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Iontophoresis of the eye - a computational approach

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Abstract: *Iontophoresis is an effective, non-invasive method of intraocular drug delivery based on electric current. However, it has many limitations that can be addressed by effective computational models based on both machine learning (a data-driven approach) and other artificial intelligence methods and techniques. To date, computational models using AI/ML are lacking, including for the iontophoresis mechanism itself. Their wider use would help facilitate the delivery of drugs to the eye, which remains a major challenge due to the multiple barriers in the eye. The aim of this paper is to explore the feasibility of developing a computational model for ocular iontophoresis using available AI methods and techniques.*

Keywords: *computational model, machine learning, iontophoresis, eye, drug delivery.*

Jonoforeza oka – podejście obliczeniowe

Słowa kluczowe: *Jonoforeza jest skuteczną, nieinwazyjną metodą wewnątrzgałkowego podawania leków opartą na prądzie elektrycznym. Ma jednak wiele ograniczeń, które można rozwiązać za pomocą skutecznych modeli obliczeniowych opartych zarówno na uczeniu maszynowym (podejście oparte na danych), jak i innych metodach i technikach sztucznej inteligencji. Do tej pory brakuje modeli obliczeniowych wykorzystujących AI/ML, w tym dla samego mechanizmu jonoforezy. Ich szersze zastosowanie pomogłoby ułatwić dostarczanie leków do oczu, co pozostaje poważnym wyzwaniem ze względu na liczne bariery w oku. Celem artykułu jest zbadanie wykonalności opracowania modelu obliczeniowego dla jonoforezy ocznej przy użyciu dostępnych metod i technik sztucznej inteligencji.*

Słowa kluczowe: *Model obliczeniowy, uczenie maszynowe, jonoforeza, oko, dostarczanie leku.*

1. INTRODUCTION

The human eye is only ostensibly an organ that is easy to directly apply drugs in a controlled and tolerable manner. In ophthalmology, the delivery of drugs to ocular lesions requires the minimisation of their systemic and local toxic effects (of the drug active ingredients as well as the method/methods of administration), with existing anatomical and physiological barriers within the eyeball presenting additional challenges, limiting the speed and extent of drug delivery here. These barriers include:

- static barriers - cornea, conjunctiva and retinal pigment epithelium,
- dynamic barriers - blood and lymphatic clearance mechanisms, tear turnover, etc.
- barriers for oral and parenteral administration - static blood-tissue barriers (epithelium, endothelium) and rapid vascular clearance mechanisms.

Together, the static and dynamic barriers limit the rate and extent of drug delivery to the eye.

One solution here is ocular iontophoresis as a non-invasive technology that increases drug penetration using low-level

electrical currents. It combines the therapeutic effect of an electric current with the pharmacological effect of drugs administered simultaneously via an electric current. It is proven for the delivery of proteins, corticoids, antibiotics and other gene drugs to the eye in various ophthalmic diseases (uveitis, herpes, cataracts, retinitis pigmentosa, cytomegalovirus retinitis, etc.). Coulomb-controlled iontophoresis (CCI), hydrogel ion circuit (HIC), EyeGate II delivery system (EGDS), among others, are used for this purpose [1]. Limitations of current ocular iontophoresis include primarily low current intensities limiting the effectiveness of macromolecule and nanoparticle delivery, but the use of higher current intensities can lead to damage to ocular tissues (Figure 1).

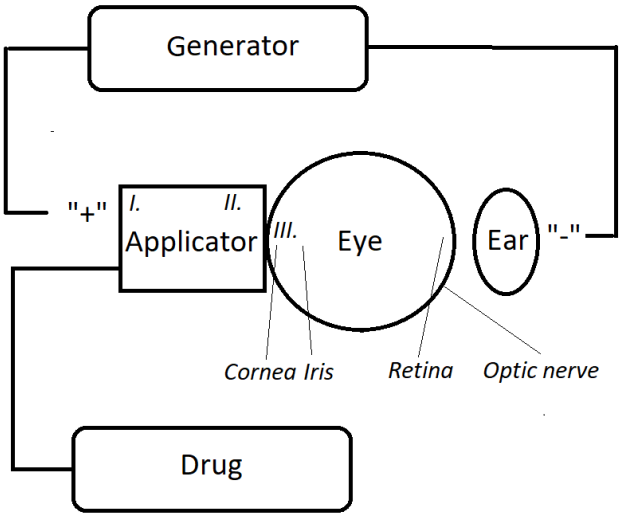

Fig. 1. Concept of eye iontophoresis.

The aim was to investigate the feasibility of developing a computational model concept for ocular iontophoresis using available artificial intelligence methods and techniques.

Data to date are incomplete. Accumulated permeability studies indicate a statistically significant effect of ionic strength on the iontophoretic transport of macromolecules: even transdermal iontophoresis with a low ionic strength preparation with a current intensity of 4 mA and a 20-minute treatment gave a permeability approximately 14 times higher compared to a conventional in vitro preparation and approximately 600 times higher than passive diffusion [2]. To date, the physical basis of the therapeutic effects of electric current on tissues and the physical and chemical mechanisms behind the delivery of drugs to human tissues through intact skin and mucous membranes by means of electric current have been understood. The clinical efficacy of such interactions has also been partially investigated [3]. There is no doubt that ocular iontophoresis:

- increases the potency of the drug,
- increases the penetration of the drug (e.g. into the cornea),

also as an emergency drug delivery method [4].

2. CONCEPT OF THE COMPUTATIONAL MODEL

A computational model of ocular iontophoresis is a type of computer simulation or mathematical model that aims to predict the effects of iontophoresis.

Such computational models are useful because they allow the prediction and optimisation of iontophoresis conditions, such as session duration, current intensity, drug type and other parameters. In practice, the creation of such a model requires the consideration of many factors, such as the electrical properties of the tissue, drug distribution, drug release kinetics, and the effect of tissue on electrical conductivity.

The guidelines for the development of a computational model concept for ocular iontophoresis are based on the following assumptions:

- Areas covered by the modelling: anatomy and physiology of the eye, pathology of ocular diseases, anterior and posterior ocular diagnostics, barriers to delivery of biological drugs to different ocular segments, ocular pharmacokinetics;
- Biological drugs are macromolecules with large size and poor stability in the biological environment;
- Changes in concept will be necessitated by new delivery systems for biologic drugs through ocular iontophoresis;
- There are a number of barriers to drug diffusion in the eye;
- The effect of increased intraocular pressure associated with (repeated) injections into the vitreous body has not been fully investigated [5].

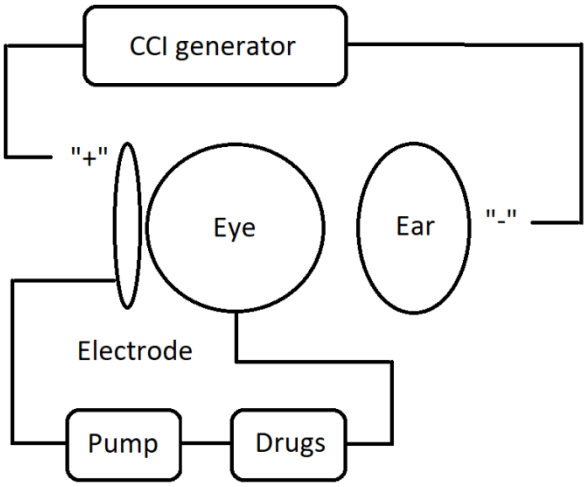

Fig 2. Idea of Coulomb controlled iontophoresis.

Such a model is useful in iontophoresis research to assess the effectiveness and safety of this technique, and to design better therapeutic protocols. It could also help to understand the mechanisms by which direct current interacts with ocular tissues and delivers substances into the eye.
Creating a sophisticated computational model of ocular iontophoresis is a complex task that requires the incorporation of advanced knowledge from physics, chemistry, biology and computer science. In addition, each model must be thoroughly verified and calibrated with experimental data to ensure its validity and usability.

3. DISCUSSION

Despite scientific and clinical advances, there is a continuing need for research into more effective drug delivery systems to the anterior and posterior segments of the eye [6]. The issues depend on the condition, the intended site and duration of effect and the type of drug, e.g. corticosteroids penetrate poorly intraocularly into the posterior segment when administered topically to the eye, but in turn their systemic administration may cause secondary side effects. Increasingly more effective ocular iontophoresis methods and techniques are being developed:

- Coulomb's transdermal controlled iontophoresis (CCI) system, whereby drug levels in the anterior and posterior intraocular tissues can be higher than those achieved by intravenous injection, modulated by current intensity and treatment duration [7],
- iontophoresis based on a hydrogel ionic circuit (HIC) for high-performance intraocular drug delivery, minimising electrode overpotential-induced heating and Joule heating and buffering pH changes generated by electrochemical (EC) reactions. This allows the safe use of current intensities of up to 87 mA/cm2 i.e., more than 10 times higher than at present. The time for the drug to reach the target tissues is 10-20 minutes [8].

As part of the directions for further research, it is necessary to:

- in-depth study of the mechanisms of pharmacokinetics of intraocular penetration for different diseases, drugs and conditions of administration,
- to compare the pharmacokinetic profiles of intraocular distribution,
- to develop computational models with significant predictive power [9-11],
- developing therapeutic approaches that allow better use of ocular iontophoresis (also as one component of therapy) [12-14],
- testing their safety [15-17].

There are a number of unproven approaches related to neuroimaging studies, among others [18-21].

4. CONCLUSIONS

Currently, iontophoresis is an effective non-invasive method of intraocular drug delivery based on electric current. However, it has many limitations that can be addressed by effective computational models based on both machine learning (a data-driven approach) and other artificial intelligence methods and techniques. To date, computational models using AI/ML are lacking, including for the iontophoresis mechanism itself. Their wider use would help facilitate ocular drug delivery, which remains a major challenge due to multiple barriers in the eye.

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