Dose and Time Controlled Electronic Insulin Pen: Bilensulin

Mana SEZDI[1], Ahmet BILEN [2]

[1]Biomedical Device Technology Programme, Istanbul University, Istanbul, Turkey
[2]Biomedical Engineering, Yeni Yuzyil University, Istanbul, Turkey
mana@istanbul.edu.tr, ahmetbilen_07@hotmail.com

Abstract: In this study, an electronic insulin pen was designed for diabetic patients dependent on insulin use in order to prevent wrong timing and wrong dosage caused from old age, vision or mental illness. During design, the patients' necessities such as easy-to-use, have been considered. The insulin pen that can be used electronically for routine dose injections, and that is called as Bilensulin, was designed to be able to used manually in the emergency. It is aimed that the patient can set the dose easily by using the fairly simple menu of the device. Additionally, the device was designed as reusable by changing the insulin cartridge. Because the tube chamber was designed to be suitable for all types of insulin, it can be used by changing cartridge without using different pen. Dose accuracy was tested by performing insulin dose measurements on a sensitive balance, and dose of Bilensulin was compared with the three types of insulin pens. The patent has been applied for this designed electronic insulin pen. The mechanism of change of cartridge has been put into the foreground in terms of ease of use and constituted the sub-structure of the patent application. Currently, the studies on the device are continuing.

Keywords: *Insulin, dose, diabetes, insulin pen***.**

1. Introduction

Insulin is a hormone secreted by the pancreas that helps the body use sugar and keeps the sugar level at the normal level. The sugar, which is the main food source of our bodies, must enter the body cells of the bloodstream (muscle cells, fat cells and liver cells) in order to provide energy. Insulin separates the blood sugar from the bloodstream and allows it to enter the cell, thus reducing the level of sugar in the blood [1].

In a non-diabetic person, after each food intake, the pancreas produces insulin to make the energy of the food taken up. This means that all people are dependent on insulin. In diabetics, the pancreas does not produce enough insulin or the insulin produced is not used by the target cells (muscle, fat and liver cells). In this case, insulin, which has a vital prescription for our bodies, needs to be taken from the outside [1].

Due to the complexity of insulin injections, insulin pens are preferred by the patients with diabetes. Several studies have demonstrated benefits of insulin pen devices for patients especially for pediatric and geriatric patients [2-4]. The studies have shown that insulin pens are preferred because of their ease of use and flexibility. Insulin pens provide more accuracy, especially for low-dose administration and the old patients [5-7].

During insulin therapy, there are some barriers presented from diabet disease in elderly patients.

Visual impairment, blindness, limited joint mobility and symptomatic peripheral neuropathy cause the difficulties on insulin theraphy [8]. These disabilities may make it more difficult for patients to use insulin pen. Visibility required to adjust a required dose and force required to inject an insulin dose are important factors for insulin pens [9]. A device with a clear dose scale, audible clicks accompanying the dialing of each dose, a large dose delivery button, and comfortable to handle device are important features for old patients [8].

There are two types of insulin pens: prefilled disposable pens and refillable pens [10]. Prefilled disposable pens are designed with a built-in and prefilled insulin reservoir containing 3ml (300 units) of insulin. Once empty, the patient must use another prefilled device. Refillable pens combine the reusable syringe and insulin container with disposable insulin cartridges containing 3ml insulin (Figure 1). These pens may be used for several years with only the needles and cartridges being replaced [5].

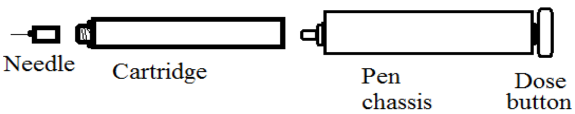

Figure 1. Schematic representation of refillable insulin pens

Before use, the refillable pens must be loaded with an insulin cartridge. The holder of cartridge is twisted from the

Received on: 31.01.2017
Accepted on: 14.03.2017

barrel and the cartridge is loaded with the piston rod fully depressed.

The aspects of the insulin pens for elderly patients must be considered as physical aspects and memory aspects separately [11].

The most important aspects of the physical feature of the insulin pen are attaching/removing cartrige holder and applying low force to inject insulin [12, 13]. But, because diseases such as hand tremor or difficulty in applying adequate force during injection affect the treatment process of elderly patients. In order to remove this negative effect, electronic insulin pens with motor system have begun to be developed.

Whether the insulin pen is mechanical or electronic, the patients and healthcare professionals want to be sure injected dosage and injection time. The insulin pens with memory function developed for this purpose are still used in the market. The feature is designed for patients who cannot remember if they administered the last dose or how much was last injected [14]. The most important aspects of the memory feature of the insulin pen according to the patients and healthcare professionals are [12];

Ability to view the units of previous insulin dose
Ability to view the time of previous insulin dose
Ability to view the date of previous insulin dose
Ability to view the previous 16 doses
Ability to confirm injection taken

In this study, considering the physical and memory features of such insulin systems, an easy-to-use electronic insulin pen was designed to prevent the wrong dose from being used in patients with mental or visual disturbances.

In this study, considering the physical and memory features of such insulin systems, an easy-to-use electronic insulin pen, named as Bilensulin (BS), was designed to prevent the wrong dose for patients with mental or visual disturbances or hand immobilities.

2. Design Modules

Bilensulin (BS) is a reusable pen for use with prefilled insulin cartridges. It is the pen that possesses a memory feature permitting the previous 16 doses to be stored with the date and time of dosing. BS designed for electronic injection, as shown in Figure 2 consists of the components listed below:

1) Motor: The self-driven driver allows the piston to move by turning. It begins to rotate with the force given to it and pushes the piston. When the cartridge is finished, it moves in the opposite direction and pulls back the piston.

2) Piston Driver: It is connected to the motor and has the cartridge on the other end. The motor moves in response to the push and applies pressure to the cartridge to inject the liquid. It is female and has a male part. It performs the movement in both directions according to the screw step.

3) Support Module: During the cartridge exchange, it prevents the piston from coming out of the moving part. It keeps the system fixed.

4) Insulin Cartridge: It is a tube with insulin liquid inside. It contains 3ml (300U) insulin.

5) Cartridge Change Mechanism: This is the part where the device doubles for replacement with the cartridge finish. It looks like a standard door hinge. The driver folds in two as the piston comes out of the cartridge and the cartridge is replaced.

6) Fixer: Half-moon constructions for fixing motor, piston driver and cartridge. It keeps the structures on top of each other and keeps them together during the operation of the device.

7) Needle: The part where insulin in the cartridge is injected into the patient.

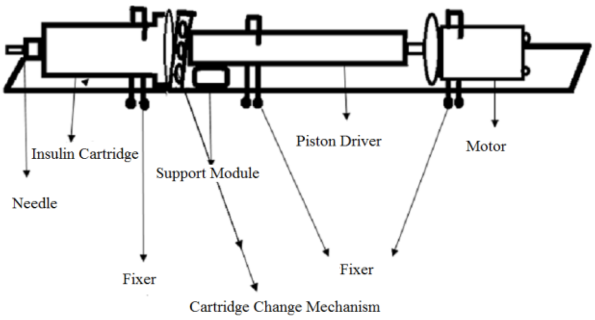

Figure 2. Cartridge change mechanism

The Arduino uno microcontroller was used for circuit design (Figure 3). Arduino is a very popular and easy to use programmable board. It consists of a simple hardware platform and a free source code editor. The Arduino board provides four basic functional elements: An Atmel ATmega328P AVR microcontroller, a simple 5 V power supply, a USB-to serial converter for loading new programs onto the board, I/O headers for connecting sensors, actuators and expansion boards.

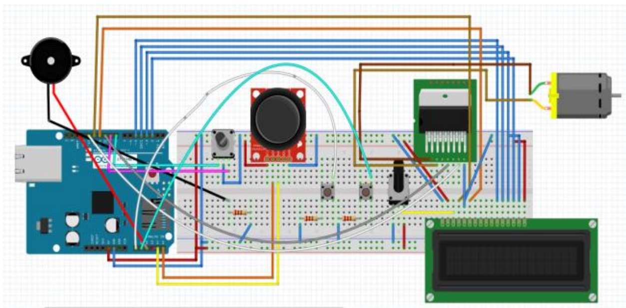

Figure 3. Circuit design of BS

In the programming used when creating the prototype, the software is based on the time taken to complete a round. The time of a tour of BS has been measured, and the software has been completed by using this account. However, in the process of converting the prototype to the final product, it will be more useful to control the device according to whether the motor is turning or not, by using an encoder. Thus, depending on the technical problems that might occur in the motor, it can be controlled whether the motor is turning or not. After all, injection of BS can be also clearly controlled by controlling motor.

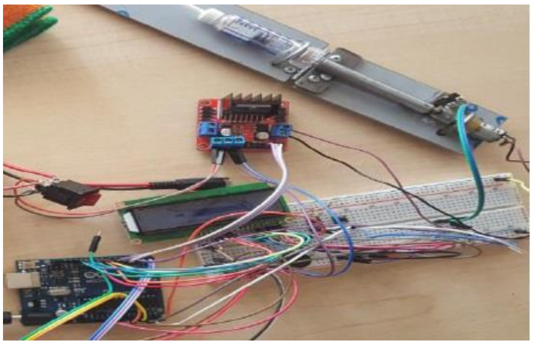

Figure 4. Bilensulin prototype

The features of Bilensulin whose prototype is given in Figure 4 can be explained as: The insulin dose which must be routinely injected by the patient during the day is entered as data at the first opening of the device. It is ensured that the insulin is automatically injected into the patient on time. First, second and third insulin dose adjusted can be followed from LCD monitor (Figure 5). The dose and time value initially entered are fixed until the next change time. In the event of a crisis, the device can be manually converted to the desired dose and manually injected. In overdose situations, the alarm of "emergency" is seen in the LCD monitor.

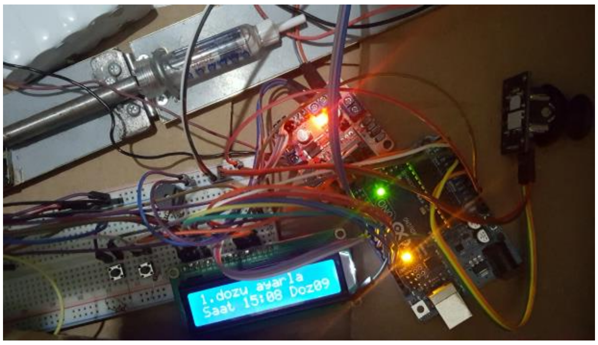

Figure 5. Bilensulin display during dose adjustment

When the insulin cartridge is finished, there is also a mechanism to switch the device to its initial position and to change the cartridge. The reservoir in which the cartridge is placed is large enough for all insulin cartridges. All possible types of insulin cartridges that are planned to be used for possible changes may be placed in this reservoir. This is a technical element that relaxes the patient both economically and in terms of ease of use. The clock module, which is located in the system, is designed in order to prevent any mistakes occurred in local clock changes or intercontinental travels, so that the patient can change it by his/her own skill or under the supervision of an individual.

3. Method of Dose Accuracy Testing

The dose of insulin injected by BS was tested by comparing with the brand insulin pens used in the marketing. The amounts of insulin injected was measured by using a sensitive balance in according to the international standard [15, 16]. Dosing accuracy was tested at 9U, 18U, 27U, 36U and 45U doses for the same type of insulin. Three insulin pens were used for comparation. The pens used in this study were the newest marketed model/technology of their brands. At the each dose, the pen was tested five times. The measurements were made by using a sensitive balance (Sartorius, ME235P-SD) calibrated before. Its measurement accuracy is 0,01mmg (the accreditation code of the calibration firm: AB-0039-K, the calibration certificate number: M15060806).

A new needle was mounted on each insulin pen according to the manufacturer's instructions before each dose. During injection, the discharging time was determined from manufacturer user manuals. The discharging of insulin must be taken for 5-10 seconds. Insulin can still be flowing out of the pen for several seconds after the button is fully depressed because of the mechanics of pen devices. Weigh measurements were taken immediately after each dose discharge in order to reduce the potential of evaporation of the expelled insulin. Environmental conditions were kept constant.

For 9U testing, the measurement was repeated five times for each insulin pen, resulting in a total of 15 measurements for three insulin pen. The same procedure was repeated for 18U, 27U, 36U and 45U. Totaly, 75 measurements were obtained. In order to eliminate potential user affect, all doses were delivered by the same person.

The related ISO standard is ISO 11608-1:2000. Specified limits based on ISO Standard were ±1 unit for a 10 unit dose and ±1,5 units for a 30 unit dose [16].

4. Results

The insulin amounts pumped in each round of the motor of BS are given in Table 1. Each measurement was repeated five times with tare measurements taken into account. The average of these five measurements were determined as the amount of each turn pumping. Again, the standard deviations of measurements were calculated.

Table 1. Amounts of insulin given in each round of the BS motor.

T	Tare (g)	Total Weight (g)	Net Weight (g)	Mean (g)	std
1	1,09899	1,17950	0,08051	0,088574	0,00526
	1,11212	1,20273	0,09061		
	1,10954	1,20170	0,09216		
	1,10886	1,20224	0,09338		
	1,10268	1,18889	0,08621		
2	1,10838	1,29720	0,18882	0,187832	0,00570
	1,10342	1,29965	0,19623		
	1,09886	1,28767	0,18881		
	1,11046	1,29446	0,18400		
	1,10652	1,28782	0,1813		

T	Tare (g)	Total Weight (g)	Net Weight (g)	Mean (g)	std
3	1,11169	1,39953	0,28784	0,29081	0,00767
	1,11308	1,41704	0,30396		
	1,10808	1,39294	0,28486		
	1,11128	1,40211	0,29083		
	1,11986	1,40642	0,28656		
4	1,10348	1,48964	0,38616	0,386978	0,00194
	1,10744	1,49558	0,38814		
	1,11320	1,49824	0,38504		
	1,11244	1,50221	0,38977		
	1,10989	1,49567	0,38578		
5	1,11317	1,59411	0,48094	0,485158	0,00708
	1,10325	1,59140	0,48815		
	1,11300	1,59438	0,48138		
	1,11011	1,58920	0,47909		
	1,10655	1,60278	0,49623		

The insulin amounts injected from the most commonly used three types of brand insulin pencils in the market can be seen in Table 2. The objective is to determine the relationship between the insulin doses injected by BS and other insulin pens.

When Table 3 are examined, it can be seen that the amount of insulin pumped in each motor tour in the BS corresponds to 9U dose in the insulin pens.

Table 3. Comparison of dosages of BS and three different insulin pens.

	BS (g)	1st pen (g)	2nd pen (g)	3rd pen (g)
9U	0,088574	0,089138	0,098554	0,095342
18U	0,187832	0,188493	0,198200	0,194522
27U	0,29081	0,269786	0,279436	0,275446
36U	0,386978	0,361322	0,369500	0,365570
45U	0,485158	0,448696	0,459684	0,455278

In Figure 5, the doses injected from BS and other insulin pens were compared by using graphic method. Figure 5 shows that BS injected insulin amounts close to the doses of other insulin pens, at all doses.

Table 2. Mean delivered doses of 9U, 18U, 27U, 36U and 45U insulin with three different insulin pens. D:dose

Dose	1st pen (g)	2nd pen (g)	3rd pen (g)
9U	0,08808	0,09782	0,09472
	0,08952	0,09964	0,09518
	0,08994	0,09655	0,09492
	0,08886	0,09984	0,09602
	0,08929	0,09892	0,09587
Mean	0,089138	0,098554	0,095342
std	0,000709	0,001371	0,000577
18U	0,189820	0,19767	0,19442
	0,187933	0,19894	0,19390
	0,188257	0,19698	0,19488
	0,189255	0,19922	0,19436
	0,187198	0,19819	0,19505
Mean	0,188493	0,19820	0,194522
std	0,001047	0,000916	0,000456
27U	0,27034	0,28004	0,27523
	0,26843	0,27983	0,27621
	0,26913	0,27827	0,27448
	0,27121	0,28109	0,27572
	0,26982	0,27795	0,27559
Mean	0,269786	0,279436	0,275446
std	0,001073	0,001306	0,000644
36U	0,36215	0,37120	0,36586
	0,36098	0,36879	0,36448
	0,36244	0,37034	0,36604
	0,35986	0,36772	0,36532
	0,36118	0,36945	0,36615
Mean	0,361322	0,36950	0,36557
std	0,001026	0,001348	0,000688
45U	0,44876	0,46024	0,45572
	0,44871	0,45986	0,45328
	0,44856	0,45879	0,45604
	0,45124	0,46008	0,45628
	0,44621	0,45945	0,45507
Mean	0,448696	0,459684	0,455278
std	0,00178	0,000581	0,001206

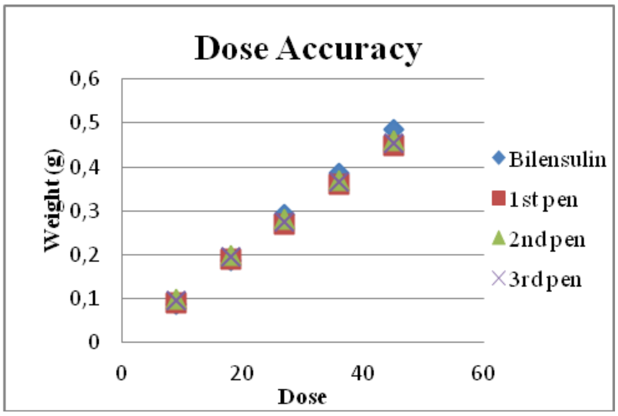

Figure 5. Comparison of mean doses for BS and the other three brand insulin pens

5. Conclusions

In this study, an easy-to-use electronic insulin pen, named as Bilensulin, was designed to prevent the wrong dose for patients with mental or visual disturbances or hand immobilities, considering the physical and memory features of such insulin systems. The dose measurements performed after design has shown that the dose accuracy of the amount of insulin injected by the BS is acceptable.

BS is an electronic insulin pen that focuses on zeroing off the error with a system that evokes the smart technology by abstracting the patient's dose completely from its own will. In addition to having a memory record like others, it also tends to keep the patient under control and reduce the risk to a minimum with an audible warning system.

The developed cartridge exchange mechanism offers an advantage in patients who have difficulty using his/her hand in terms of ease of use. In addition, the thick structure of BS allows to be easily held by such patients. The BS is different in this design structure from other insulin pens patented.

The patent of EP1095668B1 is related to the electronic insulin pen which can record the information such as insulin dosage, date and time [17]. In the patent documents numarated as US8298194 and US5688251, easy and safe methods for refilling cartridges of manually adjustable insulin pens have been explained [18, 19]. BS includes both features. It serves easy and safe methods for refilling cartridges in electronic insulin pens which adjusts dosage and time.

For this designed electronic insulin pen, the patent has been applied by putting the cartridge change mechanism into the foreground. Work is continuing to develop the device.

Acknowledgments

The patent application has been supported by The Research Fund of the University of Istanbul. The project number is FMP-2016-22534 (Property Patent Project).

6. References

[1] P. Sonksen, J. Sonksen, "Insulin: understanding its action in health and disease", *Br J Anaesth*, vol. *85*, no. 1, pp. *69-79*, July, 2000.

[2] M. P. Baruah, "Insulin pens: the modern delivery devices", *J Assoc Physicians India*, vol. *59*, pp. *38-40*, Apr, 2011.

[3] D. K. Dang, J. Lee, "Analysis of symposium articles on insulin pen devices and alternative insulin delivery methods", *J Diabetes Sci Technol.*, vol. *4*, no. *3*, pp. *558-561*, May, 2010.

[4] S. L. Schwartz, D. A. Ignaut, J. N. Bodie, "Humalog KwikPen: an insulin-injecting pen designed for ease of use", *Expert Rev Med Devices*, vol. *7*, no. *6*, pp. *735-743*, Nov, 2010.

[5] E. K. McCoy, B. M. Wright, "A review of insulin pen devices", *Postgraduate Medicine*, vol. *122*, no. *3*, pp. *81-88*, May, 2010.

[6] B. M. Rollins, D. C. Lee, M. A. Silva, "Insulin dosage preparation and administration: Prefilled pens versus syringes", *J Pharmacy Practice and Research*, vol. *43*, no. *3*, pp. *198-201*, Sept, 2013.

[7] A. Pfützner, T. Bailey, C. Campos, D. Kahn, E. Ambers, M. Niemeyer, G. Guerrero, D. Klonoff, I. Nayberg, "Accuracy and preference assessment of prefilled insulin pen versus vial and syringe with diabetes patients, caregivers and healthcare professionals", *Curr Med Res Opin*, vol. *29*, no. *5*, May, 2013.

[8] G. Spollett, "Insulin devices: addressing barriers to insulin therapy with the ideal pen", *Diabetes Educator*, vol. *34*, no. *6*, pp. *957-960, 963,967*, Nov, 2008.

[9] D. A. Ignaut, M. R. Opincar, P. E. Clark, M. K. Palaisa, S. M. Lenox, "Engineering study comparing injection force and dose accuracy between two prefilled insulin injection pens", *Curr Med Res Opin*, vol. *25*, no. *12*, pp. *2829-2833*, Dec, 2009.

[10] T. L. Pearson, "Practical aspects of insulin pen devices", *J Diabetes Sci Technol.*, vol. *4*, no. *3*, pp. *522-531*, May, 2010.

[11] A. Bode, "Development of the SoloSTAR insulin pen device: design verification and validation", *Expert Opin Drug Del*, vol. *6*, no. *1*, pp. *103-112*, Dec, 2009.

[12] D. A. Nadeau, C. Campos, M. Niemeyer, T. Bailey, "Healthcare professional and patient assessment of a new prefilled insulin pen versus two widely available prefilled insulin pens for ease of use, teaching and learning", *Curr Med Res Opin*, vol. *28*, no. *1*, pp. *3-13*, Jan, 2012.

[13] D. Burton, M. Uslan, "Diabetes and visual impairment: Are insulin pens accessible?", *AFB AccessWorld Magazine*, vol. *7*, no. *4*, July, 2006.

[14] W. J. R. R. Venekamp, L. Kerr, S. A. Dowsett, P. A. Johnson, D. Wimberley, C. McKenzie, J. Malone, Z. Milicevic, "Functionality and acceptability of a new electronic insulin injection pen with a memory feature", *Curr Med Res Opin*, vol. *22*, no. *2*, pp. *315-325*, Jan, 2006.

[15] T. Asakura, H. Seino, M. Kageyama, N. Yohkoh, "Dosing accuracy of two insulin pre-filled pens", *Curr Med Res Opin*, vol. *24*, no. *5*, pp. *1429-1434*, Apr, 2008.

[16] *Pen-injectors for Medical Use - Part 1: Pen-injectors - Requirements and Test Methods*, ISO 11608-1:2000, 2000.

[17] *Electronic medication delivery pen having a multifunction actuator*, Patent number: EP1095668B1, 2007.

[18] *Injection device and a method of changing a cartridge in the device*, Patent number: US 8298194, 2012.

[19] *Cartridge loading and priming mechanism for a pen injector*, Patent number: US5688251, 1997.

Mana Sezdi (Bandirma, Turkey, 1972) graduated from Uludag University as an electronical engineer in 1994. She received her master and Ph.D. on Biomedical Engineering from Bogazici University, in 1998 and 2005, respectively. Between 1996-2006, she worked as researcher in Biomedical Engineering Institute, Bogazici University in Turkey. She has been working in the Biomedical Device Technology Program of Istanbul University as instructor since 2007. She is also assistant director in Biomedical and Clinical Engineering Department of the Istanbul University's Medicine Faculties; Cerrahpasa Faculty of Medicine and Istanbul Faculty of Medicine since 2007. She is an author of more than 85 publications in total, including 1 book, 4 book chapters and 80 research papers in international refereed journals, national and international conference proceedings. Her book is "The quality of stored human blood" that was published by Lambert Academic Publishing in 2011. Her published book chapters; "Dose Optimization for the Quality Control Tests of X-Ray Equipment" in the book of "Modern Approaches to Quality Control" (Croatia, Intech, 2011) and "Medical Technology Management and Patient Safety" in the book of "A Broadmap of Biomedical Engineers and Milestones" (Croatia, Intech, 2012). Her research interests include biomedical instrumentation and measurements, clinical engineering, medical calibration measurements and performance tests of diagnostic imaging systems. She is the member of Association of Biomedical and Clinical Engineering in Turkey. Between 1996 and 2006, she was in the program committee of National Biomedical Conference (BIYOMUT). Since 2010, she has been serving on program committee of Health Technologies National Conference (TIPTEKNO Conferences).