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Investigation of the possibility of insulin delivering to the blood through mucous membrane of the oral cavity

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Abstract

Systems with ultrasonic nozzle tips have replaced conventional sprayers, inhalers, etc. in many industries and research applications which made many spray processes possible including medicine (the improvement of the medicines spraying). Urgent concern about environmental problems, big amounts of industrial wastes and side effects caused by taking medications forced producers to implement system with ultrasonic nozzle tips as a technology that is more accurate, controlled, environmentally friendly and harmless for patients. The development of ultrasonic nebulizer of insulin is aimed at eliminating a number of problems connected with regular insulin taking (injections). They are increasing the effectiveness of treatment for patients with diabetes (possibly accelerating treatment), replacing the painful way of insulin delivering (via injections) with the device through which the medicine will be delivered and reducing the consumption of an active drug based on insulin.

Keywords: Diabetes, dosage reduction, insulin, cavitation, fluid atomization, average droplet diameter (fraction).

1. Introduction

According to statistics in 2014 there were 3.96 million people with the diagnosis "diabetes". But the real figure is much higher. Unofficial estimates provide the information that the number of patients is more than 11 million.

The development of an ultrasonic device that sprays insulin (with the size of fractions that allow its penetration into the circulatory system through the mucous membranes of the human body) is aimed at reducing the problems associated with the need to make insulin injections. Which is a very painful process (especially for children and pregnant women). The device under development will help improve the effectiveness of treatment of patients with diabetes mellitus (possibly accelerating treatment) as well as reducing the dosage of the drug based on insulin.

The tasks associated with the research objectives are:

- calculation of permeability of insulin into mucous membrane of the oral cavity.
- decrease in the amount of the drug being sprayed.

2. Methodology

Size of the pores oral mucosa pores

The oral mucosa is an attractive alternative way to deliver macromolecules to the blood. However, hydrophilic macromolecules, as a rule, are poorly delivered through oral administration because of their hydrophilism and size. Transportation of these molecules through the mucous membrane of the oral cavity can flow through the "waterway". Knowledge of the measurement of this route is necessary to understand the process of penetration of these molecules through the mucosa of the oral cavity. Polyethylene glycols (PEG) have already been used as model hydrophilic permeants in one of the studies to establish the relationship between permeability and molecular weight in different areas of the oral mucosa. The pore radius (rp) for the passage of the "waterway" and the ratio of the area of the waterway to the length of the mucosal barrier were calculated using the Rankine equation on the basis of experimentally determined permeability and the theoretical diffusion parameters for PEG molecules. The pore sizes of the waterways for the mucosa of the cheek and the sublingual mucosa were evaluated as 18-22 and 30-53 Å, respectively (1.9-2.2 and 3.0-5.3 nm). Estimation of pore size in various areas of the oral mucosa showed that the delivery potential of therapeutically important macromolecules through the mucous membrane of the mouth is very large [2, 3].

PEGs have been selected as model permeable materials because they have good water solubility, a wide range of molecular weights, no tissue metabolism, and a low distribution coefficient in the molecular weight range. Due to its low distribution, PEG can be used to study the "waterway" transportation through the oral mucosa. The relationship between the permeability of the oral mucosa and the molecular weight of PEG has been established [5].

The pore size of the "waterway" was calculated on the basis of the experimentally determined permeability of PEG. The permeability of PEG through the oral mucosa decreased with increasing molecular weight MW for the sublingual mucosa. The permeability coefficient for PEG decreased almost 2 times from 5.31 * 10 ^ (-6) to 2.72 * 10 ^ (-6) cm /from. The molecular weight increased approximately three times from 282 to 942 Da (Table 1) [6].

Table 1. Parameters of PEG diffusion for the sublingual region of the oral cavity
ri * is the radius of the polyethylene glycol molecule based on the principle of rotational motion.
ri is the radius of the polyethylene glycol molecule based on the Stokes-Einstein equation.

Oligomer molecule weight	r_i^*(Å)	r_i(Å)	D_i*10^6 см^2/с	The experimental permeability * 106 cm2 / s (value ± error)
282	4.87	4.83	6.80	5.31±0.52
326	5.15	5.13	6.40	5.05±1.48
370	5.47	5.38	6.10	4.70±0.28
414	5.78	5.57	5.90	4.46±0.88
458	6.03	5.66	5.80	4.11±0.18
502	6.27	5.76	5.70	3.90±0.23
546	6.55	5.86	5.60	3.88±0.58
854	8.09	6.44	5.10	3.19±0.65
898	8.27	6.57	5.00	2.67±0.66
942	8.51	6.70	4.90	2.72±0.55

Using the radius values for PEG from the literature [3], the values of rp (radius) turned out to be equal to 22 Å and 53 Å. The values of Є / L were found and are equal to 1.42 and 1.24 for buccal and sublingual mucosa, respectively (Table 2). The second approach is based on the Stokes-Einstein radius. The diffusion coefficient (D) of a spherical particle with a radius ri in amides of viscosity h and at a temperature T is determined by the Stokes-Einstein relation [5, 6] as follows:

$$D = \frac{KT}{6\pi\eta r_i},$$

where K is the Boltzmann constant. If the diffusion and the viscosity of the solvent coefficients are known, the Stokes-Einstein radius (ri) can be calculated from the Stokes-Einstein equation [5, 6].

Using the Stokes-Einstein values for PEG, rp values were estimated as 18 and 30 Å system units (SU). Values of Є / L were estimated as 1.94 and 1.74 for buccal and sublingual mucous membranes, respectively (Table 2) [6].

Table 1. Values for rp (in Å) and Є / L (in cm-1) for the sublingual and buccal mucous membranes [6]

ы	Є/L(см$^{-1}$)	r_p(Å)
Using the radius of rotational motion		
Sublingual mucosa	1.24	52
Buccal mucosa	1.42	23
The use of the radius by the Stokes-Einstein equation		
Sublingual mucosa	1.74	30
Buccal mucosa	1.94	17.5

3. Discussions

As a result of the conducted studies, it can be said that the droplet size of the active preparation based on insulin, when sprayed, should be in the range: 23 - 52 Å.

When designing a device for spraying insulin, it is important to pay attention to the frequency range, power consumption, as well as the size of the spray droplets and the insulin itself, which will undergo the atomization process.

Approximate parameters of ultrasound insulin nebulizer:

Typical power is 1-10 W. Operating frequency range is 25-250kHz. Amplitude of oscillations on ultrasonic transducer is 3-9 microns. Presumed type of insulin used is "regular insulin" (average duration of action is 3-6 hours). To reduce the effect of ultrasonic cavitation it is necessary to install a self-cleaning, non-clogging filter head at the outlet.

4. Conclusion

If all these conditions are observed, it is possible to reduce the necessary dosage of insulin preparation and accelerate treatment in some cases.

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