Original Article

DOI: 10.14235/bas.galenos.2022.40427
Bezmialem Science 2022;10(6):735-41

Evaluation of Drug Release Kinetics of Temozolomide Loaded Plga Nanoparticles in Pluronic® F-127 Hydrogel

Pluronic® F-127 Hidrojel İçinde Temozolomid Yüklü PLGA Nanopartiküllerinden İlaç Salım Kinetiklerinin Değerlendirilmesi

Tansel ÇOMOĞLU

Ankara University Faculty of Pharmacy, Department of Pharmaceutical Technology, Ankara, Turkey

ABSTRACT

Objective: Controlled local release of temozolomide (TMZ) at the tumor site is a new strategy in the treatment of glioblastoma. Localized delivery systems, based on biodegradable polymers, are capable of slowing and controlling the drug release for a certain period of time. Therefore, the main objective of the study was to investigate a new approach for encapsulating TMZ in a poly(lactic-co-glycolic acid) nanoparticle (NP) system which was then formulated in 18% Pluronic® hydrogel matrix which would provide a sustained and local delivery of TMZ.

Methods: Hydrogels are investigated as local drug delivery methods due to their tunable characteristics and capacity to retain labile pharmaceuticals. The lack of established procedures for describing and evaluating drug release, on the other hand, offers considerable problems, impeding reliable evaluation of systems for defining drug release characteristics.

Results: In this part our study, we aimed to research drug release kinetics of TMZ NPs which had an encapsulation efficiency and particle size ranging between 52-69.67% and 164.4-235.5 nm from a novel hydrogel drug delivery system.

Conclusion: The application of mathematical modeling proves to be extremely beneficial for estimating the release kinetics before the release systems are implemented. The release mechanism was found to be diffusion controlled and not accompanied by dissolution of matrix.

Keywords: Hydrogel, Pluronic F-127, temozolomide, nanoparticles, drug release kinetics

ÖZ

Amaç: Tümör bölgesinde temolozomid'in (TMZ) kontrollü lokal salınımı, glioblastomanın tedavisinde yeni bir stratejidir. Biyobozunur polimerlere dayanan lokalize dağıtım sistemleri, belirli bir süre boyunca ilaç salınımını yavaşlatabilir ve kontrol edebilir. Bu nedenle, çalışmanın ana amacı, TMZ'nin sürekli ve yerel bir dağıtımını sağlayacak olan %18 Pluronic® hidrojel matrisinde formüle edilen bir poli(laktik-ko-glikolik asit) nanoparçacık (NP) sisteminde TMZ'yi kapsüllemek için yeni bir yaklaşımı araştırmaktı.

Yöntemler: Hidrojeller, ayarlanabilir özellikleri ve kararsız farmasötikleri tutma kapasiteleri nedeniyle yerel ilaç dağıtım yöntemleri olarak hızla araştırılmaktadır. Öte yandan, ilaç salımını tanımlamaya ve değerlendirmeye yönelik yerleşik prosedürlerin olmaması, ilaç salım özelliklerini tanımlamaya yönelik sistemlerin güvenilir bir şekilde değerlendirilmesini engelleyen önemli sorunlar ortaya çıkarmaktadır.

Bulgular: Yeni bir hidrojel ilaç taşıma sisteminden 164,4-235,5 nm arasında değişen partikül boyutu ve %52-69,67 kapsülleme etkinliğine sahip TMZ NP'lerin *in vitro* ilaç salım kinetiğini araştırmayı amaçladık.

Sonuç: Serbest bırakma sistemleri uygulanmadan önce serbest bırakma kinetiğini tahmin etmek için matematiksel modellemenin kullanılmasının çok faydalı olduğu ortaya çıkmıştır. Salım mekanizmasının difüzyon kontrollü olduğu ve matriksin çözünmesinin eşlik etmediği bulundu.

Anahtar Sözcükler: Hidrojel, Pluronic F-127, temozolomid, nanopartiküller, ilaç salım kinetiği

Address for Correspondence: Tansel ÇOMOĞLU, Ankara University Faculty of Pharmacy, Department of Pharmaceutical Technology, Ankara, Turkey
E-mail: tcomoglu@yahoo.com **ORCID ID:** orcid.org/0000-0002-4221-5814

Received: 24.11.2021
Accepted: 23.02.2022

Cite this article as: Çomoğlu T. Evaluation of Drug Release Kinetics of Temozolomide Loaded Plga Nanoparticles in Pluronic® F-127 Hydrogel. Bezmialem Science 2022;10(6):735-41

Introduction

Temozolomide (TMZ) is an anticancer agent with alkylating properties, included in the group of imidazotetrazine derivatives, developed in Aston University in the 1980s. TMZ was found to have antitumor activity in intracranial and extracranial tumors. It has been used for glioblastoma multiforme treatment (GBM) (1). However, treatment of GBM remains a challenge, largely due to the fast degradation of TMZ, inability to deliver an effective dose of TMZ to tumors, and lack of target specificity which may cause systemic toxicity. Nanoparticles can be a solution for the rapid degredation of TMZ and can specifically deliver TMZ to GBM cells.

Poly(lactic-co-glycolic acid) (PLGA) nanoparticles (NPs) have been used as efficient delivery vehicles for therapeutic agents to the brain. PLGA NPs can be produced in any desired shape and size and can trap molecules of any size (2). PLGA has been evaluated for encapsulating small anticancer agents used in nanoparticular cancer chemotherapy (3). Although NPs offer a number of positive properties for drug delivery, NPs have often been combined with hydrogels to further improve the therapeutic index, particularly in localized administration.

Hydrogels, like Pluronic®, excel in controlled release applications because of their tissue compatibility and ease of dispersion in the matrix (4). Hence, we hypothesized that a hydrogel, containing NPs loaded with TMZ, would provide a sustained and local delivery of the drug and destroy cancer cells that might remain in the areas that could not be reached by tumor resection during surgical intervention in the treatment of GBM.

Pluronic F-127 is a hydrophilic polymer which is capable of holding a large amount of water and showing sol-gel transition near 37 °C and the unique thermo-responsive property of the polymer is directed towards a wide area of drug delivery applications (5). In addition to Pluronics inertness and good biocompatibility, its ability to release entrapped drug in aqueous media makes Pluronics particularly suitable as drug carriers in the controlled release of pharmaceuticals (6).

The first part of the study was conducted to formulate TMZ loaded NP formulations with PLGA by emulsion-solvent evaporation method. The PLGA NP formulations were evaluated for their particle size and size distrubution, entrapment efficiency, zeta potential and *in vitro* drug release studies. Then, the optimum NP formulation was chosen to develop a thermo-responsive hydrogel formulation with Pluronic F-127. Also, hydrogel formulations were tested for their rheological and drug release properties (7).

Many manufacturing process variables affect drug release from dosage forms. To contemplate the TMZ release mechanism from Pluronic F-127 hydrogel and PLGA NPs, different kinetic models were considered to fit the experimental data (8).

After giving a brief information about the aim of the study, it was planned to focus on the kinetics of TMZ release from NPs from a Pluronic F-127 hydrogel matrice. Caccavo reviewed the trend in mathematical models used in the field of hydrogel-based drug delivery system and found that the main fit model equations used were: Zero order kinetics, first order kinetics, Korsmeyer-Peppas kinetics, Weibull and The Higuchi kinetics (9).

Methods

Materials

Temozolomide, PLGA (acid terminated; Mw =24,000-38,000; copolymer ratio 50:50), Mowiol 18-88 (Mw =130,000), and Pluronic® F-127 were supplied by Sigma-Aldrich. Ultrapurified water was obtained from the Milli-Q system. All other reagents and solvents used in this study were of analytical grade.

Methods

Formulation of TMZ Loaded PLGA Nanoparticles

The formulation method of TMZ NPs was modified from the study of Ananta et al. (7,9,10). NPs were prepared using emulsion (w/o) solvent evaporation method. TMZ and PLGA were dissolved in 1 mL dimethylformamide. The resulting solution was added in drops to 5 mL of PVA 5% solution under homogenization. The organic solvent used was evaporated. NPs were collected by centrifugation and washed with deionized water to remove free TMZ. And then NPs were collected from the resulting emulsion.

Particle Size Measurement of Nanoparticles

The mean particle size of the NPs was measured by Malvern Zeta Sizer (Malvern Instrument Ltd.). The dispersions were diluted with nanopure water and the sample was placed in a disposable cuvette at a count rate for 20 seconds. The particle size measurment data are reported in Table 1.

Determination of Encapsulation Efficiency (%)

Entrapped TMZ amount in the NPs was determined with our validated HPLC assay and calculated as equation below (7).

$$\text{Encapsulation efficiency \%} = \frac{\text{TMZ amount in formulation}}{\text{Added TMZ amount}} \times 100$$

Formulation Design of Nanoparticle Loaded Pluronic F-127 Thermoreversible Gel

The "cold method" was used in the preparation of hydrogels. Pluronic® F-127 was weighed, added to 50 mL of ultrapure water, and mixed on magnetic stirrer at 900 rpm in an ice bath until Pluronic® F-127 was homogeneously dissolved (7). Gel formulations containing 18-20 and 25% (w/v) Pluronic® F-127 were prepared.

Physicochemical Evaluation of Nanoparticle Loaded Pluronic® F-127 Hydrogels

pH Levels of Produced Hydrogels

The pH levels of the hydrogel formulations were measured with Eutech Instruments pH 700 (n=3) (9).

Sol-gel Transition Temperature

The gelation temperatures of developed formulations were determined by a modified version of the reverse-tube method (n=3) (9).

Viscosity

Sol and gel viscosities of the formulations produced were measured by running the viscometer at speeds of 5-100-5 rpm. Viscosities in gel form were measured with T96 spindle in Brookfield DVII device. Measurements were repeated three times and graphs were plotted as viscosity (cP) vs. shear rate (rpm) (9).

Mechanical Properties

Texture profile analysis (TPA) was performed in the TPA mode of the TA-XT2 Texture Analyzer (Surrey, UK). The formulations were transferred in gel form into 25 mL beakers. Measurements were recorded by puncturing the samples (11).

In vitro TMZ Release Studies

In vitro drug release experiments for all formulations were performed in a shaker bath at a temperature of 37 °C ±1 °C and pH 5 buffer containing 0.1% ascorbic acid. The amount calculated according to the data obtained from the loading capacity and which would provide the target dose was weighed and suspended in buffer with 0.1% ascorbic acid, and for hydrogel formulations, they were suspended in Pluronic® F-127 hydrogel and attached with two-end weighted clips in the dialysis membrane tube placed in a beaker. Twenty mL of buffer solution was placed in each beaker. Samples were taken at various time intervals and the release medium was replaced with new medium to prevent degradation of the active substance after 24 hours.

Kinetic Evaluation of *In Vitro* Drug Release Studies

Dissolution rate profiles were obtained by determining the amount of active substance released by conducting an *in vitro* release study from the formulations. In order to determine which mathematical model the active substance release profiles fit into, the equations of the zero-order, first-order, Higuchi, Weibull and Korsmeyer-Peppas kinetic models were applied in Excel®. Statistical evaluations were made using GraphPad Prism 6® and the findings obtained were evaluated (12).

Results and Discussion

NPs were prepared by emulsion solvent diffusion method. All formulations were produced with two different TMZ amounts, respectively 5 and 10 mg, so as to observe the effect of TMZ amount on the size and encapsulation efficiency of nanoparticles. NPs were discrete, nearly spherical with a size range of 164.4-235.5nm. NPs of 10-200 nm size are suitable for a nano-carrier systems designed for local application that will cross the blood-brain barrier in the brain and reach the tumor site. Because, nanoparticles smaller than 10 nm are excreted renally and NPs larger than 300 nm are removed from the body by RES (13,14). A2-10 formulation with least particle size had the maximum entrapment efficiency (Table 1). It was determined that increasing the amount of TMZ correlated to a higher encapsulation efficiency in all the formulations (15). This effect is explained by the fact that an excess of drug leads in a more viscous dispersed phase, making mutual dispersion of the phases problematic and resulting in the formation of large particles (16). Based on these findings A2-10 formulation was selected in the preparation of hydrogel formulations.

The Zeta potential indicates that it can generate enough repulsion to overcome the gravitational attraction between NPs and suspension dispersion has better stability (17). If formulations were observed to evaluate the effect of the amount of TMZ on the particle properties in Table 1, it was seen that particle size, polydispersity index (PDI) and zeta potential increased where the active substance was adsorbed to the terminal carboxyl groups of PLGA NPs. This is because terminal carboxyl groups are located on the surface of NPs (14). In addition, this phenomenon can be explained by the production of larger particles by causing more active substances to a more viscous oil phase and making it difficult for phases to disperse into each other (16).

The PDI value of polymeric NPs is required to be less than 0.3. According to the PDI data obtained in our study (Table 1), it

Table 1. Formulation design and particle size measurement data of TMZ nanoparticles prepared by emulsion solvent diffusion method

	Formulation code		
Component	A2	A2-5	A2-10
PLGA	2:20	5:20	10:20
DMF (mL)	1	1	1
Z-average (mV)	-13.10±0.416	-13.10±1.05	-4.16±0.337
Size (nm)	169.30±4.053	235.50±24.96	164.40±4.236
PDI	0.255±0.014	0.362±0.1	0.143±0.046
Entrapment efficiency (%)	52.63	60.69	69.67

TMZ: Temozolomide, PLGA: Poly(lactic-co-glycolic acid), PDI: Polydispersity index

was seen that the PDI value of all formulations was within the acceptable range.

Smart hydrogels are attractive because of their unique sol-gel phase transitions at body temperature, biocompatibility, safety, and injectability as a solution in the body before transforming into gel matrices. In formulations containing 18%, 19% and 20% Pluronic® F-127, which showed sol-gel transition, it was observed that the pH level increased the with increasing concentration (18). According to statistical calculations, the difference between pH levels was found to be significant ($p<0.0001$), but since the pH level of the tumor microenvironment was close to the pH level, the obtained pH level was suitable for local drug administration to the tumor site (19). In our study, increased concentration resulted with a lower transition temperature (Table 2). Sol-gel phase transition temperatures of 18%, 19%, 20% and 25% Pluronic F127 containing solutions were 32 °C, 30 °C, 26 °C and 20 °C, respectively. Elasticity and cohesiveness of gels were close for all formulations.

The importance of the sol-gel transition temperature is that the formulation remains in fluid sol state at room temperature, leaving the package or injector and transforming into an *in situ* gel and maintaining its shape. It was observed that the gelation temperature decreased with the increase of Pluronic® F-127 concentration in the formulation, and this was confirmed by the literature (18).

It was observed that the formulations were at the bottom of the tubes in the left state at room temperature (25 °C). Concentrations of 18% and above appeared to be a non-flowing gel when the gels were turned upside and incubated (37 °C). It was observed that the formulation containing 17% Pluronic® F-127 returned to its sol form, and formulations containing 15 to 16% Pluronic® F-127 remained in its left form. According to the results which was shown in Table 2, H18 was chosen as a proper injectable system with a gelation temperature of 32 °C which led to be a solution in the room and transited into a gel in the body (5). pH values of gels rangingbetween 6.80-6.94 are suitable for brain application. Also, Persi revealed that acidic pH disabled hypoxia adaptations of cancer cells and compromised tumor cell growth which indicated that pH values of formulations between 6.80-6.94 were suitable for brain cancer treatment with less damage to brain tissue (20).

The A2, A2-5, and A2-10 formulations showed a triphasic profile. In all formulations, a burst effect was observed in the first 4 hours and a plateau was detected in the following 72 hours (Figure 4). The reason for the difference in the percentage of active substance released from the formulations is thought to be proportional to the decrease in the percentage of active substance released per unit time as the encapsulation rate of the active substance increases (21). In Figure 2, the drug release of NPs from the hydrogel formulations reached approximately 25% of the total TMZ in 60 days. The *in vitro* release profile of the active substance in the hydrogel from the NP system showed an average of 10% of immediate release in the first 12 hours, then reaching a plateau in the next 60 days.

The *in vitro* release profile of TMZ in hydrogel showed an immediate release of 46% in the first 6 hours and reached a plateau in the next 18 hours. The release profile of the active substance from the NP system in the hydrogel allowed the release of TMZ at lower doses over a long period of time.

Dissolution rate profiles were obtained by determining the amount of active substance released by conducting an *in vitro* release study from the formulations. In order to determine which mathematical model the active substance release profiles fit into, the equations of the zero-order, first-order, Higuchi, Weibull and Korsmeyer-Peppas kinetic models were applied in Microsoft Office Excel and the findings obtained were evaluated (22). The applied mathematical equations used to describe release characteristics of TMZ NP from Pluronic F-127 gels are given in Table 3.

The mathematical models include: (a) zero-order model, $Q=Q_0+k_0\ t$, where Q is the cumulative release percentage, k_0 zero release rate constant, and t time; (b) first-order model, Log C_t=Log C_0-k_1t/2.303, where Log C is the cumulative release percentage, k_1 first release rate constant, t time (c) Higuchi model, $F_t=k_{Ht}^{1/2}$, where F_t is the cumulative release percentage, k_H Higuchi release rate constant, and t time (11). (d) The formula for Weibull function is F=1-exp (-atb). Where F is the drug fraction released at time t, and a and b are constants. b, as a shape parameter (18). (e) Korsmeyer - Peppas model= M_t/M_∞ = kp tn where M_t/M_α is the proportion of drug released at time t, k is the rate constant (Table 3) (11).

As can be seen in Table 4, *in vitro* release kinetics of the active substance show compatibility with the Weibull kinetic model in A2, A2-5, and A2-10 formulations. The fact that all of the calculated β values were less than 1 indicated a kinetic profile where the active substance release rate occured faster at first, then

Table 2. Properties of TMZ nanoparticles loaded Pluronic® F-127 gels

Hydrogel	Viscosity of hydrogel cP	Pluronic concentration %	pH	Gelation temperature °C	Elasticity	Cohesiveness
H18	22000.00±1833.03	18	6.80±0.01	32-33	0.9874±0.0171	0.9523±0.0030
H19	11600.00±529.15	19	6.94±0.01	28-30	0.9960±0.0148	0.9176±0.0000
H20	12666.67±665.83	20	6.94±0.01	25-26	0.9920±0.0041	0.9721±0.0000
H25	32966.67±3194	25	6.80±0.00	20-21	0.9960±0.0467	0.7668±0.0000

TMZ: Temozolomide

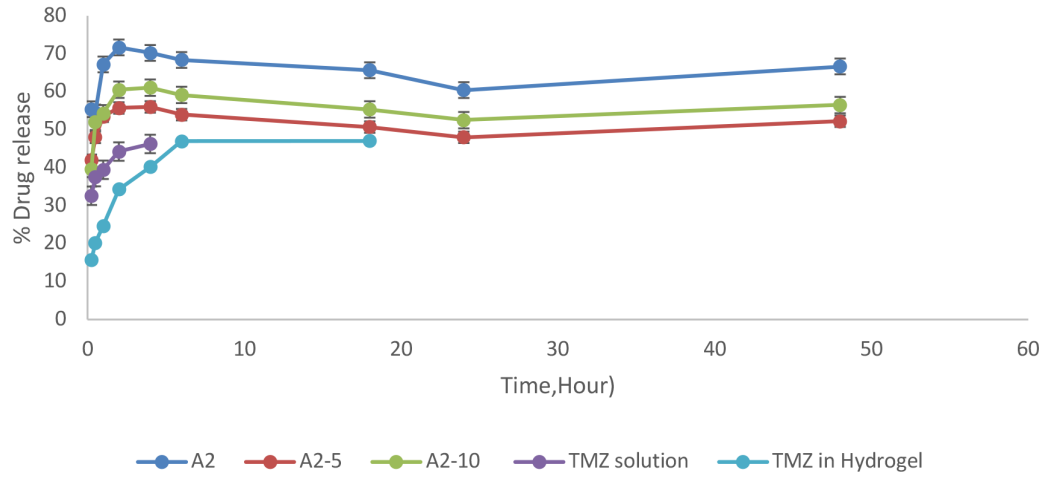

Figure 1. *In vitro* release of TMZ from nanoparticles
TMZ: Temozolomide

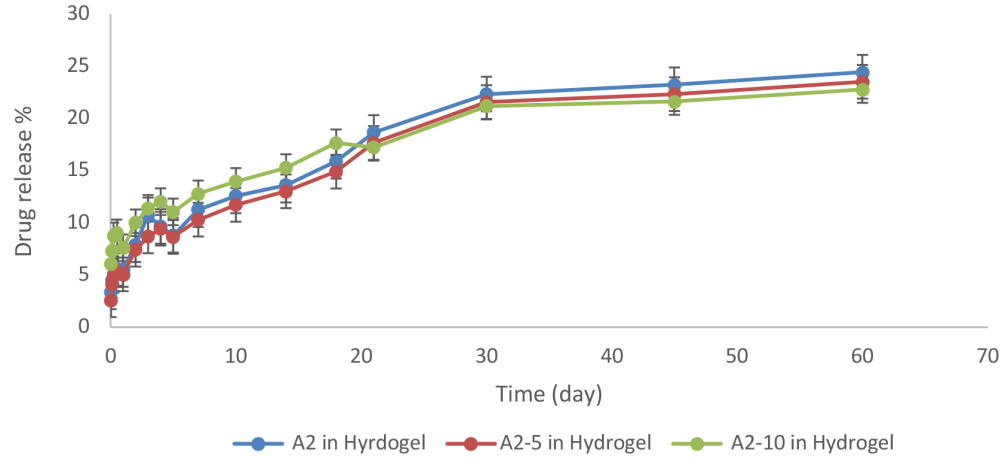

Figure 2. *In vitro* release of TMZ from nanoparticle loaded hydrogels
TMZ: Temozolomide

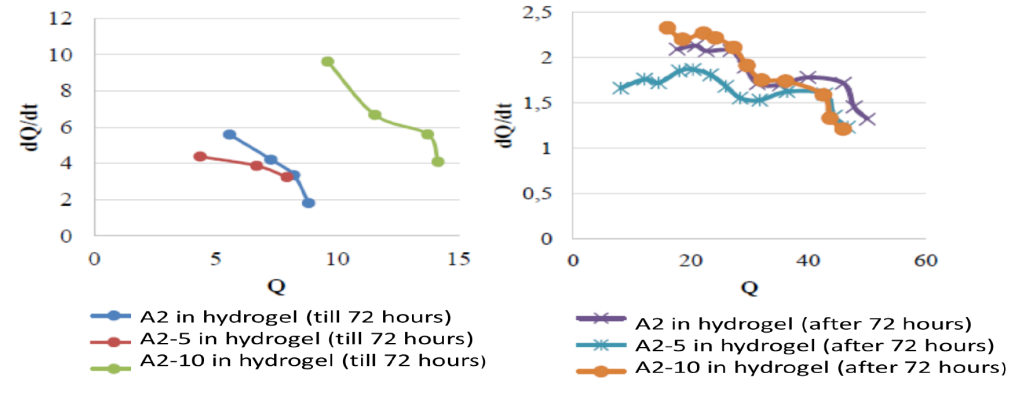

Figure 3. dQ/dt-Q plots of nanoparticle formulations in hydrogel

Table 3. Mathematical equations for the models used to describe release characteristics of TMZ from Pluronic® F-127 gels

Model	Equation
Zero-order	$Q=Q_0+k_0\ t$
First order	$Log\ C_t=Log\ C_0-k_1 t\ /2{,}303$
Higuchi	$Ft=k_H t^{1/2}$
Weibull	F=1-exp (-atb)
Korsmeyer-Peppas	Mt/M∞=kp tn

TMZ: Temozolomide

Table 4. Results of mathematical model fitting of TMZ release of nanoparticle loaded hydrogel

		A2-2	A2-5	A2-10	A2-2 in hydrogel	A2-5 in hydrogel	A2-10 hydrogel
Zero order	**k_0**	-10.433	-3.004	-0.412	-0.032	-0.030	-0.025
	r^2	0.804	0.580	0.723	0.794	0.816	0.794
	RMS	30.924	20.283	67.400	50.383	39.287	32.877
First order	**k_1**	-0.292	-0.061	-0.013	-0.001	0	0
	r^2	0.844	0.601	0.876	0.853	0.866	0.841
	RMS	0.018	0.008	0.026	0.007	0.005	0.005
$Q \rightarrow t^{1/2}$	**k**	23.344	8.637	4.122	1.326	1.243	1.042
	r^2	0.871	0.736	0.813	0.960	0.969	0.960
	RMS	20.334	12.714	45.476	9.605	6.666	6.424
Peppas	**n**	0.197	0.105	0.113	0.332	0.341	0.226
	r^2	0.915	0.872	0.904	0.961	0.967	0.959
	RMS	0.001	0.001	0.001	0.004	0.004	0.002
Weibull	**β**	0.339	0.151	0.195	0.375	0.379	0.260
	r^2	0.931	0.881	0.952	0.955	0.961	0.949
	RMS	0.002	0.001	0.002	0.006	0.005	0.004

TMZ: Temozolomide, RMS: Rhabdomyosarcoma

resembled the 1st degree kinetic profile and reached a plateau (23).

The release of active substance by diffusion and/or relaxation in the polymeric system is explained by the Korsmeyer-Peppas kinetics. According to the R^2 values obtained by the calculation made from the A2, A2-5 and A-10 formulations in the hydrogel, the release kinetics of the active substance were in accordance with the Korsmeyer-Peppas kinetics. This finding confirms the fact that Pluronic® F-127 hydrogel swells by absorbing water and the active substance is released as diffuse within the hydrogel system (24). The fact that the calculated n values were less than 0.45 indicated the Fickian diffusion profile (25).

Since the formulations showed compatibility with the Higuchi and 1st order kinetic model at the same time, a graph of the amount of active substance released (Q) versus the amount of active substance released (d_Q/d_t) in a certain time period was plotted to determine which one was compatible.

The release of water-soluble drugs from anhydrous hydrogel matrices involves simultaneous absorption of water and desorption of drug via a swelling-controlled diffusion mechanism (26). The fact that the calculated n values were less than 0.45 indicated the Fickian diffusion profile (25).

Study Limitations

Since the formulations showed compatibility with the Higuchi and First order kinetic model at the same time, a graph of the amount of active substance released (Q) versus the amount of active substance released (dQ/dt) in a certain time period was plotted to determine which one was compatible. For graphs showing biphasic characteristics, both phases and the entire profile were applied to the graph, and it was observed that the dQ/dt and Q values in all three graphs showed inverse proportion (Figure 3). This showed that the release was in accordance with the Higuchi kinetics (27).

Conclusion

A modified release drug delivery system of TMZ developed as a NP hydrogel served as a depot for sustained drug release and provided a rate-limiting barrier for modulation of drug release. Drug release from the hydrogel system was evaluated by means of mathematical modelling. The use of mathematical modeling turned out to be very useful for estimating the release kinetics before the release systems were implemented. The release mechanism was found to be diffusion controlled and not accompanied by dissolution of matrix. The release kinetics in H18 followed Korsmeyer-Peppas model.

Ethics

Ethics Committee Approval: Ethics committee approval is not required.

Peer-review: Externally peer reviewed.

Financial Disclosure: This study was supported by Ankara University BAP projects with the project number of 18L0237003.

References

1. Alphandéry E. Glioblastoma treatments: an account of recent industrial developments. Front Pharmacol 2018;9:879.
2. Makadia HK, Siegel SJ. Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier. Polymers 2011;3:1377-97.
3. Danhier F, Ansorena E, Silva JM, Coco R, Le Breton A, Préat V. PLGA-based nanoparticles: an overview of biomedical applications. J Control Release 2012;161:505-22.
4. Sharma S, S Tiwari. A review on biomacromolecular hydrogel classification and its applications. Int J Biol Macromol 2020;162:737-47.
5. Chatterjee S, Hui PCL, Kan CW, Wang W. Dual-responsive (pH/temperature) Pluronic F-127 hydrogel drug delivery system for textile-based transdermal therapy. Sci Rep 2019;9:1-13.
6. Zarrintaj P, Ramsey JD, Samadi A, Atoufi Z, Yazdi MK, Ganjali MR, et al. Poloxamer: A versatile tri-block copolymer for biomedical applications. Acta Biomater 2020;110:37-67.
7. Sayiner O, Arisoy S, Comoglu T, Ozbay FG, Esendagli G. Development and in vitro evaluation of temozolomide-loaded PLGA nanoparticles in a thermoreversible hydrogel system for local administration in glioblastoma multiforme. Journal of Drug Delivery Science and Technology 2020;57:101627.
8. Paarakh MP, Jose PA, Setty CM, Christoper GP. Release kinetics–concepts and applications. Int J Pharm Res Technol 2018;8:12-20.
9. Caccavo D. An overview on the mathematical modeling of hydrogels' behavior for drug delivery systems. International Journal of Pharmaceutics 2019;560:175-90.
10. Ananta JS, R Paulmurugan, and TF Massoud. Temozolomide-loaded PLGA nanoparticles to treat glioblastoma cells: a biophysical and cell culture evaluation. Neurol Res 2016;38:51-9.
11. Hurler J, Engesland A, Poorahmary Kermany B, Škalko-Basnet N. Improved texture analysis for hydrogel characterization: Gel cohesiveness, adhesiveness, and hardness. Journal of Applied Polymer Science 2012;125:180-8.
12. Arisoy S, Comoglu T. Kinetic evaluation of L-Dopa loaded WGA-grafted nanoparticles. Medicine 2020;9:385-8.
13. Sun SB, Liu P, Shao FM, Miao QL. Formulation and evaluation of PLGA nanoparticles loaded capecitabine for prostate cancer. Int J Clin Exp Med 2015;8:19670.
14. Lu B, X Lv, and Y Le. Chitosan-modified PLGA nanoparticles for control-released drug delivery. Polymers (Basel) 2019;11:304.
15. Derman S. Caffeic acid phenethyl ester loaded PLGA nanoparticles: effect of various process parameters on reaction yield, encapsulation efficiency, and particle size. Journal of Nanomaterials 2015;16:318.
16. Mainardes RM and RC Evangelista. PLGA nanoparticles containing praziquantel: effect of formulation variables on size distribution. Int J Pharm 2005;290:137-44.
17. Verbich SV, Dukhin SS, Tarovski A, Holt Ø, Saether Ø, Sjo J. Evaluation of stability ratio in oil-in-water emulsions. Colloids and Surfaces A: Physicochemical and Engineering Aspects 1997;123:209-23.
18. Małolepsza-Jarmołowska K. The effect of poloxamer 407 on the properties of hydrophilic gels containing lactic acid complexed with chitosan. Progress on Chemistry and Application of Chitin and its Derivatives 2010;15:143-8.
19. Kushan E. and E Senses. Thermoresponsive and Injectable Composite Hydrogels of Cellulose Nanocrystals and Pluronic F127. ACS Applied Bio Materials 2021;4:3507-17.
20. Persi E, Duran-Frigola M, Damaghi M, Roush WR, Aloy P, Cleveland JL, et al. Systems analysis of intracellular pH vulnerabilities for cancer therapy. Nat Commun 2018;9:1-11.
21. Averineni RK, Shavi GV, Gurram AK, Deshpande PB, Arumugam K, Maliyakkal N, et al. PLGA 50: 50 nanoparticles of paclitaxel: development, in vitro anti-tumor activity in BT-549 cells and in vivo evaluation. Bull Mat Sci 2012;35:319-26.
22. Zhang Y, Huo M, Zhou J, Zou A, Li W, Yao C, et al. DDSolver: an add-in program for modeling and comparison of drug dissolution profiles. AAPS J 2010;12:263-71.
23. Comoglu T, Gonul N, Dogan A, Basci N. Development and in vitro evaluation of pantoprazole-loaded microspheres. Drug delivery 2008;15:295-302.
24. Ramos DJ, Carrelo H, Borges JP, Calero Romero N, Santos García J, Cidade MT. Injectable Hydrogels Based on Pluronic/Water Systems Filled with Alginate Microparticles for Biomedical Applications. Materials 2019;12:1-13.
25. Dwivedi R, AK Singh, Dhillon A. pH-responsive drug release from dependal-M loaded polyacrylamide hydrogels. Journal of Science: Advanced Materials and Devices 2017;2:45-50.
26. Lee PI. Kinetics of drug release from hydrogel matrices. Journal of Controlled Release 1985; 2:277-88.
27. Serim TMY, ANTD Özdemir. Kontrollü salım yapan rivastigmin içeren implante partiküler sistemlerin formülasyonu üzerine çalışmalar. Ankara Üniversitesi Sağlık Bilimleri Enstitüsü Sağlık Bilimleri Enstitüsü Farmasötik Teknoloji Anabilim Dalı.