Volume 5, Issue 1, January 2011

Injection Force of SoloSTAR® Compared with Other Disposable Insulin Pen Devices at Constant Volume Flow Rates

Thomas van der Burg, B.Sc.

Abstract

Background:

Injection force is a particularly important practical aspect of therapy for patients with diabetes, especially those who have dexterity problems. This laboratory-based study compared the injection force of the SoloSTAR® insulin pen (SoloSTAR; sanofi-aventis) versus other available disposable pens at injection speeds based on the delivered volume of insulin released at the needle.

Method:

Four different prefilled disposable pens were tested: SoloSTAR containing insulin glargine; FlexPen® and the Next Generation FlexPen® (NGFP) (Novo Nordisk), both containing insulin detemir; and KwikPen® containing insulin lispro (Eli Lilly). All pens were investigated using the maximum dispense volume for each pen type [80 units (U) for SoloSTAR; 60 U for the other pens], from the free needle tip dispensing into a beaker. Twenty pens of each type were fitted with the recommended needles and tested at two dose speeds (6 and 10 U/s); each pen was tested twice.

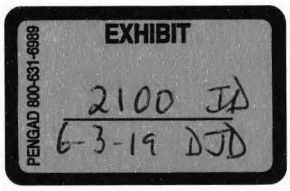
Results:

Mean plateau injection force and maximum injection force were consistently lower with SoloSTAR compared with FlexPen, NGFP, and KwikPen at both injection speeds tested. An injection speed of 10 U/s was associated with higher injection force compared with 6 U/s for all the pens tested ($p < .001$).

Conclusions:

SoloSTAR stands out because of its low injection force, even when compared with newer insulin pen devices such as the KwikPen and NGFP. This may enable patients, especially those with dexterity problems, to administer insulin more easily and improve management of their diabetes.

J Diabetes Sci Technol 2011;5(1):150-155



Author Affiliation: sanofi-aventis Deutschland GmbH, Site Frankfurt Devices/Device Industrialisation, Frankfurt, Germany

Abbreviations: (N) newton, (NGFP) Next Generation FlexPen, (U) unit

Keywords: flow rate, injection force, injection speed, insulin pen

Corresponding Author: Thomas van der Burg, sanofi-aventis Deutschland GmbH, Site Frankfurt Devices/Device Industrialisation, Industriepark Hoechst, D-65926 Frankfurt am Main, Germany; email address thomas.vanderburg@sanofi-aventis.com

Introduction

The first insulin pen device was introduced in 1985. Since then, continuing innovation has led to a steady improvement in the devices available and they now account for about half of worldwide insulin use.[1]

There are numerous disposable pen devices available on the market in the United States,[2] Europe, and Japan, such as FlexPen® (Novo Nordisk, Bagsvaerd, Denmark), more recent disposable devices such as KwikPen® (Eli Lilly, Indianapolis, IN), and the so-called Next Generation FlexPen® (NGFP) (Novo Nordisk, Bagsvaerd, Denmark).

The Lantus® SoloSTAR® disposable injection device (sanofi-aventis, Paris, France) was launched in 2007 and meets a combination of user needs that had not been previously addressed and still remain unmet by other devices on the market. These include ease of injection, differentiation of insulin type through pen body color and tactile elements, and the ability to inject up to 80 units (U) of insulin in one injection with a comparatively short dial stroke, which is particularly useful for patients with impaired manual dexterity.[3] The SoloSTAR pen was developed through a process of iterative design and feedback questionnaires involving patients, healthcare professionals, the design team, and consultants in order to comprehensively assess the needs of patients who use insulin pens.[3]

Injection force is a particularly important practical aspect of therapy for patients with type 1 or 2 diabetes, especially for those who have dexterity problems; these patients may have limited ability to self-inject insulin.[4–7]

The aim of this study, therefore, was to compare the injection force of the SoloSTAR pen with three other commonly available disposable pens at two different injection speeds based on a delivered volume of insulin released at the needle (constant volume flow rate) within a laboratory setting. This is the first study directly evaluating the injection force of these three insulin devices on the basis of the dispensed dose per time, using realistic dispense speeds for practical use.

Methods

Four different pen injection devices were tested in this investigation: SoloSTAR insulin glargine pen (batch number 40U286), FlexPen insulin detemir pen (batch number VH70215), NGFP insulin detemir pen (batch number VH70007), and KwikPen insulin lispro pen (batch number A477063).

Twenty pens of each type were tested at two dose speeds (6 and 10 U/s); each pen was tested twice, with all doses delivered into a beaker. Tests were carried out using the maximum dial stroke and dispensing the maximum dose volume of each pen type (80 U for the SoloSTAR; 60 U for the comparator pens). All investigations were conducted using the manufacturers' recommended needles with a consistent outer diameter of 0.25 mm based on the manufacturers' specifications: BD Micro-Fine 0.25 mm (31G) × 5 mm for SoloSTAR and KwikPen; NovoFine 0.25 mm (31G) × 6 mm for FlexPen and NGFP.

Laboratory tests were conducted using a tensile meter (Zwick GmbH & Co. KG, Ulm, Germany) and force cell [KAF-TC, Zwick GmbH & Co. KG, Ulm, Germany; nominal load 200 newtons (N)] under standard atmospheric conditions. The distance traveled by the push button to deliver the appropriate dose was determined to be different for each of the pens, necessitating a different push button speed to be chosen for the four devices. Before evaluating each pen, the appropriate needle was mounted and correct fitting ensured by dispensing a priming dose of 10 U. For each pen device, the injection force throughout the dose delivery was measured (**Figure 1**). The mean force value (mean plateau injection force) was calculated and the maximum injection force evaluated.

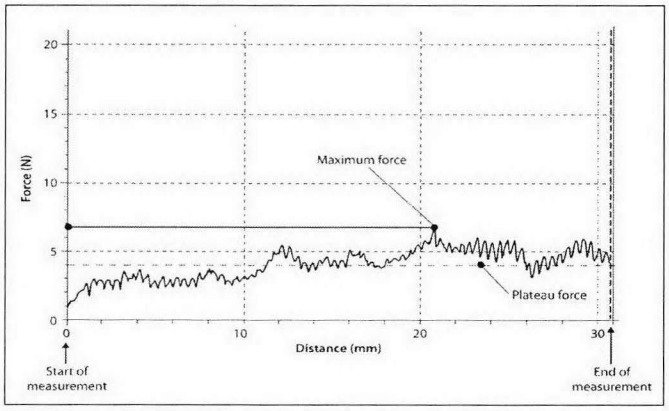


Figure 1. Example force measurement curve. Laboratory tests were carried out in order to determine the injection force of insulin pen devices at maximum insulin dose and two injection speeds (6 and 10 U/s). Injection force throughout the dose delivery was measured and mean plateau and maximum values evaluated.

Statistical analyses were carried out using Dunnett's test. A simultaneous test level of $p < .05$ was assessed with SoloSTAR as the reference group; the corresponding individual test level was $p < .012$ for each of the compared pairs. The differences in the mean maximum injection force and the mean plateau injection force between SoloSTAR and FlexPen, NGFP, and KwikPen were calculated, and the resultant confidence intervals were determined. The compared pair can be assumed to be different ($p < .012$), if the confidence interval of the respective pair is larger than 0. Due to the sufficient level of significance, no further declaration for the probability for the tested pairs was made.

Preliminary studies revealed that the injection force of insulin devices with the needle attached is mainly determined by the following factors: friction between the mechanical parts of the mechanism; friction between the bung and the glass partition of the cartridge; fluid friction of the liquid (insulin); and tissue pressure. Because tissue pressure is difficult to measure or simulate with high consistency, all tests were performed by dispensing into a beaker. Preliminary studies also showed that the fluid friction of the expelled insulin is mainly affected by changes in flow rates. Therefore, only comparisons at equal volume flow rates were pursued in this study.

Theoretical considerations were made to determine the dependence of fluid friction on the volume flow rate. Using basic fluid dynamics theory, one can demonstrate that the fluid friction of the insulin being expelled causes an accessory pressure inside the cartridge that increases the force required by the user to dispense the dose. The additional pressure can be calculated using the formula in **Equation (1)**, which is derived from the Bernoulli equation[8] by adding terms for the pressure reduction caused by fluid friction[9] and cross-section changes.[8] In **Equation (1)**, ρ represents the density of the fluid, d_{needle} the inner diameter of the needle, l_{needle} the total length of the needle, $\dot{V}$ the volume flow rate; α and ξ_2 are empiric coefficients mainly caused by crossover at the needle tip, ξ_1 is an empiric coefficient for the crossover of the fluid between cartridge and needle, and λ is the coefficient of friction for the needle (depending on viscosity, flow rate, roughness of the needle, and needle diameter).

$$\Delta p = \frac{8 \cdot \rho}{\pi^2} \cdot \dot{V}^2 \cdot \left[\left(\frac{\alpha}{d_{needle}^2} \right) + \frac{1}{d_{needle}^4} \left(\lambda \cdot \frac{l_{needle}}{d_{needle}} + \xi_1 + \xi_2 \right) \right] \quad (1)$$

As ρ, d_{needle}, l_{needle}, α, ξ_2, ξ_1, and λ are roughly constant for one needle/device combination at the used flow rate area, they can be expressed as the constant coefficient B, resulting in the simplified formula in **Equation (2)**, where the accessory pressure inside the cartridge only depends on the volume flow rate of the insulin.

$$\Delta p = B \cdot \dot{V}^2 \quad (2)$$

This formula was used to verify the theoretical approach by calculating the increase of the injection force at 10 U/s compared with 6 U/s for SoloSTAR with BD 0.25 mm (31G) × 5 mm needles. Subject to λ, an increase in the range of 2.8–4.4 N could be expected because of the higher volume flow rate.

Results

The mean plateau injection force at the maximum doses with the pens (80 U for SoloSTAR versus 60 U for the comparator pens) was significantly higher with FlexPen, NGFP, and KwikPen compared with SoloSTAR at both injection speeds tested (**Figures 2A** and **3A**). The difference in mean plateau injection force compared with SoloSTAR for the various pens was 95, 51, and 43% with FlexPen, NGFP, and KwikPen, respectively, at 6 U/s, and 87, 47, and 37%, respectively, at 10 U/s (**Table 1**). An injection speed of 10 U/s was associated with higher injection force compared with 6 U/s in all the pens ($p < .001$).

In line with the mean plateau force, the maximum injection force was also significantly higher with FlexPen, NGFP, and KwikPen compared with SoloSTAR at both injection speeds tested (**Figures 2B** and **3B**). The difference in maximum injection force compared with SoloSTAR for the various pens was 70, 26, and 29% with FlexPen, NGFP, and KwikPen, respectively, at 6 U/s, and 65, 31, and 30%, respectively, at 10 U/s (**Table 1**).

FlexPen showed the highest injection forces of all tested devices. Although KwikPen and NGFP showed comparable maximum forces, the mean plateau force of KwikPen was calculated to be significantly lower than that of NGFP ($p < .012$).

Discussion

Among the four disposable insulin pen devices compared in this study, the SoloSTAR pen had the lowest injection force irrespective of the injection speed tested. The dispense force of all pens rose when dispensing the dose at higher

speed, but injection force for SoloSTAR remained significantly lower than those of the other pens. This difference was observed for both mean plateau force and maximum force.

The empirical increase of the injection force at 10 U/s compared with 6 U/s for SoloSTAR was 3.7 N for the mean plateau force, which corresponds to the theoretical expectation with a calculated increase in the range of

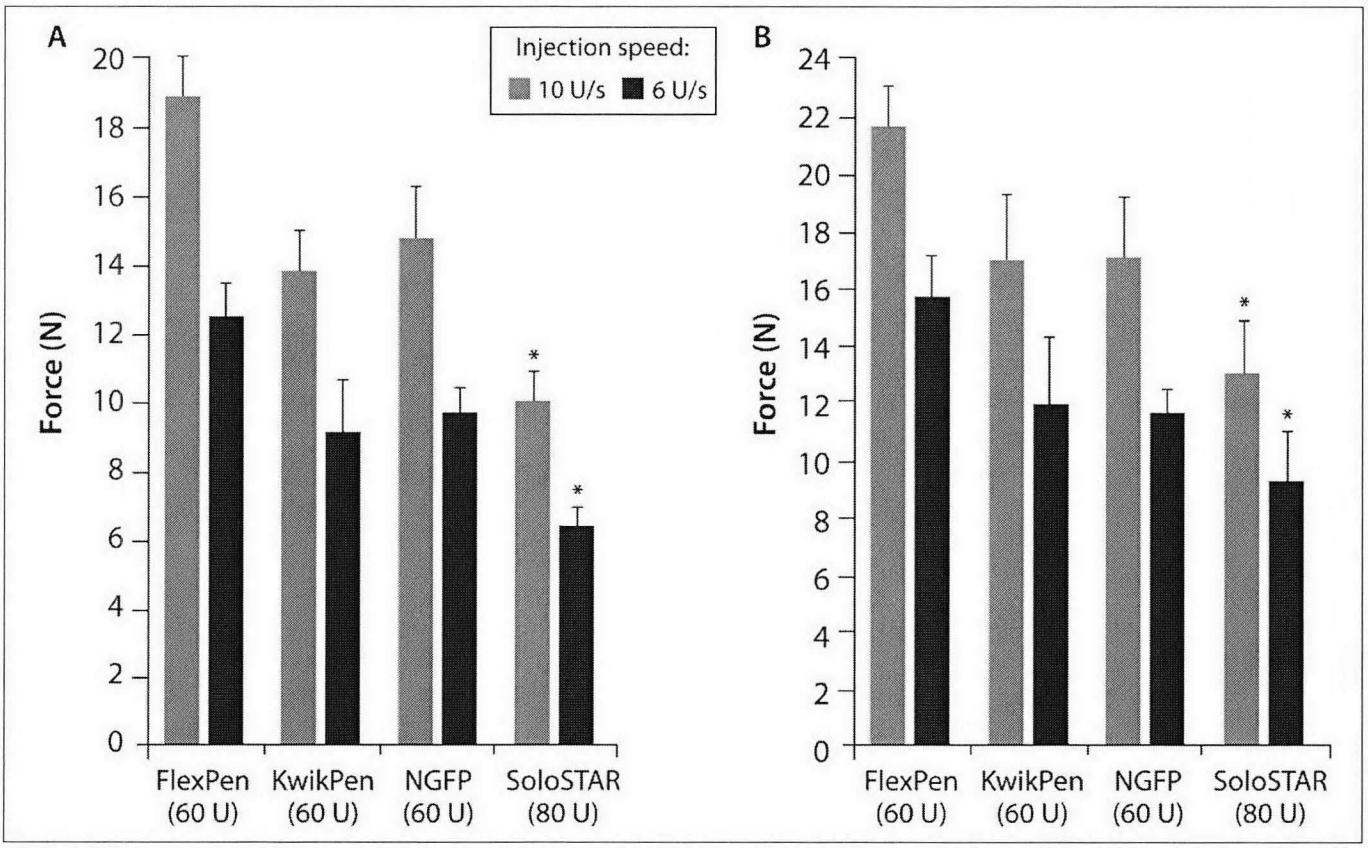


Figure 2. Comparison of mean plateau injection force **(A)** and maximum injection force **(B)** at two injection speeds for each pen and dose tested. Mean plateau and maximum injection forces of the various insulin pen devices were measured at maximum insulin dose for each pen (80 U for SoloSTAR; 60 U for the other pens and at two injection speeds (6 and 10 U/s) for each pen. Twenty pens of each type of device were tested twice for each dose and speed combination, and average values calculated. *$p < .001$ compared to comparator pens at the same injection speed.

Table 1.
Injection Force with Various Disposable Insulin Pen Types, Doses, and Injection Speed Combinations

	Dose (U)	Injection speed (U/s)	Button speed (mm/s)	Mean plateau injection force ± SD[a] (N)	Min–Max values (*n*)	Maximum injection force ± SD[a] (N)	Min–Max values (*n*)
SoloSTAR	80	6	2.6	6.43 ± 0.59	5.22–7.60	9.30 ± 1.71	6.17–14.68
	80	10	4.3	10.10 ± 0.84	8.72–12.15	13.10 ± 1.90	10.24–17.93
FlexPen	60	6	3.3	12.51 ± 0.96	10.72–14.30	15.79 ± 1.41	13.07–19.57
	60	10	5.5	18.91 ± 1.24	16.05–20.91	21.64 ± 1.52	18.46–23.72
NGFP	60	6	3.3	9.72 ± 0.72	8.44–11.87	11.71 ± 0.83	10.32–13.75
	60	10	5.5	14.79 ± 1.50	12.10–18.92	17.13 ± 2.17	13.76–25.30
KwikPen	60	6	2.8	9.17 ± 1.54	6.54–12.50	11.95 ± 2.52	6.67–16.58
	60	10	4.7	13.82 ± 1.31	11.32–16.35	16.99 ± 2.40	13.13–22.51

[a] SD = standard deviation

2.8–4.4 N. Therefore, the results of this study confirm the theoretical approach that the volume flow rate provides the main influence on the injection force for a specific pen/needle combination.

The findings from this study are in line with previously published laboratory-based studies in which the SoloSTAR pen had an improved injection force compared with the FlexPen device.[3]

The findings of this study disagree with the results of one study by Rissler and colleagues[10] and one study by Asakura and colleagues,[11] which suggested that the NGFP had a lower injection force compared with SoloSTAR. To understand the relevance of these conflicting data, it is important to recall that constant volume flow rates (U/s) were used in our study, whereas the other two studies used different injection button speeds (mm/s). The latter methodology means that, even at equal injection button speeds, the insulin flow in terms of U/s is not the same between the pen systems. Owing to the differences between the mechanisms of the pens, the volume of insulin expelled per second for SoloSTAR is 27.5% larger than that for FlexPen and NGFP. Elucidating the differences in the volume flow rates, dispensing the same volume of insulin with SoloSTAR requires a 22% smaller push-button travel and injection time (not accounting for differences in the holding time). This shorter push-button travel as the result of the shorter dial stroke extension is likely to be preferable for patients with impaired dexterity[3–7,12] as well as unimpaired patients.[13,14]

An observational, survey-based clinical study by Carter and colleagues reported high levels of acceptance of the SoloSTAR device among patients both with and without manual or dexterity impairment.[13] Participants found SoloSTAR easy to use and that using the pen had a positive impact on the management of their diabetes, such as increasing confidence and helping overcome their reluctance to use insulin.[13] In a study by Haak and colleagues where 16% of patients had dexterity problems and 19% visual impairment, more patients preferred the effort required to inject a 40 U dose with SoloSTAR versus FlexPen.[14] The findings of these studies may relate to the lower injection force characteristics of SoloSTAR versus the FlexPen device as demonstrated by Clarke and Spollett.[3] However, both of these studies demonstrated the usability and acceptance of SoloSTAR in these populations; they did not report the impact of injection force on the outcomes. Therefore, prospective studies are needed to extend these findings in patients with and without dexterity problems, and investigate whether the low injection force of available insulin pens is an important factor in their use of insulin and ultimately diabetes management.

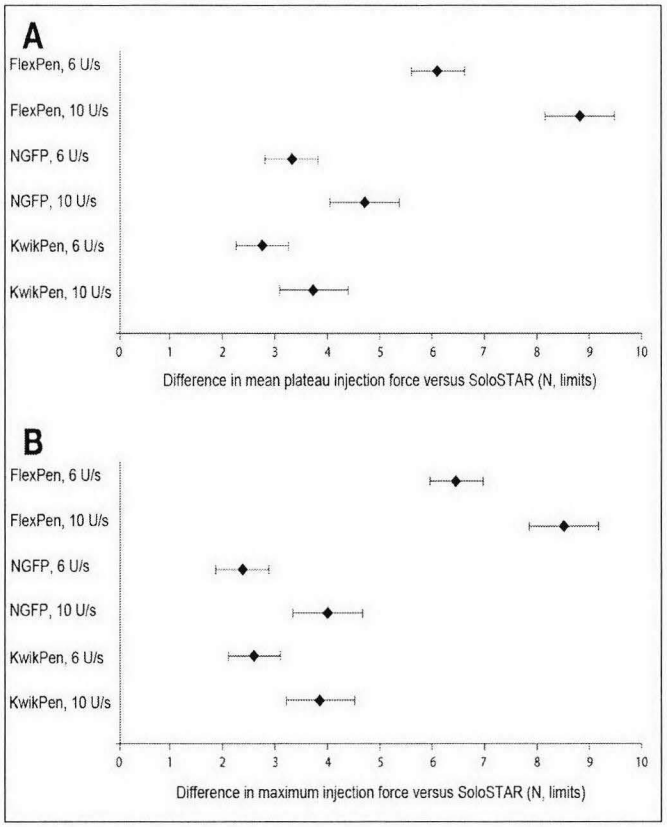


Figure 3. Interval of differences in mean plateau injection force **(A)** and maximum injection force **(B)** between SoloSTAR and the various comparators at maximum doses tested. Mean plateau and maximum injection forces of the various insulin pen devices were measured at maximum insulin dose for each pen (80 U for SoloSTAR; 60 U for the other pens) and at two injection speeds (6 and 10 U/s) for each pen. The average values for 20 pens tested twice each were calculated, and hence the difference between the average forces for SoloSTAR and each of the comparator pens as well as the limits (calculated with Dunnett's test for the difference between the respective group mean and SoloSTAR at 80 U). The differences in the mean maximum injection force and the mean plateau injection force between SoloSTAR and FlexPen, NGFP, and KwikPen were calculated with the resultant confidence intervals shown in **Figures 3A** and **B**. Only if 0 is within the confidence interval of the respective pair does the tested device show no significant difference to SoloSTAR. If 0 is not within the confidence interval, the compared pair can be assumed to be different with a probability of at least 98.8%. Due to the sufficient level of significance ($p < .012$), no further declaration for the probability for the tested pairs seems to be of value.

In order to maximize clinical relevance, we evaluated each pen together with the manufacturer's recommended needle in order to emulate real-world use. While needle outer diameters were consistent, potential variations of the inner diameter of needles within the manufacturers' specifications may have contributed to differences observed between the pens. It must also be acknowledged that

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.