
Evaluation of the FreeStyle® Lite Blood Glucose Monitoring System

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Objective: To evaluate the analytical performance and clinical accuracy of the FreeStyle® Lite Blood Glucose Monitoring system.

Method: Clinical accuracy for fingertip capillary blood testing was assessed at three diabetes clinics with three lots of FreeStyle Lite test strips. At the same clinics, lay user performance and alternative site testing (on forearm, upper arm, palm thenar, palm hypothenar, back of the hand, calf and thigh) were also evaluated. FreeStyle Lite system results in these studies were compared to the plasma equivalent glucose values of the fingertip blood samples measured by the YSI Glucose Analyzer. Subjects participating in the user performance study rated the ease of use of the FreeStyle Lite system. Laboratory studies were performed at Abbott Diabetes Care to validate analytical performance of the FreeStyle Lite system under various testing conditions.

Results: In fingertip testing, accuracy of the FreeStyle Lite system was demonstrated by comparing results from 142 patients with the YSI plasma equivalent glucose values ($r = 0.99$, mean absolute bias = 4.7 %). We found 99.3% of the individual FreeStyle Lite system results within the ISO accuracy limits. ISO 15197 specifies that 95% of the individual meter results shall fall within ± 15 mg/dL (± 0.83 mmol/L) of the reference measurement procedure at glucose concentrations < 75 mg/dL (< 4.2 mmol/L) and within $\pm 20\%$ at glucose concentrations ≥ 75 mg/dL (≥ 4.2 mmol/L). Using more stringent criteria than ISO 15197, we found that 98.6%, 92.3% and 69.7% of the individual FreeStyle Lite system results fell within ± 15 , 10 and 5 mg/dL or %, respectively of the YSI values.

Alternative site testing results obtained with the FreeStyle Lite system by 180 lay users correlated well ($r = 0.97$) with those obtained by the trained operators. When compared to the fingertip blood glucose values from the YSI Analyzer, 99.6% of the alternative site test results obtained by the lay users fell within zones A and B of the Consensus Error Grid, indicating clinical acceptability. The lay users were also surveyed on the ease of use of the FreeStyle Lite system. Using a rating scale of 1 to 6 (6 reflecting the greatest ease), the overall mean rating was 5.6, indicating that these first-time users found the new system easy to use. In the pain rating survey, 90% of the users found testing on the arm with the FreeStyle Lite system completely or virtually painless.

In the analytical performance evaluation, repeatability (within-run precision) of the FreeStyle Lite system showed an average standard deviation of 3.4 mg/dL (0.19 mmol/L) at glucose concentrations < 100 mg/dL (< 5.56 mmol/L) and an average coefficient of variation (CV) of 4.3% at glucose concentrations ≥ 100 mg/dL (≥ 5.56 mmol/L). Intermediate (day-to-day) precision showed an average standard deviation of 2.9 mg/dL (0.16 mmol/L) at glucose concentrations < 100 mg/dL (< 5.56 mmol/L) and an average coefficient of variation (CV) of 3.4% at glucose concentrations ≥ 100 mg/dL (≥ 5.56 mmol/L). The measuring range of the FreeStyle Lite system is 20–500 mg/dL (1.1–27.8 mmol/L). Linearity was verified across this range, and the appropriate results of “LO” and “HI” were obtained when glucose concentrations exceeded the range. The FreeStyle Lite system was also shown to maintain accuracy across the operating temperature range of 4°C to 40°C.

Conclusions: In the clinical studies, the FreeStyle Lite system demonstrated excellent accuracy, consistent with the FreeStyle family of products. The users also found the no-coding FreeStyle Lite system very simple to use.

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A new blood glucose monitoring system, which requires no coding by the user, has been developed based on FreeStyle® technology. The FreeStyle Lite system (Figure 1) requires the smallest sample volume (0.3 µL) among current glucose meters, provides a fast test time (averages 5 seconds), and has a backlight and test port light for testing in low light conditions. Multicenter studies were conducted to evaluate accuracy, user performance and ease of use. Additional laboratory studies were performed to verify analytical performance.

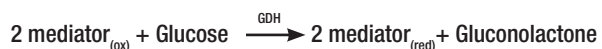


Figure 1. FreeStyle Lite Meter

MATERIALS AND METHODS

THE FREESTYLE LITE SYSTEM

The FreeStyle Lite system utilizes coulometric technology to quantify glucose, requiring 0.3 µL of whole blood for analysis. Coulometry is a patented electrochemical method available only in FreeStyle systems. Glucose in the sample is oxidized to gluconolactone via its reaction with glucose dehydrogenase (GDH) in the presence of an osmium mediator for electron transfer. The reaction proceeds as follows:



FreeStyle coulometric technology measures glucose based on the total charge generated by the reaction. More signal is measured by coulometry than by amperometry, which reads the current at a given time point or over a brief time period. This minimizes the error in the measurement and therefore coulometry is well suited for measuring glucose in a small sample size. It is also less sensitive to variations in hematocrit and temperature because

they affect the signal curve shape (the measured current) much more than the area under the curve (the measured charge). As with other products based on FreeStyle technology, the FreeStyle Lite system can be used with sample hematocrits from 15% to 65%, at altitudes from sea level to 10,000 feet (3082 meters), and for testing alternative sites including hand, forearm, upper arm, thigh and calf.

In the FreeStyle Lite system test, glucose in the blood sample reacts with glucose dehydrogenase (GDH) on the test strip and releases electrons to the enzyme. The electrons are shuttled by the electron mediator to the working electrode and are measured. The proprietary osmium-based mediator allows for the electron mediator to transfer electrons to the working electrode at a low applied potential, which minimizes the interference from reducing substances in the blood. The average test time is 5 seconds. An advantage of GDH is that it is not affected by the oxygen content in the blood sample.

The FreeStyle Lite test strip is designed to ensure reliable sampling. In addition to the working electrode, the test strip contains three other electrodes: two sample detection electrodes with a counter/reference electrode between them. The circuit connecting all three electrodes must be detected before the test will begin. This design minimizes the possibility of inaccurate results due to application of insufficient blood. Test strips for all FreeStyle systems, including the FreeStyle Lite system, requires 0.3 microliter of blood for a test. If the first drop of blood is insufficient to start the test, the user may apply a second drop of blood to the same test strip within 60 seconds of the first drop.

The FreeStyle system manufacturing process has been very consistent over a long period of time and the specification of the calibration has been constant within narrow limits and has given the users consistent and proven accuracy. This specification has been programmed into the no-coding FreeStyle Lite meter and all FreeStyle Lite test strips are manufactured to this specification to continue providing users with the accuracy they have come to expect from FreeStyle meters.

COMPARATIVE STUDIES

The YSI 2300 Stat Plus Glucose Analyzer (YSI Inc., Yellow Springs, OH) was used as the comparative method for all clinical and laboratory studies. The calibration accuracy of the YSI analyzer at each study site was validated by testing National Institute of Standards and Technology (NIST)¹ secondary reference material SRM 965a, which consists of four levels of glucose concentrations. The YSI whole blood glucose results were multiplied by 1.12 to yield plasma equivalent values.

CLINICAL STUDIES

Accuracy. The accuracy of the FreeStyle[®] Lite system for fingertip capillary blood testing was evaluated at three diabetes clinics, each using a different lot of test strips. A total of 163 subjects were enrolled. Twenty-one subjects were excluded due to protocol deviations, yielding 142 subjects. Fingertip capillary blood glucose results obtained with the FreeStyle Lite system were compared to results obtained on the YSI.

User Performance and Alternative Site Testing (AST). At the same three clinics, testing on the forearm, upper arm, palm (thenar and hypothenar), calf, thigh and back of the hand were evaluated using three lots of test strips. A total of 180 subjects participated in the study and each subject tested three of the alternative sites listed above. Five subjects were excluded due to protocol deviations and some tests were unsuccessful or gave non-numeric results, yielding more than 1000 meter tests for the seven body sites. Alternative site testing results obtained by the subjects with the FreeStyle Lite system were compared to those obtained by the trained healthcare professionals and to fingertip glucose results obtained on the YSI.

Ease-of-Use Surveys. In the user performance studies, the 180 lay users performed fingertip tests and AST on their own after reading the instructions for use. They were asked to complete a questionnaire rating various ease-of-use topics including handling of the test strips and alternative site testing. A scale of 1 to 6 was used, with a rating

of 6 reflecting the greatest ease. An overall ease of use rating was obtained by averaging all responses for the study.

Pain Rating. The 180 lay users at the three study centers participated in the pain rating survey for arm testing. After performing testing on their arms, these lay users were asked to rate the pain of testing.

LABORATORY STUDIES

The FreeStyle Lite meter utilizes the same measurement method and algorithm as the FreeStyle Freedom meter. The FreeStyle Lite test strip is identical to the FreeStyle test strip except for markings on the exterior of the strip, which enable the respective meter to recognize and accept the correct test strip. These recognition markings do not influence the analytical performances of the system. Laboratory studies were conducted at Abbott Diabetes Care to verify those analytical performances that may be influenced by the new meter electronics of the FreeStyle Lite system. These studies included precision, linearity, dynamic range, and temperature sensitivity. Other analytical performances are solely dependent on the test strip and therefore are the same as the FreeStyle Freedom system. They include the effects of hematocrit, interfering substances, humidity, altitude, sample volume and re-application. Therefore, these studies were not repeated on the FreeStyle Lite system.

Imprecision. Repeatability (within run precision) of the FreeStyle Lite system was assessed by analyzing heparinized venous blood samples at five glucose levels. Three lots of test strips and 16 FreeStyle Lite meters were used. Ten replicates were performed on each meter for each glucose level and test strip lot. For glucose concentrations < 100 mg/dL (< 5.56 mmol/L), the standard deviation values were averaged across the three strip lots. For glucose concentrations \geq 100 mg/dL (\geq 5.56 mmol/L), the coefficient of variation (CV) values of the three strip lots were averaged. Intermediate (day to day) precision of the FreeStyle Lite system was assessed with three levels of control solution. Three lots of test strips

and ten FreeStyle® Lite system meters were used over a 10 day period. Duplicate measurements were performed for 10 days on each meter for each control level and test strip lot. Both the standard deviation values and coefficient of variation values were calculated for each control level and averaged across the three test strip lots.

Linearity. Three heparinized venous blood samples were collected and each was adjusted to create nine glucose concentrations spanning the glucose measurement range. Three lots of FreeStyle Lite test strips were tested on six meters, with duplicate measurements performed for each lot of test strips, meter and glucose level.

Dynamic Range. Three venous blood samples were collected and each was adjusted to create two glucose levels: Low level at 13 ± 2 mg/dL (0.72 ± 0.11 mmol/L) and high level at 660 ± 60 mg/dL (36.7 ± 3.3 mmol/L). The six samples were tested in duplicate with 3 lots of FreeStyle Lite test strips on 6 FreeStyle Lite meters.

Temperature Sensitivity. Three heparinized venous blood samples were collected and each was adjusted to create three glucose levels at approximately 40, 90 and 360 mg/dL (2.2, 5.0, and 20.0 mmol/L). All nine samples were tested at three temperatures ($4 \pm 1^\circ\text{C}$, $25 \pm 1^\circ\text{C}$ and $40 \pm 1^\circ\text{C}$) with 3 lots of FreeStyle Lite test strips on 6 FreeStyle Lite meters. All tests were performed at a relative humidity of $50 \pm 5\%$ with $25 \pm 1^\circ\text{C}$ serving as the control condition. Duplicate measurements were performed for each lot of test strips, meter, glucose level and temperature. Averaged over three test strip lots, the difference in the bias from the YSI reference between the test conditions and the control condition ($25 \pm 1^\circ\text{C}$) was measured.

RESULTS

ACCURACY

In fingertip testing, accuracy of the FreeStyle Lite system was demonstrated by comparing results from 142 patients with the YSI plasma equivalent glucose values ($r = 0.99$, slope = 0.95, intercept = 7.2 mg/dL [0.4 mmol/L] by regression analysis;

mean absolute bias = 4.7%). We found 99.3% of the individual FreeStyle Lite system results within the ISO accuracy limits. ISO 15197 specifies that 95% of the individual meter results shall fall within ± 15 mg/dL (± 0.83 mmol/L) of the reference measurement procedure at glucose concentrations < 75 mg/dL (< 4.2 mmol/L) and within $\pm 20\%$ at glucose concentrations ≥ 75 mg/dL (≥ 4.2 mmol/L)². Using more stringent criteria than ISO 15197, we found that 98.6%, 92.3% and 69.7% of the individual FreeStyle Lite system results fell within ± 15 , 10 and 5 mg/dL or %, respectively of the YSI values.

Of the 142 test results, 141 (99.3 %) were in Zone A (clinically accurate) and 1 (0.7%) was in Zone B (clinically acceptable) of the Consensus Error Grid³ (Figure 2). The hematocrit range of the capillary blood specimens in this study was 24-56%.

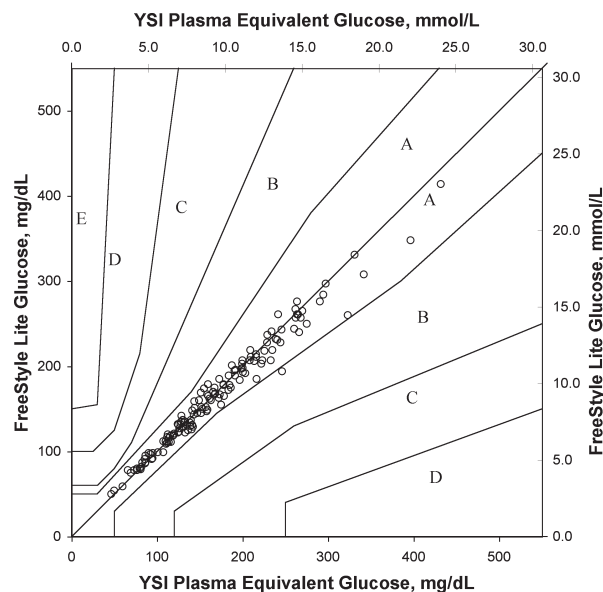


Figure 2. Consensus Error Grid Analysis of Fingertip Test Results

- Zone A: Clinically accurate (no effect on clinical action)
- Zone B: Clinically acceptable (altered clinical action—little or no effect on clinical outcome)
- Zone C: Altered clinical action—likely to affect clinical outcome
- Zone D: Altered clinical action—could have significant medical risk
- Zone E: Altered clinical action—could have dangerous consequences

ALTERNATIVE SITE TESTING

Even though the results of different blood samples were compared (FreeStyle Lite system

results on alternative site blood samples vs. YSI results on fingertip blood samples), good agreement was found between alternative site results obtained by lay users with the FreeStyle® Lite system and YSI fingertip results (slope = 1.03, intercept = 2.9 mg/dL [0.16 mmol/L], $r = 0.96$, $n = 502$). Consensus error grid analysis showed that 94.4% and 5.4% of the alternative site test results by the lay users fell within zones A and B, respectively (Table 1). In addition, results of lay users compared well with results of trained operators (slope = 1.02, intercept = -2.3 mg/dL [-0.13 mmol/L], $r = 0.97$, $n = 500$).

Table 1. Consensus Error Grid Analysis of the FreeStyle Lite System Results (AST) by Lay Users

	Percentage of AST Results				
	Zone A	Zone B	Zone C	Zone D	Zone E
n = 502	94.4	5.2	0.4	0	0

Zone A: Clinically accurate (no effect on clinical action)

Zone B: Clinically acceptable (altered clinical action—little or no effect on clinical outcome)

Zone C: Altered clinical action—likely to affect clinical outcome

Zone D: Altered clinical action—could have significant medical risk

Zone E: Altered clinical action—could have dangerous consequences

EASE OF USE

One hundred eighty lay users at the three study centers completed a questionnaire rating the FreeStyle Lite system for ease of use. A scale of 1 to 6 was used, with 6 reflecting the greatest ease. An overall ease-of-use rating of 5.6 was obtained when all responses were averaged, indicating that the lay users found the new system easy to use (Table 2).

The ages of the lay users ranged from 14 to 78 years old. Forty-eight percent of the subjects were male and 52% were female. Their education levels spanned from grade school to post graduate degrees. Twenty-five percent had type 1 diabetes, 63% had type 2 diabetes, and 12% did not have diabetes.

Table 2. Ease of use rating of the FreeStyle Lite system by Lay Users

Statement	Mean Rating*
I like that the meter does not need to be coded	5.6
It's easy to insert the test strip	5.6
It's easy to apply blood to the test strip	5.1
I had enough time to apply blood to the test strip	5.6
The test uses a small amount of blood	5.7
The display is easy to read	5.7
It's easy to understand how to use the meter	5.6
The test is fast	5.7
The meter fits comfortably in my hand	5.6
The meter is convenient to carry	5.6
The meter is easy to use	5.7
The meter is easy to learn	5.7
The test instructions are easy to follow	5.6
AST Testing: The meter is easy to use	5.4
AST Testing: The meter is easy to learn	5.7
Overall Mean	5.6

*The rating scale is 1 to 6 for each statement; (6 reflecting greatest ease).

PAIN RATING

One hundred eighty lay users at the 3 study centers completed a questionnaire rating the pain of alternative site testing with the FreeStyle Lite system. Ninety percent of lay users found arm testing with the FreeStyle Lite system completely or virtually painless (Table 3).

Table 3. Pain Rating in Arm Testing

Statement	Number (Percent) of users who selected response
Completely painless	133 (56%)
Virtually painless	82 (34%)
Slight pain	22 (9%)
Moderate pain	3 (1%)
Severe pain	0 (0%)

REPEATABILITY

In the repeatability (within-run precision) study, three lots of FreeStyle® Lite test strips, sixteen FreeStyle Lite meters and five fresh venous blood samples were tested. Averaged over the three strip lots, the standard deviation (SD) was 2.8–3.9 mg/dL (0.16–0.22 mmol/L) at glucose concentrations <100 mg/dL (< 5.56 mmol/L) and the coefficient of variation was 3.9 – 5.0% at glucose concentrations ≥ 100 mg/dL (≥ 5.56 mmol/L) (Table 4).

Table 4. Repeatability (Within-run Precision)

Mean, mg/dL (mmol/L)	29.4 (1.6)	66.2 (3.7)	138.5 (7.7)	176.8 (9.8)	386.6 (21.7)
SD, mg/dL (mmol/L)	2.8 (0.16)	3.9 (0.22)	6.9 (0.38)	7.1 (0.39)	14.9 (0.83)
CV, %			5.0	4.0	3.9

INTERMEDIATE PRECISION

In the intermediate (day-to-day) precision study, three lots of FreeStyle Lite test strips, ten FreeStyle Lite meters and three control solutions were tested. Averaged over the three strip lots, the standard deviation (SD) was 2.9 mg/dL (0.16 mmol/L) at glucose < 100 mg/dL (< 5.56 mmol/L) and the coefficient of variation was 3.3–3.5% at glucose ≥ 100 mg/dL (≥ 5.56 mmol/L) (Table 5).

Table 5. Intermediate Precision

Mean, mg/dL (mmol/L)	50.9 (2.8)	102.1 (5.7)	329.8 (18.3)
SD, mg/dL (mmol/L)	2.9 (0.16)	3.6 (0.20)	11.0 (0.61)
CV, %		3.5	3.3

LINEARITY

A total of 972 tests were conducted (duplicate tests using 3 venous samples each at 9 glucose levels, 3 lots of test strips and 6 meters). The average bias from the regression line was -0.5 mg/dL (-0.03 mmol/L) at glucose < 100 mg/dL (< 5.56 mmol/L) and -0.1% at glucose ≥ 100 mg/dL (≥ 5.56 mmol/L). A graphic presentation of the linearity data across the measurement range is shown in Figure 3.

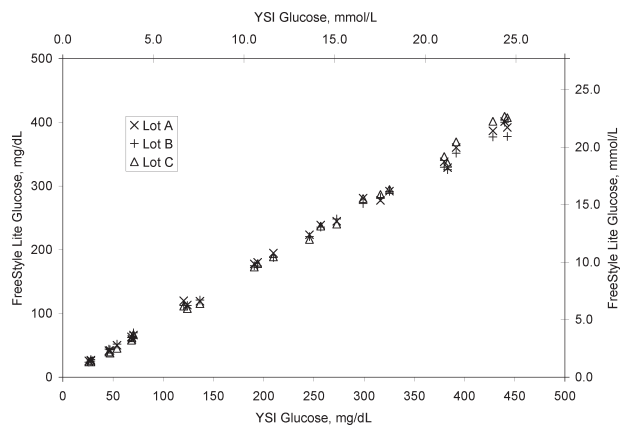


Figure 3. FreeStyle Lite System Linearity

DYNAMIC RANGE

The FreeStyle Lite system has a measuring range of 20–500 mg/dL (1.1–27.8 mmol/L). In this study, it displayed a “LO” result on all (100%) of 108 tests at the low glucose level (average: 12.6 mg/dL; 0.7 mmol/L) and a “HI” result on 100% of 108 tests at the high glucose level (average: 638.3 mg/dL; 35.5 mmol/L); no error messages were observed. Thus, the FreeStyle Lite meter displayed correct results when glucose concentrations were outside the measuring range.

TEMPERATURE SENSITIVITY

The bias (i.e., the difference between the FreeStyle Lite system result and the YSI result) at three operating temperatures ($4 \pm 1^\circ\text{C}$, $25 \pm 1^\circ\text{C}$ and $40 \pm 1^\circ\text{C}$) was measured at three glucose levels (40, 91 and 358 mg/dL; 2.2, 5.1 and 19.9 mmol/L). At glucose ≤ 75 mg/dL (≤ 4.2 mmol/L), the difference in the bias at the extreme temperatures ($4 \pm 1^\circ\text{C}$ and $40 \pm 1^\circ\text{C}$) was within 3 mg/dL (0.17 mmol/L) from the control condition ($25 \pm 1^\circ\text{C}$). At glucose > 75 mg/dL (> 4.2 mmol/L), the difference in bias was within 4% from the control condition. Thus, operating temperatures between 4°C and 40°C did not significantly affect the performance of the FreeStyle Lite system.

DISCUSSION

The no-coding FreeStyle Lite system showed excellent accuracy in the clinical studies.

Using YSI plasma equivalent glucose values as the reference, 99.3% of the FreeStyle® Lite system fingertip capillary results were within the ISO accuracy limits, thus exceeding the ISO 15197 requirement. ISO 15197 specifies that 95% of the individual meter results shall fall within ± 15 mg/dL (± 0.83 mmol/L) of the reference measurement procedure at glucose concentrations < 75 mg/dL (< 4.2 mmol/L) and within $\pm 20\%$ at glucose concentrations ≥ 75 mg/dL (≥ 4.2 mmol/L). Using more stringent criteria than ISO 15197, we found that 98.6%, 92.3% and 69.7% of the individual FreeStyle Lite system results fell within ± 15 , 10 and 5 mg/dL of the reference at glucose < 75 mg/dL (< 4.2 mmol/L) and within ± 15 , 10 and 5% of the reference at glucose ≥ 75 mg/dL (≥ 4.2 mmol/L).

This high level of accuracy can be attributed to the FreeStyle coulometry technology, which uses the total signal from the glucose reaction, thus reducing the effects of hematocrit and temperature variations. It also uses a low applied voltage in the assay to minimize interference from reducing substances such as acetaminophen (paracetamol), ascorbic acid (vitamin C) and uric acid. In addition, a pair of sample detection electrodes on each FreeStyle Lite test strip triggers the test to start when sufficient sample is detected. This is designed to minimize test errors and wasted test strips.

The lay user study validated that the FreeStyle Lite system provides simplicity for blood glucose monitoring. The 180 lay users in the study liked the fact that there is no coding with the FreeStyle Lite system, thus one less step for them to do. Furthermore, they agreed strongly that the FreeStyle Lite system is easy to learn and easy to use, and the test is fast and uses a small amount of blood. To make testing easier in dim light conditions, the FreeStyle Lite meter has a strip port light illuminating the area of test port and the inserted test strip. It also has a back light on the meter display for reading results. In the study, the lay users found the display of the FreeStyle Lite meter easy to read.

In summary, results from clinical studies with over 300 diabetic patients clearly show that the FreeStyle Lite system provides a high level of accuracy and simplicity for everyday testing.

References

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