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Evaluation of Application of Drug Modeling in Treatment of Liver and Intestinal Cancer

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ABSTRACT

In drug delivery systems, mathematical modeling plays an important role in more clearly explaining the important mechanisms of drug release profiles, so as to facilitate the development of new drug products with a regular approach rather than trial and error. Mathematical models related to known drug release mechanisms fall into three categories: infiltration, controlled inflation systems, and erosion. In the case of liposomal nanoparticles as a biodegradable nanocarrier matrix, the release control is by hydrolysis gap in the polymer chain which will lead to matrix erosion, although penetration due to slow erosion may be still predominant. On the other hand, in the case of biodegradable nanocarriers, drug release is due to the concentration gradient either in the penetration or in the penetration enhancement system by erosion. This classification allows mathematical models to be developed in different ways for each type of system. Mathematical modeling of drug release can provide good insight into chemical processes and modes of delivery in drug delivery as well as the effect of design parameters. In both biodegradable and non-biodegradable nanocarriers, design parameters such as drug loading can significantly affect drug release mechanisms. Therefore, the optimized nano-carrier design for the required drug release profile can be predicted using a regular method with a minimum number of experimental studies. Thus, mathematical modeling can help predict drug release rates; as a result, researchers can come up with much more effective drug formulations and more accurate methods that will save time and money.

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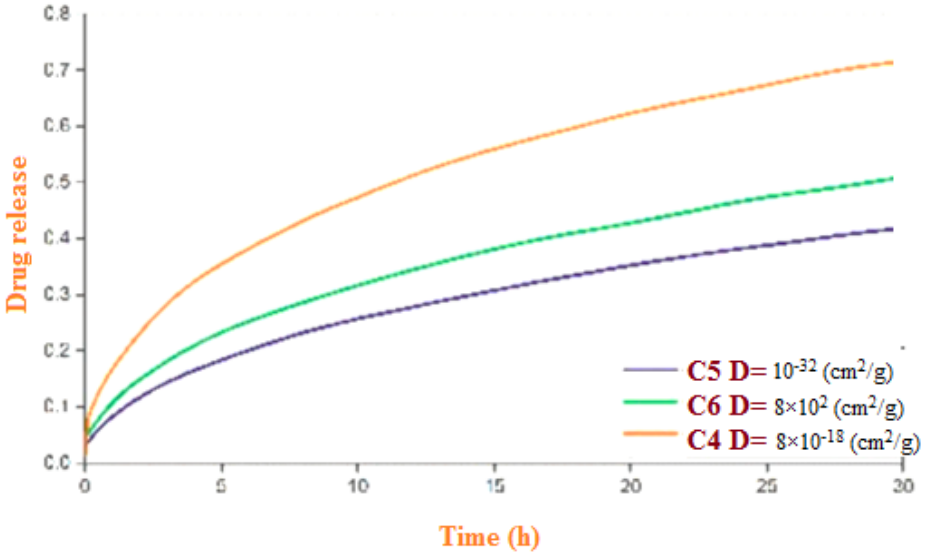
GRAPHICAL ABSTRACT



Introduction

One of the most common causes of death in today's society is cancer. The treatments used in fighting cancers have their own side effects that have created many problems in the complete treatment of cancer. In classical and conventional drug delivery systems, the drug is distributed aimlessly and generally throughout the body, and the cells take some of the drug from the blood based on their position relative to the drug [1-5]. As a result, a significant amount of the drug is wasted and eliminated without the use of the body. The most important disadvantages of the old methods of drug delivery are drug wastage, high cost of raw materials, the occurrence of side effects related to the dose, physical and chemical incompatibilities, as well as clinical drug interactions. To prevent and reduce these disadvantages, the new pharmaceutical industry took steps to produce and use modern drug delivery systems. In modern drug delivery methods, small amounts of the active ingredient can be delivered to the target point by appropriate carriers that have been produced in order to minimize the desired drug to the target cells with minimum side effects and maximum efficiency [6-8]. One of the important practical methods to reduce side effects in cancer treatments is the use of nanocarriers as a drug delivery system. Important applications of drug delivery systems include maintaining the drug concentration in the treatment range at the appropriate time, controlled drug release, and finally specific drug delivery to the target tissue [9-11]. The most important drug delivery systems are dendrimers, micelles, hydrogels, metal, polymer, and nanoliposome nanostructures noted that the performance of each of these carriers varies depending on size, shape, and other physical and chemical properties.

Nano-liposomes are nanometer-scale liposomes that are one of the most useful drug delivery systems in the field of drug release and retention, which on the one hand provides a higher level than liposomes and on the other hand increases solubility [12-14] and access to bioavailability as well as improved drug release. Important reasons for the use of nano-liposomes in the pharmaceutical industry are their similarity to cell membranes and trapping of hydrophobic and hydrophilic substances, drug delivery to the target tissue, control of drug flow in the bloodstream and good biocompatibility. Another important feature of nano-liposomes is the

coating of water-soluble drugs in the central aqueous portion and fat-soluble drugs within its bilayer membrane. Nanoliposomes can be effective in reducing drug toxicity and increasing drug efficacy [15-17].

In general, it should be noted that by adding different substances in the structure of nanoliposomes during formulation, on the one hand, the use of nanoliposomes can be improved and on the other hand, a very large volume of drugs can be introduced into the desired cell. The purpose of this study is to model and analyze the performance of lipid-polymer nanocarriers to improve the drug delivery process and cancer treatment [18-20].

Research background

Hardy Sayyahet al. (2107) used a magnetic pegylated liposome to load a hydrophobic drug and study-controlled drug release. In this study, it was predicted that magnetic pegylated liposomes would have a promising induction magnet in the presence of heat and would be used to combine chemotherapy and thermotherapy in the treatment of cancer [21].

Also, Al-Masari(2017)used scorpion venom as a therapeutic agent in a study on the efficacy of liposomal nanoparticles in the treatment of colon cancer. This in vitro study has reported the positive effect of using nanoparticles in improving the lethal function on intestinal cancer cell line [22]. Rodra Peri Tarab et al. (2018) investigated the synthesis of phytosomes with chitosan for ginger transmission in the treatment of respiratory infections both in vitro and in vivo. In this study, they successfully prepared ginger phytosomes by anti-fouling method and effectively loaded on chitosan to prepare a phytosomal drug delivery system. The characteristics of the drug composition in vitro showed a stable release of gingerol from the phytosome complex. In vitro studies also showed a dose-dependent concentration that confirmed the anti-cancer activity of the phytosome system in ginger [23].

Finally, it was shown that the combination of chitosan and phytosomes can be a good option for the treatment of respiratory infections through oral administration. Niknejad et al. (2018) investigated the ratio of lecithin to cholesterol, the time of formation and the ratio of aqueous and organic phases, which are of great importance for the efficiency of nanoliposomes [1]. They obtained the optimal conditions obtained from the preparation process by thin film hydration method; the ratio of cholesterol to lecithin was 7: 1, the formation time was 140 minutes and the ratio of aqueous phase to organic phase was 1: 4. The average size of metformin hydrochloride-based nanoliposomes based on lecithin and phosphatidylethanolamine were 52 and 83 nm, respectively. High stability was demonstrated during storage. Dave et al. (2019) investigated, synthesized, and described Celecoxib-loaded Peggy liposomal nanoparticles for biomedical applications. These nano-liposomes were prepared by thin film hydration method using different molar ratios of drug to lipids [4].

Celecoxib causes problems for the stomach when taken orally, but liposomes were able to provide a continuous combination of the drug and, after overcoming the problems caused by the drug, could be easily administered by injection [5].

Hassanzadegan et al. (2019) ran in vitro study of the anticancer effect of pegylated nanoliposome particles with carboplatin on brain cancer cell lines. The aim of this study was to evaluate the efficacy of liposomal nanocarriers containing the anticancer drug carboplatin. The effect of a platinum-based chemotherapeutic agent (carboplatin) is limited due to intracellular resistance. New therapeutic strategies are needed to improve the therapeutic effects of carboplatin. In this study, the reverse phase evaporation method was shown to be an effective method for the preparation of liposomes loaded with carboplatin. In addition, the physicochemical properties of carboplatin-containing nanoparticles were investigated. The effect of

nano-drug on A172 and C6 brain cancer cell lines showed increased cell death compared to free drug [6].

The results showed that carboplatin cell killing was associated with drug concentration and significantly increased for pegylated nanoparticles containing the drug. Zare et al. (2020) investigated pegylated liposomal nanoparticles containing autoposide using reverse phase evaporation method. The nanoparticles prepared by this technique were examined for size, size distribution, zeta potential, encapsulation efficiency and cell lethality [7]. The results showed that the synthesized nanoparticles had high encapsulation efficiency and the effects of cell lethality and nanoparticle efficiency on lung cancer cell lines were improved.

Chengchi et al. (2020) investigated the synthesis of nanophytosomes for the synthesis of silymarin phospholipids with increased bioavailability and protective effect on the liver [8]. They found that the homogenization process could significantly improve digestion and absorption in the gastrointestinal tract without causing molecular interaction. By combining phytosome and nanosuppression technologies, a drug delivery system called silymarin phospholipid nanoparticles was developed using advanced bioavailability of silymarin in both in vitro and in vivo conditions and has been shown to improve performance.

Shirzad et al. (2019) in a study investigated the role of polyethylene glycol size in cell killing and release of pegylated nanoparticles containing cisplatin. In similar studies, high molecular weight polyethylene glycol (Mw) is commonly used to coat liposomes. Experimental results showed that PEGs with higher molecular weight usually show better activity in vitro. Also, the percentage of cisplatin released from Pegylenanoliposomal cisplatin and free cisplatin after 35 hours were 46% and 97%, respectively. 64% more were reported [8].

Experiments related to the synthesis of monolayer nano liposomes

Synthesis of cisplatin-labeled pegylated liposomal nanoparticles

In this section, nanoparticles were synthesized by reverse phase evaporation. First, lecithin, cholesterol, polyethylene glycol 2000, DSPE-mPEG2000 and cisplatin were dissolved in 50 ml of 96% ethanol with a molar ratio of 1: 1: 1: 7: 10. Then a rotary evaporator was used to remove the solvent at 37 ° C and 100 rpm. Then a volume of 25 ml of phosphate buffer solution was added to the film formed on the bottom of the test balloon and the resulting mixture was suspended overnight at 40 ° C using a stirrer. Sonike operation (ultrasound) was performed for further homogenization by probe sonicator for 12 minutes non-intermittently. Because of the potential for damage to the synthesized nanodrates at high temperatures, the test vessel was placed in a cold-water bath. Finally, the mixture was stored in the refrigerator for 4 hours at 4 °C.

Non-drug or blank nano-liposomes were prepared in the same way, except that they were not added to the supra-drug medium. We checked the amount of drug loaded to check the amount of drug loaded.The standard curve was used via spectrophotometric method. Thus, 6 drug concentrations of cisplatin equal to 0.05, 0.1, 0.3, 0.5, 0.8 and 1 mg / ml were prepared in phosphate buffer, then the amount of absorption of each concentration relative to the buffer was prepared [3].

Drug-free phosphate is calculated as blank three times at a wavelength of 301 nm, thus obtaining an absorption and concentration curve. In the next step, the suspension containing the drug is centrifuged (17,000 rpm, 4 ° C for half an hour) and the supernatant is removed. By reading the absorption of the supernatant and using the standard curve, the amount of drug in the supernatant is determined. Then, the amount obtained is subtracted from the amount of drug

used, and thus the amount of drug available or loaded into the nanoparticles is obtained. The load and the amount of encapsulation are obtained using two equations (1) and (2).

$$\mathbf{EE}(\%) = \frac{(\text{amount of drug carrier})}{(\text{amount of feed initially})} \times 100 \quad (1)$$

$$\textbf{Loading efficiency}\ (\%) = \frac{\left(\text{weight of drug in nanoparticle (mg)}\right)}{\left(\text{weight of nanoparticle (mg)}\right)} \times 100 \quad (2)$$

Investigation of drug release from nanoparticles

The dialysis bag technique was used to evaluate the release kinetics of the drug. For this purpose, after calculating the drug loaded in the nanoparticles, some precipitate of nanoparticles containing the drug was poured into 5 ml of phosphate buffer to be suspended again and used for other tests. Then, to check the release of the drug, 1 ml of the suspension was poured into a dialysis bag with 13 kDa cut-off (made by Sigma) and after closing both sides of the bag, it was immersed in 20 ml of phosphate buffer solution at 37 °C for 120 h at 120 rpm. In the measurement stage, ICP-OES was used to measure the amount of drug released in phosphate buffer solution by removing 2 ml of ambient phosphate buffer at different intervals (from 1 to 48 hours) and 2 ml of buffer [9].

Fresh phosphate was substituted and then the drug release pattern from nanoparticles was calculated using the cumulative release curve. Finally, using the mathematical model in accordance with the geometric shape of the nanoparticles produced, which are based on the structure of the shell and sphere (Shell and Core), as well as the relationships in the field of drug release rate, the necessary calculations were performed. After performing the relevant calculations, the drug release rate and penetration coefficient were investigated [4].

Cytotoxicity of formulations

In order to evaluate cell viability, cisplatin-free drug formulations, cisplatin-containing nanoliposomes and cisplatin-containing pegylated nanoliposomes were used by MTT assay and two Hep-G_2 liver cancer cell lines and KATO III stomach. In summary, these two cell lines were poured at a concentration of 10,000 cells per well in 96-well plates. Then, in RPMI 1640 medium with 5% carbon dioxide, 10% fetal calf serum, 1% sodium pyruvate and/ or. Percentage of the combination of penicillin, antibiotics and glutamine was cultured at 37 °C and after 24 hours the culture medium was replaced with culture medium containing formulations in different concentrations and incubated for 24, 48 and 72 hours. Then, MTT solution with a concentration of 4 mM per well was added and after 3 hours, MTT solution was poured out and 100 l of 100% isopropanol was added to it. After 15 minutes and dissolution of formazan crystals, the amount of dye adsorption produced at 570 nm was read with Alizairder and the percentage of cell viability was calculated by dividing the amount of sample uptake by the amount of control adsorption [1]. Cytotoxicity of formulations cell viability of two formulations of pegylated nanophytosomes loaded with cisplatin and glycyrrhizic acid, uncoagulated nano phytosomes containing these two drugs and also free drug cisplatin was performed by MTT method in the presence of two colorectal cancer cell lines $(DLD)^{-1}$ and LIM-2405) were

determined,explaining that the cells were poured into 96 plates with a density of 10,000 cells in each well. The cells were then cultured at 37 ° C with 5% carbon dioxide in RPMI 1640 medium containing sodium pyruvate (1%), 10% fetal calf serum and 0.5% of the combination of glutamine and streptomycin glutamine antibiotic. In the next step, 4 mM of MTT solution was added to each well for three hours and the cells were treated with both formulations plus free cisplatin at different concentrations (1, 10, 50, 100 and 150 µM). In addition, the concentration used to treat 50% of cancer cells for each formulation was evaluated with the free drug cisplatin (IC50) after 24 hours of incubation. To calculate this factor, BIOTECH-USA ELISA reader located in Pasteur Institute of Iran was used [2].

Evaluation of cell proliferation potential Proliferation Cell Assey was performed to evaluate the proliferation rate of DLD-1 and LIM-2405 cell lines, in which a tetrazolium-1 (WST-1) assay kit was used to assess proliferation. Cells were cultured at 10,000 cells in each well in 96 plates for 24 hours. The cells were then treated with the free form of cisplatin, cisplatin and glycyrrhizic acid-loaded nanophytosomes, as well as cisplatin-loaded nano-phytosomes loaded with cisplatin and glycyrrhizic acid for 24 hours [3].

All treatments were performed at three concentrations of 50, 100 and 150 µM. In this method, untreated cells were considered as negative control and cisplatin-treated cells were considered as positive control. After the treatment period, 10 µl of WST-1 reagent was added to each well and incubated at 37 ° C for 1 hour. Cell proliferation was measured by absorption at 450 nm with a microplate reader. Modeling of effective parameters on drug release from nanoparticlesis used. This modeling focuses mainly on the penetration control mechanism in the drug release process based on mathematical modeling approaches to describe and estimate drug release from liposomal nanocarriers and simulate it using MATLAB software to study and differentiate the effect of each [4].

Factors are made on the drug release profile. As mentioned, identifying specific and complex mechanisms in the release process, as well as identifying the relevant characteristics and distinguishing between them by understanding a common mechanism and at a given time is more important. The most common design for achieving a controlled drug is to create a drug in nanoparticles. Therefore, the polymer used for this purpose can be hydrophobic or hydrophilic and based on the nature of the drug, and can also be compatible with various mechanisms of controlled release systems for drug delivery [5].

The geometry of the system in the drug-carrying matrix greatly affects the drug release profile. The diffusion profile equations are described by three different methods and using an analytical solution for unstable drug diffusion by Fick's second law of diffusion. In this study, our hypothesis is first, drug penetration and polymer relaxation, both of which are key factors in drug release rate, and second, partial absorption or solvent release rate, which is considered in equilibrium conditions. One of the most practical drug release mechanisms is the penetration control mechanism, which acts as a barrier by releasing the drug through the membrane and is evenly distributed in the biodegradable nanocarriers, which means that it is soluble in water. Nor is it for diffusion through the membrane that acts as a barrier is evenly dispersed in the biodegradable matrix, which means that it is not soluble.

In short, the nanoparticle diffusion mechanism occurs when the drug passes through the nanoparticles, which acts as a controlled diffusion system because the diffusion rate of the drug decreases with continued diffusion, which occurs when it turns out that the drug has traveled longer distances, which will lead to more time to release. Depending on the area of the matrix in which the drug penetrates primarily, the penetration control system can be classified into more

systems such as the reservoir and the matrix itself. The tank system consists of a drug tank surrounded by a polymer shell. In a drug-carrying matrix system, the drug is dissolved or dispersed in the matrix. In this study, it is assumed that the drug is dispersed in the matrix. In fact, this system is considered as an integrated solution matrix in which the loading ratio of the initial drug is higher than the solubility of the drug. Also, nanoparticles in the form of spheres and penetration are assumed to be homogeneous to help determine the penetration of drugs using existing theories [5].

Method

Using MATLAB software to apply equations to simulate matrix particle release behavior and display release curves to help understand the equation, and mathematical models and numerical simulation techniques to select the most appropriate design in drug delivery tools and rates. Drug release is effective. Infiltration is one of the most important processes in drug release and can be used by Fick's law as the best relationship, especially in matrix systems and uniform drug distribution in nanoparticles, to justify drug release even in the form of unsteady. For the release of a one-dimensional drug from the microsphere, the second law of fictitious penetration from Equation (3) is expressed:

$$\frac{\partial C}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left[Dr^2\frac{\partial C}{\partial r}\right] \quad (3$$

Where D and C are the penetration coefficient and drug concentration in the drug-carrying matrix, respectively. Boundary conditions are affected by the mass transfer process at the surface and volume of the surrounding system. Based on these conditions, there are three main points that are usually considered:

1) Resistance to mass transfer is negligible and the emission environment around it is extremely large (full sink conditions). This means that the concentration on the surface of the matrix (Cs) is constant ($Cs = K.C_b$ = constant at r = R) where, C_b is the concentration of the drug in the environment and K is the drug partition coefficient between the matrix and the environment.

2) The mass transfer resistance at the surface is limited and the volume around it is in perfect sink condition, which means that the concentration of the surrounding system is constant but the mass transfer coefficient determines the displacement of the surface concentration.

$$D\left(\frac{\partial C}{\partial r}\right)_{r=R} = h(C_{r=R} - KC_b) \quad (4)$$

3) The system around mass transfer is a limited volume and well stirred. This means that the concentration around the system changes over time and the surface resistance may or may not be negligible. As for matrix system, mathematical models are often valid for matrix systems and drug delivery tools based on biodegradable carriers. In these models, it is usually assumed that the drug is evenly distributed in the matrix carrying the indestructible drug. There are two possible cases: a) the initial loading of the drug is less than the solubility of the drug within the matrix (C0 <Cs), which becomes a dissolved or difficult-to-solve drug system, and b) the initial loading of the drug is higher than the solubility of the drug within the drug-carrying matrix (C0> Cs) indicates a dispersed drug system. Systems in which the drug is dispersed (C0> Cs) include: The drug-carrying matrix in a dispersed drug system thatcan be primarily divided into two parts. The first part is the "nucleus" in which the insoluble drug is present at a concentration of C0, and the second is the diffuser region in which the drug is dissolved and release occurs.

The distinction between the two regions is valid at C0> Cs, so the limited use of these mathematical models must be carefully considered so that C0 / Cs is not too large. Here, the "core" part differs from the "reservoir region" in the reservoir system because the former is a constant-thickness polymer region with a specific concentration of

drug charge (C0), while the drug in the reservoir region is not subject to the drug-carrying matrix.
The "core" area, on the other hand, can shrink because the drug has escaped through the infiltration process. For the controlled mathematical model of diffusion for a dispersed drug system (C0> Cs) on a flat, spherical plane was established by Higuchi on the assumption that the diffusion is quasi-stable.
The assumption of a planar system leads to a linear concentration profile of the drug in the infiltration zone, which is between the dissolution interface and the surface of the primary matrix. According to this assumption, the simplest and most popular version of the Higuchi equation for a flat system is easily obtained:

$$Mt = S\sqrt{(2C0 - Cs)CsDt} \quad (5)$$

Mt is the accumulated amount of drug released as a function of time and S is the surface area available for drug release into the environment. In the drug dispersion system, R is the outer radius and r '(t) is the radius of the internal interface between the nucleus (no penetration zone) and the matrix (penetration zone), which shrinks over time.

In the spherical system, it is assumed that the core region has a concentration of C0 and for the diffusion/ diffusion region, the quasi-stable concentration profile is in the form of relation (6):

$$\frac{C}{Cs} = \frac{r'}{r}\frac{(R-r)}{(R-r')} \quad (6)$$

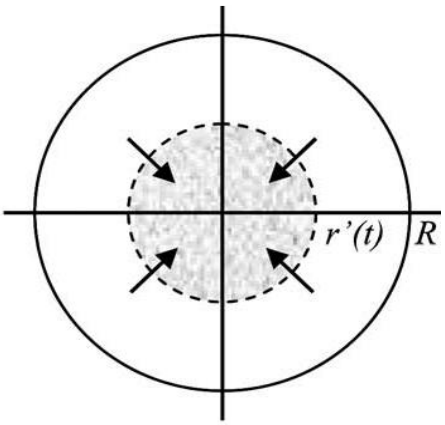


Fig. 1. Schematic representation of a drug-loaded sphere in a dispersed drug system

The integration of the mass-flux relation provides a relation (7) for the position of the moving interface (r') and time (t):

$$\mathbf{6DCsRt} = \mathbf{C0}\left(R^3 + 2r'^3 - 3Rr'^2\right) + Cs\left(4r'^2R + R^3\ln\frac{R}{r'} - R^3 - R^2r' - 2r'^3\right) \quad (7)$$

In the case of C0> Cs, this equation can be simplified and in the form of relation (8):

$$\frac{6DCs}{C0R^2}t = 1 - 3\left(\frac{r'}{R}\right)^2 + 2\left(\frac{r'}{R}\right)^3 \quad (8)$$

And when the observation time is long enough ($t \to \infty$) then the release ratio is given as Equation (9):

$$\frac{Mt}{M\infty} = 1 - \left(\frac{r'}{R}\right)^3 \quad (9)$$

Two other researchers, Quizumi and Panomsuk, used Higuchi's quasi-fixed method to obtain an approximate solution for releasing the drug from a sphere. With several series simplifications, a simple and explicit expression can be obtained for the amount of drug released as a function of time for a complete sync condition as described in Equation (10):

$$M_t = [1 - \left(1 - \frac{R - r'}{R}\right)^3 \left(1 - \frac{Cs}{C0}\right) + 3\frac{R - r'}{R}\left(\frac{Cs}{C0}\right) * \left[\left(a1 + \frac{a2}{2} + \frac{a3}{3}\right) - \left(\frac{a1}{2} + \frac{a2}{3} + \frac{a3}{4}\right)\right]\left(\frac{R - r'}{R}\right) \quad (10)$$

The concentration of drug at the matrix level (Cs) is related to the concentration of drug at the interface of the boundary layer (Ca) through the resolution coefficient K1 (Cs = K1.Ca).If there is no boundary layer or coating, then the drug concentration at the matrix surface (Cs) will be directly related to the drug concentration in the mass medium (Cb) (Cs = K.Cb). In this modeling, it is assumed that the drug penetration coefficient is constant, which is shown in Equation (11):

$$\frac{dC_A}{d} = \frac{d^2C_A}{dx^2} \quad (11)$$

We know that the drug release characteristics are significantly influenced by the system geometry in the matrices, here is an analytical method of the above equation for the release profile equations obtained in the spherical matrix:

$$\frac{Mt}{M0} = 1 - \frac{6}{\pi^2}\sum_{\pi=0}^{\infty}\frac{1}{\pi^2}\exp\left(\frac{-Dn^2\pi^2t}{R^2}\right) \quad (12)$$

Mt is the accumulated amount of drug released during time t and Mo is the initial amount of drug in the device. The parameter n is also a mock variable of the counter and R is the radius of the sphere.

Modeling results

One of the major challenges in delivering anticancer drugs is the poor solubility of many of them in water. Due to this low solubility of the drug and low diffusion in the drug-carrying matrix, the release profile is generally very slow.

The use of nanoparticles provides a way for a slow release profile by providing a much larger surface area, but is compromised by slower diffusion into the drug-carrying matrix due to its more compact structures. For an integrated system with uniform drug distribution by the drug-carrying matrix, release is generally managed by infiltration or erosion mechanisms.

Drug release from common nanoparticles is mainly due to diffusion, drug dissolution and subsequent surface erosion or mass destruction/ decomposition. The effective diffusion coefficient of the drug follows the combined effects of diffusion through particle pores and penetration through an intact matrix and is a function of the curvature and porosity of the nanocarrier.

Harland et al. (2018), developed the first dissolution model for the drug-carrying matrix that undergoes mass erosion. The model is applied for both states of unlimited and finite mass transfer boundary conditions at the matrix level. This model calculates the amount of penetration that follows Fick's law plus the dissolution of the solute in the pores filled with liquid. As mentioned, the effective physical penetration is calculated based on the continuous formula using the effective diffusion in the fluid in the fine pores. Therefore, the drug transfer model is expressed as follows:

$$\frac{\partial C}{\partial t} = De\left(\frac{\partial^2 C}{\partial r^2} + \frac{2}{r}\frac{\partial C}{\partial r}\right) + k(\varepsilon Cs - C) \quad (13)$$

C and De are the drug concentrations and effective penetration of fluid-filled pores, respectively. k is the dissolution constant of the drug and ε is the degree of porosity of the drug-carrying matrix and ε. Cs is the amount of saturation concentration of the drug in solution found in the pores. The second sentence on the right is the term of dissolution, which can be ignored when the initial load of the drug is less than its solubility.

In the case of non-constant diffusion, it is assumed that the diffusion coefficient is dependent on the exponential concentration and also the mass

transfer on the surface is displacement and under complete sink conditions. By performing dimensionless analysis with natural scale so that all variables are limited between 0 and 1, a new dimensionless number, the dissolution/ diffusion number (Di), is defined as follows:

$$\mathbf{Di} = \varphi_s^2 = \frac{kR^2}{De} \qquad (13)$$

Following the chemical engineering view, Di is the square of the Thiele modulus (ϕs / Thiele modulus) because a similar phenomenon is observed when reaction and diffusion occur together, although this occurs within the catalyst. A relation for the partial release of a drug for unlimited mass transfer at the surface is expressed as follows:

$$\frac{Mt}{\varepsilon Cs\frac{4}{3}\pi R^3} = 6\sum_{n=1}^{\infty}\frac{(Di+n^2\pi^2)Di\tau+n^2\pi^2[1-\exp[-(Di+n^2\pi^2)\tau]]}{(Di+n^2\pi^2)^2} \qquad (14)$$

Dimensionless time is defined as τ = De * t / R2.On the other hand, under transient mass transfer conditions, the Sherwood number, which is the ratio of the transfer mass to the penetration rate, appears in the relation:

$$\frac{Mt}{\varepsilon Cs\frac{4}{3}\pi R^3} = 6Sh^2\sum_{n=1}^{\infty}\frac{(Di+\alpha_n{}^2R^2)Di\tau+\alpha_n{}^2R^2[\exp[-(Di+\alpha_n{}^2R^2)\tau]-1]}{(Di+\alpha_n{}^2R^2)^2[\alpha_n{}^2R^2+Sh(Sh-1)]} \qquad (15)$$

Where αn is the roots of the higher-order Bessel equation, and at much longer release times of the drug during which dissolution controls the workflow, show that the release rate of the drug is merely a first-order equation:

$$\mathbf{Mt} = \frac{2\pi R^3\varepsilon C_s}{\sqrt{k}}\left[\sqrt{\frac{De}{R}}\coth\left(R\sqrt{\frac{k}{De}}\right)-\sqrt{k}csc^2h\left(R\sqrt{\frac{k}{De}}\right)\right]+8\pi R\varepsilon C_sDe$$
$$*\left[\frac{kR}{2De}\sqrt{\frac{De}{k}}\coth\left(R\sqrt{\frac{k}{De}}\right)-\frac{1}{2}\right]t$$

Regarding hydrophobic drugs such as cisplatin, the penetration rate of the drug in liposomal matrices has been reported in various articles from 10-15 to 10-20 square meters per second. The release profile of highly hydrophobic drugs from nano-liposomal systems is mainly influenced by the drug penetration mechanism. In the case of hydrophobic drug molecules, the dissolution constant will generally be very small due to the very low solubility of the drug in aqueous medium.

Therefore, the mechanism of drug dissolution has little effect on drug release and the dissolution rate constant (k) is very small compared with the intensity of penetration. In this regard, although it may be expected that the drug penetration from the drug-carrying microspheres be very slow, the release time scale is still faster than dissolution due to the small size of the nanoparticles, and therefore the drug retained by penetrating the case matrix Comment is released. Table 1. shows the estimated time for drug release considering the range of 10^{-15} to 10^{-20} square meters per

second for penetration coefficients from microparticle size to nanoparticles.

Table 1. Penetration time scale (t / τ) using the Harland controlled dissolution relationship, drug release from microspheres and nanospheres containing non-swellable drug.

Matrix size of hydrophobic drug carrier	**De Effective penetration coefficient** (square meters per second)	
	De =10-15	De =10-20
	t/τ (s)	t/τ (s)
$10_{\mu m}$	104*2/5	109*2/5
$1_{\mu m}$	102*2/5	107*2/5
100 nm	2/5	105*2/5

Table 2. Experimental data extracted from papers to test the effective release rate/ diffusion coefficient of a spherical nanocarrier matrix particle based on a diffusion control mechanism.

Formulation	**Effective penetration coefficient** (Square centimeters per second)	**Size** (nanometers)	**Percentage of drug loading**
C1	$2 * 10^{-18}$	1000	2
C4	$8 * 10^{-21}$	310	6
C7	10^{-21}	100	12

Table 3. Different formulations for effective release rate/ diffusion coefficient of spherical nanocarrier matrix based on diffusion control mechanism.

Formulation	**Effective penetration coefficient** (Square centimeters per second)	**Size** (nanometers)	**Percentage of drug loading**
C1	$2 * 10^{-18}$	1000	2
C2	$8 * 10^{-21}$	1000	6
C3	10^{-21}	1000	12
C4	$2 * 10^{-18}$	310	2
C5	10^{-21}	310	2
C6	$8 * 10^{-21}$	310	2
C7	$2 * 10^{-18}$	100	12
C8	$2 * 10^{-18}$	100	6
C9	$2 * 10^{-18}$	100	2

A simple diffusion model based on the Fick relation can be expected to significantly differentiate the release profile with changes in particle size. In order to evaluate the effect of penetration, size and loading percentage of the drug, we fixed two parameters and examined another change. When calculating the drug release profiles in the penetration control system for the spherical matrix of the drug carrier, by keeping the diffusion coefficient constant and changing the particle size from 100 to 1000 nm, we see an increase in drug release rate with decreasing nanocarrier size and inverse relationship between these two parameters.

Then, the size of the nanocarrier and the rate of drug loading and changes in the diffusion coefficient were investigated, which clearly showed that with increasing the release rate, the

penetration coefficient also increased with a direct relationship between them.

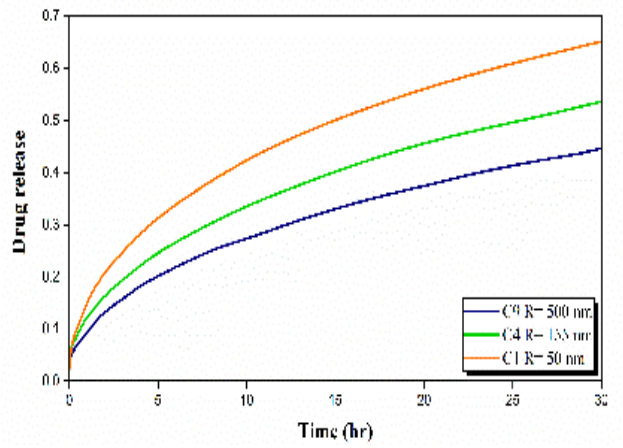


Fig. 2. The diffusion kinetics of three different nanoparticles of different sizes for spherical geometry with diffusion coefficient and constant drug loading rate (each color represents the effect of radius size on release kinetics)

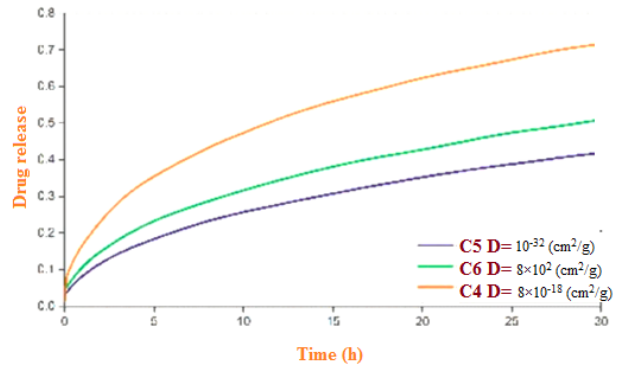


Fig. 3. Penetration kinetics of three different particles with different values of diffusion coefficient for spherical geometry with radius and constant loading of the drug (each color represents the effect of diffusion coefficient on release kinetics)

The results after keeping the particle radius and diffusion coefficient constant and changing the loading rate clearly showed that when the loading of the drug is increased to 12%, the total drug release is significantly higher after a long time compared with formulations withless load.

Conclusion

Cancer is one of the most common causes of death today.

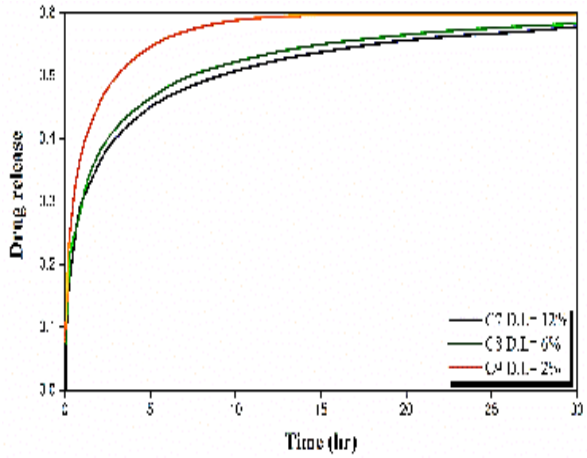


Fig. 4. Penetration kinetics of three different particles with different drug loading values for spherical geometry with constant penetration coefficient and radius (each color represents the effect of drug loading on release kinetics)

According to the National Cancer Institute, the prostate, breast, lung and intestine are the most common types of cancer, respectively. Also, the results of the most extensive and recent studies on 32 types of cancer in 195 countries show that the number of cancer deaths in Iran almost doubled from 1990 to 2016, but according to available documents, the cancer tsunami has not yet occurred in Iran. On the other hand, cancer mortality rates vary depending on when we diagnose cancer and also people's access to diagnostic and treatment services.

In general, three treatments are used to treat cancers, including surgery, radiation therapy, and chemotherapy, each with its own advantages and disadvantages. Different treatments used in the treatment of cancers are associated with their own side effects because in these types of methods, in addition to cancerous tissue in some areas, healthy tissue is also damaged. The type and extent of side effects vary depending on the treatment method, duration of use and amount. The description of drug releases is very complex, as in the case of nanoparticle-based drug delivery systems. The results of drug release through diffusion from spherical geometry and simulation

of diffusion control system mechanism for drug-carrying nanoparticles were discussed here. The purpose of this modeling was to evaluate the relationship between carrier particle size and drug diffusion coefficient when using the diffusion model. In order to validate the model, the laboratory results available in several papers for nanoparticles with a diameter of 100 to 1000 nm and previous models based on the diffusion model have been used. Based on previous studies, it can be clearly seen that when drug loading is increased to 12%, the total drug release fraction after a long time is much lower than lower loading formulations. A possible explanation for this phenomenon of drug retention as a dispersed molecular phase in the drug-carrying matrix is lower at drug loadings. When the drug load is too high (for example, 30% by weight), then the drug can exceed the solubility of the drug in the drug-carrying matrix and small drug crystals are heterogeneously embedded in the nanocarrier wall.

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