

# Development of a Single-Site Device for Conjoined Glucose Sensing and Insulin Delivery in Type 1 Diabetes Patients

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**Abstract— Goal:** Diabetes patients are increasingly using a continuous glucose sensor to monitor blood glucose and an insulin pump connected to an infusion cannula to administer insulin. Applying these devices requires two separate insertion sites, one for the sensor and one for the cannula. Integrating sensor with cannula to perform glucose sensing and insulin infusion through a single insertion site would significantly simplify and improve diabetes treatment by reducing the overall system size and the number of necessary needle pricks. Presently, several research groups are pursuing the development of combined glucose sensing and insulin infusion devices, termed single-port devices, by integrating sensing and infusion technologies created from scratch. **Methods:** Instead of creating the device from scratch, we utilized already existing technologies and introduced three design concepts of integrating commercial glucose sensors and infusion cannulas. We prototyped and evaluated each concept according to design simplicity, ease of insertion, and sensing accuracy. **Results:** We found that the best single-port device is the one in which a Dexcom sensor is housed inside a Medtronic cannula so that its glucose sensitive part protrudes from the cannula tip. The low degree of component modification required to arrive at this configuration allowed us to test the efficiency and safety of the device in humans. **Conclusion:** Results from these studies indicate the feasibility of combining commercial glucose sensing and insulin delivery technologies to realize a functional single-port device. **Significance:** Our development approach may be generally useful to provide patients with innovative medical devices faster and at reduced costs.

**Index Terms—** artificial pancreas, electrochemical glucose sensor, insulin infusion set, insulin pump, medical device development, single-port device

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## I. INTRODUCTION

PATIENTS with type 1 diabetes are unable to produce insulin due to the autoimmune destruction of the B-cells in the pancreas [1]. As a consequence, type 1 diabetes patients require insulin replacement therapy to survive. The goal of the therapy is to avoid short-term, metabolic (dangerously low or high blood glucose concentration) and long-term, vascular (renal failure, blindness, nerve damage, and myocardial infarction) complications of the disease by replicating the insulin secretion of healthy individuals as close as possible [2]. The majority of type 1 diabetes patients administer insulin in the form of multiple daily subcutaneous (under the skin) injections. However, an increasing number of patients are recently switching to the insulin pump therapy. Compared to the insulin injections, the insulin pump therapy has been shown to improve clinical outcomes by continuously administering insulin via a subcutaneous cannula [3], [4]. To adjust the insulin dosage, all forms of insulin therapy require that patients use a blood glucose meter to frequently self-monitor the glucose concentration in the blood typically obtained by finger-pricking. However, since finger-pricking cannot be performed often enough to detect the early changes in the glucose concentration and carry out immediate corrective action, the blood glucose meters are increasingly being replaced by continuous glucose monitors (CGMs) as they provide continuous, real-time data throughout the day [5]. Much of the current focus in the pursuit of better clinical outcomes in diabetes patients [6], [7] is on designing smarter insulin pumps, developing more accurate CGMs, and coupling the state-of-the-art insulin pumps and CGMs to create a mechanical artificial pancreas (AP). A mechanical AP system facilitates automated blood glucose regulation by automatically administering appropriate amounts of insulin in response to real-time blood glucose measurements (Fig. 1a). One disadvantage of the current mechanical AP systems however is that the glucose sensing and the insulin delivery are performed by stand-alone components which require separate insertion sites (dual-port AP). Due to the spatial separation, these components need individual communication and power supply units, resulting in a bulky AP system. Furthermore, having to insert the glucose sensor and the insulin infusion cannula at two different subcutaneous

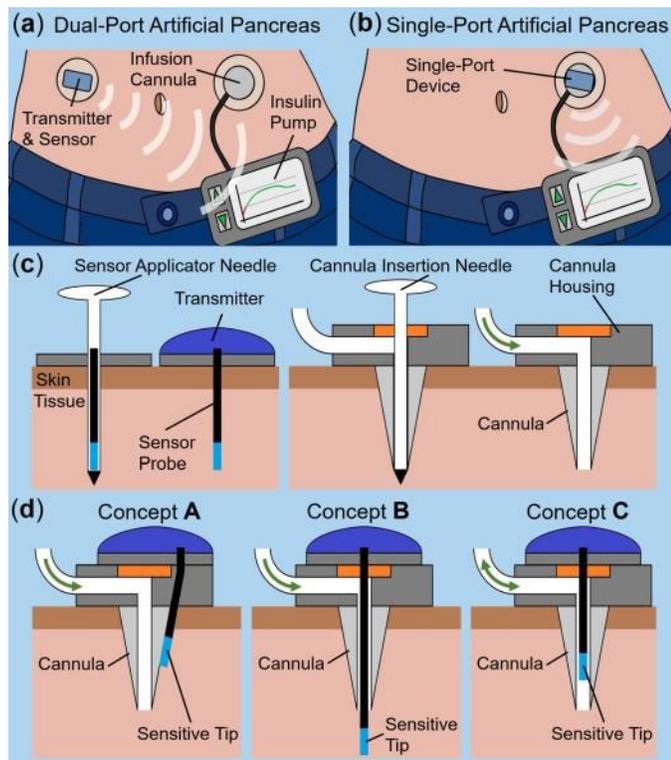


Fig. 1. Dual-port and single-port artificial pancreas (AP) systems and their constituent parts: (a) Schematic representation of a dual-port AP. (b) Schematic representation of a single-port AP. (c) Schematic cross-sectional view of commercially available needle-type continuous glucose monitors and insulin infusion sets commonly used in dual-port APs. (d) Schematic cross-sectional view of the single-port device design Concepts A, B, and C: Concept A: the sensor-probe is affixed to the outer cannula wall; Concept B: the sensor-probe is placed inside the cannula lumen so that the glucose-sensitive probe tip protrudes from the cannula tip; Concept C: the sensor-probe is placed inside the cannula housing lumen so that the glucose-sensitive probe tip resides in the cannula lumen.

tissue sites causes unnecessary pain, increases the risk of infection or skin problems [8], [9], and leads to impaired freedom of movement. In clinical studies performed to overcome these limitations [10]-[12], we have previously shown that glucose concentrations measured at the site of subcutaneous insulin infusion closely reflect the glucose levels in blood, thereby demonstrating the feasibility of conjoining glucose sensing and insulin delivery at a single subcutaneous tissue site. Integrating the glucose sensing and the insulin delivery components of an AP to perform sensing and infusion at a single tissue site (single-port AP) would allow a significant reduction in the overall system size since the number of the required system parts, such as power supply and communication units, could be decreased or some of the parts altogether eliminated. In addition, integrating the two components would also allow reducing the necessary number of treatment-related pinpricks to a minimum. Finally, managing diabetes with a single-port, as opposed to a dual-port AP (Fig. 1a,b) may result in improved patient convenience which in turn could lead to greater treatment acceptance. Several academic and industrial research groups are therefore working on a device that enables conjoined glucose sensing and insulin delivery at a single subcutaneous tissue site (single-port device). For example, the group from

Medtronic [13], and the group from Pacific Diabetes Technologies [14] are each developing a device which consists of an electrochemical glucose sensor integrated into the infusion cannula wall. Furthermore, the group from Johanneum Research and Graz University of Technology is working on a device in which an optical glucose biosensor is applied as a coating onto the infusion cannula wall and coupled to a read-out unit used to detect the glucose responsive changes in sensor fluorescence emission [15]. Finally, the group from Sensile Medical is developing a device consisting of a porous membrane that contains a glucose responsive hydrogel and a pressure sensor which measures the glucose responsive changes in fluidic resistance while insulin is being delivered through the membrane into the subcutaneous tissue [16]. All of these research groups share in common that their device development approaches are based on integrating new glucose sensor and insulin infusion technologies created from scratch. However, creating a medical device from scratch comes with high costs and risks since every stage of the highly regulated, multi-stage medical device development pathway has to be completed before a device can be brought to the market [17], [18]. Here we describe an alternative development approach that is more time- and cost-effective since it allows skipping some of these development stages. Our approach to the development of a single-port device is based on the integration of already existing glucose sensing and insulin delivery technologies. Thus, instead of creating the device from scratch, we performed a detailed analysis of the commercially available glucose sensing and insulin infusion technologies and introduced three design concepts of integrating commercial glucose sensors and infusion cannulas. Then, we built several prototypes of each concept and evaluated them according to design simplicity, ease of insertion, and sensing accuracy. Lastly, we assessed the best prototype in humans under real-use conditions.

## II. MATERIAS AND METHODS

### A. Candidate glucose sensing & insulin delivery components for the single-port device

The clinically useful state-of-the-art CGMs offered by Abbott, Dexcom and Medtronic [19]-[21] were considered as single-port device glucose sensing components. These CGMs track the glucose levels of the patients by measuring the glucose concentration in the interstitial fluid (ISF) of the subcutaneous tissue. They all consist of a subcutaneous needle-type sensor-probe which is secured in a plastic housing, a transmitter, and a receiver (Fig. 1c). Although the commercially available CGMs differ in shape, size, and insertion depth of the sensor-probe (5.5-14 mm), they share in common that the sensor-probe is inserted into the subcutaneous tissue with an applicator needle designed to protect it from the friction forces generated during insertion. Once inserted, the sensor-probe is operated with a transmitter which wirelessly sends the measured glucose concentration to a receiver (Fig. 1c).

The commercially available insulin infusion sets with soft Teflon cannulas were considered as the insulin delivery component for the single-port device, since they are more commonly used than the infusion sets with steel cannulas [22]. Infusion sets with soft cannulas consist of a subcutaneous Teflon cannula secured in a plastic housing and a tube emerging from the cannula housing (Fig. 1c). The soft cannulas are designed for either slanted or straight insertion and come in different cannula lengths (6-17 mm) as well as different cannula diameters (28-27 gauge) [23]. To insert them into the subcutaneous tissue an O-profiled steel needle housed inside the cannula is used (“over the needle insertion”). After insertion, the needle is withdrawn and the inserted cannula connected to an insulin pump.

### B. Single-port design concepts

Following the detailed analysis of the commercially available devices, we introduced three design concepts of integrating a needle-type CGM sensor-probe with a soft infusion cannula (Fig. 1d). The first concept involves affixing the sensor-probe to the outer cannula wall. The second concept involves placing the sensor-probe into the cannula lumen so that the glucose sensitive probe tip protrudes from the cannula tip. The third concept involves placing the sensor-probe into the cannula housing so that the glucose sensitive probe tip resides in the cannula lumen. Unlike the first two concepts, this concept requires a push/pull-style pump which supports infusion and withdrawal. When in push mode, the pump facilitates insulin delivery by transporting the insulin solution to the subcutaneous tissue and, when in pull mode, it facilitates glucose sensing by transporting the ISF from the subcutaneous tissue to the glucose sensitive sensor-probe tip.

### C. Building the single-port prototypes

Using commercially available CGMs and insulin infusion sets, we built several single-port device prototypes according to each concept. To build the prototypes, the CGM and the infusion set components were extracted in a laminar flow (HERAsave KS; Thermo Fisher Scientific, Massachusetts, USA) using scalpels, forceps, or scissors (Aesculap Surgical Instruments; B.Braun, Melsungen, GER), and subsequently integrated by press passing or gluing with biocompatible UV-curable glue (Vitrilit-UV; Panacol-Elosol GmbH, Steinbach, GER). Prior to integrating the components, the infusion cannulas were adapted when necessary using an excimer laser (Laser Center Hanover, Hanover, GER) or a custom-made thermal embossing device which comprised a heating element from Hasco (Cartdrige Heater; Hasco Austria Ges.m.b.H, Guntramsdorf, AUT). Finally, if necessary, custom-made components were fabricated by CNC-machining polycarbonate (KBG Kunststoff-Bearbeitung s Ges.m.b.H, Spielberg, AUT) and sterilized in an autoclave (Autoclave FVA-3; Fedegari Autoclavi SPA, Pavia, ITA) at high temperatures in pre-vacuum.

### D. Criteria to select the optimal single-port prototype

In the development of the single-port device, we placed high priority on achieving low development costs, improved

patient convenience, and high sensing accuracy during insulin delivery. We therefore introduced several criteria which reflect these priorities and desired performance characteristics. The best single-port device prototype was then selected according to these criteria. The used criteria were as follows:

*D.1. Glucose sensor function when exposed to insulin solution:* By integrating a glucose sensor with an insulin infusion cannula (Fig.1d), the glucose sensor-probe may be exposed to the infused insulin solution during insulin delivery. Therefore, several in vitro experiments were performed to determine whether the candidate commercially available CGMs are affected by insulin or the phenol and metacresol preservatives [24] contained in the rapid-acting insulin formulations commonly used in insulin pump treatment (Aspart: 100 U/ml, Aspart; Novo Nordisk, Bagsvaerd, DNK or Lispro: 100 U/ml Lispro; Eli Lilly, Indianapolis, USA). For these experiments, each CGM sensor-probe was slid into one end of an infusion set tube, while the other end was connected to a syringe filled with an insulin solution spiked with glucose (10%, Glucosteril; Fresenius Kabi GmbH, Bad Homburg, GER). After attaching the syringe to a pump (Pico Plus Elite; Harvard Apparatus, Holliston, USA) and placing the infusion set tube in a thermoregulated box (37°C, Hotbox; Med. Universität Graz, Graz, AUT), the tube was perfused with the glucose-spiked insulin solution at a constant rate. Two sets of experiments were performed. In the first set of experiments, the stability of the sensors under long-term exposure was tested by continuously exposing the sensor-probes (for 12 h) to an insulin solution containing glucose at a concentration of 200 mg/dl. In the second set of experiments, the linearity and sensitivity of the sensors under exposure to the insulin solutions was tested by sequentially exposing the sensor-probes to insulin solutions containing glucose at concentrations of 100, 50, 200, and 0 mg/dl (each for 45 min). During the experiments, the glucose sensors were either operated with their transmitters or with a potentiostat (PalmSens Handheld Potentiostat/Galvanostat, Palm Instruments BV, Houten, NL) that allowed direct access to the raw sensor signal. Detailed information on operating the glucose sensors with a potentiostat can be found in the Online Supplementary Material S1.

*D.2. Degree of required component modification:* To keep the development costs low, the sensor-probe and the cannula should be integrated in the simplest possible way. The prototypes were therefore rated with respect to the degree of modification required to integrate the two components.

*D.3. Feasibility of one-step device insertion:* To improve patient convenience, it is desirable to insert sensor and cannula of the single-port device in one step. Moreover, it would be advantageous to perform this one-step insertion with the existing CGM or cannula insertion instruments. Therefore, each prototype was rated depending on whether the design concept allows a one-step insertion with existing insertion instruments or a completely new insertion technique is needed.

*D.4. Ease of obtaining reliable glucose measurements during insulin delivery:* As mentioned above, a CGM tracks the glucose levels of the patients by measuring the glucose concentration in the ISF. By performing glucose sensing and insulin infusion at the same tissue site, the infused insulin solution may temporarily dilute the ISF surrounding the glucose-sensitive sensor-probe tip, resulting in a temporary decline of the local glucose concentration [11] and in measurements that do not reflect the blood glucose concentration of the patient. The single-port prototypes were therefore rated regarding the ease of preventing glucose sensing in diluted ISF.

*E. In-vivo experiments performed to test the selected single-port device prototype*

The selected single-port prototype was tested in two clinical trials. In the first trial, type 1 diabetes patients used the single-port device for insulin administration and glucose sensing during a 1-day stay at the Clinical Research Center (CRC). Data collected from this trial were used to inform final refinements in device assembly, insertion, and sensor operation. A detailed description of the study protocol can be found in the Online Supplementary Material S2. The second trial was conducted in type 1 diabetes patients to test the efficiency and safety of the final single-port prototype. The study protocol is described in full detail in the accompanying paper [26]. In brief, it involved an assessment of the single-port device performance during a 1-day stay at the CRC and further 6 days in the subjects' home environment. During the study day at the CRC, the single-port device was used in combination with an algorithm to perform closed-loop glucose control. During the 6 days in the subjects' home environment, the patients used the device for open-loop insulin delivery and glucose sensing.

### III. RESULTS

#### A. Selecting the optimal single-port prototype

Each single-port prototype was rated according to the criteria outlined in the material and methods section. The prototype with the highest score across all criteria was then selected for the human study.

*A.1. Glucose sensor function is not impaired by contact with insulin solutions:* Prior to the integration of the sensors of the candidate CGMs with the candidate insulin infusion cannulas, it was tested whether exposure of the sensors to rapid-acting insulin solutions impairs the sensor function. Figure 2 shows the glucose concentrations obtained during continuous and sequential sensor exposure to glucose-spiked rapid-acting insulin solutions. As can be seen, during the continuous exposure, stable signals were observed over a 12-hour period for all three sensors (Fig. 2, right column). Furthermore, during the sequential exposure, each sensor signal attained steady-state values proportional to the glucose concentrations contained in the insulin solutions (Fig. 2, left column). Taken together, these results suggest that none of the glucose sensors was impaired when exposed to insulin itself or the

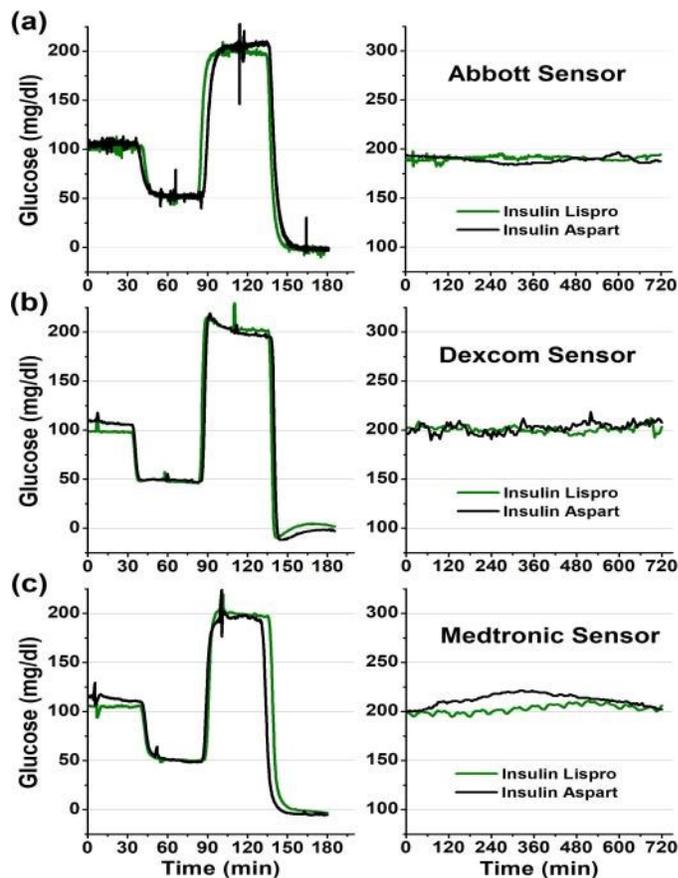


Fig. 2. Glucose concentration time courses obtained during exposing the sensors from (a) Abbott, (b) Dexcom and (c) Medtronic to rapid-acting insulin solutions (Lispro and Aspart) spiked with glucose. The left column shows the time courses obtained during sensor exposure to a sequence of insulin solutions containing glucose at concentrations of 100, 50, 200, and 0 mg/dl, whereas the right column depicts the time courses obtained during continuous sensor exposure to insulin solutions containing glucose at a concentration of 200 mg/dl.

preservatives contained in the insulin formulations. Therefore, the maximum rating was assigned to all single-port prototypes regardless of whether they are realized with a sensor from Abbott, Dexcom or Medtronic (Tab. 1).

#### A.2. Degree of required component modification varies among prototypes:

The degree of component modification required to realize a certain prototype is depending on the chosen design concept (Fig. 1d). Representative prototypes built according to each of the three concepts are shown in Figure 3. As can be seen, realizing a prototype according to Concept A (Fig. 3a) requires extensive component modifications since affixing the sensor-probe to the outer cannula wall involves carving a groove into the cannula wall and gluing the sensor-probe into the groove. In contrast, realizing a Concept B prototype (Fig. 3b) requires almost no component modifications since the sensor-probe is simply inserted into the self-sealing septum of the cannula housing and guided through the cannula lumen until it protrudes from the cannula tip. Similarly, Concept C prototypes (Fig. 3c) are also built by inserting a sensor-probe into the self-sealing septum of the cannula housing. However, here the sensor-probe is entirely placed inside the cannula lumen, making it necessary to perforate the cannula to aid transport of the ISF to the sensitive portion of the probe.

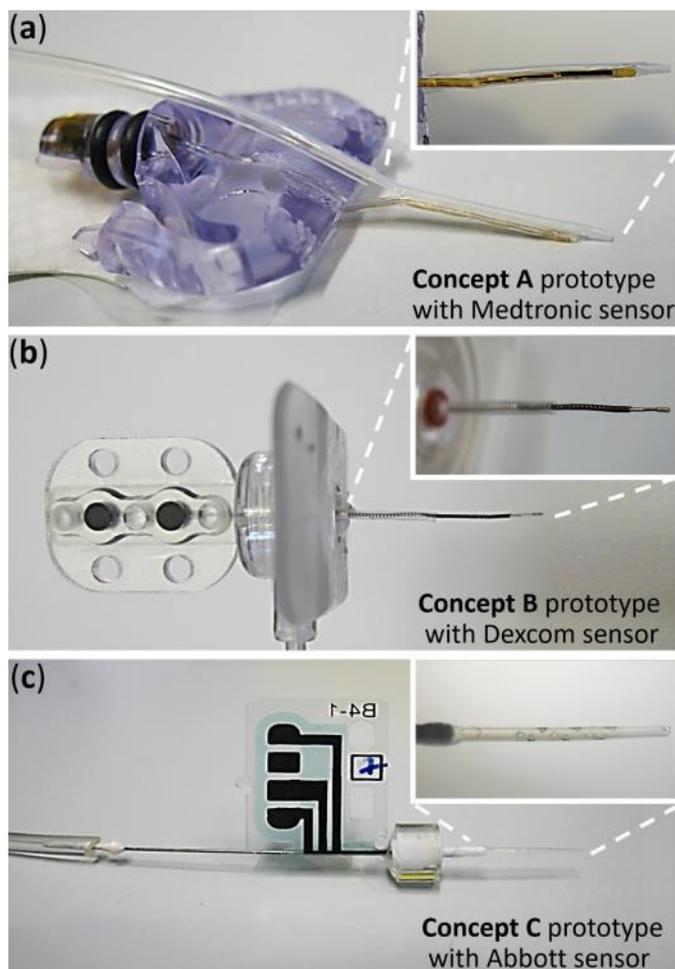


Fig. 3. Representative single-port prototypes built using each design concept: (a) A Concept A prototype with the Medtronic CGM sensor-probe affixed to the outer cannula wall. To affix the probe, a groove was carved in the outer cannula wall and the probe was glued into the carved groove. (b) A Concept B prototype with a Dexcom CGM sensor-probe protruding from the cannula tip. To house the sensor-probe inside the cannula so that its glucose sensitive tip protrudes from the cannula tip, the probe was inserted into the self-sealing septum of the cannula housing and guided through the cannula lumen until it protruded from the cannula tip. (c) A Concept C prototype with an Abbott CGM sensor-probe residing in the cannula lumen. To house the entire sensor-probe inside the cannula, the probe was inserted into the self-sealing septum of the cannula housing and placed inside the cannula lumen. Prior to placing the sensor-probe inside the cannula, the cannula was perforated with a laser to aid transport of the ISF to the sensor-probe.

Thus, Concept C prototypes still require more component modifications than Concept B prototypes. We therefore rated the single-port prototypes built applying design Concept C lower than those built applying Concept B, but higher than those built applying design Concept A.

**A.3. One-step device insertion is feasible for certain prototypes:** Basically all three concepts may allow a one-step insertion with an existing insertion instrument. For example, similar to an infusion cannula, Concept A prototypes (Fig. 1d) can be inserted using a cannula insertion needle. This cannula insertion needle resides in the lumen of the single-port cannula that has the sensor-probe affixed to its outer wall. When inserting the needle into the tissue, cannula and sensor-probe of the prototype are then following the needle through the same perforation. However, during this insertion process, the

sensor-probe is directly exposed to friction forces which may then cause damage to it. Thus, protecting the sensor-probe against the friction forces generated during the insertion process would require further design refinements, such as creating an additional lumen for the probe, which would result in increased development and manufacturing costs. In contrast, when the sensor-probe and cannula are integrated applying design Concept B or C, no further design refinement is necessary to protect the sensor since here the one-step insertion can be carried out using the sensor-containing applicator needle. To insert such a single-port device the cannula insertion needle is first replaced by the sensor applicator needle (Fig. 4a,b). Then, the applicator needle is guided into the tissue with the cannula following the needle through the same perforation. However, the cannula insertion needle can only be replaced by the sensor applicator needle if they are the same size and shape. So far, all commercially available insulin infusion sets come with an O-shaped insertion needle. However, among the commercially available CGMs, only the Dexcom CGM comes with an O-shaped sensor applicator needle. Applicator needles from the other CGM manufacturers (Abbott and Medtronic) are either V- or C-shaped. When comparing the O-shaped sensor applicator needle from Dexcom with insertion needles of commercial infusion cannulas, we found that the Dexcom applicator needle perfectly matches the cannula insertion needle of a Medtronic infusion set (Sof-Set Micro QR, cannula length: 6 mm, tube length: 610 mm; Medtronic MiniMed, Northridge, CA, USA) and thus can be used to replace it (Fig. 4a,b,c). In view of these considerations, we rated prototypes with design Concepts B and C higher than those with design Concept A as they require no additional design modifications to protect the sensor-probe during insertion. Furthermore, since only the O-shaped sensor applicator needle from Dexcom can be used for the one-step insertion, we rated Concept B and C prototypes realized with a Dexcom CGM higher than those realized with Abbott or Medtronic CGMs (Tab. 1).

**A.4 Bringing the sensor in contact with ISF not diluted by insulin solution is possible:** To measure the glucose concentration correctly, the sensor of the single-port device has to be in contact with ISF that is not diluted by the infused insulin solution. To avoid measuring the glucose concentration in diluted ISF, the sensitive probe tip and the cannula tip of Concept A or B prototypes were positioned at the maximum possible distance from each other. In Concept A prototypes, this was achieved by integrating a long cannula and a short sensor-probe, while in Concept B prototypes the maximum distance between the two was ensured by integrating a short cannula and a long sensor-probe, like the one from Dexcom (Fig. 4d). In contrast, since in Concept C prototypes the sensor is located inside the cannula, bringing the sensitive probe tip of these prototypes in contact with undiluted ISF requires switching the insulin pump to the withdrawal mode and operating it in this mode until the fluid surrounding the probe tip is free of insulin. However, the current insulin pumps would first have to be adapted to allow bidirectional flow, thus

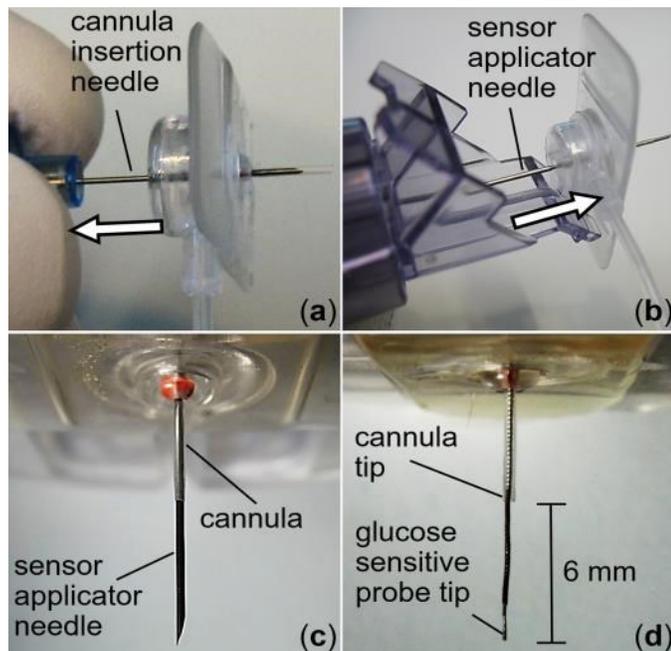


Fig. 4. Achieving the maximum distance between the sensor-probe tip and the cannula tip in a Concept B prototype: (a) The Medtronic cannula insertion needle is removed from the cannula lumen. (b) The Dexcom applicator needle is inserted through the self-sealing septum of the cannula housing. (c) and (d) Following insertion, the sensor-probe tip is positioned at the maximum distance from the cannula tip.

making a realization of a single-port device according to Concept C more costly than those according to the other two concepts. Consequently, Concept A and B prototypes were rated higher than Concept C prototypes since they do not require a push/pull-style pump to obtain reliable glucose measurements. In Concept A and B prototypes, however, a long distance between the sensitive probe tip and the cannula

tip is required to avoid measuring in diluted ISF. While this can be achieved with all sensor-probes in Concept A prototypes, Concept B prototypes can only be realized with the long sensor-probe from Dexcom. Therefore, only the Concept B prototypes with a Dexcom CGM scored equally high as the Concept A prototypes (Tab. 1).

*A.5. The single-port prototype evaluation summary:* Table 1 summarizes the rating of the single-port prototypes. For each of the established selection criteria, points were assigned to the prototypes: 2 for good, 1 for fair, and 0 for poor. With a sum of 8 points across all criteria a Concept B prototype built using the Dexcom sensor and the Medtronic infusion cannula was found to be the most suitable single-port prototype. This prototype is described in more detail below.

### B. The final single-port prototype

The selected single-port prototype consists of a Dexcom G4-Platinum CGM (G4-Platinum, Dexcom Inc., San Diego, USA), a Medtronic Sof-Set insulin infusion set (Sof-Set Micro QR, cannula length: 6 mm, tube length: 610 mm; Medtronic MiniMed, Northridge, CA, USA), and a custom-made transition piece (CNC-machined from polycarbonate; 4A engineering GmbH, Traboch, Austria; Fig. 5a). The sensor-probe of the Dexcom CGM is positioned inside the cannula of the Medtronic infusion set in such a way that the glucose sensitive probe tip protrudes 6 mm from the cannula tip (Fig 4d), [25]. The transition piece is used to mount the G4 sensor housing onto the top of the cannula, and to provide a secure attachment of the prototype to the patient's skin (Fig. 5d). Cannula and sensor of the prototype can be inserted in one step with a Dexcom sensor applicator (Fig. 5c). Furthermore, a conventional insulin pump can be used to deliver insulin via the single-port prototype (Fig. 5d).

TABLE I  
THE SINGLE-PORT CONCEPT EVALUATION SUMMARY

Selection Criteria	Concept A			Concept B			Concept C		
	ABB	DEX	MED	ABB	DEX	MED	ABB	DEX	MED
Glucose sensor function when exposed to insulin solution	2	2	2	2	2	2	2	2	2
Degree of required component modification	0	0	0	2	2	2	1	1	1
Feasibility of one-step device insertion	0	0	0	1	2	1	1	2	1
Ease of obtaining reliable glucose measurements during insulin delivery	2	2	2	1	2	1	0	0	0
Total	4	4	4	6	8	6	4	5	4

\*ABB = Abbott; DEX = Dexcom; MED = Medtronic

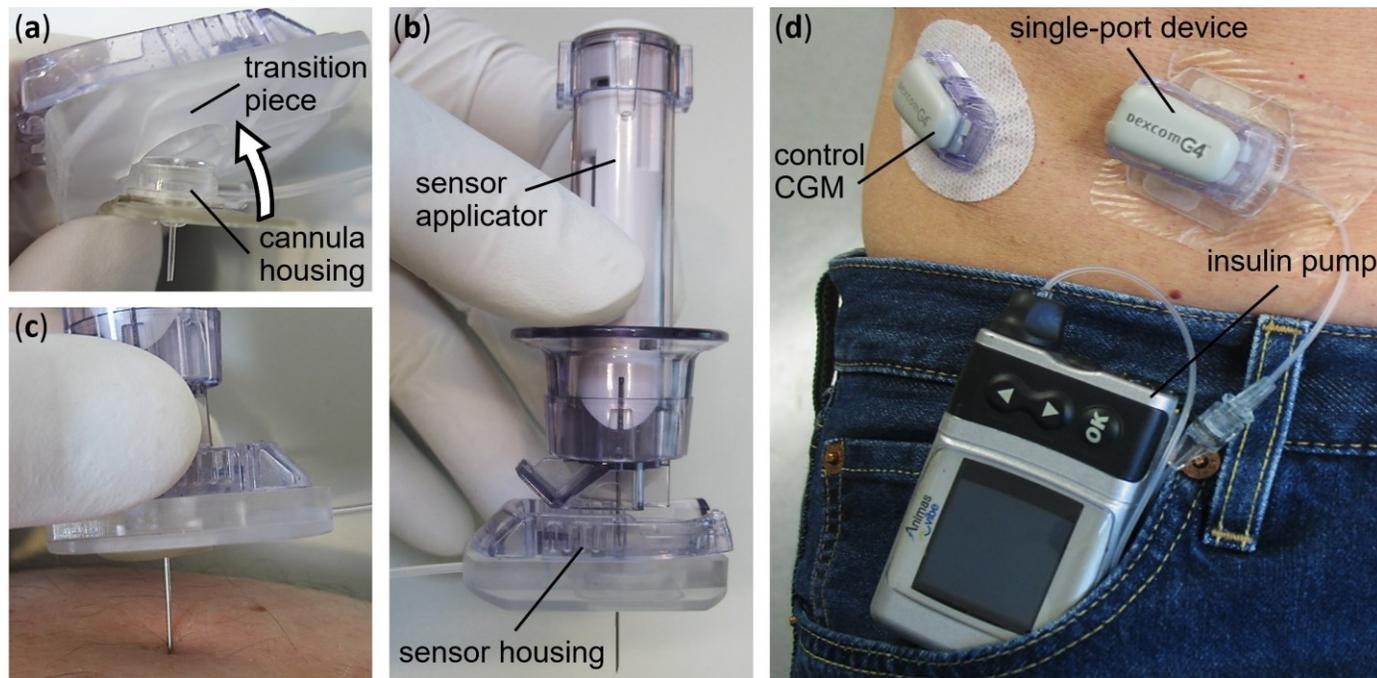


Fig. 5. Assembling and inserting the final single-port prototype: (a) The Dexcom CGM housing is mounted onto the Medtronic infusion cannula housing using a custom-made transition piece. (b) The Dexcom sensor applicator needle is inserted through the cannula housing septum and guided through the cannula until it extends 6 mm beyond the cannula tip. (c) The assembled single-port device is inserted into the subcutaneous tissue in one step. (d) After the applicator needle is removed, the Dexcom CGM transmitter is connected to the sensor-probe, making the single-port device ready for use.

### B.1. Assembling and inserting the final single-port prototype:

The assembly of the single-port prototype is performed in a laminar flow hood under sterile conditions prior to each experiment. First, the cannula insertion needle of the Medtronic Sof-Set is removed and the cannula housing pressed into the custom-made transition piece (Fig. 5a). Next, an insulin pump (Animas-Vibe Insulin Pump; Animas Corp., West Chester, USA) is connected to the infusion set and the tube filled with a glucose-spiked insulin solution. After the two are connected, the sensor housing of the Dexcom CGM is removed from the sensor applicator and the sensor-containing applicator needle inserted through the self-sealing septum of the cannula housing and guided through the cannula until it extends 6 mm beyond the cannula tip (Fig. 5b). The thus assembled single-port device is then inserted into the subcutaneous tissue in one step (Fig. 5c). After the applicator needle is removed, the Dexcom transmitter is connected to the sensor-probe, making the single-port device ready for use. The instructions on how to connect the transmitter to the sensor-probe can be found in the Online Supplementary Material S3.

### B.2. Avoiding false sensor errors during bolus insulin delivery:

During our first in vivo study with the single-port device, we found that when insulin is administered at a high infusion rate (bolus delivery), it may dilute the ISF surrounding the glucose sensitive probe tip even when the probe tip is positioned at the maximum distance from the cannula tip (Fig. 4d). Usually it takes only about 15 min until the insulin fluid has been absorbed and the ISF is again undiluted. However, the sudden drop in the glucose concentration that results from the ISF being diluted can be misinterpreted as sensor error by the CGM software. The

consequence of such false sensor errors is that the glucose values are not being displayed by the CGM receiver for up to two hours (Fig. 6a, white lines). The simplest way to avoid these false sensor errors involves instructing the CGM software to ignore the glucose sensor signal for about 15 minutes after an insulin bolus has been delivered. However, since we had no access to the source code of the CGM device, we initially avoided potential sensor errors by using the extended instead of the normal bolus delivery mode of the Animas insulin pump (Fig. 5d). In the extended bolus mode, the bolus delivery duration is increased but the insulin infusion rate decreased [3], [4]. Insulin delivered at this decreased rate did not dilute the ISF surrounding the glucose sensitive probe tip, thus no false sensor errors occurred (Fig. 6b). However, the extended bolus comes at a price of slower insulin absorption and consequently delays the re-establishment of the patients' normal blood glucose concentration. Therefore, we continued with using the regular bolus, but prevented the sudden drops in the ISF glucose concentration that caused false sensor errors by adding a small amount of glucose (200 mg/dl) to the administered insulin solutions (Fig. 6c).

### B.3. Efficiency and safety of the final single-port prototype:

A detailed description of the results from our second in-vivo study, in which the final single-port device prototype was evaluated over a 6-day period at home and during a 1-day stay at the CRC, can be found in the accompanying paper [26]. In brief, the quality of glucose sensing with the single-port device during basal and bolus insulin delivery was comparable to that of an additionally worn control CGM. Furthermore, the insulin delivery via the single-port device was reliable and safe during home use and, when performed in combination

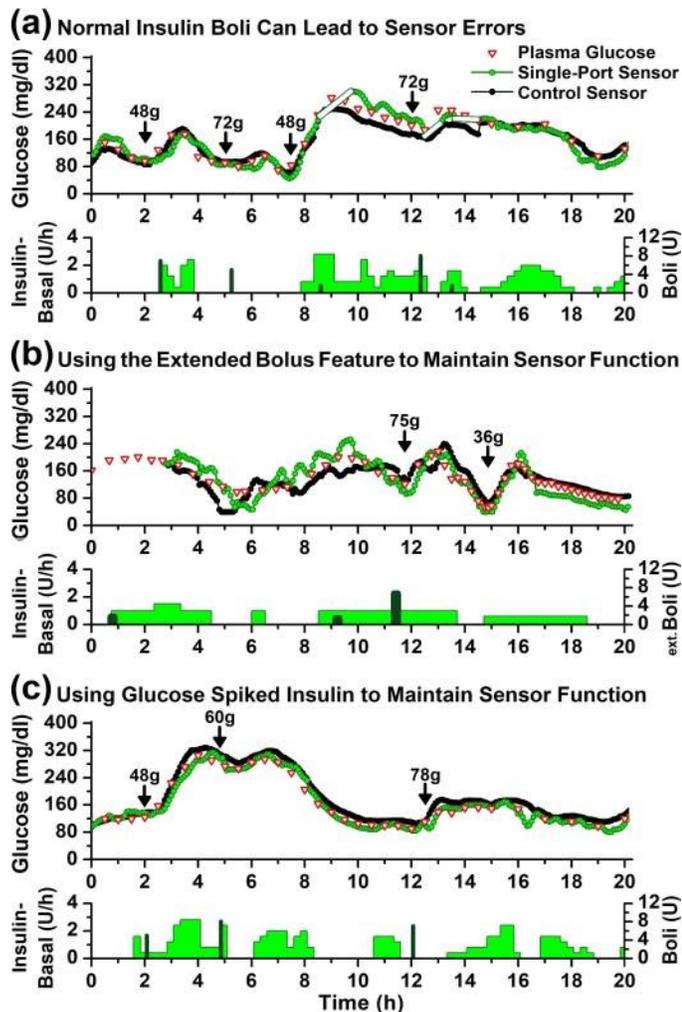


Fig. 6. Avoidance of false sensor errors during bolus delivery: Shown are the glucose concentration time courses obtained with the single-port device (green dots), the glucose concentration time courses obtained with the control CGM (black dots), the reference blood glucose concentrations (red triangles), the carbohydrate intake (black arrows), the basal insulin infusion rates (green bars), and the delivered insulin boli amounts (dark green bars). (a) The occasional sensor error (white lines) that may occur following normal bolus delivery can be prevented (b) by using the extended bolus mode or (c) by spiking the infused insulin with small amounts of glucose.

with a control algorithm, was adequate to achieve and maintain near normoglycemia. Overall, results of the trial suggest the safety and efficiency of the developed single-port device.

#### IV. DISCUSSION

The present report describes a simple and cost-effective realization of a diabetes treatment device for performing glucose sensing and insulin delivery through a single skin insertion site (the single-port device). In contrast to previous approaches based on the integration of glucose sensing and insulin infusion technologies created from scratch, we utilized already existing technologies and introduced several design concepts of integrating commercial glucose sensors and infusion cannulas. We prototyped and evaluated each concept according to design simplicity, ease of insertion, and sensing accuracy. We found that the best single-port prototype is the

one in which a Dexcom G4-Platinum sensor-probe is inserted through the self-sealing septum of a Medtronic Sof-Set infusion cannula housing and subsequently placed in the cannula lumen so that its tip extends approximately 6 mm beyond the cannula tip. Owing to the low degree of component modification required to arrive at this configuration we were able to proceed directly to testing the final prototype in vivo in humans. Results from these human studies indicate the feasibility of integrating components of commercially available glucose sensing and insulin delivery technologies to realize a functional single-port device.

A single-port device, like any new treatment modality, must be proved safe and effective before regulatory authorities will approve it for marketing [27]. Since single-port devices integrate glucose sensing and insulin infusion technologies, approval for market introduction will require clinical data demonstrating that the devices' performance is at least equivalent to that of commercially available CGMs and insulin delivery devices. Thus, to prove safety and efficiency of a single-port device, the device's manufacturer will be required to conduct clinical trials to assess the performance characteristics of the single-port device and compare its performance to that of commercially available CGMs and insulin delivery devices.

A performance characteristic that may be essential in the safe use of a single-port device is the maintenance of the device's structural integrity. Although potential issues with structural integrity may arise at any point in the single-port device lifespan, they are most likely to occur during insertion due to the device being exposed to high friction forces that arise between the tissue and the outer surface of the device. Currently, all research groups pursuing alternative approaches to the realization of a single-port device integrate the glucose sensor onto the outer wall of the infusion cannula. Hence, with such a design, high friction forces generated during the insertion process may increase the probability of sensor failure. For example, following insertion into adipose tissue of swine, Ward et al. observed fractures or short circuits in approximately one third of their electrochemical glucose sensors integrated onto the outer cannula walls [28]. To reduce the probability of experiencing such structural integrity issues Rumpler et al. pre-punctured the human skin with a large gauge needle prior to inserting the device [29]. However, a more permanent solution would require time- and cost-intensive single-port design refinements like creating an additional lumen for the sensor-probe, increasing the glucose sensor's mechanical robustness or developing completely new insertion techniques. In contrast to the integration of the sensor onto the outer wall of the infusion cannula, the sensor of the single-port device presented here is positioned in the lumen of the infusion cannula (Fig. 4). Since the sensor applicator needle precisely fits into the lumen of the infusion cannula, both sensor and infusion cannula can be simultaneously inserted using the applicator needle (Fig. 5). During insertion, the sensor is encased by the applicator needle and so protected against the generated friction forces (Fig. 4). Thus, with this design and mode of device insertion,

sensor damage and subsequent sensor failure may be avoided. Indeed, following device insertion, in no one of the type 1 diabetes patients participating in the clinical trials was any sensor failure observed [26].

Besides the maintenance of the device's structural integrity, other important performance characteristics that have to be shown to be equivalent to that of commercial CGM and insulin delivery devices are the accuracy and reliability of the glucose sensing and insulin infusion with the single-port device. A common metric used to quantify the accuracy of commercial CGM devices is the MARD value, which is defined as the mean absolute relative difference between CGM measurements and matched reference blood glucose measurements [30]. Currently, commercial CGM devices already reach MARD values below 15% [31], [32] and are therefore considered accurate enough for the use in artificial pancreas systems [33]. To our knowledge, so far only two other research groups reported the *in vivo* assessment of the accuracy of the glucose sensing with their single-port devices. In a study conducted under hospital settings, the glucose sensing accuracy of the single-port device was evaluated in type 1 diabetes subjects without however administering any insulin via the device [29]. In other *in vivo* studies, the glucose sensing accuracy of the single-port devices was assessed in anesthetized swine during either constant basal insulin delivery [15], [34], [35] or following the administration of bolus insulin [28], [34]. The MARD values reported in these studies ranged from 13.5% to 22.5% [15], [28], [29]. Unfortunately, since a retrospective calibration method was used to convert the sensor currents into blood glucose concentrations, it is difficult to directly compare the reported MARD values with those of commercial CGM devices which typically employ a prospective calibration scheme [36]. Compared to the prospective calibration of commercial CGM devices, retrospective calibration of a glucose sensing device may result in an inflation of the accuracy measures that, in turn, may lead to an overly optimistic appraisal of the device's performance [36]-[38]. Furthermore, since in the retrospective calibration all paired sensor current values and reference glucose readings generated throughout the entire experiment are used to convert sensor currents into blood glucose concentrations, retrospective calibration is only performed at the completion of the experiment and, therefore, cannot be used for real-time display of blood glucose concentrations [36]. In comparison, during our home trials, the conversion of sensor current values into glucose concentrations was carried out using the prospective calibration method incorporated in the data processing unit of the Animas pump. The obtained glucose concentrations were then displayed in real time on the pump's display module (Fig. 5d). To assess the accuracy of the glucose sensing with our single-port device, capillary blood glucose concentrations were frequently determined and a Dexcom CGM device was additionally worn by the patients (Fig. 5d). We found that the accuracy measures calculated for the single-port device were comparable to those calculated for the additionally worn CGM device [26]. For instance, the average MARD value obtained for the single-port device was

13.0% and did not differ from that obtained for the CGM device (13.9%). In addition, insulin delivery with the single-port device was found to be reliable and safe during the home-use period and, when performed in combination with a control algorithm, was adequate to achieve and maintain near normoglycemia [26]. Thus, these results indicate that the commercial glucose sensor incorporated into the single-port device maintained comparable accuracy to that of the same commercial sensor placed well apart from the tissue site of insulin delivery. Furthermore, these results also suggest that the delivery of insulin with the single-port device is equally reliable as with commercial stand-alone delivery devices.

Given these promising clinical results, we are currently focusing on improving the usability of the single-port device to allow the performance of clinical trials in which the device is evaluated under unsupervised home-use conditions over treatment periods of several weeks. Specifically, since the assembly and insertion of the current device have to be performed at the CRC and cannot be done by the patients themselves (Fig. 5), we are aiming to realize an automatic, spring-loaded insertion instrument [39] that facilitates easy insertion of the single-port device by the patients themselves. Furthermore, since a small amount of glucose had to be added to the standard insulin solutions to avoid false glucose sensor errors caused by the rapid dilution of ISF following bolus insulin delivery (Fig. 6c), we are currently evaluating alternative ways of avoiding the occurrence of these sensor errors. One way would be to simply instruct the device's data processing unit to ignore the measured glucose concentration for a short period of time after a bolus of insulin is administered (about 15 min). However, doing so may come at the price of not being able to display glucose values for a period of 15 min each time an insulin bolus is delivered. Another, more sophisticated way to avoid the occurrence of false sensor errors when boluses of insulin are delivered would be the application of the ionic reference technique [11], [12], [40]. This technique is based on the monitoring of the electrical conductivity in the ISF. When this fluid gets diluted by another fluid that has a different conductivity (e.g. insulin solutions have substantially lower conductivities than ISF), the degree to which the ISF has been diluted can be determined from the changes in the monitored conductivity. The glucose concentration in the undiluted ISF can then be calculated from the observed dilution degree and the glucose levels measured by the single-port sensor. Thus, integration of the ionic reference technique in the single-port device would allow glucose readings to be displayed also during the critical 15-min period following the bolus delivery of insulin. In addition, the ionic reference technique may be easily integrated into the single-port device, since the device's glucose sensor may additionally be used to monitor the electrical conductivity in its surrounding ISF. Both the use of the automatic insertion instrument and application of the ionic reference technique will allow the single-port device to be further evaluated under unsupervised home-use conditions and over longer periods of treatment. Next to evaluating the single-port device with regard to its safety and effectiveness, an additional aim of the

planned clinical trials will be to determine the maximum wear-time of the device. Since the sensor used in the device is approved for 7 days of continuous use, application of the single-port device would be more cost-effective if its usage time could be extended to the sensor's approved life-time of 7 days. In our previous clinical study, the achieved mean wear-time of the single-port device was 6.4 days [26]. In order to increase the mean wear-time of the single-port device to at least 7 days, we plan to apply a novel method for determining the longest possible duration of use of an insulin infusion site [41]. This method is based on the monitoring of the hydraulic tissue resistance (TR) at the subcutaneous insulin infusion site (i.e., the resistance exerted by the subcutaneous tissue on the infused insulin solution) by using a pressure sensor. We previously observed that TR is generally decreasing during the first 2 to 3 days of infusion site use but is progressively increasing as the use of the infusion site is continued, and that there is a strong inverse relationship between TR and the efficiency of insulin absorption from the site of insulin infusion [41]. Thus, because of this relationship, a too high TR value observed during infusion site use may indicate that the maximum duration of its use is reached and that a new infusion site should be established. Therefore, integration of this method in the single-port device would allow the longest possible wear-time of the device to be determined. Furthermore, the method may be easily integrated into the single-port device, since the already existing occlusion detection sensor of the insulin pump may additionally be used to monitor the TR.

Currently, most commercial CGM devices are using a subcutaneous needle-type sensor, except the novel CGM device from Senseonics, which employs a fully implantable glucose sensor [42]. It has been shown that this novel CGM device can be safely used for 90-180 days and its accuracy is comparable to that of current CGM devices using needle-type sensors [42]. Given these favorable performance features, it may seem possible that the CGM devices using fully implantable glucose sensors will replace needle-type glucose sensor devices in the near future, in which case the proposed single-port system (which integrates a needle-type sensor) may not gain substantial market traction. However, it may be argued that when a fully implantable glucose sensor device is used in combination with an insulin pump (e.g., within an AP system), the patient is still required to insert a new insulin infusion cannula every 2-3 days and surgically implant a new glucose sensor every 90-180 days. In comparison, when the single-port device is used to treat diabetes, the patient is only required to change the sensor-cannula arrangement on a weekly basis. Thus, diabetes treatment using a fully implantable glucose sensor device together with an insulin pump may still be more invasive than the treatment using the single-port device. Therefore, the market introduction of CGM devices employing fully implantable glucose sensors may not limit the market potential of the single-port device.

## V. CONCLUSION

In the present report, we describe a simple and cost-effective realization of a diabetes treatment device for performing glucose sensing and insulin delivery at a single subcutaneous tissue site (the single-port device). Instead of creating the device from scratch, we utilized already existing glucose sensing and insulin infusion technologies and introduced three design concepts of integrating commercial glucose sensors and infusion cannulas. We prototyped and evaluated each concept according to design simplicity, ease of insertion, and sensing accuracy. We found that the best single-port prototype is the one in which a Dexcom G4-Platinum sensor is housed inside a Medtronic Sof-Set cannula so that its glucose sensitive part protrudes from the cannula tip. Owing to the low degree of component modification required to build this single-port prototype, we were able to proceed directly to evaluate it in human studies. Results from these studies indicate the feasibility of integrating components of commercially available glucose sensing and insulin delivery technologies to realize a functional single-port device. Thus, using this development approach, skipping of some early stages of the medical device development pathway was possible. Skipping stages of the complicate and highly regulated medical device development pathway may significantly reduce development time and cost. Furthermore, performing a validation of a medical device under real-use conditions early on in the development pathway may help to avoid costly dead-end development paths and waste of resources. Therefore, our device development approach presented here may be generally useful to provide patients with innovative medical devices faster and at reduced costs.

## APPENDIX

This paper has Online Supplementary Material available at  
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