Acta Universitatis Apulensis,
ISSN 1582-5329, 2011,
Special Issue on Understanding Complex Systems,
Eds. Barna Iantovics, Ladislav Hluchý and Roumen Kountchev

MATHEMATICAL MODEL FOR TSPP DRUG-DELIVERY IN NANOMEDICINE

Rodica Mariana Ion, Adriana Filip,
Simona Clichici and Adriana Muresan

Abstract. Helping improve humanity is one of the promises of nanotechnology and nanomedicine. This paper will highlight some of the research findings in the nanomedicine area by creating a pharmacokinetic model of 5,10,15,20-tetra-(4-sulfonatophenyl)porphyrin (TSPP) used as sensitizer in photodynamic therapy.

Keywords: *nanomedicine, photodynamic therapy, TSPP, mathematical model*

2000 *Mathematics Subject Classification*: 05C65, 62H30.

1. Introduction

The efficiency of drug delivery to various parts of the body is directly affected by particle size. Nanostructure mediated drug delivery, a key technology for nanomedicine, has the potential to enhance drug bioavailability and a reduced drug toxicity and more efficient drug distribution. Nanostructured drug carriers help to penetrate or overcome these barriers to drug delivery. Transcutaneous permeation occurs with particles around 100 nm and 50 nm in size, respectively. Advantages of nanostructure-mediated drug delivery include the ability to deliver drug molecules directly into cells [2] and the capacity to target tumors within healthy tissue. For example, DNA and RNA that is packaged within a nanoscale delivery system can be transported into the cell to fix genetic mutations or alter gene expression profiles. Nanoscale drug delivery architectures are able to penetrate tumors due to the discontinuous, nature of the tumor microvasculature, which typically contains pores ranging from 100 to 1000 nm in diameter. The tumor tissue types can be selectively targeted by creating drug delivery nanostructures greater than the intercellular gap of the healthy tissue but smaller than the pores found within the tumor vasculature.

For a precise control of the drug carrier architecture, the release of the drug can be tuned to achieve a desired kinetic profile. Three of the most common kinetic profiles are zero order, first order, and Higuchi; these are expressed mathematically in Eq. 1, 2, 3. The ideal release profile for most drugs would follow a steady release rate so that the drug levels in the body remain constant while the drug is being administered. More recent transdermal drug delivery mechanisms follow the Higuchi model [3].

$$Zero\ order : D_t = D_0 + K_0 t \tag{1}$$

$$First\ order : lnD_t = lnD_0 - K_1 t \tag{2}$$

$$Higuchi\ order : D_t = D_0 = K_H t^{1/2} \tag{3}$$

Where:

- D_t is the amount of drug released at time t;
- D_0 is the initial amount of drug released, result of initial rapid release;

- k_0 is the zero-order release constant;
- k_1 is the first-order release constant,
- k_H is the Higuchi release constant

Photodynamic therapy (PDT) is a promising method for treating malignant tumors combining the action of a special dye - photosensitizer (PS), oxygen, and radiation on biological tissues. Treatment consists of several sequential stages: injection of the PS (intravenous or local), leaving it for up to 24 h, and irradiation for 15-20 min. In general, any coherent or incoherent light source with a proper spectrum can be used for therapy. The most widely used devices are continuous nonionizing lasers with a power density of up to 250 W/cm^2. The wavelength is, as a rule, within the limits of the "therapeutic window" of 600-1200 nm. In this case, the light penetrates deeper into the tissue compared to the remaining part of the visible spectrum. PDT is based on the photodynamic action (PA) affecting living structures, which was discovered at the end of the 19th to the beginning of the 20th centuries. At the molecular level destruction of cancer cells by PDT occurs through the formation of singlet oxygen (reaction of the second kind) - a very active oxidizer.

This paper will highlight some of the research findings in the nanomedicine area and a pharmacokinetic model of 5,10,15,20-tetra-(4-sulfonatophenyl)porphyrin (TSPP) used as sensitizer in photodynamic therapy.

2. Materials and methods

5,10,15,20-tetra-(4-sulfonatophenyl)porphyrin (TSPP), Figure 1, was synthesized and purified in the laboratory after the literature methods [4]. It was solubilized in water at 10-4 M concentration. All the stock solutions were stored at 4^oC in the dark and used in the 14 days interval.

3. Results and discussion

3.1. PDT protocol

50 male Wistar rats, weighting 200±20g were used for this study. They were anesthetized (90 mg kg^{-1} ketamine, 10 mg kg^{-1} xylazine, i.p) and grafted on the shaved right thigh with small fragments of Walker tumor. Ten rats with Walker carcinosarcoma represented the control group; the others underwent PDT with TSPP. Once the tumor reached 1 cm^3 it was treated with PDT.

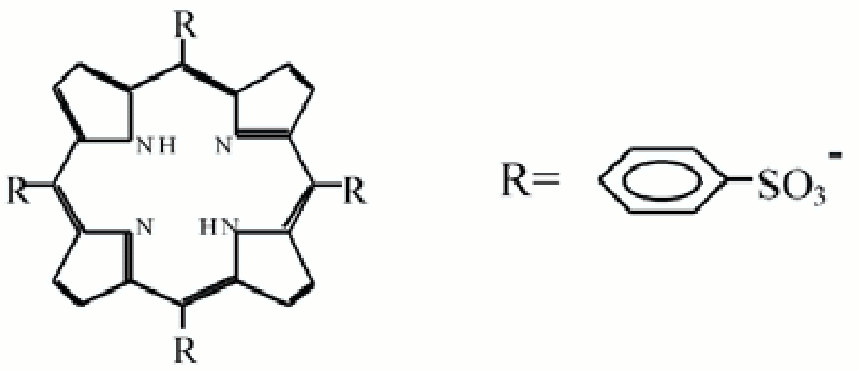


Figure 1: The chemical structure of TSPP

3.2. TSPP concentration in tumor homogenate

The tumor was homogenised with a solution containing 80% sucrose 0,25 M and 20% NaOH 0,1 N. In the supernatant obtained after centrifugation TSPP was determined fluorimetrically using a Perkin-Elmer spectrofluorimeter (excitation 412 nm and emission 643 nm), using a calibrating curve.

3.3. A Pharmacokinetic Model of TSPP

TSPP is intravenously injected at 2 mg/kg over a period of five minutes, and it attains a high saturation level from 24 to 36 hours after injection. The 12 hour period between the 24 th and 36th hour is called the treatment window, and at some time within this period a physician focuses a 630nm light on the targeted area. Different tissues absorb and expel substances from the blood at different rates, and hence the concentration of TSPP varies from tissue to tissue [5,6]. Results show that maximum tumor TSPP concentration levels were achieved at approximately 24 hours after administration. We model C_I with the following first order, linear differential equation:

$$\frac{dC_1}{dt} = \frac{k_0}{v} - kC_1 \tag{4}$$

Where:

- C_I is the plasma concentration during injection;
- k is the rate of elimination;

- k_0 is the rate of infusion;
- V is the volume of distribution.

$$C_1 = \frac{k_0}{v_k}[1 - e^{kt}] \tag{5}$$

So, assuming that the infusion ends at time $\gamma = 0.083h^{-1}$, or 5 minutes, we have that

$$dC_A/dt = -kC_A \tag{6}$$

from which we conclude that:

$$C_A = C_1(\gamma)c^{kt} = k_0[1 - e^{kt}]e^{-k(t-\gamma)} \tag{7}$$

Where C_A is the plasma concentration after infusion.

$$t_{\frac{1}{2}} = \frac{ln(2)}{k} \tag{8}$$

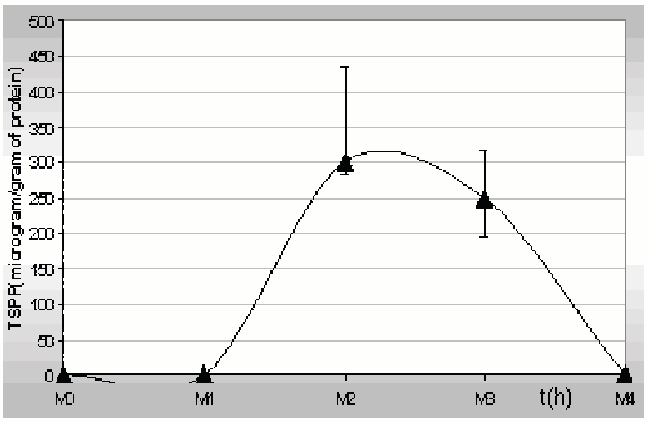
The infusion rate k_0 is based on the fact that the drug is injected at 2mg/kg over a period of 5 minutes. Under such conditions, we have that 0.4 mg/mouse of TSPP are delivered in 5 minutes, and thus k_0 is 4.8 mg/h. The rate of elimination, k, is calculated by solving:

where the half-life for TSPP is $t_{1/2}$= 336 hours. Hence, k= 0.00206 h^{-1}.

A computational reaction framework was used to model drug release in the tumor, and intracellular uptake and binding [7,8]. Numerical simulations suggest that zero-order drug release is the most applicable in this case, the slow phase corresponds to a plateau drug concentration that is proportional to the ratio of drug release from the tumor.

4. Conclusions

This paper will highlight some of the research findings in the nanomedicine area by creating a mathematical model for pharmacokinetic activity of TSPP used as sensitizer in photodynamic therapy. Results show that maximum tumor TSPP concentration levels were achieved at approximately 24 hours after administration.



M_0=controls;
M_1=5 hours;
M_2=24 hours;
M_3=48 hours;
M_4=> 48 hours.

Figure 2: Dynamic curve of TSPP tissue concentration within the tumor (Points represent absolute median TSPP concentration levels)

References

[1] LaVan DA, Lynn DM, Langer R. Moving smaller in drug discovery and delivery. Nat Rev Drug Discovery 2002;1:77-84.

[2] LaVan DA, McGuire T, Langer R. Small-scale systems for in vivo drug delivery. Nat Biotechnol 2003;21:1184- 91.

[3] Costa P, Sousa Lobo JM. Evaluation of mathematical models describing drug release from estradiol transdermal systems. Drug Dev Ind Pharm 2003;29:89-97

[4] Ravi Kumar MN. Nano and microparticles as controlled drug delivery devices. J Pharm Pharm Sci 2000;3:234- 58.

[5] Hussain N, Jaitley V, Florence AT. Recent advances in the understanding of uptake of microparticulates across the gastrointestinal lymphatics. Adv Drug Delivery Rev 2001;50:107- 42.

[6] R.M.Ion, R. C. Fierascu, and I. Dumitriu, Photonic metallic nanostructures in photodynamic therapy, Advanced Topics in Optoelectronics, Microelectronics, and Nanotechnologies IV, Proceedings of the SPIE, 7297, pp.72970H-729723 (2009).

[7] RM Ion, New trends in photodynamic therapy-review, in "Aspects of Photodynamic medicine" Biomedicine Engineering Acta, 3/2008, pp.123-159, H.Podbielska, A.Sieron, W.Strek, (Eds.), Wroclaw, Poland, 2008;

[8] R.M.Ion, L. Maresca, D. Migoni, F.P. Fanizzi, Porphyrin - Cis-Platin drug system for HeLa cells photodynamic, International Journal On Advances in Life Sciences, 1(1), 2009, pp.36-45.

Rodica Mariana Ion
National Reserch and Development Institute of Chemistry and Petrochemistry - ICECHIM Bucharest, Romania
Valahia University, Targoviste, Romania
e-mail:*rodica_ion2000@yahoo.co.uk*

Adriana Filip, Simona Clichici, Adriana Muresan
Physiology Department
University of Medicine and Pharmacy "Iuliu Hatieganu"
Cluj-Napoca, Romania