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ORIGINAL RESEARCH



Technology-derived storage solutions for stabilizing insulin in extreme weather conditions I: the ViViCap-1 device

Andreas Pfützner ^a, Gidi Pesach^b and Ron Nagar^b

^aMedical Department, Pfützner Science & Health Institute, Mainz, Germany; ^bR&D Department, TempraMed Inc., Half Moon Bay, CA, USA

ABSTRACT

Background: Injectable life-saving drugs should not be exposed to temperatures $<4^{\circ}\text{C}/39^{\circ}\text{F}$ or $>30^{\circ}\text{C}/86^{\circ}\text{F}$. Frequently, weather conditions exceed these temperature thresholds in many countries. Insulin is to be kept at $4\text{--}8^{\circ}\text{C}/\sim 39\text{--}47^{\circ}\text{F}$ until use and once opened, is supposed to be stable for up to 31 days at room temperature (exception: 42 days for insulin levemir). Extremely hot or cold external temperature can lead to insulin degradation in a very short time with loss of its glucose-lowering efficacy.

Methods: Combined chemical and engineering solutions for heat protection are employed in ViViCap-1 for disposable insulin pens. The device works based on vacuum insulation and heat consumption by phase-change material. Laboratory studies with exposure of ViViCap-1 to hot outside conditions were performed to evaluate the device performance.

Results: ViViCap-1 keeps insulin at an internal temperature $< 29^{\circ}\text{C}/84.2^{\circ}\text{F}$ for a minimum of 12 h without external power requirement, even when constantly exposed to an outside temperature of $37.8^{\circ}\text{C}/100^{\circ}\text{F}$. Bringing the device into an ambient temperature $< 26^{\circ}\text{C}/78.8^{\circ}\text{F}$ reverses the phase-change process and 'recharges' the device for further use.

Conclusions: ViViCap-1 performed within its specifications. The small and convenient device maintains the efficacy and safety of using insulin even when carried under hot weather conditions.

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KEYWORDS

Insulin injection; drug stability; extreme weather conditions; drug degradation

1. Introduction

Like many other protein drugs, insulin formulations for treatment of diabetes mellitus are required to be stored in the refrigerator at $4\text{--}8^{\circ}\text{C}/39.2\text{--}46.4^{\circ}\text{F}$ to maintain their pharmacological activity until reaching the expiration date defined by the manufacturer. A variety of chemical changes of the primary structure (yielding insulin derivatives) and physical modifications of the secondary to quaternary structures (resulting in 'denaturation,' aggregation, and precipitation) are known to affect insulin and insulin preparations during storage and use [1,2]. Chemical deterioration of insulin during storage of its pharmaceutical preparations is mainly due to two categories of chemical reactions, hydrolysis and intermolecular transformation reactions leading to high-molecular-weight products [3,4]. The predominant hydrolysis reaction is deamidation of asparagine residues, which in acidic solution takes place at residue A21 and in neutral medium occurs at residue B3. A hydrolytic cleavage of the backbone A chain has been identified in regular human insulin preparations containing rhombohedral crystals in combination with free zinc ions [1,5]. These reactions can cause substantial changes to the conformation and properties of the insulin molecule, which may finally result in isoelectric precipitation or fibrillation of the insulin in the vial, the cartridge of the insulin pen, or the container of an insulin pump [4,6].

Conformational changes to the insulin molecule promoting chemical degradation, fibrillation, and precipitation can be

induced by changes in pH, agitation, contact with hydrophobic surfaces, and – most importantly – exposure to elevated temperatures. Because of this situation, patients are educated to keep their insulin in the refrigerator until use, keep it at room temperature after opening, and consume it entirely within maximally 4 weeks [7–9]. However, room temperature can vary substantially in the different regions of the globe, and reduced efficacy because of regular exposure of the insulin pen or vial to elevated temperatures is most probably one of the major reasons for unsatisfactory treatment results and even life-threatening ketoacidosis in countries with extreme hot or cold weather conditions [10–12].

Many attempts have been made to develop heat-stable insulin formulations [13–15], which however have not yet reached the status of regulatory approval, and patients are still burdened with the requirement to store their meal insulin in bulky cool packs, e.g. containing ice cubes, when traveling or living in countries with extreme hot climate conditions [16]. New technologies and new materials, which are frequently derived from space travel, have meanwhile been identified, which have allowed the development of engineering solutions for smart and convenient devices to help patients to avoid chemical degradation of their insulin when carrying it under extreme weather conditions.

Here we report on the technological background and performance of a new temperature protection pen cap device (ViViCap-1, TempraMed Inc., Sammamish, WA, USA). This device was designed for effective thermal stabilization of the

insulin cartridge (i.e. to stay below 29°C/84.2°F) for more than 12 h, even when the pen is constantly exposed to hot outside environmental temperatures (>37.8°C/100°F).

2. Material and methods

2.1. Device description

ViViCap-1 is a replacement cap for disposable insulin pens, which can be used with the Kwikpen (Eli Lilly, Indianapolis, IN, USA), FlexPen or FlexTouch (both Novo Nordisk, Copenhagen, Denmark), and the Solostar device (Sanofi, Paris, France). It is designed to keep insulin cool within safe temperatures below 29°C/84.2°F for a minimum of 12 h even in a constant environmental temperature of 37.8°C/100°F, when the device is placed inside a personal handbag. To achieve these specifications, ViViCap-1 does not require any battery or external power supply. Cap temperature regulation is passive and combines thermal insulation with an effective heat absorbent material. The cap is 'reactivated'/'filled up' to provide safe storage conditions, whenever the ambient temperature gets below 26°C/78.8°F, for subsequent periods of less than 6 h. It can be used for up to 365 days. The device consists of the following components (see Figure 1): a thermal insulation (stainless steel) layer, held between the outer plastic cover and the inner plastic adaptor (that fixes the pen inside), and an inner filling of so-called 'phase-change material' (PCM), held between the thermal insulation and the inner plastic adaptor. Additional electronics are implemented to monitor the pen temperature and to provide a visual indication to the user about the inner pen temperature.

2.2. Engineering background for ViViCap-1

Heat is transferred from warmer to colder areas by a combination of conduction, convection, and radiation. The greater the temperature difference, the faster the heat flows to the colder

area. Insulators minimize heat transfer by affecting these ways of heat transfer. First (conduction), heat energy passes from molecule to molecule within a material. For this process, there should be physical contact between particles and some temperature difference. Thermal conductivity is the measure of the speed of heat flow passed from particle to particle. The rate of heat flow through a specific material is influenced by the difference of temperature and by its thermal conductivity. For material insulators that reduce conduction, thickness of the insulating layer is directly correlated with the effectiveness of insulation. Perfect vacuum eliminates heat conduction, which is, e.g. used to improve performance and stability of laser beams [17]. Second (convection), the moving gas or liquid particles can transfer heat from one place to the other. The efficacy is dependent on the temperature of the moving particles and the flow rate. Like for conduction, the thickness of a material convection insulator directly correlates with its thickness, and perfect vacuum eliminates convection. Finally (radiation), a third way to heat transfer occurs through radiation transmission of heat energy in the form of electromagnetic waves. This mechanism can heat surfaces that absorb the waves. It also works in vacuum, but light-reflecting shiny surfaces minimize heat absorbed from radiation.

ViViCap-1 uses a thin layer of ultrahigh vacuum encapsulated in between two thin stainless steel layers. This combination reduces all three ways of heat transfer from the ambient to the inner part of the device, through maintenance of a highly effective insulation with a small form factor.

This highly effective insulation has been combined with the action of so-called 'PCM.' PCMs are substances that absorb and release thermal energy during the process of phase transition – melting and freezing. The energy absorbed or released in this phase transition (referred to as 'latent heat') can be 100 times larger than the energy needed to change the temperature of the same substance without phase transition (referred to as 'sensible heat') [18,19]. When the PCM is exposed to ambient temperature greater than its phase transition

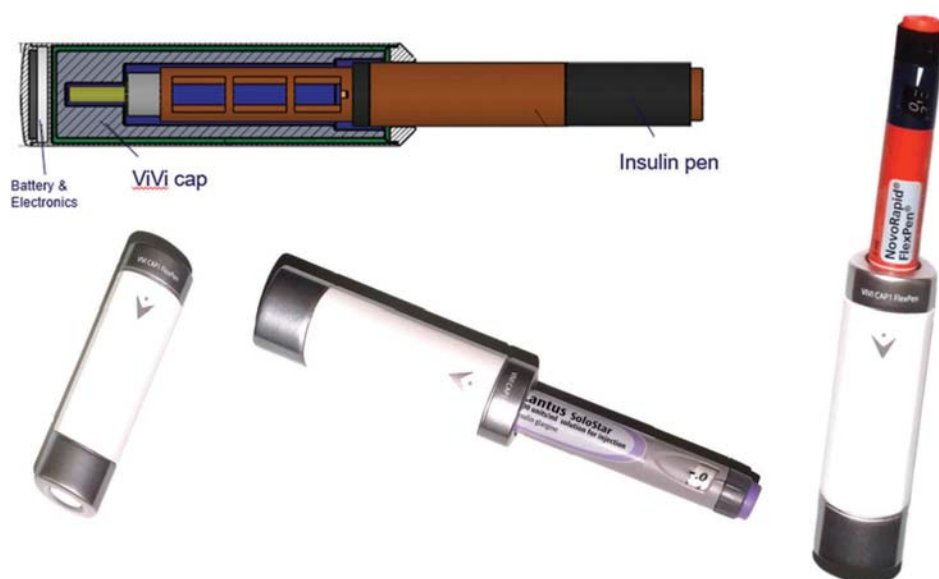


Figure 1. Engineering draws of the ViViCap-1 device and pictures of the first product generation with insulin pens in place.

temperature, it starts to melt and absorbs a large amount of heat from the environment keeping the temperature relatively constant at the melting point until it completes phase transition (see Figure 2) [20]. The time in stable thermal conditions during this process is in direct linear relation with the quantity of the PCM. The process is reversible, and when the ambient temperature falls below the phase transition temperature, the material freezes and then releases the energy into the environment at a relatively constant temperature close to the melting point.

ViViCap-1 encapsulates a volume of bulk PCM between the inner part of the insulation and the plastic pen adaptor. The PCM melting temperature (28°C/82.4°F) was chosen to be below the safe limit temperature of insulin. It has a high latent heat capacity, has a narrow melting temperature, is chemically stable and noncorrosive, and finally is also safe to use.

2.3. General considerations

The cap performance depends entirely on its structure (thermal insulation and quantity of PCM), which are the parameters that determine the capability of the cap to maintain a temperature at its inner section which is in contact with the drug cartridge of the pen. Previous thermal simulations and experiments demonstrated that heat conduction from the pen body to the drug in the cartridge through the pen walls can be neglected. Heat conduction and convection through the pen-driving mechanism and air inside that part to the drug cartridge can also be ignored. Therefore, performance of ViViCap is independent of the insulin pen. The amount of PCM used with ViViCap is in direct linear relation with the time in stable thermal conditions (i.e. doubling the PCM volume would double the time in stable thermal conditions of ViViCap, data on file, TempraMed Inc.). Measuring the temperature of the drug inside the cartridge is impossible in an actual product. It is only possible to measure the temperature on the surface of the cartridge. This temperature may be different from the temperature inside the cartridge when rapid temperature changes are induced. In real life however, temperature

variations are slow, allowing the temperature at the cartridge wall and the temperature of the drug inside the cartridge to be in equilibrium (data on file, TempraMed Inc.).

2.4. Protocol of the standard heat exposure experiment

The purpose of this experiment was to evaluate the performance of the ViViCap-1 device, comparing it to an insulin pen without any protection and to an insulin pen which employs commonly used water evaporation-based device for temperature protection.

Calibrated temperature sensors (Thermistor TDK NTC 10K OHM 1%) were attached using scotch tape and thermal conducting paste (Warmeleitpastet) to cartridges of three identical unused SoloStar per setup. Wires extending from the sensors to data logging system allowed constant tracking of the cartridge wall temperature, which represents the inside drug temperature. The ViViCap-1 devices are equipped with 16 ml of PCM (melting point: 28°C/82.4°F). They were mounted to the SoloStar pens. A second series of pens was put into a commercially available water evaporation jacket (FRIO Insulin Travel Wallet, single, Frio UK Ltd., Haverfordwest, UK), which had been prepared for use in accordance with the manufacturer's instructions. Weight of the FRIO device after preparation was 160 g. For the third condition, the SoloStar pens had no protection and were used as reference pens. To avoid any effect of water evaporation from the FRIO on the other two pens (the reference pen and the ViViCap-1 pen), they were tightly covered with a thin plastic bag. To simulate real-life conditions, the three pens were placed in an empty garment case (100% nylon/polyester 260 × 100 × 100 mm), which was placed into a standard empty backpack (Dereshete Scout Alpha 17L). During the warming cycle, the backpack was placed into a climate chamber employing a constant outside temperature of 37.8°C/100°F with circulating air inside the chamber. The temperature setting of the climate chamber was chosen to fit the operational temperature mentioned in the water evaporation-based FRIO device user manual. The temperature of all pens was recorded, and they were left to

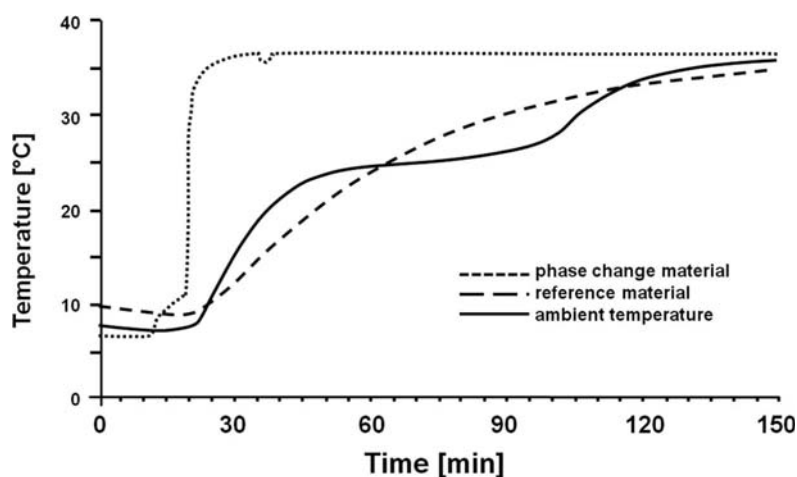


Figure 2. Typical temperature profile of a phase change material. The reference material is a similar material but with a higher melting point that was not reached in this experiment.

stabilize at room temperature conditions before the test. The backpack was placed in the climate chamber until the last of the three pens reached an insulin cartridge temperature of 34°C/93.2°F. The experiment was performed in triplicate. The time to reach an inner cartridge temperature of 30°C/86°F was recorded as primary objective in this experiment.

2.5. Protocol of a 'left-in-car' simulation experiment

The purpose of this experiment was to evaluate the performance of the ViViCap-1 device, comparing it to an insulin pen without any protection, to an insulin pen employing high-performance insulation, and to an insulin pen which was packed into a common water evaporation-based device for temperature protection. This experiment was also carried out in triplicate.

The climate chamber temperature was set in this experiment to 58°C/136.4°F, which is close to the temperature near the floor of a car on a clear sunny summer day with an outside temperature of 27°C/80.6°F [21]. The backpack was placed in the climate chamber until the last of the pens reached an insulin cartridge temperature of 34°C/93.2°F. The time to reach an inner cartridge temperature of 30°C/86°F was recorded as primary objective in this experiment.

3. Results

Both tests were conducted without deteriorations and as planned. The temperature characteristic of the selected PCM (melting point 28°C/82.4°F) is provided in Figure 2. The documented temperature curves of the insulin pen cartridges under all three conditions tested in the first experiment are provided in Figure 3. It can be seen that the unprotected reference pen insulin cartridges reached an inside temperature of 30°C/86°F in the mean already after only 95 ± 2 min. Protection of the pens with a commercial water evaporation jacket prolonged this time by about 1 h to a recorded 180 ± 3 min. When these pens were taken out from the jacket, they were observed to have water droplets on the cartridge surface and the pen body. Employing the ViViCap-1 with 16 ml of PCM kept the inner pen temperature below 30°C/86°F for more than 12 h (756 ± 4 min, $p < 0.001$ vs. both other conditions).

The documented temperature curves of the insulin pen cartridges under all three conditions tested in the second experiment are provided in Figure 4. It can be seen that the unprotected reference pen insulin cartridges reached an inside temperature of 30°C/86°F after 61 ± 2 min and of 34°C/93.2°F already after only 100 ± 2 min. Protection of the pen with a commercial water evaporation jacket prolonged this time to be 117 ± 3 min and 180 ± 3 min, respectively. Again, the pens taken out from the jacket were observed to have water droplets on the cartridge surface and the pen body. Employing the commercial ViViCap-1 device kept the inner pen temperature in this experimental setting below 30°C/86°F for 250 ± 3 min and below 34°C/93.2°F for 480 ± 5 min ($p < 0.001$ vs. the other conditions). After 480 min, the temperature that was reached in the unprotected pen cartridges was 44 ± 0.5°C/111.2 ± 1°F, spending over 6 h at average temperature of 41°C/105.8°F, and the pen cartridges in the FRIO device reached a temperature of 41°C/105.8°F, spending 5 h at an average temperature of 38.5°C/101.3°F.

It should be noted that 8 h with a temperature of 58°C/136.4°F is unlikely to occur in daily life, even for a 'left-in-car' situation. Leaving the bag on a car floor exposed to the sun on a summer day will result in the temperature of the bag to be above 41°C/105.8°F only for about 5 h at most because of natural temperature fluctuations.

4. Discussion

Use of a very effective insulation by ultrahigh vacuum in combination with the temperature-stabilizing effects of PCM has resulted in the development of an easy-to-use pen cap for storage of insulin under extreme ambient conditions. Use of PCM is not new for this purpose. The most commonly found PCM is water/ice, which is an excellent PCM for maintaining temperatures at 0°C. It is used in some of the existing bulky storage solutions for insulin in hot weather. A variety of other PCMs have been developed for use across a broad range of temperatures, from −40°C/−40°F to more than 150°C/302°F, which offer high-density energy storage within a narrow temperature range [18,19].

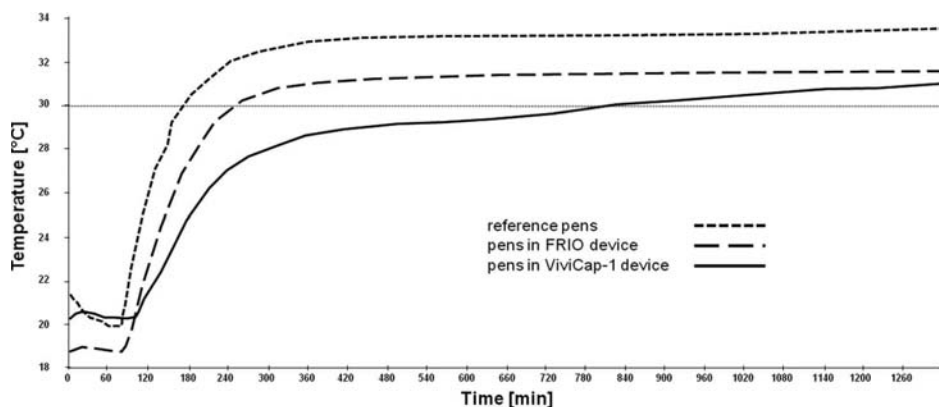


Figure 3. Temperature curves during the heat exposure experiment. After placing the devices into the climate chamber (heated to 37.8°C/100°F), the unprotected SoloStar pens reached 30°C/86°F after 95 ± 2 min and the pens in the FRIO device after 180 ± 3 min. The pens in ViViCap-1 needed 756 ± 4 min to reach the upper temperature limit.

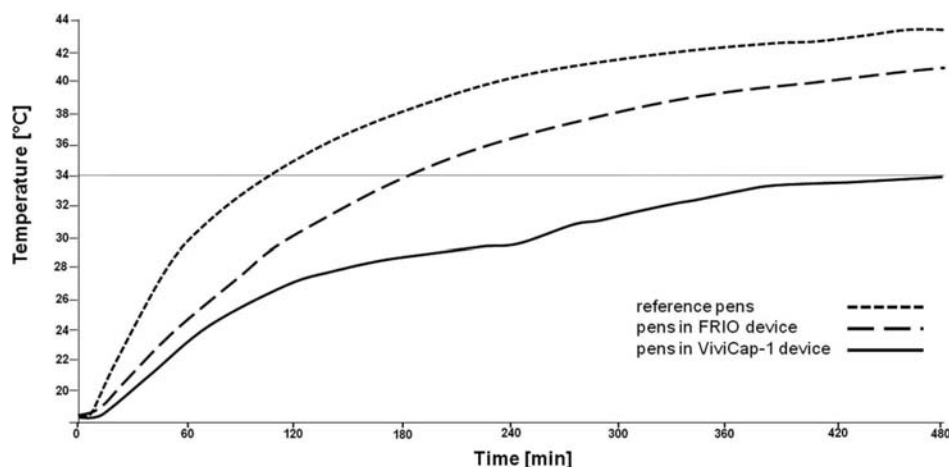


Figure 4. ViViCap-1 performance when simulating a diabetes supply bag left in a car with a bottom temperature of 58°C/136.4°F. Mean time to reach 34°C/93.2°F inside cartridge temperature in the SoloStar pens was 100 ± 2 min without heat protection, 180 ± 3 min for pens in the FRIO device, and $480 \text{ min} \pm 5$ min for pens with a mounted ViViCap-1.

Today, due to increasing demand for eco-friendly, energy-saving materials in industries such as building/construction, refrigeration, thermal energy storage, textiles, and electronics, use of PCMs is becoming popular in many applications. Refrigerators and freezers that use less energy, high-performance textiles that provide relief from hot and cold conditions, shipping containers that maintain goods at the desired temperature for longer periods, construction material that keeps living spaces comfortable and reduces heating and cooling costs, and thermal energy storage systems that shift a building's cooling and heating needs to cheaper, off-peak hours are practical examples of how PCMs have offered solutions to improve our daily-life conditions [22]. They also have the potential to improve the performance of medical devices in many applications and indications [23].

Managing diabetes in a hot (as well as below the water freezing point) environment is quite a complex task. Affected people with diabetes have greater susceptibility to adverse effects from heat (i.e. increased number of emergency department visits and hospitalizations, increased occurrence of dehydration and electrolyte abnormalities, and higher death rate) than persons without diabetes [16,24]. It has been shown that alterations in glucose homeostasis can occur and that changes in insulin kinetics and stability are additional reasons for an increased difficulty to achieve treatment targets under these conditions [16,25,26]. Having diabetes places a person already at an increased risk for heat-related health problems, but in any case, the impact of heat exposure on equipment performance (e.g. glucometers and insulin injections) has to be considered.

In a comprehensive survey, Nassar et al. [27] investigated the knowledge of patients about managing their diabetes in the heat. According to their report, patients use a variety of personal protective measures during hot weather, e.g. limiting heat exposure to less than 1 h. They also take steps to protect their diabetes medication and supplies and more than a third leave their medications and supplies at home. Although 73% of respondents had received information regarding the effect of heat on insulin, but further knowledge gaps were evident. For example, only 39% had received information about the effect of heat on oral medications, 41% on glucose meters, and 38% on glucose test strips. The

temperature at which patients took protective measures varied. Many patients had suboptimal glycemic control, placing them potentially at risk for dehydration during the hottest months [27].

These results indicate that increased public awareness of this topic is needed and that diabetes management in the heat needs to be specifically addressed in current treatment guidelines [28]. Patient educational materials have to be developed regarding self-management skills in the heat, and diabetes education programs should include information about the special heat challenges where appropriate.

Current storage solutions, however, are bulky (e.g. 'mini-fridges'), cannot be used on a daily basis, and/or show a poor performance when it comes to stabilizing the insulin at an appropriate temperature under extreme temperature conditions (e.g. cool packs and water evaporation jackets). There is clearly an increasing demand to find better solutions for insulin storage under hot weather conditions. Most recent statistics indicate that diabetes prevalence is highest in countries with extremely hot climate, such as Egypt or the Gulf region, and high incidences are seen in countries with frequent periods of extreme heat, such as India or China [29]. In parallel, global warming, regardless of whether made by man or by nature, induces abnormal weather conditions also in regions with normally predictable moderate climate conditions. In addition, more and more insulin-treated people with diabetes are traveling and also live an active life with physical activities, such as mountain climbing [30], which again increases the need of better and more suitable personal insulin storage solutions.

The use of insulin in areas with extreme weather conditions is therefore expected to go up substantially over the next decade, and companies have been founded to develop better products to the existing ones to offer solutions for this unmet medical need. However, high-performance insulation by itself does not provide an adequate solution. Adding to it, small amounts of properly defined PCM provide an extremely effective and low form factor device solution, which provides protection to insulin contained in delivery pen devices on a daily basis over long period of time (1 year) without battery recharging. It regains its protective capability without user intervention, whenever the temperature

drops (e.g. at sundown). All the ViVi devices tested regained their protection following 6 h of placement in regular room temperature conditions (22–25°C/~72–77°F).

5. Conclusion

We have demonstrated a first-generation product, ViViCap-1, which combines in one device two temperature-controlling mechanisms in a proprietary manner (perfect insulation and active temperature stabilization) to offer a light and attractive cap protective solution for insulin in extreme hot and cold weather conditions without extra power requirements. The product keeps the inner cartridge temperature conditions below 30°C/86°F for more than 12 h. Such solution can be modified to fit additional injection devices, which contain sensitive drug formulations and are carried on a daily basis by people worldwide (like EpiPen). In addition, by modifying the PCM, a version of the device can be made to maintain drugs under refrigerated conditions (2–8°C/36–46°F) for extended periods of time.

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Declaration of interest

A Pfützner and G Pesach have received consulting fees from TemptraMed Inc, R Nagar is a founder and shareholder of TemptraMed Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

ORCID

Andreas Pfützner  <http://orcid.org/0000-0003-2385-0887>

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