Conference paper

The Device for the Treatment of Diabetes with use of Infrared Radiation and Porous TiNi Based Alloy

S.V. Gunther[1,2]*, G.Ts. Dambaev[3], J.H. Kang[4], V.E. Gunther[1, 2]

[1] Tomsk State University, Tomsk, Russia

[2] Research Institute of Medical Materials and Implants with Shape Memory, Tomsk, Russia

[3] Siberian State Medical University, Department of Clinical Surgery, Tomsk, Russia

[4] Kang&Park Medical Co. Ltd., Ochang, South Korea

*Corresponding author:
S.V. Gunther, email:
guntersv@inbox.ru

🔓 OPEN ACCESS

Abstract

The research addresses the problem of design and development of a new needle-free method for diabetes treatment. New porous-permeable TiNi-based materials and new methods of IR-radiation effect on tissues of the body have been used in the research. The properties of porous alloys are similar to those of high-capacity materials that can hold a large volume of insulin solution in the porous structure of the material. With this, IR-radiation stimulates directed diffusion of insulin from the porous TiNi structure to the tissues of the body. This makes the basis for development of a needle-free device for diabetes treatment. The proposed technique does not cause skin irritation, and it is safe when used in practice. The efficiency of insulin delivery was evaluated in clinical studies. The results showed the potential of prolonged delivery for both insulin and other liquids.

1. Introduction

The main objective in diabetes treatment is to reduce the blood sugar level to the normal one. Numerous studies show that diabetes prevalence is increasing every year regardless of the age, gender and ethnicity.

The most common currently used method of diabetes treatment is intradermal insulin injections. This method causes mechanical trauma, pain and psychological discomfort. In addition, it may result in allergic reactions observed in both the local area of high drug concentration and the whole organism.

Today, researchers take great interest in the development of new methods of insulin delivery that provide a long (prolonged) effect. This is caused by the need to release the patient from the necessity of frequent injections of short action insulin (3-4 times a day). Each injection is associated with a negative emotional response to pain as well as specific difficulties of compliance with conditions of asepsis and antisepsis. One of the tendencies related to this problem is development of methods providing needle-free insulin delivery in the human organism. New methods of insulin delivery (orally or inhaled) are being actively developed.

2 Experimental

Making insulin delivery free of needle is an important factor that makes the procedure more comfortable. Therefore, new methods of transdermal (percutaneous) therapeutic systems are considered to be promising. These methods imply insulin solution diffusion through the skin. The diffusion of fluid can occur through the contact surface area without physical damage. The main obstacle for successful use of this method is the corneum layer. This layer is hardly permeable for large molecules, including insulin molecules; therefore, micropores should be created in the corneum layer. Micropores can be formed using various methods: ultrasound, laser radiation and electrical effects. Insulin molecules are packed into liposome capsules with increased penetration ability to improve diffusion.

The most promising method is needle-free injection of insulin using porous TiNi alloys and IR radiation.

The development of the powder metallurgy and self-propagating high temperature synthesis (SHS) in a combustion mode gave rise to a new class of highly permeable TiNi-based materials (Fig. 1). These materials can hold fluid media in the pore space, including insulin solution. Due to the capillary effect, diffusion processes under IR exposure, the solution can be hold in the porous TiNi volume and the liquid can be directionally released from the pores [1–3].

The analysis of interaction of porous permeable TiNi-based alloys with various tissue fluids of the organism showed the efficiency of these materials as capacitive medical materials. High-capacitive devices for effective needle-free delivery of insulin solution into the tissue system of the organism can be developed due to a

wide range of physical-mechanical properties of TiNi alloys and the possibility of producing porous structural elements. In addition, these alloys exhibit high intensity of heat transfer at low level of thermal conductivity [2, 4].
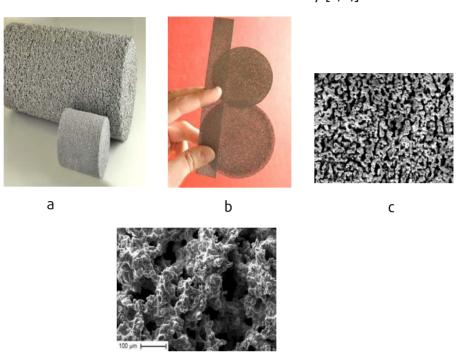

a   b   c

d

Fig. 1 The porous permeable TiNi: a – the semi-finished TiNi produced by the method SHS; b – TiNi element used in the device; c – the porous structure of TiNi with increase (x 10); d – the porous structure of TiNi with increase (x 100)

The IR sources that regulate diffusion make the basis for the design of these devices and porous permeable TiNi elements.

When the porosity of TiNi ranges from 60% to 70%, the insulin solution can take more than half of the volume of the capacitive construction element. The process of insulin diffusion of porous permeable of TiNi matrix depends on numerous factors, such as insulin viscosity, specific weight, density, permeability, pore length and size, the surface contacting with the environment, temperature of the porous matrix and others. The formula shows the dependence of the rate of change in the liquid volume of the TiNi porous structure on basic parameters of the insulin solution diffusion.

$$\Delta Q = k \cdot \frac{V_o \cdot \rho \cdot g \cdot \Delta h \cdot S \cdot P \cdot \Delta T}{\mu \cdot L} \qquad (1)$$

ΔQ – the speed of the diffusion liquid in porous TiNi; k – the coefficient of diffusion; ΔT – the gradient of temperature of porous element; µ – the viscosity of liquid; p – the density of liquid; V_0 – the initial volume of fluid in the porous material; S – the area of contact of the surface pores with tissue; Δh – the liquid lever in the porous material; L – the average length of the pores of sample; P – the porosity; g – the acceleration of gravity

IR radiation can be used to change the temperature parameter ΔT (temperature gradient). It allows control of the rate of the insulin solution diffusion relative to the power, wavelength and duration.

IR radiation in the range from 800 to 1100 µm has a distinct thermal effect that causes excitation of thermoreceptors in the skin, mucous membranes and cornea, and in the central nervous system (spinal cord and hypothalamus). This radiation penetrates up to 2 cm deep in the body tissue. The penetration depth depends on both the wavelength and the moisture content in the skin, blood content, degree of pigmentation and other individual factors [1, 3, 5].

The impulses from thermoreceptors travel into the thermoregulatory centers (hypothalamus and partially spinal cord). Further, the thermoregulation reactions cause expansion of the skin vessels and increase the volume of the blood circulating in the vessels, which results in increased sweating. Nerve-reflex reactions occur also under IR irradiation of the reflexogenic areas of the skin segments, which are connected with the internal organs. IR irradiation of the tissue leads to formation of biologically active substances such as bradykinin, kallidin, etc. These substances are crucial for humoral reactions of blood circulation (local and general).

Small and medium doses of IR radiation increase metabolism accelerate cell reproduction and enzymatic reactions that stimulate regeneration processes.

Figure 2 presents a schematic structure of the device for needle-free delivery of insulin solution in the tissue system of the body and figure 3 shows its practical use.

To prepare the device for work, the battery is charged, the element is saturated (a plate of porous permeable TiNi alloy) with insulin solution. Then, the device should be fixed to the wrist (like a bangle). The porous element should be in contact with

the skin and IR LEDs are turned on. The L-53SF6C type LEDs with wavelength λ = 920 nm and power of 120 mW by Kingbring were used as IR sources.The device is supplied with a Li-ion battery with capacity of 640 mA and total weight of about 50 g.
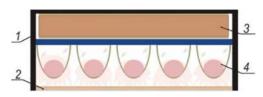

Fig. 2. The structural schematic of the device: 1 – the box of device; 2 – the removable element (the plate of porous TiNi); 3 – the power source; 4 – LEDs of IR
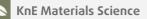
This device converts electrical energy into thermal energy to make a system of soft heat thermomechanical IR effect.

The size of the device depends on the capacity and dimension parameters of the Li-ion battery and the area of the contact surface of the porous permeable TiNi plate. The plate is a container for insulin and can be used repeatedly. For the next procedure, one needs to saturate the TiNi plate with insulin solution. This manipulation is available in any conditions, and this makes the device easy to use. The overall size of the sample plate is 48×36×16 mm. The device modifications can vary in sizes (shape of the box and porous plate).

A power button with LED indicator and a USB port for charging are located on the lateral side of the device.

Fig. 3 The device for the needleless delivery of insulin: a – the general form; b – the practical application

The procedure time (30–120 min) depends on the change in the blood glucose level. Glycemia (Fig. 4) decreases monotonically within the first 30 min and then it is followed by gradual slowdown within the next 30 min and reaches its steady-state level 120 min after the start of the procedure [3, 6].
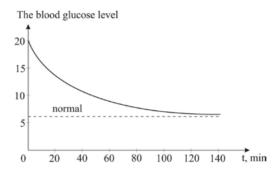

Fig. 4. The dependence of the lever of glycemia from the time operation of device

The main physical factor that stimulates the diffusion of insulin solution into the subcutaneous layer is thermophoresis, heating of the skin in contact with the moisturized surface of the porous plate of the device. The plate saturated with insulin solution and heated by IR radiation causes skin swelling. This facilitates the diffusion of insulin solution into the tissue. Experimental research has shown that the following three factors are crucial for the effective diffusion: 1 – a temperature gradient in the area of contact between the skin and insulin; 2 – heating of the adjacent skin; 3 – direct exposure of the inner layers of the skin to IR radiation. These factors facilitate the targeted diffusion of insulin into the organs to ensure a good therapeutic effect.

A temperature gradient of the liquid insulin solution in the porous element (TiNi plate) of the device occurs in the case of the element porous structure (pore walls) and the liquid insulin solution in the pores is exposed to IR radiation. Partial absorption of radiation by the plate surface creates the necessary temperature gradient due to heat removal from the opposite surface, which contacts with the skin, regulated by the body through the control of the blood flow intensity. The temperature gradient creates a driving force for insulin transfer from the area of higher temperature to the area of lower temperature. The targeted transfer of the liquid molecules to the skin, which is characterized by the excessive pressure distributed over the area of contact between the porous plate and the skin, is performed under the temperature gradient driving force. With this, insignificant

increase in the temperature of the porous TiNi containing insulin initiates diffusion and release of insulin from the material surface into the contacted tissues.

The surface skin layer is heated by the warm layer of TiNi plate (heated by IR radiation). The skin temperature in the contact surface of the plate (saturated with insulin solution) increases due to the contact with the liquid over the entire surface of the skin. This causes skin swelling and increases tissue permeability. The insulin diffused from the surface of the porous TiNi into the tissue is constantly replenished from the internal pores due to the wetting and capillary effect. The rate of insulin removal depends on the gradient of liquid concentration in the boundary layer and ability of the surface of the contacted tissues (the skin) to absorb insulin.

The third factor is the direct impact of IR radiation on tissues and the ability of the optical spectrum with the LED wavelength of 920 nm to penetrate through the skin into tissues 3–4 mm deep. The plate thickness of 0.2 to 1 mm and the pore size of 10 to 500 µm ensure partial transparency to IR radiation that has a direct effect on the skin and inner layers of tissues.

IR radiation sharply accelerates the liquid transfer from the porous TiNi to the tissue surface. Firstly, the heat fluxes cause the temperature gradient of the diffusion boundary layer on a wet surface. Secondly, the vessels are expanded being exposed to IR radiation that passes through the empty space of the porous TiNi structure, and thus accelerates insulin diffusion into the adjacent tissues. The skin integrity in the area of insulin introduction reduces risks of injury and ensures comfort of the procedure for a patient [2-4]. Once the device is turned on, the porous element starts gradual heating (about 5 min.) (Fig. 5).
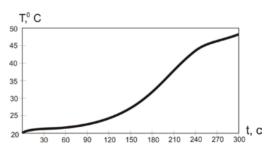

Fig. 5. The graphical time dependence the heating time of the plate

IR LEDs are used as a heating element due to the efficient control of the device and simplicity of the power source. Heating by IR radiation has an advantage over the

contact heating as the radiation penetrates into tissues, thus improving the diffusion of insulin solution. The porous TiNi samples are partially transparent within the range of 0.4 to 1 mm.

3   Results and discussion

A group of patients with different level of glycemia (blood glucose) was involved in the study. The patients aged 18 to 80 years with type 1 and 2 diabetes, with no oncopathology, hypertension and allergy to insulin were included in the study.

The blood glucose level was evaluated using a glucometer Accu-Chek Active with test strips (series 393 and 436). The device was calibrated in accordance with the manual instruction. Glycemia was visually evaluated in each measurement using test strips.

The measurements were performed after 30 and 60 min after fixing the device on a patient's wrist (fig. 6). The patients were examined under normal food-intake conditions and motor activity, no glucose-lowering tablets or insulin were allowed before the examination.

Ten units of the short-action insulin (Acropid HM and Rinosulin) were applied to the device surface and uniformly distributed over the porous TiNi plate.

A group of 52 patients was examined for the blood glucose level to test the device. The average blood glucose level was 17.3 mM/l at baseline, 9.8 mM/l after 30 min, and 8.2 mM/l after 60 min. The reduction of glucose from the baseline was about 56%, no side effects were observed.
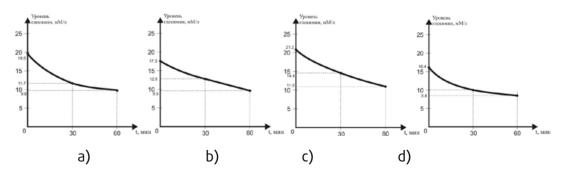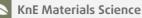

Fig. 6. The time dependence of glycemia of 4 patients

The patients were randomly chosen from the total number of patients. They proved the effectiveness of the method of needle-free introduction of insulin and the needle-free device for its delivering. The proposed method can be effectively used in medical practice for other liquids when appropriately adapted.

4   Summary

Nowadays, the main goal in the treatment of diabetes is to reduce glucose in the blood. The modes of insulin introduction simulating a natural dynamic of its concentration have been used for this purpose. The insulin secretion in healthy patients is discrete during the day. The discrete character of the secretion caused by increased blood glucose facilitates the constant release of insulin from the pancreas. The introduced long-acting insulin creates "simulated" basal secretion of insulin. The introduction of the short-acting insulin 30 min before a meal creates an additional rise of insulin in the blood, which coincides with hyperglycemia in time. Sometimes, good results can be obtained if insulin is introduced at a fixed time, but the reliable data on the discrete introduction of insulin is not reported in the scientific literature. Thus, the use of IR radiation and porous permeable TiNi (MoFe) opens the perspective for development of new needle-free devices.

References

[1] V.E. Gunther, G.Ts. Dambaev, P.G. Sysoliatin et al., Delay Law and New Class of Materials and Implants in Medicine, Northampton. MA: STT. 2000.

[2] Gunther, S.V.; Dambaev, G.Ts.; Starchenkov, D.D. *Patent RF* RU2534521 [in Russian]. 2012.

[3] Gunther S.V., Dambaev G.TS., Chekalkin T.L., Kang J-H, Kim J.S., Gunther V.E. / Porous TiNi-based material and infrared radiation in needle-free treatment of diabetic patients // Advanced Materials Letters 2016, 7 (9), 713-718.

[4] Gunther S.; Kokorev O.; Chekalkin T.; et al.; *Adv. Mater. Lett.*, 2015, 6*(9)*, 774 DOI:10.5185/amlett.2015.5882

[5] Bergenstal, R.M.; Strock, E.S.; Peremislov, D.; et al.; *Mayo ClinProc.*,2015, 90, 329. DOI: 10.1016/j.mayocp.2014.12.014

[6] Gunther S.V., Dambaev G.Ts. The needleless insulin delivery unit in diabetes with the use of infrared radiation/ International Conference "Global Science and Innovation". Materials of the VII international conference. Chicago, USA 2016, Page 260-267.