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SYMPOSIUM

FreeStyle Lite—A Blood Glucose Meter That Requires No Coding

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Abstract

Background:

Abbott Diabetes Care introduced the FreeStyle® Lite blood glucose monitoring system, which simplifies the management of diabetes. The FreeStyle Lite system relies on FreeStyle technology but eliminates the need for coding the meter for individual strip lots. The meter is precoded for the FreeStyle Lite strips. FreeStyle systems use coulometry technology where the glucose signal is calculated from the total charge generated as a result of the glucose reaction in the sample. FreeStyle strip calibration parameters can be controlled by controlling the sample volume. Coulometry technology is less sensitive to measurement conditions such as temperature and hematocrit. FreeStyle chemistry is less sensitive to interference from electroactive compounds. The ability to control calibration parameters coupled to a robust measurement technology enabled the development of a blood glucose monitoring system that does not require coding by the user.

Methods:

Laboratory studies were performed to determine analytical performance, such as linearity, precision, and sensitivity to operating temperature. Clinical accuracy for finger tip capillary blood testing was assessed with five lots of FreeStyle Lite test strips. FreeStyle Lite results in these studies were compared to the plasma equivalent glucose values of finger tip blood samples measured by the Yellow Springs Instrument glucose analyzer.

Results:

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/liter) at glucose concentrations <100 mg/dl (<5.56 mmol/liter) and an average coefficient of variation of 4.3% at glucose concentrations ≥100 mg/dl (≥5.56 mmol/liter). Linearity demonstrated across the measuring range of the FreeStyle Lite system was 20–500 mg/dl (1.1–27.8 mmol/liter) with $r^2 > 0.99$. The FreeStyle Lite system was also shown to maintain accuracy across the operating temperature range of 4 to 40°C.

Conclusions:

The FreeStyle Lite system has good analytical performance and clinical accuracy. While simplifying the process of blood glucose monitoring, the FreeStyle Lite system continues to provide the performance that users have come to expect from FreeStyle products.

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Abbreviations: (CV) coefficient of variation, (ISO) International Organization for Standardization, (SD) standard deviation, (YSI) Yellow Springs Instrument

Keywords: coulometry, FreeStyle Lite, no coding

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Introduction

Electrochemical blood glucose monitoring systems have evolved since the launch of Exactech in 1987 by MediSense Inc., now a part of Abbott Diabetes Care. The time required to complete a test has changed from over 30 seconds to just less than 5 seconds. The volume of blood volume required to perform a successful test has dropped from over 10 µl to just about 300 nl. Lower blood volume requirements have decreased the pain of blood glucose testing, making tests at alternate sites a reality.

Diabetic patients perform blood glucose testing to manage their disease. They rely on the accuracy of the measurement to make appropriate medical interventions. Clarke[1] and consensus[2] error grids have been developed to graphically represent the clinical impact of errors in glucose measurements performed using handheld devices as compared to a laboratory reference. A high degree of clinical accuracy of blood glucose measurement with handheld devices is very essential in minimizing adverse effects of the treatment.

Some of the common initiating causes of inaccuracies in an electrochemical blood glucose monitoring systems are insufficient sample provided for the test and the effect of endogenous or exogenous interfering compounds. Inaccuracies caused by insufficient sample are minimized by introducing fill indicators to ensure that sufficient sample is provided to the strip. The assay does not start until sufficient blood sample is provided to the strip. Interference from endogenous and/or exogenous compounds that may be present in the sample can be minimized by selecting chemistries with improved substrate specificity and/or mediators that require lower oxidation voltages to perform the measurement.

Each strip lot has a unique calibration parameter (e.g., slope and intercept) that defines the performance of the strips from that strip lot. The manufacturer makes multiple lots of test strips using different lots of active (e.g., enzyme and mediator) and/or inactive (e.g., buffers and polymers) reagents. The composition of reagents could vary from one lot to the other. These variations from lot to lot would result in variation of calibration parameters. Therefore, the meter has to be configured to the strip lot that is being used for the measurement. This is achieved by the user either by inserting lot-specific calibration information to the meter using a smart chip or a calibrator or by selecting a calibration code from one of the preset calibration codes from the meter appropriate for the strip lot. This process is essential to ensure analytical performance of the system. If the manufacturer can control these variations, then the need for the user to configure the meter to the strip lot can be eliminated. This simplifies the process of blood glucose monitoring.

FreeStyle Strips

TheraSense, now a part of Abbott Diabetes Care, introduced the FreeStyle® blood glucose monitoring system in 2000 to improve the lives of diabetic patients.[3] These systems require only 300 nl of blood sample to perform a test and enable alternate site testing. The FreeStyle system uses pyrroloquinoline quinone dependent glucose dehydrogenase[4] with an osmium compound as the mediator. The mediator is oxidized at a very low oxidation voltage. The reaction scheme of FreeStyle strips is provided in **Figure 1**.

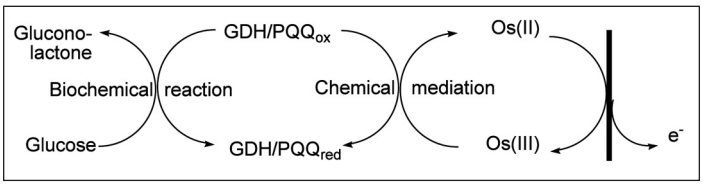

Figure 1. Reaction scheme of a FreeStyle strip.

The components of a FreeStyle test strip are shown in **Figure 2**. The strip consists of a working electrode on one of the substrates and a reference and two indicator electrodes on the other substrate. The active chemistry is coated on the working electrode. The two substrates are assembled to obtain an opposing arrangement of the electrodes by using an adhesive layer. The channel is cut out in the adhesive across the width of the strip. The strip insertion to the meter is detected by the turn-on bar located at the contact end of the strip. The dual-fill indicator electrodes across the fill channel ensure that the desired amount of the sample is provided to the strip before completion of the assay, minimizing test errors.

The FreeStyle system uses coulometry technology for glucose measurement. Coulometry is an electrochemical technique where the glucose concentration is determined from the total charge generated as a result of the reaction of the glucose in the sample. **Figure 3** shows the plot of charge as a function of time at various glucose levels. The time for completion of the reaction increases with

the glucose level. The measurement time in FreeStyle technology is dependent on the glucose concentration and increases with glucose, unlike an amperometric technique. This variable measurement time also compensates for the variations in reaction rates caused by measurement temperature, diffusion of glucose due to changes in hematocrit of the sample, and so on. FreeStyle technology also uses a low potential for the oxidation of the mediator, minimizing the interference from electrochemically active compounds, such as acetaminophen, ascorbic acid, and uric acid.

No-Coding FreeStyle Strips

In a coulometric measurement, the total charge measured from the sample at a given concentration of glucose is dependent only on the volume of the electrochemical cell. Therefore, in a coulometric technology, lot-to-lot variation can be minimized by controlling the volume of the sensor. The volume of the sample required to perform a test is defined by the channel dimensions. The length of the channel is defined by the width of the strip, which is fixed. The width and height of the channel can be varied independently to obtain the desired volume.

Abbott Diabetes Care introduced FreeStyle Lite blood glucose monitors that do not require coding. These meters are preconfigured with one set of calibration parameters representative of the FreeStyle Lite strips. Blood glucose measurement is affected by inherent imprecision in the manufacturing of the strip, as well as blood-to-blood variations in the clinical samples. Accounting for this variability in the system performance, the slope and intercept can have finite ranges without affecting the clinical accuracy of the device. When these meters are used with strips that have calibration parameters that are substantially identical (within this allowed range of slopes and intercepts) to that preconfigured in the meter, the analytical performance of the system is sufficient to give clinically accurate results.

Prior to the release of FreeStyle Lite strips that require no coding by the user, there was no control on the release of FreeStyle strip lots to the end user based on the distribution of calibration parameters. Therefore, the use of strips that are already in the marketplace with meters that require no coding had to be disabled. FreeStyle meters are activated by the turn-on bar electrode graphics on the top side of the strip. FreeStyle and FreeStyle Lite strips are differentiated by the turn-on electrode as shown in **Figure 4**. The strip port of the FreeStyle Lite meters was reconfigured not to be activated

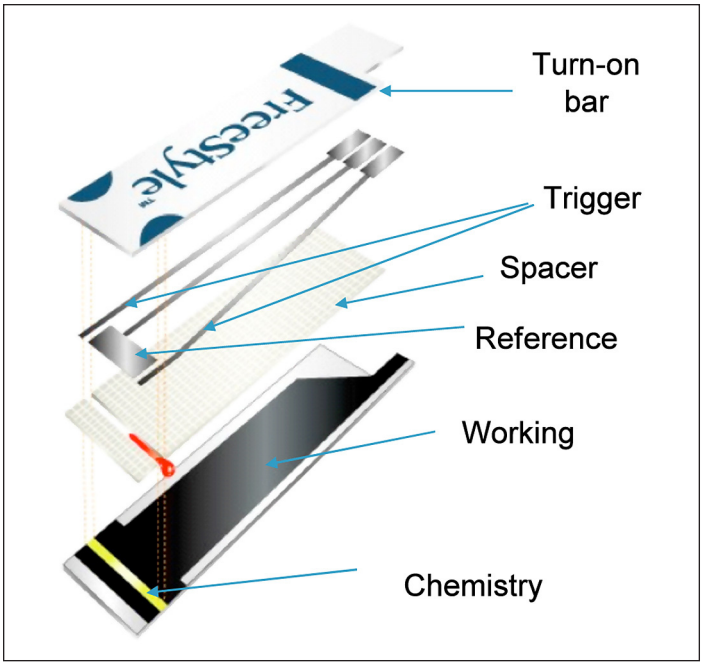

Figure 2. Construction of a FreeStyle test strip.

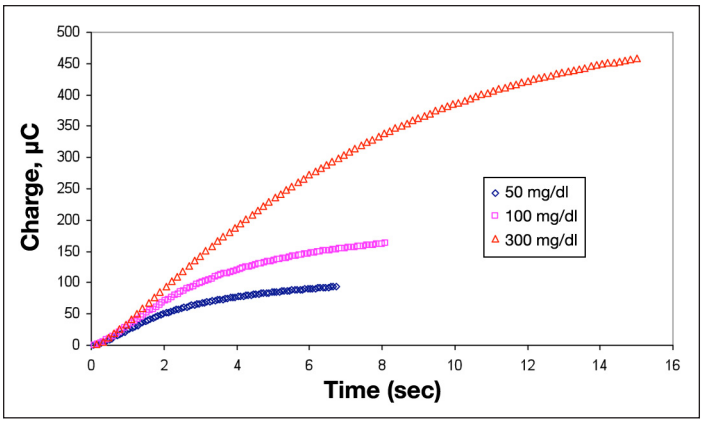

Figure 3. Signal profiles from FreeStyle strips as a function of time at different glucose levels.

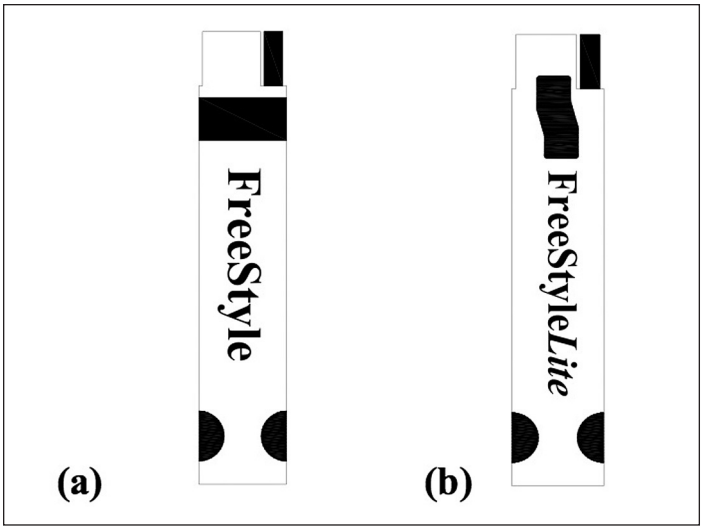

Figure 4. (a) FreeStyle and **(b)** FreeStyle Lite strips.

by the FreeStyle strips and only activated by FreeStyle Lite strips that have the correct design of the turn-on bar electrode.

Performance of a blood glucose monitoring system is determined by clinical accuracy and repeatability. Laboratory studies were performed on the FreeStyle Lite system to determine the linearity, repeatability, and sensitivity to temperature across the measurement range of 20 to 500 mg/dl. Clinical accuracy of the FreeStyle Lite system was determined by comparing the glucose results of finger capillary samples against the Yellow Springs Instrument (YSI) glucose analyzer.

Materials

Production FreeStyle Lite strips and meters were used for the study. Venous blood from healthy volunteers was drawn into heparinized tubes. The glucose concentration of the sample was adjusted to the desired level by either spiking with 1 *M* glucose solution or allowing the sample to glycolyze. Reference glucose measurements were performed using a YSI 2300 STAT Plus blood glucose analyzer.

Methods for Determining Analytical Performance

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.

Precision

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/liter), the standard deviation (SD) values were averaged across the three strip lots. For glucose concentrations ≥100 mg/dl (≥5.56 mmol/liter), the coefficient of variation (CV) values of the three strip lots were averaged.

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/liter). All nine samples were tested at three temperatures (4 ± 1, 25 ± 1, and 40 ± 1°C) with three lots of FreeStyle Lite test strips on six FreeStyle Lite meters. All tests were performed at a relative humidity of 50 ± 5% with 25 ± 1°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 ± 1°C) was measured.

Clinical Performance

The accuracy of the FreeStyle system for finger tip capillary blood testing was evaluated using five different strip lots. Each strip lot was tested with finger tip capillary blood samples from at least 50 patients in duplicate. Finger tip capillary blood glucose results obtained with the FreeStyle Lite system compared to results obtained on the YSI. Plasma equivalent glucose results were calculated from whole blood YSI measurements using the empirical relationship $YSI_{plasma} = YSI_{whole\ blood} * 1.12$.

Results and Discussion

Linearity

A total of 972 tests were conducted (duplicate tests using three venous samples each at nine glucose levels, three lots of test strips, and six meters). The average bias from the regression line was –0.5 mg/dl (–0.03 mmol/liter) at glucose <100 mg/dl (<5.56 mmol/liter) and –0.1% at glucose ≥100 mg/dl (≥5.56 mmol/liter). A graphic presentation of linearity data across the measurement range is shown in **Figure 5**.

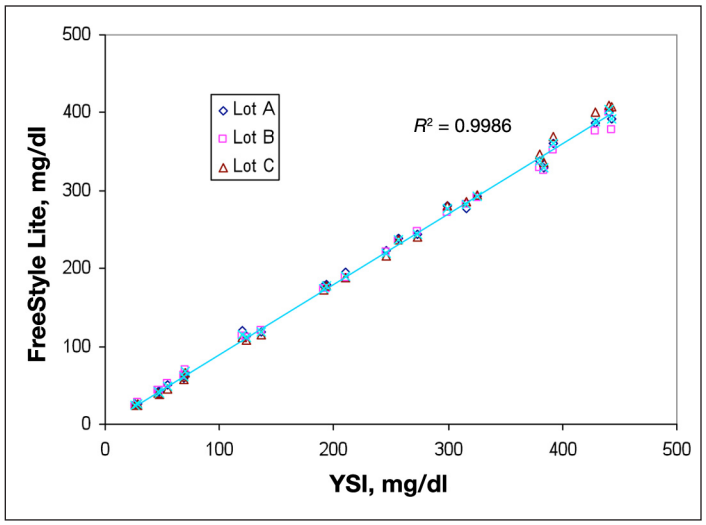

Figure 5. Linearity of FreeStyle Lite system across the measurement range.

Precision

In the repeatability (within-run precision) study, three lots of FreeStyle Lite test strips, 16 FreeStyle Lite meters, and five fresh venous blood samples were tested. **Table 1** summarizes repeatability data of FreeStyle Lite meters across the measurement range. Averaged over the three strip lots, the SD was 2.8–3.9 mg/dl (0.16–0.22 mmol/liter) at glucose concentrations <100 mg/dl (<5.56 mmol/liter) and the CV was 3.9–5.0% at glucose concentrations ≥100 mg/dl (≥5.56 mmol/liter).

Temperature Sensitivity

The bias (i.e., the difference between the FreeStyle Lite system result and the YSI result) at three operating temperatures (4 ± 1, 25 ± 1, and 40 ± 1°C) was measured at three glucose levels (40, 91, and 358 mg/dl; 2.2, 5.1, and 19.9 mmol/liter). **Table 2** summarizes temperature sensitivity data of FreeStyle Lite meters across the measurement range. At glucose ≤75 mg/dl (≤4.2 mmol/liter), the difference in the bias at the extreme temperatures (4 ± 1 and 40 ± 1°C) was within 3 mg/dl (0.17 mmol/liter) from the control condition (25 ± 1°C). At glucose >75 mg/dl (>4.2 mmol/liter), the difference in bias was within 4% from the control condition. Thus, operating temperatures between 4 and 40°C did not significantly affect the performance of the FreeStyle Lite system.

Clinical Performance

In finger tip testing, the accuracy of the FreeStyle Lite system was demonstrated by comparing results from 512 measurements with the YSI plasma equivalent glucose values [r^2 = 0.98, slope = 1.04, intercept = 1 mg/dl (0.1 mmol/liter) by regression analysis; mean absolute residual = 5.2%]. **Figure 6** shows the consensus (Parke) error grid analysis of the FreeStyle Lite results against YSI reference. We found 98.8% of the results in zone A and 1.2% of the results in Zone B of the grid. We found 96.9% of the individual FreeStyle Lite system results within the International Organization for Standardization (ISO) accuracy limits. ISO 15197 specifies that 95% of the individual meter results shall fall within ± 15 mg/dl (± 0.83 mmol/liter) of the reference measurement procedure at glucose concentrations <75 mg/dl (<4.2 mmol/liter) and within ± 20% at glucose concentrations ≥75 mg/dl (≥4.2 mmol/liter).[5]

The hematocrit range of the capillary blood specimens in the study was 31 to 52%. Over this hematocrit range, the test results did not show any hematocrit sensitivity (average sensitivity of the glucose results to the hematocrit of the sample was –0.09%/% hematocrit). This high level of clinical accuracy can be attributed to FreeStyle coulometry technology, which uses the total signal from the glucose reaction, thus reducing the effects of hematocrit.

Table 1.
Repeatability of FreeStyle Lite Meters (n = 480)

Mean glucose value (mg/dl)	29.4	66.2	138.4	176.8	386.6
SD (mg/dl)	2.8	3.9	6.9	7.1	14.9
CV (%)	9.4	6.0	5.0	4.0	3.8

Table 2.
Temperature Sensitivity of FreeStyle Lite Meters (n = 108)

Mean glucose value (mg/dl)	Bias at 4°C compared to 25°C		Bias at 40°C compared to 25°C	
	mg/dl	%	mg/dl	%
40.5	–2.9	–8.0	2.9	6.5
91.0	–1.8	–1.9	3.8	4.4
357.9	9.3	2.6	13.8	3.8

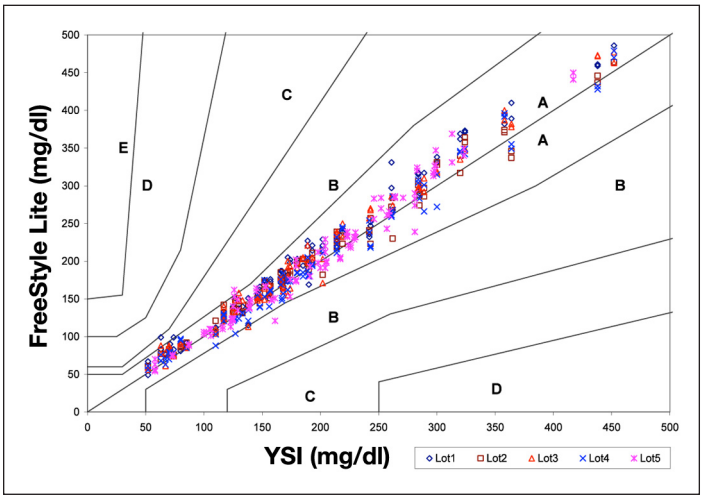

Figure 6. Clinical results from five test strip lots plotted on a Parke error grid: zone A, clinically accurate (no effect on clinical action); zone B, clinically acceptable (altered clinical action—little or no effect on clinical outcome); zone C, altered clinical action—likely to affect clinical outcome; zone D, altered clinical action—could have significant medical risk; and zone E, altered clinical action—could have dangerous consequences.

Conclusions

FreeStyle coulometry technology uses the total signal from the glucose reaction for calculating the glucose

concentration, thus minimizing the effects of hematocrit and measurement conditions such as temperature. The strip is designed with dual-fill indicators across the fill channel, minimizing test errors. Lower measurement voltage reduces interference from electroactive compounds that may be present in the sample. The charge measured in coulometry technology used in FreeStyle products is dependent on the sample volume. Precise control of the sample volume by optimizing the sample chamber dimensions allows for minimum variation between strip lots, allowing the development of FreeStyle Lite strips that require no coding.

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