repeated three times under similar conditions. In order to calculate the percentage of drug release in the determined times, after each sampling, the absorption rate of the drug was obtained using a spectrophotometer, and then the amount of drug released in the buffer medium at each stage was determined by the values obtained from the linear equation. The calibration curve of drug absorption was calculated.

3. Research results

3.1 Experiment design

Data includes figures and specifications that should be made meaningful using statistical or non-statistical methods in order to achieve the purpose of the research. Analysis as a scientific stage is one of the basic foundations of any research by which all research activities are guided until reaching the control result. In other words, analysis of the results is a method by which the entire process and research from The selection of the problem is controlled until reaching a result. In this research, for data analysis,

RSM test design techniques have been used for drug release in 12 and 168 hours for three independent parameters of Elanzapine, Water/GMO and POz/GMO. Table 1 shows the results obtained from the design of the experiment.

Table 1- The results of the experimental design

RUN	A: POZ/GMO	POZ%	%RELEASE12	%RELEASE168	EE%
1	0.4	0.3	57.54	91.9	87
2	0.6	0.2	15.75	61.8	89
3	0.4	0.4	27.34	73.8	93
4	0.2	0.4	19	85.6	90
5	0.2	0.3	15.54	61.6	86
6	0.4	0.2	36.36	81.9	92
7	0.6	0.4	43.22	88.2	86
8	0.6	0.3	55.52	89.4	85
9	0.4	0.3	41	86.3	88
10	0.4	0.4	44.74	89.2	83
11	0.6	0.3	30.07	76.4	88
12	0.4	0.3	16.95	63.5	89
13	0.2	0.3	42	87.2	86.5
14	0.2	0.2	51	86.3	90
15	0.4	0.2	33.32	78.8	94
16	0.4	0.3	9.08	54.7	96
17	0.4	0.3	44.3	89.3	88

The phase diagram of the Polyoxazoline system is shown in Figure 1. Hexagonal phase is formed in high amount of glycerol monolete and low amount of water.

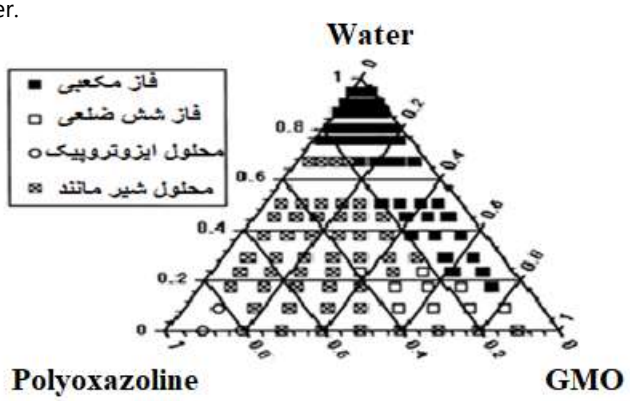


Figure 1- 3D phase diagram of glycerol monolete-water-Polyoxazoline system

A similar graph has been calculated for Polyoxazoline (Figure 2). From this graph, it can be concluded that the cubic phase can be seen in high amounts of GMO; as the amount of water increases, the range of the cubic phase increases. The hexagonal phase is more formed in high amounts of GMO and low water content. Samples with high solvent circulation are desirable for slow release injectable systems because after entering the body, it turns into a cubic phase.

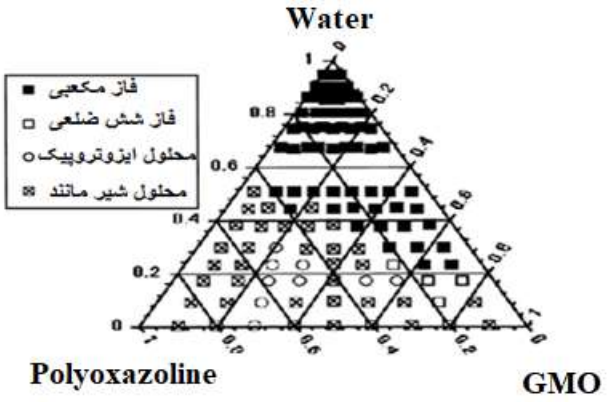
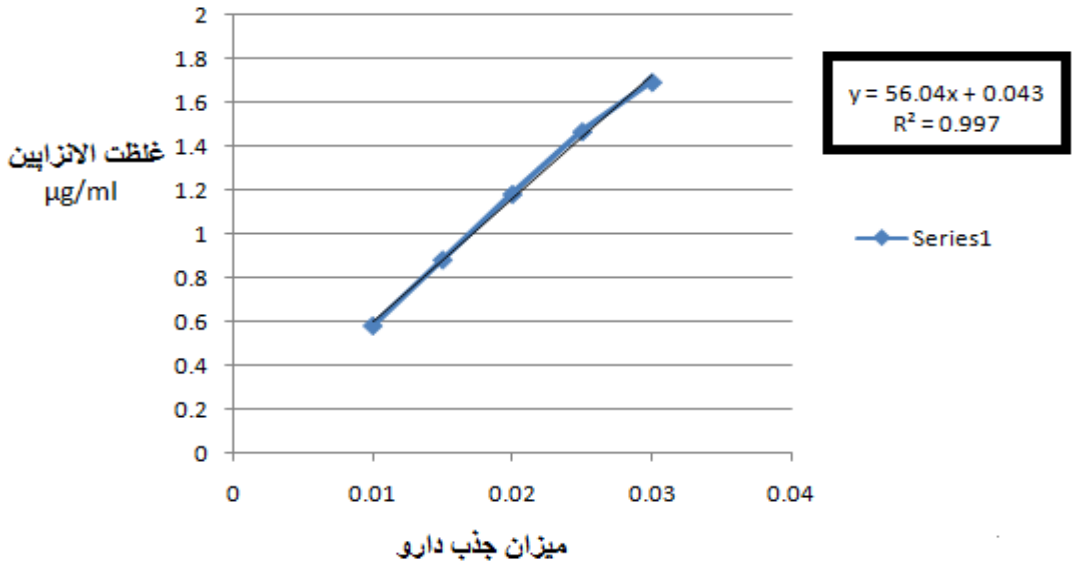


Figure 2- 3D phase diagram of glycerol monolete-water-Polyoxazoline system

3.2 Amount of Drug loading in the matrix

A solution of 2 ml of water and 1 ml of 2% acetic acid was prepared and used as a control. Then, the control was placed in the analysis cell along with the drug Elanzapine, and the absorption spectrum of the drug was obtained in the range of 200-600 nm.

Figure 3- Drug Absorption Curve



Screening by the device revealed that the Elanzapine drug has the maximum absorption rate at 265 nm wavelength. To ensure that there is no absorption interference between the polymer and the medicinal substance, solutions of glycerol monolete and Polyoxazoline with specific concentrations were prepared, and their absorbance was read at a wavelength of 265 nm, and it was observed that the said polymers do not absorb at this wavelength. To draw a standard curve, 10 mg of the drug was weighed using a balance and made up to volume in a 100 ml volumetric flask with water and acetic acid solvents. The concentration of the obtained stock solution is 100 µg/ml. From the stock solution, solutions with dilutions of 10, 15, 20, 25, 30 µg/ml of the drug were prepared by removing the appropriate volume from the original solution and diluting it with solvents, and the absorption rate of each of them during The wave of 265 nm was read, and in this way, the absorption standard curve and its equation were determined.

3.3 Determining the amount of Drug loaded in the matrix

The three-dimensional graph of drug loading percentage in different weight ratios (w/w) Water/GMO, POz/GMO (w/w) in a fixed amount of olanzapine is shown in Figure 4. The loading percentage range was observed from 96% ± 57.28% to 83% ± 1.22%, and the loading percentage was at its maximum level with the increase of the Water/GMO ratio and decreased with its decrease because with the increase in the amount of water, the percentage of phase The cube increases and the amount of drug loading increases in this phase. On the other hand, in the beginning, the percentage of drug loading increases with the increase of POZ/GMO weight ratio, and after the (w/w) ratio of POz/GMO: 0.5, it tends to decrease. The hydrophilic nature of Polyoxazoline

affects the composition of the matrix and the amount of water absorption, and with increasing the amount of Polyoxazoline added to the gel, a layered phase is formed. The coefficients of important variables for drug loading percentage are given in Equation 2.

$$\%EE = +64.93750+60.06250\ X_1-24.50000\ X_2+13.86250\ X_3 -37.50000\ X_1\ X_2 +0.62500X1\ X_3 -30.00000\ X_2\ X_3 -68.43750\ X_1^2 +188.75000\ X2^2 -0.98750\ X3^2$$

%EE, X_1, X_2 and X_3 are defined codes for drug loading percentage and Water/GMO, POz/GMO weight ratio and Elanzapine percentage, respectively. Analysis and variance regression analysis of the data showed that the linear coefficients of the independent factor, among which the POz/GMO factor, have the greatest effect on the drug loading percentage.

X1=A: POz/GMO

X2=B: Water/GMO

Actual Factor

OZ%=3.00

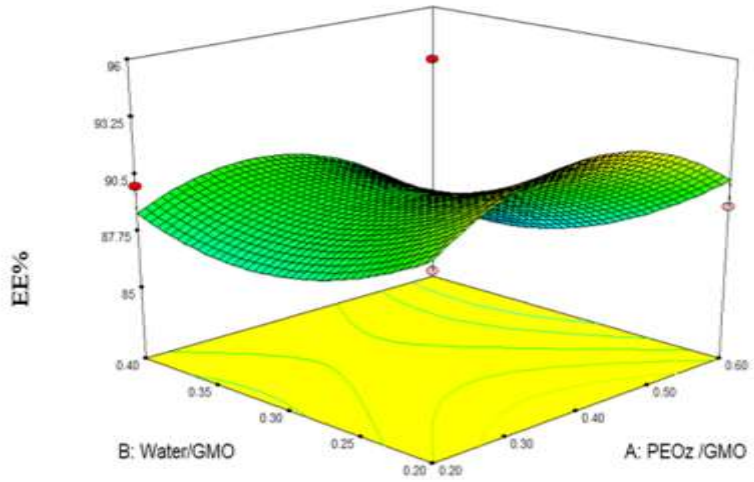


Figure 4- Three-dimensional diagram of changes in the loading percentage of drug B with the weight ratios of Water/GMO and POz/GMO in a fixed amount of Elanzapine.

3.4 Elanzapine release in the extracorporel environnement

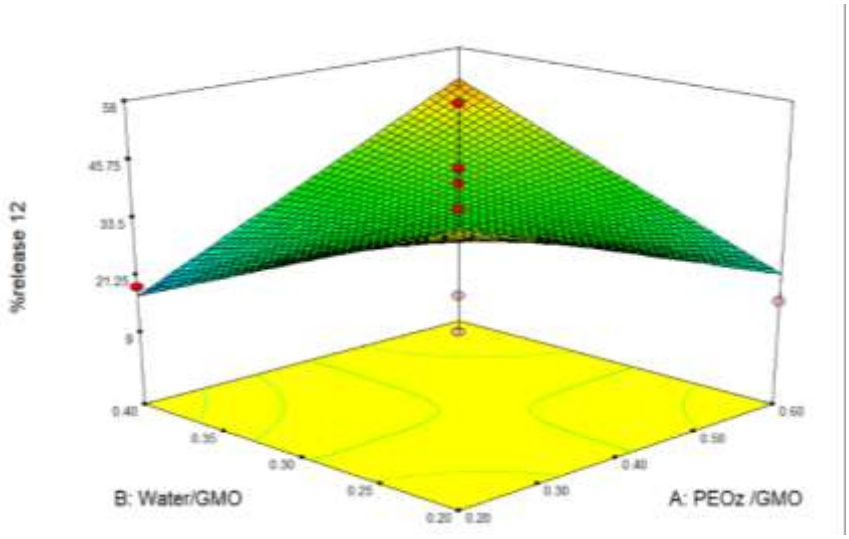
In the test plan, release at the 12th hour was considered as release 1 and release at the 168th hour as release 2. In the next step, in order to optimize the conditions, the appropriate range of release 1 was set in the range of 10-15% because the goal of this project was to create a slow release system for anzapine, and release 2 was considered at its maximum value. How to change drug release was determined by response surface diagrams. Figure 5 (a and b) shows the effect of POz/GMO and Water/GMO weight ratio on release percentages 1 and 2. As shown in Table 1, the release range was 9.08% to 57.54%, and the release range 2 was from 54.7% to 91.09%. At a fixed amount of POz/GMO, the release of the drug decreased linearly with the increase of the weight ratio of Water/GMO, and the amount of release from the gel was determined when the percentage of the drug was 3.5-3.5%, which was at its maximum value. At first, with an increasing amount of Elanzapine, the release percentage increased and then decreased. The observed reduction in the release rate at the critical dose of the drug (3.5% w/w: Elanzapine) may be due to the lipophilic nature of Elanzapine, which enters the fat layers and reduces the release rate of the drug from the matrix.

X2=B: Water/GMO

Actual Factor

X1=A: POz/GMO

OZ%=3.00



X1=A: POz/GMO

X2=B: Water/GMO

Actual Factor

OZ%=3.00

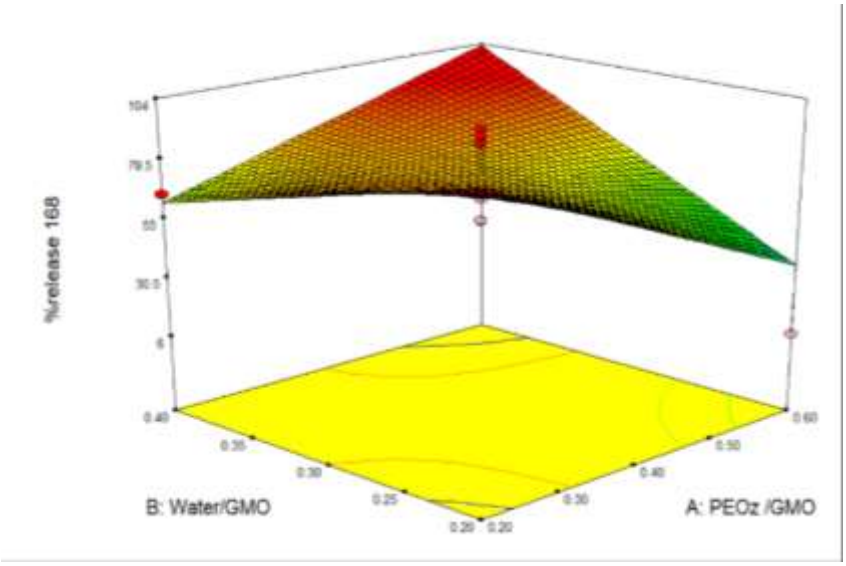


Figure 5- Three-dimensional diagram a) release percentage 1 b) release percentage 2 with the weight ratios of Water/GMO and POz/GMO in a fixed amount of Elanzapine

The coefficients of independent variables for the percentage of drug release at the 12th hour (release 1) and the percentage of drug release at the 168th hour (release 2) are shown in equations 4 and 3.

(3)- %release 12 =+82.38824-17.71250 X_1+453.31250 X_2 +12.54625X3+743.37500 X_1X_2 -64.88750 X1X3+51.10000 * X_2X_3

(4)- %release 168 =+116.69338-23.31250 X_1+364.25000 X_2+8.41250 X_3+588.75000 X_1X_2-48.00000 X_1 X_3+46.25000 X_2 X_3

X_1, X_2 and X3 are defined codes for the weight ratio of Water/GMO, POZ/GMO, Elanzapine percentage and 12% release and 168% release of the drug at the 12th hour (Release 1) and the percentage of drug release at the 168th hour (Release 2).) are. Analysis and variance regression analysis of the data showed that the linear coefficients of the independent factor, among which the Water/GMO factor, has the greatest effect on the drug loading percentage, and the negative coefficients indicate the opposite effect of the independent factors.

3.5 Check Drug release

The external release of the drug from matrices with water content and fixed drug percentage was investigated to evaluate the effect of Polyoxazoline on the release percentage, and it was shown that with the increase of Polyoxazoline concentration, the drug release increased from 61.8% to 76.4%. It is found. Polyoxazoline, due to its water-friendly property, increases the rate of water absorption and, reduces the access of water to fat layers, and causes faster drug release. In the studies done in the past, the presence of polyethylene glycol increased the release of olanzapine by 400% and similar results were also observed with the presence of Polyoxazoline 5000 (فرخزاد، ۱۳۸۸).

A) The effect of the amount of initial water on the percentage of Drug release

Comparison of drug release percentage from matrices with ratios of 0.4 and 0.2: Water/GMO and constant amount of Elanzapine and Polyoxazoline shows that the release rate of drugs with lower water content (20%) compared to samples with More water (40%) is lower (Figure 6).

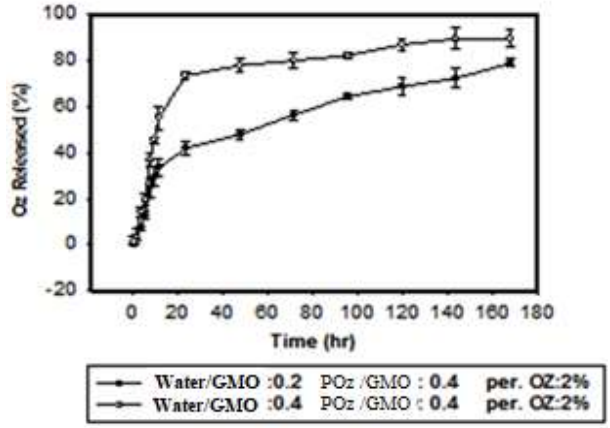


Figure 6- The effect of the amount of initial water on the percentage of drug release (N=3, Mean SD)

These observations can be due to the swelling of the 40% water samples. There are many studies to investigate the effect of water. Many studies have been conducted to investigate the effect of initial water on the drug release mechanism (رحیمی، 1390).

B) The effect of the drug on the percentage of drug release:

The type and dose of the drug is an important factor that affects the release rate of the drug and the kinetics. Due to its lipid-loving property, Elanzapine enters the lipid bilayer, and drug release decreases with increasing Elanzapine dose. The solubility and concentration of the loaded drug affect the percentage of drug release from the glycerol monolete matrix. Studies conducted on the release of polar and non-polar drugs show the effect of dose and type of drug on the release profile and mechanism (Figure 7)

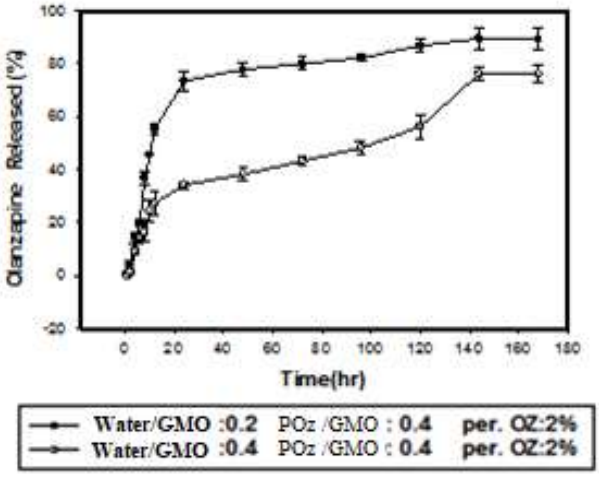


Figure 7- The effect of the amount of drug on the percentage of drug release (N=3, Mean SD)

3.6 The effect of Polyoxazoline on the percentage of Drug release

The external release of the drug from matrices with water content and fixed drug percentage has been investigated to evaluate the effect of polyethylene glycol on the release percentage, and it has been shown that with the increase in the concentration of polyethylene glycol, the drug release from 61.8% increase to 76.4% found Polyoxazoline, due to its water-friendly property, increases the rate of water absorption and reduces the access of water to fat layers, and causes faster drug release In the studies done in the past, in the presence of polyethylene glycol 400%, the release of Elazopin increased, and similar results were also observed with the presence of polyethylene glycol 1000 (B. S. Snorradottir, 2013).

3.7 The effect of the amount of initial water on the percentage of Drug release

Comparison of drug release percentage from matrices with ratios of 0.4 and 0.2: Water/GMO and constant amount of Elanzapine and Polyoxazoline shows that the release rate of drugs with lower water content (20%) compared to samples with More water (40%) is lower. These observations can be due to the swelling of the 40% water samples. There are many studies to investigate the effect of water. Many studies have been conducted to investigate the effect of initial water on the drug release mechanism (L. L. Lao, 2008).

3.8 The effect of the Drug on the percentage of Drug release

The type and dose of the drug is an important factor that affects the release rate of the drug and the kinetics. Due to its lipid-loving property, Elanzapine enters the lipid bilayer, and drug release decreases with increasing Elanzapine dose. The solubility and concentration of the loaded drug affect the percentage of drug release from the glycerol monolete matrix. Studies conducted on the release of polar and non-polar drugs show the effect of the dose and type of drug on the release profile and mechanism.

3.9 Evaluation of the Drug release mechanism

Considering the degree of convergence of the data, the best model to describe the release is Higuchi's model. In this model, the concentration of polymers, water content, and gel structure has important effects on the release mechanism [12], and also the Kroosmeyer-Papas model shows the behavior of the I mode(سیروس‌آذر، ۱۳۸۶) .

3.10 Optimisation and accuracy of the model

Optimization of jelly systems was done based on statistical analysis. The optimal formulation was obtained by using the Box-Kanken method with the weight ratio of Water/GMO at 0.31, the weight ratio of PEOz/GMO at 0.2, and the percentage of Enzopine at 2. To validate and confirm the predictability of the optimized formulation, a fresh gel with optimal conditions was prepared 3 times, and the responses were evaluated. The observed and predicted values for loading percentage were 87.88%, respectively, and this parameter was equal to 14.99% for release 1 and 64.61% for release 2. It should be noted that the predicted errors were less than 10%, which shows the correctness and predictability of the proposed model.

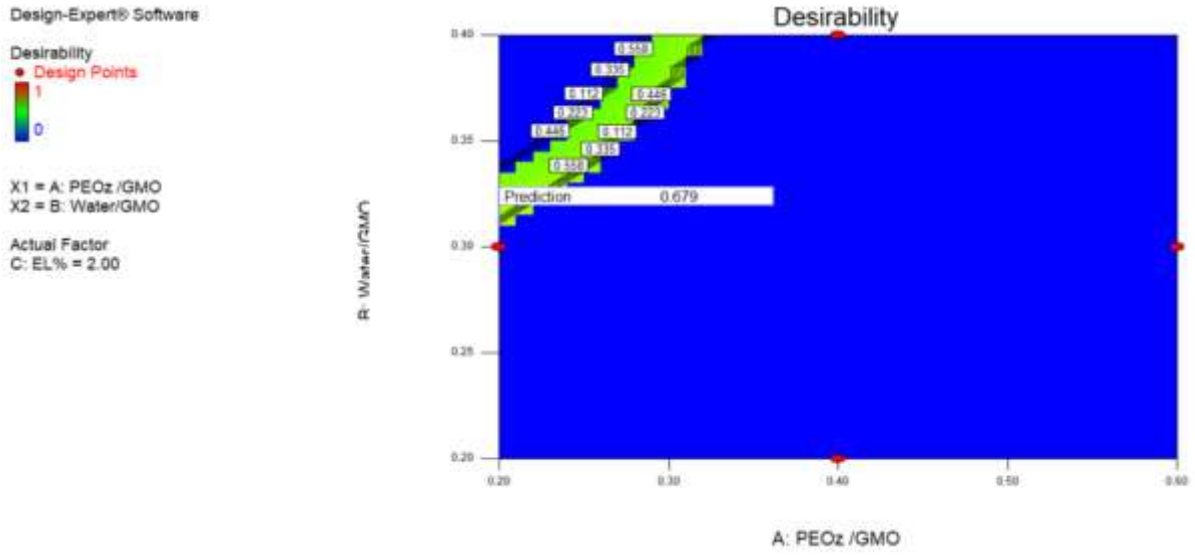


Figure 8 - Output of optimal results

4. Conclusion

Today, slow release drug systems are among the most important issues in the field of pharmaceuticals and biotechnology. Because of these systems, the amount of drug consumption can be reduced by a considerable amount, and as a result, their side effects

and toxicity caused by long-term consumption through the accumulation of drugs in the body can be reduced, and it can also prevent the unnecessary disposal of drugs. It will happen. In this study, the Elanzapine drug has been considered as a suitable drug model, and according to the type of patients who use this drug, the need to design a slow drug release system will be noticeable. This article examines the release of Elanzapine from the glycerol monolete matrix. The characteristics of the gel system, including the drug loading percentage, the release percentage, and the drug release mechanism, were investigated. The matrices were designed by using the Box-Non-Bass method, the independent variable including the weight ratio of water/glycerol monolete and Polyoxazoline/glycerol monolete and the percentage of anzapine and the effects of each of them on the percentage of leaves. The absorption and release of the drug has been investigated. The release of Elanzapine in the examined gels lasted for more than 168 hours, which was a sign of the slow release system, which is the main goal of this project. Several models were used to investigate the release kinetics of Enzopine, and among them, the Higuchi equation showed the best degree of regression with experimental data.

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References

[1] Balter A. T. J. M. (2013). Mathematical Modeling of Drug Release from Nanostructured Porous si Combining Carrier Erosion and Hindered Drug Diffiusion for predicting Release kinetics. *Acta. Biomaterialia, 9*, 8346-8353.
[2] Fu, W. J. Y. (2010). Drug Release Kinetics and Transport Mechanisms of Non- degradable and Deradable Polymeric Delivery Systems. *NIH-PA Author Manuscript, 7*, 429-444.
[3] Giri, K. K. T. K. (2012). A novel and Alternative Approach to Controlled Release Drug Delivery system Based on Solid Dispersion Technique. *Bulletin, Faculty, Pharmacy. Rev, 50*, 147-159.
[4] Korber M. (2010). PLGA Erosion: Solubility-or Diffusion- Controlled. *Pharm Res, 27*, 24142420.
[5] Lao, S. S. L. L. (2008). Modeling of Drug Release from Biodegradable Polymer Blends. *Eur. J. Pharm, 70*, 796-803.
[6] Parent M. C. N. (2013). PLGA in Situ implants formed by phase inversion Critical Physicochemical Parameters to Modulate Drug Release. *J. Controlled Release. Rev, 172*, 292-304.
[7] Snorradottir, B. S. F. J. (2013). numerical Modeling and Experimental Inestigation of Drug Release from Layered silicone Matrix System. *Eur. J. Pharm. Sci, 49*, 671-678.
[8] Soares J. S. P. Z. (2010). A mixture model for water uptake, Degradation, Erosion and Release from Polydisperse Polymeric Networks. *Biomaterials, 31*, 3032-3042.
[9] Siepmann J. N. A. (2011). Higuchi equation Derivation, Applications use and Misuse. *Int. J. Pharm, Rev, 41*, 6-12.
[10] Versypt A. N. F. D. W. (2013). Mathematical Modeling of Drug Delivery from Autocatalytically Degradable PLGA Microspheres. *J. Controlled Release. Rev, 165*, 29-37
[11] سیروس آذر، محمد؛ جعفری عنصر رودی، هاجر؛ کوکبی، مهرداد. " مدل‌سازی رهایش دارو از سامانه نوین پلیمری پاسخگو به دما ". مجله علوم و تکنولوژی پلیمر، سال 20، شماره 3، 269-257، 1386.
[12] فرخ زاد، حسین؛ موبدی، حمید؛ برزین، جلال؛ پورخلیل، علی. " بررسی اثر غظت پلیمر بر رهایش داروی داکسی سایکلین هیکلیت از سامانه تشکیل شونده در محل بر پایه پلی (لاکتید- کو- گلیکولید)". مجله علوم و تکنولوژی پلیمر، سال 22، شماره 6، 505-495، 1388.
[13] رحیمی، محمودرضا؛ قاسمی کفرودی، اسماعیل. " شبیه سازی واکنش تخریب پلیمر زیست تخریب پذیر پلی لاکتیک اسید در بدن انسان". مجله مدل‌سازی در مهندسی. سال نهم، شماره24، 1390.
[14] خوئی، سپیده؛کردانی، مریم. " هیدروژل‌ها به عنوان حامل در سامانه‌های دارورسانی کنترل شده".فصلنامه علمی- ترویجی. سال دوم، شماره4، 1391.
[15] داوران، سودابه. "تهیه سیستم‌های دارورسانی آهسته رهش نالتروکسون جهت ترک اعتیاد به مواد مخدر". ستاد مبارزه با مواد مخدر، 1392.