Journal of Diabetes Science and Technology
Volume 7, Issue 4, July 2013

TECHNOLOGY REPORT

Dosing Accuracy and Insulin Flow Rate Characteristics of a New Disposable Insulin Pen, FlexTouch, Compared with SoloSTAR

Janine Bohnet, Dipl.-Ing.Biotechnology (FH),[1] Mario Schmitz, Dipl.-Ing. (FH),[2] Stefan Kamlot, Dipl.-Bw. (FH),[2] and Mona Abdel-Tawab, Ph.D.[1]

Abstract

Background:

The introduction of the FlexTouch® (FT; Novo Nordisk; insulin aspart), a prefilled insulin pen with a spring-loaded mechanism, has created more insulin pen options. The present study compared the dosing accuracy of the FT with that of the manually operated SoloSTAR® (SS; Sanofi; insulin glulisine). The volumetric flow rate of insulin delivery with the FT was also evaluated.

Methods:

Thirty unused pens from one batch of each pen type were used to test dosing accuracy at minimum (1 U), mid (40 U), and maximum dose (80 U). Statistical analysis was performed using Student's *t*-test. Insulin flow was determined with 20 FT pens ejecting 80 U three times per pen using a mass flow meter.

Results:

Both insulin pens revealed excellent dosing accuracy, delivering all doses within the limits set by ISO 11608-1:2000. The average relative deviation of the actual dose from the target dose was +6.86% and +3.87% at the minimum, -0.72% and -1.01% at the mid, and -0.68% and -1.06% at the maximum dose for the SS and FT, respectively. The difference at maximum dose was statistically significant ($p = .006$) in favor of the SS. The FT showed a mean maximum flow rate of 15.61 U/s, with 80.52% of the total dose delivered at an injection speed exceeding 10 U/s.

Conclusions:

This study demonstrated excellent dosing accuracy for the SS and FT at all tested dosage levels. The average maximum injection speed of the FT was considerably higher than the usual range of 6–10 U/s assumed for a smooth and painless injection. Further investigations should confirm the clinical relevance.

J Diabetes Sci Technol 2013;7(4):1021–1026

Author Affiliations: [1]Central Laboratory of German Pharmacists, Eschborn, Germany; and [2]Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany

Abbreviations: (FT) FlexTouch, (ISO) International Organization for Standardization, (SS) SoloSTAR

Keywords: dosing accuracy, FlexTouch, SoloSTAR, volumetric flow rate

Corresponding Author: Mona Abdel-Tawab, Ph.D., Central Laboratory of German Pharmacists, Carl-Mannich-Str. 20, 65760 Eschborn, Germany; email address M.Tawab@zentrallabor.com

Introduction

Several studies confirm that patients with diabetes prefer insulin pens over vial and syringe for self-administering insulin.[1–3] Thus, insulin pens now account for over 60% of insulin delivery worldwide.[4] Because of the simplicity and ease of use of these devices, the conversion from the vial and syringe delivery to insulin pens is generally associated with improved medication adherence and reduced likelihood of experiencing hypoglycemic events.[4,5] Previous studies verified the accurate dosing of existing insulin pens,[4,6–13] although single doses outside the limits specified by the International Organization for Standardization standard (DIN EN ISO 11608-1:2000)[14] have been reported in some small-scale studies.[6,7,11] The existing pen options have been extended by the introduction of the FlexTouch® (FT; Novo Nordisk; insulin aspart), a prefilled insulin pen with a spring-loaded mechanism. The present study aimed to compare the dosing accuracy of the FT with that of the SoloSTAR® (SS; Sanofi; insulin glulisine) at the minimum, mid, and maximum dosage level, as recommended by the DIN EN ISO 11608-1:2000. SoloSTAR was chosen as the comparator because it is a commonly used disposable pen that has demonstrated excellent dosing accuracy and is the only disposable insulin pen that also allows delivery of 80 U in one injection like the FT.

However, dosing accuracy is not the only core aspect of a pen's function. The flow rate of insulin delivery is a key element that determines the comfort of pen use. In contrast to current disposable insulin pens such as SS, where the flow rate is controlled by the user pushing the dose button with thumb or index finger, insulin delivery with the FT is controlled by a spring force that does not allow the user to influence the injection speed. For that reason, the flow rate of insulin delivery of the FT has been evaluated as well.

Material and Methods

SoloSTAR was bought from a German pharmacy, and the FT was obtained through an international pharmacy from the United Kingdom. An overview of the included insulin pens and corresponding needles is given in **Table 1**. The needles were applied according to the manufacturer's recommendation. It is considered irrelevant for the findings of this study that the two recommended needles differ by 1 mm in length.

Table 1.
Insulin Pens and Corresponding Needles Included in the Study

Insulin pen	Manufacturer	Batch	Insulin	Needles
SoloStar	Sanofi	2F082A	glulisine (Apidra®)	BD Micro-Fine (0.25 mm [31 G] × 5 mm)
FlexTouch	Novo Nordisk	AP51446	aspart (NovoRapid®)	NovoFine (0.25 mm [31 G] × 6 mm)

Determination of Dosing Accuracy

A total of 30 previously unused insulin pens of one batch of each pen type were used to study dosing accuracy. Each of the minimum (1 U), mid (40 U), and maximum (80 U) doses were dispensed two times from each pen in a randomized manner.

The individual insulin pens were operated according to the manufacturers' instructions. Prior to starting the sequence of measurements, a priming dose of 2 U was discarded. If no drops were seen at the top of the needle, the priming dose was repeated until this was the case. All measurements were performed by a single investigator to eliminate potential user variability. As per manufacturers' instructions, the plunger was kept pressed down for 10 s (SS) and 6 s (FT) after each dose to ensure that all dialed dose had been expelled. Each dose was deposited in a beaker containing a 0.5–1 cm layer liquid paraffin, and the needle was held close to the surface of the paraffin layer. In case an insulin drop remained at the tip of the needle at the end of the relaxation time, this drop was stripped off at the paraffin surface, taking care that the needle did not strike the paraffin. Afterwards, the dose was weighed immediately using an analytical balance (XP205/M, Mettler Toledo AG, Gießen, Germany), which has an accuracy of 0.00001 g.

The balance was zeroed before each dose of insulin was deposited and weighed. The weights were corrected for the specific density of each insulin formulation determined in the run-up to the study. The relative density of insulin glulisine (SS) and aspart (FT) was determined to be 1.0072 and 1.0066, respectively, using a DMA 4500 density meter (Anton Paar GmbH, Bruchköbel, Germany). For each dose application, a new injection needle was used, which was primed in accordance with the manufacturer's recommendation before dose delivery. The whole study was carried out under good manufacturing practice conditions.

The arithmetic average of the actual doses, the standard deviation, the average deviation (percentage) from the target dose, as well as the statistical tolerance interval were calculated. The evaluation of dose accuracy was based on the guidelines of the International Organization for Standardization standard (DIN EN ISO 11608-1:2000),[14] allowing a deviation not more than ±1 U at the 1 U (0–2 U) dosage level, ±5% (2 U) at the 40 U (38–42 U) dosage level, and ±5% (4 U) at the 80 U (76–84 U) dosage level for the individual doses. In addition, the statistical tolerance interval $\bar{x} \pm (k\ s)$ for each pen should also lay within the upper and lower acceptance limits for each dosage level. The statistical analysis was performed with Minitab® 16 (Minitab Inc., State College, PA) using the Student's *t*-test with 95% confidence interval. A p value < 0.05 was considered to be of statistical significance.

Determination of the Flow Rate

The applied Bronkhorst mini CORI-FLOW™ measurement system (Bronkhorst Cori-Tech BV, Ruurlo, The Netherlands) is a compact, low flow Coriolis Mass Flow Meter. It contains a uniquely shaped, single loop sensor tube, forming part of an oscillating system. When a fluid flows through the tube, Coriolis forces cause a variable phase shift, which is detected by sensors and fed into the integrally mounted pc-board. The resulting output signal is strictly proportional to the real mass flow rate. Coriolis mass flow measurement is fast, accurate and inherently bi- directional.[15]

Twenty previously unused FTs were used to investigate the maximum flow rate while dispensing an 80 U dose. For each pen, three independent measurements were conducted.

The individual insulin pens were operated according to the manufacturers' instructions. After priming, the pen was connected to the measurement system by a replaceable 32 G 6 mm NovoFine® needle and dialed up to the maximum dose of 80 U. Once the system was zeroed, the measurement started. The dose was delivered as per the manufacturer's instruction, and the measurement was stopped after the required holding time of 6 s.

All raw data were exported to a spreadsheet program for further calculations. Mass flow was transformed into volume flow by density correction. The maximum flow, the relative dose with injection speed greater than 10 U/s, the relative dose with injection speed less than or equal to 10 U/s, and the duration of injection greater than 10 U/s was calculated.

Results

According to the delivery scheme for measuring the dosing accuracy, 60 doses were gravimetrically measured at each dosage level for each pen type, and the actual doses were calculated on the basis of the delivered masses and the relative density of the insulin solution. The arithmetic average of the actual doses, the standard deviation, and the statistical tolerance intervals are summarized in **Table 2**.

The study demonstrated consistent and accurate dose delivery at all dosage levels for both insulin pens, with none of the single values being outside the specified limits recommended by the ISO. Moreover, all calculated tolerance intervals ($\bar{x} \pm (k\ s)$) were found to lie within the acceptance range for each dosage level for each pen, where $\bar{x}$ is the average value of the actual doses for each pen at each dosage level, s is the standard deviation, and k is the tolerance limit factor, which was found to be 2.670 on the basis of the 95% confidence interval and a probability content of $p = .975$ for $n = 60$.[14]

The average values of the actual doses were closer to the target dose for the SS at the mid and maximum dose and for the FT at the minimum dose, as can be seen in **Figure 1**. The difference between the average values of both pens at

Table 2.
Overview on the Average of the Actual Doses, the Standard Deviation, and the Statistical Tolerance Interval at Each Dosage Level for SoloSTAR and FlexTouch

Pen	Target dose (U)	Actual dose		
		Average dose (U)	Standard deviation (U)	Statistical tolerance interval (U)[a]
SS	1	1.069	0.107	0.78–1.35
FT		1.039	0.072	0.85–1.23
SS	40	39.712	0.487	38.41–41.01
FT		39.597	0.246	38.94–40.25
SS	80	79.460[b]	0.737	77.49–81.43
FT		79.155[b]	0.417	78.04–80.27

[a] According to the International Organization for Standardization (DIN EN ISO 11608-1:2000), the acceptance range for the statistical tolerance interval is 0–2 U for the 1 U dosage level, 38–42 U for the 40 U dosage level, and 76–84 U for the 80 U dosage level.
[b] Statistically significant difference (p = .006).

the maximum dose was statistically significant (p = .006) in favor of SS.

The average relative deviation of the actual dose from the target dose was found to be +6.86% and +3.87% at the min dose, -0.72% and -1.01% at the mid dose, and -0.68% and -1.06% at the maximum dose for the SS and FT, respectively.

Table 3 shows the mean maximum volumetric flow rate, its standard deviation, and the flow range for 60 measurements on FT pens as well as the relative doses with a flow ≤10 and >10 U/s, respectively.

This investigation verifies the subjective high volume flow rates perceived with the spring-loaded mechanism of the FT. **Figure 2** shows the overall time versus flow diagram of all 60 measurements. The dark grey area demonstrates the dose volume with an injection speed higher than 10 U/s. This phase lasts for 4.54 s (±0.14 s) and represents 80.52% (±1.05%) of the total delivered volume.

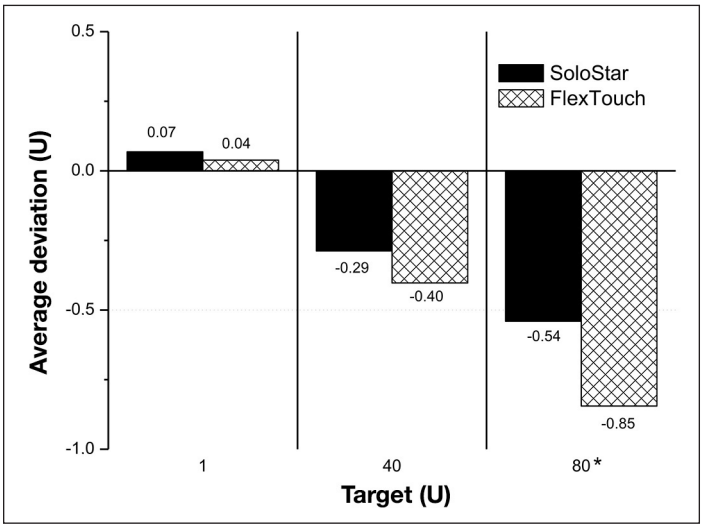

Figure 1. Average deviation (units) of actual dose from the target dose (n = 60 measurements/pen and dose). The asterisk represents p = .006.

Table 3.
Results of the Flow Analysis Using FlexTouch

	Mean (n = 60)	Standard deviation	Range (minimum– maximum)
Maximum flow (U/s)	15.61	0.60	14.26–16.87
Relative dose with flow ≤10 U/s (%)	19.48	1.05	16.74–22.41
Relative dose with flow >10 U/s (%)	80.52	1.05	77.59–83.26

Discussion

Following the recommendation of ISO 11608-1:2000, dosing accuracy was tested at the minimum, mid, and maximum dosage level, revealing excellent dosing for SS and FT. No single dose of SS and FT was detected outside the specified limits and the statistical tolerance intervals defined by the ISO standards were met by both pens at all dosage levels. Differences between the average values of the actual dose from the target dose were statistically significant at the maximum dose in favor of SS. Consequently, this study confirms the results of previous studies indicating high dosing accuracy for the SS[4,12,13] and disproves former studies reporting single doses outside ISO limits.[6,7,11] Moreover, it demonstrates that the spring-loaded mechanism of the FT does not translate into a dose accuracy advantage compared with the manually operated SS,

even though this might not have been the primary objective for the FT mode of mechanism.

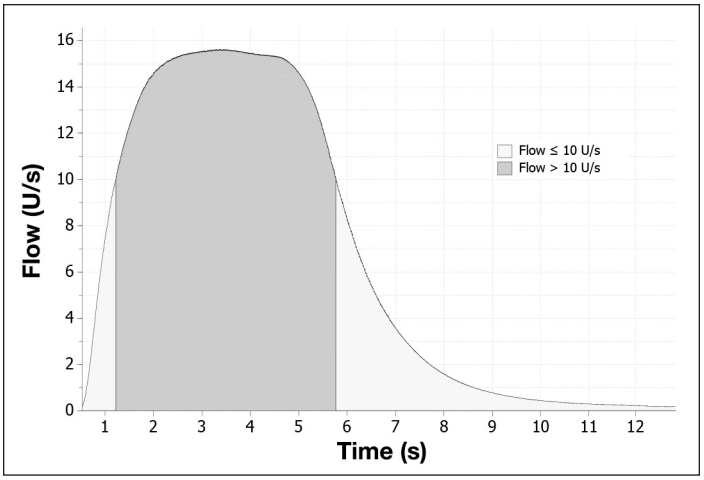

Figure 2. Average flow curve of 80 U dose dispensed with FT.

While delivering insulin doses for determining dosing accuracy, a higher injection speed was noticed for the FT in comparison with the SS. This can be attributed to the spring-loaded mechanism of the FT. In manually operated insulin pens, the user presses down on the dose button with his thumb or index finger to deliver the dose. With the FT, the user winds up a spring when dialing the dose, with the force required to dial up increasing with the spring being wound tighter. When pressing the dose button, the force stored in the spring is then released, delivering the dose at an injection speed driven by the spring load. As insulin delivery cannot be controlled individually with the FT, it was of interest to determine the flow rate of insulin at the maximum dosage level, i.e., when the spring reached its maximum compression or loading. The results of the present laboratory setting revealed that, on average, 80.52% of the 80 U dose is delivered at a mean maximum flow rate of 15.61 U/s, thus considerably exceeding an insulin delivery of 10 U/s. In this context, it should be pointed out that no empirical data exist regarding the injection speed applied by pen users for insulin delivery. However, looking at the experiments carried out to determine the injection force, several were conducted at 6 and 10 U/s.[10,16,17] Based on that background, flow rates in the range of 6–10 U/s may be regarded as realistic dispense speeds in practical use.[17] It is not known whether the increased injection speed determined in the present laboratory setting is felt as discomfort by the average patient with diabetes in daily practice. However, it cannot be excluded that this high flow rate may be accompanied by an uncomfortable feeling or pain sensation in sensitive patients, especially as it is generally recommended in the manual of the Association for Diabetes Consulting and Education Professions in Germany (Verband der Diabetes-Beratungs- und Schulungsberufe in Deutschland e.V.) and in the instructions for use of manually operated insulin pens to perform injections slowly and smoothly.[18] In the case of manually operated insulin pens like the SS, the patient can control the injection speed with his finger/thumb, adapting it to his individual needs. With the FT, however, the patient cannot influence the injection speed, which may cause pain or discomfort; consequently, the user may have no other alternative but to stop the injection by removing the finger from the button. Further investigations are warranted to establish the potential effects of the high flow rate and to confirm the clinical significance of these findings.

Conclusion

In summary, the present study demonstrates a comparable excellent dosing accuracy of the manually operated SS with the spring-operated FT at the minimum (1 U), mid (40 U), and maximum (80 U) dosage level. The SS delivered average doses nearer to the target dose than the FT at the 40 and 80 U dosage level; the difference being statistically significant at the maximum dose. Hence, the spring-loaded mechanism did not translate into a dose accuracy advantage. Moreover, the present study revealed an average injection speed of 15.61 U/s for the FT at the highest dosage level, which exceeds the flow rate of 10 U/s assumed to be relevant in daily practice. In case of discomfort or pain during injection, patients cannot adapt the injection speed of the FT, but with the SS, the flow rate can be manually controlled through the force applied to the dose button.

Funding:

This study was sponsored by Sanofi.

Disclosures:

Mario Schmitz and Stefan Kamlot are employees of Sanofi and were involved in the design of the present study.

References:

1. Korytkowski M, Bell D, Jacobsen C, Suwannasari R; FlexPen Study Team. A multicenter, randomized, open-label, comparative, two-period crossover trial of preference, efficacy, and safety profiles of a prefilled, disposable pen and conventional vial/syringe for insulin injection in patients with type 1 or 2 diabetes mellitus. Clin Ther. 2003;25(11):2836–48.
2. Molife C, Lee LJ, Shi L, Sawhney M, Lenox SM. Assessment of patient-reported outcomes of insulin pen devices versus conventional vial and syringe. Diabetes Technol Ther. 2009;11(8):529–38.
3. Ignaut DA, Schwartz SL, Sarwat S, Murphy HL. Comparative device assessments: Humalog KwikPen compared with vial and syringe and FlexPen. Diabetes Educ. 2009;35(5):789–98.
4. Perfetti R. Reusable and disposable insulin pens for the treatment of diabetes: understanding the global differences in user preference and an evaluation of inpatient insulin pen use. 2010;12 Suppl 1:S79–85.
5. Goldstein HH. Pen devices to improve patient adherence with insulin therapy in type 2 diabetes. Postgrad Med. 2008;120(3):172–9.
6. Hänel H, Weise A, Sun W, Pfützner JW, Thomé N, Pfützner A. Differences in the dose accuracy of insulin pens. J Diabetes Sci Technol. 2008;2(3):478–81.
7. Asakura T, Seino H, Kageyama M, Yohkoh N. Dosing accuracy of two insulin pre-filled pens. Curr Med Res Opin. 2008;24(5):1429–34.
8. Pfützner A, Asakura T, Sommavilla B, Lee W. Insulin delivery with FlexPen: dose accuracy, patient preference and adherence. Expert Opin Drug Deliv. 2008;5(8):915–25.
9. Penfornis A, Horvat K. Dose accuracy comparison between SoloStar and FlexPen at three different dose levels. Diabetes Technol Ther. 2008;10(5):359–62.
10. Pfützner A, Reimer T, Hohberg C, Frøkjaer LP, Jørgensen C. Prefilled insulin device with reduced injection force: patient perception and accuracy. Curr Med Res Opin. 2008;24(9):2545–9.
11. Weise A, Pfützner JW, Borig J, Pfützner AM, Safinowski M, Hänel H, Musholt PB, Pfützner A. Comparison of the dose accuracy of prefilled insulin pens. J Diabetes Sci Technol. 2009;3(1):149–53.
12. Krzywon M, Van der Burg T, Fuhr U, Schubert-Zsilavecz M, Abdel-Tawab M. Dosing accuracy of common disposable insulin pens. Curr Med Res Opin. 2010;26:901–5.
13. Krzywon M, van der Burg T, Fuhr U, Schubert-Zsilavecz M, Abdel-Tawab M. Study on the dosing accuracy of commonly used disposable insulin pens. Diabetes Technol Ther. 2012;14(9):804–9.
14. International Organization for Standardization. Pen-injectors for medical use -- part 1: pen-injectors -- requirements and test methods. ISO 11608-1:2000, version 1, 2000.
15. Bronkhorst Cori-Tech BV. mini CORI-FLOW™ Mass Flow Meters. *http://www.bronkhorst-cori-tech.com/en/products/coriolis_meters_controllers/mini_cori-flow/mass_flow_meters_mfms/*. Accessed April 23, 2013.
16. Ignaut DA, Opincar MR, Clark PE, Palaisa MK, Lenox SM. Engineering study comparing injection force and dose accuracy between two prefilled insulin injection pens. Curr Med Res Opin. 2009;25(12):2829–33.
17. Van der Burg T. Injection force of SoloSTAR® compared with other disposable insulin pen devices at constant volume flow rates. J Diabetes Sci Technol. 2011;5(1):150–5.
18. Verband der Diabetes-Beratungs und Schulungsberufe in Deutschland e.V. VDBD-Leitfaden. Die Injektion bei Diabetes mellitus *http://www.vdbd.de/Verband/VDBD_Leitfaden_Insulininjektion_PM107_FINAL.pdf*. Accessed September 14, 2012.