Expert Opinion

An assessment of dose accuracy and injection force of a novel prefilled insulin pen: comparison with a widely used prefilled insulin pen

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Objective: FlexTouch® (FT) (Novo Nordisk A/S, Bagsværd, Denmark) is a new prefilled insulin pen with a novel injection mechanism encompassing no push-button extension at any dose-setting. This study assessed the dose accuracy and injection force of FT compared with the established Next Generation FlexPen® (NGFP) (Novo Nordisk A/S Bagsværd, Denmark).
Research design and methods: Dose accuracy was measured at the minimum, medium and maximum doses (FT, 1, 40 and 80 international units (IU) and NGFP, 1, 30 and 60 IU). Injection force was measured during the injection of the maximum dose (FT, 80 IU; NGFP, 60 IU).
Main outcomes: FT and NGFP delivered insulin accurately and consistently at all doses (mean ± s.d., FT at 1 IU, 0.98 ± 0.07; 40 IU, 39.86 ± 0.33; 80 IU, 79.76 ± 0.64; NGFP at 1 IU, 1.02 ± 0.08; 30 IU, 29.69 ± 0.30; 60 IU, 59.50 ± 0.51). FT had a significantly ($p < 0.0001$) lower injection force than NGFP.
Conclusions: The study demonstrated that FT and NGFP deliver insulin accurately and consistently at low, medium and high doses. The novel torque spring injection mechanism of FT results in a significantly lower injection force than NGFP and a pen requiring less thumb-pressure to inject insulin may be welcomed by many people with diabetes.

Keywords: accuracy, diabetes, injection force, insulin pen

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1. Introduction

People with type 1 and 2 diabetes have traditionally used vial and syringe to inject insulin, with many people reporting needle phobia, injection pain and anxiety over self-injection [1-5], and facing the social embarrassment and stigma of self-injection in public. Insulin pens simplify the injection process and are the method of choice for the delivery of insulin in Europe, China and Japan but their use is less common in the US.

The use of insulin pens overcomes many of the fears of injecting, and provides a more accurate method for the delivery of insulin, especially when low doses (< 5 international units (IU)) must be administered [6,7], which is an important advance in the management of diabetes. The use of insulin pens is associated with better adherence to insulin regimens compared with the use of vial and syringe [8-11]. This may be due to increased user preference, greater convenience, more flexibility and improved quality of life with use of insulin pens [12].

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Accuracy in delivering the correct dose of insulin is an extremely important first step to ensuring consistent insulin dosing and should lead to better management of glycaemic variations [13-15]. Next Generation FlexPen® (NGFP) (Novo Nordisk A/S, Bagsværd, Denmark) is a widely used, prefilled insulin pen and trials indicate it is more accurate than other prefilled pens for delivery of insulin at low, medium and high doses [13-16]. Also, it was demonstrated to have the lowest injection force of currently available prefilled insulin pens [15,17-18]. Diabetes patients and especially elderly people who may suffer from arthritis and co-morbidities of diabetes that affect manual dexterity [19-23] may prefer a pen with reduced injection force. In fact, it has been demonstrated that use of NGFP increased medication adherence but to date this has only been shown in comparison to vial and syringe [11].

To date, all prefilled insulin pens have used the same principle of dialling up a dose, with the push-button extending as the dialled dose increases, and insulin is delivered by depression of the extended push-button. FlexTouch® (FT) (Novo Nordisk A/S, Bagsværd, Denmark) is a novel prefilled insulin pen that has no push-button extension at any dose, which is a unique feature designed to eradicate the difficulties of injection force, and make insulin administration easier, smoother and more convenient [24].

Insulin delivery from FT occurs once the user presses a release button and injection is driven by a torque spring within FT, which differs from all other available prefilled insulin pens which rely on the thumb pressure of the user [24]. Loading of the torque spring occurs during dose-setting and pressing down the push-button activates the spring energy. The spring in the push-button determines the activation/injection force. The preparation of FT for injection has the same principal steps as other prefilled pens and there are no additional steps required for injection with FT compared to other prefilled pens. The purpose of this study was to compare the dose accuracy and injection force of FT with the widely used prefilled insulin pen NGFP.

2. Methods

2.1 Materials

Pens tested were: FT filled with 3 ml Levemir® (insulin detemir; Novo Nordisk A/S, Bagsværd, Denmark) (lot number XL700018 and YP51685); FT filled with 3 ml NovoRapid® (insulin aspart; Novo Nordisk A/S, Bagsværd, Denmark) (lot number XL700014 and XL 700015); and NGFP filled with 3 ml Levemir (lot number XP52830 and YP51108).

NovoFine® (NF) 31G 6 mm needles (Novo Nordisk A/S, Bagsværd, Denmark) were used for dose accuracy measurements. A single NF 32G Tip 6 mm needle was used for injection force measurements.

2.2 Equipment

All testing was carried out in a climate-controlled laboratory at 20°C (± 2°C) and 45% (± 7.5%) relative humidity. All pens were acclimatised for at least 4 h before testing. A Mettler AX105 balance (Mettler Toledo, Glostrup, Denmark) was used for the accuracy tests. The tensile tester (Lloyd LF Plus, Lloyd Instruments Ltd, Humlebaek, Denmark) was set to compression mode, and a calibrated transducer (measuring cell) with a maximum of 50 Newton (N) was used for the injection force experiments.

2.3 Dose accuracy

For this experiment, pens were as follows: 30 pens from two different production lots (15 each) for FT with Levemir, FT with NovoRapid and NGFP with Levemir [25]. Each of the 30 pens was used to deliver each dose twice (60 measurements of each dose level with each pen type were performed) as described in the International Organization for Standardization (ISO) 11608-1, 2000 [26].

Dose accuracy was measured for the minimum, medium and maximum doses of each pen type (1, 40 and 80 IU for FT and 1, 30 and 60 IU for NGFP). An NF 31G 6 mm needle was attached to each pen and air was expelled by performing air shots until liquid appeared at the tip of the needle. The appropriate dose was discharged and the pen was held in place for 6 s according to the instructions for use of each pen type, and the dose was weighed using a sensitive pharmaceutical balance (Mettler AX105, Mettler Toledo).

Results were corrected, from mg to IU, for the specific density of the insulin formulations using the following conversion factors: FT (NovoRapid 1.005; Levemir 1.008) and NGFP (Levemir 1.014). There are two different Levemir formulations which result in different specific densities. The conversion factor was used to calculate the relative difference from target in IU.

Outcome measures were the accuracy (mean) and consistency (s.d.) of the dose delivered from the pens compared with the specified dose. Results were compared with the acceptable range, as defined in ISO regulations (ISO 11608-1, 2000): 0 – 2 IU for 1 IU, 28.5 – 31.5 IU for 30 IU, 38 – 42 IU for 40 IU, 57 – 63 IU for 60 IU and 76 – 84 IU for 80 IU.

2.4 Injection force testing for FT

Because FT has the spring-loaded mechanism for delivery of the dose, the push-button speed has no influence on the rate of insulin delivery and, therefore, the injection force of FT was measured as activation force at the maximum dose (80 IU) [24].

An NF 32G Tip 6 mm needle was attached to the pen and air was expelled by performing air shots until liquid appeared at the tip of the needle. The pen was then set to 80 IU and placed in a fixture in the tensile tester with the push-button pointing upwards, allowing free flow from the needle.

The lowest speed for depressing the injection button was set to 0.2 mm/s, which enabled a precise and highly sensitive increase in the pressure on the push-button of the pen. This pressure was increased until the 'ignition' point was reached and the torque spring was activated. The force registered at the point of 'ignition' was recorded as the activation force

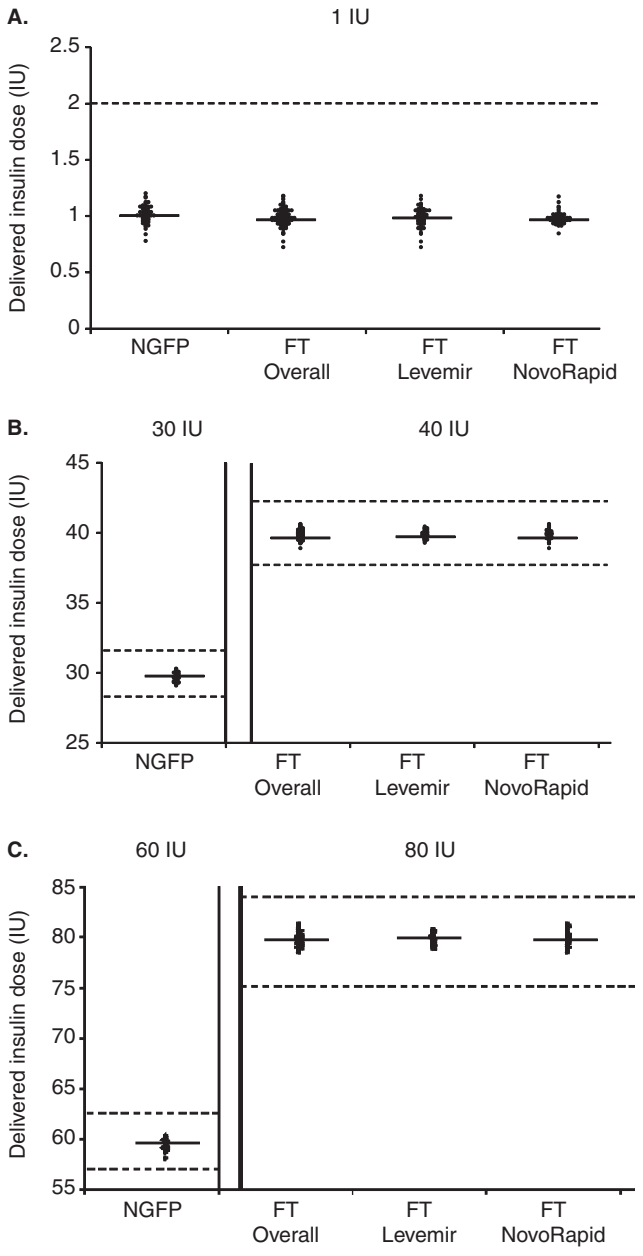

Figure 1. Accuracy of FT and NGFP under standard conditions at; A) low, **B)** medium and **C)** high target doses. Dots denote individual results for each test. Dotted lines denote the ISO limits.

FT: FlexTouch; ISO: International Organization for Standardization; IU: International units; NGFP: Next Generation FlexPen.

for FT. This procedure was conducted once with 25 pens for FT filled with Levemir and 25 pens for FT filled with NovoRapid.

2.5 Injection force testing for NGFP

The injection force of NGFP was measured as an isokinetic comparison (injection force measured at a constant push-button speed, corresponding to the speed at which a user would depress the push-button when injecting) while delivering a maximum dose of 60 IU, at three constant push-button speeds (4, 6 and 8 mm/s).

An NF 32G Tip 6 mm needle was attached to the pen and air was expelled by performing air shots until liquid appeared at the tip of the needle. The pen was set to the maximum dose (60 IU) and the first dose was discarded. The pen was then set to the maximum dose and placed in a fixture in the tensile tester with the push-button pointing upwards, allowing free flow from the needle. A dose was delivered by depressing the push-button at a speed of 4 mm/s; this was repeated at a speed of 6 mm/s and then 8 mm/s (maximum extension of the push-button was 32 mm). This procedure was conducted once for each of 25 pens.

2.6 Statistical analysis

For all calculations, the statistical software package JMP 8.02 was used. Pairwise comparisons were made via ANOVA analysis (fit model) and using Tukey's Honestly Significant Difference tests or pairwise comparisons if only two comparisons were made.

3. Results

3.1 Dose accuracy

All delivered doses from FT and NGFP were within ISO limits and both pens showed similar distributions at low, medium and high doses (**Figure 1**). The mean (s.d.; minimum–maximum) doses delivered with FT filled with NovoRapid and FT filled with Levemir when set to 1 IU were 0.98 (0.05; 0.85 – 1.17) and 0.99 (0.08; 0.72 – 1.18), respectively, when set to 40 IU the values were 39.86 (0.38; 38.90 – 40.63) and 39.87 (0.28; 39.28 – 40.45), respectively, and when set to 80 IU the values were 79.74 (0.70; 78.49 – 81.39) and 79.78 (0.58; 78.89 – 80.80), respectively. The accuracy of FT was, therefore, similar with both insulin formulations, and there were no statistically significant differences (all $p > 0.05$). Consequently, the data for both formulations were combined to give an overall value for the FT pen (**Table 1**). FT was accurate for the delivery of 1, 40 and 80 IU, and NGFP was accurate for the delivery of 1, 30 and 60 IU, both pens showing consistently low deviation from the target dose (**Table 1** and **Figure 1**). Accuracy of delivery of 1 IU was similar between FT and NGFP ($p = 0.443$).

3.2 Injection force

The mean injection force measured in Newtons (N) was significantly lower for FT than NGFP at all injection speeds ($p < 0.0001$; **Table 2** and **Figure 2**). The injection force of FT filled with Levemir and FT filled with NovoRapid were 4.9 ± 0.26 and 5.2 ± 0.60 N, respectively, with no statistically significant difference between these values ($p = 0.68$). Consequently, the data for both formulations were combined to give an overall value for the FT pen (**Table 2**). The injection force of FT was 62, 71 and 79% lower than NGFP at 4, 6 and 8 mm/s, respectively (all $p < 0.0001$; **Table 2**).

Table 1. Accuracy of FT and NGFP under standard conditions.

		Dose of insulin delivered (IU)			
Intended dose (IU)	**ISO limits (IU)**	**FT Mean ± s.d.**	**FT Min – max**	**NGFP Mean ± s.d.**	**NGFP Min – max**
1	0 – 2	0.98 ± 0.07	0.72 – 1.18	1.02 ± 0.08	0.78 – 1.20
30	28.5 – 31.5	NA	NA	29.69 ± 0.30	29.09 – 30.30
40	38 – 42	39.86 ± 0.33	38.90 – 40.63	NA	NA
60	57 – 63	NA	NA	59.50 ± 0.51	58.12 – 60.39
80	76 – 84	79.76 ± 0.64	78.49 – 81.39	NA	NA

FT: FlexTouch; ISO: International Organization for Standardization; IU: International units; NA: Not available; NGFP: Next Generation FlexPen.

Table 2. Mean difference between injection force of FT vs NGFP at three dose speeds.

Injection speed	**FT Injection force (N), mean ± s.d.**	**NGFP Injection force (N), mean ± s.d.**	**Difference in injection force FT vs NGFP mean**	**p**
Activation force	5.1 ± 0.48	NA	NA	NA
4 mm/sec	NA	13 ± 0.61	-8	< 0.0001
6 mm/sec	NA	17.8 ± 0.74	-12.7	< 0.0001
8 mm/sec	NA	23.9 ± 1.22	-18.8	< 0.0001

Note: 60 tests performed for each set dose.
FT: FlexTouch; N: Newton (N); NA: Not applicable; NGFP: Next Generation FlexPen.

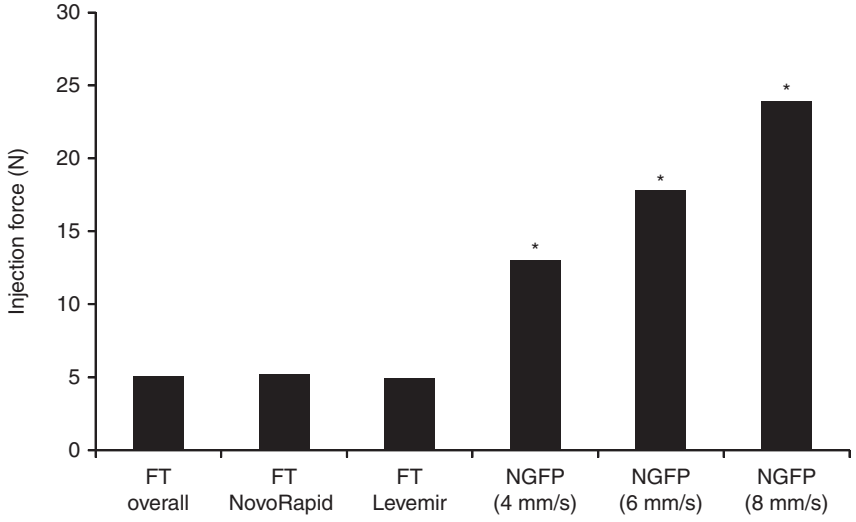

Figure 2. Mean injection force of FT and NGFP under standard conditions (mean of 25 measurements).
*All differences between FT vs NGFP $p < 0.0001$.
FT: FlexTouch; NGFP: Next Generation FlexPen.

4. Discussion

Previously, FlexPen® (FP) was shown to deliver insulin more accurately than other prefilled insulin pens at low, medium and high doses [13,14,27]. Modifications to the design of FP have resulted in the development of NGFP, which has previously been shown to have similar accuracy to FP [15]. The current study confirms previous findings on the consistently high dose accuracy of NGFP [15], and also demonstrates a similar consistent and accurate dose delivery of FT [25].

It is very important that people with diabetes and physicians have confidence in the accuracy of the insulin pen they are using, and the ability of the pen to consistently deliver insulin accurately is pivotal for good glycaemic control and

for reducing the risk of complications associated with diabetes [14,28]. Findings from this study confirm findings of a previous study and demonstrate that FT delivers insulin accurately and the delivered doses are consistently precise, as demonstrated by the small s.d. values at low, medium and high doses [25].

The injection force of NGFP has previously been shown to be lower than other commercially available injection pens at a range of injection speeds [18]. The results of this study show that the design modifications to FT have further reduced the injection force by up to 79% compared with NGFP. Injection force of FT has also been shown to be lower than for SoloStar® (Sanofi, Paris, France) and KwikPen® (Eli Lilly & Co., Indianapolis, IN, USA) [24].

The injection force of FT is determined by a torque spring within the pen, unlike other prefilled pens in which the thumb pressure on the extended push-button determines injection force; the result, as shown by the data in this study, is that FT has a considerably lower force during delivery of the dose. The lower injection force associated with FT could provide benefit to all people with diabetes who inject insulin to control blood glucose, and may have an added benefit for those with impaired manual dexterity, such as elderly people with arthritis and those with diabetes-associated neuropathy [20,21,23]. A lower injection force is preferred by insulin pen users because in general, a lower injection force makes it easier to inject the insulin [15].

A weakness of the study is that accuracy and injection force were assessed in an *in vitro* setting and it is conceivable that clinical subcutaneous administration of insulin could result in a different performance of the devices.

5. Conclusions

Insulin pens with high dose accuracy are an important aid for improving adherence and confidence in dose delivery, which may assist in the control of blood glucose levels and reduce long-term hyperglycaemia in diabetes. This study demonstrates that FT, a new prefilled pen, delivers insulin accurately and consistently at low, medium and high doses. The lower injection force associated with FT is an additional feature that may ease the injection process.

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Declaration of interest

This work was carried out at Novo Nordisk A/S, Bagsværd, Denmark. All authors are employees of Novo Nordisk A/S, Bagsværd, Denmark.

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