CONTROLLED DRUG RELEASE FROM A 3D PRINTED TABLET

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Abstract:

Introduction: In the last couple of decades, we have been working on the development of advanced drug delivery systems, which include the use of carriers of medically active substances, which enable precise and efficient therapy followed by reduction of the occurrence of side effects. The aim of this paper was to demonstrate the possibility of controlling the release of a drug substance using different carriers.

Material and methods: The experiment was performed on a 3D bioprinter Cellink +. The samples were printed from gelatin-based hydrogels. A solution of 15% concentration was used to make the hydrogel. Spectrophotometry was used to determine clindamycin.

Results and discussion: The concentration was determined by measuring the absorbance, at a wavelength of 210 nm at which clindamycin shows absorption. The standard curve was obtained by a series of dilutions and the equation was obtained from this curve. Based on those results Genetic algorithms method was used for creating a computation model for future in-silico testing.

Conclusion: Computation models based on Genetic algorithms provide a very good estimation of a drug release on time on and have the potential for in-silico testing of drugs.

Keywords: 3D print, clindamycin, genetic algorithms

1. Introduction

In the last couple of decades, we have been working on the development of advanced drug delivery systems that include the use of carriers of medically active substances, which enable precise and efficient therapy followed by reduction of the occurrence of side effects. By designing the properties of the carrier, it is possible to achieve control over the place where the drug will be released, the moment of its release, the time interval during which the drug will be released, as well as the amount of drug that will be released. This increases the accuracy and control of treatment, and thus increases efficiency, reduces the duration of treatment and alleviates or completely eliminates the possibility of side effects [1].

An ideal way of modern delivery of antibiotics is gradual release and action at a specific place in the body. The main advantages of such systems are targeted local drug delivery, control over the concentration of the drug that is released over time, lower concentration of the drug required to treat infection, minimisation or complete absence of side effects, improving treatment efficacy [2]. Clindamycin is a semi-synthetic derivative of pyranoside. It belongs to the group of lincosamide antibiotics. It acts bacteriostatically by binding to the 50S subunit of the bacterial ribosome, thereby inhibiting protein synthesis. The effectiveness of

clindamycin depends on the time during which the concentration of the active substance in the blood is above the minimum inhibitory concentration for a given pathogen [3]. It is mostly used for anaerobic bacterial infections in the abdomen and small pelvis and for the treatment of lung abscesses. It has also been shown to be effective in the treatment of periodontal and pharyngeal infections [4] – [10]. Analysis of the change in concentration over time of a drug, in this case clindamycin, is a process that is well known but requires a lot of manual work and testing on samples of different concentrations. The development of computer methods has made it possible to simulate these analyses on a computer and thus save time on testing and materials. In order for computer methods to be as accurate as possible and correspond to the real system, it is necessary to create adequate computer models. One of the ways to translate a real model into an adequate computer model is to use a genetic algorithm (GA), a type of parallel heuristic search method [11], [12], [13]. In this paper, we use the GA approach to fit the concentration-time curve and calculate the square error of the overlap of real models with the newly created GA model. We conclude with general observations about the GA method.

2. Material and methods

2.1 3D printing of tablets

The experiment was performed on a 3D bioprinter Cellink +. The samples were printed from gelatin-based hydrogels. Fifteen percent gelatin solution is used for the hydrogel. The gelatin was mixed with water at room temperature, and then the mixture was heated to 45°C. An aqueous solution of clindamycin at a concentration of 1 mg/ml was incorporated into the gelatin solution. Spectrophotometry was used to determine clindamycin.

Fig. 1. 3D printed tablets of clindamycin

2.2 Approach to curve fitting with genetic algorithm

The goals of curve fitting is to find functional coefficients (i.e. parameter values) that minimise the overall error over the collection of data points under consideration. Curve fitting becomes an optimisation problem over the set of given data points once a functional form and an error metric have been chosen. Given their effectiveness as global optimisation approaches for both continuous functions and combinatorial issues, genetic algorithms are well suited to curve fitting when structured as a parameter selection problem. We begin with a brief overview of genetic algorithms as search and optimisation approaches, followed by a description of our genetic curve fitting formulation. Explanation of GA methods for fitting curve are presented by authors in [14].

3. Results and discussion

The concentration was determined by measuring the absorbance at a wavelength of 210 nm, at which clindamycin shows absorption. The standard curve was obtained by a series of dilutions (0,1; 0,15; 0,2; and 1 mg/ml) and the results from 1mg/ml were obtained from this

curve and used for fitting with GA methods. Figure 2 shows a comparison of real measured drug concentration changing in time vs estimated results provided by the A methods.

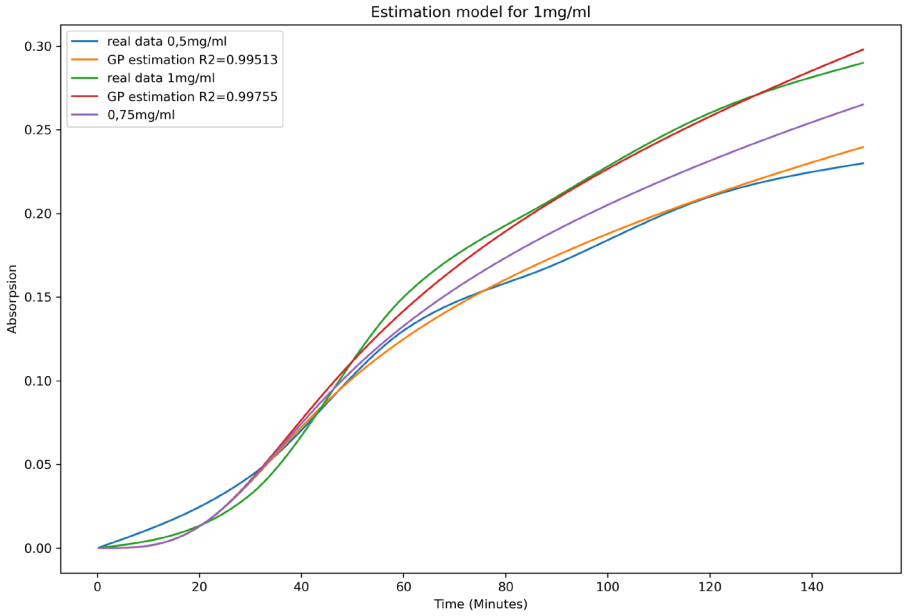

Fig. 2. Standard curve vs GA solutions

We examined two tablets using the GA method and the correlation with the real concentration of the drug. For this purpose, we developed specific GA algorithms and software. This method demonstrated a very good correlation between the real curves and estimated ones. In both cases, the coefficient of determination was very close to 1 (0.995 and 0.997). Based on these results, we can conclude that GA methods have very good estimation potential and can, therefore, be used for the estimation of drug release of some other concentrations, as presented in Figure 2 the estimation results for 0.75mg/ml.

Figure 3 shows the tablet that started releasing the drug. Absorbance was measured every minute. Based on the measured absorbance and using the equation, the concentration of the drug released was calculated.

Fig. **3.** The tablet that started releasing the drug

4. Conclusions

In this way, it is possible to achieve control over the concentration of the released drug, thus achieving the optimal concentration at the target site. It is expected that the application of modern drug delivery systems would overcome the shortcomings of traditional treatment. Computational models created on GA methods show very good estimations of drug release concentrations in time and have a huge potential for future in-silico testing. These methods could simplify the process of modeling tablets and with the use of 3D printing open the new way to targeted therapy.

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